

Toy . Girardet . Hormann . Lahoti
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CASE FILES

PEDIATRICS

- 60 Cases to excel on the boards and wards
- USMLE - style review questions
- Award-winning learning system
- Proven to increase shelf-exam scores

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PEDIATRICS

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- Elizabeth Gonston, Medical Student, Emory University

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Students Since 1938*

Case Files: Pediatrics

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Case Files: Pediatrics



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Case Files: Pediatrics

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*To my father-in-law J. Yen (Tommy) Ligh, whose inventive
genius and sense of humor is infectious, and in loving
memory of Lillie Woo Ligh, my mother-in-law whose
grace and beauty continue to shine.*

—ECT



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INTRODUCTION

Mastering the cognitive knowledge within a field such as pediatrics is a formidable task. It is even more difficult to draw on that knowledge, procure and filter through the clinical and laboratory data, develop a differential diagnosis, and finally form a rational treatment plan. To gain these skills, the student often learns best at the bedside, guided and instructed by experienced teachers, and inspired toward self-directed, diligent reading. Clearly, there is no replacement for education at the bedside. Unfortunately, clinical situations usually do not encompass the breadth of the specialty. Perhaps the best alternative is a carefully crafted patient case designed to simulate the clinical approach and decision-making. In an attempt to achieve that goal, we have constructed a collection of clinical vignettes to teach diagnostic or therapeutic approaches relevant to pediatrics. Most importantly, the explanations for the cases emphasize the mechanisms and underlying principles, rather than merely rote questions and answers.

This book is organized for versatility: it allows the student "in a rush" to go quickly through the scenarios and check the corresponding answers, while allowing the student who wants thought-provoking explanations to go at a more measured pace. The answers are arranged from simple to complex: a summary of the pertinent points, the bare answers, an analysis of the case, an approach to the topic, a comprehension test at the end for reinforcement and emphasis, and a list of resources for further reading. The clinical vignettes are purposely placed in random order to simulate the way that real patients present to the practitioner. Section III includes a listing of cases to aid the student who desires to test his or her knowledge of a certain area, or who wants to review a topic, including basic definitions. Finally, we intentionally did not primarily use a multiple choice question format because clues (or distractions) are not available in the real world. Nevertheless, several multiple choice questions are included at the end of each scenario to reinforce concepts or to introduce related topics.

HOW TO GET THE MOST OUT OF THIS BOOK

Each case is designed to simulate a patient encounter with open-ended questions. At times, the patient's complaint is different from the most

concerning issue, and sometimes extraneous information is given. The answers are organized with four different parts:

PART I:

1. **Summary:** the salient aspects of the case are identified, filtering out the extraneous information. The student should formulate his/her summary from the case before looking at the answers. A comparison with the summation in the answer helps to improve one's ability to focus on the important data, while appropriately discarding irrelevant information, a fundamental skill in clinical problem solving.
2. A **Straightforward Answer** is given to each open-ended question.
3. The **Analysis of the Case**, which is comprised of two parts:
 - a. **Objectives of the Case:** A listing of the two or three main principles that are crucial for a practitioner to manage the patient. Again, the student is challenged to make educated "guesses" about the objectives of the case upon initial review of the case scenario, which helps to sharpen the student's clinical and analytical skills.
 - b. **Considerations:** A discussion of the relevant points and brief approach to the **specific** patient.

PART II:

Approach to the Disease Process: This process has two distinct parts:

1. **Definitions:** Terminology pertinent to the disease process.
2. **Clinical Approach:** A discussion of the approach to the clinical problem in general, including tables, figures, and algorithms.

PART III:

Comprehension Questions: Each case contains several multiple-choice questions that either reinforce the material or introduce new and related concepts. Questions about material not found in the text have explanations in the answers.

PART IV:

Clinical Pearls: A listing of several clinically important points is reiterated as a summation of the text and placed at the end of each case to allow for easy review such as before an examination.

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The curriculum which evolved into the ideas for this series was inspired by two talented and forthright students, Philbert Yau and Chuck Rosipal, who have since graduated from medical school. It has been a tremendous joy to work with the excellent pediatricians at the University of Texas–Houston Medical School. I am greatly indebted to my editor, Catherine Johnson, whose exuberance, experience, and vision helped to shape this series. I appreciate McGraw-Hill's believing in the concept of teaching through clinical cases, and I would like to especially acknowledge John Williams, the director of editing. At the University of Texas–Houston Medical School, we appreciate John W. Sparks, MD, department chair of pediatrics and Maximillian Buja, MD, dean of the medical school, for their support and dedication to student education. At CHRISTUS St. Joseph Hospital, I applaud the finest administrators I have encountered: Sally Jeffcoat, Jeff Webster, Mark Mullarkey, and Dr. Benton Baker, III for their commitment to medical education, and Dorothy Mersinger for her sage advice and support. Without my dear colleagues, Drs. George T. Kuhn, Fernando Bueso, Aurora Gonzalez, and Dolar Patolia, this book could not have been written. Most of all, I appreciate my ever-loving wife Terri, and my four wonderful children, Andy, Michael, Allison, and Christina, for their patience and understanding

Eugene C. Toy

SECTION I

How to Approach Clinical Problems

PART 1. Approaching the Patient

PART 2. Approaching Clinical Problem
Solving

PART 3. Approaching Reading

PART 1. APPROACHING THE PATIENT

The transition from the textbook or journal article to the clinical situation is perhaps the most challenging in medicine. Retention of information is difficult; organization of the facts and recall of these myriad of data to apply to the patient is crucial. This text aids this process. The first step is gathering information, otherwise known as establishing the database. This consists of taking the history (asking questions), performing the physical examination, and obtaining selective laboratory and/or imaging tests.

The history is the single most important method of establishing a diagnosis. Depending on the age of the child, the information may be gathered solely from the parent, from both the parent and the child, or solely from the adolescent. The student should remember not to be misled by the diagnosis of another physician or by a family member. A statement such as "Johnnie has pneumonia and needs antibiotics" may or may not be correct; an astute clinician will keep an open mind and consider other possibilities, such as upper respiratory tract infection, aspirated foreign body, reactive airway disease, or even cystic fibrosis. The art of seeking the information in a nonjudgmental, sensitive, and thorough method cannot be overemphasized.

History

1. **Basic information:**
 - a. **Age, gender, and ethnicity** are important because some childhood illnesses occur with increased regularity at various ages, with higher frequency in one gender, or, more commonly, in one ethnic group. For instance, anorexia nervosa is more common in white adolescent females, while complications of sickle cell anemia are more common in African American children of both genders.
2. **Chief complaint.** This is usually the response that the patient or the patient's family member gives to the question: "Why are you seeing the doctor today?"
3. **History of present illness.** The onset, duration, and intensity of the primary complaint, as well as associated symptoms, exacerbating and relieving factors, and previous attempts at

therapy should be determined. For children, especially adolescents, a hidden agenda must be considered; **it is not uncommon for the adolescent to actually have questions about sexuality when the stated reason for the office visit is totally unrelated.** Both positive findings (the stool was loose, voluminous, and foul-smelling) and negative findings (without blood or mucous) are appropriate.

4. **Past history**

- a. **Pregnancy and delivery.** The age of the mother, the number of pregnancies, the route of delivery, and the gestational age of the infant can often provide clues as to the etiology of pediatric conditions. For instance, a large, full-term infant born by cesarean delivery who then develops an increased respiratory rate and streakiness on chest radiograph is more likely to have **transient tachypnea of the newborn** than is an infant born vaginally at 28-week gestation with similar symptoms. Similarly, a history of drug use (including over-the-counter, prescription, and illicit drugs) or infections during pregnancy should be obtained.
- b. **Neonatal history.** Any problems identified in the neonatal period, such as severe jaundice, infections, feeding difficulties, and prolonged hospitalization, should be reviewed, especially for the younger pediatric patients in whom residua of these problems may remain.
- c. **Surgical history.** When, where, and for what reason the surgery was performed should be explored. Complications should be noted.
- d. **Medical history.** While minor illnesses (such as occasional upper respiratory infections) can be reviewed quickly, more serious illnesses (such as diabetes mellitus) should be investigated fully. The age at diagnosis, treatments prescribed, and response to therapies can be reviewed. The number and nature of hospitalizations and complications are often important. For instance, a diabetic patient with frequent hospitalizations for ketoacidosis may indicate a lack of education of the family or underlying psychosocial issues complicating therapy. A child with a history of frequent, serious accidents should alert the physician of possible child abuse.

- e. **Developmental history.** For preschool children, a few questions about **language, fine motor, gross motor, and psychosocial skills** will provide good clues about development. For school-aged children, areas of strength and weaknesses are helpful.
- 5. **Allergies.** Reactions to medications should be recorded, including severity and temporal relationship to medications.
- 6. **Immunizations.** Dates for primary and booster series of immunizations should be recorded, preferably by reviewing the immunization cards. If the child is in school, a presumption that state laws regarding immunization completion can be made while the immunization card is being retrieved.
- 7. **Medications.** List the names of current medications, dosages, routes of administration and frequency, and durations of use. Prescription, over-the-counter, and herbal remedies are relevant.
- 8. **Sexual history of adolescents.** Details of an adolescent's sexual habits, contraceptive use, pregnancies, and sexually transmitted diseases should be determined.



CLINICAL PEARL

The adolescent must be treated with sensitivity, respect, and confidentiality to foster the optimal environment for medical care.

- 9. **Family history.** Because many conditions are inherited, the ages and health of siblings, parents, grandparents, and others can provide important diagnostic clues. For instance, an obese child with a family history of adult-onset diabetes is at high risk of developing diabetes; early intervention is warranted.
- 10. **Social history.** Living arrangements, economic situations, type of insurance, and religious affiliations may provide important clues for a puzzling diagnostic case or suggest important information about the acceptability of therapeutic options.
- 11. **Review of systems.** A few questions about each of the major body systems allows the practitioner to ensure that no problems are overlooked and to obtain crucial history about related and unrelated medical conditions.

Physical Examination

1. **General appearance.** Well- versus poorly nourished; evidence of toxemia, including lethargy (defined as poor or absent eye contact and refusal to interact with environment), signs of poor perfusion, hypo- or hyperventilation, and cyanosis; or stigmata of syndromes (such as Down or Turner).
2. **Skin.** In smaller children, the color of the skin for evidence of pallor, plethora, jaundice, or cyanosis is important. Abnormalities such as capillary hemangiomas (such as “stork bites” in a newborn), café-au-lait, pigmented nevi (such as “mongolian spots”), erythema toxicum, or pustular melanosis can be identified. In older children, macules, papules, vesicles, pustules, wheals, and petechiae or purpura should be described, and evidence of excoriation, crust formation, desquamation, hyperpigmentation, ulceration, scar formation, or atrophy should be identified.
3. **Vital signs.** Temperature, blood pressure (generally begin routine measurement after 3 years), heart rate, respiratory rate, height, weight, and head circumference (generally measured until age 3 years). Measurements are plotted and compared to normals for age.
4. **Head, eyes, ears, nose, and throat.**
 - a. **Head.** For the neonate, the size of fontanelles and presence of overriding sutures, caput succedaneum (superficial edema or hematoma that crosses suture lines, usually located over crown), or cephalohematoma (hematoma that does not cross suture lines) should be noted. For the older child, the size and shape of the head as well as abnormalities such as swellings, depressions, or abnormal hair quality or distribution may be identified.
 - b. **Eyes.** For infants, abnormalities in the size, shape, and position of the orbits, the color of the sclera (blue sclera, for instance, may indicate osteogenesis imperfecta), conjunctival hemorrhages or abnormalities, or the presence of iris defects (such as coloboma) may be found. The visual acuity of older children should also be obtained.
 - c. **Ears.** For all children, abnormalities in the size, shape, and position of the ears can provide important diagnostic

- clues. While tympanic membranes are difficult to assess in newborns, their integrity should be assessed in older children. For all children, the quality and character of discharge from the ear canal should be documented.
- d. **Nose.** The size, shape, and position of the nose (in relation to the face and mouth) can provide diagnostic clues for various syndromes, such as a small nose in Down syndrome. Patency of the nostrils, especially in neonates who are obligate nose breathers, is imperative. Abnormalities of the nasal bridge or septum, integrity of the mucosa, and the presence of foreign bodies should be noted. A butterfly rash around the nose can be associated with systemic lupus erythematosus (SLE) and a transverse crease across the anterior portion of the nose is seen with allergic rhinitis.
 - e. **Mouth and throat.** The size, shape, and position of the mouth and lips in relation to other facial structures should be evaluated. In infants, common abnormalities of the mouth include disruption of the palate (cleft palate syndrome), Epstein pearls (a tiny white papule in the center of the palate), and short frenulum ("tongue-tied"). For all children, the size, shape, and position of the tongue and uvula must be considered. The number and quality of teeth for age should be assessed, and the buccal mucosa and pharynx should be examined for color, rashes, exudate, size of tonsils, and symmetry.
5. **Neck.** The neck in infants is usually short and sometimes hard to evaluate. Nonetheless, the size, shape, and preferred position of the neck can be evaluated for all children. The range of motion may be evaluated by gentle movement. Symmetry of the muscles, thyroid gland, veins, and arteries is important. Identification of an abnormal mass such as a thyroglossal duct cyst (midline above the level of the thyroid) or brachial cleft cyst (along the sternomastoid muscle), or unusual findings, such as webbing in Turner syndrome, can be seen.
 6. **Chest.** General examination of the chest should include an evaluation of the size and shape of the structures along with identification of obvious abnormalities (such as supernumerary nipples) or movement with respirations. **Respiratory rate varies according to age** and ranges from 40 to 60 breaths per

minute in the neonate, to 12 to 14 breaths per minute in the toddler. **The degree of respiratory distress can be stratified with increasing distress noted when the child moves from subcostal to intercostal to supraclavicular to suprasternal retractions.** Palpation of the chest should confirm the integrity of the ribs and clavicles and any swelling or tenderness in the joints. Percussion in older children may reveal abnormalities, especially if asymmetry is noted. The chest should be auscultated for air movement, vocal resonance, rales, rhonchi, wheezes, and rubs. In adolescent girls symmetry of breast development and presence of masses or nipple discharge should be evaluated.

7. **Cardiovascular.** The precardium should be inspected for abnormal movements. The chest should be palpated for the location and quality of the cardiac impulse and to determine if a thrill is present. The presence and quality of the first and second heart sounds, including splitting with respirations should be noted. Murmurs, clicks, rubs, and abnormalities in rate (which varies by age) or rhythm should be identified. The peripheral perfusion, pulses, and color should be assessed.
8. **Abdominal examination.** The abdomen should be inspected to determine whether it is flat or protuberant, if masses or lesions such as striae are obvious, or if pulsations are present. In older children, the abdomen is usually flat, but in the neonate a very flat abdomen in a child with respiratory distress may indicate diaphragmatic hernia. The umbilicus, especially for neonates, should be evaluated for defects, drainage, or masses; a small umbilical hernia is often present and is normal. In the newborn, 1 umbilical vein and 2 umbilical arteries are normal. **In a neonate, palpation of the abdomen may reveal a liver edge about 2 cm below the costal margin, a spleen tip, and with deep pressure, kidneys.** In older children, these structures are not usually palpable except in pathology. Depending on the history, other masses must be viewed with suspicion for a variety of conditions. Bowel sounds are usually heard throughout the abdomen except in pathology. In adolescent females, the lower abdomen should be palpated for uterine enlargement (pregnancy).

9. **Genitalia.** Examination of the male for the size and shape of the penis, testicles, and scrotum is important. The position of the urethral opening should be assessed. In newborn girls, the labia majora is usually large and completely encloses the labia minora; the genitalia is usually highly pigmented and swollen with an especially prominent clitoris. A white discharge is usually present in the first days of life, and occasionally a blood-tinged fluid is also seen. In toddlers, examination of the genitalia can be challenging. Placing the toddler in a frog-leg position while the toddler sits in the parent's lap (or on the examination table) often allows successful viewing of external genitalia. In older girls, the knee-chest position affords an excellent view of the external genitalia. In girls outside the newborn period, the labia minora are smaller compared to the remainder of the external genitalia, and the vaginal mucosa is red and appears thin. The hymen, which is just inside the introitus, should be inspected. Abnormalities of the hymen, such as imperforation or tags, vaginal discharge or foreign bodies, and labial adhesions, may be noted. A speculum examination should be performed for sexually active adolescent girls. Tanner staging for pubertal development should be done for both boys and girls. Inguinal hernias should be identified; normalcy of anus should be confirmed.
10. **Extremities.** For all children, the size, shape, and symmetry of the extremities should be considered; muscle strength should be evaluated. Joints may be investigated for range of motion, warmth, tenderness, and redness. Normalcy of gait for age should be reviewed. For infants, recognition of dislocated hips is of critical importance, as life-long growth abnormalities may result. In contrast, identification of scoliosis in adolescents is important to prevent the debilitating complications of that condition. Athletes require evaluation of the integrity of their joints, especially those to be used in sporting activities.
11. **Neurologic.** Neurologic evaluation of the older child is similar to that in adults. The level of consciousness and orientation is determined as a starting point. The cranial nerves should be assessed. The motor system should be evaluated (including strength, tone, coordination, and involuntary

movements). Superficial and deep sensory systems, and deep tendon reflexes should be reviewed. **In younger, infants a variety of normal primitive reflexes (Moro, parachute, suck, grasp) can be found, but ensuring that these reflexes have extinguished by the appropriate age is equally important.**

Laboratory Assessment

The American Academy of Pediatrics recommends a few laboratory screening tests be accomplished for pediatric patients. These tests vary according to the child's age and risk factors.

1. **Newborn metabolic screening** is done in all states, usually after 24 hours of age, but the exact tests performed vary by state. Conditions commonly screened for include hypothyroidism, phenylketonuria, galactosemia, hemoglobin type, and adrenal hyperplasia. Other conditions that may be assessed include maple syrup urine disease, homocystinuria, biotinidase deficiency, cystic fibrosis, tyrosinemia, and toxoplasmosis. Some states require a second newborn screen be performed after 7 days of age.
2. **Hemoglobin or hematocrits** are recommended for high-risk infants (especially premature infants and those with low birth weight), at 9 to 12 months of age, and yearly on all menstruating adolescents.
3. **Urinalyses** are recommended at 9 to 12 months of age and at 5 years of age, and dipstick urinalysis for leukocytes annually for sexually active adolescents.
4. **Lead screening** is done, especially in high-risk areas, at 9 to 12 months of age, and again at 2 years of age.
5. **Cholesterol screening** is performed in high-risk patients (those with positive family histories) older than 24 months of age.
6. **Sexually transmitted disease screening** is performed yearly on all sexually active patients.

Other, specialized testing is accomplished depending on the age, risk factors, chief complaint, and conditions included in the differential diagnosis.

Imaging Procedures

1. **Plain radiographs** offer the advantage of inexpensive testing that reveals global views of the anatomy. Unfortunately, fine organ detail is not revealed sometimes, requiring further radiographic study. Bone films for fracture, chest films for pneumonia, and abdomen films for ileus are common uses of this modality.
2. **Ultrasonography** is a fairly inexpensive modality that requires little or no sedation and has no radiation risks. It offers good organ and anatomic detail, but can be operator dependent. Not all organs are accessible to sonography. Common examinations include the head for intraventricular hemorrhage in the premature infant, the abdomen for such conditions as pyloric stenosis, and the kidneys for abnormal structure.
3. **Computer tomography** provides good organ and anatomic detail and is quick, but it is fairly expensive, may require contrast, and does involve radiation. Some children require sedation to complete the procedure. This test is often performed on the abdomen or head in trauma victims.
4. **Magnetic resonance imaging** is expensive but does not involve radiation. Because it is a slow procedure, sedation is often needed for younger children, and contrast is sometimes required. It allows for superb tissue contrast in multiple planes, and excellent anatomic and now functional imaging. It is frequently used to provide detail on the brain in patients with seizures or developmental delay or on a mass located virtually anywhere to provide tissue detail.
5. **Nuclear scan** is moderately expensive and invasive. It provides functional information (usually organ specific) but provides poor anatomic detail. Radiation is involved. Common uses include bone scans for infection and renal scans for function.

PART 2. APPROACHING CLINICAL PROBLEM SOLVING

There are generally **four steps** to the systematic solving of clinical problems

1. Make the diagnosis
2. Assess the severity of the disease

3. Render a treatment based on the stage of the disease
4. Follow the response to the treatment

Making the Diagnosis

This is achieved with careful sifting of the database, analysis based on the risk factors present and the development of the list of possibilities (the differential diagnosis). The process includes knowing which pieces of information are more meaningful and which may be discarded. Experience and knowledge from reading help to guide the physician to key in on the most important concerns. **A good clinician also knows how to ask the same question in several different ways and using different terminology**, because patients at times will deny having been treated for asthma but will answer affirmatively to being hospitalized for wheezing. Reaching a diagnosis may be obtained by systematically reviewing each possible cause and reading about each disease. The patient's presentation is then matched up against each of these possibilities, and either placed higher up on the list as a potential etiology, or lower down because of the disease frequency, the patient's presentation, or other clues. A patient's risk factors may influence the probability of a diagnosis. Usually a long list of possible diagnoses can be pared down to two or three top suspicions, based on key laboratory or imaging tests. For example, an adolescent child presenting with a fever as the chief complaint can have an extensive differential diagnosis reduced to far fewer possibilities when the history reveals an uncle in the home with cough, weight loss, and night sweats and the physical examination shows an increased respiratory rate, lymphadenopathy, and right lower lobe lung crackles. In this case, it is likely that the patient has tuberculosis.

Assessing the Severity of the Disease

The next step is to characterize the severity of the disease process. In asthma, this is done formally based on guidelines promulgated by the National Heart, Lung, and Blood Institute. Asthma categories range from mild intermittent (least severe) to severe persistent (most severe). For some conditions, such as syphilis, the staging depends on the length of time, and follows along the natural history of the infection (i.e. primary, secondary, or tertiary syphilis).

Treatment Based on Stage

Many illnesses are stratified according to severity because prognosis and treatment varies based on the severity. If neither the prognosis nor the treatment were affected by the stage of the disease process, it would not make much sense to subcategorize something as mild or severe. As an example, mild intermittent asthma poses less danger than does severe persistent asthma (particularly if the patient has had to be intubated for their asthma in the past). Accordingly, with mild intermittent asthma, the management would be intermittent short-acting β -agonist therapy while watching for any worsening of the disease into more serious categories (more severe disease). In contrast, a patient with severe persistent asthma would generally require short-acting β -agonist medications as well as long-acting β agonists, inhaled steroids, and potentially oral steroids.

Group A β -hemolytic streptococcal pharyngeal infection ("strep throat") is associated with complications including poststreptococcal glomerulonephritis and rheumatic fever. The presence of group A β -hemolytic streptococcus confers an increased risk of problems, but neither the prognosis nor the treatment is affected by "more" group A β -hemolytic streptococcus or "less" group A β -hemolytic streptococcus. Hence, **the student should approach new disease by learning the mechanism, clinical presentation, how it is staged, and how the treatment varies based on stage.**

Following the Response to Treatment

The final step in the approach to disease is to follow the patient's response to the therapy. **Whatever the "measure" of response, it should be recorded and monitored.** Some responses are clinical, such as patient's pain, or temperature, or pulmonary examination. Obviously the student must work on being more skilled in eliciting the data in an unbiased and standardized manner. Other patients may be followed by imaging such as computerized tomography (CT) scan of a retroperitoneal node size in a patient receiving chemotherapy for neuroblastoma, or a marker such as the platelet count in a patient recovering from Kawasaki disease. For syphilis, it may be the nonspecific treponemal antibody test rapid plasma reagin (RPR) titer every month. The student must know what to do if the measured marker does not respond according to

the expected. Is the next step to treat further, or to repeat the metastatic work-up, or to follow-up with another more specific test?

PART 3. APPROACHING READING

The student must approach reading differently than the classic “systematic” review of a particular disease entity. Patients rarely present with a clear diagnosis; hence, the student must become skilled in applying the textbook information to the clinical setting. Everyone retains more when the reading is performed with a purpose. Experience teaches that with reading, there are several crucial questions to consider **thinking clinically**. These are:

1. What is the most likely diagnosis?
2. What should be your next step?
3. What is the most likely mechanism for this process?
4. What are the risk factors for this condition?
5. What are the complications associated with the disease process?
6. What is the best therapy?

What is the Most Likely Diagnosis?

Establishing the diagnosis was discussed in the previous section. This is a difficult task to give to the medical student; however, it is the basic problem that will confront clinicians for the rest of their careers. One way of attacking this problem is to develop standard “approaches” to common clinical problems. It is helpful to memorize the most common causes of various presentations, such as “the most common cause of mild respiratory distress in a term infant born by cesarean section is retained amniotic fluid (transient tachypnea of the newborn).”

The clinical scenario would entail something such as:

“A 3-hour-old infant is noted to have mildly increased respiratory rate and slight subcostal retractions. The infant is term, large for gestation age and was born by repeat cesarean section. The pregnancy was uncomplicated. What is the most likely diagnosis?”

With no other information to go on, the student would note that this baby has respiratory distress. Using the “most common cause” information, the student would guess transient tachypnea of the newborn. If, instead, the gestational age “term” is changed to “preterm at 30 weeks gestation,” a phrase may be added such as:

“The mother did not receive prophylactic steroids prior to birth.”

Now, the student would use the “most common cause of respiratory distress in a preterm child whose mother did not receive prenatal steroids” is surfactant deficiency (respiratory distress syndrome).

What Should Be Your Next Step?

This question in many ways is even more difficult than the most likely diagnosis, because insufficient information may be available to make a diagnosis and the next step may be to pursue more diagnostic information. Another possibility is that the diagnosis is clear, but the next step is the staging of the disease. Finally, the next step may be to treat. Hence, from clinical data a judgment needs to be rendered regarding how far along one is on the road of:

Make diagnosis → Stage disease →

Treat based on the stage → Follow response

In particular, the student is accustomed to regurgitating the same information that someone has written about a particular disease, but is not skilled at giving the next step. This talent is optimally learned at the bedside, in a supportive environment, with freedom to take educated *guesses, and with constructive feedback.* The student in assessing a child in the hospital should go through the following thinking process:

1. Based on the information I have, I believe that Cedric Johnson (a 3-month-old child with a positive respiratory syncytial virus nasal washing) has bronchiolitis.
2. I don't believe that this is severe disease (such as significant oxygen requirement, severe retractions, or carbon dioxide retention on blood gas analysis). A chest radiograph shows no lobar

consolidation (I believe this is important because a lobar consolidation would suggest a bacterial etiology).

3. Therefore, the treatment is supportive care with supplemental oxygen and intravenous fluids as needed.
4. I want to follow the treatment by assessing Cedric's respiratory status (I will follow the oxygen saturation and degree of retractions), his temperature, and his ability to maintain his hydration orally without intravenous fluids. Also, if in the first few days, Cedric does not get better, or if he worsens, I think he will need a repeat chest radiograph to assess whether he has an evolving bacterial pneumonia.

In a similar patient, when the clinical presentation is not so clear, perhaps the best "next step" may be diagnostic in nature such as blood cultures to determine if bacteremia is present. This information is sometimes tested by the dictum, "the gold standard for the diagnosis and treatment of a bacterial infection is a culture."

Sometimes the next step is therapeutic.

What is the Likely Mechanism for this Process?

This question goes further than making the diagnosis, but also requires the student to understand the underlying mechanism for the process. For example, a clinical scenario may describe a 5-year-old child with Henoch-Schönlein purpura who develops abdominal pain and heme-positive stools 1 week after diagnosis. The student first must diagnose the heme-positive stools associated with Henoch-Schönlein purpura, which occur in approximately 50% of patients. Then, the student must understand that the edema and damage to the vasculature of the gastrointestinal (GI) tract can cause bleeding along with colicky abdominal pain, sometimes progressing to intussusception. The mechanism of the pain and bleeding is, therefore, vasculitis causing enlarged mesenteric lymph nodes, bowel edema, and hemorrhage into the bowel. Answers that a student may speculate, but would not be as likely, include appendicitis, bacterial gastroenteritis, or volvulus.

The student is advised to learn the mechanisms for each disease process, and not merely to memorize a constellation of symptoms. In other words, rather than trying to commit to memory the classic pre-

sentation of Henoch-Schönlein purpura (typical rash, abdominal pain, and arthritis), the student should also understand that vasculitis of the small vessels is the culprit. The vasculitis causes edema mainly in the dependent areas that precedes the palpable purpura. This vasculitis is responsible not only for edema in the joints (mainly in dependent areas such as the knees and ankles) causing the arthritis found in approximately two-thirds of patients, but also damage to the vasculature of the GI tract leading to the intermittent, colicky abdominal pain that can manifest as heme-positive stools or even intussusception.

What are the Risk Factors for this Process?

Understanding the risk factors helps to establish a diagnosis and to determine how to interpret results. For example, understanding the risk factor analysis may help to manage a 1-year-old child with anemia found on routine screening. If the child had no risk factors for lead poisoning or thalassemia, the practitioner may choose to treat with supplemental iron, because the likelihood for more serious pathology is low. On the other hand, if the same 1-year-old child were a recent immigrant from an endemic area, lived in a older home with peeling paint, had a father who worked at a battery smelting plant, and ate meals from unglazed pottery, a practitioner should presumptively diagnose lead poisoning until proven otherwise. The physician may want to perform a serum lead level, a complete blood count with differential (looking for basophilic stippling), and thoroughly evaluate the child for developmental delay. Thus, the number of risk factors helps to categorize the likelihood of a disease process.

What are the Complications to this Process?

A clinician must understand the complications of a disease, so that the patient can be monitored. Sometimes, the student will have to make the diagnosis from clinical clues, and then apply his knowledge of the sequelae of the pathological process. For example, a child diagnosed with high fever, rash, lymphadenopathy, and oral and conjunctival changes is diagnosed with Kawasaki disease. Complications of this condition include arthritis, vasculitis of the medium-sized arteries, hydrops of the gallbladder, urethritis, and aseptic meningitis. Understanding the types of complications also helps the clinician to assess the

patient. For example, one life-threatening complication of Kawasaki disease is coronary artery aneurysm and thrombosis. **The clinical presentation in the subacute phase is desquamation, thrombocytosis, and the development of coronary aneurysms with a high risk of sudden death.** The appropriate therapy is intravenous immunoglobulin in the acute phase, and high-dose aspirin as soon as possible after the diagnosis. Nonrecognition of the risk of coronary artery aneurysm and appropriate therapy for thrombosis can lead to the patient's death. Students apply this information when they see on rounds a patient with Kawasaki disease and monitors for new murmurs, thrombocytosis, myocarditis, and development of coronary artery aneurysms. The clinician communicates to the team to watch the patient for any of these signs or symptoms so that appropriate therapy can be considered.

What is the Best Therapy?

This is perhaps the most difficult question, because not only does the clinician need to reach the correct diagnosis, assess the severity of the condition, but also weigh the situation to reach the appropriate intervention. The student does not necessarily need to memorize exact dosages, but the medication, the route of delivery, and possible complications are important. It is important for the student to verbalize the diagnosis and the rationale for the therapy. A common error is for the student to "jump to a treatment," almost like a random guess, and therefore is given a "right or wrong" feedback. In fact, the student's guess may be correct, but for the wrong reason; conversely, the answer may be a very reasonable one, with only one small error in thinking. It is crucial instead to give the steps so that feedback may be given for each step.

For example, what is the best therapy for a 15-year-old sexually active girl with severe, cystic acne? The incorrect manner of response is for the clinician to blurt out "Accutane." Rather, the student should reason it in a way such as: "Severe, cystic acne can be treated with a variety of modalities. Side effects of the medications must be considered in a sexually active teenager whose is statistically at high risk for pregnancy. Accutane causes severe birth defects and is absolutely contraindicated in pregnancy. Therefore, the best treatment for this adolescent may be a combination of oral antibiotics and topical medications that present a much lower chance of devastating side effects."

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SECTION II

Clinical Cases

◆ CASE 1

A mother brings her 12-month-old child to your clinic for a well-child examination. The child appears to be small for her age. Her weight is below the 5th percentile on standardized growth curves (50th percentile for an 8-month-old), her length is at the 25th percentile, and her head circumference is at the 50th percentile. The child's vital signs and her physical examination are otherwise normal.

- ◆ What is the next step in the management of this patient?
- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the evaluation?

ANSWERS TO CASE 1: Failure to Thrive

Summary: A 12-month-old girl has poor weight gain without obvious etiology from her physical examination.

- ◆ **Next step:** Gather more history from the mother, including birth history, past medical history, family history, social history, and developmental history. A dietary history is especially important in this case.
- ◆ **Most likely diagnosis:** Failure to thrive (FTT), most likely a result of a nonorganic cause.
- ◆ **Next step in evaluation:** Limited screening laboratory evaluation to help identify organic causes of FTT, dietary counseling, and frequent office visits to assess adequacy of weight gain.

Analysis

Objectives

1. Know the historical clues necessary to recognize organic and nonorganic causes of FTT.
2. Understand the appropriate use of the laboratory in an otherwise healthy child with FTT.
3. Appreciate the treatment and follow-up of a child with probable nonorganic FTT.

Considerations

This patient's growth pattern, including inadequate weight gain, potentially modest retardation of length, and sparing of head circumference, is suggestive of FTT. The etiology is most likely nonorganic because the physical examination is normal. The diagnosis of nonorganic FTT is made after organic etiologies are excluded, when growth resumes

normally, and when catch-up growth is demonstrated with adequate nutrition and an adequate environment is ensured. Diagnosis and therapeutic maneuvers aimed at organic causes are appropriate if supported by the patient's history (i.e. prematurity, maternal infection) or physical examination (i.e. enlarged spleen, significant developmental delay). Although organic and nonorganic FTT can occur in the same patient, attempts to differentiate between these two forms may be helpful because the evaluation, treatment, and follow-up may be very different.

Note: Had the same practitioner followed this patient since birth, earlier detection and intervention of the growth failure might have occurred.

APPROACH TO FAILURE TO THRIVE

Definitions

Failure to thrive (FTT): A physical sign and not a final diagnosis. It is suspected when growth is below the 3rd or 5th percentile on standard growth curves or a crossing of ≥ 2 major growth percentiles in a short time frame. Usually seen in a child younger than 5 years of age whose physical growth is significantly less than that of his or her peers.

Nonorganic FTT: Poor growth without a known medical etiology. Nonorganic (psychosocial) FTT is often related to poverty or poor caregiver-child interaction. Nonorganic FTT constitutes one-third to one-half of cases of FTT identified in tertiary-care settings, and in nearly all cases in primary care settings.

Organic FTT: Poor growth caused by an underlying medical condition such as inflammatory bowel disease, renal disease, or congenital heart conditions.

Clinical Approach

The goal of the history, physical examination, and laboratory testing for FTT is to establish whether the caregiver is giving enough calories,

whether the child is taking enough calories, and/or whether the child is able to use the calories for growth. Identification of which of these factors is the likely source of problem helps guide the next steps in management.

Diagnosis

A thorough history and physical examination are the clinician's most important tools in the evaluation of FTT. A detailed dietary history can offer important clues to identify an etiology for the FTT. The type of milk (breast or bottle) and frequency and quality of feeding, voiding, vomiting, and stooling are recorded when evaluating smaller infants. The milk used (commercial or homemade formula) and the mixing process (to insure appropriate dilution) is reviewed when evaluating bottle-fed infants. For example, adding too much water to a powdered commercial formula results in inadequate nutrition to the infant. The amount and type of juices and solid foods are noted when evaluating larger infants or toddlers. Significant food aversions might suggest that a child has gastric distress as a result of malabsorption. A food diary, in which the parent writes down all foods offered and taken by the child, can be useful.

Pregnancy and early neonatal histories may reveal maternal infection, depression, or drug use, intrauterine growth retardation, prematurity, or other chronic neonatal conditions. When FTT is associated with families members who are genetically small or with a history of slow growth (constitutional delay), affected children are usually normal and do not require an exhaustive evaluation. In contrast, a family history of inheritable disease associated with poor growth (such as cystic fibrosis) must be evaluated more extensively. Because nonorganic FTT is more commonly associated with poverty, a thorough social history can be useful. The living arrangements of the child including primary and secondary caregivers, type of housing, financial and employment status of caregivers, the family's social supports, and unusual stresses (such as spousal abuse) are reviewed. The astute clinician will use this time to gather history and also to observe for unusual interactions between the caregiver and the child.

All body organ systems potentially harbor an organic cause for FTT and therefore must be evaluated carefully (Table 1-1). **The develop-**

Table 1-1
MAJOR CAUSES OF INADEQUATE WEIGHT GAIN

Inadequate Caloric Intake

Lack of appetite: depression, chronic disease

Ingestion difficulties: feeding disorders, neurologic disorders (cerebral palsy), craniofacial anomalies, genetic syndromes, tracheoesophageal fistula

Unavailability of food: neglect, inappropriate food for age, insufficient volume of food

Altered Growth Potential

Prenatal insult, chromosomal anomalies, endocrine disorders

Caloric Wasting

Emesis: intestinal tract disorders, drugs, toxins, central nervous system pathology

Malabsorption: GI disease (biliary atresia, celiac disease), inflammatory bowel disease, infections, toxins

Renal losses: diabetes, renal tubular acidosis

Increased Caloric Requirements

Increased metabolism: congenital heart disease, chronic respiratory disease, neoplasms, chronic infection, hyperthyroidism

Defective use of calories: metabolic disorders, renal tubular acidosis

Source: Modified from Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ. *Rudolph's Pediatrics*. 21st ed. New York: McGraw-Hill, 2003:8.

mental status, which may be delayed in both organic and nonorganic FTT, needs evaluation. Children with nonorganic (psychosocial) FTT may demonstrate an occipital bald spot and failure to attain appropriate developmental milestones resulting from lack of parental stimulation; be disinterested in his or her environment; avoid eye contact, smiling, or vocalization; and may not respond well to maternal attempts of comforting. Children with certain types of organic FTT (such as renal tubular acidosis) and most forms of nonorganic FTT should show "catch-up" in developmental milestones with successful therapy. During the physical examination (especially of the younger infant) **the clinician should observe a feeding, which may give clues to maternal-child interaction bonding issues or to physical problems, such as cerebral palsy, oral motor or swallowing difficulties, or velum cleft palate.**

The history or the physical examination suggestive of an organic cause of FTT directs the laboratory and radiologic evaluation. For

instance, a child with an immediate family history of cystic fibrosis requires sweat chloride or genetic testing. A child with a loud, harsh systolic murmur and bounding pulses deserves a chest radiograph and electrocardiogram, and perhaps an echocardiogram and cardiology consult. Most children with FTT, however, have few or no signs or symptoms and the laboratory evaluation is usually limited to a few screening tests: a complete blood count, lead level, urinalysis, and culture, and serum electrolyte levels to include calcium, blood urea nitrogen, and creatinine are recommended. A tuberculosis skin test and testing for human immunodeficiency virus may also be indicated. Any abnormalities in these screening tests are then pursued more extensively.

Treatment and Follow-up

The treatment and follow-up for organic forms of FTT is specific for the disease process. Patients with nonorganic FTT are managed with improved dietary intake, close follow-up, and attention to psychosocial issues.

Healthy infants in the first year of life require approximately 120 kcal/kg/d of nutrition and approximately 100 kcal/kg/d after the first year of life; children with FTT require an additional 50% to 100% to ensure adequate catch-up growth. Attention to mealtime routines is important. Families should eat together in a nondistracting environment (television off!), with meals lasting between 20 and 30 minutes. Solid foods are offered before liquids, and children should not be force-fed. Low-calorie drinks, juices, and water should be limited, while high-calorie foods, such as whole milk, cheese, dried fruits, and peanut butter, can be offered (depending on the age of the child). Formulas containing more than the standard 20 calories per ounce may be necessary for smaller children, and high-calorie supplementation such as Carnation Instant Breakfast mixed in whole milk, PediaSure, or Ensure may be required for larger children. In all cases, frequent office visits or home health visits are indicated to ensure adequate weight gain in response to therapeutic maneuvers.

Successful treatment of nonorganic FTT requires not only the provision of increased calories to the child but also attention to contributing psychosocial issues. Referral to community services such as the Women, Infants, and Children (WIC) Program, the food stamp pro-

gram, and local food banks may be required. Help for the caregiver in the form of job training, substance and physical abuse prevention, parenting classes, and psychotherapy may also be available through community programs. Older children and their families may benefit from early childhood intervention and Head Start programs.

Some children with organic causes of FTT can also have nonorganic FTT. For instance, a poorly growing premature infant with special nutritional needs may be at increased risk for superimposed non-organic FTT because of psychosocial issues such as poor bonding with the family after the child's prolonged hospital stay. In this situation, care for the organic causes must be coordinated with interventions to preclude nonorganic FTT.

Comprehension Questions

- [1.1] A mother and father bring their 6-month-old son to the clinic. On examination, he is symmetrically less than the 5th percentile for height, weight, and head circumference. He was born at 30 weeks gestation and weighed 1000 g. He was a planned pregnancy and his mother's prenatal course was uneventful until she was involved in an automobile accident that initiated the labor. The child was ventilated for 3 days in the neonatal intensive care unit, but otherwise did well without residual respiratory, central nervous, or intestinal problems. He was discharged at 8 weeks of life and has no other medical problems. Which of the following is the mostly likely explanation for this child's small size:
- A. Chromosomal abnormality
 - B. Protein-calorie malnutrition
 - C. Normal ex-premie infant growth
 - D. Malabsorption secondary to short gut syndrome
 - E. Congenital hypothyroidism
- [1.2] A 13-month-old child is noted to be at the 25th percentile for weight, the 10th percentile for height, and less than the 5th percentile for head circumference. The child was born at term. She was noted to have a small head at birth, to be developmentally

delayed throughout her life, and to have required cataract surgery shortly after birth. She currently takes phenobarbital for seizures. Which of the following might explain this child's small size?

- A. Congenital cytomegalovirus infection
- B. Down syndrome
- C. Glycogen storage disease type II
- D. Congenital hypothyroidism
- E. Craniopharyngioma

[1.3] A 2-year-old child had previously been slightly less than the 50th percentile for weight, height, and head circumference, but in the last 6 months has fallen to slightly less than the 25th percentile for weight. The pregnancy was normal, the child's development is as expected, and the family reports no psychosocial problems. The mother reports that the child has become a finicky eater (wants only macaroni and cheese for each meal) but the mother insists that the child eat a variety of foods at each meal. The meals are marked by much frustration for all family members. Physical examination of the child is normal. The next step in the care of this child should be:

- A. Sweat chloride testing
- B. Examination of the eyes for retinal hemorrhages
- C. Reassurance and counseling for family about normal developmental stage of child
- D. Testing of stool for parasites
- E. MRI of the brain

[1.4] A 4-month old child is noted to be having poor weight gain. The current growth parameters include weight less than 5th percentile, height about 10th percentile and head circumference at 50th percentile. The planned pregnancy resulted in an uneventful spontaneous, vaginal delivery. The mother and child were discharged after a 48-hour hospitalization. Feeding is both breast and bottle, and the quantity seems to be sufficient. The child has had no illness. Physical examination is unremarkable except for the child's small size. On screening laboratory you find the hemoglobin and hematocrit to be 11 mg/dL and 33%, respectively, with a platelet

count of 198,000/mm³. The serum electrolytes include a sodium of 140, chloride of 105, potassium of 3.5, bicarbonate of 17, blood urea nitrogen 15, and creatinine of 0.3. The liver function tests were normal. The urinalysis had a pH of 8 with occasional epithelial cell, but no white blood cells, bacteria, protein, ketones, or reducing substances. The probable therapy for this child is:

- A. Transfusion with packed red blood cells
- B. Intravenous infusion of potassium chloride
- C. Sweat chloride analysis
- D. Growth hormone determination
- E. Oral supplementation with bicarbonate

Answers

- [1.1] C. The expected weight versus age must be modified with a preterm infant. Weight gain should be following or exceeding that of term infants. This infant's parameters, when plotted in a "premie growth chart," is likely to reveal normal growth.
- [1.2] A. The developmental delay, intrauterine growth retardation (including microcephaly), cataracts, seizures, hepatospleno-megaly, prolonged neonatal jaundice, and purpura at birth are findings consistent with a congenital infection such as cytomegalovirus (CMV) or toxoplasmosis. Calcific densities in the brain with CMV typically are found in a periventricular pattern; in toxoplasmosis, they are found scattered throughout the cortex.
- [1.3] C. It is not unusual for a child between about 18 months and 30 months of age to become "picky eaters." They sometimes slow their rate of growth, and the period can be distressing for parents (and grandparents). Calm counseling of the family to provide nutrition, avoid "force-feeding," and avoid snacks is usually effective. Close follow-up is required.
- [1.4] E. The patient described has evidence of renal tubular acidosis (probably distal tubular), a well-described cause of failure to thrive. Upon confirmation of the findings, oral supplementation

of bicarbonate would be expected to correct the elevated chloride, the low bicarbonate and potassium (although potassium supplements may be required), and poor growth.

CLINICAL PEARLS

- ◆ In the United States psychosocial FTT is far more common than organic FTT, and often is associated with poverty or poor parent-child interaction.
- ◆ Inexpensive laboratory screening tests along with dietary counseling and close observation of weight changes are usually appropriate first steps in managing an infant with FTT who appears otherwise healthy.
- ◆ Organic causes of failure to thrive are numerous and can be associated with abnormalities in any organ system. Often clues on history, physical examination, or screening laboratory tests will hint at the organ system involved.
- ◆ As many as one-third of patients with psychosocial FTT have developmental delay as well as social and emotional problems.
- ◆ Patients with renal tubular acidosis (RTA), a common organic cause of FTT, can have a defect in the proximal tubules (RTA type 2) caused by impaired tubular reabsorption of bicarbonate or in the distal tubules (RTA type 1) caused by impaired hydrogen ion secretion. Type 4 RTA is also a distal tubule problem associated with impaired ammoniogenesis.

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◆ CASE 2

An apparently healthy 16-year-old male is brought to your office by concerned parents. They report that their son's behavior has been erratic over the last several months. Much of the time he has had a great deal more energy, decreased appetite, and sleeps much less than usual; at other times he sleeps incessantly and is lethargic. He had been doing poorly in school. Last evening he appeared flushed, agitated, had dilated pupils, and complained "people were out to get him." His family notes that he has been skipping some school and reluctantly report that he was arrested for burglary 2 weeks prior to the visit. You know that this child has been in good health and has been an excellent student in the past. Today he appears to be in no distress.

- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the evaluation?
- ◆ What is the long-term evaluation and therapy?

ANSWERS TO CASE 2: Adolescent Substance Abuse

Summary: A 16-year-old previously healthy adolescent with recent behavior changes and declining school performance.

- ◆ **Most likely diagnosis:** Drug abuse (probably cocaine, possibly amphetamines).
- ◆ **Next steps in evaluation:** Thorough history, physical examination, urine drug screen, and screening for other commonly associated consequences of drug abuse (such as sexually transmitted diseases and hepatitis).
- ◆ **Long-term evaluation and therapy:** Threefold approach: (a) detoxification program; (b) follow-up with developmentally appropriate psychosocial support systems; and (c) possible long-term assistance with a professional trained in substance abuse management.

Analysis

Objectives

1. Learn the pattern of behavior found among adolescents involved with drugs of abuse.
2. Know the signs and symptoms of the more common drugs of abuse.
3. Understand the general approach to therapy for an adolescent abusing drugs.

Considerations

Although rarely a brain tumor could be an explanation for an adolescent with new onset of behavior changes, **in general, when an adolescent displays new-onset truant behavior, depression and/or declin-**

ing grades, substance abuse must be suspected. A thorough history, physical examination (with special attention to the neurologic examination), and screening laboratory will help to clarify the situation. Information about an adolescent's potential substance abuse problem can come from the patient, the patient's family, or other interested parties (teachers, coaches, or friends). Direct questioning of the adolescent alone regarding substance abuse is appropriate during routine health visits or when signs and symptoms are suggestive of abuse.

APPROACH TO THE SUBSTANCE-ABUSING ADOLESCENT

Definitions

Substance abuse: Alcohol and other drug use leading to impairment or distress resulting in failure to meet obligations at school or work, potential physical harm, substance-related legal problems, or continued use despite social or interpersonal consequences resulting from the drug's effects.

Substance dependence: Alcohol and other drug use leading to loss of control with continued use (tolerance necessitating increased dose or withdrawal upon its termination), compulsion to obtain and use the substance, and use that continues despite persistent or recurrent unpleasant consequences.

Clinical Approach

Experimentation with alcohol and other drugs is common among adolescents; some consider this experimentation to be "normal." Others argue that any level of drug or alcohol use is to be avoided because substance abuse is so frequently associated with the major causes of morbidity and mortality in the adolescent age group—homicide, suicide, and unintentional injuries. Regardless of one's viewpoint, a healthcare provider is responsible for (a) discussing facts about alcohol and drugs with the adolescent in an attempt to reduce the adolescent's risk of harm, and (b) identifying adolescents who require intervention for their alcohol or drug use.

Children at risk for drug use include those with significant behavior problems, learning difficulties, and those with impaired family functioning. Cigarettes and alcohol are the most commonly used drugs in adolescence; marijuana is the most commonly used illicit drug. Some adolescents abuse common household products such as inhalation of glue or aerosols. Others abuse their sibling's medications (such as methylphenidate, which is used to snort with cocaine).

Pediatricians are afforded the opportunity to ask about alcohol or drug use in adolescents who present for their annual health examination or in adolescents who present with signs or symptoms of substance abuse. Direct questions can identify drug or alcohol use and their affect on school performance, family relations, and peer interactions. Should any problems be identified, a thorough interview to determine the degree of drug use (experimentation, abuse, or dependency) is warranted.

Historical clues to alcohol or other drug abuse include significant behavioral changes at home, a decline in school or work performance, or involvement with the law. An increased incidence of intentional or accidental injuries may be alcohol or drug related. Risk-taking activities, such as trading sex for drugs or driving while impaired, can be particularly serious, and may indicate more serious drug or alcohol problems. The adolescent who uses alcohol or other drugs usually has a normal physical examination, especially if the previous drug use was days prior to the office visit. Needle marks and nasal mucosal injuries are rarely found.

An adolescent who has recently used alcohol or drugs can present with a variety of findings (Table 2-1). A urine drug screen can be helpful to evaluate the adolescent who (a) presents with psychiatric symptoms, (b) has signs and symptoms commonly attributed to drugs or alcohol, (c) is in a serious accident, or (d) is part of a recovery monitoring program. **An attempt to obtain the adolescent's permission and maintain confidentiality is paramount.**

Treatment of life-threatening acute problems related to alcohol or drug use follows the "ABCs" of emergency care: manage the Airway, control Breathing, and assess the Circulation. Following these initial stabilization procedures, treatment is directed at the offending agent (if known). After stabilization of the patient whose drug and alcohol use is causing undesired consequences, a treatment plan must be devised. For some patients, inpatient programs that disrupt drug and alcohol use sets

Table 2-1
CLINICAL FEATURES OF SUBSTANCE ABUSE

AGENT	SIGNS AND SYMPTOMS	RETENTION TIME FOR URINE SCREENING PURPOSES
Alcohol	Euphoria, grogginess, impaired short-term memory, talkativeness, vasodilation, and at high serum levels, respiratory depression	7–10 h (blood) or 10–13 h (urine)
Marijuana	Elation and euphoria, impaired short-term memory, distortion of time perception, poor performance of tasks requiring concentration (such as driving), and loss of judgment	3–10 d for occasional users or up to 2 mo for chronic users
Cocaine	Euphoria, increased motor activity, decreased fatigability, dilated pupils, tachycardia, hypertension and hyperthermia; sometimes associated with paranoid ideation; physical findings might include changes in nasal mucosa	2–4 d
Methamphetamine and methylene dioxymethamphetamine (ecstasy)	Euphoria, increased sensual awareness, increased psychic and emotional energy, nausea, teeth grinding, blurred vision, jaw clenching, anxiety, panic attacks, and psychosis	2 d
Opiates including heroin, morphine, and codeine	Euphoria, decreased pain sensation, pinpoint pupils, hypothermia, vasodilation, and possible respiratory depression; physical findings might include needle marks over veins	2 d

Table 2-1
CLINICAL FEATURES OF SUBSTANCE ABUSE (*Continued*)

AGENT	SIGNS AND SYMPTOMS	RETENTION TIME FOR URINE SCREENING PURPOSES
Phencyclidine (PCP)	Euphoria, nystagmus, ataxia, and emotional lability, hallucinations affecting body image that can result in panic reactions, disorientation, hypersalivation, and abusive language	8 d
Barbiturates	Sedation, pinpoint pupils, hypotension, bradycardia, hypothermia, hyporeflexia, and central nervous system and respiratory depression	1 d for short-acting agents; 2–3 wk for long-acting agents

the stage for continued outpatient therapy. For other patients, a program of intensive outpatient therapy can be initiated to help an adolescent to develop a drug-free lifestyle. In many cases, the expertise necessary to assist an adolescent through these changes is beyond the expertise of the general pediatrician. Assistance with management of this chronic problem by qualified health professionals in a developmentally appropriate setting can maximize outcome. Primary care providers can, however, assist adolescents and their families by helping families find suitable community resources.

Comprehension Questions

- [2.1] A 14-year-old is found to be ataxic on the school grounds. He is brought to the emergency department of a local hospital where he appears to be euphoric but emotionally labile and somewhat disoriented. On physical examination he has nystagmus and hyper-

salivation. Many notice his abusive language. The agent most likely responsible for his condition is:

- A. Alcohol
- B. Cocaine
- C. Barbiturates
- D. Phencyclidine (PCP)
- E. Amphetamines

[2.2] A family brings their 16-year-old daughter to your office for a “well-child” checkup. The child looks perfectly normal on examination. As part of your well-child examination you plan to do a urinalysis. The father pulls you aside and asks you to secretly run a drug screen on his daughter with extra urine. You should:

- A. Perform the screen in the manner requested.
- B. Perform the screen as requested, but call the family and adolescent back into the office to review the results.
- C. Explore the reasons for the request with the parents and the adolescent, performing a urine drug screen with the adolescent’s permission if the history warrants.
- D. Refer the adolescent to a psychiatrist for further evaluation.
- E. Tell the family to bring the adolescent back to the office for a urine drug screen when she is exhibiting signs or symptoms such as euphoria or ataxia.

[2.3] A previously healthy adolescent has a 3-month history of increasing headaches, blurred vision, and personality changes. During a previous office visit he admitted to experimentation with marijuana over a 1-year prior. Physical examination demonstrates a healthy, athletic-appearing 17-year-old with decreased extraocular range of motion and visual acuity in his left eye. The next step in his management should be:

- A. Acetaminophen and ophthalmology referral
- B. Neuroimaging
- C. Urine drug screen

- D. Trial of methysergide (Sansert) for migraine
- E. Glucose measurement

[2.4] An 11-year-old presents with dizziness, pupillary dilatation, nausea, fever, tachycardia, and facial flushing. She reports that she can “see” sound and “hear” colors. The agent likely to be responsible for this condition is:

- A. Amphetamines
- B. PCP
- C. Ecstasy
- D. Lysergic acid diethylamide (LSD)
- E. Alcohol

Answers

- [2.1] **D.** PCP is associated with hyperactivity, hallucinations, abusive language, and nystagmus.
- [2.2] **C.** The adolescent’s permission should be obtained before drug testing. Testing “secretly” in this situation destroys the doctor-patient relationship.
- [2.3] **B.** Even though this adolescent admits to experimentation with drugs in the past, his current symptoms and physical findings makes drug use a less-likely etiology. In his case, evaluation for possible brain tumor is warranted.
- [2.4] **D.** LSD is associated with symptoms that may begin 30 to 60 minutes after ingestion, peak 2 to 4 hours later, and resolve by 10 to 12 hours, including delusional ideation, body distortion, and paranoia. “Bad trips” result in the user becoming terrified or panicked; treatment is usually reassurance of the user in a controlled, safe environment.

CLINICAL PEARLS

- ◆ Cigarettes and alcohol are the most commonly used drugs in adolescence.
- ◆ Marijuana is the most common illicit drug used in adolescence.
- ◆ Behaviors associated with substance abuse include drug dealing, prostitution, burglary, unprotected sex with the risks of pregnancy and sexually transmitted infections, automobile accidents, and physical violence.
- ◆ Children at risk for drug use include those with significant behavior problems, learning difficulties, and those with impaired family functioning.

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◆ CASE 3

A 36-year-old Gravida 3 Para 2 woman with one prenatal visit at 35 weeks but otherwise uneventful prenatal course delivers a 3900 g female child. At birth the infant is noted to have decreased tone, upslanting palpebral fissures, epicanthal folds, redundant nuchal skin, clinodactyly of the fifth fingers, and brachydactyly, and the extremities show a single transverse palmar crease.

- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the evaluation?

the 15th and 20th weeks of pregnancy, which could have demonstrated a pattern suggestive of Down syndrome. Further evaluation (such as amniocentesis or chorionic villus sampling) to confirm a chromosomal abnormality could then have been offered.

APPROACH TO THE DYSMORPHIC CHILD

Definitions

Advanced maternal age: The incidence of trisomy 21 increases dramatically each year beyond 35 years of age. At 35 years of age, the incidence is 1 in 378 liveborn infants, increasing to 1 in 106 by age 40 years and to 1 in 11 by age 49 years.

Brachydactyly: Excessive shortening of tubular bones in the hands and feet resulting in a box-like appearance.

Clinodactyly: In-curving of one of the digits (in Down syndrome the fifth digit curves toward the 4th digit because of mid-phalanx dysplasia).

Dysmorphic child: One who shows a problem with generalized growth or in the formation of one or more structures of the body. Identification of dysmorphic child can lead to the diagnosis of a *syndrome* (a constellation of features having a common cause; i.e. all the features of Down syndrome being caused by extra chromosome 21 material); an *association* (sporadic occurrence of two or more features occurring together more commonly than would be expected; i.e. the features of VATER [Vertebral problems, Anal anomalies, Trachea problems, Esophageal abnormalities, and Radius or Renal anomalies] association resulting from an unknown cause), or *sequence* (a condition that results from a single defect which then leads to a series of subsequent abnormalities; i.e. Potter disease, which is a lack of normal kidney function in the infant leading to reduced urine output, oligohydramnios, and constraint deformities. Common facial features in this sequence includes wide-set eyes, flattened palpebral fissures, prominent epicanthus, flattened nasal bridge, mandibular micrognathia, and large, low-set ears that are deficient in cartilage.).

Triple screen: Measurements of α -fetoprotein (AFP), human chorionic gonadotropin (hCG), and estriol levels, usually performed at 15 to 20 weeks gestation. These tests screen for a variety of genetic problems. Approximately 60% of the babies with Down syndrome and 80% to 90% of the babies with neural tube defects will be identified by this testing.

Clinical Approach

The first evaluation of the newborn occurs in the delivery room where the attendant attempts to ensure the successful transition of an infant from an intrauterine to an extrauterine environment and focuses primarily on the “ABCs” of medicine—airway, breathing, and circulation. The infant is then evaluated for possible abnormalities, including those that might fit into a pattern such as Down syndrome.

Information gathered during the prenatal course provides some potentially important clues in the evaluation of a dysmorphic child. The age of the parents (the incidence of chromosomal abnormalities increases with increased maternal and sometimes paternal age), degree of fetal movement noted during pregnancy, maternal exposure to drugs and other teratogens, family history of dysmorphic children, and the results of prenatal testing including triple screening and chorioamniotic or chorionic villous testing may prove to be helpful. For instance, an older mother who has an abnormal triple screen with a low AFP level would be at higher risk of delivering a child with Down syndrome.

The physical examination is critical to the diagnosis of a dysmorphic child. In the case of the child with Down syndrome, a distinctive pattern of abnormalities can lead to a presumptive diagnosis. More than 90% of children with Down syndrome have characteristic features including upslanting palpebral fissures; Brushfield spots; flat facial profile; small and rounded ears; excess nuchal skin; widespread nipples; dysplasia of the pelvis; hyperflexibility of the joints; clinodactyly of their fifth fingers; a single transverse palmar (simian) crease; hypotonia; and a poor Moro reflex. Other features include brachycephaly (disproportionate shortness of the head), epicanthal folds, brachydactyly, wide spacing between first and second toes, and short stature.

In the newborn period, at least two potentially life-threatening conditions must be addressed. **Approximately 50% of infants with Down syndrome have cardiac defects—most commonly an endocardial cushion defect (60%), ventricular septal defect (32%), and tetralogy of Fallot (6%).** A cardiology consultation and echocardiogram are usually indicated. **Approximately 12% of infants with Down syndrome have intestinal (usually duodenal) atresia,** some of whom may present with a history of polyhydramnios during pregnancy. All infants with Down syndrome have a variable degree of hypotonia and sometimes slower feeding. Should an infant with presumed Down syndrome develop persistent vomiting after feeds (especially if the vomiting is bilious), an upper GI study will likely reveal the characteristic **“double-bubble” pattern of duodenal atresia** for which surgical intervention is warranted.

Confirmation of the diagnosis of Down syndrome requires a determination of the child's chromosomal configuration. A complete, extra chromosome 21 (nondysjunction [failure to segregate during meiosis]) occurs in almost 95% of cases. Two percent of cases are caused by translocations (breakage and removal of a large segment of DNA from one chromosome and attachment of that segment to a different chromosome), and 3% are mosaics (more than one type of cell in a person; usually described as a percentage of abnormal cells). Parents of children with Down syndrome caused by translocation should also be checked for chromosomal aberrations; the risk of recurrence can approach 100% when one parent has a translocation defect.

Other newborn conditions associated with Down syndrome include hearing loss, strabismus, cataracts, nystagmus and congenital hypothyroidism. Hearing is evaluated with brainstem auditory evoked response or otoacoustic emission by 3 months of age. A pediatric ophthalmologist evaluates the eyes by 6 months of age, and thyroid function is assessed as part of each state's routine newborn screening program. Longer-term consequences of Down syndrome include a higher risk for leukemia, acquired hypothyroidism, atlantoaxial (cervical spine) instability, and premature aging. All children with Down syndrome are mentally retarded, but the intelligence quotients in these children are widely variable; for example, mosaics can exhibit near-normal intelligence.

“Well-child care” takes on special meaning for children with Down syndrome. In addition to providing routine care based on the American

Table 3-1
HEALTH SUPERVISION FOR CHILDREN WITH DOWN
SYNDROME—COMMITTEE ON GENETICS*

	PRENATAL	INFANCY, 1 MONTH TO 1 YEAR				
		NEONATAL	2 MONTHS	4 MONTHS	6 MONTHS	9 MONTHS
Diagnosis						
Karyotype review†	•	•				
Phenotype review	•	•				
Recurrence risks	•	•				
Anticipatory guidance						
Early intervention services	•	•	•	•	•	•
Reproductive options	•‡	•‡	•‡			
Family support	•	•	•	•	•	•
Support groups	•	•	•			
Long-term planning	•					
Sexuality						
Medical evaluation						
Growth		o	o	o	o	o
Thyroid screening		o [†]			o	
Hearing screening		o	S/o	S/o	S/o	S/o
Vision screening		S/o	S/o [‡]	S/o	S/o	S/o [‡]
Cervical spine roentgenogram						
Echocardiogram	•	o				
Complete blood count		o				
Psychosocial						
Development and behavioral	S/o	S/o	S/o	S/o	S/o	S/o
School performance						
Socialization						

*Assure compliance with the American Academy of Pediatrics "Recommendations for Preventive Pediatric Health Care."

• = to be performed; S = subjective, by history; and o = objective, by a standard testing method.

†Or at time of diagnosis.

‡Discuss referral to specialist.

[§]Give once in this age group.

[†]According to state law.

[‡]As needed.

^{§§}See discussion.

(Used with permission of the American Academy of Pediatrics, Committee on Genetics, Health supervision for children with Down syndrome, *Pediatrics* 2001;107:443.)

Academy of Pediatrics' (AAP) guidelines for health supervision that apply to all children, the AAP has promulgated additional guidelines to address the particular needs of children with Down syndrome (Table 3-1). Periodic objective thyroid, hearing, and vision screenings are focal points of the medical evaluation. Equally important in the successful management of the patient with Down syndrome is appropriate psychosocial intervention. Appropriate home/environmental, educational, and vocational interventions can improve the level of function of chil-

EARLY CHILDHOOD. 1 TO 5 YEARS						LATE CHILDHOOD. 5 TO 13 YEARS ANNUAL	ADOLESCENCE. 13 TO 21 YEARS ANNUAL
12 MONTHS	15 MONTHS	18 MONTHS	24 MONTHS	3 YEARS	4 YEARS		
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S/o ^a			S/o ^c	S/o	S/o	S/o ^b	S/o
			:	:	:		
S/o			S/o ^c	S/o	S/o	S/o ^b	S/o
				o ^{***}			
							o
S/o	S/o	S/o	S/o	S/o	S/o	S/o	S/o
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S						S	S

dren with Down syndrome facilitating their transition to adulthood. Providing personal support to the family, assisting with applications for financial and medical support programs, and helping with submission for Supplemental Security Income (SSI) benefits are within the purview of the pediatric healthcare provider.

Comprehension Questions

- [3.1] A small-for-gestation age infant is born to a 35-year-old woman. The infant is noted at birth to have low-set and malformed ears, microcephaly, rocker-bottom feet, inguinal hernias, cleft lip and palate, and micrognathia. Chromosomal analysis is likely to reveal which of the following?

- A. Holt-Oram syndrome
 - B. Turner syndrome
 - C. Edwards syndrome (trisomy 18)
 - D. Patau syndrome (trisomy 13)
 - E. Down syndrome (trisomy 21)
- [3.2] A 15-day-old infant with respiratory distress is brought into the emergency department. A quick observation suggests that the infant has slight cyanosis, hepatosplenomegaly, and features consistent with Down syndrome. The cardiac examination demonstrates a loud first heart sound, a wide and fixed split second heart sound, a low-pitched, mid-diastolic murmur at the lower left sternal border, and a harsh apical holosystolic murmur in the mitral area. Which of the following cardiac conditions is most likely to explain the heart defect in this infant with probable Down syndrome?
- A. Complete atrioventricular (A-V) canal (endocardial cushion defect)
 - B. Transposition of the great vessels
 - C. Total anomalous venous return
 - D. Hypoplastic left heart
 - E. Tricuspid atresia
- [3.3] A small-for-gestation age and dysmorphic newborn infant with microcephaly and sloping forehead, cutis aplasia (missing portion of the skin and hair) of the scalp, polydactyly, microphthalmia, and omphalocele is likely to have which of the following:
- A. Holt-Oram syndrome
 - B. Turner syndrome
 - C. Edwards syndrome (trisomy 18)
 - D. Patau syndrome (trisomy 13)
 - E. Down syndrome (trisomy 21)
- [3.4] The parents of an 8-year-old Down syndrome boy arrive for his annual well-child check up. He wants to participate in sports, including the Special Olympics. Until further evaluation can be completed, which of the following sports would you suggest as being safe?

- A. Diving
- B. Football
- C. Tennis
- D. Tumbling
- E. Wrestling

Answers

- [3.1] C. The description is very characteristic of trisomy 18. Other features include clenched hands with overlapping digits, small palpebral fissures, prominent occiput, short sternum, and cardiac defects (including ventricular septal defect, atrial septal defect, patent ductus arteriosus, or coarctation of the aorta).
- [3.2] A. While ventricular septal defects are common heart defects in patients with Down syndrome, the most characteristic lesion is endocardial cushion defects. Slight cyanosis occurs because of the mixing of deoxygenated with oxygenated blood.
- [3.3] D. The appearance of cutis aplasia and polydactyly strongly suggests trisomy 13. Other common features include holoprosencephaly, cleft lip/palate, postaxial polydactyly, flexed and overlapping fingers, coloboma, and cardiac defects (ventricular septal defect, atrial septal defect, patent ductus arteriosus, dextrocardia).
- [3.4] C. Until lateral cervical flexion-extension films confirm normal anatomy, contact sports, and other activities that may result in forceful flexion of the neck should be avoided.

CLINICAL PEARLS

- ◆ Down syndrome is the most common autosomal chromosome abnormality in liveborn infants, increasing in incidence with advanced maternal age.
- ◆ The most common features of Down syndrome in a neonate are hypotonia with poor Moro reflex, flat faces, slanted palpebral fissures, laxity of joints, and excessive skin on back of neck.
- ◆ Common problems associated with trisomy 21 include cardiac defects and duodenal atresia.
- ◆ Common features of trisomy 18 (Edwards) syndrome include weak cry, single umbilical artery, micrognathia with small mouth and high arched palate, clenched hand with overlapping of index finger over the third finger, simian crease, rocker-bottom feet, small pelvis, and short sternum.
- ◆ Common features of trisomy 13 (Patau) syndrome include microcephaly and sloping forehead, deafness, cutis aplasia of the scalp, microphthalmia, coloboma, cardiac defect (especially ventricular septal defect), omphalocele, single umbilical artery, and hypersensitivity to agents containing atropine and pilocarpine.

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◆ CASE 4

A 3-year-old child and her family who are recent refugees from political unrest in their native east European country come to your office as new patients. The parents report their daughter to be a product of a full-term pregnancy with a birthweight of 1800 g. The child has not developed normally and does not have a diagnosis. You note that the child has short stature, hypotonia, and a small head with a round face. She has epicanthal folds, hypertelorism, and seems to be rather sensitive to loud sounds. Most impressive is her persistent, loud, high-pitched cry.

◆ **What is the most likely diagnosis?**

◆ **What is the etiology of this patient's problem?**

ANSWERS TO CASE 4: Cri-Du-Chat Syndrome

Summary: This is a developmentally delayed child with distinctive features including microcephaly, moonlike face, and a distinctive high-pitched (cat-like) cry.

◆ **Most likely diagnosis:** Cri-du-chat syndrome

◆ **Etiology:** Deletion of the short arm of chromosome 5 (85% are paternal in origin)

Analysis

Objectives

1. Know the signs and symptoms of cri-du-chat and other common chromosome deletion syndromes.
2. Understand the difference between chromosome deletion and chromosome microdeletion syndromes and the appropriate means to evaluate them.

Considerations

This child has distinctive features suggestive of a chromosomal abnormality, probably cri-du-chat. The initial evaluation focuses on the potentially life-threatening medical problems that are associated with cri-du-chat (or other chromosomal abnormalities). After this stabilization period, a thorough evaluation of the family's psychosocial environment is warranted because children with special needs can be physically, emotionally, and financially challenging.

APPROACH TO CRI-DU-CHAT

Definitions

Chromosomal deletion: Occurs when a piece of a chromosome is missing. Large (macro) deletions can be seen in routine chromo-

some preparations. A submicroscopic deletion is a small chromosome deletion that is not identified in routine chromosomal analyses; fluorescent in situ hybridization (FISH) evaluation in prophase or metaphase is required. Chromosomal deletion syndromes often result in mental retardation and a variety of malformations.

Clinical Approach

Cri-du-chat (5p-) is caused by a macrodeletion of the short arm of chromosome 5 (a deletion that is visible on routine chromosomal preparation); de novo deletions, accounting for 85% of cases, are usually paternal in origin, and the remaining 15% results from unbalanced translocations from a carrier parent. Cri-du-chat is one of many chromosomal macro- or submicroscopic deletions resulting in recognizable syndromes. Other features of cri-du-chat not listed in the case presentation include prominence of the metopic suture (the suture that runs down the midline of the forehead), high arched palate, and wide and flat nasal bridge. Congenital heart defects, scoliosis, dysplastic ears, and dental malocclusion are also described. **The high-pitched cry, commonly likened to a cat, is caused by laryngeal maldevelopment and diminishes as the child gets older.**

Although patients with cri-du-chat are developmentally delayed, appropriate psychosocial interventions can help them to communicate their wants and needs, become independently mobile, and interact with others. Home environment and educational interventions can improve the level of function in these children. Providing personal support to the family, assisting with applications for financial and medical support programs and helping with submission for Supplemental Security Income (SSI) benefits are tasks within the purview of the pediatric healthcare provider.

Comprehension Questions

- [4.1] A 2-month-old child was born in a rural hospital. At the time of birth she was noted to have distinctive facies with microcephaly, ptosis, a beaked nose, and a low-lying philtrum. Her extremities are notable for broad thumbs and large toes. The family is not

sure what evaluation was done, but they report they were told everything was “normal.” Since hospital discharge, the child’s weight gain has been slow and she has not achieved appropriate developmental milestones. The next step in the evaluation of this child should be:

- A. Thyroid function studies
- B. Urine and serum for organic acids
- C. Muscle biopsy
- D. Brain magnetic resonance imaging (MRI)
- E. FISH karyotype preparation

[4.2] A very overweight 3-year-old child presents to your office. The mother reports the child to be a product of a normal pregnancy, although she notes the baby did not “move” as much as her other two children. After birth the child was floppy and ate very poorly requiring tube feeds. During the first year of life, however, the child developed a voracious appetite and began to become very obese yet did not grow very tall. The child has been slow in gaining his milestones and appears to be developmentally delayed. The likely etiology for this child’s condition is:

- A. Prader-Willi syndrome (paternal 15q11-13)
- B. Angelman syndrome (maternal 15q11-13)
- C. Williams syndrome (7q23-)
- D. Wolf-Hirschhorn syndrome (4p-)
- E. DiGeorge syndrome (22q11-)

[4.3] A very friendly 3-year-old child was referred to you by a local pediatric cardiologist. He is followed by the cardiologist for supraventricular aortic stenosis and by an ophthalmologist for strabismus. In addition to the heart murmur and eye findings, your examination reveals a well-appearing child with mild mental retardation, a very round face with full cheeks and lips, an anteverted nose, and a long philtrum. You immediately recognize him to have:

- A. Prader-Willi syndrome (paternal 15q11-13)
- B. Angelman syndrome (maternal 15q11-13)
- C. Williams syndrome (7q23-)

- D. Velocardiofacial syndrome (22q11.21-q11.23)
- E. Alagille syndrome (20p12-)

- [4.4] A fair-haired, blue-eyed, mentally retarded 4-year-old girl is prone to fits of uncontrollable laughter. She has midface hypoplasia, prognathism (protruding jaw), an unusual gait, and a seizure disorder. She likely has:
- A. Wolf-Hirschhorn syndrome (4p-)
 - B. Angelman syndrome (maternal 15q11-13)
 - C. Williams syndrome (7q23-)
 - D. Smith-Magenis syndrome (17p11.2)
 - E. DiGeorge syndrome (22q11-)

Answers

- [4.1] E. The child has many signs and symptoms of Rubinstein-Taybi syndrome (16p13-), a microdeletion syndrome. Routine chromosome analysis may not identify this syndrome; FISH (fluorescent in situ hybridization) chromosome preparations are revealing.
- [4.2] A. Prader-Willi syndrome (15q11-15) is associated with developmental delay and defective satiety center, such that affected patients will eat constantly.
- [4.3] C. Williams' syndrome (7q23-) is associated with aortic stenosis, blue eyes, and cranial facial abnormalities.
- [4.4] B. Children with Angelman syndrome (15q11-13) have inappropriate bursts of laughter, ataxia, hypopigmented irises, and developmental delay.

CLINICAL PEARLS

Common features of cri-du-chat syndrome (5p-) include slow growth, cat-like cry, mental deficiency, microcephaly, hypertelorism, epicanthal folds, downturning of palpebral fissures, and hypotonia.

Rubinstein-Taybi syndrome often presents with a low IQ, downturning of palpebral fissures, hypoplasia of maxilla, broad thumbs and toes with radial angulation, low-set and often malformed auricles, microcephaly, short stature, and delayed osseous maturation.

Prader-Willi syndrome (paternal 15q11-13) presents with severe hypotonia in infancy but development of a voracious appetite and obesity by about 1 year of age. They have small hands and feet, micropallus, and are mentally deficient.

Patients with Angelman syndrome (maternal 15q11-13) have mental retardation, bursts of inappropriate laughter, hypopigmentation of their irises, large mouth with tongue protrusion, ataxia and jerky arm movements, and seizures.

Williams syndrome (7q23-) presents with mild microcephaly and mental retardation; blue eyes; epicanthal folds and depressed nasal bridge; supraaortic stenosis and peripheral pulmonary artery stenosis; and, occasionally, severe hypercalcemia.

DiGeorge syndrome (22q11-) presents with hypoplasia of the thymus and associated defects in cellular immunity; hypocalcemia and seizures caused by aplasia of the parathyroids; aortic arch abnormalities; and unusual facies that includes hypertelorism, short philtrum, and downturned palpebral fissures.

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◆ CASE 5

A large 15-year-old male is brought to clinic by his mother for routine care. He attends special education classes in public school where the teachers note that he is “hyperactive.” His physical examination is notable for his large size, a long face with prominent jaw and ears, and a thickened nasal bridge extending toward the tip of his nose. He has a cardiac click suggestive of mitral valve prolapse, and large testes.

- ◆ What is the most likely diagnosis?
- ◆ What is the best test to diagnose this condition?

ANSWERS TO CASE 5: Fragile X Syndrome

Summary: This is a 15-year-old male with mental retardation and a distinctive physical appearance.

- ◆ **Most likely diagnosis:** Fragile X syndrome, the most common inherited form of mental retardation, with an incidence of 1 in 2000 births.
- ◆ **Best diagnostic test:** DNA analysis demonstrating an expanded Xq27.3 region. Alternatively, a “fragile X” chromosome analysis is performed under special conditions to demonstrate the fragile site on the distal long arm of the X chromosome.

Analysis

Objectives

1. Understand the signs and symptoms of fragile X syndrome.
2. Appreciate the variety of causes of mental retardation in children.
3. Learn the signs and symptoms of syndromes involving missing or duplicate sex chromosomes.

Considerations

School system professionals have identified this adolescent's need for special education. A review of the testing performed by the school may give clues to his diagnosis. Identifying the etiology of his mental retardation impacts the psychosocial outcomes for this adolescent as well as family planning decisions for his parents. Particularly important in this case is the determination of the health and development of this patient's and his parents' siblings, especially the males on the mother's side.

APPROACH TO FRAGILE X SYNDROME

Definitions

Fragile X syndrome: A specific syndrome associated with mental retardation caused by the expansion of the familial mental retardation 1 (FMR1) gene at chromosome Xp27.3.

Mental retardation: A clinically and socially important impairment of measured intelligence and adaptive behavior that is diagnosed before 18 years of age.

Clinical Approach

Causes of mental retardation include preconceptual and early embryonic disruptions (chromosomal abnormalities, teratogens, placental dysfunction, congenital central nervous system malformations); fetal brain insults (infections, toxins, placental problems); perinatal difficulties (prematurity, metabolic disorders, infections); postnatal brain injuries (infections, trauma, metabolic disorders, toxins, poor nutrition); and miscellaneous postnatal family difficulties (poverty, poor caregiver-child interaction, parental mental illness). A category of "unknown etiology" includes children with mental retardation who do not appear to fit into the above categories.

The history of any child with possible mental retardation includes an evaluation of the child's developing psychosocial skills, and a review of school reports. The ultimate diagnosis of mental retardation may require formal testing to determine if the child's IQ falls below some set point such as 80. A determination whether formal testing should be performed is based on physical examination findings, developmental history and school history, and concerns of the family and/or teachers. All males with fragile X have developmental delay; the IQ of affected boys usually ranges from 30 to 55. Heterozygous girls are usually less affected than boys, but developmental delay and behavioral problems are often seen. **Children with fragile X syndrome often have temper tantrums and autism, in addition to having mental retardation.**

Physical findings found on patients with mental retardation include a large or small occiput, unusual color or distribution of hair, distinctive eyes, malformed ears or nose, and abnormalities in the size of the jaw, the shape of the mouth, or the height of the palate. The hands and feet may have short metacarpals or metatarsals, overlapping or supernumerary digits, and abnormal creases or nails. The skin may have café-au-lait spots or depigmented nevi, and the genitalia may be abnormally sized or ambiguous. Patients with mental retardation caused by fragile X syndrome typically exhibit macrocephaly, long face, high arched palate, large ears, macroorchidism after puberty, joint laxity, and poor motor coordination.

Laboratory testing of a child with mental retardation is based on the pattern of clinical findings and developmental milestones. A newly developed, more sensitive chromosomal analysis is now available to test for fragile X. Other testing for mental retardation may include urine and serum for amino and organic acids, serum levels of various compounds including ammonia, lead, zinc, and copper, and serum titers for congenital infections. Radiologic evaluation may include cranial CT, MRI, or electroencephalograms.

Management of all children with mental retardation includes specialized educational services, early childhood interventions, social services, vocational training, and psychiatric interventions. Further interventions for children with specific underlying etiologies may include modifying the diet, providing specific genetic counseling, or reviewing the natural course of the disease with the family.

Comprehension Questions

Match the following genetic disorders (A to E) to the clinical description [5.1 to 5.3]:

- A. Klinefelter syndrome (XXY)
- B. XYY male
- C. Turner syndrome (XO)
- D. Fragile X syndrome
- E. XXX syndrome

- [5.1] An institutionalized male juvenile delinquent appears at first glance to be normal. Upon closer examination he is noted to have severe nodulocystic acne, mild pectus excavatum, large teeth, prominent glabella, and relatively long face and fingers. His family reports that he has poor fine motor skills (such as penmanship), an explosive temper, and a low normal IQ.
- [5.2] A tall, thin 14-year-old boy has yet to have any signs of puberty. His mother reports that he was delayed in his speech development and always has done less well in school than his siblings. She reports that he is very shy, and teachers report his activity to be immature. Physical examination reveals signs of breast development, and long limbs with a decreased upper to lower segment ratio. His testes and phallus are small, and he has no evidence of pubertal development.
- [5.3] A 15-year-old with primary amenorrhea is noted to be well below the 5th percentile for height for her age. Her vital signs are significant for hypertension. On examination, she has a low posterior hairline, prominent and low-set ears, and excessive nuchal skin.
- [5.4] A 7-year-old male with mental retardation was born at home at 26 weeks' gestation to a 28-year-old mother who had received no prenatal care. A thorough evaluation of this child is likely to suggest his mental retardation related to:
- A. Brain tumor
 - B. Elevated serum lead levels
 - C. Complications of prematurity
 - D. Congenital infection with cytomegalovirus
 - E. Chromosomal aberration

Answers

- [5.1] **B.** XYY-affected males often have explosive tempers. Other findings include long and asymmetrical ears, increased length versus

breadth for the hands, feet and cranial vault, and mild pectus excavatum. By age 5 or 6 years, these boys tend to be taller than their peers, and they begin displaying aggressive/defiant behavior.

- [5.2] A. With Klinefelter syndrome (XXY), testosterone replacement allows for more normal adolescent male development, although azoospermia is the rule. The incidence of breast cancer in XXY males approaches that of women.
- [5.3] C. Other features of Turner syndrome include widely spaced nipples and broad chest; cubitus valgus (increased carrying angle of arms); edema of the hands and feet in the newborn period; congenital heart disease (including coarctation of the aorta or bicuspid aortic valve); horseshoe kidney; short fourth metacarpal and metatarsal; hypothyroidism; and decreased hearing. Mental development is usually normal.
- [5.4] C. Prematurity at birth, especially when <28 weeks' gestation, is associated with a variety of complications (such as severe intraventricular hemorrhage) that can result in developmental delay and low IQ.

CLINICAL PEARLS

◆ Males with Klinefelter syndrome (XXY) have mild mental delay, eunuchoid habitus, gynecomastia, long arms and legs, and hypogonadism.

◆ Males with XYY chromosomal configuration present with explosive (often antisocial) behavior, weakness with poor fine motor control, accelerated growth in mid-childhood, large teeth, prominent glabella and asymmetrical ears, and severe acne at puberty.

◆ Girls with Turner syndrome (45,XO) exhibit short stature, amenorrhea, excessive nuchal skin, low posterior hairline, broad chests with widely spaced nipples, cubitus valgus, and coarctation of the aorta. Hypertension is common, possibly owing to renal abnormalities (horseshoe kidney).

◆ Fragile X syndrome, the most common form of inherited mental retardation, is seen primarily in boys and can be diagnosed in mentally retarded patients (particularly boys) with macrocephaly, long face and high-arched palate, large ears, and macroorchidism after puberty.

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◆ CASE 6

A 6-month-old child is brought to your office for a well-child examination. His family recently moved to the United States from Turkey. The child's past medical and family histories are unremarkable except that goat's milk is the child's sole source of nutrition. The child appears to be healthy on examination.

- ◆ What hematologic problem is most likely to develop in this infant?
- ◆ What other concerns should a healthcare provider consider in a child fed goat's milk?

ANSWERS TO CASE 6: Megaloblastic Anemia

Summary: This is a 6-month-old child who is fed exclusively goat's milk.

- ◆ **Likely complication:** Megaloblastic anemia from folate or B₁₂ deficiency.
- ◆ **Other concerns:** Brucellosis if milk is unpasteurized.

Objectives

1. Appreciate the benefits of breast-feeding.
2. Know the nutritional supplements recommended for mothers who breast-feed.
3. Understand the special needs of infants and toddlers who are fed goat's milk or vegan diets.
4. Appreciate the clinical syndromes resulting from diets containing vitamin excesses and deficiencies.

Considerations

A wide variety of feeding regimens exist for infants and toddlers—breast-feeding, formula feeding, goat's milk, other types of nonformula milk, commercial or handmade baby foods, and table foods. An important role of the pediatric healthcare provider is to educate parents about the benefits and potential dangers of various diet choices for their infants and toddlers.

APPROACH TO INFANT NUTRITION**Definitions**

Lactovegetarians: Diet devoid of animal products but includes milk.

Omnivores: Diet includes both animal and vegetable products.

Ovovegetarians: Diet devoid of animal products but includes eggs.

Vegan: A vegetarian whose diet is devoid of all animal products.

Clinical Approach

Infant formulas containing goat's milk are not routinely available in the United States, although they are available in other countries. Goat's milk has lower sodium levels but more potassium, chloride, linoleic and arachidonic acid than does cow's milk. It is low in vitamin D, iron, folate, and vitamin B₁₂. Therefore, **infants receiving goat's milk as a primary source of nutrition should receive supplementation with folate and vitamin B₁₂ to prevent megaloblastic anemia and iron to prevent iron-deficiency anemia.** Additionally, **goat's milk** must be boiled before ingesting because goats are particularly **susceptible to brucellosis.**

Breast milk is considered the ideal food for human infants because it contains complete nutrition as well as antimicrobial properties. In developing countries, breast milk is associated with lower infant morbidity and mortality, mostly owing to a reduction in diarrhea associated with contaminated water used in formula preparation. **Breast milk contains high concentrations of IgA**, an immunoglobulin that reduces the adherence of viruses and bacteria to the intestinal wall, and macrophages that inhibit the growth of *Escherichia coli*. Many studies recognize the psychological advantages for mothers and infants who breast-feed. Breast milk provides all of the necessary nutrients for infant growth (with the possible exception of vitamin D and fluoride). **Disadvantages of breast-feeding** include the potential to **transmit HIV** and possibly other viruses, occasional **exacerbation of jaundice** because of increased levels of unconjugated hyperbilirubinemia (resolved with temporary interruption of the breast-feeding), and **its association with low levels of vitamin K**, contributing to hemorrhagic disease of the newborn (prevented by administration of vitamin K at birth).

Formula feeding has been substituted for breast-feeding for a variety of reasons including concern about appearance and personal preference. Manufacturers of commercial formulas strive to provide products as similar to human milk as possible. Growth rates of infants fed cow's

Table 6-1
EFFECTS OF VITAMIN AND MINERAL DEFICIENCY
OR EXCESS

	DEFICIENCY	EXCESS
Vitamin A	Night blindness, xerophthalmia, keratomalacia, conjunctivitis, poor growth, impaired resistance to infection, abnormal tooth enamel development	Increased intracranial pressure, anorexia, carotenemia, hyperostosis (pain and swelling of long bones), alopecia, hepatomegaly, poor growth
Vitamin D	Rickets (with elevated serum phosphatase levels appearing before bone deformities), osteomalacia, infantile tetany	Hypercalcemia, azotemia, poor growth, nausea and vomiting, diarrhea, calcinosis of a variety of tissues including kidney, heart, bronchi, stomach
Vitamin E	Hemolytic anemia in premature infants	Unknown
Ascorbic acid (vitamin C)	Scurvy and poor wound healing	May predispose to kidney stones
Thiamine (vitamin B ₁)	Beriberi (neuritis, edema, cardiac failure), hoarseness, anorexia, restlessness, aphonia	Unknown
Riboflavin (vitamin B ₂)	Photophobia, cheilosis, glossitis, corneal vascularization, poor growth	Unknown
Niacin	Pellagra (dementia, dermatitis, diarrhea)	Nicotinic acid causes flushing, pruritus
Pyridoxine (vitamin B ₆)	In infants, irritability, convulsions, anemia; in older patients (on isoniazid), dermatitis, glossitis, cheilosis, peripheral neuritis	Sensory neuropathy

Table 6-1
EFFECTS OF VITAMIN AND MINERAL DEFICIENCY
OR EXCESS (*Continued*)

	DEFICIENCY	EXCESS
Folate	Megaloblastic anemia, glossitis pharyngeal ulcers, impaired cellular immunity	Usually none
Cobalamin (vitamin B ₁₂)	Pernicious anemia, neurologic deterioration, methylmalonic acidemia	Unknown
Pantothenic acid	Rarely depression, hypotension, muscle weakness, abdominal pain	Unknown
Biotin	Dermatitis, seborrhea, anorexia, muscle pain, pallor, alopecia	Unknown
Vitamin K	Hemorrhagic manifestations	Water-soluble forms can cause hyperbilirubinemia

milk formula are similar to those of breast-fed infants. Improved sterilization procedures and refrigeration in developing countries have reduced the widespread problem of gastrointestinal infections previously associated with formula feedings.

A wide variety of formulas are available for infants with special needs. Infants with phenylketonuria require formulas low in phenylalanine (Lofenalac) and those unable to digest protein require nitrogen in the form of amino acid mixtures (Nutramigen or Pregestimil). Infants with cow's milk allergies often benefit from soybean-based formulas (ProSobee or Isomil).

Vegan diets supply all necessary nutrients if a variety of vegetables are selected. Some evidence suggests that the higher fiber of the vegetarian diet leads to faster gastrointestinal transit time, resulting in reduced serum cholesterol levels, less diverticulitis, and a lower incidence of appendicitis. Breast-feeding vegan mothers are supplemented with vitamin B₁₂ to prevent the infant's developing methylmalonic

acidemia [a disorder of amino acid metabolism, involving a defect in the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA]; patients can present with failure to thrive, seizure, encephalopathy, stroke or other neurologic manifestations. Toddlers on a vegan diet are supplemented with B₁₂ and, because of the high fiber content and rapid gastrointestinal transit time, are also supplemented with trace minerals that can be depleted.

Vitamin deficiencies and excesses can result in a variety of clinical syndromes. Although rare, these syndromes can usually be averted with appropriate nutrition (Table 6–1).

Comprehension Questions

- [6.1] A 2-day-old infant presents to the emergency room with significant bleeding from the rectum and nose. He was the product of a full-term pregnancy that appeared to be without complications. He was delivered at home by a lay midwife and had Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. He had been doing well on breast-feedings; this is his first visit to a health care professional since birth. Which of the following vitamin deficiencies might explain his condition?
- A. Vitamin A
 - B. Vitamin B₁
 - C. Vitamin C
 - D. Vitamin D
 - E. Vitamin K
- [6.2] A 6-month-old infant has been growing poorly. His parents have changed his formula three times, but he continues to grow poorly. His physical examination is remarkable for a pale, emaciated child with little subcutaneous fat and fullness to his anterior fontanelle. His laboratory screening tests are notable for a hemolytic anemia and prolonged bleeding times. Which of the following laboratory tests is an appropriate next step to diagnose his condition?

- A. Serum factor IX levels
 - B. Urine for pH and electrolytes
 - C. Serum immunoglobulins
 - D. Sweat chloride
 - E. Hemoglobin electrophoresis
- [6.3] A breast-fed infant is expected to have a lower incidence of which of the following common childhood conditions:
- A. Conjunctivitis
 - B. Impetigo
 - C. Diarrhea
 - D. Urinary tract infections
 - E. Asthma
- [6.4] A 3-week-old is admitted for failure to thrive, diarrhea, and a sepsis-like picture. He does well on intravenous fluids, but when started on routine infant formula with iron, he develops symptoms again. It is Saturday and the laboratory at the state health department is not available to assist you. The formula likely to be required in this infant is:
- A. Soy-based formula (ProSobee or Isomil)
 - B. Amino-acid based formula (Nutramigen or Pregestimil)
 - C. Low-phenylalanine formulas (Lofenalac or Phenex-1)
 - D. Low-iron, routine infant formula (Similac with low iron or Enfamil with low iron)
 - E. Low-isoleucine, -leucine, and -valine infant formula (Ketonex-1 or MSUD 1)

Answers

- [6.1] E. Newborn infants have a relative deficiency of vitamin K, especially those who are breast-fed; most infants are routinely administered vitamin K at birth to prevent bleeding complications associated with this deficiency.

- [6.2] **D.** The patient appears to have failure to thrive (FTT) with deficiencies of vitamin K (bleeding problems), vitamin A (fullness to fontanelle), and vitamin E (hemolytic anemia). Cystic fibrosis (associated with malabsorption of these vitamins) would explain the condition.
- [6.3] **C.** Breast-feeding is associated with a lower incidence of diarrhea.
- [6.4] **A.** This patient appears to have galactosemia for which a lactose-free formula is appropriate. The low-phenylalanine formulas are for infants with phenylketonuria; low-iron formulas serve no purpose other than contributing to iron-deficiency anemia, the low-isoleucine, -leucine, and -valine infant formulas are useful for patients with maple syrup urine disease, and the amino-acid-based formulas are excellent for children with malabsorption syndromes.

CLINICAL PEARLS



Breast-feeding is associated with lower morbidity and mortality (especially in developing countries) mostly owing to a reduction in enteric pathogens and diarrhea associated with contaminated water used in formula preparation.



Breast-feeding provides all of the necessary nutrients for infant growth with the possible exception of vitamin D and fluoride, which are usually supplemented.



A breast-feeding vegan (diet is totally devoid of animal products) should supplement her infant's diet with vitamin B₁₂ to prevent methylmalonic acidemia and her toddler's diet with B₁₂ and trace minerals.

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◆ CASE 7

An 8-month-old child presents to your clinic with a 24-hour history of increased crying when moving her right leg. The child has a prominent bulge over the mid-right thigh where she had received an immunization yesterday. The child has had no fever nor change in appetite, and seems to be upset only when the leg is disturbed. The child underwent a failed Kasai procedure for biliary atresia and is awaiting a liver transplant. A radiograph of the leg demonstrates a mid-shaft fracture and poor mineralization.

- ◆ What is the mechanism for this condition?
- ◆ What are the best diagnostic tests to diagnose this condition?

ANSWERS TO CASE 7: Rickets

Summary: An 8-month-old child with a chronic medical condition that likely includes biliary atresia, poor mineralization of the bones, and a fracture.

- ◆ **Mechanism:** malabsorption of vitamin D (among other fat-soluble vitamins) because of lack of intestinal secretion of bile salts, resulting in rickets.
- ◆ **Best diagnostic tests:** serum 25(OH)D, calcium, phosphorus, and alkaline phosphatase levels. Radiographs demonstrate poor mineralization of the bones.

Analysis**Objectives**

1. Become familiar with the clinical presentation of rickets.
2. Understand the pathophysiology behind nutritional and nonnutritional forms of rickets.
3. Appreciate some of the other metabolic causes for fractures in a child.

Considerations

This child has biliary atresia and underwent a failed Kasai (biliary bypass) procedure. A variety of metabolic aberrations can be expected while this child awaits liver transplantation. A thorough review of this child's medications and her compliance in receiving them is warranted. Because of the extremely brittle nature of this child's bones, it is likely that her leg was fractured while receiving immunizations.

APPROACH TO THE CHILD WITH POSSIBLE RICKETS

Definitions

Biliary atresia: A congenital condition affecting approximately 1 in 16,000 live births in which the bile ducts within the liver become blocked, resulting in reduced flow of bile from the liver. Fibrosis of the liver results, ultimately preventing any bile flow into the bowel.

Genu valgum: "Knock" knees.

Genu varum: "Bowed" legs.

Kasai procedure: An operative procedure in which a loop of bowel is used to form a duct to allow bile to drain from a liver with biliary atresia. The procedure has been named after the Japanese surgeon who pioneered the technique.

Rickets: Poor mineralization of growing bone or of osteoid tissue.

Clinical Approach

A patient with liver failure, especially biliary atresia, is at high risk of rickets because of poor bile salt secretion into the bowel lumen, resulting in poor absorption of fat-soluble vitamins, including vitamin D. The poor absorption of vitamin D leads to the typical picture of low serum 25(OH)D, occasionally reduced serum calcium levels, markedly elevated serum alkaline phosphatase, poor mineralization of the bones, and an increased incidence of bone fractures. Children with liver failure who develop ascites and are treated with loop diuretics often experience excessive urinary calcium losses. Treatment, aimed at restoring normal bone mineralization, consists of high doses of vitamin D and calcium supplementation.

Nutritional rickets results from a diet inadequate in vitamin D and/or a lack of exposure to sunlight (see Figure 7-1). It is rare in industrialized countries in otherwise healthy children. This condition is occasionally seen in dark-skinned infants who do not receive vitamin D supplementation or in breast-fed infants not exposed to sunlight. More common causes of rickets, however, are liver or renal failure or a

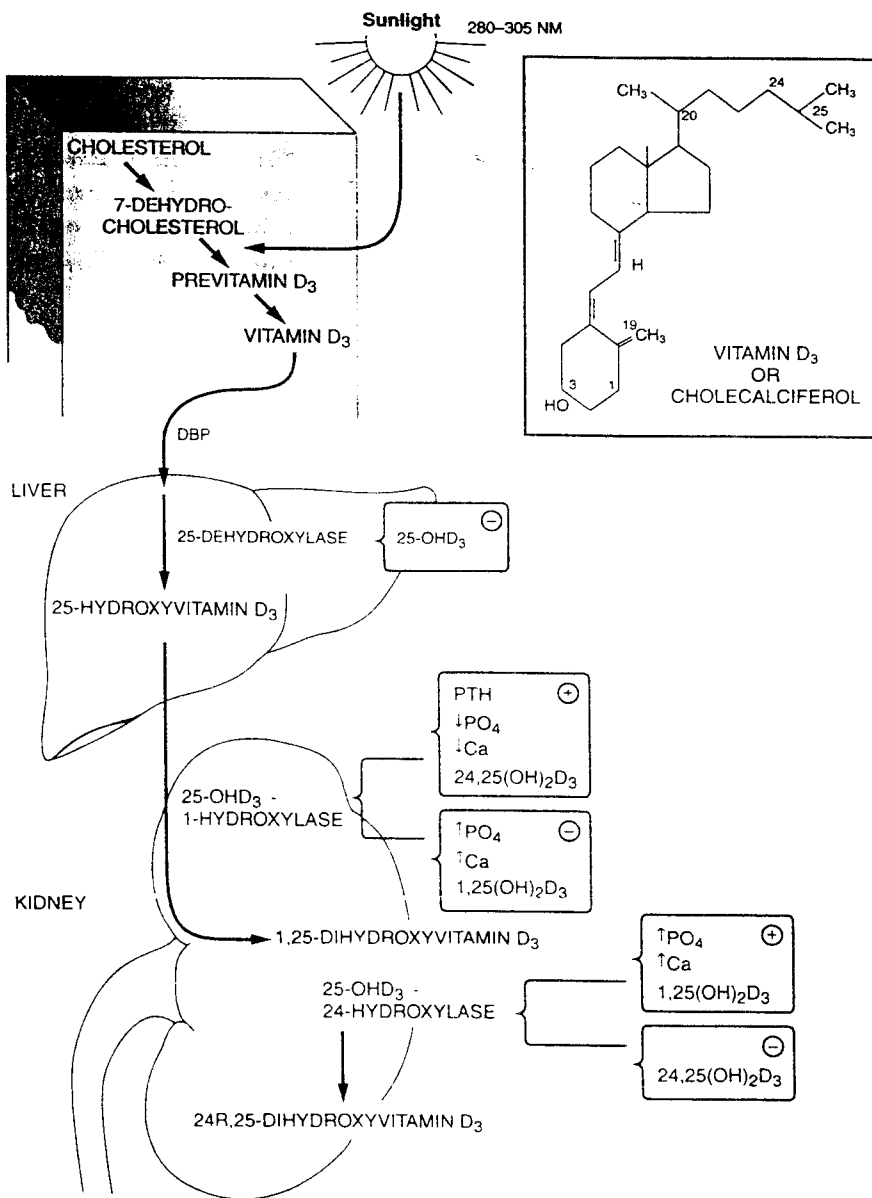


Figure 7-1. Vitamin D metabolism.

Table 7-1
COMMON CAUSES OF ABNORMAL METABOLISM OF CALCIUM
AND PHOSPHORUS

	SERUM CALCIUM	SERUM PHOSPHORUS	SERUM ALKALINE PHOSPHATASE	URINE AMINO ACIDS	COMMENTS
Calcium deficiency with 2 hyperparathyroidism [vitamin D deficiency or low 25(OH)D without stimulation of 1,25(OH) ₂ D production]	N or ↓	↓	↑	↑	Unusual except in dark-skinned infants without vitamin D supplementation, or in exclusively breast-fed infants without exposure to sunlight.
Lack of vitamin D (lack of exposure to sunlight; dietary deficiency of vitamin D, congenital)	N or ↓	↓	↑	↑	Such as in celiac disease, cystic fibrosis, or steatorrhea.
Malabsorption of vitamin D	N or ↓	↓	↑	↑	See discussion of case.
Hepatic disease	N or ↓	↓	↑	↑	Usually phenobarbital and phenytoin; patients have reduced 25(OH)D levels, possibly as a result of increased cytochrome P450 activity; treatment is with vitamin D ₂ and adequate dietary calcium.
Anticonvulsive drugs	N or ↓	↓	↑	↑	

Table 7-1
COMMON CAUSES OF ABNORMAL METABOLISM OF CALCIUM
AND PHOSPHORUS (*Continued*)

	SERUM CALCIUM	SERUM PHOSPHORUS	SERUM ALKALINE PHOSPHATASE	URINE AMINO ACIDS	COMMENTS
Renal osteodystrophy	N or ↓	↑	↑	Variable	Hypophosphaturia results in hypocalcemia that then stimulates parathyroid secretion and enhanced bone turnover. Additionally, diminished conversion of 25(OH)D to 1,25(OH) ₂ D occurs as renal damage progresses.
Vitamin D-dependent type I	↓	N or ↓	↑	↑	Autosomal recessive; felt to be reduced activity of 25(OH)D ₁ α-hydroxylase; responds to massive doses of vitamin D ₂ or low-dose 1,25(OH) ₂ D.
Phosphate deficiency without 2° hyperparathyroidism	N	↓	↑	↓	X-linked dominant; most common form of nonnutritional rickets (see text).
Genetic 1° hypophosphatemia	N	↓	↑		Includes cystinosis, tyrosinosis, Lowe syndrome, and acquired forms.
Fanconi syndrome	N	↓			Cystinosis and tyrosinosis are autosomal recessive, Lowe syndrome X-linked recessive.

Table 7-1
COMMON CAUSES OF ABNORMAL METABOLISM OF CALCIUM
AND PHOSPHORUS (Continued)

Renal tubular acidosis, type II (proximal)	N	↓	↑	N	Bicarbonaturia, hyperkalemia, hypercalcemia, hypophosphatemia and phosphaturia are common. Rickets may result from leaching of bone calcium bicarbonate in an attempt to buffer retained hydrogen ions seen in this condition.
Oncogenic hypophosphatemia	N	↓	↑	Usually N	Caused by tumor secretion of a phosphate regulating gene product (PEX) which results in phosphaturia and impaired conversion of 25(OH)D to 1,25(OH) ₂ D. The tumors are often hard to detect, but are found in the small bones of the hands and feet, abdominal sheath, nasal antrum, and pharynx. Resolution occurs after tumor removal.
Phosphate deficiency or malabsorption	N	↓	↑	N	Caused by parenteral hyperalimentation or low phosphate intake.
End-organ resistance to 1,25(OH) ₂ D ₃	↓	↓ or N	↑	↑	Autosomal recessive; very high serum levels of 1,25(OH) ₂ D ₃ ; may result from 1,25(OH) ₂ D receptor-binding disorder.

variety or biochemical abnormalities in the normal metabolism of calcium and phosphorus (Table 7-1).

The most common form of nonnutritional rickets is the X-linked dominant genetic disorder, (familial) primary hypophosphatemia. Affected individuals have defects in reabsorption of phosphate and conversion of 25(OH)D to 1,25(OH)₂D in the proximal tubules of the kidneys is abnormal resulting in low serum 1,25(OH)₂D, low-normal serum calcium, moderately low serum phosphate, elevated serum alkaline phosphatase, hyperphosphaturia, and no evidence of hyperparathyroidism. Children with this disorder present at the age of walking with smooth lower extremity bowing (as compared to angular bowing seen in calcium-deficient rickets). They also have a waddling gait, genu varum, genu valgum, coxa vara, and short stature. Other findings more common of calcium deficient rickets, such as myopathy, rachitic rosary, pectus deformities, and tetany, are not usually seen. Children with familial hypophosphatemia can have dental deformities (intraglobular dentin) in contrast to the enamel defects more commonly seen in calcium deficient rickets. Radiologic findings include coarse-appearing trabecular bone and widening, fraying, and cupping of the metaphysis of the proximal and distal tibia, the distal femur radius, and ulna.

Comprehension Questions

- [7.1] A 14-month-old child is noted to have lower extremity bowing, a waddling gait, genu varum, and to be at the 5th percentile for height. Laboratory data include low-normal serum calcium, moderately low serum phosphate, elevated serum alkaline phosphatase, hyperphosphaturia, and normal parathyroid levels. The most likely diagnosis in this child is:
- A. Genetic primary hypophosphatemia
 - B. Renal osteodystrophy
 - C. Malabsorption of vitamin D
 - D. Phosphate malabsorption
 - E. Fanconi syndrome

- [7.2] An 8-month-old black male arrives with his mother to the emergency department with the complaint of decreased movement of his left arm. The child is the product of a term pregnancy, has had no significant past medical problems, and was in good health when his mother dropped him off at daycare that morning. Radiograph of the upper arm shows a spiral fracture of his left humerus. You should:
- A. Obtain stool for analysis for fat-soluble vitamins
 - B. Obtain serum 1,25(OH)₂D levels
 - C. Admit the child and call child protective services
 - D. Send chromosomes for osteogenesis imperfecta analysis
 - E. Order serum alkaline phosphatase levels
- [7.3] The diet of a 3-year-old child with cystic fibrosis should be supplemented with:
- A. Vitamin C
 - B. Folate
 - C. Vitamin B₁₂
 - D. Sodium
 - E. Vitamin D
- [7.4] A 5-year-old girl is noted to be somewhat short for age and to have mild bowing of her legs. Her past medical history is significant only for a seizure disorder that is adequately controlled with medications. Screening serum calcium, phosphorus, and alkaline phosphatase levels and the urinary amino acid concentration are normal. A bone age of her left wrist is notable for abnormal mineralization of the distal radius and ulna. Of the following, which is most likely?
- A. Genetic first-degree hypophosphatemia
 - B. Schmid metaphyseal dysplasia
 - C. Cystic fibrosis
 - D. Rickets associated with anticonvulsive drug use
 - E. Fanconi syndrome

Answers

- [7.1] **A.** Lower extremity bowing, low to normal calcium and phosphate levels, and normal parathyroid hormone levels point to familial primary hypophosphatemia.
- [7.2] **C.** A spiral fracture of the humerus is suspicious for child abuse.
- [7.3] **E.** In addition to pancreatic enzyme replacement therapy, supplementation with fat-soluble vitamins (A, D, E, and K), often iron, and sometimes zinc is recommended.
- [7.4] **B.** All of the rickets syndromes present with elevated alkaline phosphatase levels. Schmid metaphyseal dysplasia is an autosomal dominant condition that presents in a similar way with short stature, bowing of legs, and waddling gait. Radiographs show irregular mineralization of the long bones. Biochemically, patients with Schmid-type metaphyseal dysostosis present with normal serum calcium, phosphorus, and alkaline phosphatase activity as well as with normal levels of urinary amino acids.

CLINICAL PEARLS



Nutritional rickets (a diet inadequate in vitamin D or a lack of exposure to sunlight) is rare in industrialized countries in otherwise healthy children. More commonly, a variety of other medical conditions such as liver or renal failure, or biochemical abnormalities in the normal metabolism of calcium and phosphorus are responsible.



Genetic (familial) primary hypophosphatemia is the most common causes of nonnutritional rickets. It is an X-linked dominant disorder with defects in the reabsorption of phosphate and conversion of $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ in the proximal tubules of the kidney. Findings include low serum $1,25(\text{OH})_2\text{D}$, low-normal serum calcium, moderately low serum phosphate, elevated serum alkaline phosphatase, hyperphosphaturia, in the absence of hyperparathyroidism.

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◆ CASE 8

A 5-year-old child arrives in the emergency center. His family reports that he has been increasingly confused over several hours prior to arrival. Vital signs demonstrate tachycardia, hypotension, mild hypothermia, and slow, deep respirations. A quick examination reveals poor capillary refill, tenting of his skin, and altered mental status. His mother reports that he has had a several-pound weight loss over the previous few weeks, has been increasingly tired over the several days prior to arrival, and that she has been particularly concerned about his 2- or 3-day history of thirst, frequent urination during the daytime, and new onset nocturnal enuresis.

◆ What is the most likely diagnosis?

◆ What is the best therapy?

ANSWERS TO CASE 8: Diabetic Ketoacidosis

Summary: A 5-year-old with weight loss, polydipsia, and polyuria who presents with dehydration and Kussmaul breathing.

- ◆ **Most likely diagnosis:** Diabetic ketoacidosis (DKA).
- ◆ **Best therapy:** Fluid rehydration, insulin, and close monitoring of serum glucose and acidemia.

Analysis**Objectives**

1. Understand the presentation of patients in DKA.
2. Appreciate the initial treatment strategies in the management of DKA.
3. Become familiar with pitfalls in the treatment of DKA.

Considerations

This patient presents in extremis. The “ABCs” of medicine apply. He is confused but is not obtunded, so he probably does not need his *Airway* controlled or his *Breathing* regulated. However, his clinical examination suggests at least 10% dehydration, and his *Circulatory* status is of prime interest; rapid restoration of his volume status is required. The signs and symptoms noted on the quick history and physical suggest diabetes; a finger glucose confirms the diagnosis.

APPROACH TO DIABETIC KETOACIDOSIS**Definitions**

Ketoacidosis: A condition that results from deficient insulin availability, leading to lipid oxidation and metabolism rather than glu-

cose metabolism. The absence of insulin results in free fatty acid (FFA) released from adipose tissue and in unregulated hepatic FFA oxidation and ketogenesis.

Type I diabetes: Known by a variety of names, this condition is caused by a severe deficiency of endogenous insulin and a requirement for exogenous insulin to prevent ketoacidosis.

Type II diabetes: Also known by a variety of names, but usually consists of patients who are insulin resistant at the tissue level (although exogenous insulin is often required), and rarely progress to ketoacidosis.

Clinical Approach

The patient who presents in DKA represents a medical emergency. Such patients may require intubation and control of their breathing, but these interventions are usually seen later in the disease process, with children more commonly presenting with signs and symptoms of severe dehydration and acidosis. **The history is often positive for polyuria, nausea, vomiting, and abdominal complaints. Hypothermia is a common finding, as are hypotension, Kussmaul respirations, and acetone on the breath.** As these signs and symptoms may be non-specific, especially in younger children, a high index of suspicion is required to make the diagnosis in a previously unknown diabetic child.

Laboratory data demonstrates an **elevated glucose (often 400 to 800 mg/dL), metabolic acidosis (with anion gap; i.e. excess endogenous anion production such as from lactic acid), and hyperketonemia.** Serum electrolytes usually demonstrate hyponatremia, and normal or slightly elevated serum potassium (even though intracellular potassium levels are depleted). Elevated blood urea nitrogen and serum creatinine levels are also commonly seen as a reflection of the dehydration. White blood cell counts are often elevated, especially if a bacterial infection is exacerbating the condition.

Treating a patient with DKA includes initial expansion of the vascular volume, and then correction of the hyperglycemia and hyperketonemia. Normal saline is often used to expand the vascular volume. Fluid boluses sufficient to stabilize the heart rate and blood pressure are sometimes required, and then a slower infusion (usually of

a saline solution without glucose) to replace fluid losses and to ensure adequate urine flow is initiated. Potassium is added to intravenous fluids soon **after** urine output is established to counteract the patient's total body potassium depletion; while the patient may present with normal or elevated serum potassium, treatment of the hyperglycemia and acidosis drives potassium intracellularly and hypokalemia is an avoidable complication. A continuous infusion of insulin at a rate of about 0.1 U/kg/h is also started (a bolus of 0.1 U/kg is often given initially), with the infusion rate adjusted based on the results of the child's hourly glucose measurements. Glucose is added to intravenous fluids when the serum glucose level drops to about 250 or 300 mg/dL, and additional adjustments to the insulin infusion rates are made based on serum glucose levels. **The low plasma pH and elevated serum ketone levels will correct significantly in the first 8 to 10 hours, but the serum bicarbonate level may remain low for about 24 hours or more.** Improvement is characterized by a decrease in infusion rate of insulin and resolution of the ketonuria; at this time, the patient is able to take oral feedings, and insulin therapy is converted from the intravenous to subcutaneous route.

During the treatment of DKA several pitfalls must be avoided. Infusion of intravenous fluids with insulin and **improvement in acidosis levels is often associated with a dropping serum potassium level;** addition to the intravenous fluids of potassium is usually indicated to prevent serious hypokalemia. Infusion of bicarbonate is usually avoided except in extreme situations, as it may (a) precipitate hypokalemia, (b) shift the oxygen dissociation curve to the left, worsening oxygen delivery to the organs, (c) overcorrect the acidosis, and (d) result in worsening cerebral acidosis while the plasma pH is being corrected (owing to free transfer into the cerebrum of CO₂ formed when the bicarbonate is infused in an acid serum). Cerebral edema, the etiology of which is not clearly understood, is sometimes seen manifesting as headache, changes in personality, vomiting, and decreased reflexes. Reduction in intravenous fluid, administration of intravenous mannitol, and hyperventilation are treatment modalities should cerebral edema begin to develop. **Episodes of diabetic ketoacidosis (especially in the known diabetic) can be precipitated by bacterial infection.** An evaluation for sources of infection with institution of antibiotics (if appropriate) is required.

Comprehension Questions

- [8.1] A 14-year-old girl arrives as a new patient. She was followed for 7 years in another state with a history of insulin-dependent diabetes mellitus. Her hemoglobin A₁C is 14.9%. This laboratory test indicates that:
- A. She does not have insulin-dependent diabetes.
 - B. She has an underlying infection.
 - C. Her glucose control is poor.
 - D. She is demonstrating the Somogyi phenomenon.
 - E. She has entered the "honeymoon phase" of her diabetes.
- [8.2] Six months after being diagnosed with what appears to be insulin-dependent diabetes, the 5-year-old in the case presentation demonstrates a significant decrease in his requirement for insulin. The explanation for this is most likely:
- A. His diagnosis of insulin-dependent diabetes was wrong.
 - B. He had a chronic infection that is now under control.
 - C. He has followed his diabetes diet so well that he needs less insulin.
 - D. He is demonstrating the Somogyi phenomenon.
 - E. He has entered the "honeymoon phase" of his diabetes.
- [8.3] A 15-year-old girl presents with the complaint of abdominal pain, vomiting, and lethargy for 3 days' duration. On physical examination her chest and throat are clear, but her abdominal examination is significant for right lower quadrant pain. Rectal examination is equivocal for pain, and her pelvic examination is remarkable for pain upon movement of her cervix. Laboratory data include an elevation of her white blood cell count, a serum glucose of 145 mg/dL, and a serum bicarbonate of 21 meq/dL. Her urinalysis is remarkable for 1+ white blood cells, 1+ glucose, and 1+ ketones. The most likely diagnosis is:
- A. Diabetic ketoacidosis
 - B. Pelvic inflammatory disease

- C. Gastroenteritis
- D. Appendicitis
- E. Right lower lobe pneumonia

[8.4] A 16-year-old obese girl presents with enuresis, frequent urination, a white vaginal discharge, and a dark rash around her neck. Her serum glucose is 250 mg/dL, and her urinalysis is positive for 2+ glucose, but is otherwise negative. She most likely has:

- A. Chlamydia cervicitis
- B. Urinary tract infection
- C. Psoriasis
- D. Chemical vaginitis
- E. Type II diabetes

Answers

[8.1] C. The patient in the question likely has poor diabetes control. The hemoglobin A₁C is a test commonly used to follow glucose control. It measures the average glucose levels the patient has experienced over the previous 2 or 3 months. The goal for hemoglobin A₁C for most diabetics is usually 6% to 9%. Hemoglobin A₁C levels greater than 12% suggest poor glucose control, and levels 9% to 12% represent fair control. The Somogyi phenomenon refers to a patient who has hypoglycemic episodes at night manifested as night terrors, headaches, or early morning sweating who present a few hours later with hyperglycemia, ketonuria, and glucosuria; an outpouring of counterregulatory hormones in response to the hypoglycemia is responsible for the hyperglycemic episode.

[8.2] E. A large number of newly diagnosed diabetic patients (up to 75%) have a progressive drop in the daily requirement of insulin in the months following their initial diagnosis of diabetes; a few patients require no insulin. This "honeymoon" period usually lasts a few months, but most often a requirement for insulin re-

turns. Patients should be counseled that the “honeymoon” period is not a cure, and that they almost certainly will require insulin again.

- [8.3] **B.** The patient in the question likely has pelvic inflammatory disease. The glucose in the urine is a stress-response to the infection, and does not represent glucose metabolism problems. All of the options in the question can present with abdominal pain. While diabetes mellitus is in the differential, a patient with DKA more likely presents with ketoacidosis (significantly decreased serum bicarbonate levels) and high serum glucose levels.
- [8.4] **E.** The description is of an obese child with candida vaginitis (causing the vaginal discharge) and acanthosis nigricans (the dark rash around the neck) consistent with type II diabetes. This condition is far more common in overweight children, especially those with a family history of the condition.

CLINICAL PEARLS

DKA is a medical emergency that can present with nonspecific signs of dehydration, polyuria, nausea, vomiting, and abdominal complaints. Hypothermia, hypotension, Kussmaul respirations, and acetone on the breath are also seen. A high index of suspicion is required to make the diagnosis, especially in the younger child.

Cerebral edema is a potentially life-threatening complication in the treatment of DKA presenting as headache, changes in personality, vomiting, and decreased reflexes.

Electrolyte disturbances are common in DKA. Hypokalemia can occur in the treatment phase if adequate sources are not provided. Administration of bicarbonate is usually avoided except in extreme situations for a variety of physiologic reasons.

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◆ CASE 9

A 2-month-old child arrives to your clinic for his routine “baby shots.” You have followed this child in your practice since his birth. His mother’s pregnancy was uncomplicated and he has been healthy without significant problems since his 2-week checkup.

◆ What is the next step in the care of this patient?

ANSWER TO CASE 9: Routine Well-Child Care

Summary: A healthy 2-month-old infant due for a routine well-child visit.

- ◆ **Next step:** Gather interval history, obtain appropriate measurements (length, weight, and head circumference), review results of sensory and developmental/behavioral screenings (ensure that he can see and hear and is developing normally), perform a physical examination, perform general and specialized procedures (ensure that his neonatal state screen is normal and provide immunizations), and offer anticipatory guidance.

Analysis**Objectives**

1. Become familiar with the goals of the routine well-child (or health supervision) session.
2. Become familiar with the American Academy of Pediatrics (AAP) "Recommended Childhood Immunization Schedule."
3. Learn the side effects and contraindications of common childhood immunizations.

Considerations

Well-child care for this healthy infant is relatively uncomplicated. For children with special needs, such as Down syndrome or sickle cell disease, guidelines have been developed that outline specific health supervision considerations. For children with multiple handicaps resulting from numerous complications, such as extreme prematurity, no specific guidelines may exist and the healthcare provider must adapt national "well-child care" guidelines as appropriate.

APPROACH TO CHILDHOOD WELL-CHILD CARE

Clinical Approach

Goals of the health supervision visit include evaluating the physical, developmental, psychosocial, and educational status of the child in an effort to identify problems early, so that prompt intervention can be instituted. Anticipatory guidance aims to foster good health habits, prevent illness, and assist in family communication.

Most providers follow one of the commonly available preventive healthcare guidelines for children. The American Academy of Pediatrics (AAP) periodically updates its Recommendations for Preventive Pediatric Health Care (Figures 9-1 and 9-2), which suggests a variety of questions, medical procedures, and counseling areas for children aged birth through 21 years. The Agency for Healthcare Research and Quality (AHRQ) offers extensive guidelines for preventive healthcare for children and adults. Although somewhat less-easily used in daily practice, these guidelines are extensively referenced and provide a wealth of background information. "Bright Futures" guidelines from the National Center for Education in Maternal and Child Healthcare are complete and easy to follow. Their length, however, makes it challenging for all recommended components to be completed in a timely fashion at each visit. Regardless of the source, guidelines may be modified to fit local practice and to serve best the patients' needs.

Immunizations are a cost-effective and efficacious means to improve the general health and well-being of our children. Vaccination programs have virtually eliminated conditions such as polio and smallpox worldwide. Other conditions, such as *Haemophilus influenzae* type B, measles, tetanus, rubella, and diphtheria, are now so rare that the average medical student or resident is unlikely to see even a single case. New recommendations, such as universal immunization with influenza vaccine of 6- to 23-month-old children rather than just high-risk adults, are being considered. The Recommended Childhood Immunizations Schedule, updated and released annually, is prepared and supported by a variety of organizations including the AAP, the American Academy of Family Practice, and the Centers for Disease Control and Prevention. It is widely available on these organizations' Web sites and in their publications.

Recommendations for Preventive Pediatric Health Care (RE9939)
Committee on Practice and Ambulatory Medicine

Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in satisfactory fashion. Additional visits may become necessary if circumstances suggest variations from normal.

These guidelines represent a consensus by the Committee on Practice and Ambulatory Medicine in consultation with national committees and sections of the American Academy of Pediatrics. The Committee emphasizes the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

[illegible]

- [illegible]

Key: O = to be performed S = to be performed for patients at risk
S = subjective, by history O = objective, by a standard testing method
→→→ = the range during which a service may be provided, with the dot
indicating the preferred age.

American Academy of Pediatrics



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Recommended Childhood and Adolescent Immunization Schedule for the United States, 2003

Vaccine ▼	Age ▶	range of recommended ages					catch-up vaccination					preadolescent assessment		
		Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	24 mos	4-6 yrs	11-12 yrs	13-18 yrs	
Hepatitis B		HepB #1	only if mother HBsAg (+)		HepB #2		HepB #3					HepB series		
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP	DTaP		DTaP		DTaP	Td			
Haemophilus influenzae Type b			Hib	Hib	Hib	Hib								
Inactivated Polio			IPV	IPV	IPV	IPV				IPV				
Measles, Mumps, Rubella							MMR #1			MMR #2	MMR #2			
Varicella							Varicella			Varicella				
Pneumococcal				PCV	PCV	PCV	PCV			PCV	PPV			
Hepatitis A											Hepatitis A series			
Influenza									Influenza (yearly)					

----- Vaccines below this line are for selected populations

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2002, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. [Shaded box] indicates age groups that warrant special effort to administer those vaccines not previously given. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

Figure 9-2. Recommended childhood immunization schedule.

Table 9-1
VACCINE ADVERSE EVENTS, CONTRAINDICATIONS,
AND PRECAUTIONS

AGENT	ADVERSE EVENT	CONTRAINDICATIONS OR PRECAUTIONS
<i>Haemophilus influenzae</i> type B vaccine	<ul style="list-style-type: none"> • Pain, redness, and/or swelling at the injection site in 25% of recipients 	<ul style="list-style-type: none"> • Anaphylactic reaction to vaccine
DPT/DTaP* vaccine	<ul style="list-style-type: none"> • Local and febrile reactions • Redness, edema, induration, and tenderness at the injection site • Drowsiness, fretfulness, anorexia, vomiting, crying • Slight to moderate fever • Bacterial or sterile abscesses at the site of injection (6 to 10 cases per million injections) • Allergic reactions (2 cases per 100,000 injections), transient urticarial rash • Seizures (incidence occurring within 48 h is 1 case per 1750 doses) • Hypotonic-hyporesponsive (also called "collapse" or "shock-like state") episodes (1 case per 1750 doses) • Fever of $\geq 40.5^{\circ}\text{C}$ or 105°F (0.3% of recipients) • Persistent, severe, inconsolable screaming or crying (1 case per 100 doses) 	<p>Contraindications</p> <ul style="list-style-type: none"> • Anaphylactic reaction to vaccine or vaccine constituent • Moderate or severe illness with or without a fever • Encephalopathy within 7 days of administration of previous dose of DTP/DTaP <p>Precautions</p> <ul style="list-style-type: none"> • Fever of $\geq 40.5^{\circ}\text{C}$ (105°F) within 48 h of vaccination with a prior dose of DTP/DTaP • Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 h of receiving a prior dose of DTP/DTaP • Seizures within 3 days of receiving a prior dose of DTP/DTaP (acetaminophen given prior to administering DTaP or DTP and every 4 h thereafter for 24 h should be considered for children with a personal or family history of convulsions in siblings or parents). • Persistent, inconsolable crying lasting >3 h within 48 hours of receiving a prior dose of DTP/DTaP

Table 9-1
VACCINE ADVERSE EVENTS, CONTRAINDICATIONS,
AND PRECAUTIONS (*Continued*)

AGENT	ADVERSE EVENT	CONTRAINDICATIONS OR PRECAUTIONS
		<ul style="list-style-type: none"> Guillain-Barré syndrome within 6 weeks after a dose of DTP/DtaP
Hepatitis B vaccine	<ul style="list-style-type: none"> Pain at injection site and temperature $>37.7^{\circ}\text{C}$ (1% to 6% of recipients) Anaphylaxis reported to be 1 in 600,000 doses 	<ul style="list-style-type: none"> Anaphylactic reaction to vaccine or vaccine constituent Moderate or severe illness with or without a fever Anaphylactic reaction to baker's yeast
Measles vaccine	<ul style="list-style-type: none"> Fever up to 39.4°C (103°F) occurs in 5% to 15% of vaccinees 7 to 12 days after injection, lasting 1 to 2 days Rash in about 5% of vaccinees Transient thrombocytopenia Encephalitis and encephalopathy occurs in less than 1 per million doses, less often with revaccination Allergic reaction: reactions to the measles-mumps-rubella vaccine are rare even in children with documented egg-allergy Clinically apparent thrombocytopenia within 2 months of the vaccine occurs in less than 1 per 25,000 to 40,000 vaccinated children, clustered about 2 to 3 weeks after the vaccine, and is generally transient and benign in nature Subacute sclerosing panencephalitis is possibly a rare complication 	<p>Contraindications</p> <ul style="list-style-type: none"> Anaphylactic reaction to neomycin or gelatin Pregnancy Known altered immunodeficiency (hematologic and solid tumors, severe HIV infection, congenital immunodeficiency, and long-term immunosuppressive therapy) <p>Precautions</p> <ul style="list-style-type: none"> Recent immunoglobulin administration (within 3 to 11 months depending on product) Thrombocytopenia or history of thrombocytopenic purpura

Table 9-1
VACCINE ADVERSE EVENTS, CONTRAINDICATIONS,
AND PRECAUTIONS (Continued)

AGENT	ADVERSE EVENT	CONTRAINDICATIONS OR PRECAUTIONS
Poliovirus vaccine (IPV)	<ul style="list-style-type: none"> • None 	<p>Contraindications</p> <ul style="list-style-type: none"> • Anaphylactic reaction to streptomycin, polymyxin B, and neomycin <p>Precautions</p> <ul style="list-style-type: none"> • Pregnancy
Varicella vaccine	<p>Adverse reactions</p> <ul style="list-style-type: none"> • Rash within 1 month of immunization, a mild maculopapular or varicelliform rash (median of about 2 to 5 lesions) at the injection site or elsewhere develops in about 7% of children and about 8% of susceptible adolescents/adults • Pain, redness, and/or swelling at the injection site in 20% of children and 25% to 35% of adolescents • Transmission of the vaccine virus from healthy vaccinees to other persons is rare (<1%) and appears to occur only if vaccinee develops rash. Transmission of this vaccine virus appears to cause mild or no disease • Zoster-like illness (rash and minimal or absent system symptoms) has been reported in vaccinees (about 18 cases per 100,000 persons years); no cases have been severe 	<p>Contraindications</p> <ul style="list-style-type: none"> • Anaphylactic reaction to neomycin and gelatin • Infection with HIV • Known altered immunodeficiency (hematologic and solid tumors, congenital immunodeficiency, and long-term immunosuppressive therapy) <p>Precautions</p> <ul style="list-style-type: none"> • Recent immunoglobulin administration (within 5 months) • Family history of immunodeficiency

Table 9-1
VACCINE ADVERSE EVENTS, CONTRAINDICATIONS,
AND PRECAUTIONS (Continued)

AGENT	ADVERSE EVENT	CONTRAINDICATIONS OR PRECAUTIONS
Pneumococcal vaccine	<ul style="list-style-type: none"> • Up to about 1 of 4 infants had redness, tenderness, or swelling where the shot was given • About 1 of 3 infants had a fever $>38^{\circ}\text{C}$ ($>100.4^{\circ}\text{F}$), and up to about 1 in 50 had a higher fever ($>39^{\circ}\text{C}$ [$>102.2^{\circ}\text{F}$]) • Some children also became fussy or drowsy, or had a loss of appetite 	<ul style="list-style-type: none"> • Known anaphylactic reaction
Hepatitis A vaccine	<ul style="list-style-type: none"> • Soreness where the shot was given (about 1 of 2 adults, and up to 1 of 5 children) • Headache (about 1 of 6 adults and 1 of 20 children) • Loss of appetite (about 1 of 12 children) • Tiredness (about 1 of 14 adults) • If these problems occur, they usually come 3–5 days after vaccination and last for 1 or 2 days 	<ul style="list-style-type: none"> • Known anaphylactic reaction

*In general, only the acellular (DTaP) pertussis vaccine is available; all of the adverse events listed are far more common with the cellular (DTP) form.

Sources: Adapted from American Academy of Pediatrics. Guide to contraindications and precautions to immunizations, January 2000. In: Pickering LK, ed. 2000 Red book: Report of the Committee on Infectious Diseases, 25th ed. Elk Grove Village, IL: American Academy of Pediatrics. 2000:755–758, and MMWR 45(RR-12); 1–35, 1996.

Pediatric immunizations are extraordinarily safe. The risk of potential side effects is extremely low, especially when compared to the benefit of preventing morbidity and mortality of a communicable disease. Despite this, the safety of vaccines is occasionally scrutinized by the news media and worried parents. The health care provider must have access to updated side effect data to effectively respond to a family member's concerns (Table 9-1).

Many American children are incompletely (or inadequately) immunized for their ages because of a lack of access to immunizations, poor family understanding of the need for immunizations, cost, or fear of side effects. True contraindications to giving immunizations are rare. **Mild upper respiratory infections, gastroenteritis, and low-grade fever are *not* contraindications for receiving vaccinations.**

True contraindications to future administration with a particular vaccine include **immediate hypersensitivity** reactions to the given vaccine, the vaccine component, or the preservative in the agent. **True egg hypersensitivity is a contraindication for influenza and yellow fever vaccination** (both are grown in chick embryo tissue cultures), but not for measles-mumps-rubella (MMR) (which contains only minute amounts of egg products). Patients who have encephalopathy or encephalitis after receiving the diphtheria, tetanus, and pertussis (DTP) or diphtheria, tetanus, and acellular pertussis (DTaP) vaccine should not receive subsequent doses. In general, **pregnant and severely immunocompromised patients should not receive live virus vaccinations**, but administration of live vaccines to a child living in the home with a pregnant woman and giving MMR or varicella to an asymptomatic patient with HIV is permitted; expert consultation in these cases is often warranted.

Comprehension Questions

[9.1] A 6-year-old child arrives as a new patient to your clinic. He is a healthy, well-developed toddler. His immunization card reveals that he received an immunization at birth and some when he was 2-months old, but none since. He obviously requires several immunizations. Which of the following statements is correct?

- A. He should receive the live oral polio virus vaccine rather than the inactivated (injectable) poliovirus vaccine.
- B. The pertussis vaccine is contraindicated at his age and should be replaced with the tetanus-diphtheria vaccine.
- C. He is too old to receive the *Haemophilus influenzae* type B vaccine.

- D. His vaccinations at birth and 2 months of age should be repeated, since too much time has elapsed for them to be effective.
- E. He is too young for the varicella vaccine.

[9.2] Appropriate advice for a mother who has brought her 2-week-old child to you for a routine "well-child" visit includes:

- A. Sleep in the supine position is recommended.
- B. Half-strength fruit juices can be initiated at 2 months of age.
- C. By 1 month of age the child should be sleeping through the night.
- D. Children should be able to roll over by 2 months of age and sit by 4 months of age.
- E. Potty training should begin at 1 year of age.

[9.3] During a "well-child" visit, the parents of an apparently healthy 5-month-old offer a great amount of information. Which of the following bits of information is of most concern?

- A. Intermittent tugging on the ears
- B. A diet that includes baby cereal, 5 different baby vegetables, and 1 baby fruit
- C. Consuming 32 ounces of infant formula per day
- D. Rolling from front to back but not back to front
- E. Limited eye contact with parents

[9.4] Screening tests are included as part of the "well-child" examination. Which of the following statements about screening tests is true?

- A. All children should undergo tuberculosis skin testing at 12 months of age.
- B. Pelvic examinations should be part of the examination of a sexually active adolescent.
- C. Universal cholesterol screening should begin at 11 months of age.

D. Screening hematocrits should be obtained on all infants at 2 months of age.

E. Lead testing is obtained on all 12- and 14-month-old infants.

Answers

[9.1] C. The *Haemophilus influenzae* type B (HIB) vaccine generally is not recommended for children at or older than 5 years of age.

[9.2] A. Juices are avoided until approximately 6 months of age (in a cup and not in the bottle) and diluting is usually not required. Infants do not usually sleep through the night until 2 to 3 months of age. More realistic targets for development include rolling over at 4 months of age and sitting by 6 months of age. Potty training should be initiated when the child shows interest, usually no earlier than 2 years of age. Parents are advised to place healthy children on their backs (or side) for sleep; the incidence of sudden infant death syndrome (SIDS) is reduced in this sleep position.

[9.3] E. Almost from the time of birth, children fix and follow on the human face. A 5-month-old child who does not engage eye contact with his or her parents is clearly abnormal.

[9.4] B. Tuberculosis and lead testing are performed only on children at risk, or as required by law. Pelvic examinations are done when adolescents become sexually active, or by 18 to 21 years of age. Screening hematocrits should commence at 9 to 12 months of age, and cholesterol screening is done for children with familial risk factors.

CASE 10

CLINICAL PEARLS

True contraindications for vaccinations are rare and include immediate hypersensitivity reactions to the given vaccine, the vaccine component, or the preservative in the agent.

Conditions that are *not* contraindications for vaccinations include mild upper respiratory infections, gastroenteritis, and low-grade fever.

In general, pregnant and severely immunocompromised patients should not receive live virus vaccinations, but administration of live vaccines to a child living in the home with a pregnant woman and giving MMR or varicella to an asymptomatic patient with HIV is permitted.

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◆ CASE 10

A 3-year-old child is left under the supervision of his 6-year-old sibling while the parents are outside of the home. About 2 hours later the parents return to find the 3-year-old child alone lying on the floor with several opened bottles of medicines and loose pills surrounding him. They rush him to a nearby hospital but forget to bring any of the medication containers. In the emergency department, he is disoriented, vomiting, has an increased respiratory rate, and is hyperpyrexic. Shortly after arrival he has a generalized tonic-clonic seizure. His laboratory data reveal mild hyperglycemia, metabolic acidosis, and a respiratory alkalosis.

◆ What is the most likely diagnosis?

◆ What is the most appropriate next step?

ANSWERS TO CASE 10: Ingestion

Summary: A 3-year-old child is found among opened bottles of pills with acute, new-onset symptoms of disorientation, vomiting, increased respiratory rate, hyperpyrexia, a nonanion gap acidosis, and seizures.

- ◆ **Most likely diagnosis:** Ingestion. This child has many symptoms of salicylate ingestion.
- ◆ **Next step:** After initiating resuscitation measures (maintain Airway, control Breathing, and ensure adequate Circulation) immediately commence efforts to reduce absorption and effects of the possible offending agent(s).

Analysis

Objectives

1. Understand the signs and symptoms of salicylism.
2. Become familiar with the accepted emergency treatment of unknown ingestions.
3. Become familiar with signs, symptoms, and antidotes of common drugs of ingestion in children.

Considerations

The most important goal in managing this patient is to ensure adequate resuscitation (maintaining the Airway, controlling the Breathing, and ensuring adequate Circulation). The next critical goal is to control the patient's seizures. After the patient is stabilized, the health care provider should immediately order urine or blood for drug screening and initiate decontamination of the gastrointestinal tract. After an offending agent is identified from the urine and blood drug screening or from symptomatology, administration of appropriate antidotes can begin.

APPROACH TO INGESTIONS

Clinical Approach

Approximately 50% of ingestions, defined as accidental or intentional intake of a potentially harmful substance, **occur in children age 5 years or younger, and are usually accidental**. Young children put things into their mouths without consideration for the consequences. Approximately 90% of accidental ingestions occur in the home and usually consist of a single agent. While exposures occur through dermal, ophthalmic, and inhalation routes (6%), the majority of exposures occurs via ingestion (75% of cases).

Children between the ages of 6 and 12 years rarely ingest substances. The incidence of exposure to toxic agents begins to increase at age 13 and is either **intentional (suicide attempt or substance abuse) or occupational**. **Any suicidal ideations in this age range must be taken seriously**, and psychiatric intervention must be arranged immediately.

Efforts to reduce further absorption of a toxic substance depend upon the method of absorption. Patients with inhalation exposures should be moved to fresh air and given oxygen. Patients with transdermal absorptions should have their skin cleaned with soap and water. Decontamination of the stomach for ingested substances is controversial. Some experts feel that induced emesis via syrup of ipecac to physically remove the offending agent is best; other feel that gastric (sometimes whole-bowel) lavage is a better option. Activated charcoal with or without a cathartic (an agent included in the charcoal to increase bowel movements) is often administered to prevent further absorption. Each of these methods has its own risks and benefits; consultation with a local poison control center is recommended.

Attempts to enhance urinary elimination may be useful for certain agents. Techniques include diuresis through alteration of the urine pH, hemodialysis, peritoneal dialysis, and hemoperfusion. **Dialysis and hemoperfusion are effective for a relatively small number of agents, for older children, and the procedure carries an increased risk for smaller children.**

Table 10–1
AGENTS OF INGESTION

AGENT	COMMENT	ANTIDOTE OR SPECIFIC TREATMENT
Acetaminophen	Toxicity results when glutathione stores are depleted and toxic metabolites accumulate. Early-on patients have anorexia, nausea, vomiting, malaise, and diaphoresis. Symptoms resolve over 24 to 48 h, being replaced by right upper quadrant abdominal pain and elevated liver function studies, and oliguria. These symptoms peak at 3 to 4 days of age resulting in either resolution of hepatic damage or progression to complete liver failure. Comparing serum acetaminophen levels to nomogram levels is helpful in dictating treatment and prognosis.	<i>N</i> -acetylcysteine (Mucomyst)
Antidepressants	Tricyclic antidepressants are usually more serious ingestions than selective serotonin reuptake inhibitors (SSRI). SSRI ingestion is usually mild with drowsiness or hyperactivity and agitation, nausea, vomiting, and abdominal pain occurring in a minority of patients. Tricyclic antidepressants can cause central nervous system excitation, extrapyramidal signs, blurred vision, mydriasis, dry mouth, hyperpyrexia, tachycardia and arrhythmias, urinary retention, decreased intestinal peristalsis. Severe findings include seizures, coma, severe arrhythmias, and cardiorespiratory arrest.	
Benzodiazepine	Central nervous system alterations, including sedation, somnolence, diplopia, dysarthria, apnea ataxia, and intellectual impairment, are seen. If ingested with other agents, severe central nervous system depression and coma is more common.	Flumazenil

Table 10-1
AGENTS OF INGESTION (*Continued*)

AGENT	COMMENT	ANTIDOTE OR SPECIFIC TREATMENT
Carbon monoxide	Early symptoms include headache, malaise, and nausea (low exposure) progressing toward severe headaches, dizziness, visual changes, weakness, syncope, coma, seizures, and death (higher exposures). A late sign is cherry-red lips.	Hyperbaric oxygen
Caustics	Upon ingestion acidic agents coagulate proteins (tissue necrosis) while alkaline agents dissolve proteins (liquefaction necrosis). Symptoms include oral lesions, pain, refusal to swallow, drooling, and vomiting. The degree of injury is dependent on the pH extreme and the duration of the exposure.	
Cyanide	Onset is within seconds or minutes of exposure (ingestion or inhalation) resulting in giddiness, severe and pulsating headache, anxiety, palpitations, hyperventilation and shortness of breath, vomiting, coma, seizures, apnea, bradycardia, hypotension, and severe metabolic acidosis.	Sodium nitrite or sodium thiosulfate
Digoxin	Early findings in a patient with an acute ingestion of digoxin include vomiting, bradycardia, and hyperkalemia. Ventricular arrhythmias are less commonly seen in an acute ingestion in a patient not previously exposed to digoxin. When they occur, however, heart block and supraventricular arrhythmias are seen.	Antidigoxin antibody (Digibind)
Ethylene glycol (antifreeze)	Included among the early symptoms are nausea and vomiting, as well as drowsiness and inebriation. Later, metabolic acidosis, arrhythmias, tetany (caused by hypocalcemia) and finally cardiac failure, seizures, renal failure, and cerebral edema can be seen.	Ethanol or fomepizole

Table 10–1
AGENTS OF INGESTION (*Continued*)

AGENT	COMMENT	ANTIDOTE OR SPECIFIC TREATMENT
Hydrocarbons (gasoline, furniture polish)	Toxic effect is most commonly an aspiration pneumonitis occurring at the time of ingestion or during vomiting the agent later; ipecac is contraindicated. Transient, mild central nervous system depression can be seen. Chest radiographs initially can be normal but become abnormal 8–12 h later. Some hydrocarbons have specific toxicities including cancer (benzene), liver failure (carbon tetrachloride), and methemoglobinemia (aniline).	Avoid emesis as this exposes the airway to further aspiration.
Ibuprofen	Nausea, vomiting, abdominal pain, drowsiness, lethargy, ataxia, and acidosis. Supportive care is mainstay of therapy.	
Iron	Abdominal pain, nausea, vomiting and diarrhea (both often becoming bloody). Patients with early hypotension, drowsiness, or severe gastrointestinal symptoms at higher chance of developing severe liver damage, metabolic acidosis, coagulopathies, coma, and death. Four phases are described, but with much overlap between phases. Comparing serum iron levels compared to nomogram levels is helpful in dictating treatment and prognosis.	Deferoxamine
Isoniazid (INH)	Seen as a clinical triad of repetitive seizures not responsive to usual therapies, metabolic acidosis, and coma. Can present with slurred speech, hallucination, respiratory failure, hypotension, fever, rhabdomyolysis, and prior to the onset of seizures the gastrointestinal symptoms of nausea and vomiting.	Pyridoxine
Methanol	Sleepiness with mild inebriation symptoms, and nausea and vomiting develop early. Later, visual disturbances and severe metabolic acidosis are seen.	Ethanol

Table 10-1
AGENTS OF INGESTION (*Continued*)

AGENT	COMMENT	ANTIDOTE OR SPECIFIC TREATMENT
Opiates	Hypothermia, central nervous system depression, hypoventilation, hypotension, miosis.	Naloxone
Organophosphates	Cholinergic symptoms of SLUDGE (Salivation, Lacrimation, Urination, Defecation, Gastrointestinal Effects [nausea and vomiting]). Also can see muscle fasciculations, miosis, weakness, seizures, and bronchospasm. Absorption of agents such as pesticides transdermally can result in symptoms.	Atropine, pralidoxime
Phenothiazine (Phenergan)	Extrapyramidal symptoms including oculogyric crisis, dysphonia, torticollis, rigidity, tremors, and opisthotonus.	Diphenhydramine
Salicylate	See case.	
Warfarin	External or internal bleeding including epistaxis, gingival (or other mucocutaneous) bleeding, petechial rash ecchymoses, hematuria, and melena.	Vitamin K

Clinicians must become familiar with the symptomatology and laboratory findings of commonly ingested agents so that rapid identification and treatment can be initiated (Table 10-1). Consultation with the local poison control center can assist in the identification, dosage, and timing of antidote administration.

The patient in this case has salicylism. While the use of salicylates as an antipyretic in children has declined, use of these agents in the adult population as a preventive measure for myocardial infarction makes them more accessible to an unsupervised toddler. Table 10-2 summarizes the stages of ingestion.

Table 10–2
STAGES OF SALICYLATE INTOXICATION

Phase 1	Lasts about 12 h, results in stimulation of the respiratory center (respiratory alkalosis, alkaluria, and urinary potassium losses), but may be inapparent in toddlers.
Phase 2	Onset often occurring in fewer than 12 h in a young child, is remarkable for continued respiratory alkalosis, aciduria (resulting from exchange of potassium for hydrogen in the urine), and the development of hypokalemia.
Phase 3	May occur rapidly in the young child; is notable for dehydration, hypokalemia, and the development of metabolic acidosis owing to the accumulation of lactic acids. Other findings during this phase include pulmonary edema, hyper- or hypoglycemia, severe electrolyte imbalance, seizures, and cardiovascular collapse.

Treatment of this toddler, in addition to the initial resuscitation efforts of rehydration and gastric decontamination, includes administration of potassium and alkalization of the urine that enhances excretion of the salicylate ion.

Comprehension Questions

- [10.1] A 14-year-old girl, upset after a fight with her family, reports that she took a bottle of acetaminophen 6 hours previously. The most appropriate initial therapy for her includes:
- A. Administration of syrup of ipecac
 - B. Gastric lavage
 - C. Administration of activated charcoal
 - D. Measurement of serum acetaminophen level
 - E. Whole-bowel irrigation
- [10.2] A 2-year-old child is brought into the emergency center with the complaint of coughing, which developed approximately 1 hour prior to admission. The mother reports that the child was found

with a bottle of “Old English Furniture Polish” a few hours earlier in the day. The most likely explanation for this child’s condition is:

- A. Organophosphate poisoning
- B. Hydrocarbon aspiration
- C. Methanol ingestion
- D. Ethylene glycol ingestion
- E. Chlorine inhalation

[10.3] An adolescent arrives to the emergency center with tachycardia, nausea, vomiting, and abdominal pain. His family says that he was found in his room about an hour ago “talking out of his head about bugs crawling on him.” His electrocardiogram (EKG) shows tachycardia and various arrhythmias. The most likely agent causing these symptoms is:

- A. Opiate
- B. Benzodiazepine
- C. Carbamate insecticide
- D. Methanol
- E. Cocaine

[10.4] An 8-year-old was flown into your emergency center from a rural hospital. He had been helping his father on their family farm. The sketchy history obtained was that the child developed nausea and vomiting, had profuse sweating, and began to “foam at the mouth” before he became weak, confused, and had a seizure. Approximately 15 minutes after his arrival to the emergency center a nurse and respiratory therapist who were caring for him begin to complain of nausea and vomiting, blurred vision, and increased lacrimation. The most important next step in this situation is:

- A. Closure and quarantine of the emergency center
- B. Administration of serum immunoglobulin (Ig) G to all staff
- C. Rifampin prophylaxis for the child, his family, and all exposed healthcare workers

- D. Removal of all clothing from the child and the affected staff followed by thorough cleansing of all body surfaces
- E. Hyperbaric oxygen to all symptomatic persons

Answers

- [10.1] **D.** Administration of charcoal or ipecac and gastric or whole-bowel lavage might have been indicated earlier in the postingestion period. However, 6 hours after the ingestion of a relatively rapidly absorbed agent none of these procedures would be expected to be of great benefit. Measurement of the serum acetaminophen level 4 or more hours after ingestion can give an indication as to the probability of liver toxicity and the need for the antidote, *N*-acetylcysteine (Mucomyst).
- [10.2] **B.** The agent in the question is one of many hydrocarbon products used in the home. The onset of the pulmonary symptoms can be delayed for several hours.
- [10.3] **E.** Cocaine intoxication can result in all of the symptoms referenced in this question, including lethal cardiac arrhythmias, even myocardial infarction, and cerebral vascular accidents.
- [10.4] **D.** The child in the question was likely exposed to organophosphate poison on the farm. His clothing was contaminated, and contact with the child without appropriate barriers allowed absorption of organophosphate from the child's clothing through the staff's skin allowing them to develop symptoms. Appropriate therapy for organophosphate exposure is to remove the clothing and cleansing of all skin surfaces.

CLINICAL PEARLS

Children younger than about 5 years of age often accidentally ingest substances. Beginning at about age 13 years the incidence of exposure to toxic agents is either intentional (suicide attempt or substance abuse) or occupational.

See Table 10–1 for a quick reference of common agents of ingestions, symptoms, and treatment options.

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CASE 11

A 3-year-old boy is brought to the emergency center after having had a seizure. The family reports that they moved to Baltimore from the Midwest 3 months ago. The child was the product of a normal pregnancy and delivery, and has had no medical problems until moving to Baltimore. The family reports that he has developed emotional lability, abdominal pain, "achy bones," and intermittent vomiting and constipation. They initially attributed his change in behavior to the move and to the chaos in their house, which is being extensively renovated.

- ◆ **What is the most likely diagnosis?**
- ◆ **What is the best test to diagnose this condition?**
- ◆ **What is the best therapy?**

ANSWERS TO CASE 11: Lead Toxicity

Summary: A 3-year-old, previously healthy child now living in a home undergoing extensive renovations has developed seizures, neurologic changes, and abdominal complaints.

- ◆ **Most likely diagnosis:** Lead toxicity.
- ◆ **Best test:** Serum lead level.
- ◆ **Best therapy:** Remove child from lead source and initiate chelation therapy.

Analysis**Objectives**

1. Understand the signs, symptoms, and treatment of lead poisoning.
2. Be familiar with the environmental sources of lead.
3. Understand the sources of other environmental exposures.

Considerations

This child is demonstrating signs and symptoms of lead poisoning. Confirmation of the diagnosis awaits the measurement of a blood lead level, but therapy should be initiated immediately while awaiting those results. During the evaluation and treatment of this patient, attention should be paid to other children in the home who may also be at risk for lead poisoning.

Note: Sources of lead exposure vary dramatically in various parts of the country. In the northeastern United States, older homes undergoing renovation are common sources of lead exposure. Leaded-paint is far less common in other parts of the country. A thorough history includes a travel history and history of pos-

sible exposures to lead paint through hobbies (such as stained glass), home renovation, and the like.

APPROACH TO LEAD POISONING

Definitions

Chelating agent: A soluble compound that binds a metal ion (in this case lead) so that the new complex is excreted in the urine.

Plumbism: Alternate name for lead poisoning.

Clinical Approach

The incidence of lead poisoning in the United States has decreased dramatically over the last 20 years. **Sources of lead**, such as leaded gasoline, foods, and beverage cans, have been eliminated, leaving **lead-containing paint in older homes as the major source**. Rarer sources include imported foodstuffs from countries where regulations are not as strict as in the United States, **unglazed lead-containing dishes, ingestion of leaded items such as jewelry or fishing equipment**, or exposure **through burning of lead-containing batteries** or through **hobbies where smelting of lead** occurs.

The signs and symptoms of lead poisoning vary from none (especially at lower lead levels) to those listed in this case. However, symptoms may be seen at low blood lead levels and a child with very high blood lead levels occasionally may be asymptomatic. **Anorexia, hyperirritability, altered sleep pattern, and decreased play activity are commonly seen**. **Loss of developmental milestones, especially in speech, is sometimes seen**. Abdominal complaints including occasional vomiting, intermittent pain, and constipation are sometimes noted. Persistent vomiting, ataxia, altered state of consciousness, coma, and seizures are signs of **encephalopathy**. **Permanent, long-term consequences of lead poisoning include learning and cognitive deficits and aggressive behavior**.

The serum lead level is the diagnostic test of choice. Other tests such as free erythrocyte protoporphyrin, qualitative urinary coproporphyrin.

basophilic stippling, glycosuria, hypophosphatemia, "lead lines" in the end of long bone, and radiopaque flecks in the gastrointestinal tract in a patient with signs and symptoms of lead poisoning are less specific than blood lead levels.

Treatment varies depending on the blood lead level and the patient's symptoms. Admission to the hospital, stabilization, and chelation are appropriate for symptomatic patients. Therapy for asymptomatic patients varies depending on the blood lead level and could involve simple investigation of the child's environment, outpatient chelation, or immediate hospitalization (Table 11-1). Close contact with local health agencies is important, as they are usually charged with ensuring that the child's environment is lead-free.

Chelation therapy in an asymptomatic child may consist of intramuscular injections of calcium disodium ethylenediaminetetraacetate (CaEDTA) or more commonly with oral doses of meso-2,3-dimercapto-

Table 11-1
RECOMMENDED FOLLOW-UP SERVICES BY DIAGNOSTIC
BLOOD LEAD LEVELS (BLLs)

BLOOD LEAD LEVEL ($\mu\text{g}/\text{dL}$)	ACTION
<10	<ul style="list-style-type: none"> • No action required
10-14	<ul style="list-style-type: none"> • Obtain a confirmatory venous BLL within 1 month; if still within this range, provide education to decrease blood lead exposure • Repeat BLL test within 3 months
15-19	<ul style="list-style-type: none"> • Obtain a confirmatory venous BLL within 1 month; if still within this range, take a careful environmental history • Provide education to decrease blood lead exposure and to decrease lead absorption • Repeat BLL test within 2 months
20-44	<ul style="list-style-type: none"> • Obtain a confirmatory venous BLL within 1 week; if still within this range, conduct a complete medical history (including an environmental evaluation and nutritional assessment) and physical examination • Provide education to decrease blood lead exposure and to decrease lead absorption

Table 11-1
RECOMMENDED FOLLOW-UP SERVICES BY DIAGNOSTIC
BLOOD LEAD LEVELS (BLLs) (Continued)

BLOOD LEAD LEVEL ($\mu\text{g/dL}$)	ACTION
	<ul style="list-style-type: none"> • Either refer the patient to the local health department or provide case management that should include a detailed environmental investigation with lead hazard reduction and appropriate referrals for support services • If BLL is $>25 \mu\text{g/dL}$, consider chelation (not currently recommended for BLLs $<45 \mu\text{g/dL}$), after consultation with clinicians experienced in lead-toxicity treatment
45-69	<ul style="list-style-type: none"> • Obtain a confirmatory venous BLL within 2 days; if still within this range, conduct a complete medical history (including an environmental evaluation and nutritional assessment) and a physical examination • Provide education to decrease blood lead exposure and to decrease lead absorption • Either refer the patient to the local health department or provide case management that should include a detailed environmental investigation with lead hazard reduction and appropriate referrals for support services • Begin chelation therapy in consultation with clinicians experienced in lead toxicity therapy
≥ 70	<ul style="list-style-type: none"> • Hospitalize the patient and begin medical treatment immediately in consultation with clinicians experienced in lead toxicity therapy • Obtain a confirmatory BLL immediately • The rest of the management should be as noted for management of children with BLLs between 45 and 69 $\mu\text{g/dL}$

Used with permission from the American Academy of Pediatrics, Committee on Environmental Health, screening for elevated blood lead levels. Pediatrics 1998;101:1075.

succinic acid (DMSA, succimer). Hospitalized symptomatic patients are often treated with 2,3-dimercaptopropanol (BAL) and CaEDTA. Close attention is paid to fluid and electrolyte balance; urine output must be maintained because CaEDTA is excreted in the kidneys, but encephalopathy may be exacerbated if the patient is overhydrated.

Because lead poisoning in the United States occurs most often in children who are exposed to lead paint in older homes, targeted blood lead screening of at-risk children rather than universal screening is recommended. Questionnaires used to assess the risk of lead exposure query the age of the home or daycare, the possibility of exposure to high-lead environments (battery recycling plant, lead smelter, etc.), or environments in which others (siblings, playmates, etc.) have been identified with elevated blood lead levels. Some state and federal programs such as Early Periodic Screening, Diagnosis, and Treatment (EPSDT) and Healthy Kids provide specific guidance for lead screening.

Comprehension Questions

- [11.1] Students attending school built in 1951 are at risk for which of the following?
- A. Dichlorodiphenyltrichloroethane (DDT)
 - B. Mercury
 - C. Asbestos
 - D. Polychlorinated biphenyls (PCBs)
 - E. Arsenic
- [11.2] An 8-year-old mentally delayed child ingests the contents of a mercury thermometer. Which of the following symptoms are most likely to be seen?
- A. No symptoms
 - B. Chest pain and dyspnea
 - C. Ataxia, dysarthria, and paresthesias
 - D. Gingivostomatitis, tremor, and neuropsychiatric disturbances
 - E. Pulmonary fibrosis
- [11.3] A 4-year-old child is found with a bottle of insecticide that contains arsenic. Symptoms most likely to occur include:
- A. Constipation
 - B. Bradycardia with third-degree heart block

- C. Hemorrhagic gastroenteritis with third spacing of fluids
 - D. Hyperreflexia
 - E. Hypothermia
- [11.4] Exposure to environmental toxins can occur in a number of ways. Which of the following is the most likely mechanism of exposure?
- A. Transplacental exposure to benzene
 - B. Exposure of a child to beryllium from the child's parents' clothing
 - C. Iron intoxication from vehicular emissions
 - D. Asbestos exposure from hazardous arts and crafts materials
 - E. Lead toxicity from ingesting pieces of a pencil

Answers

- [11.1] C. Between 1947 and 1973 asbestos was commonly sprayed on school ceilings as a fire retardant. Deterioration of this substance results in microscopic fibers being released into the air. Drop ceilings or placement of barriers is usually sufficient protection against this carcinogen.
- [11.2] A. The child in the question is likely to develop no symptoms (the quantity of mercury would be small) but an acute ingestion of elemental mercury might include a variety of gastrointestinal complaints. If the elemental mercury were in vapor form the gastrointestinal complaints would be seen along with fever, chills, headaches, visual changes, cough, chest pain, and possibly pneumonitis and pulmonary edema. Ingestion or exposure to inorganic mercury salts (as found in pesticides, disinfectants, explosives, and dry batteries) would result in gastroesophageal burns, nausea, vomiting, abdominal pain, hematemesis, hematochezia, cardiovascular collapse, or death. Ataxia, dysarthria, and paresthesias are seen in methyl mercury intoxication such as after exposure to contaminated fish. Gingivostomatitis, tremor, and neuropsychiatric disturbances are seen with chronic inorganic mercury intoxication.

- [11.3] **C.** The acute ingestion of arsenic would result in nausea, vomiting, abdominal pain, and diarrhea. The third spacing and hemorrhage in the gut can lead to cardiovascular hypovolemic shock. The cardiac symptoms include ventricular tachycardia (QT prolongation) and congestive heart failure. These patients can develop seizures, cerebral edema, encephalopathy, and coma. Early on, patients develop loss of deep tendon reflexes, paralysis, painful dysesthesias, and respiratory failure similar to Guillain-Barré syndrome. Fever, anemia, alopecia, hepatitis, and renal failure can also be seen.
- [11.4] **B.** Fat-soluble compounds can be transmitted transplacentally (but benzene would be unusual). Parents' work clothes can transmit potentially hazardous compounds to children. It is unlikely that asbestos would be contained in arts and crafts supplies. Vehicular emissions are responsible for any number of pollutants, many of which are carcinogens, but iron intoxication would be unusual. Pencil "lead" is actually graphite (carbon) and not elemental lead.

CLINICAL PEARLS

Lead-containing paint in older homes is the major source of lead exposure in pediatric patients in the United States.

Behavioral signs of lead toxicity include hyperirritability, altered sleep patterns, decreased play activity; loss of developmental milestones, especially in speech and altered state of consciousness. Physical symptoms include vomiting, intermittent abdominal pain, constipation, ataxia, coma, and seizures.

Chelation therapy in an asymptomatic child with elevated lead levels consists of intramuscular injections of CaEDTA or more commonly oral doses of meso-2,3-dimercaptosuccinic acid (DMSA, succimer). Hospitalized patients with symptomatic disease are often treated with 2,3-dimercaptopropanol (BAL) and CaEDTA.

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◆ CASE 12

A mother brings her 8-year-old daughter to your office because she has noticed that the child's panties have a yellowish stain on them. The mother reports the girl has started using many adult sexual words, that her grades at school have dropped over the previous few months, and that the child has become quiet and reluctant to interact with her. The mother tells you that her boyfriend stays with the child while she works during the evenings; he is not present at the clinic visit, but has not mentioned any new problems at home. When interviewed alone and asked about whether she has been touched in any private places on her body when she did not want to be touched, the child begins crying and states that "he touches me." She explains that her mother's boyfriend touches her "private with his private part." She was afraid that her mother would get angry if she told her about it. On physical examination her abdomen is soft and nontender, and her anogenital examination reveals erythema of the fossa navicularis, a hymenal transection at 5 o'clock, and a copious amount of yellowish-white vaginal discharge. A wet-mount microscopic examination is negative for trichomonas, bacterial vaginosis, and yeast. A culture of the vaginal discharge is negative for *Chlamydia trachomatis* but is positive for *Neisseria gonorrhoeae*.

◆ **What is the best management for this condition?**

◆ **What is your next step in the evaluation?**

ANSWERS TO CASE 12: Sexual Abuse

Summary: An 8-year-old female has a positive vaginal culture for *Neisseria gonorrhoeae*. Her anogenital examination reveals erythema of the fossa navicularis and a hymenal transection at 5 o'clock. She disclosed that her mother's boyfriend has sexually abused her.

- ◆ **Best management:** Treatment for her infection with a single dose of ceftriaxone 125 mg intramuscularly.
- ◆ **Next step:** A blood test for human immunodeficiency virus (HIV) antibody, hepatitis B antibody, and rapid plasma reagin (RPR) for syphilis should be done. Children's Protective Services and/or law enforcement must be notified of this child's abuse. Each state has its child abuse reporting requirements.

Analysis

Objectives

1. Know the most common physical and behavioral signs and symptoms of sexual abuse in children.
2. Know the sexual abuse "look-alikes"-nonsexual explanations for genital-anal symptoms.
3. Know the physical findings that are clear evidence of sexual abuse.

Considerations

This prepubertal child has a positive vaginal gonococcal culture, which is diagnostic of sexual abuse, as a girl cannot contract gonorrhea without genital-genital contact. She has a hymenal transection, which is clear evidence of penetrating vaginal trauma. Blood work for human immunodeficiency virus should be obtained 3 months and 6 months after genital contact. The most important issue at this point is to avoid sending the child back into the same at-risk situation. Chil-

dren's Protective Services and law enforcement officials generally work in tandem to ensure safety of the child and to perform criminal investigations of child sexual abuse cases. This child should be referred to child sexual abuse specialists so that a full evaluation and colposcopic photos of her anogenital injuries may be taken.

APPROACH TO SEXUAL ABUSE IN THE CHILD

Definitions

Hymenal transection: A tear in the hymen, which is evidence of penetrating vaginal trauma.

Sexual abuse: Sexual activity a child engages in that the child cannot comprehend, cannot give consent to, is not developmentally prepared for, or that violates the law or societal taboos. Coercion, power imbalance, or a significant age gap may also be present.

Clinical Approach

One in four women and one in six men in the United States are victims of sexual abuse by the age of 18 years. Abuse can be noncontact forms, such as exhibitionism, voyeurism, and pornographic photographing, as well as contact forms such as fondling and anogenital contact. **Most victims of sexual abuse know their abusers; they may be family members, friends, or acquaintances.**

Physical complaints associated with sexual abuse include **dysuria, enuresis, frequent urinary tract infections, genital irritation and itching, vaginal or penile discharge, vaginal bleeding, genital or anal pain, abdominal pain, and encopresis.** Behavioral findings include nightmares, sleep disorders, sexual behaviors inappropriate for developmental level, regressive behaviors, eating disorders, acting out aggressively, poor school performance, and poor peer relationships.

Nonsexual explanations for genital-anal symptoms include psoriasis of the vulva, vulvar lichen sclerosus, pinworms, scabies, pubic lice, perianal streptococcal dermatitis, and candidiasis. **Anogenital bruising can be seen with straddle injuries (falls onto bicycle bars, toys,**

trampolines), but while they may cause impressive external anogenital trauma, they rarely cause damage to the hymen and internal structures. Rectal bleeding can be caused by constipation, and a vaginal discharge can be caused by a foreign body, such as toilet paper.

Supportive and sensitive history taking, detailed documentation of the child's disclosure, and careful physical examination are imperative when evaluating a child who has been sexually abused. **The child's disclosure should be written verbatim rather than paraphrased.** A thorough physical examination is then conducted, with special attention to the neck, mouth, and anogenital area. The examination is most effectively performed in the **frog-leg position** (full abduction with feet in apposition) for young girls and lithotomy (flat on her back with legs spread apart in stirrups) position for older girls. Any abnormality noted in the frog-leg position in the prepubertal girl is verified in the knee-chest position, as the change in gravitational pull can clarify the appearance of the hymenal edge. Bite marks or ecchymotic sucking injuries should be measured and photographed, and wiping for saliva is done to aid in DNA identification of the perpetrator. The external genitalia and anus are then examined for signs of trauma. The labia are separated and gentle traction (pulling forward) used with gloved fingers; a **speculum examination is generally avoided in prepubertal girls.**

Acute injuries to the hymen occur primarily between the 3 o'clock and the 9 o'clock positions. Ecchymoses, bleeding, and discharge should be noted. **Children who have been abused in the past often have no physical findings since adequate time for healing has lapsed.** A detailed anogenital examination is described or sketched if a colposcope (an instrument with a strong light and magnifier) is unavailable.

If the suspected child abuse occurred less than 72 hours prior to evaluation, forensic evidence should be collected in an evidence collection kit. Healthcare providers must be trained to appropriately collect forensic evidence. Laboratory studies are performed depending on the history of the assault. If a history of genital-genital, genital-anal, or genital-oral contact is found, gonorrhea and *Chlamydia* cultures are obtained, and blood tests for HIV antibody, syphilis, and hepatitis B serology are performed.

All victims of sexual abuse require psychological support. The consequences and appropriate therapy of sexual abuse vary, depending on the type of abuse, the age and other physical and emotional factors in the victim, the frequency of abuse, and identity of the abuser.

Healthcare professionals who examine sexually abused children are often called to testify in court. Referral to child sexual abuse specialists ensures that a complete examination is performed, appropriate laboratory studies are done, proper forensic evidence is collected, and effective testimony is delivered.

Comprehension Questions

- [12.1] A developmentally delayed 18-year-old female tells her mother that someone at her daycare has been “messing with her.” The mother brings her to your clinic to be evaluated for sexual abuse. Which of the following statements about this child’s possible sexual abuse is more likely to be true?
- A. This developmentally delayed girl is at a lower risk for abuse than her nondelayed counterparts.
 - B. This girl was most likely sexually abused by a stranger.
 - C. If this child is a victim of chronic sexual abuse, she is unlikely to have physical evidence of abuse.
 - D. Most children, like this girl, immediately disclose their sexual abuse.
 - E. If this nonsexually active adolescent develops a culture positive for chlamydia, herpes, or gonorrhea, a nonsexually transmitted infection source must be sought out.
- [12.2] An 18-month-old male child is brought to clinic by his father because the child has “skin tags” growing around his anus. He has had the tags for several months and they are growing. The child lives with his mother and father, and the father reports no history of potential sexual abuse. The mother has a 15-year history of venereal warts. Examination reveals cauliflower-like warts in the perianal area. What is the most likely cause of this finding?

- A. Condyloma acuminata (human papillomavirus [HPV]) acquired at sexual abuse
- B. Herpes type II
- C. Molluscum contagiosum
- D. Condyloma acuminata (HPV) acquired from birth
- E. Herpes type I

[12.3] A 7-year-old girl complains of itching for 1 week in her “front and back private parts.” She has no history of skin disorders. She has not changed her soap, clothing detergents, or clothing. She states that no one has touched her in her private places inappropriately. Examination reveals an intensely erythematous perianal area without skin breakdown, depigmentation, or scaling. The remainder of the physical examination is normal. What is the most likely cause of her problem?

- A. Pinworms
- B. Gonorrhea
- C. Eczema
- D. Psoriasis
- E. Lichen sclerosus

[12.4] A 9-year-old boy comes to clinic with rectal bleeding. He states that he has had bright red bleeding off and on for a few months. He has a history of constipation and intermittent encopresis. He denies any inappropriate touching in the area. Upon examination, the child’s anus has lost its stellate pattern and its tone. He has three deep fissures in the anus and a scar at 8 o’clock. What is a likely cause of the boy’s findings?

- A. Penetrating anal trauma
- B. Constipation
- C. Eczema
- D. Hirschsprung disease
- E. Hemorrhoids

Answers

- [12.1] **C.** The majority of children who have been abused over a period of time do not report the abuse and show no physical evidence of penetrating vaginal trauma. This could be due to the child's ability to heal tissues in this area or to the perpetrator's lack of total penetration of the female sexual organ or anus. The perpetrator in most cases of sexual abuse are known to the victim. Finding, in a nonsexually active patient, a sexually transmitted disease, such as *Chlamydia*, gonorrhea, and herpes, is diagnostic of sexual abuse.
- [12.2] **D.** Anal condylomata in children younger than age 3 years are often acquired at birth through direct contact with genital condylomata involving the birth canal. A full history is important to determine the risk of abuse versus the risk of acquiring the infection at birth.
- [12.3] **A.** Pinworms cause intense itching and erythema. Placing tape over the anus often identifies the eggs of the worm (and, less likely, a tiny, thread-like worm). Treatment consists of a single dose of mebendazole (100 mg) which is repeated in 2 weeks; family members are also treated. Eczema would involve more than just the perianal region.
- [12.4] **A.** Repeated penetrating anal trauma causes loss of stellate pattern of the anus, loss of tone, and deep fissures. Constipation would be less likely to cause such dramatic findings. Sexual abuse must be suspected and further history is indicated.

CLINICAL PEARLS

- ◆ One in four women and one in six men in the United States are victims of sexual abuse by the age of 18 years.
- ◆ Most victims of sexual abuse know their abusers; they may be family members, friends, or acquaintances.
- ◆ Physical complaints associated with sexual abuse include dysuria, enuresis, frequent urinary tract infections, genital irritation and itching, vaginal or penile discharge, vaginal bleeding, genital or anal pain, abdominal pain, and encopresis.
- ◆ Behavioral indicators of sexual abuse include nightmares, sleep disorders, sexual behaviors inappropriate for developmental level, regressive behaviors, eating disorders, acting out aggressively, poor school performance, and poor peer relationships.

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◆ CASE 13

A 4-year-old child complains of ear pain. He has a temperature of 102.1°F (38.9°C), has had a cold for several days, but has been eating well and his activity has been essentially normal.

◆ What is the most likely diagnosis?

◆ What is the best therapy?

ANSWERS TO CASE 13: Acute Otitis Media

Summary: A toddler presents with ear pain and fever.

◆ **Most likely diagnosis:** Acute otitis media

◆ **Best therapy:** Oral antibiotics

Analysis**Objectives**

1. Be familiar with the epidemiology of otitis media in children.
2. Understand the treatment option for this condition.
3. Learn the consequences of severe infection.

Considerations

Otitis media is high on the diagnostic differential for this child who has an upper respiratory infection and ear pain. Confirmation of the diagnosis can be made with pneumatic otoscopy, and then treatment can commence. A “telephone diagnosis” should be avoided. Figure 13–1 illustrates the anatomy of the middle ear.

APPROACH TO ACUTE OTITIS MEDIA**Definitions**

Acute otitis media: A condition of otalgia (ear pain), fever, and other systemic symptoms associated with the findings of a red, opaque, bulging tympanic membrane that moves poorly.

Myringotomy and placement of pressure equalization (PE) tubes: A surgical procedure involving incision of the tympanic membrane and placement of “pressure equalization” tubes, which

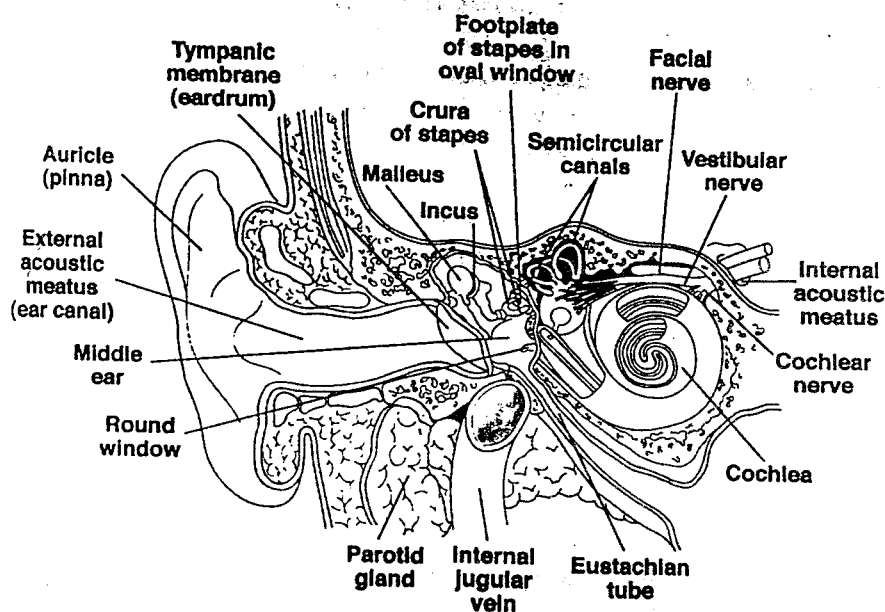


Figure 13-1. Anatomy of the middle ear. From Rudolph's Pediatrics, 21st ed. (with permission).

consist of tiny plastic or metal tubes anchored into the tympanic membrane, to ventilate the middle ear and help prevent reaccumulation of fluid in the middle ear.

Otitis media with effusion: A condition in which the ear demonstrates fluid collection behind the tympanic membrane but without signs and symptoms of acute otitis media. Sometimes also called serous otitis media.

Pneumatic otoscopy: The process of obtaining a tight seal in the ear canal with an ear speculum and then applying very slight positive and negative pressure with a rubber bulb to determine the mobility of the tympanic membrane.

Tympanocentesis: A minor surgical procedure in which a small incision is made into the eardrum to allow pus and fluid to drain from the middle ear space.

Clinical Approach

Otitis media is an extremely common diagnosis in the pediatric population. The **bacterial pathogens** most commonly responsible for this condition include *Streptococcus pneumoniae*, **nontypeable *Haemophilus influenzae***, and *Moraxella catarrhalis*. A variety of other organisms including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* can be seen in neonates and patients with immune deficiencies. Viruses can cause acute otitis media, and in many cases, the etiology of otitis media is unknown. Acute otitis media is diagnosed by identifying a child with fever (usually less than 104°F [40°C]), ear pain (often nocturnal awakening child from sleep), and generalized malaise. Systemic symptoms can include anorexia, nausea, vomiting, diarrhea, and headache. Findings on physical examination include a **red, bulging tympanic membrane that does not move well with pneumatic otoscopy**. The tympanic membrane may be opaque with pus behind it, the middle ear landmarks may be obscured, and if the tympanic membrane has spontaneously ruptured, pus may be found in the ear canal (see Figure 13–2 for normal landmarks).

Because of the development of resistant bacterial organisms over the past decade, the treatment of otitis media has become challenging. Currently (and depending on resistance patterns in a particular community), amoxicillin in either the traditional 40 to 50 mg/kg/d or at higher doses up to 80 to 90 mg/kg/d for 7 to 10 days are customary initial treatments. If clinical failure is noted after 3 days of treatment, many clinicians change to amoxicillin-clavulanate, cefuroxime axetil, azithromycin, cefixime, ceftriaxone, or consider tympanocentesis. A variety of other agents previously used in the treatment of otitis media, such as trimethoprim-sulfamethoxazole, erythromycin-sulfisoxazole, and penicillin, are usually ineffective. Adjuvant therapies, such as analgesics or antipyretics, are often used, but other measures, such as antihistamines, decongestants, and corticosteroids, are ineffective.

After an episode of acute otitis media, middle-ear fluid often persists for a prolonged period lasting up to several months. If hearing remains normal, middle-ear effusion is often treated with observation alone, although some practitioners treat with another course of an-

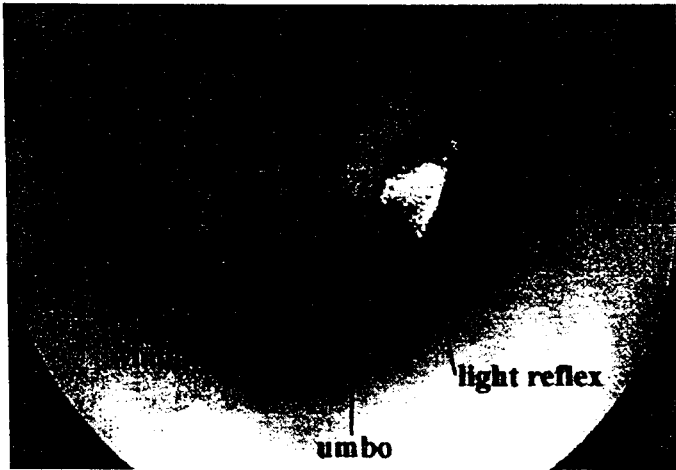


Figure 13–2. The tympanic membrane. From Rudolph's Pediatrics, 21st ed. (with permission).

tibiotics. When the fluid does not resolve or recurrent episodes of suppurative otitis media occur, especially if hearing loss is noted, myringotomy with PE tubes is often used.

Rare but serious complications of otitis media include mastoiditis, osteomyelitis of the temporal bone, and facial nerve paralysis. Epidural and subdural abscess formation, meningitis, lateral sinus thrombosis, and otitic hydrocephalus (evidence of increased intracranial pressure with otitis media) are occasionally seen. A patient diagnosed with acute otitis media whose clinical course is unusual or prolonged should be evaluated for one of these conditions.

Comprehension Questions

- [13.1] An 8-year-old boy complains of severe pain with the movement of his ear. He has no fever, nausea, vomiting, or other systemic symptoms. He has been in good health, having just returned from summer camp where he swam, rode horses, and water-skied. Examination of his ear reveals a somewhat red pinna that

is extremely tender with movement, a very red and swollen ear canal, but an essentially normal tympanic membrane. The most appropriate next course of therapy is:

- A. High dose oral amoxicillin
- B. Intramuscular ceftriaxone
- C. Tympanocentesis and culture
- D. Administration of topical mixture of polymyxin and corticosteroids
- E. Intravenous vancomycin

[13.2] Three days after beginning oral amoxicillin for otitis media, a 4-year-old boy is noted to have continued fever, ear pain, and swelling with redness behind his ear. His ear lobe is pushed superiorly and laterally. He seems to be doing well otherwise. The most appropriate course of action includes:

- A. Myringotomy and parenteral antibiotics
- B. Tympanocentesis
- C. Change to oral amoxicillin-clavulanate
- D. Topical steroids
- E. Nuclear scan of the head

[13.3] A 5-year-old girl developed high fever, ear pain, and vomiting 1 week ago. She was seen in the emergency center, diagnosed with otitis media, and started on amoxicillin-clavulanate. Her symptoms continued, and on the third day of this medication she was seen with persistent findings of otitis media, fever, and pain. She was given a dose of ceftriaxone intramuscularly and switched to oral cefuroxime. After an additional 48 hours she continued to have fever, pain, and no improvement in her otitis media, but otherwise was doing well. The next logical step in her management is:

- A. Tympanocentesis and culture of middle ear fluid
- B. High-dose oral amoxicillin
- C. Oral trimethoprim-sulfamethoxazole
- D. Addition of intranasal topical steroids to the oral cefuroxime
- E. Adenoidectomy

- [13.4] A 1-month-old boy has a fever to 102.7°F (39.3°C), is irritable, has diarrhea, and has not been eating well. On physical examination he has a red tympanic membrane that does not move and has pus behind it. The appropriate course of action is:
- A. Oral high-dose amoxicillin
 - B. Oral amoxicillin-clavulanate
 - C. Oral cefuroxime
 - D. Intramuscular ceftriaxone and close outpatient follow-up
 - E. Admission to the hospital with complete sepsis evaluation

Answers

- [13.1] D. The patient in the question likely has an otitis externa that was caused by his swimming (also known as swimmer's ear). Treatment is the application of a topical agent as described. Insertion of a wick may assist in the absorption of the excess fluid in the macerated ear canal.
- [13.2] A. The child has mastoiditis. The diagnosis can be made clinically, but CT scan is sometimes needed if the case is not so obvious. Appropriate treatment includes myringotomy and culture of the fluid with initiation of parenteral antibiotics. If rapid improvement does not occur in the next 24 to 48 hours, surgical drainage of the mastoid air cells may become necessary.
- [13.3] A. After failing several antibiotic regimens, tympanocentesis and culture of the middle ear fluid are indicated.
- [13.4] E. Children with otitis media at very young age, especially with irritability or lethargy, are at a higher chance of bacteremia or other serious infection. Hospitalization and parenteral antibiotics are likely indicated in this child.

CLINICAL PEARLS

The most common bacterial pathogens responsible for otitis media are *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Findings of otitis media on physical examination include a red, bulging tympanic membrane that does not move well with pneumatic otoscopy; an opaque tympanic membrane with pus behind it, obscured middle-ear landmarks; and if the tympanic membrane has spontaneously ruptured pus may be found in the ear canal.

Initial treatment for otitis media often includes amoxicillin (depending on local rate of resistant *S. pneumonia*). Should clinical failure be seen on day 3, a change to amoxicillin-clavulanate, cefuroxime axetil, ceftriaxone, or a tympanocentesis is indicated.

Complications are rare but include mastoiditis, osteomyelitis of the temporal bone, facial nerve paralysis, epidural and subdural abscess formation, meningitis, lateral sinus thrombosis, and otitic hydrocephalus.

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◆ CASE 14

You are called STAT to the delivery room. The obstetrician who is resuscitating the infant informs you that the child was born by a spontaneous vaginal delivery to a 24-year-old gravida 1 woman. Her pregnancy was uncomplicated. Fetal heart tones were stable throughout the labor. Spinal anesthesia was partially effective and was supplemented with intravenous meperidine (Demerol) and promethazine (Phenergan). The amniotic fluid was not bile-stained and the mother had no evidence of intraamniotic infection. The infant was floppy and blue when born, and has not responded well to stimulation and blow-by oxygen. The child is now approximately 2 minutes old.

► What is the next step?

ANSWER TO CASE 14: Neonatal Resuscitation

Summary: A newborn infant who was born floppy, blue, and poorly responsive to initial resuscitation efforts.

- ◆ **Next step:** Evaluate for heart rate and respirations. If no respirations are found or if the heart rate is less than 100 beats per minute (bpm), initiate positive pressure ventilation (by bag and mask). Because this mother was given meperidine during the labor process, administration of naloxone (Narcan) is an important step in resuscitation.

Analysis**Objectives**

1. Understand the steps of delivery room resuscitation of a newborn.
2. Become familiar with the use of the Apgar score.
3. Become familiar with other conditions that may result in difficult transitioning from the intrauterine to extrauterine life.

Considerations

This depressed infant was born to a healthy mother without prenatal or delivery complications other than failed epidural anesthesia. Positive pressure ventilation was initiated and naloxone was administered. The key to understanding what is likely occurring with this infant is appreciating the timing of the administration of maternal meperidine and the continued effects it has on the infant.

APPROACH TO NEONATAL RESUSCITATION**Definitions**

Narcosis: The condition of deep stupor or unconsciousness produced by a chemical substance such as a drug or anesthesia.

Perinatal hypoxia: Inadequate oxygenation of a neonate that, if severe, can lead to brainstem depression and secondary apnea unresponsive to stimulation.

Positive pressure ventilation: The process of mechanically breathing for a child with a bag and mask.

Clinical Approach

Resuscitation of a neonate in the delivery room follows the "ABC" rules of resuscitation used for patients of all ages: establish and maintain the **Airway**; control the **Breathing** of the patients; and maintain the **Circulation** with medications and chest compressions (if necessary). In this case, meperidine (Demerol) was given during the labor and is probably responsible for the infant's apnea and poor respiratory effort. Children who have narcosis usually have a good heart rate response but poor respiratory effort in response to bag and mask ventilation. **The therapy for narcotic-related depression is the intravenous (IV), intramuscular (IM), subcutaneous (SQ), or endotracheal administration of naloxone (Narcan).** Infants who require administration of naloxone are at risk for recurrent respiratory compromise and further doses of this medication may be required.

Table 14-1
APGAR EVALUATION OF A NEWBORN

SIGN	0	1	2
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Flexed, active motion
Reflex irritability (response to catheter in nose)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, acrocyanosis (extremities blue)	Completely pink

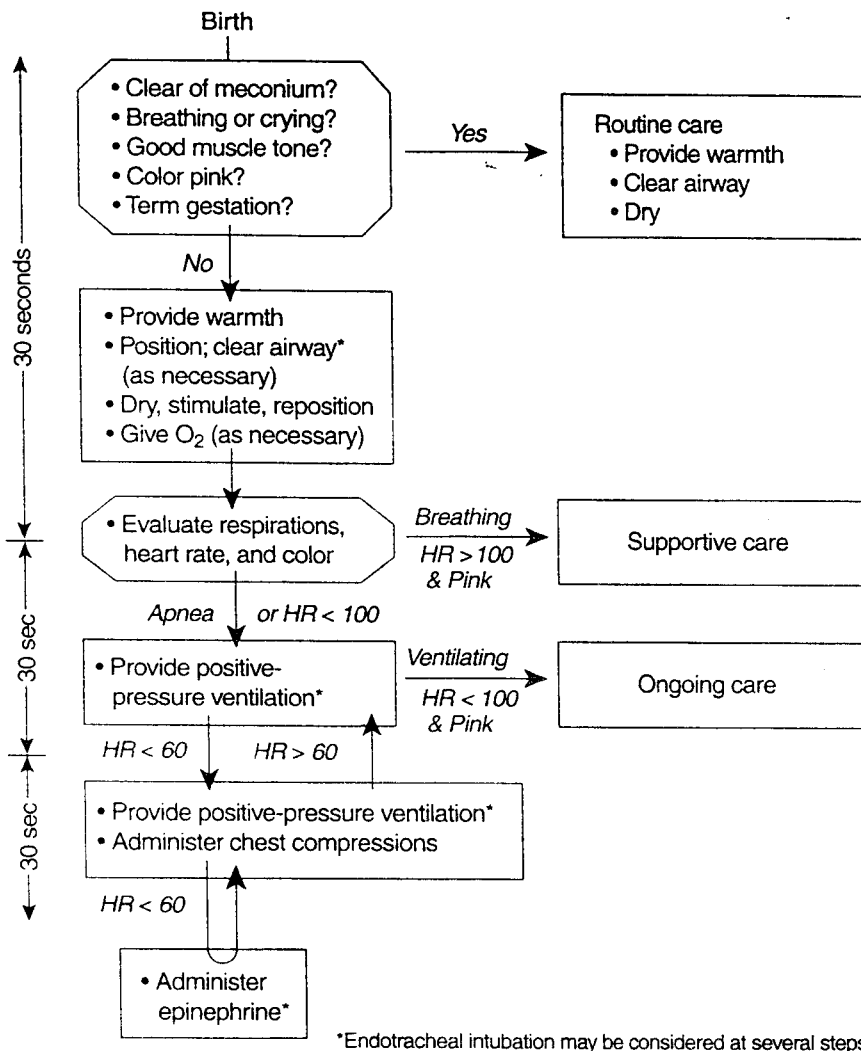


Figure 14–1. Algorithm for neonatal resuscitation. Used with permission from The American Academy of Pediatrics, International Guidelines for Neonatal Resuscitation: an excerpt from the guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 2000;106:7.

The Apgar score (Table 14–1) is widely used to evaluate a neonate's transition from the intrauterine to extrauterine environment. Scores of 0, 1, or 2 are given at 1 and 5 minutes of life for the listed signs. The 1-minute score helps to determine the well-being of the infant, and scores of less than 3 have historically been used to indicate that the infant required immediate resuscitation. In current practice the infant's heart rate, color, and respiratory rate rather than the 1-minute Apgar score (Figure 14–1) are used to determine the need for resuscitation. The 5-minute score is one indicator of how successful the resuscitation efforts were. Some continue to measure Apgar scores beyond the 5-minute period to determine the continued effects of resuscitation efforts. The Apgar score alone cannot determine neonatal morbidity or mortality.

Comprehension Questions

- [14.1] A large infant is born via STAT cesarean section to a 34-year-old mother whose pregnancy was complicated by hypertension and abnormal fetal heart monitoring. At the time of delivery the infant is covered in thick, green meconium and is limp, apneic, and bradycardic. The first step in resuscitation of this infant is to:
- A. Initiate bag and mask intubation.
 - B. Administer intravenous naloxone.
 - C. Administer bicarbonate intravenously.
 - D. Intubate with an endotracheal tube and suction meconium from the trachea.
 - E. Initiate chest compressions immediately.
- [14.2] A term infant is delivered vaginally to a 22-year-old gravida 2, para 1 mother. Immediately after birth the child is noted to have a scaphoid abdomen, cyanosis, and respiratory distress. Heart sounds are heard on the right side of the chest, and the breath sounds seem to be diminished on the left side. The next step in resuscitation in this child is to:
- A. Initiate bag and mask intubation.
 - B. Administer intravenous naloxone.

- C. Administer bicarbonate intravenously.
 - D. Intubate with an endotracheal tube.
 - E. Initiate chest compressions immediately.
- [14.3] A 37-week gestation infant is born to a 33-year-old gravida 3 mother. The pregnancy was uncomplicated, but the infant was noted at birth to be lethargic and with a slow heart rate. Oxygen was administered via bag and mask and the child was intubated, but the infant's heart rate remained at 40 bpm. The most appropriate next step is to:
- A. Begin chest compressions.
 - B. Administer intravenous bicarbonate.
 - C. Administer intravenous atropine.
 - D. Administer intravenous epinephrine.
 - E. Administer intravenous calcium chloride.
- [14.4] A term infant is born by vaginal delivery after an uncomplicated pregnancy. The child appears to be normal but develops respiratory distress each time he stops crying. When crying, he is pink. When he is not crying, he makes vigorous respiratory efforts but becomes dusky. The likely explanation for this child's symptoms is:
- A. Choanal atresia
 - B. Diaphragmatic hernia
 - C. Neonatal narcosis
 - D. Meconium aspiration
 - E. Pneumothorax

Answers

- [14.1] **D.** An attempt should be made to remove the meconium from the oropharynx and the airway prior to initiation of respirations. Ideally, the obstetrician will begin suctioning of the meconium as soon as the head is delivered and the pediatrician will further remove meconium with a meconium aspirator or through endotracheal intubation with suction. Ventilation is initiated after meconium is removed. The goal of the described therapy is to

remove meconium from the airway and to prevent its being aspirated into the small airways where ventilation-perfusion mismatch may occur with deleterious effects.

- [14.2] D. The case describes a child with diaphragmatic hernia. As a result of herniated bowel contents into the chest, children with this condition often have pulmonary hypoplasia. Bag and mask ventilation will cause accumulation of gas into the bowel (which is located in the chest) and further respiratory compromise. Therefore, endotracheal intubation is the best course of action.
- [14.3] A. If the heart rate is still below 60 bpm despite positive pressure ventilation with 100% oxygen, then chest compressions are used for 30 seconds. If the heart rate is still below 60 bpm, then drug therapy (usually epinephrine) is indicated.
- [14.4] A. Infants are obligate nose breathers. When crying they can breathe through their mouth, but when quiet they must have a patent nose. Choanal atresia is demonstrated by attempting to pass a feeding catheter through each nostril. Should choanal atresia be diagnosed by failure to pass the feeding tube, endotracheal intubation bypasses the airway obstruction until surgical repair can be completed.

CLINICAL PEARLS

- ◆ An infant with slow heart rate, poor color, and inadequate respiratory effort requires immediate resuscitation.
- ◆ The therapy for narcosis (respiratory depression in a newborn caused by maternal pain medications) is the IV, IM, SQ, or endotracheal administration of naloxone (Narcan).
- ◆ A child with diaphragmatic hernia often presents with immediate respiratory distress, scaphoid abdomen, cyanosis, and heart sounds displaced to the right side of the chest.
- ◆ Choanal atresia results in respiratory distress each time a child stops crying; immediate treatment is intubation until surgical correction can be completed.

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◆ CASE 15

A 6-month-old boy whom you have been following for routine visits since birth comes to you for a well-child visit. The mother's major concern is that the baby is "floppy" when placed in a sitting position, and that he does not seem to be interested in reaching for toys. You noted at his 4-month well-child visit that his head support appeared weak and that he had a persistent stepping reflex. The mother's pregnancy and vaginal delivery were uneventful, and the child did not appear to have any abnormalities at the 2-week or 2-month check-ups.

- ◆ What is the initial step in the evaluation of this child?
- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the evaluation?

ANSWERS TO CASE 15: Cerebral Palsy

Summary: A 6-month-old boy with reported postural hypotonia and who does not reach for toys.

- ◆ **Initial step:** Gather a more detailed history, focusing particularly on developmental questions, social and family histories, and perform a detailed neurologic examination to further delineate the child's deficits.
- ◆ **Most likely diagnosis:** Cerebral palsy.
- ◆ **Next step:** Consider further evaluation, including sensory testing (vision, hearing), and a brain magnetic resonance scan (MRI), and arrange for immediate initiation of therapy with a developmental specialist.

Analysis

Objectives

1. Know the definition of cerebral palsy.
2. Recognize the classifications of cerebral palsy.
3. Know the basic therapeutic approach to cerebral palsy.

Considerations

This baby's postural hypotonia and failure to reach for toys by 6 months of age are clearly abnormal, and highly suggestive of cerebral palsy. He has gross motor and possibly fine motor delay, cognitive and sensory deficits. Determining the full extent of his deficits is crucial for developing therapies that will help him achieve maximal functional outcome. Although often of low yield, an attempt should be made to identify the etiology of the child's cerebral palsy. Knowing the etiology can aid in developing a treatment plan for this child, family plan-

ning (especially if the cause is inherited), and assuaging parental guilt for this child's condition.

APPROACH TO CEREBRAL PALSY

Definitions

Cerebral palsy: A disorder of movement and posture that results from an insult to or anomaly of the immature central nervous system. This definition recognizes the central origin of the dysfunction, thus distinguishing it from neuropathies and myopathies.

Developmental delay: Failure of a child to reach milestones of development at normally anticipated ages. Development is categorized as gross motor, fine motor, language and social-adaptive skills.

Neurologic deficit: Abnormal functioning or lack of function of a part of the nervous system.

Clinical Approach

With an estimated prevalence of 1 to 2 cases per 1000 live births, **cerebral palsy is the most common movement disorder of childhood.** The true prevalence is likely higher if one considers the number of children who have cerebral palsy, but are labeled by their comorbid diagnoses of seizure disorders, mental retardation, or developmental delay. **One-third of patients with cerebral palsy also experience seizures, and approximately 60% are mentally retarded.** Deafness, visual impairments, swallowing difficulty with concomitant aspiration, limb sensory impairments, and behavioral disturbances are not uncommon comorbidities. The effect of aggressive neonatal medical intervention on the prevalence of cerebral palsy is unclear; overall improved outcomes of premature infants may mitigate the impact of increased survival of very low birth weight infants.

Cerebral palsy has been associated with events during pregnancy, and less commonly from effects of the labor or delivery. It may be a result of prematurity, and be associated with intrauterine

growth retardation. However, most children with the disorder have no identifiable risk factors. **Current research indicates that cerebral palsy is most likely the result of antenatal insults.** Difficulties during the pregnancy, delivery, and the perinatal period are thought to reflect these insults, and are probably not themselves the primary cause of cerebral palsy.

Cerebral palsy is often referred as “static” encephalopathy, as it is the result of a one-time insult to the central nervous system. This is in contrast to progressive encephalopathies, which continue to destroy brain function with time. The term “static” is misleading, however, as the manifestations of cerebral palsy change with age. Contractures and postural deformities may become more severe with time, or they may improve with therapy. Also, a child’s changing developmental stages early in life can alter the expression of his or her neurologic deficits.

The immaturity of the central nervous system at birth makes it impossible to diagnose cerebral palsy in a neonate. Normal newborn infants have a number of primitive reflexes, variable muscular tone, and hyperresponsive reflexes. If a central nervous system insult is suspected, head imaging (most simply by ultrasound if the fontanelle is still open) can be helpful in recognizing cerebral palsy early in life. Periventricular cysts are specific for cerebral palsy, but are uncommon. Beyond the newborn period, the diagnosis is suspected whenever a child fails to meet developmental milestones at the anticipated age.

Practically speaking, the diagnosis of cerebral palsy often is not made until after one year of life, when developmental deficits are more obvious than in a younger child. **Asymmetry or lack of spontaneous movement in a young infant is often the earliest indicator of a central nervous system problem.** After a period of quiet observation, the **clinician should try to elicit a number of primitive reflexes** that can help pinpoint the child’s developmental stage. Examples of concerning findings are:

- a stepping response after the age of 3 months
- a Moro reflex beyond 6 months
- an asymmetric tonic neck reflex beyond 6 months.

The diagnosis of cerebral palsy should be considered when there is a significant discrepancy between the child’s motor developmental age and his or her chronologic age.

Cerebral palsy may be classified in terms of physiologic or topographic categories. Physiologic descriptors identify the major motor abnormality, and are divided into pyramidal (spastic) and extrapyramidal (nonspastic) categories. **Pyramidal types have persistent neurologic findings**, and are characterized by "clasp knife" rigidity (high resistance followed by sudden relaxation as the limb is moved) and pathologic reflexes (e.g. Babinski). The neurologic findings of **extrapyramidal types** vary with changes in activity, emotions, and alertness. Tone is variable, and is usually decreased when the child is asleep. Pathologic reflexes (e.g. Babinski) are absent, but primitive reflexes (i.e. those which are normally present at birth but disappear by late infancy, such as the Moro) are a prominent feature. Extrapyramidal types can be further subdivided into:

Choreoathetoid—spontaneous, slow muscle movement but without normal control. Often described as a rhythmic, snakelike movement.

Ataxic—muscle coordination is poor and the child's movements are shaky.

Dystonic—uncontrollable and rapid changes in body tension or tone.

Rigid or spastic—the muscles are stiff and weak.

The **topographic classification** categorizes cerebral palsy types according to limb involvement. *Hemiplegia* refers to involvement of a **single lateral side of the body, with greater impairment of the upper extremities than the lower ones**. *Bilateral hemiplegia* indicates involvement of both sides of the body, with upper extremities more impaired. *Diplegia* describes **four-limb involvement**, with greater impairment of the lower extremities. *Spastic quadriplegia* is **four-limb involvement with significant impairment of all extremities**, although the upper limbs may be less impaired than lower ones. Quadriplegia is considered by some to represent a furtherance of diplegia. The terms *monoplegia* and *triplegia* are also sometimes used. (The term *paraplegia* is reserved for spinal and lower motor neuron disorders.)

An "expanded classification" of cerebral palsy relies on the motor quotient to place patients into minimal, mild, moderate, and severe (profound) categories and includes children with milder deficits than the traditional physiologic labels. The motor quotient is derived by dividing

the child's "motor age" (i.e. motor skills developmental age) with his or her chronologic age. A motor quotient of 75 to 100 is considered to represent minimal impairment, a quotient of 55 to 70 mild impairment, 40 to 55 moderate impairment, and lesser quotients severe (profound) impairment. Use of the motor quotient is helpful to clinicians to identify children with less obvious impairments so early treatment can be provided.

The initial evaluation of the child with cerebral palsy is dictated by the history and physical findings. The evaluation may include brain imaging and metabolic or genetic testing. The yield of these tests is often low. When a cause is identified, however, the information can be helpful in managing the patient, future family planning and offering parents peace of mind. An attempt to identify comorbid conditions includes cognitive testing for mental retardation and electroencephalography for seizures.

Treatment goals for a child with cerebral palsy include **maximizing motor function** and **preventing secondary handicaps**. During the preschool years, providers should pay careful attention to maximizing the child's ability to communicate. Efforts to **enhance communication** focus on cognitive skills in some children, whereas for others, the therapy targets oral motor function. School performance and peer acceptance become important issues for older children. Physical therapy for motor deficits is often supplemented with pharmacologic and surgical interventions. Occupational therapy improves positioning and allows the child to interact better with the environment and eases care as the child grows. Finally, the psychological and social needs of the family should never be overlooked, as many children with cerebral palsy require extensive physical and emotional support.

Comprehension Questions

- [15.1] You are called to examine a term infant who required resuscitation after a spontaneous vaginal delivery. The Apgar scores at 1, 5, and 10 minutes were 2, 7, and 9, respectively. The mother's records show that she received routine prenatal care, and that her prenatal ultrasonogram, triple screen, and glucose tolerance tests were all within normal limits. The nurse tells you that the

father seemed very agitated and that he mentioned possibly suing the obstetrician if the baby does not "turn out normal." Your thorough examination of the baby reveals no abnormalities. In counseling the family, which one of the following is most appropriate?

- A. Tell them that your examination findings indicate that everything is fine.
- B. Tell them that the low Apgar scores at 1 and 5 minutes indicate that the baby suffered perinatal asphyxia.
- C. Tell them that as the pregnancy was uncomplicated, and that any neurologic deficit that the baby may develop is likely to be attributable to events at delivery.
- D. Tell them that your examination findings are reassuring, and that you will perform a careful developmental assessment at every well-child visit.
- E. Avoid speaking to the parents until you have had a chance to speak with the obstetrician and see the cord blood gas results.

[15.2] A 4-year-old child with cerebral palsy comes to your clinic for the first time for a routine visit. He walks with the help of leg braces and a walker, and his speech is slow and slurred. His mother tells you that he has never been hospitalized, and he has never had any problems with swallowing. He began walking at age 2.5 years, his speech is limited to short phrases, and he is unable to take off his clothes or use the toilet without assistance. On examination, you find that the boy has only minimally increased tone in the upper extremities and that he has good fine motor coordination, but that he has significantly increased tone and deep tendon reflexes in the lower extremities. How would you categorize this child's cerebral palsy?

- A. Mild, diplegic
- B. Mild, hemiplegic
- C. Moderate, diplegic
- D. Moderate, quadriplegic
- E. Severe, diplegic

- [15.3] An infant girl is born via spontaneous vaginal delivery at 28 weeks' gestation because of an incompetent cervix. Which of the following features of her clinical course in the neonatal intensive care unit is most likely to correlate with her clinical outcome 5 years from now?
- A. Grade IV intraventricular hemorrhage
 - B. Administration of surfactant
 - C. Retinopathy of prematurity stage 1 on initial ophthalmologic examination
 - D. Apnea of prematurity
 - E. Umbilical artery catheterization
- [15.4] The parents of a 2-year-old girl, recent immigrants from Guatemala, bring their child to you for the first time. The child was born at term after an uncomplicated pregnancy and delivery, and her neonatal course was uneventful. She sat without support at 6 months of age, pulled to a stand at 10 months, and began walking at 14 months. She has a 10-word vocabulary, and she is able to drink from a cup and feed herself with a spoon. You also learn that a previous child in the family died at the age of 5 years from "heart trouble." On physical examination, you note contractures of the lower extremities, stiffness of the hands, somewhat coarse facial features, and an enlarged liver and spleen. The child's growth is within normal limits, and her examination is otherwise normal. What is the most appropriate next step to diagnose this child's condition?
- A. Abdominal computerized tomography
 - B. A brain MRI (magnetic resonance imaging)
 - C. Tests for a storage disorder
 - D. Chromosomes
 - E. Thyroid function studies

Answers

- [15.1] **D.** The Apgar score at 1 minute reflects the neonatal environment immediately prior to birth and the 5-minute score corre-

lates with the infant's response to resuscitation. The Apgar scores are not an accurate reflection of morbidity. Your examination is a much better indicator of the child's outcome, but you cannot rule out the possibility of cerebral palsy on the basis of a normal neonatal physical examination. It is always best to leave discussion of the events of delivery to the obstetrician, keeping in mind that the majority of difficult deliveries are the result of a previously unidentified antenatal insult. Avoidance of the parents at this emotional time will likely only further their anxiety and may impede your future efforts to provide for the child.

- [15.2] C. Diplegia means all four extremities are affected, more in the lower extremities.
- [15.3] A. Intraventricular hemorrhage is a frequent complication in preterm infants, and is associated with seizures, hydrocephalus and periventricular leukomalacia (PVL). A grade IV bleed involves the brain parenchyma and puts this child at higher risk for neurodevelopmental handicap.
- [15.4] C. The enlarged liver and spleen, the coarse facies, and the history of the death of a previous child from "heart trouble" all point to a storage disorder as the most likely diagnosis in this case. Her joint contractures and hand stiffness may be explained by an abnormal metabolism, rather than a central nervous system deficit as in cerebral palsy.

CLINICAL PEARLS

◆ Cerebral palsy is a disorder of movement or posture that is the result of an insult to or an anomaly of the central nervous system.

◆ Most children with cerebral palsy have no identifiable risk factors for the disorder.

◆ Optimal treatment plans for the child with cerebral palsy use a multidisciplinary approach.

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◆ CASE 16

A 5-year-old white girl comes to your clinic for the first time. Her mother reports that the child has had fever, malaise, and a cough for the past 2 days. The girl has a history of asthma for which she uses a steroid inhaler every day as well, and an albuterol inhaler as needed. The child has also been given various over-the-counter cold and allergy remedies, but despite all of her medications, her symptoms have been worsening over the past several months. The mother reports that her daughter was treated for "sinusitis" during each of the past two winter seasons, and that she has "always been small for her age." Your examination reveals a child whose height and weight are at the 5th percentile for age and who appears moderately ill. Her temperature is 101°F (38.3°C) orally, and her respiratory rate is 32 breaths per minute. She has scant purulent rhinorrhea from both nostrils. Her breath sounds are wheezy in all lung fields and diminished on the right side. Heart sounds and capillary refill are normal, yet she has digital clubbing.

- ◆ Describe the diagnostic approach in the evaluation of this child?
- ◆ What is the most likely diagnosis?
- ◆ What is the next step in evaluation?

ANSWERS TO CASE 16: Cystic Fibrosis

Summary: A small-appearing 5-year-old girl previously diagnosed with asthma and sinusitis now presents with fever, scant purulent rhinorrhea, abnormal breath sounds and digital clubbing.

- ◆ **Diagnostic approach:** Gather more information including perinatal, past medical, family and dietary histories. A careful review of systems will be important in this case. Plot the child's height and weight on a standard growth curve.
- ◆ **Most likely diagnosis:** Cystic fibrosis.
- ◆ **Next step in evaluation:** Obtain a chest radiograph and perform a sweat chloride test.

Analysis**Objectives**

1. Know the historical clues and physical signs necessary to distinguish cystic fibrosis from other more common conditions.
2. Know how to accurately diagnose cystic fibrosis.
3. Have a basic understanding of the implications and limitations of genetic testing for cystic fibrosis.

Considerations

A careful review of this child's frequency and severity of respiratory symptoms, response to medications, and general health is warranted. Her small size and digital clubbing (both unusual findings for asthma) indicate that asthma may not be the etiology of her respiratory problems. Furthermore, recurrent sinusitis is uncommon in young children whose nasal passages are not fully pneumatized. This girl was either incorrectly diagnosed with sinusitis or she has an underlying condition that predisposes her to this problem.

APPROACH TO CYSTIC FIBROSIS

Definitions

Clubbing: Increase in the angle between the nail and nail base of 180 degrees or greater, and softening of the nail base to palpation. This is an uncommon finding in children and usually indicates the presence of chronic pulmonary, hepatic, cardiac or gastrointestinal disease, although it can also be familial.

Cystic fibrosis (CF): The major cause of chronic debilitating pulmonary disease and pancreatic exocrine deficiency in the first three decades of life. Generally characterized by the triad of chronic obstructive pulmonary disease, pancreatic exocrine deficiency, and abnormally high sweat electrolyte concentrations. Characteristic changes in the pancreas give the disease its name.

Clinical Approach

CF afflicts approximately 1 of 3300 whites, but only 1 of 16,300 African Americans and 1 of 32,100 Asian Americans. **An affected individual has a defect in mucus secretion and the function of eccrine sweat glands, resulting in the obstruction of various visceral lumen and excessive electrolyte secretion.**

CF almost always involves the respiratory tract. **Most patients develop bronchiectasis by the age of 18 months**, although some may not experience respiratory difficulty until several years of age. It is not uncommon for children with CF to be initially misdiagnosed as asthmatic, but a careful history and physical examination usually demonstrate the presence of other clues to the diagnosis of CF. **Persistent bronchial obstruction from impaired mucus secretion predisposes the patient with CF to secondary bacterial infection, which then leads to a cycle of inflammation, tissue damage, further obstruction, and chronic infection.** Often, bacterial pneumonia is initially caused by *Staphylococcus aureus*, but subsequent infections are caused by *Pseudomonas aeruginosa*. Most patients with advanced disease harbor heavy, **slime-producing variants of *P. aeruginosa* called mucoid variants** that are rarely found in other conditions. Once established, these bacteria are virtually impossible to eradicate.

Airway reactivity is present in 50% of patients, but the response to bronchodilators is unpredictable and varies over time. Pneumothorax, hemoptysis, and cor pulmonale are frequent complications in patients with advanced disease. Pulmonary involvement advances at a variable rate, but eventually leads to respiratory and/or cardiac failure. Upper respiratory tract manifestations such as chronic nasal congestion, sinusitis, and nasal polyps are common in CF.

Children with CF tend to have poor growth as a result of impaired intestinal absorption of nutrients, because of the pancreatic duct obstruction leading to inadequate enzyme secretion. These children may also have abdominal distention, rectal prolapse, deficiency of subcutaneous fat and muscle tissue, and frequent passage of oily, malodorous stools. Abnormal stool composition may also predispose the patient with CF to intestinal obstruction, volvulus, or intussusception.

Fatty infiltration of the liver or focal biliary cirrhosis occurs in many patients with CF, but they may be asymptomatic for many years. Hepatomegaly, esophageal varices, and hypersplenism caused by portal hypertension develop in a small proportion of teens, and infants may present with prolonged neonatal jaundice. Abnormalities of the gallbladder are common in adult patients.

Other symptoms of CF include **osteoarthropathy; impaired fertility**, particularly in males as a result of obstructive azoospermia; enlarged submaxillary glands; and a “salty taste” on the skin. Patients and their families require extensive psychosocial support.

Cystic fibrosis is caused by abnormalities in the protein called the cystic fibrosis transmembrane conductance regulator (CFTR); defects in this protein result in abnormal chloride transport. Thus, **CF is diagnosed by documenting an elevated sweat electrolyte concentration.** It is important that experienced personnel perform the test, as false negative and false positive results are usually the result of testing error. Appropriate testing technique is particularly important for infants, in whom the collection of an adequate quantity of sweat may be difficult. **Elevated sweat electrolytes (false positives) have been reported in conditions such as anorexia nervosa, hypothyroidism, and nephrogenic diabetes insipidus.** False-negative results can occur in patients with edema and hypoproteinemia as presenting signs of CF. Because the implications of a false positive or false negative result are great, the test is most appropriately obtained in patients for whom a reasonable clinical suspicion of CF exists (see Table 16-1 for indications).

Table 16-1
INDICATIONS FOR SWEAT TESTING

Gastrointestinal

Chronic diarrhea

Steatorrhea

Meconium ileus or plug syndrome

Rectal prolapse

Cirrhosis/portal hypertension

Prolonged neonatal jaundice

Pancreatitis

Deficiency of fat-soluble vitamins (especially A, E, K)

Respiratory Tract**Upper**

Nasal polyps

Pansinusitis on radiographs

Lower

Chronic cough

Recurrent "wheezing" bronchiolitis

Recurrent or intractable asthma

Obstructive pulmonary disease

Staphylococcal pneumonia

Pseudomonas aeruginosa (esp mucoid) from throat, sputum or bronchoscopy cultures

Other

Digital clubbing

Family history of CF

Failure to thrive

Hyponatremic, hypochloremic alkalosis

Severe dehydration or heat prostration incompatible with history

"Tastes salty"

Male infertility

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Sweat electrolyte levels should be repeated whenever there is a doubt about the initial results.

Genetic testing for CF can be helpful for some families. Available tests have a high specificity but may have a low sensitivity. A positive result is diagnostic for the disease but a negative result may not entirely preclude the diagnosis due to the heterogeneous nature of the genetic

Table 16–2
ABDOMINAL PAIN IN CYSTIC FIBROSIS

ETIOLOGY	CHARACTERISTICS	TREATMENT
Constipation	Difficult stooling	Oral lactulose; prune juice; fiber
DIOS (Distal intestinal obstruction syndrome)	Crampy pain, feels well between waves of pain No stools, with or without emesis	Oral or nasogastric GoLytely; Gastrografin enema
Fibrosing colonopathy	Abdominal pain Bloody diarrhea Signs of obstruction	Surgery
Gastroenteritis	Vomiting and diarrhea	Supportive therapy
Pancreatitis	Largely restricted to those with intact pancreatic function	Initially NPO, then low-fat diet Pain control, pancreatic enzymes
Intussusception	Intermittent, crampy pain May have “currant jelly” stools	Contrast enema or surgery
Gall stones	Epigastric pain worse after fatty meal	Surgery
Peptic ulcer disease	Epigastric pain, may have emesis	Antacids, H ₂ blockers, proton pump inhibitors
Appendicitis	Fever, anorexia, right lower quadrant abdominal pain May become chronic	Surgery
Abdominal wall (from coughing)	Abdominal muscles are tender to palpation	Supportive

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basis of this disease. Thus, in whites of northern European background, approximately 70% of all cystic fibrosis mutations are accounted for by deletion of three specific base pairs at the $\Delta F508$ position of the CFTR, and an additional 20% can be detected with additional genetic testing. More genetic heterogeneity exists in non-whites, making this method of screening of little use for these populations. Universal screening of newborns for CF is currently performed in only a few states, and its appropriateness has been the subject of wide debate. False test results can cause significant anxiety for families, and the long-term benefits of early detection are unclear.

Therapy for CF patients is best coordinated by experienced pediatric pulmonary specialists. Long-term management includes minimizing airway reactivity and infections, optimizing nutritional status, and ongoing psychosocial support. The prognosis for patients with this condition varies depending on the severity of the disease. Infants with severe lung disease can die in early childhood, but most patients reach adolescence or adulthood. Abdominal pain is relatively common (see Table 16-2 for a listing of etiologies). Mean duration of survival is approximately 30 years.

Comprehension Questions

- 6.1] A term-appearing infant delivered vaginally after an uneventful pregnancy develops vomiting and abdominal distention at 10 hours of life. No passage of stool has been recorded since birth. An abdominal radiograph shows distended bowel loops and a "bubbly" pattern in a portion of intestine, and the colon appears narrow. What do you tell the parents?
- A. You would like to consult a geneticist because you suspect that their child has an unusual genetic defect that may involve other associated anomalies.
 - B. The child most likely has necrotizing enterocolitis, a condition more commonly seen in premature infants. You therefore question the child's supposed gestational age.

- C. You are concerned about the possibility of meconium ileus, and would like to obtain some family history.
 - D. You believe that the child is simply constipated and would like to change to a soy-based formula to see whether the baby tolerates this better.
 - E. The child's symptoms and radiograph findings are most likely normal.
- [16.2] Appropriate clinical management of the patient in the above question includes:
- A. Change from enteral feeds to intravenous fluids and obtain a genetics consult for the next morning.
 - B. Change from enteral feeds to intravenous fluids, obtain a blood culture, and initiate antibiotics.
 - C. Change from enteral feeds to intravenous fluids and obtain a STAT pediatric surgery consult.
 - D. Change from cow milk to soy-based infant formula and continue to observe the infant.
 - E. Do not change your current management.
- [16.3] A 10-year-old boy presents to you with a history of recurrent sinusitis and multiple episodes of pneumonia. You obtain a sweat electrolyte test, and the result is within the normal range. Your differential diagnosis now includes atopy, primary ciliary dyskinesia, and:
- A. Severe combined immunodeficiency
 - B. Cystic fibrosis
 - C. Aspergillosis
 - D. Chronic granulomatous disease
 - E. Coccidioidomycosis
- [16.4] A 2-month-old infant presents to the emergency center for recent onset of bulging of his anterior fontanelle. The child is fussy and refuses to nurse or take a bottle, and he vomited once en route to the emergency department. He has not had any fever. Computerized tomography scan of the head is negative for

trauma or tumor. In addition to meningitis, your differential diagnosis includes:

- A. Colic
- B. Sinusitis
- C. Pneumonia
- D. Vitamin A deficiency
- E. Intussusception

Answers

- [16.1] C. Meconium ileus occurs when inspissated meconium obstructs the distal ileum. It is thought to be caused by deficiency of proteolytic enzymes. Obstruction begins in utero, resulting in underdevelopment of distal lumina. It is almost always associated with cystic fibrosis. Intestinal atresia and Hirschsprung (congenital aganglionic megacolon) cause clinical pictures similar to this baby's, but the radiographic findings for this child are most consistent with meconium ileus. Necrotizing enterocolitis also causes emesis and abdominal distension, but would be unlikely in a term infant with no history of ischemic injury, and the colon would be expected to be of normal size. Constipation would not be consistent with the severity of this baby's clinical picture, nor would it produce the described radiographic picture.
- [16.2] C. Meconium ileus is a surgical emergency, as volvulus and perforation peritonitis are not uncommon complications.
- [16.3] B. Because of the possibility of a false negative sweat electrolyte test, cystic fibrosis cannot be ruled out. The test should be repeated and/or consideration given to other diagnostic modalities. Bronchiectasis and chronic sinusitis are characteristic of ciliary dyskinesia syndromes. If associated with visceral situs inversus, the diagnosis of Kartagener disease is given.
- [16.4] D. Malabsorption of fats and protein are major causes of morbidity for patients with cystic fibrosis. In addition to carefully

planned diets, most children with CF take supplements of the fat-soluble vitamins D, E, K, and A. Disorders of vitamin A metabolism can result in pseudotumor cerebri, which causes headache, vomiting, and neurologic abnormalities due to increased intracranial pressure. Thus, a bulging fontanelle may be the presenting sign of CF in an infant.

CLINICAL PEARLS

- ◆ Cystic fibrosis involves a defect in mucus secretion and the function of eccrine sweat glands resulting in the obstruction of various visceral lumen and excessive electrolyte secretion.
- ◆ Extrapulmonary signs and symptoms such as digital clubbing, recurrent sinusitis, growth retardation, and fat malabsorption are often clues to the diagnosis of cystic fibrosis.
- ◆ A negative sweat chloride test does not preclude cystic fibrosis and should be repeated and further testing should be considered whenever clinical manifestations suggestive of CF are present.
- ◆ Meconium ileus in the newborn period is nearly pathognomonic for cystic fibrosis.

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◆ CASE 17

A mother brings her previously healthy 6-year-old son into your clinic because he has been limping and complaining of left leg and knee pain for 1 week. He has experienced no recent trauma and his past medical history is unremarkable. His physical examination reveals a temperature of 100°F (37.8°C) orally with no swelling, misalignment, or weakness of the lower extremities. He demonstrates tenderness over the right knee, hepatomegaly, and petechiae on his cheeks and chest.

- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the evaluation?

ANSWERS TO CASE 17: Acute Lymphoblastic Leukemia

Summary: A 6-year-old boy with a 1-week history of leg pain and limping. He has a low-grade temperature, hepatomegaly, and petechiae on his face and chest.

- ◆ **Most likely diagnosis:** Acute lymphoblastic leukemia (ALL).
- ◆ **Next step in the evaluation:** Complete blood count with platelets and differential.

Analysis

Objectives

1. Describe the clinical manifestations of ALL.
2. Describe the laboratory and radiologic tests used in diagnosing ALL.
3. Know the treatment plan for a child with newly diagnosed ALL.
4. Understand the long-term survival and follow-up issues in children diagnosed with ALL.

Considerations

This patient has several clinical manifestations of acute lymphoblastic leukemia—**leg and joint pain, fever, splenomegaly, and petechiae**. Most of the clinical signs and symptoms of ALL are a result of either replacement of normal bone marrow components with uncontrolled proliferation of immature lymphoid cells or infiltrates of extramedullary sites by immature lymphoid cells. Rapid diagnosis and referral to a pediatric cancer center can increase survival in this condition.

APPROACH TO ACUTE LYMPHOBLASTIC LEUKEMIA

Definitions

- Extramedullary:** Areas of the body outside of the bone marrow.
Granulocytopenia: A reduction in total circulating leukocytes.

Lymphoblast: A large, primitive, undifferentiated precursor cell not normally seen in the peripheral circulation.

Pancytopenia: A reduction in circulating erythrocytes, leukocytes, and platelets secondary to a decrease in blood cell production in the bone marrow.

Thrombocytopenia: A reduction in circulating platelets.

Clinical Approach

Leukemia is the most common childhood cancer, accounting for approximately one-third of pediatric cancers. Acute lymphoblastic leukemia affects the lymphoid cell line and comprises approximately 75% of leukemia cases in children. Acute myeloblastic leukemia (AML) affects the myeloid cell line (granulocytes, monocytes, erythrocytes, or megakaryocytes) and comprises approximately 20% of childhood leukemia cases. The clinical manifestations of AML are similar to those of ALL. **In the United States, childhood ALL has a peak incidence at age 4 years and occurs more frequently in boys than in girls.**

ALL is often called the "great imitator" because of its nonspecific symptoms—anorexia, irritability, lethargy, pallor, bleeding, petechiae, leg and joint pain, and fever. Differential diagnoses include idiopathic thrombocytopenic purpura (ITP), aplastic anemia, mononucleosis, juvenile rheumatoid arthritis, and leukemoid reaction. A careful history and physical examination can help exclude these other causes:

- Idiopathic thrombocytopenic purpura (ITP) is a common cause of bruising and petechiae due to low platelet levels in children; however, anemia, leukocyte disturbances, and hepatosplenomegaly are not typical findings.
- Aplastic anemia causes pancytopenia and fever; lymphadenopathy, arthralgias, bone pain, and hepatosplenomegaly are unusual findings in aplastic anemia.
- Children with infectious mononucleosis (i.e. Epstein-Barr virus) or other acute viral illnesses may present with fever, malaise, adenopathy, splenomegaly, and lymphocytosis. Atypical lymphocytes that resemble leukemic lymphoblasts are characteristic of these viral illnesses.

- Leukemoid reactions may be observed in bacterial sepsis, pertussis, acute hemolysis, granulomatous disease, and vasculitis. The leukemoid reaction resolves as the underlying disease is treated.

Children with ALL presenting with fever, arthralgias, arthritis, or a limp are frequently diagnosed initially with juvenile rheumatoid arthritis (JRA). Anemia, leukocytosis, and mild splenomegaly may also be seen in JRA, causing even more confusion in the differential diagnosis. **A bone marrow examination can differentiate ALL from an atypical presentation of JRA.**

Infiltration of the marrow by other types of malignant cells (neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, and retinoblastoma) occasionally can produce pancytopenia. These tumor cells are usually found in clumps in the normal marrow but may occasionally replace the marrow completely.

Important questions to differentiate ALL from other diagnoses include:

- How long have the symptoms been present?
- Has the child had unexplained bleeding (gums, nosebleeds) or bruising?
- Has the child sustained any trauma that could explain bone and joint pain, bruising or petechiae?
- Does the child have fatigue or pallor?
- Is the child taking medication that could lead to easy bruising (aspirin)?
- Is there a family history of juvenile rheumatoid arthritis?
- Has the child had abdominal pain or anorexia?

A physical examination should include the general appearance and energy level, vital signs (note if antipyretic has been given), bleeding, bruising, petechiae, pallor, pain upon palpating bones or joints, and hepatosplenomegaly.

Almost half of the children with newly diagnosed leukemia have total leukocyte counts less than $10,000/\text{mm}^3$. Leukemic blasts may or may not be seen in the peripheral blood smear; therefore the diagnosis of leukemia must be established by bone marrow examination rather than by peripheral blood examination alone. The bone mar-

row specimen is aspirated most commonly from the posterior iliac crest. **A normal marrow contains less than 5% blasts; a minimum of 25% blasts is required to make the diagnosis of ALL.**

Approximately two-thirds of the children with ALL have karyotypic abnormalities involving the leukemic cell. These abnormalities include changes in chromosome number (i.e. hypo- or hyperdiploidy) or chromosome structure (translocation, deletions, inversions). The most commonly found translocations include t(12;21), t(1;19), t(9;22) or Philadelphia chromosome, and t(4;11).

A variety of markers can be used to gauge prognosis. **In general, girls have a better prognosis than boys. African American and Hispanic populations have lower remission rates and higher relapse rates.** Children with ALL who are younger than age 1 year and those older than age 10 years have a worse prognosis. **Higher leukocyte counts, especially if higher than 50,000/mm³, have an unfavorable prognosis.** Patients with mature B-cell or T-cell immunophenotypes typically have a worse outcome than patients with B-precursor ALL. The karyotypes of leukemic cells have diagnostic, prognostic, and therapeutic significance. Patients with hyperdiploidy generally have a more favorable prognosis, while those with hypodiploidy and pseudodiploidy do less well. Translocations with a poor outcome include t(8;14) which is associated with B-cell ALL, t(9;22) or Philadelphia chromosome, t(1;19) found in pre-B-cell ALL, and t(4;11) seen commonly in younger infants.

A **lumbar puncture**, performed to examine the central nervous system for early leukemic involvement, has **important therapeutic implications**. A higher number of blasts in the CSF is associated with a worse prognosis. A **chest radiogram** is performed to detect a mediastinal mass. Bone radiographs may show altered medullary trabeculation or cortical defects as well as transverse radiolucent lines. However, these radiologic findings lack clinical or prognostic significance, and a skeletal survey is usually unnecessary.

Combination chemotherapy is the principal therapy for childhood ALL. The therapy involves remission induction and consolidation, prophylactic central nervous system therapy, and maintenance. Induction therapy, a combination of prednisone, vincristine, and asparaginase, produces remission in approximately 98% of children with non-high-risk ALL within 4 weeks. Consolidation treatment,

aimed at further reducing residual leukemia, is designed to deliver multiple chemotherapies in a relatively short period of time. Prophylactic central nervous system therapy with intrathecal chemotherapy (\pm craniospinal irradiation) has decreased the incidence of central nervous system leukemia as a primary site of relapse from 50% to about 3% to 6%. Maintenance therapy with methotrexate and 6-mercaptopurine, vincristine, and prednisone is given for 2 to 3 years to prevent relapse. Therapy is discontinued for children who remain in complete remission for 2 to 3 years on maintenance therapy.

The overall cure rate for childhood ALL is 80%. With prolonged survival, monitoring for late effects of therapy has become increasingly important. Late effects include neuropsychological deficits, seizures and endocrine disturbances (i.e. growth hormone deficiency) related to central nervous system prophylaxis; spermatogenesis dysfunction related to cyclophosphamide; delayed sexual maturation in boys who received irradiation of gonadal tissue due to leukemic invasion of the testes; leukoencephalopathy and neurodevelopmental problems (especially in postcentral nervous system radiation patients); and secondary malignancies.

Comprehension Questions

- [17.1] A mother brings her 3-year-old son who has Down syndrome to the clinic because his gums have been bleeding for a week. Further history reveals that he has been less energetic than usual. Examination reveals that the child has a temperature of 100°F (37.8°C) orally, pallor, splenomegaly, gingival bleeding, and bruises on the lower extremities. Which of the following is the most likely explanation for this child's symptoms?
- A. Idiopathic thrombocytopenia
 - B. Aplastic anemia
 - C. Leukemia
 - D. Leukemoid reaction
 - E. Megaloblastic anemia
- [17.2] A father brings in his 6-year-old son to the clinic who is taking induction chemotherapy for ALL. The school will not allow the

child to register until his immunizations are up to date. The best course of action is to:

- A. Call the school nurse or principal to inform them that this child cannot receive immunizations while he is taking chemotherapy.
- B. Update all immunizations except for measles-mumps-rubella (MMR) and varicella.
- C. Update all immunizations except for oral polio vaccine.
- D. Update all immunizations.
- E. Call the school nurse or principal to inform them that this child will never receive immunizations because of the alteration in his immune system.

[17.3] A mother brings to the clinic her 4-year-old son who began complaining of right knee pain 2 weeks ago, is limping slightly, is fatigued, and has had a fever to 100.4°F (38°C). Which of the following is the most important diagnostic laboratory test to perform?

- A. Epstein-Barr virus titer
- B. Sedimentation rate
- C. Antinuclear antibodies
- D. Complete blood count (CBC) with differential and platelets
- E. Rheumatoid factor

[17.4] Two weeks after a viral syndrome, a 2-year-old develops bruising and generalized petechiae, more prominent over the legs. He has neither hepatosplenomegaly nor lymph node enlargement. Laboratory testing reveals a normal hemoglobin, hematocrit, and white blood cell count and differential. The platelet count is 15,000/mm³. The most likely diagnosis is:

- A. Von Willebrand disease
- B. Acute lymphoblastic leukemia
- C. Immune thrombocytopenia
- D. Aplastic anemia
- E. Thrombotic thrombocytopenic purpura

Answers

- [17.1] **C.** A high susceptibility to leukemia is associated with certain heritable diseases (including Klinefelter syndrome, Bloom syndrome, Fanconi, ataxia telangiectasia, and neurofibromatosis) and chromosomal disorders such as Down syndrome. Children with Down syndrome have a 10- to 15-fold increased risk for developing leukemia compared with normal children. Siblings of an ALL patient have a two- to fourfold increase in chance of developing ALL. A few cases are associated with aberrations in the p53 gene. Overall, these genetic links account for a small number of total ALL cases.
- [17.2] **A.** Live virus vaccines are contraindicated for the child with ALL (and all members of the household) during chemotherapy and for at least 6 months after completion of treatment. Although the viruses in the MMR and varicella vaccine are attenuated, immunosuppression from treatment can be profound and actual viral disease can result. While immunizations that do not contain live virus (diphtheria, tetanus, inactivated poliovirus vaccine, hepatitis B, hepatitis A) are not directly contraindicated for the child receiving chemotherapy, the associated immunosuppression often inhibits antibody responses.
- [17.3] **D.** This child has symptoms of JRA as well as leukemia. The CBC with differential and platelets is the best initial screening test. The leukocyte count is normal to increased in JRA and the platelet count is normal to increased; there are no blast cells. Frequently, blast cells are found on the peripheral smear in children with ALL. The child in the question may ultimately require a bone marrow aspiration.
- [17.4] **C.** In children, immune thrombocytopenic purpura (ITP) is the most common form of thrombocytopenic purpura. In most cases a preceding viral infection can be documented. The platelet count is frequently less than $20,000/\text{mm}^3$, but other laboratory tests yield normal results, including the bone marrow aspiration. Treatment consists of gamma globulin.

CLINICAL PEARLS

Leukemias are the most common childhood cancers, and ALL represents approximately 75% of all leukemia cases in children.

ALL has a peak incidence at age 4 years, and boys are affected more frequently than girls.

ALL is often called the "great imitator" because of its non-specific symptoms-anorexia, irritability, lethargy, pallor, bleeding, petechiae, leg and joint pain, and fever.

Combination chemotherapy is the principal therapy for childhood ALL. Induction therapy, a combination of prednisone, vincristine, and asparaginase, produces remission in approximately 98% of children with average risk ALL within 4 weeks.

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◆ CASE 18

You are called to the operating room to manage an infant recently born by emergency cesarean delivery. The mother is 18 years old and has one previous child. She received no prenatal care for the current pregnancy, arriving at the hospital in active labor approximately 1 hour prior to delivery. At delivery you note the infant to be very large (4500 g). The infant has poor tone, a grayish color, and demonstrates no spontaneous respirations. You detect a pulse of 100 beats per minute (bpm).

- ◆ What is the first step in the evaluation of this child?
- ◆ What is the most likely diagnosis?
- ◆ What is the next step in evaluation?

ANSWERS TO CASE 18: Infant of a Diabetic Mother

Summary: A very large, disproportionate infant with respiratory depression.

- ◆ **First step:** Resuscitation of the infant begins immediately following the **A** (airway), **B** (breathing), and **C** (circulation) method of neonatal resuscitation. Oxygen is administered via blow-by simultaneously with attempts to stimulate the infant to breathe on his own. If the infant does not respond to these simple measures, bag-mask ventilation and endotracheal intubation may be required. The infant's poor tone, color, and slow heart rate should resolve once the child is adequately oxygenated.
- ◆ **Most likely diagnosis:** Infant of a diabetic mother.
- ◆ **Next step:** Once the infant's cardiorespiratory status is stabilized, frequent checks for hypoglycemia are indicated.

Analysis

Objectives

1. Recognize the clinical features of the infant of a diabetic mother (IDM).
2. Know the management of the infant of a diabetic mother.
3. Know the infant anomalies that are associated with pregestational diabetes.

Considerations

The fetal hyperinsulinism which is a response to poorly controlled maternal hyperglycemia can result in fetal macrosomia. Hyperinsulinism can also result in increased fetal oxygen requirements. These two factors can make the birth process difficult and result in neonatal distress. This mother's lack of prenatal care precluded management of her poorly controlled gestational diabetes. The baby's high insulin lev-

els cause him to become **hypoglycemic** when he is removed from the high-sugar environment that he experienced in utero. Infant hypoglycemia must be managed immediately and monitored frequently to prevent further complications. This should be done within the first 45 minutes of life. A blood glucose level of 25 to 40 mg/dL requires immediate feeding. A level less than 25 mg/dL (or in infants with higher levels but with symptoms of hypoglycemia which might include lethargy, listlessness, poor feeding, temperature instability, apnea, cyanosis, jitteriness, tremors, seizure activity and respiratory distress) should be treated with an intravenous glucose bolus followed by a constant glucose infusion. **Polycythemia, hypocalcemia, and hyperbilirubinemia** are other common early sequelae of gestational diabetes that may require further management.

APPROACH TO THE INFANT OF A DIABETIC MOTHER

Definitions

Gestational diabetes: Persistent hyperglycemia during pregnancy, with untreated serum glucose levels >100 mg/dL in the fasting state or >130 mg/dL otherwise.

Hypoglycemia: A blood glucose level less than 40 mg/dL is the usual definition although other definitions exist.

Macrosomia: A baby that is considerably larger than normal, usually exceeding the 90th percentile for gestational age.

Polycythemia: Elevated hematocrit that can lead to thrombosis if the level is significant and remains untreated. Levels in a newborn greater than 65% are often treated by partial exchange transfusion.

Caudal Regression Syndrome: Rare malformation of poorly developed legs, associated with pregestational diabetes.

Clinical Approach

Diabetes during pregnancy is a common occurrence, affecting more than 3% of pregnancies. For most women, diabetes is a transient problem that occurs during pregnancy and disappears after delivery. Generally, all pregnant women are screened for gestational diabetes

between 24 and 28 weeks of pregnancy. Gestational diabetes is classified according to the age at which the mother is first diagnosed, the duration of her symptoms, and the presence of vasculopathy, as these factors have been shown to significantly influence perinatal outcome (Table 18-1). Among pregnant women without a history of pregestational diabetes, those who require insulin therapy (class A2) are distinguished from those whose carbohydrate intolerance can be managed by diet alone (class A1), as the risk for a poor perinatal outcome is greater for the former. Women with diabetes prior to becoming pregnant should be followed closely by their health care provider, as **many of the congenital malformations associated with diabetes are thought to be the result of hyperglycemia early in the pregnancy.**

Fetal glucose levels reflect those of the mother. The fetal pancreas begins to produce insulin during the fourth month of gestation but does not become functionally significant until sometime after week 26, when macrosomia may first be appreciated. Increased infant weight and length occur because of increased adipose tissue deposition and the growth hormone effects of insulin. Increased glycogen is stored in the infant liver, kidney, skeletal muscle, and heart. Head circumference, however, is less significantly affected as insulin does not affect brain growth.

Macrosomia, increased oxygen requirements, and placental insufficiency are factors that can lead to perinatal asphyxia in the IDM. More severe cases may result in premature birth or be an indication for early induction of delivery. **Prematurely born IDMs are at particularly high risk for hyaline membrane disease.** In some cases, intrauterine growth retardation may occur as the result of severe fetal oxygen deprivation due to maternal vascular disease.

Hyperbilirubinemia occurs in the IDM as a result of the relative immaturity of the liver and of fetal polycythemia. Hyperglycemia and hyperinsulinism can result in increased fetal oxygen requirements and lead to increased production of erythropoietin. The resultant polycythemia further contributes to elevated bilirubin levels and can also cause renal vein thrombosis. **Hypocalcemia** is a common occurrence in IDMs resulting in irritability and rarely in decreased myocardial contractility; treatment is necessary only in severe cases. **Hypomagnesemia** can occur but is almost never clinically significant.

Infants born to mothers with poor diabetic control are at increased risk for congenital malformations including **congenital heart disease, neural tube defects, and the caudal regression syndrome.** The latter

Table 18-1
WHITE CLASSIFICATION OF DIABETES IN PREGNANCY

CLASS	DIABETES ONSET AGE (YR)		DURATION (YR)	VASCULAR DISEASE	INSULIN NEED
Gestational diabetes					
A1	Any		During Pregnancy	0	0
A2	Any		During Pregnancy	0	+
Pregestational diabetes					
B	>20		<10	0	+
C	10-19	or	10-19	0	+
D	<10	or	>20	+	+
F	Any		Any	+	+
R	Any		Any	+	+
T	Any		Any	+	+
H	Any		Any	+	+

Note: Classes D, F, R, T, and H refer to gestational diabetics with the following vascular complications: benign retinopathy (D), nephropathy (F), proliferative retinopathy (R), status postrenal transplant (T), and ischemic myocardial disease (H).

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is characterized by general hypoplasia of the sacrum and lower extremities, and is sometimes associated with a small left colon. IDMs may be small in childhood, but are often overweight in adolescence and may be at risk for problems associated with obesity later in life.

Comprehension Questions

- [18.1] An infant is delivered via cesarean section at 35 weeks gestation because of macrosomia and fetal distress. The mother has class

D gestational diabetes. Despite regular visits at a high-risk obstetrics clinic, her hemoglobin A_{1C} level is 20% (normal <8%). This infant is particularly at risk for birth asphyxia, cardiac septal hypertrophy, polycythemia, and:

- A. Hyperglycemia
- B. Pneumothorax
- C. Hyaline membrane disease
- D. Congenital dislocated hip
- E. Dacryostenosis

[18.2] A term infant weighing 9 pounds 3 ounces is born without complication to a mother with class A gestational diabetes. His initial bedside glucose measurement is 30 mg/dL, but a subsequent glucose level after the baby takes 30 cc of infant formula orally is 50 mg/dL, and a subsequent test 30 minutes later gives a glucose value of 55 mg/dL. His physical examination is unremarkable except for his large size. On the proposed day of discharge 48 hours later, the baby appears mildly jaundiced. Vital signs are stable, and mother reports that he is eating well. Which laboratory tests are most likely to help you evaluate this infant's jaundice?

- A. Total and direct bilirubin and liver transaminases
- B. Total and direct bilirubin, liver transaminases, and a hepatitis panel
- C. Total bilirubin and a hematocrit
- D. Total bilirubin and a complete blood count
- E. Total and direct bilirubin and a complete blood count with differential and platelets

[18.3] A premature infant of a Class B diabetic mother who received late prenatal care is delivered via cesarean section due to fetal distress. The mother's axillary temperature just prior to delivery is 98.6°F (37°C). The child has poor color and tone at birth, and no spontaneous cry. Respiratory effort is minimal, and the pulse is weak and slow at 80 beats per minute. After endotracheal intubation, the color and tone improve somewhat, but the baby still has perioral cyanosis and the heart rate is 90 beats per

minute. What is the most likely cause of this infant's persistent distress?

- A. Sepsis
- B. Impaired cardiac function
- C. Renal failure
- D. Hypoglycemia
- E. Hypocalcemia

[18.4] A term infant is born to a mother with class C gestational diabetes. The mother had only intermittent prenatal care. The child requires endotracheal intubation at delivery for poor respiratory effort, tone and color. His initial serum glucose level is 10 mg/dL, which resolves over the first 36 hours of life with intravenous administration of dextrose solution. On the third day of life, his physical examination is remarkable for macrosomia and an abdominal mass. The most likely cause of this abdominal mass is:

- A. Liver engorgement
- B. Infarction of the spleen
- C. Small left colon syndrome
- D. Hydronephrosis
- E. Intraintestinal air

Answers

- [18.1] C. Infants of diabetic mothers, especially when poorly controlled during pregnancy, are at risk for respiratory distress syndrome.
- [18.2] C. This baby most likely has hyperbilirubinemia secondary to liver immaturity, possibly complicated by polycythemia. You would expect him to have a high level of unconjugated bilirubin (included in the total bilirubin test), but his conjugated (or direct) portion should be normal in the absence of intrahepatic disease.

- [18.3] **B.** Infants born to mothers with poorly controlled gestational diabetes are at risk for congenital heart anomalies, cardiomyopathy, septal hypertrophy, and subaortic stenosis. This child's symptoms of failure of heart rate and color to fully respond to resuscitation efforts and the maternal history of diabetes are clues that suggest the infant is at higher risk of cardiac problems. Sepsis can present in a similar fashion, and certainly should remain in the differential diagnosis until further evaluation is complete, but no particular risk factors for infectious disease are known in this case. This child is also at high risk for hypoglycemia in the first hours of life, but hypoglycemia alone would be a less likely explanation for his constellation of symptoms.
- [18.4] **D.** Renal vein thrombosis can present as an abdominal mass (hydronephrosis) in neonates after an episode of asphyxia. Such infants may have gross hematuria (or no hematuria at all), but microscopic hematuria is more common. Hypertension is uncommon in the acute period following renal vein thrombosis, but may occur as a late complication. The affected kidney may recover normal function, or it may atrophy. Bilateral renal vein thrombosis can lead to chronic renal failure. If the infant in this question had delayed passage of its first stool, small left colon syndrome, another complication of the infant of a diabetic mom, might also be considered as a cause of the abdominal mass.

CLINICAL PEARLS

Infants of diabetic mothers are at increased risk for perinatal complications including hypoglycemia, hyperbilirubinemia, birth trauma, and congenital malformations.

Infants of diabetic mothers are generally heavier and longer than other infants at the same gestational age, but head circumference is usually normal. IDMs can be small for gestational age if placental insufficiency is present.

All pregnant women should be screened for gestational diabetes weeks 24 and 28 weeks of pregnancy.

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◆ CASE 19

A mother is concerned that the skin on her 4-day-old son's face and chest is turning yellow. The infant is the product of a full-term uncomplicated vaginal delivery. He is of Japanese origin and the family history is unremarkable. With the exception of a large cephalohematoma, the infant's physical examination is normal. He is breast-feeding well and shows no signs of illness.

◆ What is the most likely diagnosis?

◆ What is the next step in evaluating this patient?

ANSWERS TO CASE 19: Neonatal Hyperbilirubinemia (Icterus Neonatorum)

Summary: A 4-day-old breast-feeding male infant of Japanese descent with a cephalhematoma is jaundiced but shows no signs of illness.

◆ **Most likely diagnosis:** Neonatal hyperbilirubinemia.

◆ **Next step:** Total serum bilirubin level.

Analysis

Objectives

1. Understand the etiology of physiologic neonatal jaundice.
2. Identify the causes of pathologic jaundice in a newborn.
3. Know the treatment for neonatal jaundice.

Considerations

Neonatal hyperbilirubinemia results from higher rates of bilirubin production and a limited ability to excrete it. It includes physiologic jaundice and nonphysiologic jaundice. **This infant has several risk factors for neonatal physiologic jaundice: male gender, cephalohematoma, Japanese origin, and breast-feeding.** Other risk factors to consider include maternal diabetes, prematurity, polycythemia, trisomy 21, cutaneous bruising, delayed bowel movement, and a sibling who had physiologic jaundice. Nonphysiologic jaundice is diagnosed when excessive amounts of unconjugated bilirubin accumulate as a result of a variety of pathologic conditions in which red blood cells are:

- Lysed at too rapid a rate
- Interruption occurs during the transmission of unconjugated bilirubin to the liver
- Enzymatic deficiencies in the liver preclude appropriate metabolism of the unconjugated material

Jaundice may be present at birth or may appear at any time during the neonatal period. **Untreated severe unconjugated (indirect) hyperbilirubinemia is potentially neurotoxic (kernicterus).** Conjugated (direct) hyperbilirubinemia, although not neurotoxic, often signifies a serious underlying illness (Table 19-1).

APPROACH TO NEONATAL JAUNDICE

Definitions

Conjugated bilirubin: Also known as “direct” bilirubin, includes bilirubin that has been chemically attached to a glucuronide by an enzymatic process in the liver.

Erythroblastosis fetalis: Increased rate of red blood cell (RBC) destruction secondary to transplacental passage of maternal antibody active against the infant’s RBC antigens.

Table 19-1

DIFFERENTIAL DIAGNOSIS OF NEONATAL JAUNDICE

Hemolytic disease (isoimmune)—ABO, Rh, or minor group incompatibility
Structural or metabolic red cell abnormalities
Hereditary spherocytosis
Glucose-6-phosphate dehydrogenase deficiency
Hereditary defects in bilirubin conjugation
Crigler-Najjar syndrome
Gilbert disease
Bacterial sepsis
Breast-milk jaundice
Physiologic jaundice
Congenital biliary atresia
Extrahepatic biliary obstruction
Neonatal hepatitis—bacterial, viral, nonspecific
Inspissated bile syndrome
Postasphyxia
Neonatal hemosiderosis

Source: Reproduced with permission from Cashore WJ. Neonatal hyperbilirubinemia. In: McMillan JA, DeAngelis CD, Fegin RD, Warshaw JB, eds. *Oski's Pediatrics: Principles and practice*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999:200, Table 26-1.

Hemolysis: Rapid breakdown of red blood cells. Clinical and laboratory findings include a rapid rise of serum bilirubin (>0.5 mg/dL/h), anemia, pallor, reticulocytosis, and hepatosplenomegaly.

Kernicterus: A neurologic syndrome resulting from the deposition of unconjugated bilirubin in brain cells, especially the basal ganglia, globus pallidus, putamen, and caudate nuclei. The less-mature or sick infant has greater susceptibility to kernicterus. Lethargy, poor feeding, and loss of Moro reflex are common initial signs.

Polycythemia: A central hematocrit of 65% or higher; can lead to hyperviscosity of the blood.

Unconjugated bilirubin: Also known as “indirect” bilirubin, includes bilirubin that has yet to be enzymatically attached to a glucuronide in the liver.

Clinical Approach

Physiologic jaundice is comprised of primarily unconjugated hyperbilirubinemia observed during the first week of life in approximately 60% of full-term infants and 80% of preterm infants. The diagnosis of physiologic jaundice is established by precluding known causes of jaundice on the basis of history as well as on clinical and laboratory findings. Newborn infants have a limited ability to conjugate bilirubin and cannot readily excrete unconjugated bilirubin. Jaundice results from accumulation in the skin of unconjugated bilirubin pigment; it usually begins on the face and then progresses to the chest, abdomen and feet. **The average full-term newborn infant has a peak serum bilirubin concentration of 5 to 6 mg/dL between the second and fourth days of life.**

Findings suggestive of nonphysiologic jaundice include (1) it appears in the first 24 to 36 hours of life; (2) serum bilirubin is rising at a rate greater than 5 mg/dL/24 h; (3) serum bilirubin is greater than 12 mg/dL in a full-term infant without other risk factors for physiologic jaundice listed above; and (4) jaundice persists after 10 to 14 days of life. Nonphysiologic etiologies are common when there is a family history of hemolytic disease, or concomitant pallor, hepatomegaly,

splenomegaly, failure of phototherapy to lower bilirubin, vomiting, lethargy, poor feeding, excessive weight loss, apnea, or bradycardia. Causes of **nonphysiologic jaundice** are numerous and include **septicemia, congenital atresia of the bile ducts, hepatitis, galactosemia, hypothyroidism, cystic fibrosis, congenital hemolytic anemia (e.g., spherocytosis, maternal Rh or blood type sensitization), or hemolytic anemia caused by drugs.**

Jaundice that presents within the first 24 hours of life requires immediate attention; it may be caused by erythroblastosis fetalis, hemorrhage, sepsis, cytomegalic inclusion disease, rubella, or congenital toxoplasmosis. The primary concern of unconjugated hyperbilirubinemia is the potential for neurotoxic effects (kernicterus). The signs and symptoms of kernicterus may be subtle and similar to those of sepsis, asphyxia, hypoglycemia, and intracranial hemorrhage. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill, with diminished tendon reflexes and respiratory distress.

An estimated 2% of breast-fed full-term infants develop significant elevations in unconjugated bilirubin (breast-milk jaundice) after the seventh day of life, reaching maximum concentrations as high as 10 to 30 mg/dL during the second to third week. If breast-feeding is continued, the serum bilirubin gradually decreases. Cessation of breast-feeding for 12 to 24 hours and substitution of formula for breast milk results in a rapid decline in serum bilirubin, after which breast-feeding can be resumed without a return of the hyperbilirubinemia.

Low-risk jaundiced infants who are full-term and asymptomatic may be evaluated by monitoring serum total bilirubin levels. Regardless of the gestational age or time of appearance of jaundice, significant hyperbilirubinemia requires a complete diagnostic evaluation, including a determination of indirect and direct bilirubin fractions, hemoglobin, reticulocyte count, blood type, Coombs test, and an examination of the peripheral blood smear. Estimates of serum bilirubin concentrations that are based solely on clinical examination are not reliable. Noninvasive techniques for transcutaneous measurement using multiwavelength spectral reflectance are quite reliable. These devices help to reduce the need to draw blood and improve follow-up for infants at home.

Phototherapy is often used in the **treatment of unconjugated hyperbilirubinemia** in infants. An infant undergoing phototherapy is

placed unclothed under a bank of lights (eight fluorescent bulbs), the eyes are shielded, and hydration is maintained. The light changes the isomerization of the bilirubin in the skin so that it may be excreted. The time at which phototherapy is initiated varies according to the infant's gestational age and the cause of the jaundice. For full-term infants with no evidence of hemolysis, the American Academy of Pediatrics recommends initiating phototherapy at the following bilirubin levels: 15 mg/dL at an age of 25 to 48 hours; 18 mg/dL at 49 to 72 hours; and 20 mg/dL at 72 hours or more. Phototherapy may be discontinued after the serum bilirubin concentration is reduced by 4 to 5 mg/dL.

Exchange transfusion is required in a small percentage of infants with hyperbilirubinemia that fails to respond to more conservative measures. This technique rapidly eliminates bilirubin from the circulation. Small aliquots of the infant's blood are removed via a catheter in a peripheral artery or an umbilical vessel and replaced with similar aliquots of donor red cells mixed with plasma. The risks related to this procedure include air embolus, volume imbalance, arrhythmias, acidosis, respiratory distress, electrolyte imbalance, anemia or polycythemia, fluctuation in blood pressure, infection, and necrotizing enterocolitis.

Comprehension Questions

- [19.1] Which of the following factors decreases the risk of neurologic damage in a jaundiced newborn?
- A. Hypoalbuminemia
 - B. Displacement of bilirubin from binding sites by such drugs as sulfasoxazole
 - C. Acidosis
 - D. Sepsis
 - E. Maternal ingestion of phenobarbital during pregnancy
- [19.2] Gilbert syndrome is caused by:
- A. Increased production of bilirubin
 - B. Impaired conjugation of bilirubin
 - C. Deficient hepatic uptake of bilirubin

- D. Severe deficiency of uridine diphosphate glucuronosyl-transferase
- E. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

[19.3] An infant with Crigler-Najjar syndrome type I has developed bilirubin encephalopathy at 1 month of life. The hyperbilirubinemia is caused by:

- A. Increased production of bilirubin
- B. Impaired conjugation of bilirubin
- C. Deficient hepatic uptake of bilirubin
- D. Severe deficiency of uridine diphosphate glucuronosyl-transferase
- E. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

[19.4] A 30-hour-old full-term infant has jaundice of the face and chest. He is breast-feeding well and has a normal physical examination except for the jaundice. His serum bilirubin level is 15.5 mg/dL. The best course of action is to:

- A. Recommend discontinuation of breastfeeding for 48 hours and supplement with formula
- B. Start phototherapy
- C. Wait 6 hours and retest the serum bilirubin level
- D. Start an exchange transfusion
- E. No action is needed

Answers

- [19.1] E. Administration of phenobarbital induces glucuronyl transferase in newborn infants, thus reducing rather than exacerbating neonatal jaundice.
- [19.2] C. Gilbert disease is associated with an abnormality of bilirubin transport in the hepatocyte.
- [19.3] D. Although all newborn infants are relatively deficient in the enzyme, uridine diphosphate glucuronosyl transferase; those

with Crigler-Najjar syndrome type I have a severe deficiency, leading to high bilirubin levels and encephalopathy; the mainstay of therapy is phototherapy, although research for other treatment options is ongoing. Encephalopathy is rare in infants with Crigler-Najjar syndrome type II, in which serum bilirubin levels rarely exceed 20 mg/dL.

- [19.4] **B.** Although the etiology of the hyperbilirubinemia must be investigated, phototherapy should be started.

CLINICAL PEARLS



Physiologic jaundice, which is observed during the first week of life in approximately 60% of full-term infants and 80% of preterm infants, results from higher rates of bilirubin production and a limited ability to excrete it. The diagnosis of physiologic jaundice is established only by precluding known causes of jaundice on the basis of the history as well as with clinical and laboratory findings.



Causes of nonphysiologic jaundice include septicemia, congenital atresia of the bile ducts, hepatitis, galactosemia, hypothyroidism, cystic fibrosis, congenital hemolytic anemia (spherocytosis), or hemolytic anemia due to drugs, or antibodies directed at the fetal red blood cell.



High levels of unconjugated bilirubin may lead to kernicterus, an irreversible neurologic syndrome resulting from the deposition of bilirubin in brain cells, especially the basal ganglia, globus pallidus, putamen, and caudate nuclei. The less-mature or sick infant has greater susceptibility to kernicterus. The signs and symptoms of kernicterus may be subtle and similar to those of sepsis, asphyxia, hypoglycemia, and intracranial hemorrhage.

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◆ CASE 20

A 10-year-old boy in obvious respiratory distress arrives late in the evening to the emergency department (ED). His mother says that he awoke approximately 2 hours earlier breathing rapidly and complaining that his chest hurt. She gave him two nebulizer treatments but his symptoms did not improve. She also tells you that this is the fourth time in 3 months that he has required emergency department visits for similar symptoms. Your initial examination reveals an afebrile male with a respiratory rate of 60 breaths per minute and a heart rate of 120 beats per minute (bpm). You note that his pulse varies in amplitude with respiration. His blood pressure is within normal limits for his age, but his capillary refill is somewhat sluggish at 1 to 2 seconds. He is pale and appears drowsy. He has mild perioral cyanosis and he is using accessory chest muscles to breathe. You hear only faint wheezing on chest auscultation.

- ◆ What are the initial steps in evaluating this patient?
- ◆ What is the most likely diagnosis?
- ◆ What is the next step in evaluation?

ANSWERS TO CASE 20: Asthmatic Exacerbation

Summary: A 10-year-old boy with a recent history of multiple episodes of respiratory difficulty presents to you with tachypnea, perioral cyanosis, likely pulsus paradoxus, use of accessory muscles of breathing, slight wheezing, delayed capillary refill, and drowsiness.

- ◆ **Next step: Treating this patient's respiratory distress is of immediate concern.** The patient's airway is evaluated first, followed by evaluation of his breathing, and finally assessment of his circulatory status (the "ABCs"). Initial management includes the administration of a β agonist such as albuterol via nebulizer, oxygen, and a dose of systemic prednisone to combat likely airway inflammation. Intravenous access for the administration of fluids and medications is indicated for a patient with this degree of distress. A stat blood gas determination and monitoring of his oxygen saturation levels aids in further managing this patient.
- ◆ **Most likely diagnosis:** Asthma exacerbation.
- ◆ **Next step in evaluation:** After initial stabilization, further history is obtained to include past medical history, family history, medications, and a review of systems. What triggers these episodes, how often do they occur, and how severe have the episodes been in the past? Has the patient ever been hospitalized for asthma, and has he ever required care in an intensive care unit or endotracheal intubation? Your physical examination, the patient's blood gas report, and your assessment of his response to your initial treatments will determine subsequent management.

Analysis

Objectives

1. Know the acute management of asthma exacerbation.
2. Know how to classify the severity of an asthma exacerbation.

3. Know the approach to long-term management of asthma and prevention of exacerbations.

Considerations

This child's recent history of repeated episodes of ED visits for respiratory difficulty and his presenting symptoms point to asthma as the most likely diagnosis; less likely conditions include cystic fibrosis, foreign body aspiration, and congestive heart failure can also present similarly. The history from the child's mother helps to rule out these other conditions. According to the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) guidelines for asthma, this child's exacerbation is severe and requires immediate, intensive treatment. **His drowsiness is particularly concerning, as it indicates possible impending respiratory failure.** His respiratory and circulatory status must be frequently assessed during his stay in the emergency department. The **paucity of wheezes** in this child is explained by the **severe airway obstruction and reduced air movement.** **As his asthma improves and the airways begin to open, the wheezing is likely to become more pronounced.**

APPROACH TO ASTHMA EXACERBATION

Definitions

Asthma: The diagnosis of asthma is established when it is determined that (1) episodic symptoms of airflow obstruction are present; (2) airflow obstruction is at least partially reversible; and (3) alternative diagnoses are excluded.

Asthma exacerbation: Characterized by the triad of bronchoconstriction, airway inflammation, and mucus plugging.

Pulsus paradoxus: A pulse pressure that varies more widely with respiration than normal. A variance of greater than 10 mmHg between inspiration and expiration suggests obstructive airway disease, pericardial tamponade, or constrictive pericarditis.

Spirometry: A test of pulmonary function. For patients with asthma, this test demonstrates reversibility and can be used to determine an individual's response to treatment.

Clinical Approach

The prevalence of asthma has been steadily rising in Western countries since the 1970s, perhaps secondary to increased urbanization, increased pollution, and better diagnostic techniques. Some have even suggested that children raised in “too clean” of an environment are at increased risk for developing asthma. The disease currently accounts for approximately 3 million pediatrician visits per year in the United States, and is the reason most often cited for school absenteeism. **Asthma is the most frequent reason for admission of children to many urban hospitals.** Although rare, deaths secondary to asthma have been rising in recent years. **Risk factors for increased morbidity and mortality relate primarily to urbanization and poverty.**

The median age of onset of asthma is 4 years, but 20% of children develop symptoms within the first year of life. Atopy and a history of asthma in the immediate family are strong risk factors for developing the disease. Respiratory infections early in life are associated with later development of asthma; **between 40% and 50% of children with respiratory syncytial virus (RSV) bronchiolitis later develop chronic asthma.** More than half of children with asthma will have resolution of symptoms by the time they reach young adulthood, but many will continue to have abnormal tests of pulmonary function and some will become symptomatic again later in adulthood. Heavy exposure to pollution, allergens, or cigarette smoke makes resolution less likely.

Airway inflammation in asthma is a result of mast cell activation. In atopic individuals, immunoglobulin (Ig) E antibodies are released in response to environmental triggers such as dust mites, plant pollens, foods, or animal dander. An immediate response occurs within 15 to 30 minutes and includes vasodilation, increased vascular permeability, smooth-muscle constriction, and mucus secretion. Two to four hours after allergen exposure, a late-phase reaction (LPR) begins. **The LPR is characterized by infiltration of inflammatory cells into the airway parenchyma, and is responsible for the chronic inflammation seen in asthma.** Airway hyperresponsiveness may persist for days to weeks after the LPR.

Bronchoconstriction is typically precipitated by a variety of stimuli in a given individual. **Common triggers include cigarette smoke,**

Table 20-1
SEVERITY OF ASTHMATIC EXACERBATION
BY SYMPTOMS

Clinical Features Before Treatment*

	SYMPTOMS [†]	NIGHTTIME SYMPTOMS	LUNG FUNCTION
STEP 4 Severe Persistent	<ul style="list-style-type: none"> • Continual symptoms • Limited physical activity • Frequent exacerbations 	Frequent	<ul style="list-style-type: none"> • FEV₁ or PEF $\leq 60\%$ predicted • PEF variability $> 30\%$
STEP 3 Moderate Persistent	<ul style="list-style-type: none"> • Daily symptoms • Daily use of inhaled short-acting β_2-agonist • Exacerbations affect activity • Exacerbations ≥ 2 times a week; may last day 	> 1 time a week	<ul style="list-style-type: none"> • FEV₁ or PEF $> 60\%$–$< 80\%$ predicted • PEF variability $> 30\%$
STEP 2 Mild Persistent	<ul style="list-style-type: none"> • Symptoms > 2 times a week but < 1 time a day • Exacerbations may affect activity 	> 2 times a month	<ul style="list-style-type: none"> • FEV₁ or PEF $\geq 80\%$ predicted • PEF variability 20%–30%
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> • Symptoms ≤ 2 times a week • Asymptomatic and normal PEF between exacerbations • Exacerbations brief (from a few hours to a few days); intensity may vary 	≤ 2 times a month	<ul style="list-style-type: none"> • FEV₁ or PEF $\geq 80\%$ predicted • PEF variability $< 20\%$

*The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable.

[†]Patient at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

Abbreviations: FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

NAEPP Expert Panel Report: Guidelines for the diagnosis and management of asthma—update on related topics 2002. Website: www.nhlbi.nih.gov.

Table 20-2
SUGGESTED MANAGEMENT OF ASTHMA

STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE*			
	LONG-TERM CONTROL	QUICK RELIEF	EDUCATION
STEP 4 Severe Persistent	<p>Daily medications:</p> <ul style="list-style-type: none"> • Antiinflammatory: inhaled corticosteroid (high dose) • Long-acting bronchodilator: either long-acting inhaled β_2-agonist, sustained-release theophylline, or long-acting β_2-agonist tablets AND, if needed • Corticosteroid tablets or syrup long term (2 mg/kg/d, generally do not exceed 60 mg/d) 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled β_2-agonist as needed for symptoms • Intensity of treatment will depend on severity of exacerbation • Use of short-acting inhaled β_2-agonists on a daily basis, or increasing use, indicated the need for additional long-term-control therapy 	<p>Steps 2 and 3 action plus:</p> <ul style="list-style-type: none"> • Refer to individual education/counseling
STEP 3 Moderate Persistent	<p>Daily medication:</p> <ul style="list-style-type: none"> • Either Antiinflammatory: inhaled corticosteroid (medium dose) OR Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for night- 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled β_2-agonists as need for symptoms • Intensity of treatment will depend on severity of exacerbation • Use of short-acting inhaled β_2-agonists on a daily basis, or 	<p>Step 1 action plus:</p> <ul style="list-style-type: none"> • Teach self-monitoring • Refer to group education if available <p>Review and update self-management plan</p>

STEP 2 Mild Persistent	<p>time symptoms: either long-acting inhaled β_2-agonist, sustained release theophylline, or long-acting β_2-agonist tablets.</p> <ul style="list-style-type: none"> • If needed <p>Antiinflammatory: inhaled corticosteroids (medium-high dose)</p> <p>AND</p> <p>Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled β_2-agonist, sustained-release theophylline, or long-acting β_2-agonist tablets.</p>		<p>increasing use, indicated the need for additional long-term-control therapy</p>
	<p>One daily medication:</p> <ul style="list-style-type: none"> • Antiinflammatory: either inhaled corticosteroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil) • Sustained-release theophylline to serum concentration of 5–15 $\mu\text{g/mL}$ is an alternative, but not preferred, therapy; zafirlukast or zileuton may 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled β_2-agonists as needed for symptoms • Intensity of treatment will depend on severity of exacerbation; see component 3: Managing Exacerbations • Use of short-acting inhaled β_2-agonists on a daily basis, or increasing use, indicated the need 	

Table 20-2
SUGGESTED MANAGEMENT OF ASTHMA (*Continued*)

	LONG-TERM CONTROL	QUICK RELIEF	EDUCATION
	also be considered for patients ≥ 12 years of age, although their position in therapy is not fully established	for additional long-term-control therapy	
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> No daily medication needed 	<ul style="list-style-type: none"> Short-acting bronchodilator: inhaled β_2-agonists as needed for symptoms Intensity of treatment will depend on severity of exacerbation Use of short-acting inhaled β_2 agonists more than 2 times a week may indicate the need to initiate long-term control therapy 	<ul style="list-style-type: none"> Teach basic facts about asthma Teach inhaler/spacer/holding chamber technique Discuss roles of medications Develop self-management plan Develop action plan for when and how to take rescue actions especially for patients with a history of severe exacerbations Discuss appropriate environmental control measures to avoid exposure

		to known allergens and irritants
<ul style="list-style-type: none"> • Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible 	<ul style="list-style-type: none"> • Step up If control is not maintained, consider step up. First, review patient medication technique or other factors that contribute to asthma severity 	

* Preferred treatments are in bold print.

- **The stepwise approach presents general guidelines to assist clinical decision-making; it is not intended to be a specific prescription. Asthma is highly variable; clinicians should tailor specific medication plants to the needs and circumstances of individual patients.**
- Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition or starting at a higher level of therapy (e.g., a course of systemic corticosteroids or higher or dose of inhaled corticosteroids).
- A rescue course of systemic corticosteroids may be needed at any time and at any step.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may be especially common with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- At each step, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diagnosis and education.
- Referral to an asthma specialist for consultation or co-management is *recommended* if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be *considered* if the patient requires step 3 care.

Source: NAEPP Expert Panel Report. Guidelines for the diagnosis and management of asthma -- update on related topics 2002. Website: www.nhlbi.nih.gov.

odors, pollution, sulfite preservatives, weather changes, emotions, and upper respiratory infections. Certain drugs, such as β -adrenergic antagonists, aspirin, and some other nonsteroidal antiinflammatory agents, also cause obstruction. **Exercise** can cause bronchoconstriction, particularly when performed in a **cold environment**.

Management of asthma involves identifying and minimizing exposure to environmental triggers. In some situations allergy testing can be helpful. Pharmacotherapy for the child's asthma symptoms should follow NHLBI guidelines and is based on the frequency and severity of symptoms (Table 20–1). In children old enough to cooperate, **spirometry is used to measure the child's response to therapy**. A description of symptoms may not be a reliable indicator of severity in an individual with chronic asthma; therefore, older children should be taught home use of a **peak expiratory flow meter to provide an objective assessment of lung function**. Adequate long-term management of asthma depends on repeat objective assessment of lung function and reinforcement of the goals of therapy with the patient and family.

Pharmacotherapy for asthma includes **β -adrenergic agonists, anticholinergics, antiinflammatory agents, and leukotriene modifiers**. The NHLBI guidelines provide a stepwise approach to administration of these medications (Table 20–2). **Methylxanthines** (theophylline, theobromine, and caffeine), previously a mainstay of asthma therapy in the United States, have fallen out of favor because of their **toxicity** and the availability of other more target-specific alternatives.

β -Adrenergic agonists cause rapid reversal of bronchoconstriction via β_2 receptors on bronchial smooth muscle cells but do not significantly inhibit the LPR. Because of its **selectivity for the β_2 receptor**, albuterol is the β -adrenergic agonist of choice for quick relief therapy. It may also be used immediately prior to exercise or exposure to allergens in an effort to minimize the acute asthmatic response. Metaproterenol and terbutaline are β -adrenergic agonists with selectivity and duration similar to albuterol, but are generally reserved for use in hospital settings. Epinephrine also is effective, but is less selective than albuterol, metaproterenol, and terbutaline, and it has a shorter duration of action. **Use of epinephrine is generally limited to subcutaneous administration for infants who are initially unable to cooperate with nebulization.** Salmeterol is β_2 -selective, has duration of action of 12 to 18 hours, and is a good drug for use as a prophylac-

tic agent in moderate and severe asthma; it is not used as a rescue medication for acute symptoms.

Toxicity of β -adrenergic agonists includes tachycardia and muscle tremor. Increased levels of drug are delivered to the lungs and toxicity is decreased when these medications are delivered via inhalation routes (nebulizer or inhaler) as compared to the oral route. When inhalers are used, a reservoir device ("spacer") should be used to increase the quantity of drug delivered to the lungs. Adolescents must be cautioned about overreliance on short-acting inhalers, as this is associated with death in severe asthma attacks.

Anticholinergics may be useful in the **acute management of asthma exacerbation, but are of little value in chronic therapy.** These agents cause bronchodilatation through inhibition of the vagal reflex at smooth muscle. Currently available drugs in this category include atropine, ipratropium, and glycopyrrolate. Side effects include mydriasis, abdominal pain, and tachycardia.

Cromolyn and nedocromil, antiinflammatory drugs that act by limiting or preventing the immune response to allergen exposure, become effective after 2 to 4 weeks of chronic therapy, but are **successful in only 75% of patients.** Except for a rare allergic reaction, these drugs are nontoxic. The **most potent available antiinflammatory drugs available for asthma are the corticosteroids,** which are **useful both for acute exacerbations and for chronic therapy.** Prednisone and prednisolone are used for acute situations, and the inhaled corticosteroids are administered for long-term therapy. Chronic oral therapy and high-dose inhaled steroids have been associated with growth retardation and decreased serum cortisol concentrations. **Hypokalemia** may occur with high-dose steroid administration in the acute setting.

Comprehension Questions

- [20.1] A 12-year-old girl with a history of asthma presents to the emergency department with tachypnea, intracostal retractions, and perioral cyanosis. Minimal wheezing is auscultated. You immediately begin administration of oxygen, nebulized albuterol, and 2 mg/kg of intravenous prednisone. Upon reassessment, wheezing increases in all fields, but the child appears slightly more

alert and her color has improved. Which of the following is the appropriate explanation for these findings?

- A. The girl is not having an asthma attack.
- B. The girl is not responding to the albuterol, and her symptoms are worsening.
- C. The girl is responding to the albuterol, and her symptoms are improving.
- D. She did not receive enough albuterol.
- E. The albuterol was inadvertently left out of the nebulizer treatment, and the patient received only saline.

[20.2] A 2-year-old girl presents to the office with the complaint of acute onset of wheezing. Her mother reports that she has never wheezed before, and states that their family history is negative for asthma and atopy. The mother says that she left the child playing in her older brother's room and approximately 20 minutes later was alerted by the sound of the child coughing and wheezing. The girl has been healthy recently except for a slight runny nose. The best next step includes:

- A. Determining what the girl was playing with and ordering a chest radiograph
- B. Referring the child to a pulmonologist
- C. Prescribing antibiotics for a likely pneumonia
- D. Administering an injection of intramuscular prednisone and sending her home
- E. Accusing the mother of poor supervision of her child's health, as this is obviously not the first time that the child has had these symptoms

[20.3] A 4-month old boy presents to the emergency department on a cold winter night with the complaint of worsening wheezing. He has been receiving nebulized albuterol treatments at home since the age of 2 months for wheezing episodes. The father has given the baby 2 treatments at home prior to arrival in your center, but the baby's respiratory difficulty has not significantly improved. The father notes that the baby always sounds "congested." On

your primary survey of the child, you note pallor and perioral cyanosis, a respiratory rate of 60 breaths per minute, and loud wheezes throughout the chest that obscure the heart sounds. The examination is otherwise unremarkable. The most likely diagnosis is:

- A. Bronchiolitis
- B. Congenital anomaly
- C. Cystic fibrosis
- D. Gastroesophageal reflux
- E. Tracheoesophageal fistula

[20.4] A 15-year-old boy uses his albuterol inhaler shortly after mowing the lawn because of a mild feeling of "tightness" in his chest. He is required to return home early from dinner at a friend's house when about 3 hours later he has the sudden onset of wheezing, persistent cough, and chest pain. The most likely explanation for these circumstances is:

- A. He likely aspirated a piece of grass.
- B. His albuterol inhaler must be empty.
- C. His albuterol inhaler must be outdated.
- D. He is having a "late-phase reaction."
- E. He has been exposed to a new allergen that is more irritating to his immune system than grass.

Answers

[20.1] C. This child presented in severe respiratory distress. Her improved color and level of alertness indicate that her asthma attack is reversible. Increased wheezing is auscultated after the initial nebulizer treatment because areas of lung that were "shut down," that is, obstructed, are now opening allowing additional airflow in those areas. Additional airflow in these areas is now able to produce wheezing. Prior to initiation of treatment wheezing was impossible because an inadequate quantity of air moved through these obstructed airways. Unfortunately,

less-experienced examiners may misinterpret lack of air movement as "clear" breath sounds, further delaying appropriate medical management.

- [20.2] A. The most likely diagnosis in this case is foreign-body aspiration. Young children, generally between the ages of 4 months and 3 years, are particularly prone to putting objects into their mouths. Oral exploration is a normal part of development, but can be a significant cause of morbidity. A pulmonologist may ultimately be needed to retrieve the object, but this would not be a first step.
- [20.3] A. While bronchiolitis is the most frequent diagnosis in a wheezing infant in the winter months, all of the choices are possibilities in this case. Because respiratory infections are so common and many chronic conditions present for the first time in infancy, the differential diagnosis for wheezing is more extensive in a baby than in an older child. Initial treatment in this baby is oxygen, nebulized albuterol or epinephrine, and a STAT chest radiograph. Infants with wheezing caused by bronchiolitis do not always respond as well to β agonists as do older children so failure to respond will not rule out this possibility. Chest radiographs may assist in identification of a congenital anomaly such as congenital heart disease, a vascular ring, or a tracheoesophageal fistula, although often the films may appear deceptively normal in these conditions. A careful history may provide important clues concerning the possibilities of cystic fibrosis and gastroesophageal reflux.
- [20.4] D. A late-phase reaction occurs hours after an initial wheezing episode caused by inflammatory cell accumulation in the airway.

CLINICAL PEARLS

The prevalence of asthma in Western countries has been steadily increasing since the 1970s, making this now the most frequent admission diagnosis for children in many urban hospitals.

Atopy and a family history of asthma are risk factors for development of asthma, and exposure to pollutants including cigarette smoke make resolution less likely.

The LPR begins 2 to 4 hours after allergen exposure, and is responsible for the chronic inflammation seen in asthma.

Acute and long-term management of asthma should follow the guidelines published by the National Heart, Lung and Blood Institute.

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◆ CASE 21

The parents of a healthy 8-year-old child are concerned that he is the shortest child in his class. His height and weight growth curves are shown (see Figure 21-1). A thorough history reveals that he was a full-term infant, has had no significant medical problems, and he is *developmentally appropriate*. Other than being small for his age, no abnormalities are noted on physical examination. Careful measurements of his upper and lower body segments demonstrate normal body proportions for his age. His father is 6 feet, 4 inches tall and began his pubertal development at 13 years of age; his mother is 5 feet, 11 inches tall and had her first menstrual cycle at 14 years of age.

- ◆ What is the most likely diagnosis?
- ◆ What is the best diagnostic test?
- ◆ What is the best therapy?

ANSWERS TO CASE 21: Growth Hormone Deficiency

Summary: An 8-year-old child with no significant past medical history and a normal physical examination presents with failure to grow.

- ◆ **Most likely diagnosis:** Growth hormone deficiency.
- ◆ **Best diagnostic test:** Screening tests might include a complete blood count (CBC) and erythrocyte sedimentation rate (ESR), electrolytes and general health chemistry panel, urinalysis, serum thyroid function studies, serum insulin-like growth factor 1 (IGF1), and binding protein 3 (IGF-BF3), bone age radiograph, and if this were a girl, possibly chromosomal karyotype.
- ◆ **Best therapy:** Replace growth hormone via injection.

Analysis**Objectives**

1. Understand the common causes of growth delay in children
2. Appreciate the evaluation strategies for the various forms of growth failure
3. Learn treatment options for common causes of childhood growth delay.

Considerations

This patient is growing at a rate less than expected. He has no medical problems by history or on physical examination. His parents are tall and, importantly, their pubertal development were not delayed. An evaluation to determine the reason for his growth failure is appropriate.

APPROACH TO GROWTH HORMONE DEFICIENCY

Definitions

Bone age: The bone development of a child occurs in a predictable sequence. Radiographs of the left wrist on children older than 2 years of age (or the knee in those younger) can be compared to “normals” to determine how old the bones appear as compared to chronologic age, thus providing an estimate of the bones’ remaining growth potential.

Constitutional growth delay: A condition in which an otherwise healthy child’s growth is slower than expected, but for whom one or more parents demonstrated a delay in pubertal development but later demonstrated normal adult height. In these children the “bone age” equals the “height age.”

Familial short stature: A condition in which a short child is born to short parents who had normal timing of their pubertal development.

Height age: The age at which a child’s measured height is at the 50% percentile.

Idiopathic short stature: A condition in which a specific diagnosis for a child’s short stature cannot be determined.

Clinical Approach

Many parents become concerned if their child is noticeably shorter than his or her peers. A wide variety of conditions can result in short stature; a thorough history including growth history, social history (to identify psychosocial growth failure), physical examination, and selected screening tests usually help to identify the etiology of the problem.

In the first year of life, children grow at a rate of about 23 to 28 cm per year. This rate drops to about 7.5 to 13 cm per year for children aged 1 to 3 years. Until just before puberty, children grow at a rate of about 4.5 to 7 cm per year. At puberty, growth increases to 8 to 9 cm per year for girls and to about 10 to 11 cm per year for boys. By about 24 months of age, most children settle into a percentile growth channel, remaining there for the remainder of their childhood.

Significant deviations from these expectations alert the clinician to potential growth problems.

Constitutional growth delay is a common cause of short stature. These children have no abnormalities identified in their past medical history and their physical examinations are unremarkable. In contrast to children with growth hormone deficiency, a child with constitutional delay has a **growth rate that is normal**; their family history is positive, however, for one or more parents who had delays in pubertal development ("late bloomers") but ultimately developed normal adult height. A short child in a family with a classic history of "late bloomers" often requires no laboratory or radiographic evaluation. Sometimes a bone age is helpful to reassure the patient and his or her family that while the child appears small, much growth remains in the bones and eventually normal height will be achieved. For some of these children, testosterone injections will hasten the start of pubertal changes (which will eventually begin on their own without treatment); consultation with pediatric endocrinologist can be helpful.

The child born to short parents is often short, a condition called **familial short stature**. A review of the growth curve of such a child shows **his or her growth to parallel a growth line at or just below the 3rd to 5th percentile**. Laboratory and radiographic testing is usually not necessary; a **bone age equals the chronologic age**, indicating no "extra" growth potential. An estimate of a child's ultimate height potential can be calculated using his or her parent's heights. A boy's final height can be predicted as: $(\text{father's height in cm} + [\text{mother's height in cm} + 13])/2$. A girl's final height can be predicted as: $(\text{mother's height in cm} + [\text{father's height in cm} - 13])/2$. Reassurance is indicated for children with familial short stature.

Growth hormone deficiency is estimated to occur in about 1 in 4000 school-aged children. **Children with growth hormone deficiency demonstrate a growth rate that is slow, usually falling away from the normal growth curve (in contrast to constitutional delay where the growth parallels the 3rd to 5th percentile curve)**. On physical examination these children often appear to be younger than their stated ages and are frequently chubby in appearance (weight age is higher than height age). **Bone ages in these children are delayed**, indicating catch-up growth potential with therapy. Screening tests for growth hormone deficiency include serum insulin-like growth factor 1 (IGF-1 or

somatomedin C) and insulin-like growth factor binding protein 3 (IGF-BP3). Confirmation of the diagnosis of growth hormone deficiency often requires growth hormone stimulation testing and interpretation by a pediatric endocrinologist. Growth hormone replacement therapy involves injections with recombinant growth hormone several times a week until the child reaches full adult height.

Clues that growth failure may be caused by an underlying condition not already mentioned include poor appetite, weight loss; abdominal pain or diarrhea; unexplained fevers; headaches or vomiting; weight gain out of proportion to height; or dysmorphic features. Screening tests for challenging cases might include a complete blood count (anemia), erythrocyte sedimentation rate (chronic inflammatory diseases), electrolytes (acidosis or renal abnormalities) and general health chemistry panel (hepatitis, liver dysfunction), urinalysis (infection, renal disease), serum thyroid function studies (hypothyroidism), serum IGF-1 and IGF-BP3 (growth hormone deficiency), and if the patient is a female, possibly chromosomal karyotype (Turner syndrome). Children with failure of growth who do not fall into another, more appropriate category listed above are classified as having idiopathic short stature.

Comprehension Questions

[21.1] An 8-year-old boy is evaluated for short stature. His mother reports that he has begun to gain quite a bit of weight over the last year, that he has little or no energy, he sleeps more than normal, and he complains of being cold all the time. His growth curve demonstrates that he has fallen from the 50th percentile for height to the 5th percentile for height, but his weight has increased to the 90th percentile for height. On physical examination he is obese, has an immature facies, thin hair, and slow reflexes. The most appropriate course of action for this child is to:

- A. Order Epstein-Barr virus titers
- B. Measure thyroid function
- C. Reassure the mother that the child has normal prepubertal development

- D. Determine bone age
- E. Order a somatomedin C level

[21.2] A 16-year-old boy complains that he is the shortest boy in his class. He has a normal past medical history, and although he was always a bit small for age, he has really noticed that he has fallen behind his peers in the last 2 years. He is Tanner stage 3, and is at the 5th percentile for height. His father reports that he began puberty at age 16 and completed his growth in college at age 19; he is now 6 feet, 2 inches tall. His mother began her pubertal development at age 10 and had her first menstrual period at age 13; her height is 5 feet, 4 inches. Of the following, the single most appropriate intervention is:

- A. Measurement of bone age
- B. Measurement of somatomedin C
- C. Liver function studies
- D. Pediatric endocrinology referral
- E. Chromosomal analysis

[21.3] A 17-year-old girl is 4 feet, 10 inches tall while her parents are of normal height. Her past medical history is significant for lifelong short stature and cardiac surgery when she was 1 year old. She has never had a menstrual period. The most appropriate action would be to order:

- A. Serum testosterone levels
- B. Ultrasonogram of the abdomen
- C. Thyroid function studies
- D. Referral to a pediatric endocrinologist
- E. Chromosomal analysis

[21.4] You see a 14-year-old male in the juvenile detention center where he is currently living after he set a fire in an abandoned building. The boy is tall, slim, underweight, and appears to have especially long legs. His testes are very small for his age and his phallus seems somewhat undersized. His mother reports that he

had difficulty with reading, spelling, and mathematics early on, but now seems to be having difficulty in all of his classes. The diagnostic test most likely to identify his problem is:

- A. Serum testosterone levels
- B. Ultrasonogram of the abdomen
- C. Thyroid function studies
- D. Referral to pediatric endocrinology
- E. Chromosomal analysis

Answers

- [21.1] **B.** This child has classic symptoms of acquired hypothyroidism. A bone age would be delayed, but the tests necessary to diagnose his condition are thyroid function studies. Thyroid hormone replacement therapy should resolve these symptoms and growth should resume normally.
- [21.2] **A.** This boy likely has constitutional growth delay, similar to that experienced by his father. Bone age would be delayed, indicating much potential growth. This child will eventually enter puberty, but the psychosocial ramifications of remaining shorter and more immature-appearing than his peers may warrant treatment. Monthly injections of testosterone over several months "jump starts" the pubertal process without altering final growth potential. Ultimately, a pediatric endocrinologist might be required to assist in the dosing should testosterone injections be chosen.
- [21.3] **E.** Chromosomal analysis is likely to demonstrate Turner syndrome in this patient. The heart defect that required surgery might have been a coarctation of the aorta. Common features of Turner syndrome include female phenotype, short stature, sexual infantilism, streak gonads, broad chest, low hairline, webbed neck, congenital lymphedema of the hands and feet, and a variety of other anomalies. Some children with Turner syndrome benefit from growth hormone therapy.

- [21.4] E. Boys with Klinefelter syndrome are tall for their age; the testes are smaller than normal and feel firm and fibrotic. Physical examination often reveals a eunuchoid body habitus and reduced upper-to-lower body segment ratio secondary to a long lower segment. Diagnosis is established by karyotyping.

CLINICAL PEARLS

Constitutional growth delay is a condition in which an otherwise healthy child's growth is slower than expected, and for whom at least one parent demonstrated a delay in pubertal development but later demonstrated normal adult height. These children are "late bloomers." Growth parallels the 3rd or 5th percentile growth curve; bone age is delayed.

Familial short stature is a condition in which a short child is born to short parents who had normal timing of their pubertal development. Growth parallels the 3rd or 5th percentile growth curve; bone age is normal.

Idiopathic short stature includes children with short stature for whom a more appropriate diagnosis cannot be found.

Growth hormone deficiency is a condition in which inadequate secretion of growth hormone results in growth failure, delayed bone age, and catch-up growth upon initiation of replacement hormone therapy.

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◆ CASE 22

A 2800 g infant is born at 36 weeks gestation to a 19-year-old mother via spontaneous vaginal delivery. Delivery was 19 hours after spontaneous rupture of membranes; the pregnancy was uncomplicated according to the mother, but her prenatal records are not available at the time of delivery. At 6 hours of age the infant is noted by the mother to be breathing harder and that he would not latch on to the breast for feedings. The nurses find his respiratory rate to be 60 breaths per minute and that he “grunts” with expiration. They also report to you that his temperature is 96.5°F (35.8°C) and that his blood pressure is lower than normal. You ask them to obtain a complete blood count (CBC) while you drive in from home. Upon arrival you confirm that the infant is in respiratory distress and that his perfusion is poor. The CBC demonstrates a white blood cell (WBC) of 2500 with 80% bands. The child’s radiograph is shown (see Figure 22–1).

◆ What is the most likely diagnosis?

◆ What is the best therapy?

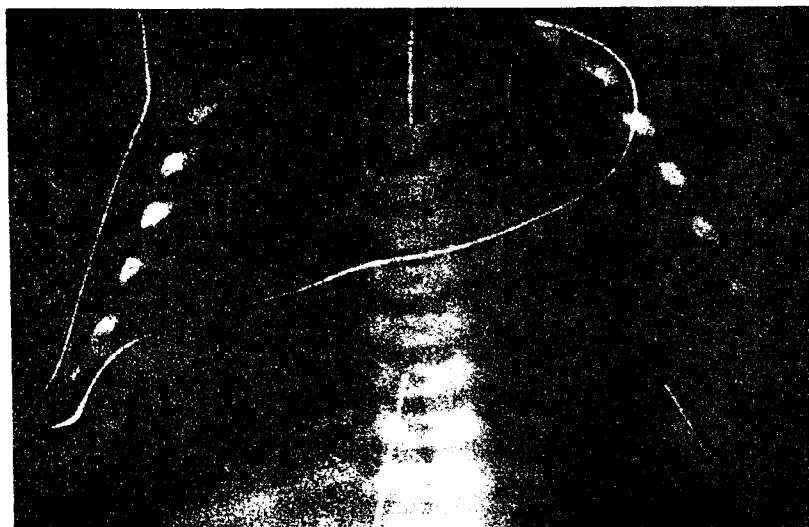


Figure 22–1. Chest radiograph of an infant. From Pretest in Pediatrics, 2003, with permission. (Courtesy of Susan John, MD.)

ANSWERS TO CASE 22: Group B Streptococcal Infection

Summary: A 2800-g infant born by vaginal delivery at 36 weeks gestation is found to have poor feeding, tachypnea, hypothermia, and poor perfusion at 6 hours of age.

- ◆ **Most likely diagnosis:** Group B streptococcal infection.
- ◆ **Best therapy:** Intravenous antibiotics (after addressing ABC's).

Analysis

Objectives

1. Understand the common presentations of sepsis in a neonate.
2. Understand the maternal risk factors for group B streptococcal infection in the infant.

3. Appreciate the variety of organisms responsible for neonatal infections.
4. Learn treatment options for the common infections in the neonate.

Considerations

The rapid onset of the symptoms, the low WBC count with left shift, and the depicted chest x-ray findings are typical of a patient with group B streptococcus pneumonia. At this point in the patient's care, management would include rapid application of the **ABCs** of resuscitation (maintain **A**irway, control **B**reathing, and ensure adequate **C**irculation) followed by rapid institution of appropriate antibiotics after cultures are obtained. Despite these measures, mortality from this infection is not uncommon.

APPROACH TO GROUP B STREPTOCOCCAL INFECTION

Definitions

Early-onset sepsis syndrome: Sepsis in the neonate that occurs in the first 6 days of life. The majority of infection (approximately 85%) occurs in the first 24 hours, 5% by about 48 hours of life, and the remainder occurring throughout the next 4 days of life. The source of infection is usually acquisition of microorganisms from the mother's genitourinary tract.

Group B streptococcal colonization: Group B streptococcal infection is limited to mucous membrane sites in a healthy adult; the gastrointestinal tract is the most common reservoir of colonization.

Late-onset sepsis syndrome: Sepsis in a neonate that occurs usually after about 7 days of life but before about 90 days of life. The source of infection is often from the caregiving environment.

Intrapartum antibiotic prophylaxis: Intravenous penicillin or ampicillin given during labor to prevent group B streptococcal disease in the newborn.

Clinical Approach

Signs and Symptoms of Sepsis

The signs and symptoms of sepsis in the neonate can be subtle and nonspecific, often overlapping with findings in other conditions, such as respiratory distress syndrome (RDS), metabolic disorders, intracranial hemorrhages, and traumatic deliveries. Temperature instability, tachypnea, hypotension, and bradycardia are common findings in sepsis and meningitis. **Overwhelming shock is manifest with findings of pallor and poor capillary refill.** Neurologic findings of impaired level of consciousness, coma, seizures, bulging anterior fontanelle, focal cranial nerve signs, and nuchal rigidity are unusual, but when present hint at meningitis, a condition more commonly seen in late-onset disease. Physical examination findings that tend to be seen more frequently with pneumonia (more commonly seen in early onset disease) include tachypnea, grunting, nasal flaring, retractions (costal or substernal), decreased breath sounds, and cyanosis.

Evaluation of the Potentially Septic Child

Some of the laboratory findings of neonatal sepsis can be nonspecific including hypoglycemia, metabolic acidosis, and jaundice. The complete blood count (CBC) is often used to help guide therapy, although the sensitivity and specificity of this test is low. Evidence of infection on CBC includes:

- Markedly elevated or lowered levels of white blood cell (WBC) count
- Increased neutrophil count
- Increased immature to total neutrophil (I:T) ratios
- Thrombocytopenia with platelet counts less than $100,000/\text{mm}^3$

The C-reactive protein (an acute phase protein that is increased with tissue injury) can be elevated in infants with sepsis; some use it as an adjunct to other tests to assess for neonatal sepsis.

A blood culture is crucial for all patients with suspected sepsis. Controversy exists as to the utility of routine examination of cerebral

spinal fluid (CSF) in all infants with suspected sepsis. Some argue that the low incidence of meningitis, especially in early onset disease, does not warrant routine testing but rather reserving this testing for patients with documented (i.e., positive cultures) or presumed (patients so sick that a full course of antibiotics are to be given regardless of culture results) sepsis. Urine cultures usually are included in the evaluation only of late-onset disease. Chest radiologic findings include segmental, lobar, or diffuse reticulogranular patterns, the later being easily confused with respiratory distress syndrome (lack of surfactant).

Pathogens

The organisms commonly causing early onset sepsis colonize in the mother's genitourinary tract and are acquired transplacentally, from an ascending infection or as the infant passes through the birth canal. **Specific organisms include group B *Streptococcus*, *Escherichia coli*, *Haemophilus influenzae*, and *Listeria monocytogenes*.** Late-onset disease occurs when the infant becomes infected with organisms in the postnatal environment, such as from the skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus. For the hospitalized infant, sources of bacteria include catheters (vascular or urinary) or contact with healthcare workers. Organisms most commonly seen causing late-onset disease in this situation include coagulase-negative staphylococci, *Staphylococcus aureus*, *E. coli*, *Klebsiella species*, *Pseudomonas species*, *Enterobacter species*, *Candida*, group B *Streptococcus*, *Serratia species*, *Acinetobacter species*, and anaerobes.

Group B *Streptococcus* is the most common cause of sepsis in infants from birth to 3 months of age; this organism has received a great deal of attention from researchers and public health policymakers in an attempt to reduce the significant morbidity and mortality associated with it. The **majority of cases** (approximately 80%) occur as early onset disease (septicemia, pneumonia, and meningitis), resulting from **vertical transmission from mother to infant during labor and delivery.** Respiratory signs (apnea, grunting respirations, tachypnea or cyanosis) are the initial clinical findings in more than 80% of neonates, regardless of the site of involvement, while hypotension is an initial finding in approximately 25% of cases. Other signs are similar to those associated with other bacterial infections described above.

Neonates with group B *Streptococcus* meningitis rarely have seizures as a presenting sign, yet 50% develop seizures within the first 24 hours of infection. The median age at diagnosis for early onset group B *Streptococcus* infection is 13 hours, which is earlier than that for the other bacterial infections described above. Clinical history and findings suggestive of early onset group B *Streptococcus* disease (rather than of a noninfectious etiology for pulmonary findings) include prolonged rupture of membranes, apnea, hypotension within the first 24 hours of life, a 1-minute Apgar score of less than 5, and an unusually rapid progression of pulmonary disease.

Factors associated with increased risk for early-onset group B *Streptococcus* disease are rupture of membranes more than 18 hours prior to delivery, chorioamnionitis or intrapartum temperature $>100.4^{\circ}\text{F}$ ($>38^{\circ}\text{C}$), previous infant with group B *Streptococcus* infection, mother younger than 20 years of age, and low birth weight or prematurity (<37 weeks gestation). Mortality as a result of group B *Streptococcus* disease is close to 10%. Major neurologic sequelae, consisting of cortical blindness, spasticity, and global mental retardation, occur in 12% to 30% of infants who survive meningitis.

The incidence of early onset group B *Streptococcus* infection decreased from 1.7 per 1000 live births in 1993 to 0.6 per 1000 live births in 1998. The decline in incidence is largely attributed to the widespread implementation of the Center for Disease Control's 1996 group B *Streptococcus* risk-reduction guidelines. These guidelines recommend screening women at 35 to 37 weeks' gestation and offering intrapartum antibiotic prophylaxis to women with positive risk factors or positive group B *Streptococcus* cultures at 35 to 37 weeks gestation. Infants whose gestational ages are less than 35 weeks or who are born to women who received inadequate intrapartum prophylaxis undergo a limited evaluation often including a complete blood count and blood culture.

Treatment

Treatment for the infant with suspected early onset disease includes antibiotics directed at the common pathogens listed above, often consisting of a combination of intravenous aminoglycosides (gentamicin or tobramycin) and penicillin (often ampicillin). For patients with late-onset disease,

therapy often consists of β -lactamase-resistant antibiotics (such as vancomycin) and second- or third-generation cephalosporins. For early and late-onset disease, antibiotic coverage is adjusted depending on the organism identified and the specific antibiotic sensitivities of the organism.

The duration of antibiotic therapy is at least 48 to 72 hours. If cultures are negative after that period of time and the patient is otherwise well, antibiotics are often stopped. For infants presenting with **convincing signs and symptoms of sepsis, antibiotics may be continued even if the culture results prove to be negative.** For infants with positive cultures, therapy continues for 10 to 21 days depending on the organism and the site of the infection. For all infants close observation for signs of antibiotic toxicity is important.

Comprehension Questions

[22.1] A newborn infant was born at home. At 2 days of life he is noted to have puffy, tense eyelids, red conjunctivae, a copious amount of purulent ocular discharge and chemosis. The most likely diagnosis is:

- A. Dacryocystitis
- B. Chemical conjunctivitis
- C. Pneumococcal ophthalmia
- D. Gonococcal ophthalmia
- E. Chlamydial conjunctivitis

[22.2] A full-term 3500-g female newborn delivered by cesarean section develops a respiratory rate of 70 breaths per minute and expiratory grunting at 1 hour of life. She has good tone, good color, and a strong suck. The most likely diagnosis in this infant is:

- A. Sepsis
- B. Transient tachypnea of the newborn
- C. Respiratory distress syndrome
- D. Meconium aspiration syndrome
- E. Tracheoesophageal fistula

- [22.3] An infant is born at term to a 23-year-old known HIV-positive mother. The mother has been followed closely during the pregnancy, and she has been taking antiretroviral medications for the weeks prior to the delivery of her infant. Routine management of the healthy infant should include:
- A. Admission to the neonatal intensive care unit for close cardiovascular monitoring
 - B. HIV enzyme-linked immunosorbent assay (ELISA) on the infant to determine if congenital infection has occurred
 - C. Beginning a course of zidovudine for the infant
 - D. Chest radiographs to evaluate for congenital *Pneumocystis carinii*
 - E. Administration of intravenous immunoglobulin (IVIG) to the baby to decrease the risk of perinatal HIV infection
- [22.4] A 2150-g infant is delivered at 34 weeks gestation. The mother had prenatal care in Mexico and states that she had no problems during her pregnancy. The mother's highest temperature during labor was 100.8°F (38.2°C). The amniotic fluid had a brown-stained appearance. The infant had a disseminated erythematous pustular rash at birth and had pallor, poor feeding, tachypnea, and cyanosis. The infant's CBC reveals a marked monocytosis. The infant died at 4 hours of life soon after initiation of antibiotics. This infant most likely had:
- A. Disseminated herpes
 - B. Congenital syphilis
 - C. Listeriosis
 - D. Group B streptococcal disease
 - E. Congenital varicella

Answers

- [22.1] **D.** The time of onset of symptoms in a neonate with conjunctivitis is somewhat helpful in the diagnosis of ophthalmia neonatorum. Chemical conjunctivitis is a self-limited condition that presents within 6 to 12 hours of birth; it is a consequence

of irritation secondary to silver nitrate or erythromycin prophylaxis applied to the eyes. Gonococcal conjunctivitis usually has its onset within 2 to 5 days of birth and is the most serious of the bacterial infections; prompt and aggressive topical treatment and systemic antibiotics are indicated to prevent serious complications such as corneal ulceration, perforation and resulting blindness. Parents should be treated for gonococcal disease to avoid the risk to the child of reinfection. Chlamydial conjunctivitis often presents 5 to 14 days after birth and is usually treated with systemic erythromycin (in part, to reduce the risk of the infant's developing chlamydial pneumonia at 2 to 3 months of age). The benefits of using oral erythromycin in infants must be weighed with the increased risk of their developing hypertrophic pyloric stenosis, a condition found to be more common in children having received oral erythromycin. Both parents of a child with chlamydial conjunctivitis must also be treated.

[22.2] **B.** Transient tachypnea of the newborn (TTN) is a respiratory condition that results from incomplete evacuation of fetal lung fluid in full-term infants. It is more common in cesarean deliveries. It usually disappears within 24 to 48 hours of life. Often no treatment is indicated unless the infant requires low amounts of supplemental oxygen.

[22.3] **C.** HIV transmission from mother to infant has decreased by more than 50% over the past 15 years, probably as a result of perinatal administration of antiretroviral medications to the mother and a course of zidovudine to the exposed infant. ELISA is an antibody test that will be positive in the infant because maternal antibodies for her HIV disease are passed through the placenta; it is not a useful test in the newborn infant to determine neonatal infection. IVIG has not been shown to have a role in decreasing perinatal transmission. Healthy infants born to HIV-infected mothers do not need special monitoring nor do they need routine radiographs.

[22.4] **C.** *Listeria* is a gram-positive rod isolated from soil, streams, sewage, certain foods, silage, dust, and slaughterhouses. The

food-borne transmission of disease is related to Mexican (soft ripened) cheese, whole and 2% milk, undercooked chicken and hot dogs, raw vegetables, and shellfish. The newborn infant acquires the organism transplacentally or by aspiration or ingestion at the time of delivery. The mortality rate of early onset disease is approximately 30%.

CLINICAL PEARLS

Sepsis in the neonate can present with nonspecific findings of temperature instability, tachypnea, poor feeding, bradycardia, hypotension, and hypoglycemia.

Early-onset neonatal infection (that occurring in the first 6 days of life) is usually caused by organisms found in the maternal genitourinary system, including group B *Streptococcus*, *Escherichia coli*, *Haemophilus influenzae*, and *Listeria monocytogenes*. Pneumonia and sepsis are common presentations; group B *Streptococcus* is the leading cause.

Late-onset neonatal infection (that occurring between 7 and 90 days of life) is often caused by organisms found in the infant's environment, including coagulase-negative staphylococci, *Staphylococcus aureus*, *E. coli*, *Klebsiella*, *Pseudomonas* species, *Enterobacter* species, *Candida*, group B *Streptococcus*, *Serratia* species, *Acinetobacter* species, and anaerobic bacteria.

Treatment of early-onset neonatal infection usually includes a penicillin and an aminoglycoside, while treatment of late-onset disease is with a β -lactamase-resistant antibiotic (such as vancomycin) and often a third-generation cephalosporin.

The incidence of early-onset group B *Streptococcus* infection decreased from 1.7 per 1000 live births in 1993 to 0.6 per 1000 live births in 1998. The decline in incidence is largely attributed to the widespread implementation of the Center for Disease Control's 1996 group B *Streptococcus* risk-reduction guidelines.

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◆ CASE 23

A 3-month-old boy is brought to the emergency center by ambulance after his parents discovered him not breathing in his crib this morning. Cardiopulmonary resuscitation was begun by the parents and was continued by paramedics en route to the hospital. You continue to try to revive the child, but pronounce the child dead after 20 minutes of resuscitation. You carefully review the history with the family and examine the child, but are unable to detect any apparent cause of death.

- ◆ What is the first step in the management of this situation?
- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the evaluation?

ANSWERS TO CASE 23: Sudden Infant Death Syndrome

Summary: A 3 month-old boy discovered not breathing by his parents.

- ◆ **First step:** Tell the boy's parents that despite everyone's best efforts, their son has died. Ask the parents if they would like you to call a friend, family member, religious leader, or other support person. Provide them with a quiet room where they can be left alone.
- ◆ **Most likely diagnosis:** Sudden infant death syndrome (SIDS).
- ◆ **Next step:** Discuss with the parents that routine protocol is followed after the unexplained death of an infant. A coroner will perform an autopsy and police investigators will examine their home for any clues related to the death. Emphasize that these measures can help to bring closure for the family and may yield important information for preventing future child deaths should the couple have more children.

Analysis

Objectives

1. Know the definition of SIDS.
2. Know the factors that are associated with SIDS.
3. Know how to counsel parents about measures they can take to reduce the risk of SIDS.

Considerations

Sudden infant death syndrome (SIDS) is one of the most tragic and frustrating diagnoses in medicine. It is a diagnosis of exclusion that can be assigned only after the postmortem investigation, postnatal history, and the crime scene investigation fail to yield another explanation.

At the time that the family is in the emergency center, other possible causes of death, such as child abuse or inherited disorders cannot be excluded. Your role as the presiding clinician is to remain objective concerning these other possibilities, yet sympathetic to the parents' grieving. As always, meticulous documentation of the history and physical examination of this child is imperative.

APPROACH TO SIDS

Definitions

Apparent life-threatening event (ALTE): A complex of observations and events that are perceived by the child's caregiver as life-threatening. By definition, the event is observed. A myriad of conditions may be responsible, including cardiac, respiratory, central nervous system, metabolic, infectious, and gastrointestinal causes. In approximately 50% of cases, a cause is never found.

Near-miss SIDS/aborted SIDS: Terms used historically to describe ALTE. They are no longer used because they confuse a syndrome that usually occurs when an infant is alone (SIDS) with an event that is observed (ALTE).

SIDS: The sudden death of an infant that cannot be explained by results of a postmortem examination, death scene investigation and historical information.

Clinical Approach

SIDS is the most common cause of death in infants between the ages of 1 week and 1 year of life. In the United States, about 2500 infants die each year due to SIDS, with an incidence of 0.8 per 1000 live births. The majority of SIDS deaths occur between 1 and 5 months of age, with a peak incidence between 2 and 4 months of age. SIDS deaths rarely have been reported in infants older than 1 year of life. **Most SIDS victims are boys.** More cases are reported in winter, and the vast majority of cases occur when the infant is (or is presumed to be) asleep.

Despite extensive research on the subject, **no cause of SIDS has been identified.** Epidemiologic studies have demonstrated that **prone-position sleeping and exposure to cigarette smoke increase the risk of SIDS.** Some investigators suggest that the prone sleeping positioning puts infants at risk for suffocation and asphyxiation, while other investigators cite alveolar collapse or brainstem abnormalities as possible mechanisms. The higher risk of SIDS in cigarette-exposed infants is poorly understood. Statistics suggest that infants born to mothers who smoked during pregnancy as well as those exposed to tobacco smoke after birth are at greater risk for SIDS; the risk is dose dependent. Maternal anemia has also been shown to enhance the risk of SIDS in infants of smoking mothers, suggesting that hypoxemia or prenatal nutrition may play a role in SIDS.

SIDS is more common in premature and low-birth-weight infants. However, apnea of prematurity is not related to SIDS. SIDS is **more common among African American and Native American** infants, and least common among Asian infants, but it is unclear whether these associations are a function of race or reflective of other environmental factors. A higher incidence of SIDS is seen in infants born to substance-abusing mothers; the etiology of the relationship is unclear. Other proposed associations with SIDS, such as infection, immunizations, and poor infant nutrition, have not been shown to increase a child's risk. The risk of SIDS is higher in families with a previous SIDS death. Since the early 1990s, the incidence of SIDS has decreased dramatically in countries instituting public education campaigns targeted at limiting these risk factors.

The investigation of the unexpected death of an infant includes a clinical history, a postmortem examination, and a death scene investigation. In some infants, autopsy reveals mild pulmonary edema and scattered intrathoracic petechiae; these findings are supportive but not diagnostic of SIDS. Explainable causes of death may be divided into congenital and acquired conditions. **Congenital conditions** that may result in sudden, unexpected death include **cardiac anomalies** (arrhythmia, congenital heart disease), **metabolic disorders**, and **central nervous system etiologies.** **Acquired causes** of sudden death include **infection and both accidental and intentional trauma** (e.g., homicide).

The association between ALTEs and SIDS is unclear. While most parents of SIDS victims do not report a previous ALTE, infants with a

previous history of an idiopathic apparent life-threatening event (*IALTE* or *ALTE* of unknown etiology) are thought to be at risk for SIDS. The evaluation of an infant reported to have had an ALTE should be guided by a carefully obtained history and physical. A report of feeding difficulties or emesis would indicate the need for swallowing studies and a pH probe, whereas unusual posturing or movements should lead the examiner to obtain an electroencephalogram. A complete blood count and serum bicarbonate level obtained close to the time of the event may help to uncover an infectious or metabolic etiology. An electrocardiogram may be considered to look for prolonged QT syndrome or other cardiac anomaly. Documented cardiorespiratory monitoring and polysomnography can also be helpful in some cases.

Comprehension Questions

- [23.1] Which of the following infants most warrants home cardiorespiratory monitoring?
- A. A healthy 3-month-old infant who was born at term and whose weight is at the 5th percentile for age.
 - B. A healthy infant who was born at 29 weeks gestation and whose weight is at the 50th percentile for age.
 - C. A 5-month-old infant with a history of recurrent bouts of wheezing.
 - D. A premature infant with abnormal apnea and bradycardia.
 - E. A healthy term infant whose older sibling died of SIDS.
- [23.2] A pregnant woman comes to you for a prenatal visit: As her family pediatrician, your advice to her should include which one of the following information about reducing the risk of SIDS:
- A. Reduce the infant's exposure to prenatal and environmental smoke, and always place the baby in the supine position when she sleeps.
 - B. Always keep her in the prone position, even while awake.
 - C. Administer supplemental infant vitamins.

- D. Attempt to make breast milk the infant's primary source of nutrition.
- E. Protect the infant from people who are ill.

[23.3] Which of the following is a true statement?

- A. Most SIDS victims are girls.
- B. The incidence of SIDS is lowest among African Americans and Native Americans.
- C. Home monitoring reduces the risk of SIDS.
- D. Most cases of SIDS are attributable to a metabolic defect.
- E. SIDS is the most common cause of death between the ages of 7 and 365 days.

[23.4] The investigation of the unexpected death of an infant must include a clinical history, a postmortem examination, and:

- A. DNA studies.
- B. An arterial blood gas measurement.
- C. A venous blood gas measurement.
- D. A death scene investigation.
- E. Stool studies.

Answers

- [23.1] **D.** Home cardiorespiratory monitoring has not been shown to decrease the incidence of SIDS. Therefore, the potential benefits of decreased caregiver anxiety and possible avoidance of an adverse event must be considered against the inconvenience and cost involved. Symptomatic premature infants (i.e., those with apnea and bradycardia events) are among those who are considered to be at higher risk for an adverse event, and for whom monitoring is therefore recommended. Monitors are also recommended by some, but not all experts when more than one child in a family has died from SIDS. Monitoring is not recommended for the infants in choices A, B, or C.

- 3.2] A. Although your advice to this woman might also include choices C, D, and E, these measures have not been shown to reduce the infant's risk of SIDS.
- 3.3] E. SIDS is the most common cause of death of infants between 1 week and 1 year of age, more commonly affects boys, and Native American or African American children.
- 3.4] D. A death scene investigation is crucial to rule out trauma, both intentional and accidental.

CLINICAL PEARLS

- SIDS is a diagnosis of exclusion that can be assigned only after the postmortem investigation, postnatal history, and crime scene investigation fail to yield another explanation.
- Prone sleep position and exposure to cigarette smoke are significant risk factors for SIDS.
- ALTEs (Apparent life-threatening events), previously termed "near-miss SIDS," are observed occurrences that can be caused by any of a myriad of etiologies.

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◆ CASE 24

A 29-week-old, 1000-g baby boy is born vaginally after spontaneous rupture of membranes to a 17-year-old primigravida mother who received no prenatal care. The infant is admitted to the neonatal intensive care unit where he receives routine care for low-birth-weight infants including mechanical ventilation, umbilical catheterization, and sepsis evaluation. The infant does well until day of life 5, when he develops an increased respiratory rate, mild subcostal retractions, a widened pulse pressure, but no significant increase in oxygen requirement and is not clinically cyanotic. A continuous murmur is heard along the left sternal border. Chest radiography shows pulmonary vascular congestion.

◆ What is the most likely diagnosis?

◆ What is the treatment for this condition?

ANSWERS TO CASE 24: Patent Ductus Arteriosus

Summary: A preterm infant develops respiratory distress on day of life 5. He is acyanotic, has a continuous heart murmur along the left sternal heart border, and his chest radiograph shows pulmonary vascular congestion.

◆ **Most likely diagnosis:** Patent ductus arteriosus (PDA).

◆ **Treatment:** Indomethacin or surgical closure.

Analysis**Objectives**

1. Recognize the presenting signs and symptoms of patent ductus arteriosus.
2. Know the major acyanotic congenital heart lesions.
3. Be familiar with the fetal circulation (see Figure 24–1).

Considerations

A noncyanotic heart lesion should be suspected in this child who has a new heart murmur without a corresponding increase in oxygen requirements. The murmur, which was not heard at birth, becomes evident after the pulmonary vascular resistance falls. His age, history, and physical findings are entirely consistent with a PDA. If untreated, the PDA can lead to further respiratory compromise and increased chances of developing other complications associated with prematurity.

APPROACH TO ACYANOTIC HEART LESIONS**Definitions**

Eisenmenger's syndrome: Pulmonary hypertension resulting in right-to-left shunting of blood. This may occur with large ventricular

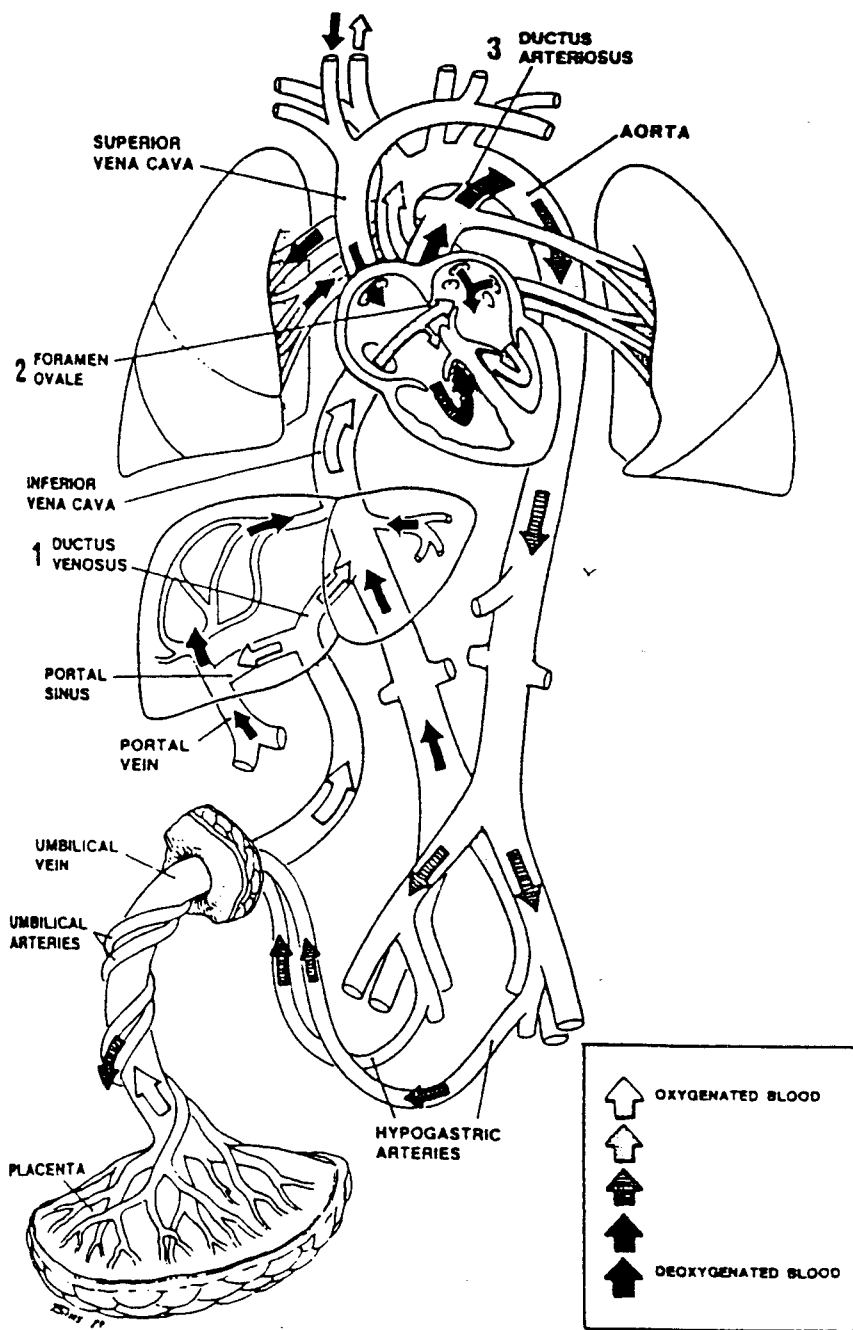


Figure 24-1. Fetal circulation. (From William's Obstetrics, 21st edition, with permission).

septal defects, atrioventricular canal lesions, and patent ductus arteriosus.

Left-to-right shunt: Flow of blood from the systemic circulation into the pulmonary circulation across an anomalous connection, such as a patent ductus arteriosus. Such lesions result in pulmonary congestion and systemic hypoperfusion, but do not cause cyanosis.

Widened pulse pressure: A large, bounding arterial pulse. Many conditions may cause this finding, including fever, hyperthyroidism, anemia, arteriovenous fistulae, and patent ductus arteriosus.

Clinical Approach

The common feature of acyanotic congenital heart lesions is shunting of blood from the systemic system into the pulmonary circulation. If the volume of flow is significant and is allowed to continue for a prolonged period of time, the shunt can reverse as a result of an increased pulmonary vascular pressure, resulting in clinical cyanosis. **PDA is most commonly encountered in preterm infants,** but also occurs in children without a history of prematurity. **In utero, the ductus arteriosus shunts blood away from the quiescent lungs via the pulmonary artery to the descending aorta.** The increase in plasma oxygen tension that occurs at birth is associated with vasoconstriction of the ductus. **Closure of the ductus in term infants usually occurs within 10 to 15 hours after birth, but almost always by 2 days of life.** Closure is delayed in premature infants, perhaps as the result of an impaired vasoconstrictor response to increased oxygen tension. Pulmonary resistance falls when a ductus fails to close, allowing shunting of blood from left (the systemic circulation) to right (the pulmonary circulation), with resultant myocardial stress, pulmonary vascular congestion, and respiratory difficulty.

A small PDA usually results in no symptoms. An infant with a **large PDA** typically has a **systolic or continuous heart murmur** that is described as being like **“machinery” or “rolling thunder” in quality.** The precordium is active, the pulses are bounding, and the pulse pres-

sure is widened due to runoff of blood into the pulmonary artery during diastole. **If heart failure ensues, tachycardia, hepatomegaly, decreased urinary output, and worsening respiratory distress with cyanosis may occur.** Chest radiography shows pulmonary congestion and may also reveal cardiomegaly.

Occasionally, a PDA is present in association with another congenital cardiac lesion. In such cases the PDA may be difficult to detect clinically. For patients with coarctation or interruption of the aortic arch, patency of the ductus arteriosus is vital to maintaining blood flow to the systemic circulation. Likewise, a PDA in the presence of an obstructed pulmonic valve is essential for providing blood flow to the lungs (see Figure 24-2). Such lesions are called *ductus dependent*. In all other cases, however, closure of the PDA is desirable in order to prevent the complications of pulmonary congestion and systemic undercirculation. **Closure of the ductus may be achieved by administering indomethacin**, an inhibitor of prostaglandin synthesis. Potential complications of indomethacin are renal, cerebral and gastrointestinal hypoperfusion, and impaired platelet aggregation. **A PDA also may be closed surgically**, but this approach involves the potential risks of patient transport, anesthesia, blood loss, and infection. This technique is usually reserved for patients whose ductus does not close with medical treatment.

Pulmonary overcirculation and systemic hypoperfusion resulting from a PDA may increase the risk of developing or worsening many of the complications of prematurity, including bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis. **If left untreated, a patent ductus arteriosus can eventually result in pulmonary hypertension with resultant right-to-left shunting of blood and cyanosis (Eisenmenger syndrome).** Infective endocarditis and growth failure are also possible complications of PDA. Other complications of prematurity, such as periventricular leukomalacia and retinopathy of prematurity, are not associated with PDA.

Other acyanotic congenital heart lesions include ventricular septal defects (VSDs) and atrial septal defects (ASDs). **VSDs are the most common acyanotic heart lesions in children, accounting for 25% of all congenital heart disease.** The majority of VSDs occur in the membranous portion of the septum, and small VSDs with minimal left-to-right

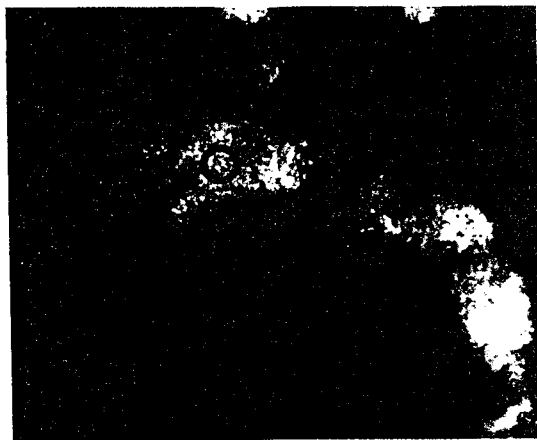


Figure 24–2. Angiography of persistent Patent Ductus Arteriosus (PDA) Aorta (AO) and Pulmonary artery (PA) shown. (From Rudolph's Pediatrics, 21st edition, with permission).

shunts are the most common. These children are usually asymptomatic, and a harsh holosystolic murmur at the left lower sternal border is detected incidentally on routine physical examination. The murmur of a large VSD is less harsh than that of a small lesion caused by the absence of a significant pressure gradient across the defect. Large VSDs are accompanied by symptoms of dyspnea, feeding difficulties, growth failure, and profuse perspiration in young infants, and may lead to recurrent infections and cardiac failure. Although these infants are generally not cyanotic, they may become dusky during feeding or crying. VSDs may not be detected during the first few days of life because of high right-sided pressures; they become audible as pulmonary vascular resistance drops and left-to-right shunting of blood increases across the defect.

Chest radiography and electrocardiography in children with small VSDs are usually normal, but may reveal evidence of mild left ventricular hypertrophy. Children with large VSDs have enlarged hearts and pulmonary vascular congestion on chest radiograph, and biventricular hypertrophy on electrocardiogram. Echocardiography is used to con-

firm and further describe a VSD. Because up to 50% of small VSDs close spontaneously, **management for small, asymptomatic defects requires only close monitoring.** Closure usually occurs during the first 2 years of life, with the vast majority closed by age 4 years. Most of these children remain asymptomatic, but may be at increased risk for infective endocarditis. **Children with larger defects require medical management to minimize pulmonary congestion and to maintain adequate cardiac function.** Large defects are closed surgically, generally by 1 year of age.

Children with ASDs are often asymptomatic, and are discovered inadvertently on routine physical examination. **Children with large defects may have mild growth failure and exercise intolerance** that are not appreciated except in retrospect after closure of the defect. Physical findings of an ASD include **splitting of the second heart sound that does not vary normally with respiration (“fixed splitting”)**, and a systolic murmur at the left upper and mid sternal borders that is caused by high-volume flow of blood from the right ventricle into the normal pulmonary artery; the murmur is not blood flowing across the ASD itself. A diastolic murmur at the lower left sternal border produced by increased flow across the tricuspid valve may also be present. The chest radiograph reveals an enlarged right atrium, right ventricle and pulmonary artery and increased pulmonary vascularity, and electrocardiography shows right ventricular hypertrophy and sometimes right axis deviation. **ASDs are well tolerated during childhood, but can lead to pulmonary hypertension in adulthood.** Infective endocarditis is rare, and thus routine prophylaxis is not recommended. **Surgery is recommended for symptomatic and large defects;** this is usually done during early childhood because of the greater risks of surgery in adults. **An isolated patent foramen ovale (PFO) is usually not clinically significant and is not considered an ASD.**

Another common acyanotic heart lesion is the **atrioventricular (AV) septal defect** (also known as AV canal or endocardial cushion defect) consisting of a contiguous atrial and ventricular septal defect as well as abnormal AV (i.e., mitral and tricuspid) valves. A **systolic murmur of large pulmonary flow is present,** and there is a **diastolic murmur** at the lower left sternal border. The second heart sound may be widely split. The chest radiograph and electrocardiogram show

cardiac enlargement; and pulmonary vascularity is increased on the chest film. **If untreated, these children develop cardiac failure, growth failure, and recurrent pulmonary infections in infancy.** Pulmonary hypertension develops with eventual right-to-left shunting and cyanosis. Surgical correction is performed in infancy.

Comprehension Questions

- [24.1] At her 2-month-old well-child examination, an infant girl with Down syndrome is noted to have both a systolic and a diastolic heart murmur, and the second heart sound is split. The liver edge is palpable 4 cm below the right costal margin. Her mother reports that lately the baby has been sweaty and sometimes bluish around the mouth when she nurses, and she seems to be eating less than previously. The most likely diagnosis is:
- A. Ventricular septal defect
 - B. Atrial septal defect
 - C. AV canal defect
 - D. Patent ductus arteriosus
 - E. Patent foramen ovale
- [24.2] A 2-year-old African American girl presents to the emergency center with a complaint of sudden onset of abdominal pain and weakness. She is afebrile, but is tachypneic and tachycardic. Her mucous membranes are pale. Lung sounds are clear. A III/VI systolic murmur is noted at the lower left sternal border. The spleen tip is palpable 2 cm below the right costal margin. The initial work-up for this patient should include:
- A. Electrocardiogram
 - B. Chest radiograph
 - C. Magnetic resonance imaging (MRI) of the abdomen
 - D. Complete blood count with peripheral smear
 - E. Liver function tests.

[24.3] A 12-month-old boy with a moderate-sized ventricular septal defect is treated for his first episode of a urinary tract infection. Following completion of a 7-day course of oral antibiotics, he is scheduled for a voiding cystourethrogram (VCUG). Prior to the procedure, he should receive:

- A. Acetaminophen
- B. Amoxicillin
- C. Digoxin
- D. Ditropan
- E. Furosemide

[24.4] A 4-month-old boy with a moderate-sized ventricular septal defect presents to the emergency center with a 12-hour history of multiple episodes of vomiting and diarrhea. His temperature is 101.8°F (38.8°C) rectally, his heart rate is 120 beats per minute, and he is normotensive. His mucous membranes appear dry, and his capillary refill is 3 seconds. His mother reports that his last wet diaper was 5 hours prior. Two intravenous infusions of 100 cc/kg normal saline are administered over a 1-hour period. Following the fluid boluses, the child's mucous membranes and capillary refill have improved, but he develops an increased respiratory rate. The most likely explanation for the increased respiratory rate is:

- A. Pulmonary congestion
- B. Pneumonia
- C. Pneumonitis
- D. Bronchiolitis
- E. Bronchitis

Answers

[24.1] C. AV canal is common among children with Down syndrome. This infant's symptoms and clinical findings are most consistent with this diagnosis.

- [24.2] **D.** The most likely and also the most urgent diagnosis for this child is splenic sequestration. Rapid pooling of blood in the spleen, as can occur in sickle cell disease, can lead to hypovolemia with significant morbidity and even death if not addressed quickly. This child's heart murmur is most likely due to chronic anemia associated with sickle cell disease.
- [24.3] **B.** The American Heart Association recommends prophylactic antibiotics prior to invasive procedures for patients with VSDs or other heart lesions that are considered to put the patient at risk for infective endocarditis. Urinary catheterization, bronchoscopy, dental procedures likely to induce gingival bleeding, surgical drainage of an abscess, and other procedures are among those that require prior antibiotic prophylaxis.
- [24.4] **A.** Pulmonary vascular congestion ("fluid overload") is a potential complication of intravenous fluid administration in any patient. Persons with cardiac lesions that involve a left-to-right shunt are at particular risk for this problem. Diuretic administration (furosemide) may be required if the respiratory distress is significant.

CLINICAL PEARLS



Acyanotic heart lesions are characterized by shunting of blood from the systemic circulation to the pulmonary circulation ("left-to-right shunt").



The most common congenital acyanotic heart lesion is the ventricular septal defect (VSD). Patent ductus arteriosus (PDA), atrial septal defects (ASD), and arteriovenous (AV) canal are other left-to-right shunt lesions.



Left-to-right shunts can eventually reverse direction (right-to-left) and cause cyanosis if pulmonary hypertension develops (Eisenmenger syndrome).

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◆ CASE 25

A 39-week gestation, 3700-g infant is delivered vaginally without complications. The infant breast-feeds well, voids and passes meconium within the first 12 hours of life. At 15 hours of life the infant is no longer interested in feeding and he appears dusky. The infant's respiratory rate is 65 breaths per minute, and the capillary refill is 3 seconds. No heart murmur is audible on cardiac examination, but a loud single second heart sound is noted.

- ◆ What is the most likely diagnosis?
- ◆ What is the best management for this condition?

ANSWERS TO CASE 25: Transposition of the Great Arteries

Summary: A healthy-appearing term infant suddenly loses interest in feeding, and develops cyanosis, poor peripheral perfusion and tachypnea at 15 hours of life. The cardiac examination reveals a loud second heart sound and no heart murmur.

- ◆ **Most likely diagnosis:** Cyanotic congenital heart disease, likely transposition of the great arteries.
- ◆ **Best initial management:** Administer prostaglandin E_1 to maintain patency of the ductus arteriosus.

Analysis

Objectives

1. Know the major types of cyanotic congenital heart lesions and their most common clinical presentations.
2. Understand why some congenital heart lesions result in cyanosis, while others do not.
3. Understand the importance of maintaining patency of the ductus arteriosus in some types of congenital heart disease.

Considerations

This child has symptoms consistent with congenital cyanotic heart disease, and likely has transposition of the great arteries (TGA). In this condition, the cardiac origins of the aorta and the pulmonary artery are switched, thus creating two parallel circuits of blood flow rather than the normal series circuit (Figure 25–1). This situation is **incompatible with life unless a connection between the pulmonary and systemic circuits exists**. During the first hours of life, **the ductus arteriosus and the foramen ovale provide this connection**; symptoms develop when this connection begins to close. Some patients with TGA also have a defect in the ventricular septum (VSD), and may first show

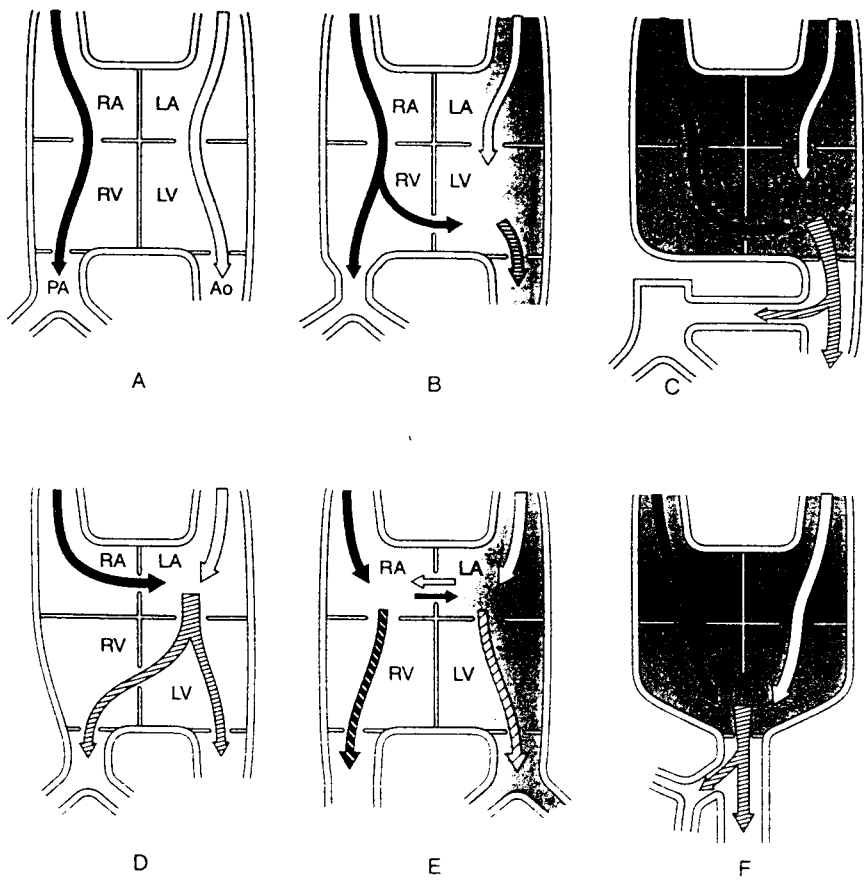


Figure 25-1. Schematic drawing of circulation of various cardiac defects. (A) = Normal circulation; (B) = tetralogy of Fallot; (C) = pulmonary atresia; (D) = tricuspid atresia; (E) = transposition of the great arteries; (F) = truncus arteriosus. Black arrows = deoxygenated blood, White arrows = oxygenated blood, cross-hatched arrows = mixed.

signs of heart disease later in infancy than babies without VSDs. **In this case, management of the infant consists of immediate steps to maintain patency of the ductus arteriosus.**

APPROACH TO CONGENITAL CYANOTIC HEART DISEASE

Definitions

Cyanosis: Bluish discoloration of the skin and mucous membranes caused by unsaturation of the blood with oxygen.

Ductus-dependent lesions: Cardiac defects that are incompatible with life in the absence of a patent ductus arteriosus.

Right-to-left shunt: Abnormal flow of blood from the pulmonary system to the systemic circulation across a cardiac defect. These lesions result in cyanosis.

Clinical Approach

Cyanotic heart disease in a newborn often manifests itself after the ductus arteriosus begins to close, and are termed *ductus dependent*. Patency of the ductus maintains a connection between the pulmonary and systemic circulations; closure normally occurs on the first or second day of life. In the past, management of neonatal cyanotic heart lesions involved emergency surgical repair on very sick infants. This changed in the 1980s with the introduction of **prostaglandin E₁**, a medication **administered intravenously that keeps the ductus open**, thus allowing stabilization of the infant prior to attempting more definitive correction.

The cyanotic congenital heart lesions are characterized by decreased pulmonary blood flow. Unsaturated blood returning to the heart from the periphery is shunted back into the systemic circulation, thus bypassing the lungs. This occurs whenever blood flow into the pulmonary system is compromised, as in stenosis of the pulmonary valve or if the origins of the pulmonary artery and aorta are switched (TGA).

Transposition typically causes an “egg-on-a-string” appearance on chest radiography, but the chest radiograph often appears normal

in the first few days of life. Electrocardiography (EKG) shows right axis deviation and right ventricular hypertrophy, which are normal findings in a newborn because of the normal minimal flow of blood in the pulmonary circuit prior to birth. Diagnosis is confirmed with echocardiography.

Initial management of TGA after the administration of prostaglandins involves creation of an aperture in the atrial septum ("atrial septostomy"). This procedure is performed via cardiac catheterization, and provides immediate palliation of symptoms. Surgical techniques for TGA repair include "atrial baffle" procedures (where systemic venous drainage is channeled to the mitral valve and pulmonary venous blood to the tricuspid valve) and arterial switch repair (where the origins of the great arteries are reversed). Stenosis at the sites of anastomosis is a potential long-term complication of surgical repair.

Pulmonary valve stenosis occurs in approximately 20% to 30% of children with congenital heart disease. Cyanosis and exercise intolerance are directly proportional to the degree of stenosis, and are not present in milder forms. Cardiac examination reveals a systolic murmur along the upper left sternal border that radiates to the back, and a systolic click. The EKG is frequently normal in mild cases, but greater degrees of stenosis usually show right axis deviation and right ventricular hypertrophy. Valvuloplasty is achieved via cardiac catheterization. Pulmonary valve stenosis may occur in association with other diseases or syndromes, such as glycogen storage disease or Noonan syndrome (a congenital syndrome with a low posterior hairline and characteristic facial features).

When **pulmonary stenosis occurs in association with a large VSD**, the result is the spectrum of abnormalities known as **tetralogy of Fallot (TOF)**. In these cases, the intraventricular septum is displaced anteriorly, resulting in the right ventricular outflow obstruction, and also overriding of the aorta over the right ventricle. Hypertrophy of the right ventricle develops as a result of the hemodynamic changes caused by the other abnormalities. The characteristic chest radiograph finding is a boot or wooden shoe appearance (*coeur en sabot*). If pulmonary stenosis is mild at birth, neonates have normal color (so-called pink tetralogy), but most children become cyanotic by early childhood as a result of the progression of the stenosis. **Many children with TOF also**

experience hypercyanotic spells (“tetralogy spells”), caused by a sudden increase in right-to-left shunting of blood. These spells may be brought on by activity or agitation, or may occur without apparent precipitant. Children with TOF are often seen assuming a squatting posture, which compresses peripheral blood vessels, thus increasing pulmonary blood flow and systemic arterial oxygen saturation. With current surgical management, 90% of patients with TOF survive to adulthood.

Cyanosis is also a hallmark of children who have abnormalities of the tricuspid valve, such as tricuspid atresia or Epstein anomaly. In tricuspid atresia, no outlet exists between the right atrium and the right ventricle, forcing systemic venous return to enter the left atrium via the foramen ovale or an associated atrial septal defect. A ventricular septal defect is also often present. The tricuspid valve of Epstein anomaly is usually regurgitant and often obstructs ventricular outflow due to a large anterior leaflet. Both conditions are often “ductal dependent” in the neonate, and both require surgical correction.

Comprehension Questions

- [25.1] A 12-year-old boy presents to his pediatrician for a sports physical examination. He denies any chronic health problems, including any adverse symptoms with exertion. The clinician notes a I-II VI systolic murmur at the left upper sternal border that does not radiate. The second heart sounds splits normally, and no audible click is appreciated. Peripheral perfusion is normal, and the fingers are not clubbed. What should the clinician recommend to this patient?
- A. He should not play any strenuous sport.
 - B. He may participate in sports without restrictions.
 - C. He should have a chest radiograph and an EKG before any further recommendation can be made.
 - D. He should be evaluated by a cardiologist.
 - E. He may participate in sports activities, but should seek immediate medical attention if he experiences dyspnea or other adverse symptoms.

- [25.2] A term, 3700-g infant is born vaginally without complications. At 24 hours of life, a II/VI systolic murmur is noted in the mitral area that radiates to the back. A similar murmur is also noted in the right axilla. The infant is pink and breathing easily, and his bedside chart shows that he has been taking 30 cc of formula approximately every 2 hours. Initial management of this infant should include:
- A. Chest radiography, EKG, and four extremity blood pressures.
 - B. Immediate administration of prostaglandin E₁.
 - C. Transfer to a neonatal intensive care unit.
 - D. Consultation by a pediatric cardiologist.
 - E. Discharge home with follow-up in the pediatric clinic at 3 days of life.
- [25.3] A 4-year-old boy presents for the first time to a family practice clinic for a routine well-child visit. On review of systems, his mother notes that he breathes fast and his lips turn "dusky" when he runs or plays hard. The symptoms resolve once he stops the activity. On physical examination, the boy is noted to have a II/VI systolic murmur at the left upper sternal border that radiates to the back, and a faint click is heard. What is the most likely cause of this child's exercise intolerance?
- A. Asthma
 - B. Ventricular septal defect
 - C. Atrial septal defect
 - D. Pulmonary valve stenosis
 - E. Tricuspid atresia
- [25.4] A 15-month-old child is playing with blocks in a squatting position in the clinic waiting room. The skin around her mouth is faintly blue, but she appears comfortable. She then begins running after her 3-year-old brother, when she suddenly becomes dyspneic and cyanotic. She returns to a squatting position and soon is breathing comfortably again with only slight perioral cyanosis. You expect to see the following on her chest radiograph:

- A. A “boot-shaped” heart
- B. An “egg on a string”
- C. Pneumonia
- D. Pulmonary congestion
- E. Lung hyperinflation

Answers

- [25.1] **B.** This child has a benign pulmonary flow murmur. It is differentiated from a pathologic pulmonary murmur by the fact that it does not radiate, there is no click, and there are no signs and symptoms of cardiac disease such as digital clubbing, cyanosis, and exercise intolerance.
- [25.2] **E.** This infant has peripheral pulmonic stenosis, another benign murmur of childhood. The other benign childhood murmurs that are frequently encountered are the venous hum (a low-pitched murmur heard at the sternal notch only when the child is upright) and the Still vibratory murmur (a high-pitched “musical” systolic murmur heard best at the left sternal border in the supine position). While it may be difficult to diagnosis the multitude of pathologic heart sounds, it certainly behooves the general clinician to know the characteristics of the common benign murmurs of childhood.
- [25.3] **D.** Although both pulmonary stenosis and tricuspid atresia are cyanotic heart lesions, the clinical presentation of exercise-induced cyanosis and systolic murmur are characteristic of pulmonary stenosis.
- [25.4] **A.** This child has tetralogy of Fallot, with improvement when squatting, and “tet” (hypercyanotic) spells when running. The “boot shaped heart” is a characteristic chest radiographic finding.

CLINICAL PEARLS

Cyanotic congenital heart lesions are characterized by decreased pulmonary blood flow (right-to-left shunt). Transposition of the great arteries and defects of the tricuspid valve and pulmonary outflow tract are examples of cyanotic heart defects.

Lesions that are incompatible with life except in the presence of a patent ductus are termed "ductus dependent."

Prostaglandin E₁ is often used in infants with cyanotic congenital heart disease to maintain patency of the ductus arteriosus until more definitive surgical correction can be attempted.

The heart defects in tetralogy of Fallot are (1) ventricular septal defect; (2) pulmonic stenosis; (3) overriding aorta; and (4) right ventricular hypertrophy.

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◆ CASE 26

A 3-year-old boy is admitted to the hospital with a 20-day history of high fevers that spike twice daily. He was diagnosed with otitis media by his private practitioner on the fifth day of fever and was prescribed a 7-day course of amoxicillin, but the fever persisted despite antibiotic therapy. The fever is associated with the appearance of a faint rash on the trunk and proximal extremities and complaints of "body aches." A chest radiograph performed prior to admission is normal, but a complete blood count shows leukocytosis, thrombocytosis, and anemia. On the day prior to admission, the child developed an aversion to bearing weight. On admission, the child has a temperature of 102.5°F (39.2°C), but otherwise has normal vital signs. His physical examination is remarkable for scattered lymphadenopathy, hepatosplenomegaly, and mild swelling of his interphalangeal joints and knees.

- ◆ What is the most likely diagnosis?
- ◆ What is the best diagnostic test for this disorder?
- ◆ What is the treatment for this condition?

ANSWERS TO CASE 26: Juvenile Rheumatoid Arthritis (JRA)

Summary: A 3-year-old boy with daily high-spiking fevers of nearly 3 weeks duration. A rash and "body aches" wax and wane with the fevers. He also has a 1-day history of refusal to bear weight. His physical examination is significant for lymphadenopathy, organomegaly, and joint swelling. His chest radiograph is negative, but the complete blood count (CBC) reveals lymphocytosis, thrombocytosis, and anemia.

- ◆ **Most likely diagnosis:** Systemic-onset juvenile rheumatoid arthritis (Still disease).
- ◆ **Best diagnostic test:** No laboratory studies are diagnostic for juvenile rheumatoid arthritis, but a thorough patient history plus a CBC, blood cultures, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), antinuclear antibody (ANA), and synovial fluid assessment can aid in establishing or eliminating this diagnosis.
- ◆ **Treatment:** Nonsteroidal antiinflammatory drugs (NSAIDs), hydroxychloroquine, methotrexate, and glucocorticoids may be used to control symptoms. Physical and occupational therapy are important for preserving function and preventing deformity.

Analysis**Objectives**

1. Know the three forms of juvenile rheumatoid arthritis and their most common presenting signs and symptoms.
2. Recognize systemic-onset JRA as an important consideration in the differential diagnosis of fever of unknown origin in a child.

Considerations

The **differential diagnosis for fever of unknown origin** in a child is long and includes **infectious, hematologic, and rheumatologic etiologies**. The characteristics of the fever pattern can sometimes aid in narrowing the diagnostic possibilities. In this case, the history of **quotidian high-spiking fevers associated with a characteristic rash** is highly suggestive of **systemic JRA**. Organomegaly and lymphadenopathy are also characteristic of systemic JRA. Arthritis may develop after the onset of other symptoms, as in this case, sometimes appearing as late as months or even years into the disease course.

Definitions

Arthralgia: Any pain that affects a joint.

Arthritis: Swelling or effusion or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat in one or more joints.

Pauciarticular JRA (oligoarthritis): JRA with involvement of one to four joints.

Polyarticular JRA (polyarthritis): JRA with involvement of five or more joints.

Clinical Approach

JRA is the most common rheumatologic disorder in children, affecting approximately 250,000 persons in the United States. The diagnosis of JRA specifies an age of onset prior to 16 years old, and duration of symptoms of 6 weeks or longer. Other causes of arthritis in children, such as infectious etiologies and other rheumatologic conditions, must be excluded; **in the sexually active adolescent, gonococcal arthritis must be considered**. Three diverse entities fall under the JRA rubric, classified according to symptoms that appear during the first 6 months of illness: (1) **systemic-onset disease**; (2) **polyarticular disease**; and (3) **pauciarticular disease**.

Systemic symptoms dominate the clinical picture in (**systemic-onset JRA**), and making the diagnosis may be difficult if frank arthritis is not initially present. Daily high-spiking fevers, a rash and arthralgias that wax and wane with the fever, lymphadenopathy, and organomegaly are characteristic of systemic-onset disease. Pericarditis, hepatitis, pleural effusion, and encephalopathy may also occur. Chronic inflammatory arthritis occurs in approximately 25% of patients with systemic-onset disease, and is a poor prognostic sign.

Polyarticular disease is diagnosed when five or more joints are involved and systemic signs and symptoms are mild or absent. Girls predominate in this type of JRA. Onset usually occurs in the teen years, but symptoms may appear as early as 8 years of age. Patients with this disease are stratified by rheumatoid factor (RF). Patients with a negative RF generally have a better prognosis, although 5% to 10% progress to severe joint destruction. More than half of patients with RF-positive disease progress on to chronic disease. The latter group is believed to be nearly identical to the adult entity of rheumatoid arthritis.

Pauciarticular JRA is defined as onset of disease in fewer than five joints, and is divided into early and late-onset categories. Early onset disease is predominant in females, and the serum ANA is often positive. Half of the children with early onset disease develop iridocyclitis (inflammation of the iris and ciliary body; also called “anterior uveitis”) that is often asymptomatic. Eye disease does not parallel the activity of the arthritis. Late-onset pauciarticular JRA primarily affects boys older than 8 years of age. Late-onset disease sometimes progresses to lumbar and sacral joint involvement, in which case the diagnosis is changed to ankylosing spondylitis.

The initial laboratory evaluation for the child with suspected systemic JRA includes a CBC, an ESR, and blood cultures. **Leukocytosis, thrombocytosis, and anemia support the diagnosis of systemic JRA.** The ESR is elevated, and blood cultures are negative. **Evaluation of synovial fluid may be necessary to rule out septic arthritis,** particularly in the presence of exquisitely tender joints or when only a single joint is involved. **Rheumatoid factor and antinuclear antibody are usually negative** in systemic JRA.

Medications for JRA include NSAIDs, steroids, hydroxychloroquine, methotrexate, and other immunosuppressive agents. A pediatric rheumatologist should oversee the administration of these medications.

Physical and occupational therapy are vital for maintaining joint function and preventing further deformities. Other important aspects of care include **routine slit-lamp ophthalmic examinations to monitor for uveitis**, dietary interventions to ensure adequate calcium intake, and social support for the patient and family. Although approximately 50% of patients with systemic JRA eventually recover completely, another 25% of patients develop chronic and destructive arthritis. **Death can occur, usually from overwhelming infection.**

Comprehension Questions

- [26.1] A 14-year-old girl presents with a 3-day history of swollen "neck nodes" and a diffuse salmon-colored rash. On review of systems, she reports that she had a sore throat and a cough with low-grade fever 5 days ago, but these symptoms resolved 2 days ago. On physical examination, she is noted to have enlarged posterior auricular and suboccipital lymph nodes, as well as tender swelling of multiple large and small joints. The most likely diagnosis is:
- A. Pauciarticular JRA.
 - B. Polyarticular JRA.
 - C. Rubella.
 - D. Systemic lupus erythematosus.
 - E. Systemic-onset JRA.
- [26.2] A 5-year-old girl is referred to a pediatric rheumatologist with a 4-week history of mild swelling and decreased range of motion in the left knee and right elbow. She is afebrile and appears otherwise well. The procedure most likely to be helpful in the diagnosis of her condition is:
- A. Arthrocentesis
 - B. A complete blood count
 - C. A computerized tomography (CT) scan of the involved joints.
 - D. A slit-lamp examination of both eyes.
 - E. A bone scan.

- [26.3] An obese 12-year-old African American boy presents to the emergency center complaining of right knee pain. He denies any history of trauma to the right leg. He has a notable limp favoring the right lower extremity. Initial evaluation of his condition should include:
- A. Range of motion of the right hip.
 - B. Magnetic resonance imaging of both knees.
 - C. ANA.
 - D. Rheumatoid factor.
 - E. Complete blood count.
- [26.4] A 3-year-old boy with suspected systemic-onset JRA develops tachycardia and dyspnea on the fifth day of hospitalization. He complains that his chest hurts. Auscultation of the heart reveals a “friction rub” sound. The most likely diagnosis is:
- A. Heart failure.
 - B. Pneumonia.
 - C. Asthma.
 - D. Pericarditis.
 - E. Mitral valve prolapse.

Answers

- [26.1] C. The differential diagnosis for arthritis in a child includes infectious etiologies in addition to rheumatologic disorders. This girl's signs and symptoms are typical of rubella. Vaccination against rubella is given at 1 year of age and again at school entry. The major reason for vaccination is to prevent congenital rubella syndrome, a devastating neonatal condition, as the disease is usually mild in older patients.
- [26.2] D. Slit-lamp findings consistent with JRA are likely to be most helpful (most specific). The other choices, and a variety of other tests such as an erythrocyte sedimentation rate, are also helpful but are often nonspecific.

- [26.3] A. Careful attention must always be paid to the hips when evaluating knee complaints, as pain from a hip problem can be referred to the knee. Slipped capital femoral epiphysis occurs most commonly in obese African American boys. JRA rarely affects the hip in the initial course of the disease.
- [26.4] D. A friction rub is characteristic of pericarditis.

CLINICAL PEARLS

The spectrum of juvenile rheumatoid arthritis is comprised of three entities: (1) systemic-onset disease; (2) polyarticular disease; and (3) pauciarticular disease.

Systemic-onset JRA is an important consideration in the differential diagnosis of fever of unknown origin in a child.

The diagnosis of JRA is based on clinical criteria and by excluding other possibilities; no single laboratory test confirms the diagnosis.

Sometimes a bone marrow aspiration is required to differentiate JRA from leukemia.

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◆ CASE 27

A 6-month-old girl comes to your office for an initial visit. The parents have been reluctant to seek routine medical care because they are concerned about the safety of immunizations. However, the child's daycare insisted that the child undergo immunization, and the parents have reluctantly agreed. The child was the 4-kg (9-lb) product of a normal pregnancy and has no prior medical history. The child drinks only goat's milk and has not started solid foods yet. The parents report the child has an average of 9 to 10 watery stools per day. On physical examination you find a pale, irritable infant; her weight is less than the 5th percentile and her height is at the 5th percentile. She is mildly tachycardic. The remainder of her physical examination is normal. You order a complete blood count and a reticulocyte count as initial screening laboratory tests. The lab calls back with the results: hemoglobin is 5 g/dL, platelet count is $98,000/\text{mm}^3$, mean corpuscular volume is 105 fL, and the reticulocyte count is 2.0%.

◆ What is the most likely cause of this child's anemia?

◆ How should she be treated?

ANSWERS TO CASE 27: Macrocytic Anemia Secondary to Folate Deficiency

Summary: A 6-month-old girl, who has been drinking goat's milk exclusively, displays pallor, tachycardia, irritability, chronic diarrhea, and poor growth; her weight has fallen from about the 95th percentile at birth to below the 5th percentile for a 6-month-old infant. Her labs reflect a macrocytic anemia with poor bone marrow response.

- ◆ **Most likely cause:** Folic acid deficiency secondary to exclusive use of goat's milk for nutrition.
- ◆ **Treatment:** Folic acid replacement for 3 to 4 weeks and dietary changes.

Analysis

Objectives

1. Describe the typical findings in macrocytic anemia.
2. List the potential causes of macrocytic anemia.
3. Understand the treatment of this disease.

Considerations

This infant has poor growth but has not been evaluated by a medical professional since birth. Inadequate weight gain may result from a large number of disorders, including inadequate caloric intake, increased metabolic needs, and abnormal absorption in the gastrointestinal tract (see also Case 1). The history of using goat's milk exclusively is the clue, as unaltered goat's milk provides little folic acid. Goat's milk also has less vitamin B₁₂ than do commercial formulas and breast milk.

APPROACH TO MACROCYTIC (MEGALOBLASTIC) ANEMIA

Definitions

Mean corpuscular volume (MCV): The average size of a red blood cell. Normal values vary by age; large cells are macrocytic, small cells are microcytic.

Red cell distribution width (RDW): The variability of red cell size. The red blood cell (RBC) can be increased with abnormally large red cells (seen in folic acid deficiency), as well as with abnormally small cells.

Reticulocyte count: The percentage of red blood cells that are immature (new) reticulocytes.

Clinical Approach

Anemia is typically distinguished by the size of the red blood cells. Children with **iron deficiency** develop a **microcytic anemia**; their red blood cells are smaller than normal because of the decreased amount of hemoglobin in each cell. Children who lose a large amount of blood quickly have a **normocytic anemia**; the cells are normal, but there are fewer of them.

A number of conditions may result in a **macrocytic (or megaloblastic) anemia** with *inadequate marrow response (low reticulocyte count)*, including **hypothyroidism, congenital bone marrow dysfunction (including Blackfan-Diamond syndrome), aplastic anemia, trisomy 21, vitamin B₁₂ deficiency, and folate deficiency**. A macrocytic anemia may also be seen with active hemolysis, but this also results in an elevated reticulocyte count.

Folate is absorbed in the small intestine and is used as a cofactor in many metabolic processes, including DNA synthesis. It is commonly found in **meats, leafy green vegetables, and citrus fruits**. Folate supplementation **decreases neural tube defects and women of child-bearing age** are encouraged to take folate supplements.

The child in this case was drinking goat's milk. Goat's milk is used in many areas of the world as a replacement for cow's milk in children with suspected or proven cow's milk allergy; a number of commercially available goat's milk based formulas are available. Goat's milk has the reputation of being easier to digest than cow's milk, possibly owing to its lack of agglutinin, a compound that encourages the fat in cows' milk to clump. Thus, the fat from goat's milk may be more easily digested. **Goat's milk is nutritionally deficient, however, in folate and vitamin B₁₂.** Infants exclusively fed goat's milk will develop folate deficiency and subsequent megaloblastic anemia. Goats are also susceptible to brucellosis, making unpasteurized goat's milk a potential infectious risk. The American Academy of Pediatrics has noted in a policy statement on hypoallergenic infant formulas that goat's milk is not an appropriate substitute for cow's milk in the child with milk protein allergy. Although the protein structure is slightly different between the two milks, large amounts of animal protein remain in goat's milk and may cause similar symptoms. Vitamin and mineral supplementation is required for infants drinking goat's milk.

In addition to dietary deficiencies, a number of rare congenital defects may cause macrocytic anemia by preventing the absorption or utilization of folic acid. A degenerative or inflammatory disease of the intestine can impair folate absorption as well. Anticonvulsants interfere with folate absorption, but macrocytic anemia in patients on these medications is uncommon. Methotrexate interferes with tetrahydrofolate production and can lead to macrocytic anemia; trimethoprim and pyrimethamine occasionally cause folate deficiency and anemia.

Vitamin B₁₂ is also an important factor in DNA synthesis. Dietary deficiency or lack of intrinsic factor (which is secreted in the stomach and is required for absorption of B₁₂ in the ileum) can result in megaloblastic anemia. Vitamin B₁₂ is available in many foods and a pure dietary deficiency is rare; however, diets devoid of all animal products may result in deficiency. **Breast-fed infants of mothers adhering to the vegan diet are also at risk for vitamin B₁₂ deficiency.** Children with the rare condition juvenile pernicious anemia are unable to secrete intrinsic factor and, thus, become vitamin B₁₂ deficient between the ages of 1 and 5 years, when the supply of vitamin B₁₂ passed transplacentally to the child from the mother is exhausted. These children will exhibit worsening irritability, loss of appetite,

and decreased activity. Affected children are at risk for permanent neurological damage resulting from spinal cord demyelination. Therapy is intramuscular vitamin B₁₂ replacement; oral replacement is not helpful.

The fish tapeworm *Diphyllobothrium latum* uses vitamin B₁₂. Thus, infestation in the intestinal lumen can result in vitamin B₁₂ deficiency. Surgical removal of the terminal ileum, as well as any generalized intestinal inflammatory process, also can result in vitamin B₁₂ deficiency and subsequent megaloblastic anemia.

Comprehension Questions

- [27.1] A 19-year-old mother has just delivered a healthy term infant and is asking about the baby's nutrition. She was fed goat's milk as a child and wants to do the same for her infant. You respond that goat's milk is acceptable as infant nutrition only when:
- A. The goat's milk proteins are hydrolyzed before feeding the baby.
 - B. The infant is provided supplemental vitamins and minerals.
 - C. The milk is freshly obtained from the goat.
 - D. The milk comes from Nigerian Dwarf goats.
 - E. The milk is diluted 1:1 with water.
- [27.2] A premature infant born at 28 weeks gestation develops necrotizing enterocolitis and intestinal perforation requiring the removal of a small portion of his colon and 20 cm of small intestine, including the ileocecal junction. Future nutritional support will likely include:
- A. Vitamin B₁₂ oral supplementation.
 - B. Long-term parenteral nutrition.
 - C. Vitamin B₁₂ injections every 1 to 3 months.
 - D. Liquid-only diet.
 - E. Supplemental oral folate.

[27.3] The parents of a previously healthy 3-year-old bring the child to your office because she is complaining that her tongue hurts. The parents also report she has seemed weak and listless over the last several months and has not been eating well. Just recently she has had trouble walking. The family usually eats a regular diet including meats and vegetables. On physical examination her tongue is smooth, red, and tender. She is pale and tachycardic. Her complete blood count reveals a macrocytic anemia. The most likely diagnosis in this child is:

- A. Iron deficiency
- B. Nutritional deficiency
- C. Transcobalamin deficiency
- D. Juvenile pernicious anemia
- E. Folate deficiency

[27.4] A 16-year-old Alaskan adolescent girl comes to the office for an evaluation of lethargy. Her father notes that recently she has seemed pale. She eats a regular diet and has no significant past medical history. Her menses are regular and have not changed. During the last 2 years she has helped her mother in the family seafood restaurant after school. Her complete blood count reveals a megaloblastic anemia. The next appropriate study is:

- A. Stool for ova and parasites
- B. Transcobalamin levels
- C. Iron levels
- D. Gastric endoscopy
- E. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) assay for Lesch-Nyhan syndrome

Answers

[27.1] **B.** Infants taking goat's milk must have nutritional supplementation with folate, B₁₂, and iron. Several goat's milk-based formulas are available that include these nutrients. Fresh, un-

pasteurized goat's milk can contain *Brucella ovis* and cause brucellosis. Diluting the milk will also dilute the caloric content.

- [27.2] C. The terminal ileum is the location of B₁₂ absorption; the child in this case has had the terminal ileum resected. Oral replacement of vitamin B₁₂ would be ineffective. Folate is absorbed throughout the small intestine. The amount of resected intestine is insufficient to cause the need for long-term parenteral nutrition, as the infant still has an adequate amount of small intestine remaining.
- [27.3] D. This is the typical presentation for juvenile pernicious anemia, a rare autosomal recessive condition in which the child is not able to secrete intrinsic factor and thus cannot absorb vitamin B₁₂. Supplies of vitamin B₁₂ passed to the fetus from the mother are typically sufficient for at least the first year or two of life. A deficiency in transcobalamin results in megaloblastic anemia in infancy, as transcobalamin is required for B₁₂ transport and utilization; therefore, the vitamin B₁₂ provided by the mother cannot be used effectively.
- [27.4] A. The fish tape worm *Diphyllobothrium latum* uses vitamin B₁₂ for growth and egg production; as many as 1 million eggs a day may be produced. The parasite also inactivates the B₁₂-intrinsic factor complex, inhibiting absorption in the terminal ileum. The fish tapeworm is the longest tapeworm to infect humans, sometimes growing to more than 10 meters in length. In 2% to 9% of infestations, megaloblastic anemia may result; otherwise, most infestations are asymptomatic. Risk factors include eating raw or undercooked fish. In North America, it is most commonly seen in the northern United States, Alaska, and Canada. Eggs have a unique morphology and are easily found in stool samples.

CLINICAL PEARLS

Goat's milk is deficient in folate and infants drinking goat's milk must be supplemented.

Antineoplastic agents can induce folate deficiency.

Vitamin B₁₂ dietary deficiency is rare.

Vitamin B₁₂ deficiency can lead to permanent neurologic damage.

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◆ CASE 28

The parents of a 3-year-old girl bring her to your office for routine well-child care. A quick review of her chart reveals that she was delivered at term without prenatal or postnatal problems. Her development thus far has been normal. The family reports that she is a rather “picky” eater; she does not like meats, but loves to drink large quantities of whole milk. On physical examination the child is normal with perhaps a bit of paleness to her mucous membranes. The family has not traveled, they live in a new home, and they report no family history of anemias. As part of your evaluation you obtain a complete blood count (CBC) and are informed that the peripheral smear shows microcytosis with hypochromia; her hemoglobin is 8 g/dL.

- ◆ What is the most likely etiology for this child’s microcytic anemia?
- ◆ What is the most appropriate test to confirm this etiology?
- ◆ What is the treatment?

ANSWERS TO CASE 28: Microcytic Anemia Secondary to Iron Deficiency

Summary: A 3-year-old previously healthy girl does not eat meats, consumes excess quantities of milk, and appears to be a bit pale on physical examination. She has a microcytic, hypochromic anemia on her CBC.

- ◆ **Most likely diagnosis:** Microcytic anemia caused by iron deficiency.
- ◆ **Best confirmatory test:** Probably no testing is required; an appropriate increase in blood count with a trial of iron is both diagnostic and curative. Alternatively, serum iron and total iron-binding capacity (TIBC) could be measured.
- ◆ **Treatment:** Administration of an oral iron preparation for several months to increase the blood count and to restore the total body iron stores.

Analysis

Objectives:

1. List causes, both acquired and genetic, of microcytic anemia.
2. Describe the typical laboratory findings of microcytic anemia.
3. Understand the individual treatments for the different causes of microcytic anemia.

Considerations

Many children are “picky” eaters, and, occasionally, a child’s dietary intake results in a medical condition. In this case, the consumption of large quantities of whole milk (low in iron) and the avoidance of iron-containing foods (red meats) has resulted in a dietary deficiency of iron

and anemia. Lead toxicity should also be considered, but this child's environment (a new home) is unlikely to contain lead-based paint, which is more commonly found in an older home.

APPROACH TO MICROCYTIC ANEMIA

Definitions

Mean corpuscular hemoglobin (MCH): Calculated value describing the amount of hemoglobin in a red cell as obtained by the formula: hemoglobin \div red blood cell count.

Mean corpuscular volume (MCV): The average size of a red blood cell. Normal values vary by age; large cells are termed macrocytic, small cells are termed microcytic.

Red cell distribution width (RDW): The variability of red cell size; can be increased with abnormally large red cells (seen in folic acid deficiency), as well as with abnormally small cells.

Reticulocyte count: The percentage of red blood cells that are immature (new) reticulocytes.

Clinical Approach

Iron deficiency is by far the most common cause of microcytic anemia in the pediatric population. Iron is required for hemoglobin synthesis, and a lack of iron will result in **small (microcytic), pale (hypochromic)** red blood cells with less hemoglobin than normal and subsequent impaired oxygen transport. Iron stores in a newborn infant are sufficient for hemoglobin synthesis until **6 to 9 months of age**, after which the child will become anemic unless adequate iron intake is maintained. Iron is found in many foods, but is not absorbed well (only about 10% of dietary iron is absorbed). Gastric acidity helps make iron more soluble; thus, medications or conditions that affect gastric pH will have an adverse effect on iron absorption in the proximal small intestine.

Commercially available infant formulas usually have iron supplementation. Breast milk typically has less iron than does formula, but

the iron in breast milk is absorbed more effectively. **Cow's milk and goat's milk have little iron content;** children exclusively fed these milks will develop iron-deficiency anemia.

In addition to nutritional deficiency, chronic occult blood loss must be considered as a possible etiology in a child with iron-deficiency anemia. Children may have ongoing occult blood loss with peptic ulcer disease, a Meckel diverticulum, polyps, or hemangiomas. Infection with the hookworms *Necator americanus* or *Ancylostoma duodenale* is the most common cause worldwide of microscopic blood loss and iron-deficiency anemia.

Clinical symptoms of iron deficiency are typical of anemia. Pallor is usually the most obvious sign. If the anemia is long-standing, tachycardia, cardiomegaly, and splenomegaly may result. In addition to these findings, behavior changes and irritability are attributable to iron deficiency. Pica (eating of nonfood items such as dirt and paint) is occasionally seen in iron-deficient children. Laboratory findings consistent with iron-deficiency anemia include microcytic, hypochromic red blood cells. **Ferritin, serum iron, and percent iron saturation are typically decreased,** while the **TIBC and RDW are increased.** The reticulocyte count is usually low. Thrombocytosis may occur, and thrombocytopenia rarely occurs.

Treatment of iron-deficiency anemia simply requires replacement of body stores with an oral iron preparation. The usual dose is 6 mg/kg/d of elemental iron. A reticulocytosis is expected in 3 to 4 days; the medication should be continued for 8 weeks following the return to normal hemoglobin levels to replenish total body stores.

In the 1970s, children were exposed to significant amounts of lead in the environment, including exposure to lead-based paints and leaded gasoline. In that era, **children with lead poisoning presented with acute encephalopathy,** at times preceded by a prodrome of **intermittent emesis and abdominal pain, constipation, and behavioral changes.** Diagnostic tests typically reveal an increased serum lead level and a microcytic anemia with coarse basophilic stippling on microscopy. Lead has since been eliminated from both paints and gasoline, and cases of pediatric lead toxicity have subsequently dropped as well. In a renovation of an older house, **lead paint chips may be ingested and dust contaminated with lead may be inhaled.** Children with severe lead poisoning must be removed from the situation until ap-

appropriate environmental changes are made. According to the Centers for Disease Control (CDC), a blood lead level greater than 10 $\mu\text{g/dL}$ requires environmental investigation and removal of the source of lead. Symptomatic children and children with a lead level greater than 25 $\mu\text{g/dL}$ require medical attention and chelation therapy (see also Case 11).

The **thalassemias** are a group of **genetic disorders** that generally manifest as **microcytic, hypochromic anemias** of varying severity. The underlying disorder is defective production of a polypeptide chain of hemoglobin resulting in unstable hemoglobin complexes and subsequent red cell death. Many different mutations are known to cause thalassemia. Patients with β -thalassemia major (also called Cooley anemia or β^0 -thalassemia) develop a severe hemolytic anemia in their first year of life and are transfusion dependent. This is because no β -globin chains are produced. Individuals with **thalassemia trait** are more difficult to diagnose; these patients typically have a **mild microcytic anemia** and often have been **treated with extended courses of iron replacement therapy without success**. Those affected with α -thalassemia are usually of southeast Asian descent. Iron deficiency may be distinguished from thalassemia trait by **hemoglobin electrophoresis**. Patients with thalassemia trait usually have **elevations of hemoglobin A₂** and occasionally elevations of hemoglobin F. In addition, iron studies will usually be normal in patients with thalassemia trait and the reticulocyte count will be normal or elevated.

Other, rarer causes of microcytic anemia include anemia of chronic disease, copper deficiency, aluminum toxicity, protein malnutrition, and sideroblastic anemia.

Comprehension Questions

- [28.1] A 3-year-old plump, healthy-appearing toddler comes to your office for her health maintenance examination. In discussing her dietary history with her mother, you find that the child refuses solid food, instead preferring to drink cow's milk almost exclusively. The parents tried to cut her off once, but could not endure the subsequent whining and gave in to her demands for milk. Her blood pressure, heart rate, and respiratory effort are normal. Her complete blood count is significant for

a hemoglobin of 7 g/dL and an MCV of 60 fL (normal 70–90). Appropriate therapy should include:

- A. Transfusion of packed red blood cells to get her to a normal hemoglobin, and then initiation of oral iron replacement.
- B. Discussion with the family about dietary changes, and then initiation of oral iron replacement.
- C. Intramuscular iron injection and follow-up visit in 1 week.
- D. Hospital admission to monitor vital signs.
- E. Reassuring the parents that the behavior and laboratory findings are normal.

[28.2] You are asked to see a patient in consultation with his primary doctor. The 2-year-old boy was admitted to the hospital this morning with severe iron-deficiency anemia (hemoglobin of 2 g/dL). He is tachycardiac and lethargic. The patient's physician wants to transfuse him with packed red cells. You suggest:

- A. Transfusion of 1 unit of packed red blood cells over 4 hours.
- B. Transfusion of 20 cc/kg of packed red blood cells.
- C. An initial transfusion of 2 or 3 cc/kg of packed red blood cells over 4 hours.
- D. He does not need transfusion of packed red blood cells; instead, iron supplementation only should be initiated.
- E. Transfusion of 1 L of normal saline.

[28.3] You are caring for a child with homozygous β -thalassemia (thalassemia major) who requires monthly blood transfusions. What ongoing medication is vital to the health of this patient?

- A. Penicillin
- B. Iron
- C. Hydroxyurea
- D. Deferoxamine
- E. Prednisone

[28.4] A father brings his 10-year-old child to you for evaluation of a rash and fatigue. The child was healthy child until about 2

months ago when he first developed a vesicular rash and swelling in his right foot. The rash seemed to coincide with a barefoot run through the family's farm, so the father thought little of it. At about the same time as the rash developed the child developed a cough. The father reports that while the cough has resolved the child has seemed ill and has not been able to do his chores. The boy has had occasional abdominal pain and diarrhea, but has no specific complaint today aside from fatigue. His physical examination is significant for pallor and mild abdominal tenderness without rebound. Laboratory studies reveal a microcytic, hypochromic anemia with an elevated percentage of eosinophils. The next step in arriving at this patient's diagnosis is:

- A. Iron studies
- B. Hemoglobin electrophoresis
- C. Serum chemistries
- D. Vitamin B₁₂ level
- E. Stool for ova and parasites

Answers

- [28.1] **B.** The child in the question has iron deficiency secondary to excessive cow's milk ingestion. Cow's milk contains little iron. The child's vital signs are normal, suggesting transfusion of blood is not necessary. Intramuscular iron can cause fever, anaphylaxis, hypotension, rash, and arthralgias; oral replacement is preferred. The best long-term management is dietary counseling for the family.
- [28.2] **C.** Patients with acute hemorrhage may be given red cell transfusion as quickly as necessary to maintain cardiovascular stability. In contrast, patients with severe iron-deficiency anemia or any other long-standing anemia have adapted to the persistently lower intravascular volume. Aggressive administration of fluids or packed red blood cells in such patients could quickly lead to heart failure; therefore, transfusion must start slowly. The

patient in the question requires transfusion because he is symptomatic with his anemia.

- [28.3] **D.** Patients requiring hypertransfusion will ultimately develop hemosiderosis if not treated with the iron-chelating medication deferoxamine. Each unit of packed red blood cells delivers 200 mg of iron; left untreated, the patient develops a significant iron overload.
- [28.4] **E.** This patient is on a farm, has been barefoot, developed a rash in his feet, developed cough, and now has microcytic anemia with eosinophilia. He is likely infected with a hookworm. Routine microscopy on a stool specimen for eggs will confirm that.

CLINICAL PEARLS



Iron-deficiency anemia is the most common microcytic anemia and is easily treated.



Worldwide, occult blood loss is the most common cause of iron-deficiency anemia.



Suspected iron-deficiency anemia that does not respond to prolonged courses of iron may be instead caused by a thalassemia trait.

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◆ CASE 29

A 14-year-old Hispanic boy comes to your office with a complaint of “brown urine” for the previous 3 days. He has been your patient since birth and has had no major illnesses or injuries, is active in band and cross-country track, and denies drug use or sexual activity. Three days prior he noticed his urine was tea colored, but he did not have dysuria or other symptoms and thought little of it until the color change persisted. Two weeks ago he stayed home from school for 2 days because of fever and a sore throat, but he seemed to get better spontaneously and has been well since. His review of systems is remarkable only for his eyes being a little puffy; he attributes it to late-night studying for final examinations. On physical examination, he is afebrile, his blood pressure is 135/90 mmHg. He is active and nontoxic in appearance and his only examination finding is some periorbital edema. The urine dipstick has a specific gravity of 1.035 and contains 2+ blood and 2+ protein. You spin the urine, resuspend the sediment, and identify red blood cell casts under the microscope.

- ◆ What is the most likely cause of this child’s hematuria?
- ◆ What laboratory tests would support this diagnosis?
- ◆ What is the prognosis in this condition?

ANSWERS TO CASE 29: Acute Poststreptococcal Glomerulonephritis

Summary: A healthy teenage boy develops tea-colored urine, which on microscopy reveal red blood cells, periorbital edema, and mild hypertension with a preceding pharyngitis.

- ◆ **Most likely diagnosis:** Acute poststreptococcal glomerulonephritis (APSGN).
- ◆ **Laboratory studies:** C₃ (low in 90% of cases), C₄ (usually normal): antistreptolysin-O (ASO) enzyme antibodies and antideoxyribonuclease B (anti-DNase B) antibodies provide evidence of recent streptococcal infection.
- ◆ **Prognosis:** Excellent, with 95% to 98% of affected children recovering completely.

Analysis

Objectives

1. Describe the typical presentation of APSGN.
2. List the different diagnostic possibilities for a patient with dark urine.
3. Discuss appropriate follow-up care for the patient with APSGN.

Considerations

This child is otherwise healthy, had a pharyngitis that was not evaluated at the time, and now has hematuria, proteinuria, edema, and hypertension. While APSGN is the most probable explanation for this boy's condition, other possibilities must be considered. Strenuous activity can cause rhabdomyolysis and subsequent dark urine, but patients with this condition often will have muscle aches, fatigue, nausea and vomiting,

and fever. Immunoglobulin (Ig) A (Berger) nephropathy is characterized by recurrent painless hematuria, usually preceded by an upper respiratory tract infection; if this boy has recurrent episodes, this diagnosis should be entertained. Henoch-Schönlein purpura (HSP) is a relatively common cause of nephritis in the pediatric population; however, most of these cases occur in younger children, peaking in incidence between 4 and 5 years of age. Lupus nephritis can present as described in the case, and should be considered if the hematuria does not resolve or if his C_3 does not become normal in 6 to 12 weeks.

APPROACH TO APSGN

Definitions

Glomerulonephritis: Inflammation of the glomeruli resulting in the classic triad of hematuria, proteinuria, and hypertension.

Red cell casts: Injured glomeruli have increased permeability and leak red cells and proteins into the proximal convoluted tubule. These substances subsequently clump in the distal convoluted tubule and in the collecting ducts; when passed, these clumps of cells retain the shape of the tubule in the urine. Casts are markers for glomerular injury.

Clinical Approach

Acute poststreptococcal glomerulonephritis is the most common of the postinfectious nephritides, comprising 80% to 90% of cases. Other bacteria, viruses, parasites; and fungi have also been implicated in postinfectious glomerulonephritis (PIGN). The group A β -hemolytic streptococcal (GABHS) infection can be in the form of either pharyngitis ("strep throat") or a superficial skin lesion (impetigo). Not all GABHS infections result in APSGN; certain strains of GABHS have been identified as "nephritogenic" (M type 12 and M type 49) and are more likely to result in APSGN. The other well-known complication of GABHS infection, rheumatic fever, only rarely occurs concomitantly with APSGN. **Administering antibiotics during the initial GABHS**

infection may reduce the subsequent risk of developing rheumatic fever, yet has not been shown to prevent APSGN. The risk of nephritis after infection with a nephritogenic strain of GABHS remains 10% to 15%.

Males are more commonly affected with APSGN than are females. This condition is most common in children between the ages of 5 and 15 years of age; it is rare in toddlers and infants.

Generally the interval between GABHS pharyngitis and APSGN is 1 to 2 weeks; the interval between GABHS impetigo and APSGN is 3 to 6 weeks. Onset of symptoms is abrupt. Although almost all patients with APSGN have microscopic hematuria, only 30% to 50% develop gross hematuria. In addition, 85% present with edema and 60% to 80% develop hypertension. Hypertension is rarely severe enough to result in hypertensive encephalopathy.

The most important laboratory test in APSGN is measurement of the serum C_3 and C_4 levels. C_3 is low in 90% of APSGN cases, while C_4 is usually normal. If both are low, an alternate diagnosis must be considered. Urinalysis typically reveals high specific gravity, low pH, hematuria, proteinuria, and red cell casts. Documentation of a recent streptococcal infection is helpful to confirm the diagnosis. Serum markers of recent streptococcal infection include the presence of ASO enzyme antibodies and anti-DNase B antibodies. ASO antibodies are found in 80% of children who recently had GABHS pharyngitis, but in less than 50% of children who recently had GABHS skin infection. Unfortunately, ASO titers are positive in 16% to 18% of normal children. Anti-DNase B antibodies assays are more reliable; they are present in almost all patients after GABHS pharyngitis and in the majority of patients after GABHS skin infection. Antibodies to other streptococcal antigens, such as NADase, hyaluronidase, and streptokinase may be assayed as well. Renal biopsy for children suspected of having APSGN is no longer routine. Treatment of APSGN is generally supportive. Fluid balance is crucial; diuretics, fluid restriction, or both may be necessary. Sodium and potassium intake may require restriction. Hypertension is usually easily controlled with calcium-channel blockers. Strict bed rest and corticosteroid medications, often used in the past, are not helpful. Dialysis is rarely required.

Resolution is rapid and complete in most cases. The edema resolves in 5 to 10 days, and patients are usually normotensive within 3 weeks.

C₃ levels are usually normal in 2 to 3 months; persistently low C₃ is uncommon in APSGN, and should prompt a search for an alternate diagnosis. The urinalysis in APSGN, however, may be persistently abnormal for several years.

Comprehension Questions

- [29.1] A 16-year-old boy comes to your office complaining of intermittent cola-colored urine of several years, usually when he has a "cold." He is otherwise well and has no other complaints. When the dark-colored urine is present, he does not have dysuria. None of his family members has similar complaints, nor is the family history positive for renal disease. On physical examination he is normotensive and has no obvious abnormalities. The most likely cause of this teen's intermittent hematuria is:
- A. Acute poststreptococcal glomerulonephritis.
 - B. Henoch-Schönlein purpura nephritis.
 - C. IgA nephropathy.
 - D. Recurrent kidney stones.
 - E. Rapidly progressive glomerulonephritis (RPGN).
- [29.2] The parents of a healthy 12-year-old girl recently moved to your town and bring her to you for a physical examination prior to summer camp. They have no complaints and the girl denies any problems. Her last menses was normal 2 weeks prior. The camp requires a urine screen. To your surprise, the clean-catch urine screen is found to have significant hematuria. Red cell casts are noted on centrifuged urine. You discuss your findings with the parents and they respond that "everyone on dad's side of the family has blood in their urine and they are all doing well." The family history is negative for deafness and for renal failure. Microscopy of renal tissue from this patient or her father will likely reveal:
- A. Thinning of the basement membrane.
 - B. Immune complex deposition in the mesangium.

- C. Endothelial cell swelling and fibrin in the subendothelial space.
- D. Large numbers of crescentic glomeruli.
- E. Renal cell carcinoma.

[29.3] A 17-year-old girl comes to the office complaining of persistent joint tenderness for the previous 2 months that has limited her summer job of lifeguarding at the neighborhood pool. In the morning, she awakens with bilateral knee pain and swelling and right hand pain. The pain eases during the day but never completely resolves. Nonsteroidal antiinflammatory medications help slightly. She also wants a good “face cream” because she reports that the sun exposure at the pool “has worsened her acne.” On physical examination you notice facial erythema involving the cheeks and nasolabial folds. She has several ulcers in her mouth that she calls cold sores, bilateral knee effusions, and her distal interphalangeal joints on her right hand are swollen and tender. Her liver is palpable 3 cm below the costal margin. You perform a urinalysis and find microscopic hematuria and proteinuria. What is the likely cause of this young woman’s arthritis?

- A. Juvenile rheumatoid arthritis
- B. Osteoarthritis
- C. Postinfectious arthritis
- D. Lyme disease
- E. Systemic lupus erythematosus

[29.4] You are not surprised to see again one of your most challenging patients, a 16-year-old adolescent girl who has been in the office several times a week over the last 2 months complaining of cough, occasional hemoptysis, malaise, and intermittent low-grade fever. Thus far you have identified a microcytic, hypochromic anemia for which she has been taking iron (without response) and migratory patchy infiltrates on chest radiograph that seem unaffected by antibiotic treatment. She has no tuberculosis exposure risks and her tuberculin skin test was neg-

ative. Today she also complains of facial edema and tea-colored urine. You suddenly realize her symptoms can be grouped as:

- A. Alport syndrome.
- B. Hemolytic-uremic syndrome.
- C. Nephrotic syndrome.
- D. Goodpasture syndrome.
- E. Denys-Drash syndrome.

Answers

- [29.1] C. Recurrent painless gross hematuria, frequently associated with an upper respiratory tract infection, is typical of IgA nephropathy. These patients may develop chronic renal disease over decades. If proteinuria, hypertension, or impaired renal function were found, a biopsy would be necessary.
- [29.2] A. This history is consistent with benign familial hematuria, an autosomal dominant condition that causes either persistent or intermittent hematuria without progression to chronic renal failure. Biopsy reveals a thin basement membrane; in some cases, however, the biopsy is normal. Immune complex deposition with IgA in the mesangium is seen in Henoch Schönlein purpura and IgA nephropathy; endothelial cell swelling with fibrin deposition is seen in hemolytic-uremic syndrome, and crescentic glomeruli are seen in rapidly progressive glomerulonephritis.
- [29.3] E. Systemic lupus erythematosus affects more women than men and nephritis is one of the more common features seen at presentation. Her rash, photosensitivity, oral ulcers, hepatomegaly, arthritis, and nephritis combine to make this a likely diagnosis. A positive antinuclear antibody and low C_3 and C_4 would help to confirm the diagnosis.
- [29.4] D. Goodpasture syndrome is the clinical diagnosis when patients exhibit nephritis and pulmonary hemorrhage. It can be

secondary to a number of conditions, including systemic lupus erythematosus and Henoch-Schönlein purpura. Alport syndrome is a genetic defect in collagen synthesis that leads to abnormal basement membrane formation; patients will develop hematuria, proteinuria, and renal failure. Denys-Drash syndrome is a group of findings composed of Wilms tumor, gonadal dysgenesis, and nephropathy.

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◆ CASE 30

A mother and father bring their 5-year-old daughter to your clinic because she started developing breasts 3 months ago and recently started growing pubic hair. Physical examination reveals a girl whose height and weight are above the 95th percentile on standardized growth curves. She has Tanner stage II breast and pubic hair development, oiliness of the skin, and facial acne.

- ◆ What is the most likely diagnosis?
- ◆ What is the best next step in the evaluation?

ANSWERS TO CASE 30: Precocious Puberty

Summary: A 5-year-old girl has breast and pubic hair development, tall stature, and facial acne.

- ◆ **Most likely diagnosis:** Idiopathic central precocious puberty.
- ◆ **Next step in the evaluation:** Gather a history, including birth history, illnesses, hospitalizations, medications, other siblings' health status, family history of early puberty, and diseases that run in the family. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and bone age radiographs of the left hand and wrist are helpful.

Analysis**Objectives**

1. Understand the underlying causes of precocious puberty.
2. Describe which laboratory and radiologic tests are most helpful in determining the etiology of precocious puberty.
3. Establish the treatment and follow-up necessary for a child with precocious puberty.

Considerations

This patient has several signs of precocious puberty—breast development, pubic hair development, and tall stature for 5 years of age. It is unclear whether this child has gonadotropin-dependent (true, central) precocious puberty or gonadotropin-independent precocious pseudo-puberty (puberty resulting from noncentral sources). An organic central nervous system cause of true precocious puberty must be ruled out in this child because she is younger than 6 years of age (it must be ruled out in boys of any age).

APPROACH TO PRECOCIOUS PUBERTY

Definitions

Delayed puberty: No signs of puberty in a girl by 13 years of age and in a boy by 14 years of age. May be caused by gonadal failure, chromosomal abnormalities (Turner syndrome, Klinefelter syndrome), hypopituitarism, chronic disease, or malnutrition.

Gonadotropin-dependent (true, central) precocious puberty: Stems from hypothalamic-pituitary-gonadal activation and leads to all of the secondary sex characteristics.

Gonadotropin-independent' precocious pseudopuberty: No hypothalamic-pituitary-gonadal activation; the hormones are usually either exogenous (birth control pills, estrogen creams) or from adrenal/ovarian tumors.

Gonadotropin-releasing hormone: Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus. GnRH stimulates the pituitary to produce LH and FSH.

Incomplete (partial) precocious puberty: Premature thelarche (early breast development), premature adrenarche (pubic hair related to adrenal hormones), or premature menarche (early menstruation).

Precocious puberty: The onset of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys; this definition is somewhat arbitrary because of the marked variation in the age at which puberty begins in normal children in different ethnic groups. In general, African American girls show signs of puberty earlier than do white girls.

Premature adrenarche: Early activation of adrenal androgens, causing pubic and axillary hair development and body odor. Typically occurs in girls 6 to 8 years of age. The pubic and axillary hair gradually increases. Congenital adrenal hyperplasia must be ruled out in these children.

Premature thelarche: Breast development at an early age, typically between 1 and 4 years of age. Pubic/axillary hair does not develop and linear growth acceleration does not occur.

Clinical Approach

True precocious puberty, which is far more common in girls than boys, stems from **secretion of hypothalamic GnRH**. Although the onset of sexual maturation is at a young age, **the pattern of progression of pubertal events is normal**. **Sexual precocity is idiopathic in more than 90% of girls**, whereas a structural central nervous system abnormality is present in 25% to 75% of boys.

Girls with precocious puberty, **independent of pituitary gonadotropins**, have a nongonadotropin-stimulated or independent source of estrogens causing their pubertal changes. An exogenous source of **estrogen** (skin creams and medications, particularly birth control pills and hormone-replacement therapies) or estrogen-producing **tumor of the ovary or adrenal gland must be considered**. Central nervous system lesions causing precocious puberty without neurologic symptoms are rarely malignant and seldom require neurosurgical intervention.

A detailed history offers important clues regarding the onset of puberty. Three main patterns of precocious pubertal progression can be identified, particularly for girls. Most girls who are younger than 6 years of age at onset have rapidly progressive sexual precocity, characterized by rapid physical and osseous maturation, leading to a loss of ultimate height potential. Other girls, who are generally older than 6 years of age at onset, have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. A third group, representing a small percentage of girls, has spontaneously regressive or unsustained central precocious puberty at a young age, with normal pubertal development at an expected age.

The age at which pubertal changes were first noticed as well as the type and sequence of changes (breast, pubic hair, axillary hair, maturation of external genitalia, menstruation) give valuable information regarding the etiology of the problem. Important questions include:

- Does the child show evidence of linear growth acceleration; that is, is the child outgrowing shoes and clothes rapidly?
- Has the child's appetite increased?
- Has the child developed a body odor?

- Is there a possibility that the child was exposed to an exogenous source of sex steroids (oral contraceptives, hormone replacement medications, anabolic steroids)?
- At what ages did the parents and siblings develop pubertal changes?
- Is there a known or suspected family history of congenital adrenal hyperplasia?

A neurologic history determines past medical problems (hydrocephalus, severe head trauma, encephalitis, meningitis) and the presence of headaches, visual problems, or behavior changes.

The physical examination offers further important information (Figures 30-1 and 30-2). Current and previous height measurements are critical for determining the child's growth velocity. The skin should be examined for signs of oiliness, acne, and café-au-lait spots (the latter being associated with neurofibromatosis). The presence of axillary hair and body odor, the amount of breast tissue, and whether the nipples and areolae are enlarging and thinning should be documented. The amount, location, and character of pubic hair should be noted. The abdomen is palpated for masses. Boys are examined for enlargement of the testes (>2.5 cm in precocious puberty) and penis, as well as thinning of the scrotum (prepubertal scrotum is thick and nonvascular). If the testes are different in size and consistency, a unilateral mass must be considered. Transillumination of the testes may be helpful. In girls, the clitoris, labia, and vaginal orifice are examined to determine whether there is maturation of the labia minora, estrogenization of the vaginal mucosa (pink and dull rather than shiny and red), and vaginal secretions. A complete neurologic examination should be performed.

In children with precocious puberty, serum sex hormone concentrations are usually appropriate for the stage of puberty, but inappropriate for the child's chronologic age. When compared to expected levels for a child's age, serum estradiol concentrations are elevated in girls and serum testosterone levels are elevated in boys with precocious puberty. Because LH and FSH levels fluctuate, single samples are often inadequate. A sensitive immunometric assay for LH offers more sensitivity than the radioimmunoassay when using random blood samples. With this immunometric assay, serum LH concentrations are undetectable in prepubertal children and detectable in 50% to 70% of girls, and in a

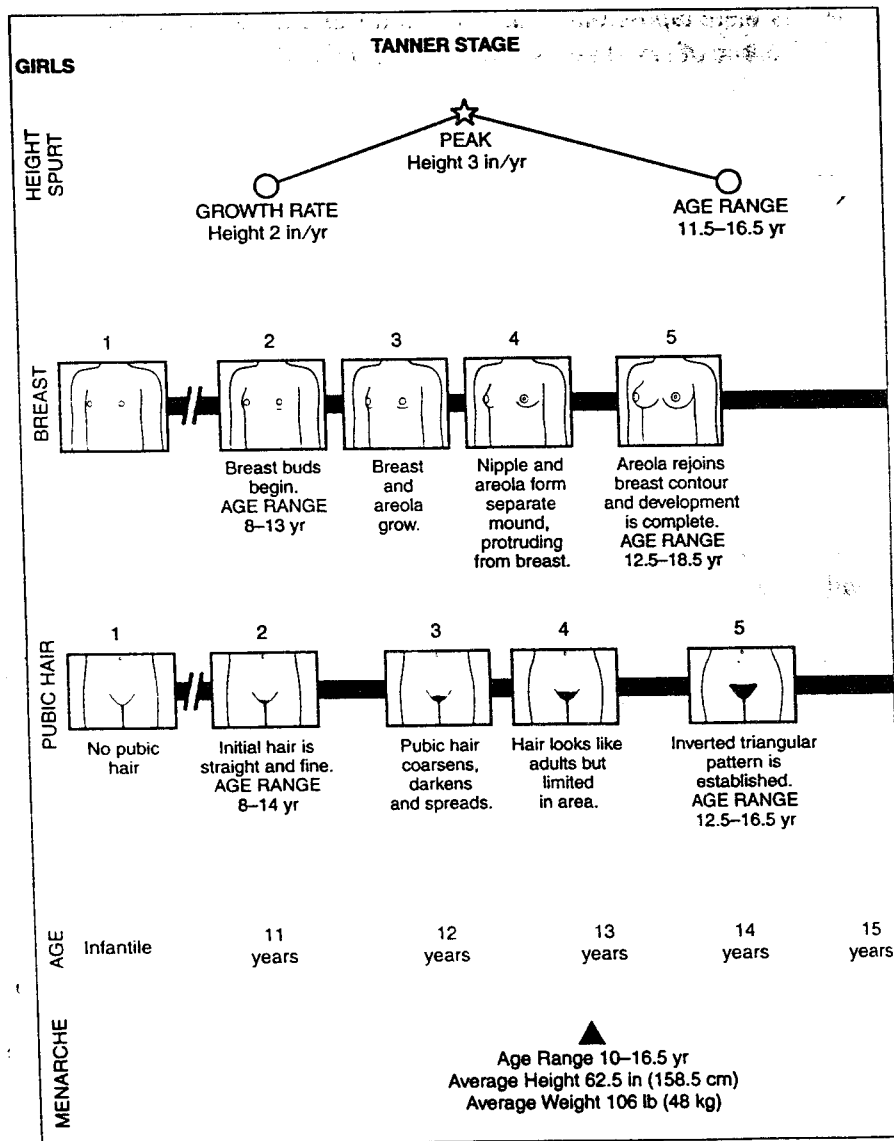


Figure 30–1. Female Tanner staging.

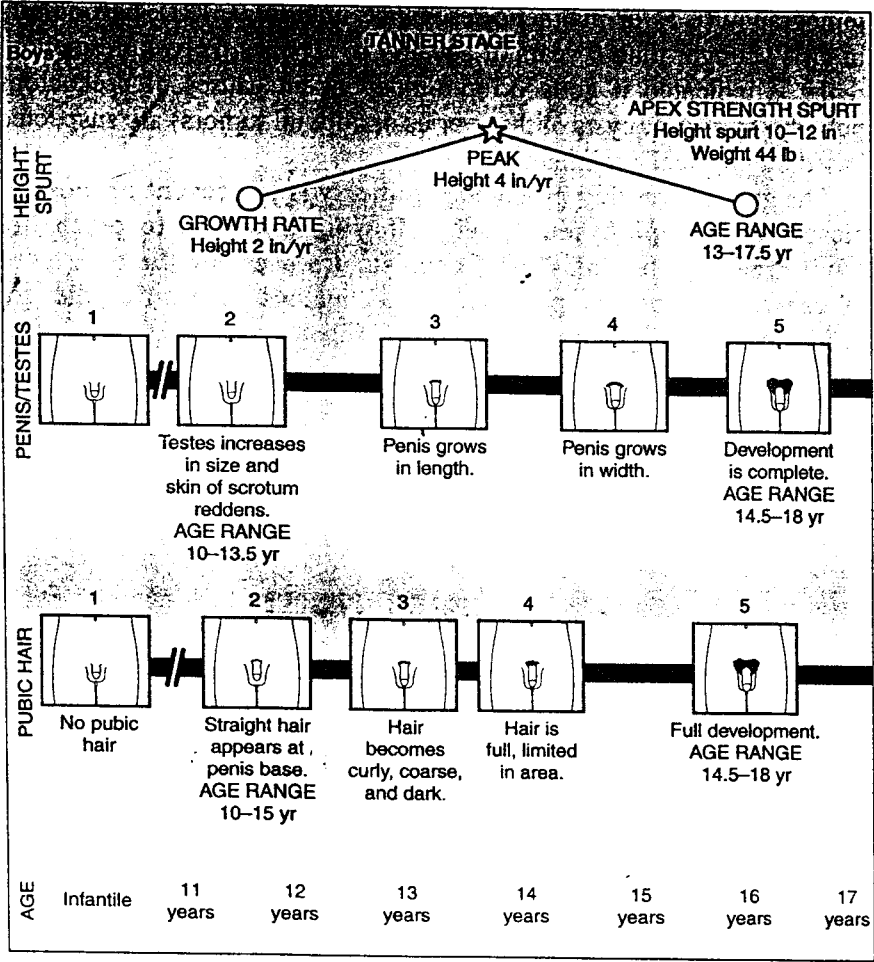


Figure 30-2. Male Tanner staging.

higher percentage of boys with central precocious puberty. A GnRH stimulation test, which measures briskness of response as well as peak values of LH and FSH after intravenous administration of gonadotropin-releasing hormone, is a helpful diagnostic tool.

Bone age radiographs are advanced beyond chronologic age in children with precocious puberty. Organic central nervous system causes of central sexual precocity are ruled out by computerized

tomography (CT) or magnetic resonance imaging (MRI), particularly in girls younger than 6 years of age and in all boys. Pelvic ultrasonography is indicated if gonadotropic-independent causes of precocious puberty (tumors or cysts of the ovaries or adrenal tumors) are suspected based on physical examination.

The goal of treating precocious puberty is to prevent premature closure of the epiphyses, thereby allowing the child to reach full adult growth potential. GnRH agonists are used for the treatment of central precocious puberty. These analogs desensitize the gonadotropic cells of the pituitary to the stimulatory effect of GnRH produced by the hypothalamus. Nearly all boys and most girls with rapidly progressive precocious puberty are candidates for treatment. Girls with slowly progressive puberty do not seem to benefit from GnRH agonist therapy in adult height prognosis. A pediatric endocrinologist should evaluate children considered for GnRH agonist treatment.

Comprehension Questions

[30.1] A mother brings her 4-year-old girl to your clinic. The girl has bilateral breast development that was first noticed 6 months ago. The child takes no medications and there is no source of exogenous estrogen in the home. The family history is unremarkable. The physical exam reveals a female who is 50th percentile for height and weight, has normal blood pressure, normal skin without oiliness, Tanner stage II breasts, soft abdomen without palpable masses, no body odor, neither pubic nor axillary hair, a mild estrogenization of the vagina. Which of the following is the most likely explanation for the child's breast development?

- A. Central precocious puberty
- B. Premature thelarche
- C. Congenital adrenal hyperplasia
- D. An adrenal tumor
- E. Premature adrenarche

[30.2] A father brings in his 4-year-old son who has started growing pubic hair. The child has also recently exhibited aggressive

“bullying” behavior at his preschool. History reveals that the child was a full-term infant who had no postnatal complications. The child takes no medications. Family history is unremarkable. He has one younger sister who is well. Physical exam reveals a white male who is above the 95th percentile for weight and height, with marked muscular development, Tanner stage II pubic hair development, scant axillary hair, prepubertal testicular size (<2.5 cm), a voice with a masculine quality, and skin with oiliness. The abdominal examination is normal. The child’s bone age is 6 years old. The next step in the care of this child is:

- A. Magnetic resonance imaging (MRI) of the brain.
- B. Serum 17α -hydroxyprogesterone level.
- C. Ultrasonogram of the testes.
- D. Reassurance to the family.
- E. Dexamethasone challenge test.

[30.3] A mother brings in her 13-year-old daughter who is “falling behind” in growth and who has not yet exhibited pubertal changes. Physical examination reveals a height less than the 5th percentile on standardized growth charts, no signs of secondary sexual characteristics, a small mandible, low posterior hairline, prominent ears, and a broad chest. The next step in the care of this child is:

- A. Treat with a short series of growth hormone injections.
- B. Bone age radiograph.
- C. Chromosome analysis.
- D. Ultrasonograph of abdomen.
- E. Reassurance to the family and recommendation to return in 6 months for remeasurement of height.

[30.4] A mother brings in her 14-year-old son into clinic because his teacher has expressed repeated concerns about his poor school performance and maladjusted behavior. He has poor grades in math, spelling, and reading. The boy is extremely shy and has always had difficulty in adjusting socially. Physical examination reveals a slim boy at the 95th percentile for height and the 5th

percentile for weight on standardized growth curves. It is very difficult to engage him in conversation. The testes are prepubertal (<2.5 cm) and he has mild hypospadias. He has no secondary sexual characteristics. Which of the following is the most likely cause of this boy's delay in puberty?

- A. Testicular tumor
- B. Hypopituitarism
- C. Noonan syndrome
- D. Klinefelter syndrome
- E. Marfan syndrome

Answers

- [30.1] B. All of this child's findings are estrogen related. She has no virilization. Postulated causes of premature thelarche include ovarian cysts and transient gonadotropin secretion. No treatment is necessary.
- [30.2] B. Boys with congenital adrenal hyperplasia have virilization despite prepubertal testicles. The virilization results from a disorder of steroid synthesis, leading to a deficiency of cortisol and an overproduction of androgenic intermediary metabolites such as 17 α -hydroxyprogesterone.
- [30.3] C. This child has Turner syndrome (45,XO). Other features include webbed neck, high-arched palate, increased nevi, renal anomalies, an increased arm-carrying angle, and edema of the hands and feet. Treatment includes recombinant human growth hormone and replacement therapy with estrogens.
- [30.4] D. Klinefelter syndrome (47,XXY) usually comes to attention because of gynecomastia and small testes. These male infants are usually clinically normal at birth. Treatment involves replacement therapy with a long-acting testosterone beginning at age 11 to 12 years.

CLINICAL PEARLS

True precocious puberty is the onset of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys. It stems from secretion of hypothalamic GnRH and is much more common in girls than boys.

Precocious puberty is idiopathic in more than 90% of girls, whereas a structural central nervous system abnormality is present in 25% to 75% of boys.

When compared to expected levels for a child's age, serum estradiol concentrations are elevated in girls and serum testosterone levels are elevated in boys with precocious puberty. Bone age radiographs are advanced beyond chronologic age.

The goal of treating precocious puberty is to prevent premature closure of the epiphyses, thereby allowing the child to reach full adult growth potential.

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◆ CASE 31

A 3740-g infant is vaginally delivered after an uncomplicated 38 weeks gestation. Upon initial physical examination, healthcare providers have immediate difficulty in determining whether the infant is a boy or a girl. The infant has what appears to be small scrotal sacs that resemble enlarged labia and no palpable testes and either a microphallus with a hypospadias or an enlarged clitoris. No vaginal opening is apparent. The remainder of the exam is normal.

◆ What is the most likely diagnosis?

◆ What is the next step in evaluation?

ANSWERS TO CASE 31: Ambiguous Genitalia

Summary: A full-term newborn with ambiguous genitalia and an otherwise normal examination.

- ◆ **Most likely diagnosis:** Congenital adrenal hyperplasia.
- ◆ **Next step in evaluation:** A karyotype analysis and a serum 17 α -hydroxyprogesterone level.

Analysis

Objectives

1. Understand the underlying causes of ambiguous genitalia.
2. Describe factors that influence assignment of sex in infants with ambiguous genitalia.
3. Describe the treatment and follow-up of infants after sex is assigned.

Considerations

This neonate with sexual ambiguity represents a true pediatric psychosocial emergency. Upon proper assignment of gender for rearing and appropriate continued medical management, individuals born with ambiguities of the genitalia should be able to lead well-adjusted lives and ultimately satisfactory sex lives. To obtain this favorable outcome, **making a correct diagnosis as early as possible is critical.** The assignment of gender in the neonate born with sexual ambiguity should be strongly influenced by the possibilities that exist for achieving unambiguous and sexually useful genital structures. Clear and comprehensive discussions with the parents, taking into account their level of understanding, anxieties, and religious, social, and cultural beliefs are critical for an appropriate gender assignment. Once the sex for rearing is assigned, the gender role should be reinforced by appropriate surgical, hormonal, and psychological measures.

The major treatment consideration for infants with ambiguous genitalia is the possibility of achieving cosmetically and functionally normal external genitalia by surgical and hormonal means. **Because the presence of ambiguous external genitalia may reinforce doubt about the sexual identity of the infant, reconstructive surgery is performed as early as medically and surgically feasible, usually before 6 months of age.** Feminizing genitoplasty is the most common surgical procedure performed in the female pseudohermaphrodite, and in the true hermaphrodite and the male pseudohermaphrodites reared as females. The goal of this surgery is to reduce the size of the clitoris while maintaining vascularity and innervation, feminizing the labioscrotal folds, and ultimately creating a vagina. A high incidence of gonadal tumors in individuals with certain forms of gonadal dysgenesis makes it mandatory to do a gonadectomy concurrently with the initial repair of the external genitalia. **A male with hypospadias often requires multiple procedures to create a phallic urethra. Circumcision is avoided in these individuals because the foreskin tissue is commonly used for reconstruction.**

If steroid production is the underlying etiology of the intersex problem, treatment is provided to prevent further virilization. **Administration of hydrocortisone to individuals with CAH helps to inhibit excessive production of androgens and further virilization.** Hormone substitution therapy in hypogonadal patients is prescribed in a manner so that secondary sexual characteristics develop at the expected time of puberty. Oral estrogenic hormone substitution is initiated in females and repository injections of testosterone are given to males. With the exception of some female pseudohermaphrodites and true hermaphrodites reared as females, disorders that cause ambiguous genitalia usually lead to infertility.

Comprehension Questions

- [31.1] A 3650-g term infant is delivered to a 27-year-old female. The infant has ambiguous genitalia including an enlarged clitoris/microphallus and one palpable testis in the labioscrotal folds. Radiologic studies reveal that the infant has a uterus and ovaries. Which of the following is the most likely explanation for the child's ambiguous genitalia?

- A. True hermaphroditism
- B. Male pseudohermaphroditism
- C. Congenital adrenal hyperplasia
- D. Female pseudohermaphroditism
- E. Aromatase deficiency

[31.2] A mother brings in her 1-week-old son who has vomited four times over the last 24 hours. He has no fever or diarrhea and no one in the home has been ill. The infant is breast-feeding poorly and appears to be “floppy” to the mother. He has had only one wet diaper in the last 12 hours. The physical examination reveals a lethargic ill-appearing infant who has lost 250 g since birth; his pulse is 110 beats per minute; his buccal mucosa is dry, and he lacks skin turgor. In addition to stabilization procedures and measurement of his serum electrolytes, what endocrinologic test would be reasonable to consider?

- A. Serum cortisol level
- B. Urine cortisol level
- C. Serum 21-hydroxylase level
- D. Serum 17α -hydroxyprogesterone level
- E. Serum testosterone level

[31.3] A mother brings in her 15-year-old daughter because she has never started her periods. She otherwise is healthy and takes no medications. Her past medical history is unremarkable except for inguinal hernia repair as an infant. Family history is unremarkable. Physical examination reveals a white female who is at the 75th percentile for height and weight. She has Tanner stage IV breast development and no pubic or axillary hair development. Her anogenital examination reveals a short pocket-like vaginal opening. Which of the following is the most likely explanation for the child’s amenorrhea?

- A. Congenital adrenal hyperplasia
- B. Turner syndrome
- C. Testicular feminization
- D. Pituitary tumor
- E. Adrenal tumor

[31.4] You examine a full-term 3780-g newborn in the nursery and notice that he has marked hypotonia, a very small penis, and unilateral cryptorchidism. Which of the following is the most likely explanation for this infant's findings?

- A. Maternal treatment with steroids
- B. Congenital adrenal hyperplasia
- C. Mixed gonadal dysgenesis
- D. Male pseudohermaphroditism
- E. Prader-Willi syndrome

Answers

- [31.1] A. The gonad in the labioscrotal fold suggests a testis; however, the presence of a uterus and an ovary on sonography is seen, which is highly suggestive of a true hermaphrodite. The assignment of sex to a true hermaphrodite should be based on the possibilities for surgical correction of the external genitalia. In general, assignment of female sex and an attempt to preserve an ovary or ovarian tissue are appropriate.
- [31.2] D. Male infants with salt-losing congenital adrenal hyperplasia develop clinical symptoms that are easily confused with those of pyloric stenosis, intestinal obstruction, heart disease, cow's milk intolerance, or other causes of failure to thrive. Their genitalia appear normal. A serum 17α -hydroxyprogesterone level would be elevated in this infant. Without appropriate treatment (hydrocortisone, mineralocorticoid and sodium supplementation), cardiovascular collapse and death may occur within a few weeks. Many states have neonatal screening programs for CAH, yet infants with salt-losing CAH (21-hydroxylase deficiency) can become very ill and die before the screening results are known.
- [31.3] C. Testicular feminization is a result of decreased androgen binding to target tissues or androgen insensitivity. These individuals have 46,XY karyotypes yet appear as phenotypically

normal females with a short or atretic vagina. Androgen insensitivity is the most common form of male pseudohermaphroditism. Maintaining female gender assignment is appropriate; and vaginoplasty is frequently needed after puberty.

- [31.4] E. Although severe hypotonia, failure to thrive, and hypogonadism characterize Prader-Willi syndrome in early life, hyperphagia, obesity, mental retardation, and the appearance of bizarre behavior become manifest by age 6 years. The insatiable appetite leads in many cases to morbid obesity, limited sexual function, and severe behavioral abnormalities. Mixed gonadal dysgenesis is a reasonable choice because of the unilateral cryptorchidism and hypogonadism, yet unlike infants with Prader-Willi syndrome, these infants do not exhibit severe hypotonia.

CLINICAL PEARLS

The goal of the evaluation of a neonate with sexual ambiguity (a psychologic emergency) is to determine the etiology of the intersex problem, assign gender, and intervene with surgical or other treatment as soon as possible.

The major treatment consideration for infants with ambiguous genitalia is the possibility of achieving cosmetically and functionally normal external genitalia by surgical and hormonal means.

Reconstructive surgery for a patient with ambiguous genitalia is performed as early as medically and surgically feasible, usually before 6 months of age.

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◆ CASE 32

A 13-year-old boy arrives at your office with the chief complaint of fatigue and leg pain. He notes several months of feeling listless and stopped participating in his school's soccer team as the star goalie because his legs are persistently sore. He remembers no antecedent illness, and he has no new stressors at home or at school. His past medical history is unremarkable. His mother and father immigrated to the United States, having grown up together in the same small town in Hungary. They have no known health problems.

On physical examination he is afebrile and is slightly tachycardic with a normal blood pressure. His conjunctivae and nail beds are pale. His head, neck, chest, and heart examinations are normal. His spleen is palpable 7 cm below the costal margin and his liver is palpable 5 cm below the costal margin. He has multiple bruises in varying stages of healing on his arms and legs, and both femurs seem diffusely tender to palpation.

The family returns from the laboratory with a printed set of results. His white blood cell count is $2500/\text{mm}^3$ with a normal differential and no blasts on the peripheral smear. His hemoglobin is 5.6 g/dL, and his platelet count is $56,000/\text{mm}^3$. His aspartate aminotransferase (AST) and alanine transaminase (ALT) levels are slightly elevated.

- ◆ What is this patient's most likely diagnosis?
- ◆ How can this diagnosis be confirmed?
- ◆ What treatment can be offered?
- ◆ What is this patient's prognosis?

ANSWERS TO CASE 32: Gaucher Disease (Type I)

Summary: A teenage boy of Eastern European origin presents with abdominal organomegaly, easy bruising, fatigue, and bone pain. His laboratory studies reflect pancytopenia without evidence of leukemic cells on peripheral smear, along with mildly elevated liver enzymes. His parents are from the same small town, increasing the possibility of consanguinity and making autosomal recessive disease more likely.

- ◆ **Most likely diagnosis:** Gaucher disease (type 1).
- ◆ **Confirmation:** Bone marrow biopsy showing characteristic cytology; white cell or fibroblast assay for specific enzyme activity.
- ◆ **Treatment:** Replacement of the deficient enzyme, β -glucocerebrosidase.
- ◆ **Prognosis:** With enzyme replacement, this patient should live well into adulthood.

Analysis**Objectives**

1. Recognize the signs and symptoms of lysosomal storage diseases.
2. Distinguish the natural history of the three types of Gaucher disease.
3. Describe the typical findings in patients with other lysosomal storage diseases.

Considerations

This 13-year-old boy complains of fatigue and bone pain, which might be common complaints in an adolescent, even without surrounding life stressors, and might be discounted as typical adolescent “growing

pains.” However, two points in the case suggest a more serious problem: (1) the patient has stopped participating in a sport that he apparently enjoys; and (2) he has organomegaly. Leukemia should also be high in the differential; the lack of lymphoblasts on his peripheral smear does not completely eliminate this diagnostic possibility, and therefore a bone marrow study will be required in most cases. Other storage diseases should also be considered in patients with organomegaly, but most would have presented long before adolescence.

APPROACH TO LYSOSOMAL STORAGE DISEASES

Definitions

Lysosomal storage disease: A disease in which a lysosomal enzyme is deficient or absent, including Gaucher, Tay-Sachs, mucopolysaccharidoses, Niemann-Pick, Fabry, and Krabbe disease (see Table 32-1).

Lysosome: An organelle in eucaryotic cells designed to break down sugars, proteins, bacteria, and old cellular material.

Clinical Approach

Lysosomes contain many different enzymes that assist in the destruction of cellular mucopolysaccharides, glycoproteins, and sphingolipids. A deficiency of one of these enzymes leads to progressive build-up of partially degraded material, thus disrupting lysosomal activity. Lysosomal storage diseases have a variety of presentations, dependent on the type of material stored and the material's usual distribution in the body.

Gaucher disease is the most common lysosomal storage disease, and is characterized by a deficiency in β -glucocerebrosidase and subsequent accumulation of glucocerebroside in the reticuloendothelial system, leading to organomegaly and infiltration of the marrow. The gene for β -glucocerebrosidase is encoded on chromosome 1. The disorder is **autosomal recessive**, and is subdivided into three groups:

Type 1, or nonneuronopathic Gaucher disease, accounts for almost all cases of this disorder. It is most common among those of Eastern

Table 32-1
SELECTED LYOSOMAL STORAGE DISEASES

DISEASE	DEFICIENCY	DEPOSITED SUBSTANCE	ONSET OF SYMPTOMS	CLINICAL PRESENTATION	NATURAL HISTORY	INHERITANCE
Gaucher	β -Glucocerebrosidase	Glucocerebroside	Variable forms	Organomegaly, bone pain, anemia, thrombocytopenia, fatigue; type 2 has early neurologic involvement	Type 1 can be normal; type 2 death within first 2 years; Type 3 death within 10-15 years	Autosomal recessive
Tay-Sachs	Hexosaminidase A	GM ₂ gangliosides	Variable	Decreased eye contact, increased startle, macrocephaly, seizures, cherry-red spot on macula (not in juvenile form), ataxia	Neurologic degeneration and death within several years of diagnosis	Autosomal recessive
Niemann-Pick group	Sphingomyelinase	Sphingomyelin	6 months to 2 years	A & C: organomegaly, failure to thrive, neurologic degeneration, seizures, discolored skin; B: pulmonary disease, but little neurologic involvement	Type A: rapidly progressive degeneration and death by 3 years; type B: survival to adulthood; type C: may survive to adulthood	Autosomal recessive

Fabry	α -Galactosidase A	Neutral glycosphingo-lipids	<10 years	Angiokeratomas, hypohidrosis, corneal opacities, vascular disease, pain crises	Survival to adulthood, death from vascular disease	X-linked, 1/40,000
Hurler syndrome (MPS I-H)	α -L-iduronidase	Heparan sulfate, dermatan sulfate	6-12 months	Coarse facies, corneal clouding, gingival hyperplasia, deafness, developmental regression, organomegaly, hernias, cardiomyopathy, congestive heart failure	Death in adolescence, may be sooner with cardiac involvement	Autosomal recessive 1/100,000 births
Scheie syndrome (MPS I-S, formerly called MPS V)	α -L-iduronidase	Dermatan sulfate	>5 years	Mildly coarse facies, cloudy corneas, deafness, joint problems, aortic valve problems, normal intelligence and near normal stature	Mild form of MPS, normal life span	Autosomal recessive
Hunter syndrome (MPS II)	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	1-2 years	Similar to MPS I-H without corneal clouding, onset more gradual	Death in the second or third decade; mild	X-linked

(Continues)

Table 32-1
SELECTED LYSOSOMAL STORAGE DISEASES (Continued)

DISEASE	DEFICIENCY	DEPOSITED SUBSTANCE	ONSET OF SYMPTOMS	CLINICAL PRESENTATION	NATURAL HISTORY	INHERITANCE
Sanfilippo syndrome (MPS III)	Heparan <i>N</i> -sulfatase, α - <i>N</i> -acetylglucosaminidase, acetyl CoA: α -glucosaminide acetyl-transferase, or <i>N</i> -acetylglucosaminide-6-sulfatase	Heparan sulfate	2-4 years	Developmental delay, behavior problems with aggression and hyperactivity, coarse facies, joint involvement, organomegaly, hernias (no corneal clouding), normal stature, can have cardiac involvement	Death in third or fourth decade form can have, normal life span	Autosomal recessive
Morquio syndrome (MPS IV)	Galactose-6-sulfatase or β -galactosidase	Keratan sulfate, chondroitin-6-sulfate	1 year	Primarily skeletal involvement with short stature, flared ribs, pectus carinatum, genu valgum, mild corneal clouding, organomegaly	Death in third or fourth decade, type A more severe with earlier death	Autosomal recessive

Abbreviation: MPS = mucopolysaccharidosis

European Jewish descent. In this population, the incidence is 1 in 1000 and the carrier rate is 1 in 18. Patients with type 1 have a variable time of onset of clinical symptoms, ranging from early childhood to adulthood. Some patients may not have any symptoms, and are only diagnosed when a routine examination reveals organomegaly. Patients typically present with chronic fatigue from anemia, easy bruising from thrombocytopenia, bone pain, and hepatosplenomegaly. More than 50 percent have radiographic evidence of bony changes, such as the abnormal cortex of the distal femur described as an "Erlenmeyer flask" abnormality. Patients usually have normal intelligence.

Gaucher disease type 2, also called **infantile Gaucher disease**, usually presents within the first 2 years of life. There is no ethnic predisposition, and this form is much less common than type 1. Presenting symptoms may include increased tone, trismus, strabismus, and organomegaly. These patients have progressive neurological deterioration, seizures, feeding problems, failure to thrive, and respiratory difficulties including stridor. They usually die from respiratory compromise by the age of 2 years.

Type 3, also called **juvenile or the Norrbottnian type** of Gaucher disease, is between types 1 and 2 in severity. This type is most prevalent in people with ancestry from the county of Norrbotten in northern Sweden. Death usually occurs in adolescence or early adulthood.

The **diagnosis of Gaucher disease is made by demonstrating a deficiency in β -glucocerebrosidase enzyme activity in either fibroblasts or leukocytes**. Samples of bone marrow, spleen, and liver of affected patients will usually demonstrate the characteristic Gaucher cell. The cell is not pathognomonic for Gaucher disease, however, as it can be seen in other disorders such as myeloma and granulocytic leukemia.

Treatment options for patients with Gaucher disease include enzyme replacement and bone marrow transplantation. Gaucher disease was the first lysosomal storage condition to have available enzyme replacement therapy; several other storage diseases now have enzyme replacement available or in development. **After enzyme replacement an improvement in the organomegaly occurs in all types of Gaucher disease.** Neurologic symptoms do not improve after enzyme replacement in patients with type 2 disease, yet do improve in patients with type 3 disease. Bone marrow transplantation is associated with a

myriad of complications and may not be the best treatment option for many patients with Gaucher disease.

Comprehension Questions

- [32.1] You are asked by a general practitioner to see a 3-year-old boy admitted for failure to thrive, recent mild tachypnea, and a cough. He has grown poorly throughout his first 3 years of life despite attempts at nutrition counseling. His parents report that he can no longer walk or feed himself, and his speech has become garbled with a hoarse voice. His physical examination reveals an afebrile, developmentally delayed boy with mild tachypnea. He is macrocephalic, has coarse facial features, and has a normal eye examination. He has mild contractures of his elbows and knees with decreased range of motion. His pulmonary examination is significant for fine crackles in the lung bases. His cardiac examination reveals a hyperactive precordium with tachycardia. He has organomegaly on abdominal examination. As you review these findings with his mother, she relates that both of her sisters had sons with the same problem; these boys died in their first decade of life, but no one knows why. She reports that her sisters have normal appearing, healthy daughters. The most likely disease afflicting this family is:
- A. Tay-Sachs disease
 - B. Gaucher disease
 - C. Hunter syndrome
 - D. Niemann-Pick disease
 - E. Morquio syndrome
- [32.2] Parents bring an 8-month-old infant to your office for a well-child checkup. The parents recently immigrated from Israel. The child has been in good health, but the parents are concerned that the child has been losing developmental milestones. She can no longer reach for objects and no longer rolls over. On physical examination you witness an exaggerated startle response to mild stimulation. She has no abdominal organomegaly, but her fun-

oscopic examination reveals a bright red spot with a surrounding grayish halo in the center of her macula. This child most likely has:

- A. Tay-Sachs disease
- B. Gaucher disease
- C. Hunter syndrome
- D. Niemann-Pick disease
- E. Morquio syndrome

[32.3] The parents of an infant boy newly diagnosed with type 2 Gaucher disease have questions about the prognosis of their child. In addition, they want to know if they can have more children and what the risk would be of having another child with the disease. You respond:

- A. The child can be expected to have a good prognosis with enzyme replacement; low risk of recurrence in another child.
- B. The child can be expected to have a good prognosis with enzyme replacement; 25% chance of recurrence in another child.
- C. A poor prognosis even with enzyme replacement can be expected; low risk of recurrence in another child.
- D. A poor prognosis even with enzyme replacement can be expected; 25% chance of recurrence in another child.
- E. A poor prognosis even with enzyme replacement can be expected; 100% chance of recurrence in another child.

[32.4] A 5-year-old boy is referred from the local elementary school for evaluation of behavioral difficulties. His development had been normal until 1 year ago when he became aggressive with his siblings. His father thought enrollment in kindergarten would help with discipline but his behavior has worsened, he seems unable to learn many of the concepts taught in school, and seems to have lost some of his vocabulary. His father notes that the boy has a history of sleeping difficulty. Both parents are from the Cayman Islands, but the father knows of no other family members with behavior difficulties or developmental delay.

The physical examination reveals a boy with normal stature, coarse facial features, and hirsutism. He has decreased range of motion in his elbows and knees, abdominal organomegaly, and an inguinal hernia. The most likely diagnosis in this boy is:

- A. Gaucher disease
- B. Sanfilippo syndrome (MPS III)
- C. Morquio syndrome (MPS IV)
- D. Tay-Sachs disease
- E. Fabry disease

Answers

- [32.1] **C.** This 3-year-old child with failure to thrive, developmental regression, heart failure, organomegaly, and coarse facial features has a lysosomal storage disease. The familial pattern is consistent with an X-linked disorder, thus Hunter syndrome (mucopolysaccharidosis [MPS] type II) is the most likely diagnosis. Most lysosomal storage diseases are autosomal recessive, but MPS II and Fabry disease are both X-linked.
- [32.2] **A.** This child likely has Tay-Sachs disease, a lysosomal storage disease common among those of Ashkenazi Jewish heritage. A cherry red spot in the center of the macula is characteristic. Cherry red spots may also be seen in some forms of Niemann-Pick disease; however, these patients typically have organomegaly.
- [32.3] **D.** Gaucher disease is inherited in an autosomal recessive manner. Therefore, each child of the same parents has a 25% chance of having the enzymatic defect leading to Gaucher disease. Infantile, or type 2, Gaucher disease has a poor prognosis. While enzyme replacement may help decrease organomegaly, the therapy does not seem to affect the neurologic symptoms. These patients frequently die in the first 2 years of life.
- [32.4] **B.** This child has a typical presentation of Sanfilippo syndrome; carrier rates in the Cayman Islands are 1 in 10 for Sanfilippo

type A. The behavior problems and developmental delay are frequently the first manifestations.

CLINICAL PEARLS

Gaucher disease is the most common lysosomal storage disease, caused by a deficiency of β -glucocerebrosidase enzyme, with increased incidence in persons of Eastern European Jewish descent.

Most lysosomal disorders are autosomal recessive; Hunter syndrome (MPS II) and Fabry disease are X-linked.

In general, lysosomal storage diseases are progressive; deposition of accumulated material leads to organomegaly and tissue injury.

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◆ CASE 33

A 6-year-old boy with no significant past medical history complains of a persistently runny nose without fever. His family notes that he has tried many over-the-counter cold remedies with only marginal and temporary success. When questioned further, his mother reports the symptoms are worse in the spring and summer. His complaints include paroxysms of sneezing, an itchy throat, and tearing of his eyes. His mother notes persistent mouth breathing and loud snoring. His physical examination reveals dark circles under his eyes and a crease across the bridge of his nose. His nasal turbinates are pale bluish in color and are boggy. He has clear nasal drainage.

◆ What is the most likely diagnosis?

◆ What is the best management for this condition?

ANSWERS TO CASE 33: Allergic Rhinitis

Summary: A 6-year-old boy with clear rhinorrhea and allergic symptoms including itchy throat, tearing eyes, an allergic crease, and allergic shiners.

- ◆ **Most likely diagnosis:** Allergic rhinitis.
- ◆ **Best management:** Avoidance of suspected allergens, systemic antihistamines, nasal steroids.

Analysis

Objectives

1. Describe the physiology of allergic rhinitis.
2. Become familiar with the differential diagnosis of persistent rhinitis.
3. Contrast the possible treatments of allergic rhinitis.

Considerations

This patient's symptoms are consistent with allergic disease. **The crease on his nasal bridge is the result of the "allergic salute," a characteristic upward rubbing of the nose.** His allergic "shiners" are likely caused by nasal mucosal edema interfering with **venous drainage and resulting in venous pooling in the area under the eye.** His family history is positive for allergic disease further suggesting this as the etiology of his chronic problem.

APPROACH TO ALLERGIC RHINITIS

Definitions

Allergic crease: A hypo- or hyperpigmented line across the bridge of the nose that results from chronic rubbing of the nose (also known as an "allergic salute").

Allergic salute: A characteristic upward rubbing of the nose with the palm of the hand.

Rhinitis: Inflammation of the nasal mucosa.

Sinusitis: Inflammation of the mucous membranes of a sinus cavity.

Clinical Approach

Allergic rhinitis is a common diagnosis in a pediatric practice, occurring in nearly 10% of children and increasing in prevalence with age. Allergic rhinitis must be distinguished from other causes of rhinitis. Viral and bacterial upper respiratory tract infections usually cause congestion and mucopurulent drainage. A foreign body in the nose can cause unilateral purulent, foul smelling, and sometimes bloody drainage. Persistent clear drainage, especially after trauma, can be indicative of a cerebrospinal fluid leak, and can be distinguished from other causes by the presence of glucose in the drainage. Cocaine abuse can lead to chronic clear or bloody rhinitis. Malignancy can cause a persistent bloody discharge.

Diagnostic testing is usually unnecessary; the diagnosis can be made by history and physical examination alone. The presence of eosinophils in a Hansel stain of nasal drainage lends support for the diagnosis of allergic rhinitis, but sinus imaging is rarely helpful. Allergy testing may be helpful in selected patients who have severe symptoms; the results are useful only if the inciting allergen(s) can be removed from the environment, or if immunotherapy (allergy injections) is being contemplated.

The management of rhinitis depends on the underlying etiology. **Viral upper respiratory tract infections do not require specific treatment, and the parents should be reassured about the self-limited nature of the disease.** Bacterial sinusitis usually improves with antibiotic therapy aimed at common upper respiratory pathogens such as *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and nontypeable *Haemophilus influenza*. Less commonly, *Staphylococcus aureus*, *Streptococcus viridans*, and anaerobes may be encountered. **Vasomotor rhinitis, symptoms similar to allergic but more related to weather changes, physical stimuli, or emotion in patients lacking atopic histories or eosinophilia in nasal smears, requires no specific treatment.** Nasal congestion caused by medications, including oral contraceptives,

reserpine, beta-blockers, methyldopa (Aldomet), aspirin, nonsteroidal antiinflammatory drugs, and overuse of decongestant nasal sprays, can be treated by elimination of the offending agent.

The principal treatment for allergic rhinitis is allergen avoidance. If the allergen is unidentified (or pervasive in the environment, like tree pollen), medications may be necessary. Antihistamines can control many of the allergic symptoms such as sneezing, itching, and nasal drainage. Many first-generation antihistamines, such as diphenhydramine (Benadryl), are sedating, thus limiting their usefulness in the school-aged child; **some of the newer antihistamines, such as loratadine (Claritin), are nonsedating, and are preferable alternatives.**

Decongestants are indicated in patients with significant nasal obstruction. These medications may be given alone or in conjunction with antihistamines. Pseudoephedrine is the most commonly used decongestant in pediatric medications. The United States Food and Drug Administration recently requested that pharmaceutical firms remove another decongestant, phenylpropanolamine, from all products after researchers demonstrated a link with stroke in older patients. Adverse effects of oral decongestants include hypertension, agitation, insomnia, and occasionally hallucinations. Topical decongestants in nasal sprays can be useful initially if significant obstruction exists, but these medications should only be used for a few days at a time. Chronic use of topical decongestants leads to rebound edema known as "rhinitis medicamentosa."

Nasal steroids are currently a mainstay of treatment in allergic rhinitis. Most can be used once or twice a day after the initial acute symptoms are under control. Adverse effects of these medications may include epistaxis, irritation, and burning; in general, however, they are well tolerated. Little or no systemic effect is expected, although some studies have suggested a slight effect on growth in patients who chronically use nasal or inhaled steroids.

Comprehension Questions

- [33.1] A 4-year-old boy presents to the emergency center with nasal drainage for 2 months. His mother has asthma and his father has eczema, otherwise his family history is negative. On examina-

tion, you find left sided nasal drainage that is foul smelling and blood tinged. He is completely obstructed on that side, but his other nostril is clear without drainage or edema. The next step in managing this patient should be:

- A. Nasal steroids and oral antihistamines
- B. Computerized tomography of the sinuses
- C. Oral antibiotics
- D. Otolaryngology evaluation for possible foreign body
- E. Reassurance that his condition is benign and observation only

[33.2] A 16-year-old girl arrives to your office as a new patient complaining of monthly upper respiratory tract infections over the last few years. She said her last doctor would always prescribe antibiotics, and she would eventually improve. She complains of clear nasal drainage with congestion, itchy eyes, itchy nose, and cough. The next step in managing this patient should be:

- A. Nasal steroids and oral antihistamines
- B. Computerized tomography of the sinuses
- C. Oral antibiotics
- D. Evaluation for possible foreign body
- E. Reassurance that her condition is benign and observation only

[33.3] A 4-year-old boy presents with a 3-month history of bilateral purulent nasal drainage. His father reports that he is afebrile and has no other complaints. Your examination reveals several small shiny gray pedunculated masses partially occluding the nasal meatus on both sides. A diagnostic workup should include:

- A. Nasal smear for eosinophilia
- B. Total immunoglobulin levels
- C. Nitroblue tetrazolium (NBT) test
- D. Sweat chloride test
- E. Complete blood count with peripheral smear

- [33.4] A 10-year-old girl complains of 5 months of left-sided nasal congestion. She has tried decongestants and antihistamines without success. She denies placing any object in her nose. Her mother brought her in today because she noticed increasing swelling and tenderness over the left side of her face. Her examination reveals a pink, nontender, fleshy mass in her left nares that is completely occluding the airway. Initial management should include:
- A. Sweat chloride test
 - B. Nasal steroids with antihistamines
 - C. Computerized tomography of the face
 - D. Foreign-body removal with alligator forceps
 - E. Reassurance and observation

Answers

- [33.1] **D.** This young patient with unilateral purulent nasal discharge is likely to have a foreign body in his nostril that should be removed as soon as possible. Although a malignancy is possible, a foreign body is more likely.
- [33.2] **A.** This patient has a classic history for allergic rhinitis. Patients frequently are told they have recurrent colds when in fact they have allergic symptoms. Although occasionally difficult to distinguish, a careful history and physical will usually distinguish allergic rhinitis from other causes of rhinitis.
- [33.3] **D.** While nasal polyps can result from chronic inflammation associated with allergic rhinitis and chronic sinusitis, a child with polyps who is less than 10 to 12 years old should be tested for cystic fibrosis. Approximately 25% of patients with cystic fibrosis have nasal polyps. The child in this case has no other symptoms of cystic fibrosis, but his age and the presence of nasal polyps make testing for cystic fibrosis a priority. Immotile cilia syndrome (Kartagener syndrome: situs inversus, chronic sinusitis and otitis media, and airway disease) is another diagnostic possibility in this patient, but the test to confirm this choice (electron microscopy of cilia) was not listed in the question.

- [33.4] C. Rhabdomyosarcoma is the most common pediatric soft-tissue sarcoma, and the head and neck location accounts for approximately half of these tumors. Rhabdomyosarcomas typically present as a mass that is sometimes tender, causing symptoms relating to the displacement of normal structures. When arising from nasal tissue, rhabdomyosarcomas can obstruct the nares and extend into the skull, causing cranial nerve involvement. The first logical step in evaluating such a patient is a computerized tomography or magnetic resonance imaging scan to determine the size and location of the tumor. A rhabdomyosarcoma that is completely resectable has the best prognosis.

CLINICAL PEARLS

◆ Allergic rhinitis is allergen mediated; thus, allergen avoidance is the best treatment.

◆ Nasal steroids offer the best treatment for chronic allergic rhinitis, often in conjunction with antihistamines.

◆ Nasal polyps can be sequelae of chronic inflammation and allergic rhinitis, but younger patients with polyps must be screened for cystic fibrosis.

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◆ CASE 34

A 16-year-old boy arrives in the emergency center by ambulance. He is a resident at the local police department's boot camp, serving a sentence for assault. He was in his normal state of health until early this morning, when he complained of a headache. At that time his temperature was 105.8°F (41°C). Over the course of the next 2 hours, he developed a stiff neck and began vomiting. The officers brought him in when he developed altered mental status. No one else in the boot camp is ill. In the emergency center, his heart rate is 135 beats per minute, blood pressure is 120/70 mmHg, respiratory rate is 25 breaths per minute, and temperature is 104°F (40°C). He is combative, unaware of his surroundings, and does not follow instructions. Kernig and Brudzinski signs are present.

- ◆ What is the most likely diagnosis?
- ◆ How would you confirm the diagnosis?
- ◆ What treatment is indicated?
- ◆ What are possible complications?

ANSWERS TO CASE 34: Bacterial Meningitis

Summary: A 16-year-old adolescent has fever, headache, a stiff neck, and altered mental status. He is tachycardic but normotensive.

➤ *Most likely diagnosis:* Bacterial meningitis.

◆ **Confirm diagnosis:** Lumbar puncture.

◆ **Treatment:** Intravenous antibiotics.

◆ **Complications:** Deafness, cranial nerve palsies, and, rarely, hemiparesis or global brain injury.

Analysis

Objectives

1. Describe the typical presentation of bacterial meningitis.
2. Describe how a patient's age affects the presentation and outcome of bacterial meningitis.
3. List typical pathogens and appropriate treatment strategies by age group.

Considerations

This teen has the typical triad of symptoms seen with meningitis: fever, headache, and a stiff neck. In addition, he has an altered mental status, a common finding in meningitis. Other considerations for altered mental status include viral meningoencephalitis, trauma, intentional or accidental ingestion, and hypoglycemia. Of these, only viral meningitis would be expected to explain the fever and stiff neck.

APPROACH TO BACTERIAL MENINGITIS

Definitions

Brudzinski sign: A physical finding consistent with meningitis; while the patient is supine, the neck is passively flexed resulting in involuntary flexion of the knees and hips.

Encephalitis: Inflammation of the brain parenchyma causing brain dysfunction.

Kernig sign: A physical finding consistent with meningitis; while the patient is supine, the legs are flexed at the hip and knee at 90-degree angles resulting in pain with extension of the leg.

Meningitis: Inflammation of the leptomeninges, typically infectious in origin, but may also be caused by foreign substances.

Clinical Approach

The microbiology and clinical presentation of meningitis varies based on the age of the patient. The incidence of neonatal meningitis is between 0.2 and 0.5 cases per 1000 live births. In the neonatal period, *Escherichia coli* and group B streptococcus (*Streptococcus agalactiae*) are common pathogens; *Listeria monocytogenes* is seen less commonly. Other organisms that may cause meningitis in neonates include *Citrobacter species*, *Staphylococcus species*, group D streptococci, and *Candida species*. Infants at risk for meningitis include low-birth-weight and preterm infants, as well as those born to mothers with chorioamnionitis, after a prolonged rupture of the amniotic membranes, or by a traumatic delivery. Most neonatal bacterial meningitis occurs from hematogenous spread; occasionally, a sinus tract (such as a pilonidal sinus or sacral dimple) or an infected skin structure will extend and cause meningitis. Clinical symptoms of meningitis in infants are not the typical triad of headache, fever, and stiff neck; symptoms in neonates are nonspecific. Infants with meningitis may have thermal instability (often hypothermia), poor feeding, emesis, seizures, irritability, and apnea. The infant may have a bulging fontanelle on physical examination, and may be either hypotonic or hypertonic.

Bacterial meningitis in older children is usually caused by *Streptococcus pneumoniae* or *Neisseria meningitidis*. Until recently, *Haemophilus influenza* type B was a common cause of pediatric meningitis, but immunization has all but eliminated this pathogen. Other less-common causes of meningitis in this age group include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella* species, and *Listeria monocytogenes*.

The incidence of pneumococcal meningitis is 1 to 6 cases per 100,000 children per year, with a predominance of cases occurring in the winter months. Pneumococcus is an encapsulated pathogen; therefore, children with either a poorly functioning or absent spleen are at increased risk of disease. African American children are more likely to contract pneumococcal meningitis. **Children with sickle cell disease are at particularly high risk**, with an incidence 300 times greater than in white children. Other risk factors for pneumococcal meningitis include sinusitis, otitis media, pneumonia, and head trauma with a subsequent cerebral spinal fluid (CSF) leak.

Neisseria meningitidis colonizes in the upper respiratory tract in approximately 15% of normal individuals, with nasal carriage as high as 30% detected during outbreaks of invasive *Neisseria* disease. Disease appears to be caused by "new" infection, and is not thought to occur in children with long-term carriage. In the United States, most disease is caused by serotypes B and C. Family and close daycare contacts of children with disease are at a 100- to 1000-fold increased risk of contracting disease. A plethora of other bacterial, viral, fungal, and mycobacterial agents can cause meningitis.

The classic symptoms of bacterial meningitis in older children and adults are fever, stiff neck, and headache. Other symptoms may include mental status changes, nausea, vomiting, lethargy, restlessness, ataxia, back pain, Kernig and Brudzinski signs, and cranial nerve palsies. **Approximately one-third of patients have a seizure during the course of the illness.** Patients infected with *N. meningitidis* often have a petechial or purpuric rash.

The diagnostic test of choice for patients with suspected meningitis is a lumbar puncture to examine the cerebrospinal fluid. The test is fairly safe in the pediatric population, with few complications. Contraindications to the procedure include a **skin infection over the site of the planned puncture**; evidence of or clinical concern for in-

creased intracranial pressure; and a critically ill patient who may not tolerate the procedure. Laboratory analysis of the CSF includes routine Gram stain and culture, white and red blood cell counts, and protein and glucose analysis. Bacterial antigen screens are usually performed in patients already receiving antibiotics at the time of the lumbar puncture because these antigens may persist for several days, even after the culture would be negative. Typical spinal fluid findings in bacterial meningitis include an elevated opening pressure. The fluid usually contains several hundred to several thousand white blood cells per cubic millimeter, with polymorphonuclear cell predominance. Typically, the protein is elevated and glucose is decreased.

Treatment strategies for the patient with meningitis reflect the age of the patient and the likely pathogens, in addition to the local resistance patterns of the possible pathogens. A Gram stain of the CSF can be an invaluable tool in the decision-making process. In the neonatal period, ampicillin often is combined with a third-generation cephalosporin or an aminoglycoside to cover infections caused by group B streptococcus, *L. monocytogenes*, and *E. coli*. Neonates in an intensive care setting may be exposed to nosocomial infections; prevalent pathogens in the specific nursery must be considered.

The increasing antibiotic resistance of *S. pneumoniae* in older children has changed initial management over the last decade. In many major cities, more than half of the pneumococcal isolates are either immediately sensitive or completely resistant to penicillin; 5% to 10% of the organisms are resistant to cephalosporins. Therefore, in suspected cases of pneumococcal meningitis a third-generation cephalosporin combined with vancomycin is typically recommended. Most strains of *N. meningitidis* are susceptible to penicillin or cephalosporins.

Acute complications of meningitis may include seizures, cranial nerve palsies, cerebral infarction, cerebral or cerebellar herniation, venous sinus thrombosis, subdural effusions, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with hyponatremia, and central diabetes insipidus. The most common long-term sequela of bacterial meningitis is hearing loss occurring in up to 30% of patients with pneumococcal meningitis and in up to 20% of children with *H. influenza* B infection. All patients with bacterial meningitis should undergo a hearing evaluation at the conclusion of antibiotic therapy. Less-common long-term complications include mental retardation or

neuropsychiatric and learning problems, epilepsy, behavioral problems, vision loss, and hydrocephalus.

Comprehension Questions

- [34.1] A 13-year-old boy arrives in the emergency center by emergency medical services (EMS). His parents report a 1-day history of fever, lethargy, and inability to awaken him this morning. In the emergency center his respiratory rate is 7 breaths per minute, his heart rate is 55 beats per minute, his temperature is 105.8°F (41°C), and his blood pressure is 60/40 mmHg. He has altered mental status, a stiff neck, and a purpuric rash over his trunk. The next step in the management of this patient should be:
- A. Computerized tomography of the head
 - B. Lumbar puncture
 - C. Intravenous antibiotics
 - D. Serum chemistries
 - E. Intubation
- [34.2] An 8-year-old child arrives in the emergency room with his parents complaining of persistent fever and headaches. Her parents report that for the 2 weeks prior she has complained of frontal headache, recently significant enough to keep her out of school. Her parents also note intermittent temperature elevation to 101°F (38.3°C). She started vomiting a nonbloody, nonbilious fluid a few days prior to arrival. The family has no history of headache or migraine. Her past medical history is significant for frequent episodes of otitis media and sinusitis, with her last episode of otitis media about 5 weeks ago. On physical examination you find a lethargic girl who appears to be in no respiratory distress. She has a temperature of 100°F (37.7°C), a heart rate of 109 beats per minute, and a blood pressure of 100/60 mmHg. She has nuchal rigidity and frontal sinus tenderness. The next step in managing this patient is:

- A. Computerized tomography of the head
- B. Intravenous promethazine for emesis
- C. Trial of subcutaneous sumatriptan for migraine
- D. Sinus radiographs
- E. Lumbar puncture

[34.3] A 2-week-old infant develops a temperature to 102°F (38.9°C). The infant was the product of an uncomplicated term gestation and has been at home since the second day of life. The irritable, fussy infant has a heart rate of 170 beats per minute and a respiratory rate of 40 breaths per minute. The infant's anterior fontanelle is full, but demonstrates no nuchal rigidity; the rest of the physical examination is unremarkable. Appropriate management of this infant is to:

- A. Encourage oral fluids and office follow-up in 24 hours.
- B. Prescribe oral amoxicillin and office follow-up in 1 week.
- C. Perform a lumbar puncture, blood culture, urine culture, and admit to the hospital.
- D. Order computerized tomography of the head followed by lumbar puncture.
- E. Prescribe intramuscular ceftriaxone and office follow-up in 1 week.

[34.4] A fully immunized 14-year-old boy complains of fever and stiff neck for 2 days. He also complains of a sore throat, and has not been able to eat anything for 1 day because of the pain. On physical examination he is alert and oriented, but he has nuchal rigidity and midline fullness in the posterior oropharynx. He is drooling to avoid the pain associated with swallowing. The next step in managing this patient is to:

- A. Order computerized tomography of the head
- B. Perform a lumbar puncture
- C. Order lateral neck radiographs
- D. Prescribe intravenous antibiotics
- E. Prescribe intramuscular antibiotics

Answers

- [34.1] E. This patient is in shock and in grave danger of impending death. The ABCs of airway, breathing, and circulation should take precedence over any diagnostic study. Because he is critically ill, the patient's lumbar puncture should be deferred until he is clinically stable. He likely has meningococcal meningitis; intravenous fluids to support his cardiovascular status and antibiotics should be administered as soon as possible after resuscitation is begun.
- [34.2] A. This girl has a history of sinusitis and a prolonged headache with worsening emesis and nuchal rigidity. She likely has an intracranial abscess as a complication of her sinusitis. In this instance, imaging (preferably with contrast) is performed prior to a lumbar puncture; performing a lumbar puncture in a patient such as this who may have a mass lesion causing increased intracranial pressure can result in herniation of the brain and death of the patient.
- [34.3] C. This infant potentially has a serious bacterial infection, and a complete evaluation including a lumbar puncture is performed. Infants do not reliably demonstrate Kernig or Brudzinski signs; thus, a lack of nuchal rigidity should not preclude a lumbar puncture. Performing a computerized tomography scan before lumbar puncture in an infant with an open anterior fontanelle is rarely necessary as herniation of the brain is exceedingly rare.
- [34.4] C. This boy has a retropharyngeal abscess causing his neck stiffness; he does not have meningitis. He has a normal mental status, dysphagia, and fullness in his oropharynx. Lateral neck films are a simple way to confirm this diagnosis.

CLINICAL PEARLS

The typical presentation of meningitis in older children consists of fever, headache, and nuchal rigidity.

Nuchal rigidity is rarely seen in infants with meningitis; nuchal rigidity is not a reliable finding until 12 to 18 months of age.

Pneumococcal disease (including meningitis) is more common in patients with functional or anatomic asplenia.

Approximately one-third of patients with meningitis have a seizure at some point in the course of the disease.

Typical CSF findings of bacterial meningitis include elevated protein, reduced glucose, and several hundred to several thousand white blood cells per cubic millimeter.

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◆ CASE 35

You receive a telephone call from the mother of a previously healthy 2-year-old boy. Yesterday, the boy developed a temperature of 104°F (40°C), cramping abdominal pain, emesis, and frequent large watery stools. The mother kept him hydrated, assuming that he had the same viral gastroenteritis like many other children in his daycare. Today, however, the boy developed bloody stools with mucous and he seemed more irritable. In addition to the daycare, potential contacts include an aunt who visited 2 days ago who was recovering from an illness with an elevated temperature, abdominal pain, and watery diarrhea. While you are discussing the boy's current hydration status, the mother reports that he is having a seizure. You tell her to call the ambulance, and then notify the local hospital's emergency center of the child's imminent arrival.

- ◆ What is the most likely diagnosis?
- ◆ How can you confirm this diagnosis?
- ◆ What is the best management for this illness?
- ◆ What is the expected course of this illness?

ANSWERS TO CASE 35: Bacterial Enteritis

Summary: This child was exposed in daycare and at home to gastrointestinal illnesses. He has fever, abdominal pain, and watery diarrhea that progressed to a bloody diarrhea with mucous. In addition, he had a new-onset seizure.

- ◆ **Most likely diagnosis:** Bacterial enteritis with neurologic manifestations.
- ◆ **Diagnostic tools:** Fecal leukocytes, fecal blood, and stool culture using appropriate media.

Management: Varies with age and suspected organisms; hydration and electrolyte correction is first priority. *Salmonella* intestinal infections are self-limited and generally not treated except in patients ≤ 3 months old or in the immunocompromised; *Shigella* infections, while self-limited, are generally treated to shorten the illness and decrease excretion of the organism. Antimotility agents generally are not used.

- ◆ **Course:** Untreated, *Salmonella* and *Shigella* gastrointestinal infections in normal healthy children will spontaneously resolve. Extraintestinal infections are more likely in immunocompromised individuals.

Analysis

Objectives

1. Describe the typical clinical presentation of bacterial enteritis.
2. List potential pathogens for gastroenteritis, considering the age of the patient.
3. Discuss treatment options, and when treatment is necessary.
4. Discuss potential complications of bacterial enteritis.

Considerations

Bloody stools may be caused by a number of diseases, not all of which are infectious. In this child, the differential for his apparent gastrointestinal bleeding must include a Meckel diverticulum, intussusception, Henoch-Schönlein purpura, hemolytic uremic syndrome, *Clostridium difficile* colitis, and polyps. The case presentation is most consistent, however, with infectious enteritis typical of *Salmonella* or *Shigella*.

APPROACH TO BACTERIAL ENTERITIS

Definitions

Colitis: Inflammation of the colon.

Diarrhea: Frequent passage of unusually soft or watery stools.

Dysentery: An intestinal infection resulting in severe bloody diarrhea with mucous.

Enteritis: Inflammation of the small intestine, usually resulting in diarrhea; may be a result of infection, immune response, or other causes.

Clinical Approach

Salmonella organisms are gram-negative rods. The organisms grow aerobically, and can survive as facultative anaerobes. They are motile and do not ferment lactose. Infections with *Salmonella* are more common in warmer months. *Salmonella* infections may be separated into nontyphoidal disease (including gastroenteritis, meningitis, osteomyelitis, and bacteremia) and enteric (or typhoid) fever, caused primarily by *S. typhi*. ***Salmonella* outbreaks usually occur sporadically, but can also be food-related and occur in clusters.** Many animals harbor *Salmonella*, with certain serotypes characteristically harbored by different animals. **Exposure to poultry and raw eggs is probably the most common source of human infection;** other sources include iguanas and turtles. The ingestion of many organisms is required to induce disease, so person to person spread is uncommon.

Gastroenteritis is the most common manifestation of nontyphoidal disease. Typically, children have a sudden onset of nausea, emesis, cramping abdominal pain, and watery or bloody diarrhea. Most develop a low-grade fever; some manifest neurologic symptoms, such as confusion, headache, drowsiness, and seizures. Fecal leukocytes and occult blood tests are typically positive, and a mild leukocytosis is common. Between 1% and 5% of patients with *Salmonella* infection develop transient bacteremia. Subsequent extraintestinal infections may develop in this case, such as osteomyelitis, pneumonia, meningitis, gall bladder and arthritis. These findings are more common in patients with immune system dysfunction and in infants.

Shigella organisms are small gram-negative bacilli. They are facultative anaerobes, are nonmotile, and are nonlactose fermenting. The four species responsible for human disease are *S. dysenteriae*, *S. boydii*, *S. flexneri*, and *S. sonnei*. Infections most commonly occur in warmer months. **Infection is usually transmitted person to person, but may be transmitted by food and water.** Relatively few *Shigella* organisms are required to cause disease. Infection is more common in the first 10 years of life, with a peak in the second and third years of life. Typically, children present with fever, cramping abdominal pain, watery diarrhea, and anorexia. Children appear to be ill when infected with *Shigella*. In most cases, the disease progresses to frequent small bloody stools, but some children will continue with watery stools. Untreated, the diarrhea typically will last 1 to 2 weeks and then resolve. *Shigella* infections result in neurologic findings in as many as 40% of children ill enough to require hospitalization. Symptoms may include headache, confusion, seizure, or hallucinations. *Shigella* meningitis is infrequent. Uncommon complications of disease include rectal prolapse, cholestatic hepatitis, arthritis, conjunctivitis, and cystitis. Rarely, *Shigella* causes a rapidly progressive septic-like presentation (Ekiri syndrome) that quickly results in death.

Diagnostic studies for *Salmonella* or *Shigella* should include a bacterial stool culture, although cultures are frequently negative even in test subjects known to be infected. **Fecal leukocytes are usually positive in bacterial enteritis,** but this is a nonspecific finding that suggests colonic inflammation. An occult blood assay is frequently, but not always, positive. In ***Shigella* infection,** the peripheral white count is usually normal, but a remarkable left shift is often present, with *more*

bands than polymorphonuclear cells. *Salmonella* infection usually results in a mild leukocytosis.

Treatment is always focused on correcting fluid and electrolyte balance. Antibiotic treatment of *Salmonella* gastroenteritis is generally not necessary. Treatment has not been shown to shorten the disease course and may increase the risk of hemolytic uremic syndrome. Infants younger than 3 months of age and individuals with compromised immune systems are usually treated if they have a *Salmonella* intestinal infection, as they are at increased risk for disseminated disease. *Shigella* is self-limited as well, but antibiotic treatment shortens the course of the illness and decreases the length of time the organisms is shed. Antimotility agents are not indicated in either type of infection.

In addition to *Salmonella* and *Shigella*, enteroinvasive *Escherichia coli*, *Campylobacter* sp., and *Yersinia enterocolitica* can cause a dysentery-like illness, with fever, abdominal cramps, and bloody diarrhea. *Yersinia* is well-known to cause an "acute abdomen"-like picture and is always considered in the patient with possible appendicitis. Enterohemorrhagic (or Shigatoxin-producing) *E. coli* can cause bloody diarrhea, but usually without fever. Infection with *Vibrio cholera* produces vomiting and profuse watery diarrhea with little or no fever and no blood in the stool.

Hemolytic-uremic syndrome (HUS) develops in 5% to 8% of children with diarrhea caused by enterohemorrhagic *E. coli*; it is seen less commonly following infections with *Shigella*, *Salmonella*, and *Yersinia*. HUS is the most common cause of acute renal failure in children. The disorder is most common in children younger than 4 years of age. The underlying process is thought to be endothelial cell injury resulting in a microangiopathic hemolytic anemia and consumptive thrombocytopenia. Renal involvement results from deposition of an unidentified material in the glomerulus that leads to thickening of the capillary walls with subsequent narrowing of the lumen. The typical presentation is the acute onset of pallor, irritability, and decreased or absent urine output; children may also develop petechiae and edema. These symptoms usually follow the diarrheal illness by 1 to 2 weeks. Treatment is usually supportive; some children require dialysis. With careful management, most children recover and regain normal renal function; however, the child must have long-term surveillance for hypertension and chronic renal failure.

Comprehension Questions

- [35.1] A 2-year-old boy without significant medical history developed emesis and intermittent abdominal pain yesterday, with several small partially formed stools. His parents were not overly concerned, as the child seemed fine between the episodes of pain. Today, however, the child has developed persistent bilious emesis and has had several bloody stools. The examination reveals a lethargic child in mild distress that is tachycardic and febrile. The abdominal examination reveals a diffusely tender abdomen with a vague tubular mass in the right upper quadrant. The next step in managing this condition should be:
- A. IV antibiotics for *Shigella*
 - B. Computerized tomography of the abdomen
 - C. Parental reassurance
 - D. Contrast enema
 - E. Stool cultures
- [35.2] A previously healthy 2-year-old girl had 3 days of bloody diarrhea last week that spontaneously resolved. She is now in your office because her mother thinks she looks pale. On physical examination you see that she is afebrile, her heart rate is 150 beats per minute, her systolic blood pressure is 150 mmHg and her diastolic is 80 mmHg. She is pale and irritable, has pitting edema of the lower extremities, and has scattered petechiae. After appropriate laboratory studies, initial management of her condition should include:
- A. Intravenous antibiotics and platelet transfusion
 - B. Careful management of fluid and electrolyte balance
 - C. Intravenous steroids and aggressive fluid resuscitation
 - D. Contrast upper gastrointestinal series with small bowel delay films
 - E. Intubation and mechanical ventilation
- [35.3] A family reunion picnic went awry when the majority of attendees developed emesis and watery diarrhea with streaks of

blood. Those who were unaffected did not eat the potato salad. A few of the ill family members are mildly febrile. They come as a group to your office, seeking medications. After you examine them all and wash your hands thoroughly, the most appropriate step in managing their condition is:

- A. Oral amoxicillin
- B. Oral metronidazole
- C. Antimotility medication
- D. Intramuscular ceftriaxone
- E. Hydration and careful follow-up

[35.4] You are asked to see a 1-month-old infant to provide a second opinion. During a brief, self-limited, and untreated diarrheal episode last week, his primary physician ordered a stool assay for *Clostridium difficile* toxin, which has subsequently come back positive. The infant now is completely asymptomatic, active, smiling, and well hydrated. His physician told the mother treatment was not necessary, but the mother was concerned and is asking what you think should be done. You correctly respond:

- A. *Clostridium difficile* commonly colonizes the intestine of infants, and treatment is not warranted in this case.
- B. The infant should take a 7-day course of oral metronidazole to prevent future complications.
- C. The infant should take a 10-day course of oral vancomycin to prevent future complications.
- D. The infant should be admitted to the hospital for intravenous metronidazole to prevent future complications.
- E. A repeat study needs to be performed to look for the *Clostridium difficile* organism.

Answers

[35.1] **D.** This child has an intussusception. Although the child has bloody stools, the child also has bilious emesis, colicky abdominal pain, and a tubular or “sausage-shaped” mass in the right

upper quadrant. A contrast enema may be diagnostic as well as therapeutic when performed by an experienced radiologist. A surgeon and a prepared operating room must be available should the attempt at reduction via contrast enema fail or result in intestinal perforation.

- [35.2] **B.** HUS is typically seen after an episode of bloody diarrhea, and presents with anemia, thrombocytopenia, and nephropathy. The child in question is hypertensive and has edema, so large amounts of fluids may be counterproductive. Steroids are not typically helpful in HUS. The thrombocytopenia in HUS is consumptive; thus, unless the patient is actively bleeding, platelet transfusion is not helpful. Most of the care for patients with HUS is supportive, concentrating on fluids and electrolytes. Early dialysis may be needed as well. Hypertensive patients should have appropriate control of their blood pressure.
- [35.3] **E.** This family probably has *Salmonella* food poisoning. Antibiotics are not indicated for this healthy family and antimotility agents may prolong the illness. Frequent hand washing should be emphasized.
- [35.4] **A.** *C. difficile* colonizes approximately half of normal healthy infants in the first 12 months. In this infant with no history of antibiotic treatment and no current symptoms, treatment is unnecessary. *C. difficile* colitis rarely occurs without a history of recent antibiotic use.

CLINICAL PEARLS

In normal children older than age 3 months, isolated intestinal *Salmonella* infections do not require antibiotic treatment; antibiotics do not shorten the course of illness.

Suspected *Shigella* intestinal infections are usually treated to shorten the course of the illness and to decrease the shedding of organisms.

Hemolytic-uremic syndrome is the most common cause of acute renal failure in children and is a potential sequela of bacterial enteritis.

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◆ CASE 36

A 15-year-old girl presents to the emergency department complaining of periumbilical pain that began 8 hours prior to presentation. She reports that she vomited once a couple of hours ago, and that she has had one small, loose, bowel movement. She denies dysuria or urinary frequency. Her last meal was 12 hours ago, and she says she is not hungry. Her last menses was 1 week ago and was normal; she denies any sexual activity. On physical examination she appears moderately uncomfortable. Her temperature is 101.5°F (38.6°C) orally, respiratory rate 24 breaths per minute, heart rate 70 beats per minute, and her blood pressure 120/80 mmHg, systolic and diastolic. Her abdominal examination reveals hypoactive bowel sounds, rigidity of the rectus muscles, and tenderness to palpation, particularly in the periumbilical area. Breath sounds are clear, and she has no skin rash. On pelvic examination, she has no visible vaginal discharge, but she complains of abdominal pain with gentle bimanual examination. She also complains of pain with digital examination of the rectum.

◆ What is the most likely diagnosis?

◆ What is the next step in the management of this patient?

ANSWERS TO CASE 36: Appendicitis

Summary: A 15-year-old girl with periumbilical pain of 6 hours duration. She has vomited and had one small, loose, bowel movement since the pain began. She denies dysuria, and there is no apparent relation to her menses. She denies any history of sexual activity. Her physical examination is remarkable for fever, a quiet, rigid and tender abdomen, and pain with digital rectal examination.

- ◆ **Most likely diagnosis:** Appendicitis.
- ◆ **Next step in management:** She should be told not to take anything by mouth and be given intravenous fluids to maintain adequate hydration. A surgeon should be consulted once the diagnosis of appendicitis is suspected. An abdominal ultrasonogram may demonstrate an inflamed appendix (but the surgeon may not request one if the symptoms are classic). A urinalysis is useful to eliminate a urinary tract infection as the cause of the patient's discomfort, and a complete blood count often shows a leukocytosis if the patient has an appendicitis. Despite this adolescent's denial of sexual activity, a urine β -human chorionic gonadotropin should be obtained to rule out pregnancy.

Analysis

Objectives

1. Recognize the presenting clinical signs for appendicitis.
2. Know the differential diagnosis for appendicitis.
3. Recognize the importance of maintaining a high index of suspicion for appendicitis in order to prevent possible complications.

Considerations

Because of the multitude of possible causes of abdominal pain, sometimes it is not possible to make a definitive diagnosis until the time of surgery. **This patient's triad of fever, vomiting, and abdominal pain**

are most consistent with **appendicitis**. Of particular historical significance in this patient is her pain **preceding** the onset of vomiting and diarrhea. She also had periumbilical pain in the early phase that subsequently migrates to the right lower quadrant. Variations of pain include that associated with a retrocecal appendix, which can result in pain more laterally, and a perforated appendix, which often causes diffuse abdominal tenderness. The utility of routine rectal examinations for all children with suspected appendicitis is debatable, but it can be helpful for localizing the source of pain in a female adolescent.

The girl in this scenario is early in the course of her disease process, and arguably might be safely observed for a few hours if the diagnosis remains in question. Once the diagnosis of appendicitis is considered strongly, however, surgical management should occur in a timely fashion, as the perforation rate exceeds 65% if diagnosis is delayed beyond 36 to 48 hours from the onset of symptoms. The possible complications of appendicitis—wound infection, abscess formation, intestinal obstruction, and adhesions—are rare following uncomplicated appendectomy, but do occasionally occur secondary to appendiceal perforation.

Definitions

Appendicitis: Inflammation of the appendix that occurs following luminal obstruction. If the appendix is not removed, necrosis of the wall results in perforation and contamination of the peritoneum.

McBurney's point: The junction of the lateral and middle third of the line joining the right anterior superior iliac spine and the umbilicus (Figure 36–1). This is typically the area of greatest discomfort in patients with acute appendicitis.

Typhlitis: Necrotizing enterocolitis involving the terminal ileum and cecum. This condition most typically occurs in children with neutropenia.

Clinical Approach

A person's lifetime risk for developing appendicitis is estimated to be between 6% and 20%, with the **peak incidence occurring in adolescence**.

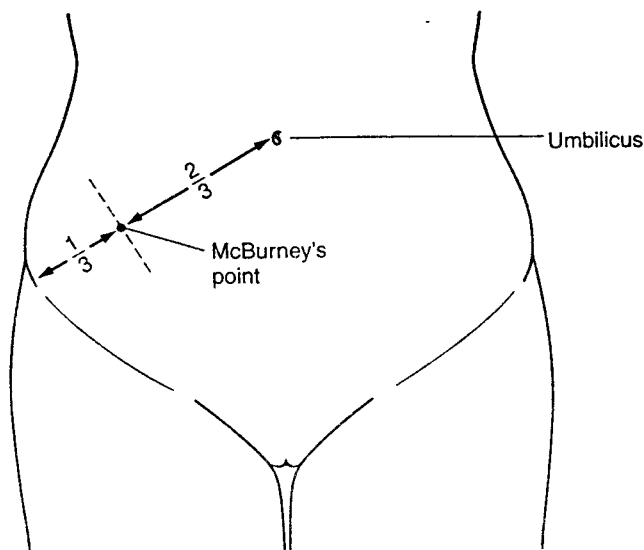


Figure 36-1. McBurney's point.

The appendix becomes inflamed secondary to either intrinsic or extrinsic luminal obstruction. Intrinsic obstruction caused by inspissated fecal material (appendicolith) is found in 30% to 50% of patients at the time of surgery. Extrinsic compression is usually caused by enlarged lymph nodes associated with bacterial or viral infections. Obstruction is followed by vascular thrombosis and ischemia, and, ultimately, with perforation.

The differential diagnosis for acute abdominal pain in childhood is long (Table 36-1), but often, a careful history and physical examination can suggest the correct etiology. A history of worsening abdominal pain that starts in the periumbilical area and subsequently migrates to the right lower quadrant is characteristic of acute appendicitis. Likewise, anorexia, nausea, and vomiting that begin after the onset of pain is strongly indicative of this diagnosis.

A gentle approach can be used to obtain an abdominal examination that is both meaningful and not frightening to the child. Observation of the child as they get on and off the examination table can be revealing; the child with appendicitis avoids sudden movements such as jumping off the table. The abdomen should be auscultated for bowel sounds first. This is followed by gentle palpation for the area of maximal ten-

Table 36-1
PARTIAL DIFFERENTIAL DIAGNOSIS OF ACUTE
ABDOMINAL PAIN IN CHILDREN BEYOND INFANCY

CONDITION	SIGNS AND SYMPTOMS
Appendicitis	Right lower quadrant pain, abdominal guarding, and rebound tenderness
Bacterial enterocolitis	Diarrhea (may be bloody); fever, vomiting
Cholecystitis	Right upper quadrant pain, often radiating to subcapsular region of the back
Constipation	Infrequent, hard stools
Diabetic ketoacidosis	History of polydipsia, polyuria, and weight loss
Ectopic pregnancy	Lower abdominal pain, vaginal bleeding, and an abnormal menstrual history
Gastroenteritis	Fever, vomiting, and hyperactive bowel sounds
Hemolytic-uremic syndrome	Irritability, petechiae, and edema
Henoch-Schönlein purpura	Purpuric lesions and joint pain
Hepatitis	Right upper quadrant pain and jaundice
Inflammatory bowel disease	Weight loss, diarrhea, and malaise
Mittelschmerz	Sudden onset of right or left lower quadrant pain with ovulation, copious mucoid vaginal discharge
Nephrolithiasis	Hematuria, colicky abdominal pain
Ovarian cyst	White blood cell count less than 11,000/mm ³ ; vomiting rare
Pancreatitis	(Severe) epigastric abdominal pain, fever, and persistent vomiting
Pelvic inflammatory disease	Cervical motion tenderness; white blood cells in the vaginal secretions

Table 36-1
PARTIAL DIFFERENTIAL DIAGNOSIS OF ACUTE
ABDOMINAL PAIN IN CHILDREN BEYOND
INFANCY (*Continued*)

CONDITION	SIGNS AND SYMPTOMS
Pneumonia	Fever, cough, and crackles on auscultation of the chest
Sickle cell crisis	Anemia, and extremity pain
Streptococcal pharyngitis	Fever, sore throat, and headache
Urinary tract infection	Dysuria, fever, vomiting, and back pain

derness and rigidity. Gentle finger percussion can be used to assess for peritoneal irritation ("rebound tenderness"). If performed, a rectal examination should occur last.

A peripheral blood count can be helpful for discriminating the cause of abdominal pain. **Although not a specific finding, a leukocytosis with a predominance of polymorphonuclear cells (a "left shift") supports an inflammatory process.** Hematuria and pyuria on urinalysis raise the possibility of a genitourinary etiology, although these signs can occur with acute appendicitis if the inflamed appendix is also causing irritation of the bladder or ureter wall. Plain radiographs of the abdomen can be helpful if the diagnosis is in doubt or if an abscess or perforation is suspected. Radiographic signs that support appendicitis are obliteration of the psoas shadow, dilatation of the intestine in the right lower quadrant, scoliosis toward the affected region, and the presence of an appendicolith. The appendicolith is visualized in only 10% to 20% of cases, however. Plain radiographs of the chest eliminate pneumonia as an alternate diagnosis. **Ultrasonography is more sensitive than plain films for appendicitis, and is particularly useful in female adolescents.** The ultrasonograph image can determine the thickness of the bowel wall and its compressibility, and will also show other etiologies of abdominal pain, such as ovarian cysts, tumors, or pregnancy. **Computerized tomography is a helpful adjunct in patients who are neurologically impaired, immunologically suppressed, or**

obese, and it is the preferred modality when perforation is suspected. Computerized tomography can also be used to guide drainage of a periappendiceal abscess.

The definitive treatment for appendicitis is surgical removal of the appendix, which must be accomplished as soon as the diagnosis is strongly suspected to prevent perforation (if it has not already occurred). Postoperative hospitalization for an uncomplicated appendectomy is brief (less than 3 days). For appendicitis involving perforation, recovery requires intravenous antibiotics and fluid replacement, and may be complicated by sepsis, abscess formation, or prolonged (4 to 5 days) paralytic ileus.

Comprehension Questions

- [36.1] A 7-year-old boy presents to the emergency department with a chief complaint of right-sided abdominal pain and fever to 102°F (38.9°C). His mother reports that he has had poor appetite and a cough for 2 days, and he had two loose bowel movements earlier on the day of presentation. On physical examination, he has a temperature of 101.7°F (38.7°C), his heart rate is 120 beats per minute, and his respiratory rate is 50 breaths per minute. Breath sounds are diminished, and the abdomen is diffusely tense with hypoactive bowel sounds. His examination is otherwise normal. The initial diagnostic work-up should include:
- A. Chest radiograph
 - B. Stool leukocytes
 - C. Stool for culture, ova, and parasites
 - D. Liver function tests
 - E. Abdominal computerized tomography
- [36.2] A 14-year-old girl with a 3-day history of abdominal pain, anorexia, and vomiting, and a 1-day history of fever, underwent laparoscopic surgery for suspected appendicitis. The appendix was found to be perforated at the time of surgery. Intravenous ampicillin, gentamicin, and clindamycin were initiated prior to

surgery and continued postoperatively. On the third postoperative day, she continues to spike fever to 102°F (38.9°C). The next most appropriate step in her management is to:

- A. Add metronidazole to the antibiotic regimen.
- B. Change the antibiotic coverage to amikacin and a cephalosporin.
- C. Order a STAT computerized tomography scan.
- D. Send a urinalysis and urine culture.
- E. Perform a pelvic examination.

[36.3] A previously healthy 8-year-old boy presents to his primary care provider with a complaint of abdominal pain, anorexia, and vomiting that have progressively worsened over the past 24 hours. He localizes the pain to the umbilical region. Despite the emesis, he appears well-hydrated. A complete blood count obtained in the office shows a white blood count of 17,000 cells/mm³ with 50% polymorphonuclear cells. A urine dipstick on a clean-catch specimen shows 2+ leukocytes and 1+ protein, but no nitrites. Appropriate management at this point is to:

- A. Obtain a complete chemistry panel and continue to observe the patient in the office.
- B. Send the patient immediately to the hospital for an abdominal ultrasonogram.
- C. Give the patient a prescription for trimethoprim-sulfamethoxazole and schedule a follow-up visit in 2 days to reevaluate the urine.
- D. Admit the patient to the hospital for intravenous antibiotics to treat presumed pyelonephritis.
- E. Schedule a computerized tomography scan of the abdomen for the next morning.

[36.4] A 4-year-old girl presents to the emergency department with a fever of 102.4°F (39.1°C), difficulty swallowing, vomiting, and abdominal pain. The diagnostic test that is most likely to yield the appropriate diagnosis is:

- A. A streptococcal antigen test (“rapid strep test”).
- B. An antigen test for Epstein-Barr virus (“monospot”).
- C. A lateral neck radiograph.
- D. An abdominal ultrasonograph.
- E. A complete blood count.

Answers

- [36.1] **A.** Pneumonia in the lower lobes can cause abdominal pain, which may be the most distressing symptom in a young patient. This child has cough, fever, tachypnea, and diminished breath sounds, which together make pneumonia the most likely diagnosis.
- [36.2] **C.** This girl is at risk for an intraabdominal abscess despite her recent appendectomy and intravenous antibiotics. Furthermore, it would be unusual for a urinary tract infection or pelvic inflammatory disease to cause persistent fever in the face of broad-spectrum intravenous antibiotics.
- [36.3] **B.** This boy’s symptoms and signs are most consistent with a diagnosis of acute appendicitis. A urinary tract infection in an otherwise healthy boy would be unusual. His pyuria is most likely the result of irritation of the bladder wall or ureter caused by an inflamed appendix.
- [36.4] **A.** This child’s symptoms are most consistent with a diagnosis of strep throat. In addition to throat pain and fever, acute infection with Group A streptococcus commonly causes abdominal pain and emesis in children.

CLINICAL PEARLS

Acute appendicitis typically causes periumbilical abdominal pain that eventually migrates to the right lower quadrant. Emesis usually follows the onset of pain, rather than precedes it.

Surgical management of appendicitis should occur as soon as the diagnosis is suspected in order to minimize the risk of potential complications such as perforation and intraabdominal abscess formation.

The diagnosis of appendicitis is often not certain until the time of surgery. A carefully obtained history and physical examination, a urinalysis, a complete blood count, and an abdominal ultrasound or computerized tomography scan are generally the most useful tools for eliminating other diagnostic possibilities prior to surgery.

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◆ CASE 37

A 19-year-old college student presents to the University Health Center with complaints of fever, sore throat, and malaise. She developed a rash today, which prompted the visit to the clinic. She first started feeling ill 10 days ago when she noted a general malaise, headache, and nausea. Four days ago she developed a temperature of 103°F (39.4°C) that has persisted. She also complains of a gradually worsening sore throat, and difficulty swallowing solid foods; she is, however, drinking well. She denies emesis or diarrhea, and recalls no recent sick contacts. Her medication history includes a daily oral contraceptive and two doses of ampicillin taken yesterday (left over from a prior illness). The physical examination reveals a well-developed young woman with a diffuse morbilliform rash. She appears to be tired but in no distress. Her temperature is 102.2°F (39°C). Pertinent findings on physical examination include mild supraorbital edema; bilaterally enlarged tonsils that are coated with a shaggy grey exudate; a few petechiae on the palate and uvula; bilateral posterior cervical lymphadenopathy, and a spleen that is palpable 3 cm below the costal margin. Laboratory data includes a white blood cell count of 17,000 cells/mm³ with 50% lymphocytes, with 15% atypical, and a platelet count of 100,000/mm³.

- ◆ What is the most likely diagnosis?
- ◆ What is the best tool to quickly confirm this diagnosis?
- ◆ What is the best management for this condition?
- ◆ What is the expected course of this condition?

ANSWERS TO CASE 37: Acute Epstein-Barr Viral Infection (Infectious Mononucleosis)

Summary: A female college student has a 10-day prodrome of malaise, headache, and nausea. She more recently developed a fever, sore throat, and morbilliform rash after taking ampicillin. Her physical examination is significant for a fever, rash, tonsillar hypertrophy with exudate, posterior cervical lymphadenopathy, and splenomegaly. She has an elevated white blood cell count with a lymphocytic predominance, and a mild thrombocytopenia.

- ◆ **Most likely diagnosis:** Epstein-Barr virus (EBV) infection (infectious mononucleosis).
- ◆ **Best tool:** Assay for heterophil antibodies (Monospot).
- ◆ **Best management:** Symptomatic care, avoidance of contact sports while the spleen is enlarged (usually 1 to 3 months).
- ◆ **Expected course:** Acute illness may last 2 to 4 weeks, with gradual recovery; splenic rupture is a rare but potentially fatal complication; rarely, some patients have persistent fatigue.

Analysis

Objectives

1. Describe the presenting signs and symptoms of acute EBV infection.
2. Contrast symptoms of acute infection in young children with those in adolescents and adults.
3. List potential complications of acute EBV infection.

Considerations

This case is typical of an adolescent with a primary EBV infection, although the supraorbital edema only occurs in approximately 10% to

20% of patients. Differential considerations for this patient include group A β -hemolytic streptococcal pharyngitis; however, streptococcal pharyngitis typically does not have a prodrome similar to this case, nor does streptococcal pharyngitis have splenomegaly as an associated examination finding. Acute cytomegalovirus (CMV) infection in this patient is another possibility; similarities include splenomegaly, fever, and atypical lymphocytosis. However, sore throat with exudate and posterior cervical lymphadenopathy occur less frequently with CMV. Although the patient in the case denies ill contacts, EBV infection has an incubation of 30 to 50 days; further questioning would have revealed that her boyfriend was seen at the clinic 6 weeks ago for similar symptoms. Rash is seen less commonly in adolescents; however, many patients with acute EBV infection develop a morbilliform rash in response to ampicillin, amoxicillin, or penicillin.

APPROACH TO EPSTEIN-BARR INFECTION

Definitions

Epstein-Barr virus: A virus in the family of Herpesviridae (the fifth human herpes virus identified). It is a double-stranded DNA virus that infects human oropharyngeal and salivary tissues as well as B lymphocytes. It can cause persistent viral shedding in humans, is associated with oral hairy leukoplakia in HIV-infected individuals, and causes several malignancies.

Infectious mononucleosis: This is the typical presentation of EBV infection in older children and adolescents. Fever, posterior cervical adenopathy, and sore throat are present in greater than 80% of cases.

Clinical Approach

EBV is ubiquitous in humans. In developing nations, EBV infection occurs in almost all children by 6 years of age. In the industrialized world, only about half of adolescents have serologic evidence of previous EBV infection. The adolescent period is a common time to acquire EBV, with 10% to 15% of previously uninfected college students seroconverting

each year. The virus is excreted in saliva, and infection results from mucosal contact with an infected individual or contact with a contaminated fomite. Shedding of EBV in saliva after an acute infection can continue for more than 6 months, and occurs intermittently thereafter for life.

After an EBV infection occurs, the virus initially replicates in the oropharyngeal epithelium, and then later in the B lymphocytes. After infection a prodromal period may last for 1 to 2 weeks with vague findings of fever, nausea, malaise, headache, sore throat, and abdominal pain. The sore throat and fever persist and gradually worsen; these symptoms frequently are the cause for a patient to seek medical help. Physical findings during an acute EBV infection may include generalized lymphadenopathy, splenomegaly, and tonsillar enlargement with exudate. Less-common findings include a rash and hepatomegaly.

Primary EBV infection presents as typical infectious mononucleosis in older children and adults (as in this case), but this presentation is seen less frequently in young children and infants. In small children, many infections are asymptomatic. In others, fever may be the only presenting sign of EBV. Additional findings in acutely infected small children include otitis media, abdominal pain, and diarrhea. Hepatomegaly and rash are seen more often in small children with acute EBV than in older individuals.

The heterophil antibody test (Monospot) is useful in the diagnosis of EBV infection in children older than about 5 years of age; in younger children, the test results are unreliable. In some children, early in their course of the illness, the monospot test may be falsely negative. More definitive testing includes assays of EBV viral capsid antigen (EBV-VCA), early antigen (EA), and Epstein-Barr nuclear antigen (EBNA). Typically, immunoglobulin (Ig) G and IgM antibodies to EBV-VCA are first to appear. Anti-EBNA antibodies appear 1 to 2 months following infection and persist for years in all patients. Anti-EA antibodies are seen in most children during acute infection, and may also persist for years in approximately one-third of patients. Past infection is indicated by the presence of VCA-IgG and EBNA-IgG antibodies. Other common laboratory findings include a leukocytosis with a lymphocytic predominance; approximately 20% to 40% of the lymphocytes are atypical. Mild thrombocytopenia is common, but this abnor-

maity only rarely precipitates bleeding or purpura. **More than half of patients with EBV infection develop mildly elevated liver function tests, but jaundice is uncommon.**

Complications of an EBV infection are rare but can be life-threatening. Neurologic sequelae can include Bell palsy, seizures, aseptic meningitis or encephalitis, Guillain-Barré syndrome, optic neuritis, and transverse myelitis. Parotitis, orchitis, or pancreatitis may develop. Airway compromise may result from tonsillar hypertrophy, and may require treatment with steroids. Fulminant hepatitis, hemolytic anemia, myocarditis, pericarditis, and central nervous system involvement may also require steroid therapy. **Splenomegaly occurs in about half of those with infectious mononucleosis; rupture, while rare, can cause life-threatening blood loss.**

Typical infectious mononucleosis requires no therapy aside from rest. Strict bed rest, while prescribed historically, is not useful except for patients with debilitating fatigue. Children with splenomegaly should avoid contact sports, that may precipitate splenic rupture, until the splenomegaly resolves. Acyclovir, while effective in slowing viral replication, does not affect the severity or outcome of the disease.

EBV was initially identified from Burkitt lymphoma tumor cells, and was the first virus associated with human malignancy. Other malignancies associated with EBV include Hodgkin disease, nasopharyngeal carcinoma, and lymphoproliferative disorders. EBV can also stimulate hemophagocytic syndrome. Individuals already infected with HIV may develop oral hairy leukoplakia, smooth muscle tumors, and lymphoid interstitial pneumonitis with EBV infection.

Comprehension Questions

- [37.1] A 17-year-old boy presents to the emergency center with left shoulder and left upper quadrant tenderness and vomiting. He reports having "mono" last month, but claims to be completely recovered from that illness. He was playing flag football with his friends when the pain started an hour ago, but he does not remember being hit in his back or abdomen. His exam reveals a heart rate of 150 beats per minute and a blood pressure of 80/50 mmHg. He is pale, weak, and seems disoriented. He has diffuse

rebound abdominal tenderness. Emergent management should include:

- A. Laparoscopic appendectomy
- B. Fluid resuscitation and blood transfusion
- C. Intravenous antibiotics
- D. Hospital admission for observation
- E. Synchronized cardioversion for supraventricular tachycardia

[37.2] You are asked to see a 2-year-old boy in consultation. His general practice doctor admitted the toddler to the hospital 2 days ago because of 3 days of fever. The child has generalized lymphadenopathy, but is otherwise well. A Monospot, HIV enzyme-linked immunosorbent assay (ELISA), and CMV antigen tests are negative, but his liver function tests are mildly elevated. His physician diagnosed the toddler's 7-year-old sibling with "mono" the month prior, but he is puzzled by the negative Monospot. You suggest:

- A. Starting intravenous immunoglobulin (IVIG) and obtaining an echocardiogram, as the patient likely has Kawasaki disease.
- B. Sending an EBV culture for confirmation of the physician's suspicions.
- C. Treatment with acyclovir empirically, because he has a positive exposure history for EBV.
- D. Obtaining EBV-VCA IgG and IgM, EBV-EA, and EBV-NA tests.
- E. Liver imaging with ultrasonography or computerized tomography.

[37.3] The mother of a 15-year-old girl recently diagnosed with infectious mononucleosis calls for more information. She reports that her daughter, while tired, seems comfortable and is recovering nicely. She remembers that her 20-year-old son had "mono" when he was 10 years old, and at that time he received an oral medicine, reportedly to help him get better faster. She requests the same medication for her daughter. You:

- A. Explain that medications are not routinely used in EBV infection and would not be useful in her daughter's case.
 - B. Call the local pharmacy and order oral prednisone, 50 mg daily for 5 days (1 mg/kg/d).
 - C. Call the local pharmacy and order oral acyclovir 250 mg four times a day (20 mg/kg/d).
 - D. Have her come to the office for a single dose of 50 mg of intravenous methylprednisolone (1 mg/kg).
 - E. Call the local pharmacy and order oral amoxicillin 250 mg three times a day for 7 days.
- [37.4] A teen-aged boy comes to the office for a check-up. He mentions that his friend was recently diagnosed with mononucleosis. He is worried that he will contract this as well. You explain that transmission of EBV:
- A. Is common among casual friends.
 - B. Only occurs in immunodeficient individuals.
 - C. Requires close contact with saliva as in kissing or drinking from the same cup.
 - D. Is only passed through heterosexual or homosexual contact with an infected individual.
 - E. Does not occur after the infected person recovers from the initial infection.

Answers

- [37.1] **B.** The patient described is in shock, and likely has splenic rupture with intraperitoneal bleeding. He will die shortly if not aggressively resuscitated with fluids and blood. Evaluation by surgery for potential removal of the ruptured spleen should follow quickly.
- [37.2] **D.** The Monospot heterophil antibody test, while useful in older children, is not as reliable in younger children for making the diagnosis of EBV infection. Antibodies against specific EBV antigens are more helpful for diagnosis in younger children.

- [37.3] A. Supportive care is usually all that is required in a patient with an acute EBV infection. Although steroids have been used historically, current literature suggests their use only in impending airway compromise or other life-threatening complications. Acyclovir does suppress viral shedding acutely, but has no long-term benefit and is not routinely recommended. Amoxicillin (and ampicillin) is not an effective antiviral medication, and is known to induce a rash in some patients infected with EBV.
- [37.4] C. EBV is excreted in saliva, and is thus transmitted through mucosal contact with an infected individual (as in kissing) or through a contaminated object. Virus is shed for a prolonged period after the clinical symptoms resolve, and is intermittently reactivated and shed for years (without any symptoms associated with this reactivation).

CLINICAL PEARLS

- ◆ Most adults show evidence of past EBV infection; it is a common infection worldwide.
- ◆ Children in industrialized nations often show symptoms of infection later than children in developing countries.
- ◆ Diagnosis of EBV infection in young children is done best by specific antibody assays; children older than age 5 years have fewer false-negative results with the heterophile antibody test (Monospot).
- ◆ Infectious mononucleosis is self-limited and does not require treatment. Occasional complications of EBV infection may require steroid administration.

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◆ CASE 38

A mother brings her 2-year-old daughter to your office with a complaint of 1 to 2 weeks of perineal and perianal itching. The mother notes that the itching occurs mostly at night, and that she has no fevers, diarrhea, emesis, or other symptoms. The girl spends time in a “Mother’s Day Out” program 3 days a week, but is otherwise always with the mother. On physical examination, you find the perianal area to be red and irritated; the anal sphincter tone is normal and you find no evidence of penetrating trauma. The perineal area is similarly red and excoriated. Other than a slight whitish vaginal discharge, the child’s diaper area is clean.

- ◆ What is the most likely diagnosis?
- ◆ How can you confirm the diagnosis?
- ◆ What is the best management for this condition?

ANSWERS TO CASE 38: Pinworms

Summary: A 2-year-old healthy girl with several weeks of mainly nocturnal perianal and perineal pruritus.

- ◆ **Most likely diagnosis:** Infection with *Enterobius vermicularis* (pinworms).
- ◆ **Confirm the diagnosis:** Cellophane tape test with microscopy to look for pinworm eggs (see Figure 38–1).
- ◆ **Best management:** Mebendazole, pyrantel pamoate, or albendazole in a single dose, treating the entire family.

Analysis

Objectives

1. Describe the typical presentation of *Enterobius vermicularis* infection in the pediatric population.

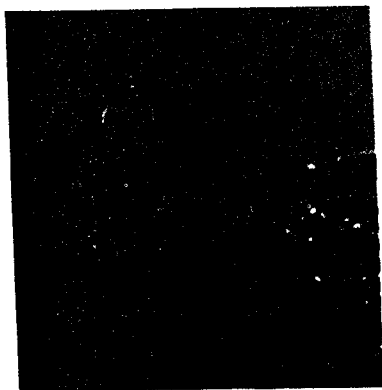


Figure 38–1. Pinworm (*Enterobius vermicularis*) ova on microscopy. From Rudolph's Pediatrics, 21st ed. (with permission).

2. Explain the methods of treatment and prevention of further infection.

Considerations

This patient has the typical history for a pinworm infection. Although sexual abuse is always a possibility, it is unlikely given the history and physical examination. Poor personal hygiene is a common problem in 2-year-olds who are toilet training and not cleaning themselves adequately. This results in perianal itching and irritation, yet the genital examination is essentially normal.

APPROACH TO *ENTEROBIUS VERMICULARIS* INFECTION

Definition

Nematode (roundworms): Cylindrical organisms, with thousands of different species, only a few of which are parasitic (Table 38–1). Nematode infection is one of the most common types of infection in humans.

Clinical Approach

A patient with a complaint of perianal itching, especially at night, should be evaluated for *Enterobius vermicularis* infection. Unlike many other parasites, direct visualization of the feces for ova is not useful because the eggs are small and few. Some parents may report seeing a worm in the stool, but *Enterobius vermicularis* is difficult to positively identify with the naked eye. Instead, **a piece of cellophane tape may be applied to the perianal region in the early morning;** from this tape *Enterobius vermicularis* eggs may be identified. These eggs are infectious and proper infection control practices must be exercised in performing this diagnostic procedure.

Enterobius vermicularis infection is **the most common nematode infection in North America**, occurring more commonly in the late fall and in the winter; humans are the only natural host. Risk factors include

Table 38-1
COMMON NEMATODE INFECTIONS IN HUMANS

COMMON NAME	PARASITE NAME(S)	SOURCE OF INFECTION	SIGNS AND SYMPTOMS	DIAGNOSIS	TREATMENT
Ascariasis	<i>Ascaris lumbricoides</i>	Egg ingestion, usually from soil contaminated with human feces	Most asymptomatic; hemoptysis, pulmonary infiltrates, abdominal pain, distension; occasional intestinal obstruction	Embryonate and nonembryonate eggs in stool; occasionally see adult worms in stool or coughed up	Albendazole single dose, mebendazole for 3 days or a single dose of pyrantel pamoate; obstruction may be cleared with piperazine salts (causes worm paralysis and expulsion)
Hookworms	<i>Ancylostoma duodenale</i> <i>Nector americanus</i>	Larvae in soil penetrate exposed skin	Pruritus and rash at site of entry; epigastric pain and diarrhea; anemia from blood loss; respiratory symptoms	Characteristic ovoid eggs in stool	Mebendazole for 3 days, or albendazole single dose, or pyrantel pamoate; include iron supplement
Pinworms	<i>Enterobius vermicularis</i>	Egg ingestion	Many asymptomatic; nocturnal perianal itching most common	Microscopy of cellophane tape to anus will reveal eggs; routine stool ova and parasites not useful	Pyrantel pamoate, or mebendazole, or albendazole single dose with a second dose 2-3 weeks later

Strongyloides	<i>Strongyloides stercoralis</i>	Larvae penetrate skin and move to lungs and then intestines; also autoinfectious, larvae can move from intestines into blood stream, to lungs, and back to intestines	Can be asymptomatic; can cause epigastric pain, emesis, diarrhea, malabsorption, weight loss	Larvae in feces, or sample of duodenal fluid by a string test	Ivermectin for 1-2 days, or thiabendazole for 2 days; may require up to 2 weeks of therapy, based on subsequent stool exams
Visceral and Ocular Larva Migrants	<i>Toxocara canis</i> <i>Toxocara cati</i> <i>Toxocara leonina</i> <i>Baylisascaris procyonis</i>	Egg ingestion, usually from soil contaminated with dog or cat feces	Fever, cough occasional abdominal pain; hepatomegaly, rhonchi, and skin lesions on exam	Clinical presentation and serologic testing: microscopy of affected tissue occasionally reveals larvae	Visceral: none, self-limited disease Ocular: diethylcarbamazine, albendazole for 3-5 days, or mebendazole for 5 days; use with caution, as death of organisms may precipitate inflammatory reaction
Whipworms	<i>Trichuris trichiura</i>	Egg ingestion	Most asymptomatic; can cause proctitis, bloody diarrhea, abdominal pain, rectal prolapse	Lemon-shaped eggs in the stool	Mebendazole or albendazole for 3 days (single dose for light infections)

exposure to other children in a daycare environment or in the home. The adult worm is about 1 cm long and lives in the human gastrointestinal tract, rarely migrating to the appendix, spleen, liver, bladder, and vagina. The life cycle of the pinworm begins when pregnant female worms migrate to the perianal region to deposit their eggs. These ova are flattened on one side and are approximately $30 \times 60 \mu\text{m}$ in size. Within 6 hours a larva is present in each ovum; the larvae are viable for up to 20 days. These eggs are subsequently transferred to clothes, fingers (from perianal itching), and bed sheets. A pinworm infection results when these eggs are ingested. The larvae “hatch” in the duodenum and grow to adult worms in 4 to 6 weeks.

Many patients infected with pinworms are asymptomatic. The symptom described most frequently is **nocturnal perianal itching**, a result of a hypersensitivity to the worms and the ova. The gravid worms may occasionally migrate to the perineal area resulting in vaginal itching and discharge. Other symptoms of pinworm infection, most notably bruxism, historically are related to pinworm infection. However, there is no association between pinworm infection and symptoms other than perianal itching.

Once the diagnosis of pinworm infection is clear, all members in the household should be treated. Although asymptomatic, others in the household may be harboring pinworm infections as well and should be treated. Treatment can be with **mebendazole, albendazole, or pyrantel pamoate in a single dose**. Often a second dose is needed 2 weeks after the first dose to eliminate any new worms released from ova ingested around the time of treatment.

Comprehension Questions

- [38.1] A mother brings her 4-year-old boy to the office with the complaint of 2 days of “buttocks pain.” She reports several blood-streaked stools, and that he is frequently scratching the area. His temperature is 98.8°F (37.1°C), but his perianal region is bright red with a clearly demarcated border of erythema. The area is diffusely tender to palpation, but you find no area of nodularity, fluctuance, or trauma. Appropriate diagnostic testing and therapy in this patient includes:

- A. Stool sample for ova and parasites and treatment with albendazole.
- B. Cellophane tape test for ova and treatment with albendazole.
- C. Rapid streptococcal test of the anal area and oral antibiotics.
- D. Blood culture and parenteral antibiotics.
- E. Administration of diaper rash ointment.

[38.2] A 6-year-old boy who recently moved from the southeastern United States complains of "something coming out" of his buttocks while straining during defecation; it seems to resolve when he relaxes. He also complains of abdominal pain and bloody stools for the last week. Physical examination reveals a normal external anus without evidence of trauma. When asked to strain, he produces a pink mucosal mass from his anus that returns into the anus when he relaxes. Initial diagnostic evaluation should include which of the following studies?

- A. Cellophane tape test upon morning awakening
- B. Stool for ova and parasites
- C. Rectal culture
- D. Abdominal ultrasonography
- E. Herpes culture

[38.3] A mother brings a stool sample to your office for your review. In the stool are several 15- to 20-cm long, round, whitish worms. You initiate treatment with:

- A. Amoxicillin
- B. Mebendazole
- C. Praziquantel
- D. Niclosamide
- E. Paromomycin

[38.4] A 14-year-old boy with HIV and AIDS presents for a routine physical prior to traveling to Southeast Asia to visit his grandparents. In counseling him on health risks in the area, you mention that he must always wear shoes to help avoid *Strongyloides* infection. This type of infection would be particularly dangerous to him because:

- A. His antiretroviral medications make him more susceptible.
- B. His immune deficiency will make eradication impossible.
- C. Antiparasitic agents are not available in Southeast Asia.
- D. Teenagers typically have severe disease when infected.
- E. *Strongyloides* can develop a “hyperinfection” in immune compromised hosts.

Answers

- [38.1] C. Although diagnostic considerations should include pinworm infestation for this case (as well as sexual abuse, contact diaper rash, and candidal diaper rash), the presentation is more consistent with perianal cellulitis. Pinworm infection does not usually cause blood-streaked stool and any erythema associated with pinworms is not well demarcated. Perianal cellulitis is commonly caused by *Streptococcus* and usually responds to oral or topical (mupirocin; Bactroban) antibiotics.
- [38.2] B. Pinworms are not known to cause rectal prolapse; whipworms (*Trichuris trichiura*) are. The whipworm nematode lives in warm and humid areas, and is commonly found in the southeastern United States. Routine microscopy for ova is sufficient for the diagnosis because whipworms produce many more ova than do pinworms. Treatment is albendazole or mebendazole. Cystic fibrosis should also be a consideration in any child with rectal prolapse, although their history might include frequent pneumonias, failure to thrive, or foul-smelling stools.
- [38.3] B. Worms of this size and description are typically *ascaris*. Ascariasis is treated with mebendazole or albendazole. Amoxicillin is an antibacterial. Praziquantel, niclosamide, and paromomycin are effective against cestodes (tapeworms) and are not recommended for nematodes.
- [38.4] E. The life cycle of *Strongyloides* does not require a period outside the host; therefore, the organism can “autoinfect” the host as larvae that develop in the intestines move through the walls

of the intestine, into the circulation, through the lungs and back into the intestines. This autoinfection can lead to overwhelming disseminated strongyloidiasis in immunocompromised hosts with massive invasion of organs with tissue destruction, and can lead to sepsis with gram-negative intestinal organisms.

CLINICAL PEARLS

Patients with nocturnal perianal itching should be evaluated for *Enterobius vermicularis* infection.

Typical stool studies for ova and parasites may not identify *Enterobius vermicularis* ova, as the egg count is usually low. A cellophane tape test is more useful in confirming the diagnosis of pinworm infection.

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◆ CASE 39

A 5-month-old infant arrives at the emergency center strapped to a backboard with a cervical collar in place. The father was holding the infant in his lap in the front passenger seat of their sedan when the driver lost control and collided with a tree. The child was ejected on to the median through the front windshield. The paramedics report the child's modified Glasgow Coma Scale score to be 6 (opens eyes to pain, moans to pain, and demonstrates abnormal extension). The paramedics intubated the child without sedation at the scene. The child had a 2-minute generalized tonic-clonic seizure en route to the hospital; the seizure stopped spontaneously.

Your initial assessment reveals a child with altered mental status. His endotracheal tube is in the correct position, and his arterial blood gas reflects effective oxygenation and ventilation. He is eutermic and tachycardic. He has no clinical evidence of fractures, and his abdominal examination is benign. He has several lacerations on the face and scalp, one that will require surgical closure. His anterior fontanelle is bulging, his sutures are slightly separated, and his fundoscopic examination reveals bilateral retinal hemorrhages.

- ◆ **What is the most likely etiology for this child's altered mental status?**
- ◆ **What is the most appropriate study to confirm this etiology?**

ANSWERS TO CASE 39: Subdural Hematoma

Summary: An unrestrained infant is ejected through the windshield after a motor vehicle accident. The child has altered mental status, has had seizure activity, and his physical examination is consistent with increased intracranial pressure.

- ◆ **Most likely diagnosis:** Subdural hematoma.
- ◆ **Best study:** Urgent computerized tomography (CT) of the head.

Analysis**Objectives**

1. Describe typical findings in head trauma.
2. Compare the typical findings of subdural hematoma with those of epidural hematoma.
3. Discuss the possible treatment options for intracranial hemorrhage.

Considerations

The child in this case is younger than 1 year of age, and subdural hematomas are more common in this age group; epidural hematomas are more common in older children. Seizures are more common with subdural hematomas, occurring in 75% of affected patients; seizures occur in less than 25% of patients with epidural hematoma. The child's altered mental status could be caused by a simple cerebral concussion; the CT scan would be normal or show nonspecific changes. The motor vehicle accident with subsequent ejection of the infant through the windshield provides an appropriate mechanism of action, making other considerations such as shaken baby syndrome much less likely. This child was not in an infant car seat, and thus this case demonstrates parental neglect of the child's safety while traveling in the automobile.

APPROACH TO SUBDURAL HEMATOMA

Definitions

Concussion: Altered mental state immediately after blunt trauma to the head; no consistent brain abnormality is seen; these injuries can cause varying degrees of memory loss, both retrograde and anterograde

Epidural hemorrhage: Bleeding between the dura and the skull; commonly occurs with skull fracture and laceration of the middle meningeal artery, but is frequently of venous origin in children from disruption of dural sinuses or middle meningeal veins (Figure 39-1).

Glasgow Coma Scale: A clinical tool developed to assist in prediction of head injury severity, but as initially described in 1974, it is inappropriate for infants and toddlers. Several "modified"

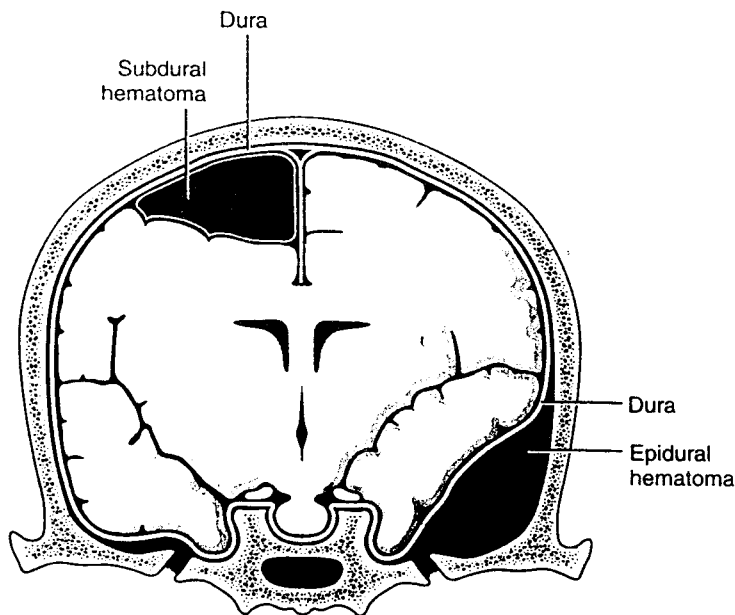


Figure 39-1. Anatomy of subdural and epidural hematomas.

Glasgow Coma Scales have been proposed, attempting to adapt the verbal portion of the scale to reflect language development, and some modify the motor component to reflect the lack of purposeful movement in early infancy (Table 39-1).

Subdural hemorrhage: Bleeding between the dura and the arachnoid space; occurs with disruption of bridging veins connecting cerebral cortex and dural sinuses (see Figure 39-1).

Table 39-1
MODIFIED GLASGOW COMA SCORE FOR CHILDREN
YOUNGER THAN 3 YEARS OF AGE*

Eye opening:

- 1 None
- 2 To pain
- 3 To speech
- 4 Spontaneous

Verbal communication:

- 1 No response
- 2 Incomprehensible sounds
- 3 Inappropriate words
- 4 *Confused conversation, cries
- 5 *Oriented, cries to indicate needs

Motor response

- 1 None
 - 2 Abnormal extension
 - 3 Abnormal flexion
 - 4 Withdraws from pain
 - 5 Localizes pain
 - 6 *Spontaneous movement in infants <6 months and goal-directed movements in children 6-36 months
-

*The Glasgow Coma Scale has been an effective tool to assist in prediction of head injury severity, but as initially described by Teasdale and Jennett in 1974, it is inappropriate for infants and toddlers. The "modified" Glasgow Coma Scale attempts to adapt the verbal portion of the scale to reflect language development and modify the motor component to reflect the lack of purposeful movement in early infancy.

The modified Glasgow Coma Scale can be found at Prasad MR, Ewing-Cobbs L, et al. Predictors of outcome following traumatic brain injury in young children. *Pediatr Neurosurg* 2002; 36:64-74.

The original Glasgow Coma Scale can be found at Teasdale G, Jennett B. Assessment of coma and impaired consciousness: A practical scale. *Lancet* 1974;2(7872):81-84.

Clinical Approach

The child presented above is seriously ill, with evidence of increased intracranial pressure and retinal hemorrhages. Some form of cerebral hemorrhage must be considered. Initial management of this child follows the "ABCs" of resuscitation: the patient's Airway is evaluated first, followed by evaluation of his Breathing, and then assessment of his Circulatory status. After these initial steps are accomplished, care should be directed at his injuries.

Subdural hemorrhage is more common in children younger than 1 year of age, and is much more common than an epidural hemorrhage in the supratentorial space. **Approximately one-third of subdural hemorrhages identified by CT scan have an associated skull fracture**; almost all are venous in origin, and **approximately three-fourths are bilateral**. Computerized tomography images typically show a crescentic hematoma. **Subdural hemorrhage causes seizures in 60% to 90% of afflicted patients**, and retinal hemorrhages are a frequently associated finding. Increased intracranial pressure is typical. Subdural hemorrhage is generally associated with less mortality than that seen with epidural hemorrhage, but long-term morbidity is more significant with subdural injury as the brain parenchyma is more often involved.

Subdural hematomas may be acute, subacute, or chronic. In acute hematomas, symptoms occur in the first 48 hours after injury. Patients with subacute subdural hematomas display symptoms between 3 and 21 days after injury, while chronic hematomas cause symptoms after 21 days. **Chronic subdural hematomas are more common in older children and in teens than in infants**; symptoms may include chronic emesis, seizures, hypertonicity, irritability, personality changes, inattention, poor weight gain, fever, and anemia. Magnetic resonance imaging is more useful than CT in the evaluation of subacute and chronic hematomas, as the age of the hematoma may be estimated by signal intensity.

Epidural hemorrhages are more commonly seen in older children and adults. Epidural lesions are more commonly seen in the infratentorial space, and, in contrast, subdural hemorrhages are more commonly seen in the supratentorial space than are epidural lesions. **Two-thirds of epidural hemorrhages are associated with skull fracture**. While most epidural hemorrhages are arterial in origin in adults,

about half originate from venous injuries in children. Most epidural hemorrhages are unilateral, usually are located in the temporoparietal region of the skull, and present on CT scan images as a lens-like, or bi-convex, hematoma. In contrast to subdural hematoma, fewer than 25% of patients with epidural hemorrhage have seizures, and retinal hemorrhages are uncommon. **Mortality is greater with epidural hemorrhage than with subdural, but long-term morbidity is low.**

Increased intracranial pressure, which may be caused by both forms of hemorrhage, is important to recognize and treat. Epidural hematomas are frequently rapidly progressive, and may require urgent surgical evacuation with identification of the source of bleeding. Subdural hemorrhage usually does not require urgent evacuation, but may necessitate evacuation at a later date.

Comprehension Questions

- [39.1] You are the team physician for a high school varsity football team. On a Friday night during the first quarter of the game, you watch as your star quarterback is sacked with a helmet-to-helmet tackle. He does not get up from the initial impact, and the other players are waving frantically. You sprint on the field and assess the injured player. He is breathing and has a steady pulse, but he is unconscious. As you begin your evaluation, he wakes up. He remembers his name but cannot remember the day, his position on the team, the coach's name, or how he got to the game. He has no sensory or motor deficit that would suggest a cervical spine injury, and eventually you assist him off the field. After 10 minutes he is fully oriented (although he still cannot remember what he had for breakfast) and wants to go back in. The coach tells him he is sitting out for the rest of the game. The player appeals to you. Which of the following is the most appropriate management?
- A. Affirm the coach's decision and tell the player that he will need sequential evaluations before he can come back to practice.
 - B. Affirm the coach's decision and tell the player he can come back and practice tomorrow.

- C. Refute the coach's decision and tell the player he can resume playing now.
- D. Refute the coach's decision and tell the player he can resume playing after half-time.
- E. Strap the player to a backboard and take him to the hospital.

[39.2] A 17-year-old woman is brought to the hospital by ambulance after a motor vehicle accident. She and her boyfriend had been drinking beer at a party and were on their way home when she lost control of the car and hit the wall of the local police station. She reportedly had a brief loss of consciousness but is currently oriented to name, place, and time. She responds appropriately to your questions. While waiting for her cervical spine series, however, she vomits and lapses into unconsciousness. She becomes bradycardic and develops irregular respirations. The brain injury most likely in this case is:

- A. Subdural hemorrhage
- B. Epidural hemorrhage
- C. Intraventricular hemorrhage
- D. Posttraumatic epilepsy
- E. Concussion

[39.3] Several days after emergent management of her injury, the adolescent in the above case is transferred to you from the intensive care unit. She is concerned about her prognosis. You tell her:

- A. She will need extensive neuropsychiatric evaluation before she can return to school.
- B. She will likely have headaches, fatigue, nausea, and sleep disturbances.
- C. She will likely develop seizures and will need to take prophylactic anticonvulsants for 2 years.
- D. She can no longer be legally permitted to drive because she has had brain surgery.
- E. She should have few long-term problems.

[39.4] A 7-month-old child presents to the emergency room after reportedly falling from his high chair. The parents report no loss of

consciousness, and no other trauma or medical problems. Your physical examination reveals a few old bruises but no evidence of acute trauma or fracture. The child is irritable, however, and you request a CT scan of the brain without contrast. The pediatric radiologist reports bilateral frontal subdural hematomas, and notes two healing skull fractures that she estimates to be about 2 weeks old. The best next step in this child's management is to:

- A. Observe him for 6 hours in the emergency center.
- B. Assess bleeding time and prothrombin time.
- C. Order magnetic resonance imaging of the head.
- D. Discharge him from the emergency center with head injury precautions.
- E. Order an electroencephalography and a neurology consultation.

Answers

- [39.1] **A.** Although there is debate as to the proper length of time a player needs to refrain from sports activities after a concussion, most organizations recommend that a player who sustains a concussion resulting in loss of consciousness refrain from play the remainder of the day. The American Academy of Pediatrics currently endorses findings of the 1997 Concussion Workshop sponsored by the American Orthopaedic Society for Sports Medicine. Despite a paucity of data, this report suggests that individualized and frequent reassessment of the player over time is more useful than a predetermined length of time to refrain from additional sports.
- [39.2] **B.** This teen displays the typical adult course in epidural hemorrhage, with an initial period of altered mental status (initial concussion), followed by a period of lucidity, and then finally redevelopment of altered mental status and symptoms of increased intracranial pressure (hematoma effect). Younger children typically do not display this pattern. Immediate neurosurgical evaluation is appropriate for her.
- [39.3] **E.** Although the mortality for patients with acute epidural hemorrhage is higher than that for patients with acute subdural hem-

orrhage, long-term morbidity is minimal. The complaints in answer B are common after a subdural hemorrhage. While a seizure disorder may preclude driving, simply having had cranial surgery does not.

- [39.4] C. This child has evidence of old skull fractures with subdural hematomas. Magnetic resonance imaging of the head would help to determine the age of the hematomas. Should the age of the blood in the hematomas correlate with the estimated age of the skull fractures, child abuse should be considered. Neurology may be helpful later in the child's evaluation, but a consultation would be of limited benefit before additional data were gathered. Discharge with the information presented in the case would be dangerous; the child likely requires admission to the hospital. Bleeding studies are unlikely to be helpful; the child has no history consistent with a bleeding disorder, nor would a bleeding disorder explain the old fractures.

CLINICAL PEARLS

Subdural hemorrhage is more common in children younger than 1 year of age and in the supratentorial space. About one-third of subdural hemorrhages are associated with skull fractures, and on CT scan show a crescentic hematoma; seizures and retinal hemorrhages are frequently associated findings. Increased intracranial pressure is typical.

Epidural hemorrhages are more commonly seen in older children and adults and in the infratentorial space. About two-thirds of epidural hemorrhages are associated with skull fracture and present on CT scan images as a lens-like, or biconvex, hematoma. Fewer than 25% of patients have seizures; retinal hemorrhages are uncommon.

Mortality with subdural hemorrhage is generally less than that seen with epidural hemorrhage, but long-term morbidity is more significant with subdural injury as the brain parenchyma is more often involved.

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◆ CASE 40

A mother brings her 12-year-old son to your office for the evaluation of behavioral problems. The school sent home a letter suggesting that the boy had features consistent with attention deficit hyperactivity disorder (ADHD), and encouraged the family to have the boy tested. His teacher noted that the boy frequently stares off into space and does not seem to be concentrating on his work. Yet after about 10 seconds, he resumes his work as if nothing had happened. When the mother tries to get his attention by calling his name or touching him he takes a moment to respond, seemingly daydreaming. She notes that he is not disruptive, nor does he seem to be overly active. The mother has also noticed that he daydreams frequently when he is at home on the weekends; she has always written it off as “being in his own world.” The boy does not think anything is wrong, but does report his friends mention he frequently “zones out.” Past medical history, family history, and social history are negative.

While discussing the child’s situation with the mother, you notice the boy to be staring out the window and holding a magazine without looking at it. He exhibits a blank facial expression, rhythmically blinking eyes, and slightly twitching hands. After about 10 seconds, he resumes reading the magazine.

◆ **What is the most likely diagnosis?**

◆ **What is the next step in evaluating this patient?**

ANSWERS TO CASE 40: Absence Seizures

Summary: A 12-year-old boy has frequent, brief episodes of cessation of activity. During these episodes, he has subtle rhythmic movements; verbal and tactile stimulation do not rouse him.

◆ **Most likely diagnosis:** Absence (petit mal) seizures.

◆ **Next step:** Electroencephalograph (EEG).

Analysis

Objectives

1. Describe a typical absence seizure.
2. Distinguish absence seizures from other kinds of epilepsy (see Table 40-1).

Considerations

This patient has classic signs of absence seizures—a sudden cessation of activity, a blank facial expression, and a flickering of the eyelids. He does not have symptoms of a tonic-clonic seizure—a preceding aura, loss of bowel or bladder function, tonic-clonic contractions, and postictal confusion. His teachers suggested testing for the inattentive form of ADHD. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), the child must have six of the following symptoms to be diagnosed with the inattentive form of ADHD: (1) makes careless mistakes; (2) cannot sustain school or play activities; (3) does not seem to listen when spoken to; (4) cannot follow tasks through to completion; (5) has difficulty organizing; (6) avoids tasks that require persistent effort; (7) loses needed items; (8) is distractible; and (9) is forgetful. Although children with absence seizures can display several symptoms of ADHD, a careful history will usually distinguish inattention from absence seizures.

APPROACH TO ABSENCE SEIZURES

Definitions

Absence seizure: A seizure with few physical manifestations, typically represented by an abrupt cessation of activity for 5 to 10 seconds during which the child is unresponsive. The seizure rapidly resolves without postictal confusion and activity resumes as if no pause has occurred.

Epilepsy: Recurrent seizure activity that may or may not have an identifiable cause.

Seizure: Abnormal electrical activity of the brain resulting in altered mental status or involuntary neuromuscular activity.

Clinical Approach

Absence seizures are short and frequent. The typical absence seizure lasts 5 to 10 seconds, but may last up to 30 seconds; hundreds of seizures may occur in a single day. **Typically, the onset of absence seizures occurs after age 3 to 5 years, with most first seizures occurring prior to the age of 10 years.** Girls are more often affected. Absence seizures are frequently familial, with multifactorial inheritance. Additional forms of seizures occur in 30% to 50% of children with absence seizures. During the seizure, the child may occasionally have rapid blinking and subtle arm movements, and the head may droop slightly. The child has **no preceding aura, is not aware of a pause in activity, does not lose bowel or bladder control, and does not have a postictal state;** instead, the child merely resumes activity after the seizure as if no pause had occurred. These children typically are thought to be “daydreaming” but they have no recollection of a “daydream.” In contrast to children who daydream, a child having absence seizures cannot express what they were doing, and do not respond to verbal or tactile stimulation until the seizure is over.

Hyperventilation is used in the diagnostic setting to induce an absence seizure. The child is asked to breathe rapidly and deeply for 3 to 4 minutes. **Electroencephalograph findings are characteristic and diagnostic, demonstrating a three per second spike and wave pattern with a normal background (Figure 40-1).**

Table 40-1
SELECTED GENERALIZED EPILEPTIC SEIZURES IN CHILDHOOD

SEIZURE	AGE OF ONSET	TYPICAL MANIFESTATIONS	EXPECTED COURSE	NOTES
Absence (petit mal)	4-12 years	Staring, occasional eye blinking and hand twitching, lasts 5-10 seconds	Approximately 90% of patients with normal intelligence and isolated absence seizures will become seizure free	Characteristic EEG is three-per-second spike and wave with normal or near-normal background
Infantile spasm (West syndrome)	Most between 4 to 8 months	Sudden and brief flexion spasms of head, torso, and limbs with adduction ("salaam seizure"), usually mixed with extensor spasms	Rarely persist past 5 years, but most develop profound mental retardation and epilepsy; only 5-10% have normal intelligence	Difficult to treat; occur in clusters; characteristic EEG is hypsarrhythmia
Lennox-Gastaut syndrome	In the first 3 years of life	Younger children have tonic, atonic, and atypical absence	Most have mental retardation; 80% will continue to have seizures into adulthood.	Usually secondary to other causes such as anoxic brain injury, head injury, central

		Older children have tonic-clonic convulsions		nervous system infection; no cause identified in a third of patients; EEG has long runs of generalized two-per-second sharp-wave and slow-wave complexes with abnormal background; difficult to treat
Benign myoclonus of infancy	Infancy	Clusters of myoclonic movements of neck, trunk, and extremities	Normal development, cessation of myoclonus by 2 years	Normal EEG; can be confused with infantile spasms
Juvenile myoclonic epilepsy (Janz syndrome) (impulsive petit mal)	Between 12 and 16 years	Early morning myoclonic jerks and tonic-clonic seizures, made worse by sleep deprivation, photic stimulation; no impairment of consciousness	Normal intelligence, easily treated, usually need medication for life, relapse common with cessation of antiepileptics	EEG with four- to six-per-second irregular spike and wave pattern

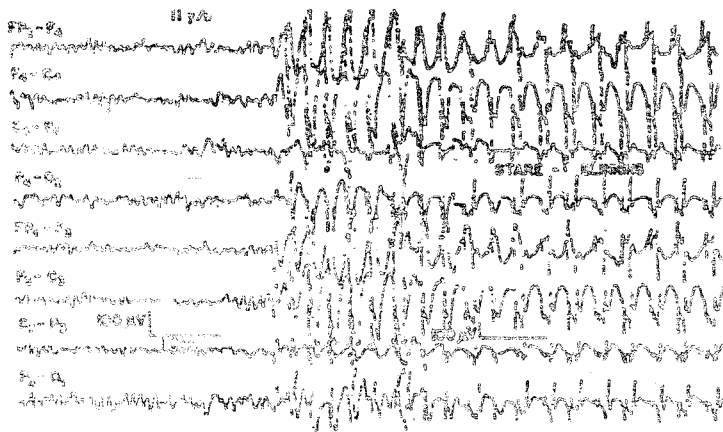


Figure 40-1. EEG of typical absence seizure with three per second spike and wave pattern. From Rudolph's Pediatrics, 21st ed. (with permission).

In general, the prognosis is favorable for children with simple absence epilepsy. Factors predictive of a good outcome include a normal background EEG, no history of tonic-clonic seizures in the child or family, normal intelligence, and a normal neurologic examination. Absence seizures in this group of children become less frequent with the age of the patient, and many patients are seizure free as adults. Current **therapy** for the patient with absence seizures includes **ethosuximide** and **valproate**.

Comprehension Questions

- [40.1] A 7-year-old girl presents with poor school performance. She is repeating the first grade because she did poorly in reading. Her mother reports that she cannot finish her homework without repeated encouragement and occasional threats. She notes that the girl does not like to go to school, and every morning the girl complains of a headache or stomachache to avoid attending school. Her teachers report that she does not pay attention in class, that she gets up frequently and walks around the classroom, and that she is always misplacing her school supplies. She

frequently leaves her backpack at school. Her physical examination, including a funduscopic examination, is normal. The best way to evaluate this child is:

- A. Electroencephalograph (EEG)
- B. Magnetic resonance imaging of her brain
- C. Electrolytes and a complete blood count
- D. Parental reassurance
- E. Parent and teacher input into an ADHD evaluation tool

[40.2] The parents of a 1-year-old boy come to the office for a second opinion. The boy has a history of infantile spasms beginning at 6 months of age. He was born via emergency cesarean section at 30 weeks gestation after his mother was in a motor vehicle accident and developed placental abruption. His previous doctor tried many different antiepileptic medications with little success for seizure control. The child's most recent EEG demonstrated hypsarrhythmia. The parents are interested in the possibility of new medications and ask about their child's long-term prognosis. You tell them:

- A. Infantile spasms are difficult to treat. While the child will likely outgrow them, he will have significant mental retardation and may have other types of seizures.
- B. Infantile spasms are best treated with phenobarbital, which will decrease the child's seizures and improve his prognosis.
- C. Most children grow out of infantile spasms and develop normally; medication for seizure control is unnecessary.
- D. The EEG finding indicates the child does not have infantile spasms; the movements that the parents are seeing are likely caused by gastroesophageal reflux and he will be completely cured with reflux medication.
- E. Infantile spasms are best prevented by antipyretic medication, and usually resolve by 5 years of age.

[40.3] The emergency center physician admits a 17-year-old boy for new onset seizures. A first semester freshman at the local college, he awoke to go to class but then had a generalized

tonic-clonic seizure, witnessed by his roommate. He reports that he spent the night before studying and denies illicit drug use. With prompting he reports that for several years he has had isolated muscle twitches in the mornings, but because they always resolved after an hour or so he did not seek medical attention. He has no family history of seizures. He is currently afebrile, and his physical examination is completely normal. He questions why he had the seizure and what is wrong with him. Which of the following is the best diagnosis and treatment plan?

- A. Absence seizures; 1 to 2 years of antiepileptic medications
- B. Febrile seizures; no need for medications
- C. Lennox-Gastaut syndrome; lifelong antiepileptic medication
- D. Juvenile myoclonic epilepsy; lifelong antiepileptic medication
- E. Benign myoclonus; no need for medications

[40.4] A 7-year-old girl, born at 26 weeks gestation, has global developmental delay and functions at the level of a 4-year-old child. She has a history of staring spells that last several minutes and include unilateral upper extremity jerking. Treatment has been difficult, requiring two antiepileptic medications to achieve adequate control. The parents have read information suggesting that most children with absence seizures improve with age and are developmentally normal. They ask if they can expect the same from their child. You respond that they can expect:

- A. Complete resolution of the absence seizures and normal development.
- B. Complete resolution of the absence seizures and continued developmental delay.
- C. Persistent seizures but eventual normal development.
- D. Persistent seizures and continued developmental delay.
- E. Partial resolution of the seizures and normal development.

Answers

- [40.1] E. The history suggests attention deficit hyperactivity disorder. Rating scales that include parent and teacher questionnaires can

be helpful in this evaluation. Laboratory evaluation would not be helpful, and a central nervous system neoplasm is unlikely in this child with a normal physical examination. Reassurance in this situation without more information would be a disservice to the child.

- [40.2] **A.** An EEG demonstrating hypsarrhythmia is typical of a patient with infantile spasms. Infantile spasms are notoriously difficult to treat. Only a small percentage of children with infantile spasms will have normal development; this patient, with probably underlying central nervous system injury secondary to perinatal asphyxia, will probably have persistent developmental delay. Phenobarbital is not usually effective in this disorder, and there is no evidence suggesting that medications will affect long-term prognosis.
- [40.3] **D.** This is a typical presentation of Janz syndrome, or juvenile myoclonic epilepsy. Prognosis is generally excellent with medication, but cessation of medication frequently results in relapse.
- [40.4] **D.** The child described has atypical, or complex, absence seizures. These children usually do not have resolution of seizure activity as they get older; rather, they commonly develop other types of seizures.

CLINICAL PEARLS



Absence seizures should be considered in children who have repeated episodes of diminished awareness.

Absence seizures occur many times throughout the day and are usually no more than 10 seconds long.

The electroencephalography finding of three-per-second spike and wave pattern is characteristic of absence seizure.

Children who have a normal background EEGs, no personal or family history of convulsions, normal intelligence and a normal neurologic exam have a good chance of being seizure free as adults.

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◆ CASE 41

The emergency department (ED) notifies you that one of your patients is being evaluated for new onset seizures. The 2-year-old boy was in his normal state of good health until this morning, when he complained of a headache and then fell to the floor. While waiting for the ED physician to come to the phone, you review his chart and find that the child had normal development at his 2-year-old visit. His family history is significant for a single seizure of unknown etiology that his father had at age 4 years. According to the ED physician, the boy's mother saw jerking movements of both his arms and legs. When the ambulance arrived 5 minutes later, the child had stopped jerking, was sleeping, and was not arousable. The paramedics reported a heart rate of 108 beats per minute, a respiratory rate of 16 breaths per minute, a blood pressure of 90/60 mmHg, and a temperature of 104°F (40°C). His blood sugar was 135 mg/dL. By the time the child arrived at the hospital, he was awake and recognized his parents. His physical examination by the ED physician is completely normal. Screening laboratory data including a complete blood count and urinalysis are normal.

- ◆ What is the most likely diagnosis?
- ◆ What is the best management for this condition?
- ◆ What is the expected course of this condition?

ANSWERS TO CASE 41: Simple Febrile Seizure

Summary: An otherwise normal 2-year-old boy, with a family history of seizure in his father, has a brief, generalized, self-limited seizure associated with an elevated temperature. His examination is nonfocal. He has completely recovered within 1 to 2 hours of the seizure.

- ✦ **Most likely diagnosis:** Simple febrile seizure.
- ✦ **Best management:** Parental education about seizures, injury prevention during a seizure, and fever control.
- ✦ **Expected course:** More seizures with fever may occur, but this child is likely to "grow out" of the condition by 5 to 6 years of age. He is likely to have no sequelae and is expected to have normal development.

Analysis**Objectives**

1. Describe a typical febrile seizure.
2. Explain the typical course of febrile seizures.
3. List factors that increase the risk of further seizure activity.

Considerations

This patient had a simple febrile seizure. The seizure was short, self-limited, and generalized with no focal findings. The child had an elevated temperature at the time, and is between the ages of 6 months and 6 years. The child had a short postictal state and then quickly returned to normal. He is old enough to have reliable neck examination findings, and has no evidence of meningeal irritation. The father has a history of a single seizure at a young age, which may have been febrile, but the data are insufficient to make that conclusion.

APPROACH TO FEBRILE SEIZURE

Definitions

Epilepsy: Recurrent seizure activity; may or may not have identifiable cause.

Febrile seizure: A seizure occurring in the absence of central nervous system (CNS) infection with an elevated temperature in a child between the ages of 6 months and 6 years of age.

Seizure: Abnormal electrical activity of the brain resulting in altered mental status or involuntary neuromuscular activity.

Clinical Approach

A diagnosis of febrile seizure must be made only after considering the possibility of central nervous system infection as the cause of the seizure. There are **two classic physical findings that suggest meningeal irritation: Kernig sign** (patient is supine, leg flexed at the hip and knee at 90-degree angles, pain is induced with extension of the leg), and **Brudzinski sign** (while supine, passive flexion of the neck results in involuntary flexion of the knees and hips). If the **neurologic examination is abnormal** after the seizure, or if the child is **unable to provide adequate feedback during a neck examination, a lumbar puncture may be necessary**. The meningeal signs described above are usually not reliable in children younger than 1 year of age; therefore, a lumbar puncture is recommended in children in this age group when they present with fever and seizure. **Contrast-enhanced imaging of the brain should occur before lumbar puncture when a space-occupying lesion, such as a brain abscess, is a diagnostic possibility.**

Febrile seizures are a uniquely pediatric entity, typically occurring between the ages of 6 months and 6 years, these convulsions may be extremely distressing to the parent but only occasionally pose a threat to the child. Febrile seizures are common, occurring in 2% to 4% of all children. Peak incidence for the first febrile seizure is between 14 and 18 months of age. Febrile seizures seem to have a genetic basis, as many children have a history of febrile seizure in their siblings or their

parents. An increased risk of febrile seizure (10% to 20%) is found when a **first-degree relative** was diagnosed with the same.

Febrile seizures are frequently classified as **simple or complex**; this distinction helps to clarify the risk of recurrence as well as prognosis. Simple febrile seizures are described as lasting no more than 15 minutes and demonstrating no focal or lateralizing signs. If more than one seizure occurs in a brief period, the total episode lasts no more than 30 minutes. No sequela in a simple febrile seizure is found. A complex febrile seizure lasts more than 15 minutes and may have lateralizing signs. If several seizures occur in a brief period, the entire episode may last longer than 30 minutes (see Figure 41-1 for algorithm).

The timing of the febrile seizure in relation to the temperature elevation is variable. While many children will have a febrile seizure during the initial temperature upswing (many parents are unaware that the

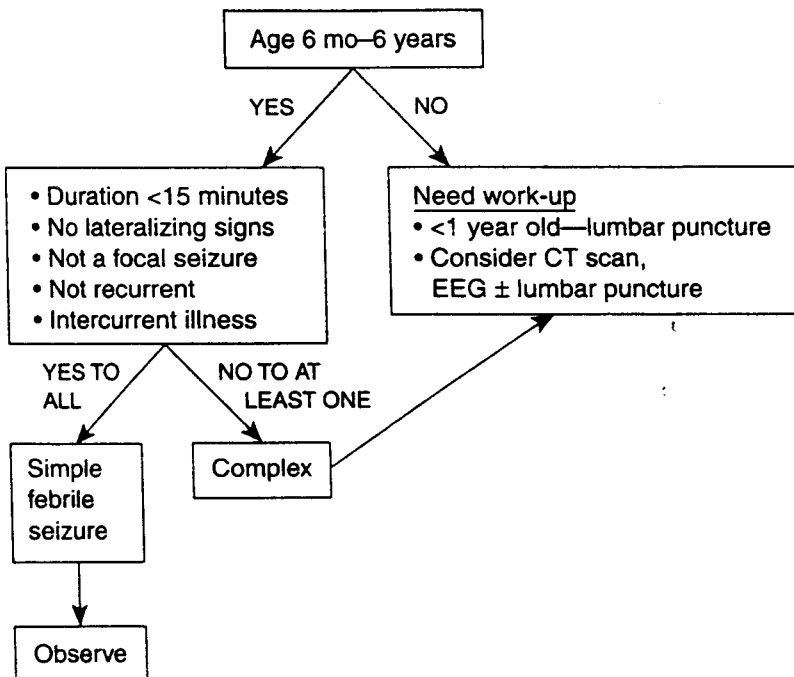


Figure 41-1. Algorithm for managing febrile seizures.

child is ill until the seizure and the subsequent recording of the temperature), other children will have seizures at other points during the febrile illness.

A febrile seizure is usually self-limited. If the seizure lasts longer than 5 minutes, lorazepam or diazepam may be used to interrupt the seizure. Airway management must remain a priority; although most children tolerate benzodiazepine medications well, an occasional child may develop respiratory depression. Ongoing seizures unresponsive to lorazepam or diazepam may be interrupted with fosphenytoin.

The evaluation of a simple febrile seizure need not be extensive. Electroencephalography (EEG) is not recommended unless focal findings were present during or after the seizure, or if the seizure was prolonged. EEG is not predictive of future febrile or afebrile seizures. Laboratory studies (except to workup the fever) are not helpful in most cases of simple febrile seizure. Similarly, brain imaging is usually unnecessary in a simple febrile seizure. Imaging may be indicated in a complex febrile seizure or in patients with evidence of increased intracranial pressure. A lumbar puncture is indicated in a child younger than 12 to 18 months of age, in a child with an unreliable or abnormal neurologic exam, and in a patient who experience the seizure several days into a febrile illness. Routine lumbar puncture in other groups is usually not helpful.

Prophylactic medications are usually not necessary. Some experts recommend prophylactic diazepam during febrile illness, but this practice is not widespread. In the practice parameter published in 1999, the American Academy of Pediatrics emphasized that prophylactic medications for the usually benign condition of febrile seizures were not routinely useful.

Prognosis is generally good, as the majority of children who develop febrile seizure will not develop neurologic or developmental consequences. The age at the time of the first seizure is predictive of recurrence: **children younger than 12 months of age at the time of their first seizure have a 50% to 65% chance of having another febrile seizure**; older children have a 20% to 30% chance of recurrence. While having a febrile seizure does increase the chance of developing epilepsy, this factor only increases the chance from 0.5% in the general population to 1% in the child with a febrile seizure history. Children at highest risk of developing epilepsy after having had febrile seizures often have preexisting neurologic or developmental problems and

develop complex febrile seizures; these children have 30 to 50 times the baseline risk of developing epilepsy.

Comprehension Questions

- [41.1] Paramedics bring a 7-month-old infant to the emergency room with seizure activity. The father reports the infant was in a normal state of health until about 3 days ago when she developed a febrile illness, diagnosed by her physician as a viral upper respiratory tract infection. Approximately 30 minutes ago the child began having left arm jerking, which progressed to whole-body jerking. The infant stopped having the seizure activity in the ambulance on the way to the hospital. Vital signs include a heart rate of 90 beats per minute, a respiratory rate of 25 breaths per minute, and a temperature of 100.4°F (38°C). Your examination reveals a sleeping infant in no respiratory distress with an intravenous catheter in the left arm. The child's anterior fontanelle is full. The oropharynx is clear, and crusted mucous is found in the nares. The tympanic membranes are dark. The lungs are clear, and the heart and abdominal examinations are normal. The skin examination is significant for a bruise over the occiput and several parallel bruises along the spine. The next step in management is:
- A. Observation
 - B. Lumbar puncture
 - C. Computerized tomography of the head
 - D. Phenobarbital
 - E. Electroencephalogram
- [41.2] A 2-year-old boy who had a simple brief febrile seizure comes to your office one day after his emergency center visit. He is currently afebrile, is happily pulling the sphygmomanometer off the wall, and from the mother you learn that he is taking antibiotics for an ear infection diagnosed the previous day. She wants to know what to expect in the future regarding his neurologic status. You tell her that:

- A. He has no risk of further seizures because he was age 2 years at the time of his first febrile seizure.
- B. He will need to take anticonvulsant medications for 6 to 12 months to prevent further seizure activity.
- C. You want to schedule an EEG and a magnetic resonance scan of his head.
- D. While he does have a risk of future febrile convulsions, seizures of his type are generally benign and he is likely to outgrow them.
- E. This is an isolated disorder and his children will not have seizures.

41.3] A 10-month-old boy presents to the ED with a 1-day history of fever to 104°F (40°C), increased irritability, decreased breast-feeding, and refusal of solid foods. The parents brought him in after two 30-second episodes of generalized jerking that occurred over a 20-minute span. Your examination reveals an awake but lethargic infant. The anterior fontanelle is flat, the tympanic membranes and oropharynx are moist and not erythematous, the lungs are clear, and the heart and abdominal examinations are normal. He has no focal neurologic findings. The next step in management should be:

- A. Intravenous ceftriaxone
- B. Admission overnight for observation
- C. Computerized tomography of the head
- D. Discharge from ED to follow-up with his primary care provider in 24 hours
- E. Lumbar puncture

41.4] The father of a 4-year-old girl calls your office to report her second febrile seizure. He states that this seizure was identical to the first one that happened 4 months ago: she developed an elevated temperature and within a short time had a generalized convulsion lasting 90 seconds. She was sleepy for about 2 minutes after the seizure. When she woke up, the family gave her ibuprofen suspension. She is now running around the house chasing her younger brother. The parents wonder if she needs to

be on anticonvulsants now that she has had another seizure. You tell the father that:

- A. Febrile seizures are frequently recurrent, but they usually have no significant long-term effect.
- B. You will prescribe an anticonvulsant because they reduce the risk of epilepsy in the future.
- C. You will order an EEG and CT scan of her head to be done on an outpatient basis.
- D. He needs to take his daughter to the hospital for inpatient admission.
- E. He should stop the ibuprofen and observe the fever curve.

Answers

- [41.1] C. This child's history is worrisome for trauma. The fontanelle is full, bruises are found along the spine and on the occiput, and he has evidence of hemotympanum. A CT scan is of paramount importance, as this child likely had a seizure as a result of acute intracranial hemorrhage associated with physical abuse. While this child is febrile and is within the proper age range for febrile seizure, the history and physical examination findings are more consistent with a diagnosis other than febrile seizure.
- [41.2] D. Part of the anticipatory guidance for parents of children with febrile seizures is to impress upon them that the child may have another seizure; it is similarly important to emphasize the usual benign nature of this condition. In a simple febrile seizure, imaging and EEG generally are not recommended, nor are prophylactic anticonvulsants. Because febrile seizures seem to have a genetic basis, it is possible that your patient's children will also have febrile seizures.
- [41.3] E. While this child may ultimately be diagnosed as having had a simple febrile seizure, the patient's age (younger than 1 year) is such that a neck examination will not be reliable. A lumbar puncture is required to evaluate the child for meningitis. Ad-

ministering antibiotics before the lumbar puncture (or other cultures are obtained) is inadvisable unless the patient's condition is such that he would not tolerate the procedure.

- [41.4] A. Some children will develop recurrent febrile seizures. Data suggest that anticonvulsant medications will decrease the risk of further febrile seizures; however, no evidence suggests the notion that anticonvulsant therapy will decrease the risk of developing epilepsy. The possible adverse reactions with antiepileptic medications are numerous, including severe allergic reactions and interference with school performance, and in most cases, the benefit is not worth the risk. Fever reduction with medications is generally encouraged in children with a history of febrile seizure.

CLINICAL PEARLS

- ◆ Febrile seizures are usually benign and self-limited. They do not require an extensive diagnostic evaluation unless they are prolonged or focal.
- ◆ A diagnosis of febrile seizure must be made only after considering the possibility of central nervous system infection as the cause of the seizure.
- ◆ Febrile seizures only rarely lead to epilepsy; risk factors for the development of nonfebrile seizures include preexisting developmental abnormalities and complex febrile seizures.

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◆ CASE 42

The parents of a 4-year-old boy have a long-standing concern about their child's walking. They noted that he first walked at about 16 months of age. They reported that he was clumsier than other children as he was beginning to walk, but they were reassured by another pediatrician that he would "outgrow it." More recently, they noticed that he continues to be clumsier than his peers (frequently falling during simple tasks such as walking or running) and that he has begun to develop a "waddling" gait. Within the last month the child has had increasing difficulty trying to get up from a sitting position on the floor.

- ◆ What is the most likely diagnosis?
- ◆ What is the diagnostic test of choice?
- ◆ What is the mechanism of disease?

ANSWER TO CASE 42: Muscular Dystrophy

Summary: A 4-year-old boy has delayed onset of walking and, more recently, the development of a waddling gait, clumsiness, and proximal muscle weakness.

- ◆ **Most likely diagnosis:** Muscular dystrophy, probably Duchenne type.
- ◆ **Diagnostic test:** DNA analysis of peripheral blood or immunocytochemical detection of abnormal dystrophin on a section of muscle biopsy tissue.
- ◆ **Mechanism of disease:** Duchenne muscular dystrophy is an X-linked recessive trait. The abnormal gene is at the Xp21.2 locus and encodes for an aberrant form of the protein, dystrophin.

Analysis**Objectives**

1. Know the presentation of children with inherited forms of muscular dystrophy.
2. Understand the inheritance pattern of the common muscular dystrophies.
3. Understand the progression of the muscular dystrophy.

Considerations

This 4-year-old boy exhibits classic signs of Duchenne muscular dystrophy (DMD): waddling gait and progressive proximal muscle weakness. Initial testing includes serum assessment of creatinine kinase and DNA analysis of peripheral blood for diagnosis. When the diagnosis of DMD is made, the family should be introduced to support organiza-

tions such as the Muscular Dystrophy Association (MDA), and genetic counseling is offered. Ongoing cardiac evaluation is required to monitor for the development of cardiomyopathy. Medical therapy is supportive, with orthopedic intervention as needed to prolong ambulation and to slow the progression of scoliosis. As the disease progresses, patients are at increasing risk for severe complications from respiratory infection. Hence, they should be followed closely with early initiation of treatment.

APPROACH TO MUSCULAR DYSTROPHY

Definitions

Gower sign: Describes the manner in which patients with proximal muscle weakness arise to a standing position from the floor. The legs are brought under the torso and weight is then shifted to the hands and feet. The hands are walked toward the feet and up the thighs as the patient attempts to rise.

Trendelenburg gait: The pelvic waddling gait that results from proximal muscle weakness.

Clinical Approach

DMD is the most common hereditary neuromuscular degenerative disease. It is an X-linked recessive disease, having an incidence of 1:3,000 to 1:3,600 male births; 30% of cases are new mutations. DMD is the most severe progressive primary myopathy of childhood.

The prenatal history may reveal relatively less fetal movement or polyhydramnios. Affected males are generally asymptomatic during infancy with developmental milestones achieved early in life. Boys with DMD typically present between 3 and 5 years of age with increasing lumbar lordosis secondary to gluteal weakness, frequent falling or difficulty climbing stairs, inability to release after a hand grip, hip waddle, and proximal muscle weakness often manifest in a **Gower sign**. **Muscular enlargement**, caused by hypertrophy of muscle fibers, as well as by infiltration of fat and collagen proliferation, leads to a

pseudohypertrophy of calf, gluteal, and deltoid muscles; **on examination, these muscles feel woody or rubbery in nature.** Contractures of hip flexors, heel chords, and iliotibial bands develop, limiting the range of motion of affected joints. Myocardial involvement can lead to cardiomyopathy with electrocardiographic findings of tall R waves in right precordial leads and deep Q waves in the left precordial leads. Nonprogressive brain atrophy may be seen on computerized tomography, and intellectual impairment is common, with a mean IQ of 80.

Patients with DMD generally become wheelchair dependent between 10 and 12 years of age, and demonstrate rapid progression of scoliosis after the loss of ambulation. Distal muscles, however, remain functional, permitting adequate manual dexterity. As the degenerative process continues, respiratory muscle involvement, coupled with the scoliosis, results in diminished pulmonary function and a high risk for recurrent pulmonary infections. Oropharyngeal dysfunction secondary to muscle weakness can lead to aspiration, further compromising respiratory capacity. Gastroparesis is sometimes treated with metoclopramide, and phenytoin or carbamazepine is sometimes used to treat myoclonia (inability to relax muscles). Boys with DMD usually succumb to respiratory failure, heart failure, or airway obstruction late in the second decade of life.

DNA analysis of peripheral blood samples using polymerase chain reaction (PCR) technology is diagnostic in two-thirds of cases. Immunocytochemical testing of muscle biopsy tissue for abnormal dystrophin can be performed when peripheral blood samples are not diagnostic. Findings on muscle biopsy include endomysial connective tissue proliferation, inflammatory cell infiltrates, areas of regeneration interspersed with areas of degeneration, and areas of necrosis.

Other laboratory findings include an elevation of the serum creatinine kinase (CK) levels. Levels of this enzyme are elevated prior to clinical presentation and can be especially helpful in the early diagnosis of familial cases. **In 80% of cases, female carriers can be identified by detection of elevated levels of CK.** Electromyogram (EMG) findings reveal myopathy. However, these findings are not diagnostic of DMD, as patients with Becker muscular dystrophy (BMD) also have a genetic defect at the Xp21.2 locus, resulting in similar, but less severe, disease. At this time, there is no cure for DMD or medical treatment to slow progression of the disease. Orthopedic intervention, including

bracing and tendon lengthening, can prolong the duration of ambulation and slow the progression of scoliosis. Physiotherapy may delay the onset of contractures, but is not intended for muscle strengthening because significant exercise can hasten muscle degeneration.

All patients with DMD have some degree of **cardiomyopathy**, but the severity of cardiac dysfunction does not correlate with the degree of skeletal involvement. Thus, boys with DMD require routine cardiac evaluation from the time of diagnosis. Early cardiac dysfunction may be responsive to digoxin.

Respiratory failure is often the cause of death in patients with DMD. Pulmonary infections are treated early and aggressively; exposure to respiratory illnesses should be limited when possible. Routine immunizations are supplemented with yearly influenza vaccine.

The nutritional status of boys with DMD is carefully monitored to ensure appropriate caloric intake. For wheelchair-bound patients, caloric needs are lower owing to decreased activity, but calcium supplementation may be required to minimize osteoporosis. Patients with DMD are at risk for depression, often resulting in overeating, weight gain, and added burden to their already limited muscle function.

Comprehension Questions

[42.1] The parents of a 3-year-old child are worried about the child's apparent clumsiness with frequent falls and a waddling gait. Which of the following is consistent with DMD?

- A. Female sex
- B. Hypertrophy of the quadriceps
- C. 22-year-old sister with DMD
- D. Gower sign
- E. Positive antinuclear antibodies in the blood

[42.2] The best screening test for the child mentioned above is:

- A. A muscle biopsy
- B. Measurement of serum creatinine
- C. An electromyogram

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◆ CASE 43

A 2-week-old infant presents to the emergency department with a 12-hour history of fever, irritability, and decreased oral intake. She was delivered vaginally at 39 weeks' gestation to a gravida 2 para 1 woman, whose pregnancy was uncomplicated except for a hospitalization for 2 days because of acute urinary retention. The mother had routine prenatal care. The infant went home from the hospital on day of life 2. She has surpassed her birth weight of 3.7 kg, and she has been well until today. On physical examination, the infant has a temperature of 101.5°F (38.6°C) and she is fussy. Her physical examination is otherwise unremarkable, but during the course of her evaluation, she has an episode of shaking that begins on the right side of her body and then generalizes to the remainder of her body. The episode lasts approximately 2 minutes, and the infant is subsequently somnolent.

◆ **What is the most likely diagnosis?**

◆ **What are the potential complications of this condition?**

ANSWERS TO CASE 43: Congenital Herpes

Summary: A 2-week-old previously healthy infant with fever, irritability, and decreased oral intake has one episode of seizure-like activity in the emergency department. The pregnancy was remarkable for urinary retention as a consequence of probable herpes virus. The vaginal delivery and early neonatal course were uncomplicated.

- ◆ **Most likely diagnosis:** Congenital herpes.
- ◆ **Potential complications of this condition:** If untreated, the majority of infants with disseminated or central nervous system infection die. Even with appropriate management, the mortality and morbidity of disseminated herpes infection are substantial: more than 50% of infants with disseminated disease die, and 40% of survivors have sequelae at 1 year of age. Among treated infants with central nervous system disease, the mortality rate is 15%, and only 30% are normal at 1-year follow-up.

Analysis

Objectives

1. Recognize the importance of early recognition of congenital herpes infection.
2. Know how to diagnose congenital herpes infection.
3. Know the appropriate management of congenital herpes infection.

Considerations

A young infant with fever and irritability should be presumed to have a serious bacterial or viral infection. Bacterial causes of sepsis and meningitis in a child of this age include group B streptococcus, listeria, and gram-negative pathogens. The **primary viral pathogen to consider in this case is herpes simplex virus (HSV)** because the child

is having **focal seizures**. The absence of a history of herpes in the mother of this infant is not unusual, but the episode of acute urinary retention is suspicious for HSV. Primary and recurrent herpes outbreaks in women may be asymptomatic or associated with only nonspecific symptoms. The risk of maternal passage of the infection to the neonate is higher in cases of primary herpes outbreaks, as the viral inoculum in the genital tract is high and the protective antibody is not present. Neonatal infection in the setting of a recurrent maternal outbreak is only 5% or less.

Blood, urine, and cerebrospinal fluid (CSF) specimens should be obtained for routine bacterial cultures; HSV cultures should be obtained from the blood, nasopharynx, eyes, urine, stool or rectum, and CSF. CSF should also be obtained for polymerase chain reaction (PCR) testing for HSV. This infant should be placed on intravenous antibiotics and antiviral therapy pending test results.

APPROACH TO SUSPECTED CONGENITAL HERPES INFECTION

Definitions

First HSV infection, nonprimary: Infection with one type of HSV (e.g., type 2) in a person with immunity to another type of HSV (e.g., type 1). These infections are usually less severe than symptomatic primary infections, but maternal passage of first nonprimary disease can result in severe disease in the neonate.

Genital herpes: Infection of the genital tract with HSV type 1 or 2. The majority of genital herpes infections are caused by HSV-2.

Primary herpes infection: HSV infection in the previously seronegative host. Most instances of primary infection are subclinical, but they can manifest as localized lesions or severe systemic symptoms.

Recurrent infection: Reactivation of a latent infection in an immune host. Lesions tend to be localized and not associated with systemic symptoms.

Clinical Approach

The prevalence of herpes antibodies is higher among people in lower socioeconomic groups and correlates with crowded living conditions. Overall, it is estimated that 20% to 30% of American women of childbearing age have antibodies to HSV-2, but that **only 5% of these women have a history of genital herpes**. Thus, the majority of neonates who become infected with HSV are born to women with no known history of herpes. In the United States, approximately 75% of cases of congenital herpes are caused by HSV-2. HSV-2 is associated with greater morbidity among survivors of congenital infection than HSV-1. HSV-2 is usually transmitted via sexual contact, and most genital diseases are the result of type 2 infection, although HSV-1 can be transmitted sexually and is occasionally found in the genital tract.

The majority of neonates with congenital herpes acquire the infection through **direct contact with infected vesicles during a vaginal birth**. For this reason, cesarean delivery usually is indicated in pregnant women who have an outbreak of genital herpes or symptoms of HSV infection (paresthesias, dysesthesias) at the time of delivery. The infant's **risk of acquiring an HSV infection is increased significantly** if the outbreak represents **primary infection** in the mother. Approximately 40% of infants in this setting will become infected if delivered vaginally, whereas only 5% or fewer will acquire the disease if the outbreak represents recurrent disease. HSV surveillance cultures are no longer recommended in pregnant women, as the women who are at greatest risk of infecting their infants are those who have no prior history of infection.

Neonatal HSV disease can result in premature delivery, and can manifest in the neonate as localized skin, eye, and mouth involvement, central nervous system disease, disseminated disease, or a combination of these. Asymptomatic infection can also occur in the neonate, but it is uncommon. **Approximately 80% of infected infants develop skin, eye, or mouth lesions, and 50% have central nervous system disease**. Disseminated disease accounts for 25% of neonatal infection, and primarily involves the liver and adrenal glands. Nonspecific, presenting clinical signs and symptoms often occur in the absence of lesions, and can include fever, lethargy, irritability, anorexia, vomiting, respiratory

distress, apnea, jaundice, a bulging fontanelle, seizures, decerebrate posturing, and coma. Shock and disseminated intravascular coagulation can occur in severe cases. Organomegaly, pneumonitis, and pleural effusion also may occur. The risk of death is highest among infants with disseminated or central nervous system disease, particularly if pneumonitis and disseminated intravascular coagulopathy occur. Among survivors, morbidity is associated with a history of disseminated disease, central nervous system involvement, HSV-2 infection, seizures, and frequent cutaneous recurrences.

Cell culture of samples taken from various body sites and **PCR of cerebrospinal fluid** are the **most useful diagnostic tests** for HSV infection. Culture samples should be taken from the nasopharynx, eyes, urine, blood, stool or rectum, CSF, and skin vesicles (if present). Serologic tests for herpes virus are not helpful in the acute setting, as titers tend to rise late in the course of infection. **Histologic examination of lesions (e.g., Tzanck preparation) and antigen detection** methods applied to the specimens can aid in rapid diagnosis of herpes infection, but the **sensitivity of this approach is low**. Infected individuals often have a moderate peripheral leukocytosis, elevated serum liver transaminases, hyperbilirubinemia, and thrombocytopenia. When the central nervous system is involved, the cerebrospinal fluid frequently contains an elevated number of red cells, lymphocytes, and protein; the CSF glucose is usually normal but may be reduced. Electroencephalography (EEG) and magnetic resonance imaging (MRI) may show temporal lobe abnormalities in cases of early encephalitis, and computerized tomography (CT) of the brain will become abnormal as the disease progresses. The most definitive method for diagnosis of HSV encephalitis is brain biopsy with histologic examination and viral culture of the tissue.

Parenteral acyclovir is the preferred treatment for all types of congenital herpes infection. Treatment is usually given for 14 days for children with skin, eye, and mouth disease and 21 days for central nervous system or systemic infection. **Topical antiviral ophthalmic therapy** is added for **infants with ocular involvement**. Children with isolated skin, eye, and mouth disease generally have the best outcomes, whereas **the majority of infants with central nervous system disease develop neurologic sequelae**. Half of infants with systemic infection die despite antiviral therapy.

Comprehension Questions

- [43.1] A 10-day-old infant presents to the pediatric clinic with a painful, red vesicular rash in the diaper area. He is mildly fussy but afebrile, and he has good oral intake. What is the appropriate management of this infant?
- A. Prescribe an antifungal cream and follow up by telephone in 24 hours.
 - B. Perform a Tzanck smear and send the patient home if no multinuclear giant cells or intranuclear inclusions are found.
 - C. Obtain specimens for HSV culture and admit to the hospital for parenteral acyclovir pending test results.
 - D. Schedule an appointment with a pediatric dermatologist.
 - E. Order a STAT EEG and brain MRI.
- [43.2] A woman presents for her first prenatal visit at 9 weeks' gestation. She reports that she is generally healthy, except that she has an outbreak of genital herpes approximately once a year. To prevent transmission of the virus to her infant, her physician should:
- A. Place her on oral acyclovir for the remainder of the pregnancy.
 - B. Perform weekly genital viral cultures starting at 36 weeks' gestation.
 - C. Anticipate a cesarean section delivery.
 - D. Offer a cesarean delivery if herpetic lesions or prodromal symptoms are present when labor has begun.
 - E. No change in management is indicated, as the risk of transmission to the infant is low even if she has an outbreak at the time of delivery.
- [43.3] A 5-year-old with a complaint of dysuria is found on examination to have herpetic genital lesions. The next step in management is to:
- A. Ask the parent to leave the room and then ask the girl in an open-ended fashion whether she has ever been **inappropriately** touched in her private area.

- B. Prescribe oral acyclovir and ask her to follow-up in 2 days.
- C. Admit her to the hospital for parenteral antiviral therapy.
- D. Ask how often the mother has outbreaks of genital herpes.
- E. Send a urine culture and suggest that the mother apply petroleum jelly to the lesions until they heal.

[43.4] PCR results of cerebrospinal fluid from a 15-year-old boy with encephalitis reveal that he is infected with HSV. The parents want to know what this means in terms of his prognosis. Which of the following is the most appropriate statement to tell them?

- A. He will most likely die.
- B. He will likely survive, but will almost certainly have serious neurologic impairment.
- C. Most children with HSV encephalitis survive, although many (but not all) are left with some permanent neurologic deficits.
- D. They should consider placing him in a long-term care facility following this hospitalization.

Answers

[43.1] C. Unlike older children and adults with localized cutaneous disease, infants with suspected herpes skin lesions require parenteral antiviral therapy to prevent more serious sequelae.

[43.2] D. Even though the risk of viral transmission in the setting of a recurrent outbreak of herpes is low, cesarean section is indicated if lesions are present at the time of delivery. Surveillance cultures are not likely to be helpful as negative results obtained a few days prior do not preclude an outbreak at the time of delivery, and results of a more recently obtained specimen may not be available. Culture specimens may be indicated at 48 hours of life from the infant born to a herpes positive mother and treatment with acyclovir initiated if any culture is positive or there are signs of neonatal HSV.

- [43.3] A. The possibility of sexual abuse must always be considered in a child who presents with genital herpes beyond the neonatal period. It is important to know who helps to bathe the child, and whether these persons have ever had herpes, as nonsexual transmission is also possible.
- [43.4] C. Although the majority of children with HSV encephalitis suffer permanent neurologic impairment, good outcomes are possible with appropriate medical and rehabilitative therapy.

CLINICAL PEARLS



Most infants with congenital herpes are born to mothers who have no prior history of HSV infection.



The presenting signs and symptoms of congenital HSV may be nonspecific, without any visible herpetic lesions.



Infants with suspected HSV infection should be hospitalized for HSV testing and parenteral antiviral therapy pending test results.



Children with HSV skin, eye, and mouth disease generally have the best outcomes, whereas the majority of infants with central nervous system disease develop neurologic sequelae. Half of infants with systemic infection die despite antiviral therapy.

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◆ CASE 44

A mother brings her 11-month-old daughter into clinic because of a persistent rash on the face. The child has become restless and agitated at night and scratches in her sleep. She is otherwise healthy; immunizations are up to date. Physical examination reveals a well-nourished, healthy appearing white female with dry, red, scaly areas on the cheeks, chin, and around the mouth. The areas on the cheeks have a plaque-like weepy appearance. The diaper area is spared. The remainder of the child's examination is normal.

◆ What is the most likely diagnosis?

◆ What is the most appropriate next step in the evaluation?

ANSWERS TO CASE 44: Atopic Dermatitis

Summary: A well-appearing 11-month-old white female has dry, red, scaly areas on the cheeks, chin, and around the mouth and sparing of diaper area.

- ◆ **Most likely diagnosis:** Atopic dermatitis.
- ◆ **Next step in evaluation:** Further history to determine duration of the rash and factors that exacerbate it. A complete family history for atopic dermatitis, allergic rhinitis, and asthma also gives clues to the child's underlying condition, and may be predictive of future health problems.

Analysis

Objectives

1. Describe the incidence, etiology, and risk factors for atopic dermatitis.
2. Discuss diagnostic criteria and differential diagnoses for atopic dermatitis.
3. Describe treatment and follow-up of children with atopic dermatitis.
4. Be familiar with other conditions associated with atopic dermatitis.

Considerations

In this child, the history and physical examination are consistent with the diagnosis of atopic dermatitis. Further history from the family may reveal additional risk factors for allergic disease. Treatment for this child consists of avoidance of factors that exacerbate the condition and intensive hydration of the skin.

APPROACH TO ATOPIC DERMATITIS

Definitions

Eczema: Another term for atopic dermatitis.

Emollient: Creams and lotions that restore water and lipids to the epidermis. Preparations that contain urea or lactic acid have special lubricating properties and may be the most effective. Creams are thicker and more lubricating than lotions.

Flexural areas: Areas of repeated flexion, extension, and perspiration with exertion (antecubital fossae, neck, wrists, and ankles).

Lichenification: Thickening of the epidermis; in this condition, normal skin lines are accentuated to resemble a washboard.

Clinical Approach

Atopic dermatitis is an eczematous eruption that is itchy, recurrent, and **flexural** in older children and **symmetric** in adults. The term “atopy” was coined to describe a group of patients who had a personal or family history of one or more of the following diseases: hay fever, asthma, very dry skin, and eczema. More than 15 million American adults and children have atopic dermatitis. The highest incidence is among children, and the lifetime prevalence of atopic dermatitis is 20% in children ages 3 to 11 years. In 65% of patients, symptoms develop in the first year of life; in 90%, symptoms develop before 5 years of age. The etiology is unknown but is hypothesized to be related to immune factors. Seventy percent of atopic patients have a family history of asthma, hay fever, or eczematous dermatitis.

Atopic dermatitis can be divided into **three phases: infant** (birth to 2 years), **childhood** (2 to 12 years), and **adult** (12 years to adult). Infants are rarely born with atopic dermatitis but typically develop the first signs of inflammation during the third month of life. The most common scenario is that of a baby who, during the winter months, develops dry, red, scaling areas confined to the cheeks but sparing the perioral and paranasal areas. The chin is often involved and initially may be more inflamed than are the cheeks. The diaper area is usually

spared. The infant is uncomfortable due to pruritus and is often aggravated during sleep. Atopic dermatitis resolves in approximately 50% of infants by 18 months of age, but progresses in some to the childhood phase. The most common symptom in the childhood phase is inflammation in flexural areas. Perspiration stimulates burning and intense itching and initiates an itch-scratch cycle. The rash begins with papules that rapidly coalesce into plaques that ultimately become lichenified when scratched. The exudative lesions typical of the infant phase are not so common in the childhood phase. The adult phase (12 years to adult) begins near the onset of puberty. The reason for the resurgence of inflammation may be related to hormonal changes of early adolescence. The pattern of flexural inflammation continues, often accompanied by hand dermatitis, inflammation around the eyes, and lichenification of the anogenital area.

Atopic dermatitis may become secondarily infected with *Staphylococcus aureus*, *Streptococcus* species, or herpes simplex. The child may present with constitutional symptoms indicative of sepsis such as fever, nausea, vomiting, and lethargy.

Two misconceptions about atopic dermatitis are commonly seen. The first is that eczema is an emotional disorder. Patients with skin inflammation lasting for months or years seem to be irritable, but this is a normal response to a frustrating disorder. The second misconception is that atopic skin disease is precipitated by an allergic reaction. Atopic individuals frequently have respiratory allergies and, when skin tested, are informed that they are allergic to "everything." Individuals with atopy may react with a wheal when challenged with a needle during skin testing, but this is a characteristic of atopic skin and is not necessarily a manifestation of allergy. Evidence to date indicates that most cases of atopic dermatitis are precipitated by environmental stress on genetically compromised skin and not by interaction with allergens.

Evaluation of the child with atopic dermatitis involves ruling out other potential causes of the child's rash through a complete personal history, family history, and physical examination. The goal of the evaluation is to make a proper diagnosis so that treatment can be initiated.

A careful history offers valuable information regarding the etiology of the child's skin condition (see Table 44-1).

A physical examination includes vital signs to identify fever or other evidence of infection. The skin is evaluated for locations of affected ar-

Table 44-1
QUESTIONS TO ASK WHEN INVESTIGATING RASHES

How long have the symptoms been present? Were there previous episodes of similar outbreaks?

How itchy are the affected areas? Is the child becoming irritable or awakening at night because of itching and scratching?

Do symptoms appear to get worse with exposure to cold weather, wool, perspiration, or stress?

Do other family members have eczema, asthma, or allergic diseases?

Has the child had fever or other signs of infection?

eas, nature of the affected areas (patches, erythema, weepiness, lichenification), general degree of skin dryness, and warmth or erythema (possibly indicative of bacterial superinfection). The eyes, nose, and throat are examined for evidence of allergic rhinitis (drainage at posterior pharyngeal wall, runny nose, watery eyes, dark circles under eyes). The lungs are examined for wheezing.

Laboratory studies are not particularly helpful in diagnosing atopic dermatitis. Serum immunoglobulin (Ig) E levels are often elevated, but are rarely helpful in diagnosing or treating the condition. Culture of the skin is done if superinfection is suspected.

The differential diagnosis includes seborrheic dermatitis (cradle cap), which usually begins on the scalp in the first few months of life and may involve the ears and contiguous skin, nose, eyebrows, and eyelids. The greasy brown scales of seborrheic dermatitis are in contrast to the erythematous weeping, crusted lesions of infantile atopic dermatitis. Other considerations include scabies, primary irritant dermatitis (nonallergic irritation such as perioral fruit juice dermatitis), allergic contact dermatitis (i.e., poison ivy), and infectious eczematoid dermatitis (i.e., a weepy lesion that develops near a draining ear).

Treatment goals consist of attempting to preserve and restore the skin barrier by using emollients, eliminating inflammation and infection with medications, reducing damage to the skin due to scratching by using antipruritics, and controlling exacerbating factors. Some recommend limiting bathing to brief baths or showers of moderate temperature with mild and preferably unscented soap or nonsoap cleansers (Dove unscented, Tone, Caress, Keri, Purpose, Basis, Oil of Olay, Lever

2000, Cetaphil, and Aquaphil). Drying soaps, such as Ivory and Pure and Natural, are avoided. Lubricants are applied immediately after bathing and air- or pat-drying. Effective lubricants include Eucerin cream or lotion, Moisturel cream or lotion, Curel cream or lotion, Complex 15 cream or lotion, Vaseline, Aquafor, and Crisco. Some products contain urea (e.g., Nutraplus) and others contain lactic acid (e.g., Lac-Hydrin, LactiCare). Urea and lactic acid have special hydrating qualities and may be more effective than other moisturizers. Lotions and creams may sting shortly after application. This may be a result of the base or of a specific ingredient, such as lactic acid. If itching and stinging continue with each application, another product should be selected.

Topical corticosteroids used to control inflammation vary in potency (Table 44-2); the percent number behind the name of the topical corticosteroid is *not* an indication of potency. Lower-potency preparations (groups VI and VII) can be used for longer periods of time to treat chronic symptoms involving the trunk and extremities. Lower-potency steroids are generally used for infants. Steroids (such as triamcinolone 2.5%) can be added to moisturizers to cover large areas of affected skin. Fluticasone propionate (Cutivate) is the only FDA-approved topical corticosteroid cream for infants as young as 3 months of life. **Fluorinated corticosteroids are generally avoided on the face, genitalia, and the intertriginous area because they may cause depigmentation and thinning of the skin.** Group I agents are used for only very short periods of time and only in lichenified areas; the face and skin folds are avoided. Group II agents are used for less than 3 weeks and for exacerbations only. Ointment preparations are generally preferable because they result in better penetration of the corticosteroid and the incidence of irritant and hypersensitivity reactions is reduced. Administration of agents is usually twice daily unless the chosen agent (such as fluticasone propionate) requires only once-daily application. Lubrication is continued after corticosteroids are discontinued.

Tacrolimus (Protopic) is a nonsteroidal immunomodulator topical ointment for the treatment of atopic dermatitis. The 0.1% concentration is approved for use in adults; the 0.03% preparation is approved for use in children ages 2 years and older. Use of tacrolimus is recommended for long-term intermittent therapy in patients not adequately responsive to, or intolerant to, conventional therapy. Dosing is twice daily until at least 1 week after signs and symptoms have cleared.

Table 44-2
TOPICAL GLUCOCORTICOID POTENCY RANKING

Group I (superpotent)

Augmented betamethasone dipropionate 0.05% (ointment)
 Clobetasol propionate 0.05% (cream & ointment)
 Diflorasone diacetate 0.05% (ointment)
 Halobetasol propionate 0.05% (cream & ointment)

Group II (high potency)

Amcinonide 0.1% (ointment)
 Betamethasone dipropionate 0.05% (cream & ointment)
 Desoximetasone 0.25% (cream & ointment)
 Desoximetasone 0.05% (gel)
 Fluocinonide 0.05% (cream, gel, ointment, & solution)
 Halcinonide 0.1% (cream)
 Halobetasol propionate 0.05% (cream & ointment)

Group III to V (medium potency)

Amcinonide 0.1% (cream & lotion)
 Betamethasone dipropionate 0.05% (cream & lotion)
 Betamethasone valerate 0.1% (cream & ointment)
 Desoximetasone 0.05% (cream)
 Diflorasone diacetate 0.05% (cream)
 Fluocinolone acetonide 0.05% (cream)
 Halcinonide 0.1% (ointment & solution)
 Hydrocortisone butyrate 0.1% (cream, solution, & ointment)
 Hydrocortisone valerate 0.2% (cream & ointment)
 Flurandrenolide 0.5% (ointment)
 Fluticasone propionate 0.05% (cream & ointment)
 Fluocinolone acetonide 0.025% (ointment)
 Mometasone furoate 0.1% (cream, lotion, & ointment)
 Prednicarbate 0.1% (cream)
 Triamcinolone acetonide 0.1% (ointment & cream)
 Triamcinolone acetonide 0.1% (ointment)

Group VI (mild potency)

Aclometasone dipropionate 0.05% (cream & ointment)
 Betamethasone valerate 0.05% (lotion)
 Desonide 0.05% (cream & ointment)
 Fluocinolone acetonide 0.01% (cream & solution)

Group VII (low potency)

Hydrocortisone hydrochloride 2.5% (cream, lotion, & ointment)
 Hydrocortisone hydrochloride 1% (cream & ointment)
 Hydrocortisone acetate 2.5% (cream, lotion, & ointment)
 Hydrocortisone acetate 1% (cream & ointment)
 Pramoxine hydrochloride 1% (cream, lotion, & ointment)
 Pramoxine hydrochloride 2.5% (cream, lotion, & ointment)

Oral antihistamines are used to reduce itching. Because symptoms of atopic dermatitis are often worse at night, oral antihistamines with sedating side effects (hydroxyzine or diphenhydramine) may offer an advantage over nonsedating agents. Less-sedating agents include cyproheptadine, clemastine, chlorpheniramine, loratadine, and cetirizine. Doxepin has tricyclic antidepressant and antihistamine effects and may be useful in some cases. Topical antihistamines (Benadryl, Caladryl, Calamycin, Ivarest) are avoided because of the potential for skin irritation or toxicity owing to absorption. Fingernails should be cut short to avoid further skin damage via scratching.

Patients with secondary bacterial infections often require antibiotic therapy. Topical antibiotic therapy with mupirocin (Bactroban) may be used for limited areas of infection or in the nose to reduce chronic *Staphylococcus aureus* carriage. Oral antibiotics are indicated for more extensive areas of infection. First-generation cephalosporins, erythromycin, penicillinase-resistant penicillins, or clindamycin are chosen based on local susceptibility patterns. Patients with evidence of superinfection with herpes simplex virus may require oral or intravenous acyclovir.

The role of food allergies in the management of atopic dermatitis is controversial. Dietary manipulation in a child with a strong history of exacerbation of symptoms upon exposure to a particular food may be helpful. A 4- to 6-week trial excluding egg and milk in infants followed by a rechallenge may be justified, especially in a child who does not respond to first-line treatment.

Consultation with a pediatric dermatologist may be warranted for patients with an unclear diagnosis, who fail to respond to treatment or who have extensive exfoliation. Consultation may also be appropriate for patients with ocular or serious infectious complications and for patients requiring oral steroid therapy.

Comprehension Questions

- [44.1] A mother brings her 2-week-old son to the clinic for a well-baby visit. Her only concern about the infant is a "rash" on his face and scalp that began approximately 1 week earlier. Examination

reveals a healthy white male with normal vital signs and a normal examination except for the skin. He has yellowish, waxy-appearing, adherent plaques on the scalp, forehead, cheeks, and nasolabial folds. Which of the following is the most likely explanation for the infant's skin findings?

- A. Lichen planus
- B. Tinea versicolor
- C. Atopic dermatitis
- D. Seborrheic dermatitis
- E. Psoriasis

[44.2] An 8-year-old girl arrives at your school-based clinic with the chief complaint of a rash on her chest, abdomen, and arms. It started with one small scaly red area on her chest and then spread. It itches "a little." She had a sore throat and headache last week, but now feels better. She is taking no medications and knows nothing of her family history. Physical examination reveals salmon-colored, flat, finely scaly oval eruptions on her chest, abdomen, back, and upper arms, stopping at her umbilicus and elbows. Which of the following is the most likely explanation for this child's findings?

- A. Tinea versicolor
- B. Pityriasis rosea
- C. Syphilis
- D. Atopic dermatitis
- E. Contact dermatitis

[44.3] A father brings his 8-month-old daughter to your office because her eczema is "out of control" and is causing her to feel bad and have fever. He is following your recommendations of bathing her with gentle soaps, using topical emollients and steroids, and oral antihistamines. The examination reveals a lethargic child with an oral temperature of 103°F (39.4°C). The child's cheeks are red and contain numerous red, punched-out, and umbilicated vesicles; some lesions are pustular. What is the best course of action at this point?

- A. Prescribe oral corticosteroids and have the child return in the morning.
- B. Initiate outpatient tacrolimus.
- C. Admit immediately to the hospital for intravenous acyclovir.
- D. Prescribe oral antibiotics.
- E. Prescribe outpatient topical acyclovir.

[44.4] An 8-month-old child has had difficult-to-treat eczema that was first noticed at 2 months of age. He has had six episodes of otitis media, one previous episode of pneumonia (thought to be viral), and has now developed severe nosebleeds. His complete blood count is normal except for a platelet count of $15,000/\text{mm}^3$. He most likely has:

- A. DiGeorge anomaly
- B. Severe combined immunodeficiency
- C. Bruton agammaglobulinemia
- D. Wiskott-Aldrich syndrome
- E. Job syndrome

Answers

- [44.1] **D.** Seborrheic dermatitis presents in infancy ("cradle cap") and adolescence. The chronic symmetric eruption, characterized by overproduction of sebum, affects the scalp, forehead, retroauricular region, auditory meatus, eyebrows, cheeks and nasolabial folds. The treatment includes softening the scales with mineral oil and daily shampooing with a mild shampoo; some suggest shampoos containing ketoconazole (Nizoral). Low to medium potency topical corticosteroids may be used. Avoid scrubbing the affected areas.
- [44.2] **B.** Pityriasis rosea may mimic tinea versicolor, yet is preceded by a "herald patch," an annular, scaly erythematous lesion. The lesions are salmon-colored and in a Christmas-tree formation, following the lines of the skin. The cause is unknown. Treatment may include antihistamines, topical antipruritic lotions and

creams, topical corticosteroids, and phototherapy, none of which is very effective. The rash usually lasts up to 6 weeks and then resolves. It can be confused with a form of eczema (called nummular eczema) and in the sexually active adolescent syphilis should also be considered.

- [44.3] **C.** Certain atopic infants may develop the rapid onset of diffuse cutaneous herpes simplex. The disease is most common in areas of active or recently healed atopic dermatitis, particularly the face. High fever and adenopathy occur 2 to 3 days after the onset of vesiculation. Viremia with infection of internal organs can be fatal. Eczema herpeticum of the young infant is a medical emergency. The child should be admitted immediately for intravenous acyclovir.
- [44.4] **D.** Wiskott-Aldrich syndrome is an X-linked condition with recurrent infections, thrombocytopenia, and eczema. Infections and bleeding usually is noted in the first 6 months of life. The recurrent infections these children have are both common infections (otitis media and pneumonia caused by a poor antibody response to capsular polysaccharides) and rare infections (fungal and viral septicemias caused by T-cell dysfunction). The thrombocytopenia is usually in the 15,000 to 30,000/mm³ range and platelets are noted to be small or microthrombocytes (usually not seen in other thrombocytopenic disorders). In addition to eczema, these children also have autoimmune disorders and a very high incidence of malignancy (often lymphoma).

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◆ CASE 45

A 5-year-old female comes to clinic with a several-week history of abdominal pain. She describes that her "tummy hurts a lot everywhere for a little while, then it goes away, and then it comes back." The pain is not associated with other symptoms. She is growing and gaining weight appropriately. Upon physical examination she has a blood pressure of 130/88 mmHg, heart rate of 82 beats per minute, respiratory rate of 14 breaths per minute, and a temperature of 98.9°F (37.2°C). She has a smooth, firm, 7-cm by 7-cm mass palpated in the right upper quadrant of her abdomen; the mass does not cross the midline. The remainder of the examination is normal.

- ◆ What is the most likely diagnosis?
- ◆ What is the best management for this condition?

ANSWERS TO CASE 45: Wilms Tumor

Summary: A 3-year-old female with abdominal pain, a firm, smooth abdominal mass that does not cross the midline, and hypertension.

- ◆ **Most likely diagnosis:** Wilms tumor.
- ◆ **Best management for this condition:** Immediate treatment is surgical excision of the tumor followed by multiagent chemotherapy for all patients and radiation for selected patients with tumor in a more advanced stage.

Analysis

Objectives

1. Recognize the signs and symptoms of Wilms tumor.
2. Describe the diagnosis and treatment of this tumor.

Considerations

Wilms tumor must be suspected in any young child with an abdominal mass. This 3-year-old girl has a typical presentation—an abdominal mass, abdominal pain, and hypertension. Masses are often discovered by parents or on routine physical examination. Hypertension, reported in 60% of patients, results from renal ischemia caused by pressure on the renal artery.

APPROACH TO WILMS TUMOR

Definitions

Aniridia: Lack of iris.

Hematuria: Blood cells in the urine; this is an abnormal finding.

Hemihypertrophy: One side of the body is larger than the other side.

Clinical Approach

Wilms tumor is the most common primary malignant renal neoplasm of childhood. The annual incidence rate is 8 cases per 1 million children younger than 15 years of age, representing 6.3% of childhood cancers. It occurs with approximately equal frequency in both genders and in all races. An important feature of Wilms tumor is its association with **congenital anomalies**, the most common being **genitourinary anomalies** such as horseshoe kidney or hypospadias, hemihypertrophy, and sporadic aniridia. Chromosome 11 deletions have been noted in cells of about 30% of Wilms tumors.

The **median age at diagnosis** of unilateral Wilms tumor is about 3 years. The signs and symptoms of Wilms tumor, in decreasing order of frequency, are **abdominal or flank mass, pain, hematuria, hypertension, and fever**. The mass is generally smooth and firm and **rarely crosses the midline**. Masses vary greatly in size. Masses are often discovered by family members (parents or grandparents) or on routine physical examination by a health care provider.

The major differential diagnostic consideration is neuroblastoma. In general, patients with Wilms tumor are slightly older and appear less ill than do patients with neuroblastoma. Neuroblastoma produces urinary vanillylmandelic acid and homovanillic acid, levels of which are increased in more than 90% of patients with neuroblastoma; other markers include elevated serum levels of enolase, ferritin, and lactate dehydrogenase (LDH).

Urinalysis reveals gross or microscopic hematuria in 10% to 25% of Wilms tumor cases. Computerized tomography (CT) or magnetic resonance imaging (MRI) is useful in identifying the tumors and assessing the extent of disease. In 5% of patients, the tumor is bilateral, and in 15% of patients metastases are present at the time of diagnosis. The most common sites of metastases are the lungs and liver.

Treatment involves surgical excision of the tumor, followed by multiagent chemotherapy for all patients and radiation therapy for patients with tumor in a more advanced stage. Overall cure rates for Wilms tumor exceed 85%.

Comprehension Questions

- [45.1] While bathing her 3-year old son, a mother feels a mass in his abdomen. You consider Wilms tumor. A thorough medical evaluation of the child might reveal which of the following:
- A. Coloboma
 - B. Hemihypertrophy
 - C. Epispadias
 - D. Duplication of the urinary collecting system
 - E. Cataracts
- [45.2] A 1-week-old infant presents with a right mid-quadrant abdominal mass, failure to thrive, and decreased urinary output. What is the most likely diagnosis?
- A. Neuroblastoma
 - B. Hydronephrosis
 - C. Wilms tumor
 - D. Sepsis
 - E. Intussusception
- [45.3] A 2-year-old child is brought to the emergency center by the father who felt a mass in the child's abdomen this morning while bathing her. She has had less energy than usual, a decreased appetite, and is pale with dark circles under her eyes. Physical examination reveals a large abdominal mass that crosses the midline. She also has periorbital ecchymoses and proptosis. What is the most likely diagnosis?
- A. Wilms tumor
 - B. Lymphoma
 - C. Neuroblastoma
 - D. Teratoma
 - E. Hepatoblastoma
- [45.4] In an effort to determine whether an abdominal mass is a neuroblastoma or a Wilms tumor, which of the following tests would be most helpful?

- A. Routine urinalysis
- B. Abdominal film
- C. Chest radiograph
- D. Urinary catecholamines
- E. Complete blood count

Answers

- [45.1] **B.** Genitourinary anomalies such as hemihypertrophy is relatively common in patients with Wilms tumors.
- [45.2] **B.** Urinary tract obstruction is often silent. In the newborn, a palpable abdominal mass is commonly a hydronephrotic or multicystic dysplastic kidney.
- [45.3] **C.** Children with neuroblastoma develop periorbital metastases, leading to periorbital ecchymoses and proptosis.
- [45.4] **D.** Approximately 90% of patients with neuroblastomas have elevated urinary catecholamines.

CLINICAL PEARLS

Wilms tumor presents with an abdominal mass, abdominal pain, and hypertension.

Masses are often discovered by family members or on routine physical examination.

The major differential diagnostic consideration for a patient with Wilms tumor is neuroblastoma. In general, patients with Wilms tumor are slightly older and appear less ill than do patients with neuroblastoma. Neuroblastoma produces urinary vanillylmandelic acid and homovanillic acid, levels of which are increased in more than 90% of patients with neuroblastoma.

An important feature of Wilms tumor is its association with congenital anomalies, including horseshoe kidney, hypospadias, hemihypertrophy, and sporadic aniridia.

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◆ CASE 46

A 15-year-old male complains of right knee pain and swelling for the last 2 weeks. The pain, which he describes as “deep in the bone,” is awakening him at night and is not responding to ibuprofen or acetaminophen. He plays football yet has sustained no injuries in the last few months. His past medical history is unremarkable. Physical examination reveals normal vital signs. The patient limps when he walks, and the right knee is swollen, warm, tender, and with reduced range of motion. He has a palpable mass over the head of his right tibia. The remainder of the physical examination is normal. A radiograph of the extremity is shown (Figure 46–1).

- ◆ What is the most likely diagnosis?
- ◆ What is the best management for this condition?

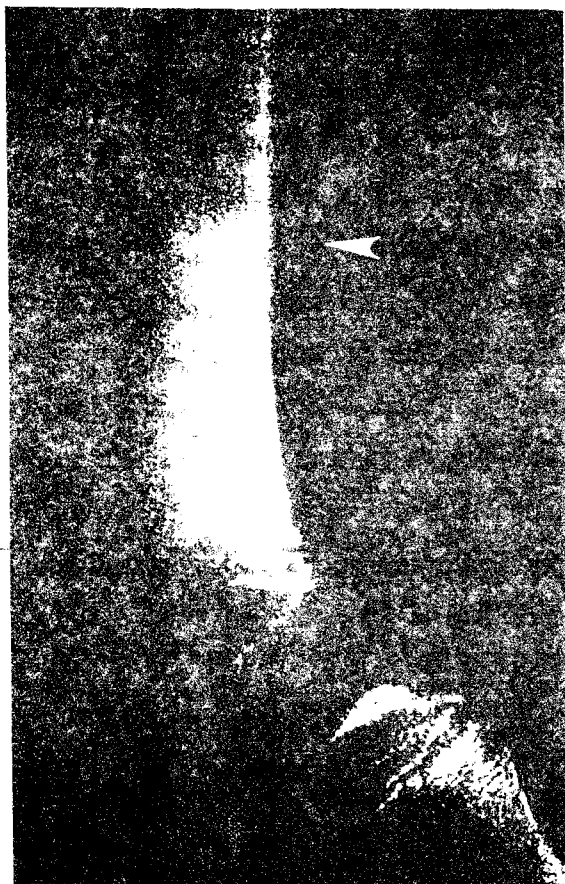


Figure 46–1. Radiograph of the femur. From: Rudolph's Pediatrics, 21st ed., with permission.

ANSWERS TO CASE 46: Osteosarcoma

Summary: A 15-year-old boy has right knee pain that is not responding to conventional analgesia. He had a palpable mass over the proximal head of the tibia. The right knee is swollen, warm, tender, with reduced range of motion.

◆ **Most likely diagnosis:** Osteosarcoma.

- ◆ **Best management for this condition:** Treatment with preoperative chemotherapy is given in an attempt to facilitate limb salvage surgical procedure and to treat micrometastatic disease. Complete local surgical excision is followed by systemic multiagent chemotherapy.

Analysis

Objectives

1. Recognize the signs and symptoms of osteosarcoma.
2. Describe the diagnosis and treatment of osteosarcoma.

Considerations

This adolescent has classic symptoms of osteosarcoma—bone pain, swelling, tenderness, and decreased range of motion. The pain is not responding to conventional treatment. A palpable mass over the head of the tibia is suggestive of a bone tumor and must be evaluated further.

APPROACH TO OSTEOSARCOMA

Definitions

Blastic: Undifferentiated; immature.

Ewing sarcoma: A malignant bone tumor that is generally less common than osteosarcoma. However, in children younger than 10 years of age, Ewing sarcoma is more common than osteosarcoma.

Lytic: Destructive; cellular breakdown.

Clinical Approach

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. Most osteosarcomas occur during the first 2 decades of life, a period characterized by rapid skeletal growth,

suggesting an association between rapid bone growth and malignant transformation. **Males** are affected more commonly than females, but when female patients develop osteosarcoma, they do so at earlier ages, perhaps reflecting difference in timing of onset of puberty and growth spurts. Patients with osteosarcoma are generally taller than their peers of similar age.

Most pediatric osteosarcomas arise spontaneously in long bones, with the majority of the tumors occurring around the knee area. The **most frequent sites** of involvement are the **distal femur, the proximal tibia, and the proximal humerus**. Certain genetic or acquired conditions, such as **hereditary retinoblastoma**, predispose patients to development of osteosarcoma. Osteosarcoma can also be induced by radiation for Ewing sarcoma, craniospinal radiation for brain tumors, or high-dose irradiation for other tumors. Paget disease is a benign condition that is associated with malignant transformation into osteosarcoma. Metastatic disease, seen in 20% of cases, carries a grave prognosis for osteosarcoma.

Pain and swelling are the most common presenting manifestations of osteosarcoma. The pain is often insidious and usually involves the area affected by the tumor. Other clinical findings include limping, limitation of motion, joint effusion, tenderness, and warmth. Because these tumors occur more frequently in active adolescents, initial complaints may be attributed to a sports injury. Any bone or joint pain that does not respond to conservative therapy within a reasonable amount of time should be investigated thoroughly.

Routine laboratory studies are often unrevealing. **Elevations of serum lactate dehydrogenase (LDH) and alkaline phosphatase** are the most common laboratory abnormalities, but are nonspecific. **Plain radiography is the most effective method** to detect bone tumors. Radiologic findings characteristic of osteosarcoma include a metaphyseal lesion with periosteal new bone formation as well as destruction of the preexisting cortical bone. A soft tissue mass is present in more than 90% of cases. A baseline chest radiograph is obtained to detect lung metastases. Computerized tomography (CT) of the primary tumor offers accurate assessment of the degree of tumor calcification and ossification.

Children with tibial and distal femur primary tumors appear to have a more favorable prognosis than those with axial primaries. The frac-

tion of tumor necrosis following preoperative chemotherapy is the most consistent and important factor associated with outcome. A favorable response (90% necrosis) correlates with excellent overall survival.

The treatment of osteosarcoma includes the use of preoperative chemotherapy and surgical resection of the primary tumor, followed by postoperative chemotherapy. Before the development of limb-sparing procedures (surgical techniques in which the tumor is removed but vital limb structures are preserved), amputation was the standard surgical method. Limb-sparing procedures have dramatically increased over the past several years, and amputation is now generally reserved for patients whose primary tumor is deemed unresectable. The role of radiation therapy is limited. Localized disease is curable with combined therapy of chemotherapy and additional surgery in more than 70% of cases, whereas metastatic disease is curable in 30% to 40% of cases.

Comprehension Questions

- [46.1] A 13-year-old male complains of left knee pain, swelling, warmth, and tenderness for 1 week. He has sustained no trauma and has never had knee pain in the past. He has a temperature of 101.8°F (38.8°C). Examination reveals an erythematous, warm, swollen knee with reduced range of motion. A complete blood count (CBC) reveals a leukocyte count of 18,700/mm³ and a erythrocyte sedimentation rate (ESR) of 100 mm/h. What is the most likely diagnosis?
- A. Ewing sarcoma
 - B. Osteomyelitis
 - C. Osteosarcoma
 - D. Eosinophilic granuloma
 - E. Neuroblastoma
- [46.2] A 6-year-old male complains of right knee pain for 2 weeks. He has been fatigued and has developed bruising on his arms and thighs. Examination reveals a temperature of 99.8°F (37.7°C), gingival bleeding, and hepatomegaly. What is the most likely diagnosis?

- A. Osteomyelitis
- B. Osteosarcoma
- C. Paget disease
- D. Juvenile rheumatoid arthritis
- E. Acute lymphoblastic leukemia (ALL)

[46.3] A 4-year-old female developed progressive swelling, warmth, stiffness and pain in her left knee beginning two weeks ago. She has become fatigued in the afternoons and has developed fevers spikes to 102.2°F (39°C) over the last week. Examination reveals a right knee that is swollen, nonerythematous, warm to the touch, and with decreased range of motion. She has a faint erythematous macular rash over her trunk and proximal extremities. What is the most likely diagnosis?

- A. Juvenile rheumatoid arthritis (JRA)
- B. Acute lymphoblastic leukemia (ALL)
- C. Osteosarcoma
- D. Lymphoma
- E. Osteomyelitis

[46.4] Which of the following factors is associated with an increased risk of developing osteosarcoma in children?

- A. Prior radiation therapy
- B. Medulloblastoma
- C. Delayed adolescent growth spurt
- D. Prior trauma to or abnormality of the involved bone
- E. Short stature

Answers

[46.1] **B.** Osteomyelitis. He has an elevated temperature and high white blood cell (WBC) count, indicating infection.

[46.2] **E.** This child has the classic signs of acute lymphoblastic leukemia (ALL) bone pain, low-grade fever, fatigue, bruising, bleeding of gums, and hepatomegaly. Although each of the di-

agnoses listed may exhibit one or two of this child's symptoms, only ALL is likely to be responsible for all of the symptoms.

[46.3] A. Intermittent fever in association with a rash and arthritis is highly suggestive of systemic-onset JRA.

[46.4] A. Prior radiation, certain growth conditions such as retinoblastoma, and malignant transformation of Paget disease are risk factors for developing osteosarcoma.

CLINICAL PEARLS

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. Most osteosarcomas occur during the first two decades of life, arising spontaneously in long bones, most commonly around the knee area.

Plain radiography is the most effective method to detect bone tumors.

Treatment includes preoperative chemotherapy, surgical resection of the primary tumor, followed by postoperative multiagent chemotherapy. Limb-sparing procedures have dramatically increased over the past several years; amputation of the limb is now rarely required.

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◆ CASE 47

A 3700-g male is born at term by spontaneous vaginal delivery to a 27-year-old gravida 2 para 1 mother following an uncomplicated prenatal course. Shortly after birth, the neonate begins to cough followed by what appears to be a choking episode and cyanosis. During the resuscitation, placement of an orogastric tube meets resistance at 10 cm. His Apgar scores are 8 and 6 at 1 and 5 minutes, respectively; he is transferred to the Level II nursery for evaluation and management of respiratory distress.

- ◆ What is the most likely diagnosis?
- ◆ What is the best test for evaluation?

ANSWERS TO CASE 47: Esophageal Atresia

Summary: A newborn infant presents with coughing, choking, and cyanosis, with inability to have an orogastric tube passed.

- ◆ **Most likely diagnosis:** Esophageal atresia, probably with a tracheoesophageal fistula.
- ◆ **Best test for diagnosis:** A radiograph of the chest and abdomen with the orogastric tube in place will demonstrate a coiled tube in the esophageal blind pouch. Low volume (1 cc), water-soluble contrast material is occasionally used to define the anatomy, and should be withdrawn immediately after the study because the infant is at high risk for aspiration.

Analysis**Objectives**

1. Become familiar with the presentation of a newborn and older children with tracheoesophageal fistula.
2. Understand the anatomic variants of tracheoesophageal fistula.
3. Understand emergency management of newborns with tracheoesophageal fistula.

Considerations

In this newborn with choking and coughing, esophageal atresia should be suspected when an orogastric tube does not pass. Infants with esophageal atresia cannot tolerate oral secretions and require constant drainage of the esophageal pouch to prevent aspiration. They should be monitored in the neonatal intensive care unit while awaiting emergent surgical intervention.

Definitions

Association: Sporadic occurrence of two or more features occurring together more commonly than would be expected but without an identifiable cause (such as VATER [vertebral (defects), (imperforate) anus, tracheoesophageal (fistula), radial and renal (dysplasia)]).

Polyhydramnios: Diagnosis of an abnormal amount of amniotic fluid.

Syndrome: A constellation of features having a common cause (such as the features of Down syndrome being caused by a trisomy 21).

Clinical Approach

Esophageal atresia occurs in 1 in 2000 to 5000 live births; in 75% of cases it is accompanied by some form of tracheoesophageal fistula (TEF). The prenatal course may be complicated by a history of polyhydramnios (50%). While five different anatomic variants occur, the most common (87%) includes a proximal atresia with a distal fistula (Figure 47-1).

Infants with TEF usually present in the newborn period with **excessive oral secretions and coughing, choking, and cyanosis secondary to aspirated oral secretions** or with initial feeds. Infants with the **“H-type” fistula**, which accounts for about 5% of cases, often **present later in life as recurrent aspiration pneumonia or feeding difficulty**. In this form of TEF, the esophagus and trachea are intact but are connected by the fistula; symptoms are less dramatic and diagnosis may be difficult.

Other congenital anomalies occur in about 30% of patients with TEF. The most common association is the VATER or VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) association that includes vertebral anomalies, anorectal malformation, cardiac defects, tracheoesophageal fistulas, renal abnormalities, radial anomalies, and limb defects. All patients with TEF are evaluated for these

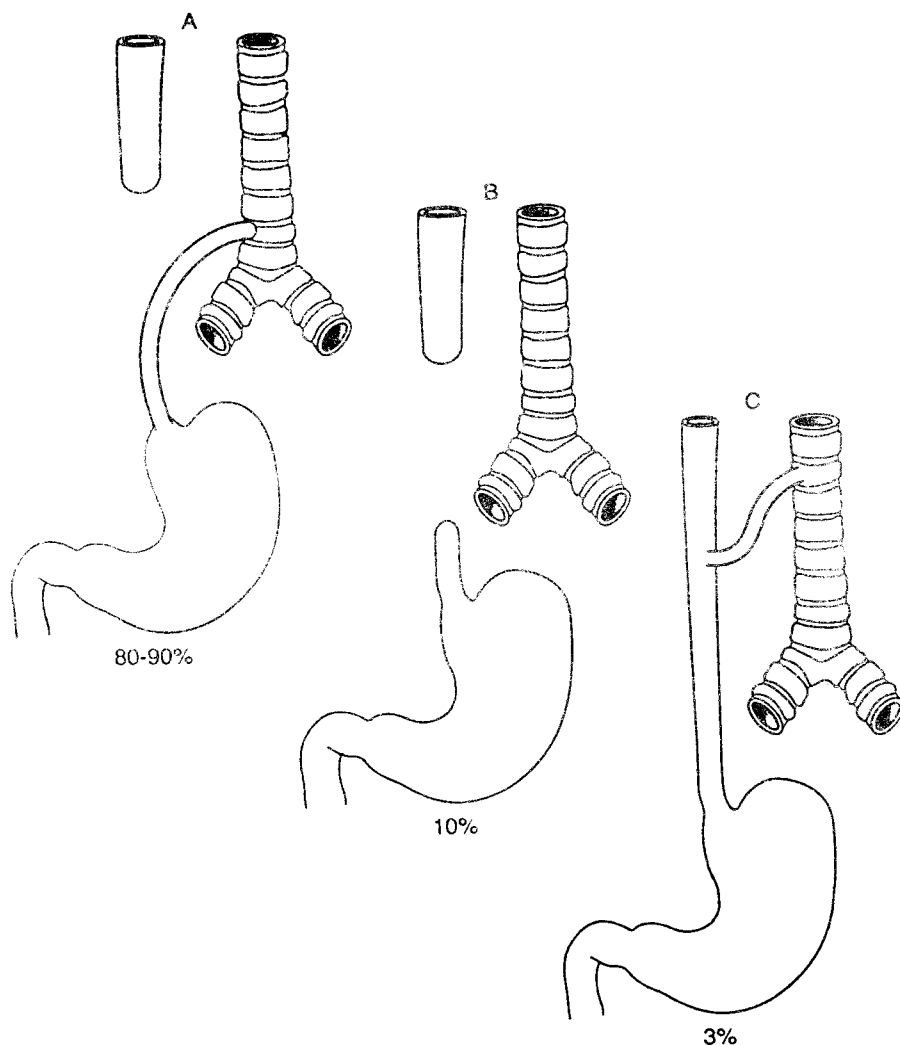


Figure 47-1. Types of tracheoesophageal (TE) fistulas.

associated malformations. Neonates with tracheoesophageal fistula/esophageal atresia are at high risk for respiratory compromise secondary to aspiration. The esophageal pouch requires constant suctioning while awaiting emergent surgical intervention. The goal of surgery is to ligate the fistula and to anastomose the esophagus. If anatomic

conditions preclude primary anastomosis, staged surgical procedures may be required. Esophageal dysmotility may persist after surgical correction and these children are predisposed to chronic gastroesophageal reflux.

Comprehension Questions

- [47.1] A 2-hour-old term newborn male has coughing, choking, and cyanosis prior to feeding. A nasogastric tube is placed and meets resistance at 10 cm. Prenatal history is significant for polyhydramnios. Which of the following is most likely to be found in this infant?
- A. Congenital cataracts
 - B. Microcephaly
 - C. Gingival hyperplasia
 - D. Hepatosplenomegaly
 - E. Vertebral anomaly
- [47.2] An infant with a history of recurrent pneumonia is diagnosed with tracheoesophageal fistula at the age of 8 months. Which of the following statements is correct?
- A. The infant most likely has a "H-type" tracheoesophageal fistula.
 - B. The infant most likely has proximal esophageal atresia with distal fistula.
 - C. The infant is likely to have a previously undetected, associated finding of imperforate anus.
 - D. The infant is unlikely to have gastroesophageal reflux.
 - E. The infant is likely to have cystic fibrosis.
- [47.3] A 2-year-old girl with a history of esophageal atresia and a ventricular septal defect is hospitalized with *Pneumocystis carinii* pneumonia. She is most likely to have immunodeficiency as a result of which of the following conditions?

- A. DiGeorge syndrome
- B. Severe combined immunodeficiency syndrome
- C. Bruton agammaglobulinemia
- D. Hyperimmunoglobulin E syndrome
- E. Chronic granulomatous disease

[47.4] A 2-year-old boy presents to your office with his foster parents. The child has been living with his foster parents for 3 weeks and during that time has become progressively short of breath. When he first arrived at their home, the child was active and playful. Now he appears too tired to play. They are aware that he had surgery as an infant, for a problem with “esophagus being connected to his lungs” and that he is not on any medication currently; however, they are unable to provide any specific details. Upon examination the child is afebrile, diaphoretic, tachycardic, and tachypneic. His symptoms can most likely be attributed to:

- A. Adjustment disorder
- B. Reactive airway disease
- C. Rheumatic heart disease
- D. Kawasaki disease
- E. Heart failure secondary to ventricular septal defect


Answers


- [47.1] E. This infant is likely to have esophageal atresia. The VATER or VACTERL association of congenital anomalies includes vertebral anomaly, anorectal malformation, tracheoesophageal fistula, cardiac (congenital heart disease), renal abnormalities, and limb defects.
- [47.2] A. This infant is most likely to the H-type fistula that often presents later in infancy with recurrent pneumonias and/or feeding difficulty. Patients with esophageal atresia and distal fistula will present within the first hours of life secondary to their inability to swallow oropharyngeal secretions. Infants with imperforate


anus will also present early in the neonatal period. All patients with tracheoesophageal fistula are at high risk for gastroesophageal reflux.

- [47.3] A. DiGeorge syndrome or thymic hypoplasia results from abnormal formation of the third and fourth pharyngeal pouches during fetal development. The cell-mediated deficiency is associated with *Pneumocystis carinii* pneumonia. Neighboring structures formed during the same period of fetal growth are often affected. Associated conditions include anomalies of the great vessels, esophageal atresia, bifid uvula, congenital heart disease, short philtrum, hypertelorism, antimongoloid slant palpebrae, mandibular hypoplasia, and low set, notched ears. Infants with DiGeorge syndrome may present with hypocalcemic seizures in the neonatal period secondary to parathyroid hypoplasia.
- [47.4] E. This child most likely has a history of repaired tracheoesophageal fistula with associated congenital heart disease with symptoms of heart failure.

CLINICAL PEARLS

 VATER or VACTERL association—**vertebral anomalies, anorectal malformation, cardiac defects, tracheoesophageal fistulas, renal abnormalities, radial anomalies, and limb defects**—is often seen in a patient with a tracheoesophageal fistula.

 Esophageal atresia is associated with DiGeorge syndrome.

 The H-type fistula often presents later in infancy as recurrent pneumonitis and can be difficult to diagnose.

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◆ CASE 48

A term male is born to a 35-year-old woman after an uncomplicated pregnancy. Immediately after birth, the child is noted to have tachypnea, nasal flaring, grunting, and retractions, and cyanosis. Apgar scores were 4 and 4 at 1 and 5 minutes, respectively. Auscultation of the chest reveals right-sided heart sounds and the neonate is noted to have a scaphoid abdomen.

- ◆ What is the most likely diagnosis?
- ◆ What is the best management for this condition?

ANSWERS TO CASE 48: Congenital Diaphragmatic Hernia

Summary: A term newborn presents with respiratory distress, shifted heart sounds, and a scaphoid abdomen.

◆ **Most likely diagnosis:** Congenital diaphragmatic hernia.

◆ **Treatment:** Cardiorespiratory support and surgical correction.

Analysis**Objectives**

1. Know the presentation of congenital diaphragmatic hernia (CDH).
2. Understand the preoperative care for CDH.
3. Be familiar with common reasons for respiratory distress in the term newborn infant.

Considerations

This child presents at birth with respiratory distress. The resuscitation of this infant begins immediately and follows the basic principles of resuscitation (the “ABCs”) including establishing an **A**irway, controlling **B**reathing, and assessing the **C**irculation. After stabilization of the infant, further evaluation of the causes can be undertaken.

APPROACH TO DIAPHRAGMATIC HERNIA**Definitions**

ECMO (extracorporeal membrane oxygenation): A system using a modified heart-lung machine that is used in severe pulmonary failure. Cannulation of the carotid artery and jugular vein is required to link the neonate to the system. An “ECMO team”

usually includes a pediatric surgeon, neonatologist, perfusionists, respiratory therapists, and nurses.

Clinical Approach

CDH results from herniation of abdominal contents through the posterolateral foramen of Bochdalek into the thoracic cavity. The incidence of this condition is about 1 in 2500 to 5000 live births. **Left-sided hernias predominate** (70% to 85%) and bilateral hernias occur in 5% of cases. **Pulmonary hypoplasia and intestinal malrotation are present in almost all cases.** Twenty percent to 30% of cases have associated anomalies including central nervous system lesions, congenital heart disease, esophageal atresia, and omphalocele, or have associated chromosomal aberrations, including **trisomy 21, trisomy 13, and trisomy 18.**

By the eighth week of gestation, the abdominal and thoracic cavities of the fetus are separate because of the closing of the posterolateral pleuroperitoneal canals. Some authors believe that failure of this developmental step leads to CDH. Bilateral pulmonary hypoplasia often results in decreased lung volume, decreased number of alveoli and bronchial generations, and abnormal vasculature. Pulmonary arterioles have increased musculature and patients have pulmonary hypertension.

Other diaphragmatic hernias include those in the paraesophageal and foramen of Morgagni locations. Hernias through the foramen of Morgagni are located in the anteromedial diaphragm and patients generally become symptomatic after the neonatal period. Paraesophageal hernias are uncommon and should be repaired rapidly because patients are at risk of gastric incarceration and strangulation.

The diagnosis of CDH is often made by prenatal ultrasonography. Upon diagnosis, fetal echocardiography and amniocentesis are performed to identify other anomalies. After complete evaluation, parents are counseled about CDH and other associated anomalies (if any) so that delivery preparation can be made. Neonates with CDH are delivered at specialized facilities where adequate neonatal and pediatric surgical services are available.

Most neonates with CDH have a scaphoid abdomen at birth because of the dearth of intestinal contents and develop respiratory failure within

24 hours of life. Radiographs of the chest may be diagnostic if intestinal contents are present in the thoracic cavity (Figure 48-1). Ultrasonography may be required to differentiate intestinal contents from a cystic lesion.

The presentation of CDH in the neonatal period must be differentiated from pneumothorax. In both cases, the patient may have respiratory collapse and shifted heart sounds. However, if a scaphoid abdomen is present and CDH is being considered, thoracentesis should be deferred to avoid intestinal perforation.

Immediate resuscitation of CDH includes placement of a nasogastric tube to minimize aeration of the gastrointestinal tract. If the patient has any respiratory difficulty, an endotracheal tube is placed as bag-mask

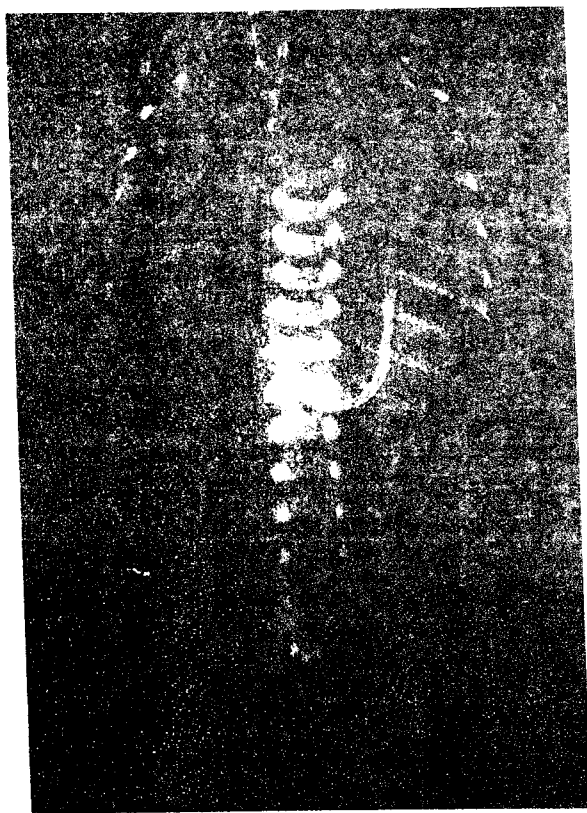


Figure 48-1. Radiograph of child with congenital diaphragmatic hernia. Courtesy of Susan John, MD.

ventilation can lead to further respiratory compromise by causing gastric distension. Ventilatory strategies vary from moderate hyperventilation to permissive hypercapnia. Volume expanders, inotropic agents and alkalization may be useful adjunctive therapy.

When the increased pulmonary vascular resistance commonly seen in this condition is **not** associated with right-to-left shunting, the infant may be a candidate for **surgical repair between 24 and 72 hours of life**. If pulmonary vascular resistance does lead to **significant shunting, the patient will likely require ECMO**. ECMO may be required for up to 4 weeks. Surgical repair may be attempted shortly after initiation of ECMO with a significant duration of postoperative ECMO, or the surgery may be postponed until the infant has tolerated some weaning from ECMO support. Patients unable to be fully weaned from ECMO following surgical repair may require trials of high-frequency jet ventilation, oscillatory ventilation, nitric oxide, lung transplant, and, in some cases, withdrawal of all support.

Fetal surgery to reduce the herniated gastrointestinal contents has been attempted, but overall morbidity and mortality were unaffected and postnatal repair is more common. Even with the use of ECMO and sophisticated neonatal care, the survival rate for live born infants with CDH is 42% to 66%. **Especially poor prognostic factors include respiratory distress within 24 hours, major associated anomaly, and the need for ECMO.**

Neonates with **prior group B streptococcal sepsis** early in life may present weeks later with **right-sided CDH**. A small percentage of patients with CDH have a milder clinical course presenting later in infancy or childhood with symptoms of intestinal obstruction or respiratory symptoms. Diagnosis in these unusual cases usually requires contrast radiography.

Follow-up

In the past, most patients surviving CDH had only mild abnormalities on pulmonary function testing. With current more advanced and aggressive therapies, however, survival of infants with more severe pulmonary disease is more common. Long-term sequelae include restrictive lung disease, airway reactivity, neurologic abnormalities, gastroesophageal reflux, and growth retardation; all are more common

following need for ECMO. All patients surviving CDH require long-term, careful follow up of their pulmonary, nutritional, and neurologic status.

Comprehension Questions

- [48.1] A term male infant is born to a 33-year-old woman. She had little prenatal care, but denies having had any problems. Immediately after birth the infant is noted to have cyanosis and respiratory distress. Auscultation of the chest in the delivery room reveals right-sided heart sounds and absent breath sounds on the left. The most appropriate next step is to:
- A. Perform a needle thoracostomy for possible pneumothorax.
 - B. Assess the abdomen to evaluate for possible congenital diaphragmatic hernia.
 - C. Order ultrasonography of the chest.
 - D. Prepare the infant for extracorporeal membranous oxygenation.
 - E. Order a computerized tomography of the chest.
- [48.2] The next step in stabilizing the infant in the above question [48.1] is to:
- A. Perform endotracheal intubation and begin ventilatory support.
 - B. Begin bag-mask ventilation.
 - C. Perform a needle thoracostomy.
 - D. Call the ECMO team to initiate extracorporeal membranous oxygenation.
 - E. Administer intravenous sodium bicarbonate solution.
- [48.3] A male neonate is born at 39 weeks' gestation by spontaneous vaginal delivery to a 22-year-old primigravida woman following an uncomplicated pregnancy. Just prior to delivery, fetal bradycardia was noted and at delivery thick meconium is present. The infant is found to be hypotonic and have bradycardia. The first step in resuscitation should be:

- A. Bag-mask ventilation
- B. Administration of epinephrine via endotracheal tube
- C. Endotracheal intubation with direct suction
- D. Oxygen delivered by cannula in close proximity to the nares
- E. Endotracheal intubation with immediate ventilation

[48.4] After the infant discussed in the above question [48.3] is stabilized and admitted to the neonatal intensive care unit, a chest radio-graph is performed that reveals bilateral patchy infiltrates with coarse streaking and flattening of the diaphragm. The infant abruptly has an increased oxygen requirement. Physical examination reveals decreased breath sounds on the right side. Which of the following statements is true?

- A. The infant is likely to have hyperresonance of the chest on the left side.
- B. Transillumination of the chest is likely to transmit excessive light on the right side.
- C. Needle thoracostomy is contraindicated.
- D. High positive end-expiratory pressure (PEEP) is useful in this condition.
- E. Repeat chest radiography is likely to reveal congenital diaphragmatic hernia.

Answers

[48.1] **B.** Evaluation of the neonate born with respiratory distress with unilateral breath sounds must include examination of the abdomen. With asymmetric breath sounds both pneumothorax and congenital diaphragmatic hernia must be urgently considered. In this case, the infant was found to have a scaphoid abdomen increasing the likelihood that the infant has congenital diaphragmatic hernia; needle thoracostomy is contraindicated as intestinal perforation may occur. The patient must be stabilized immediately and the need for ECMO can only be ascertained after evaluating the infant's response to initial therapy.

- [48.2] **A.** Endotracheal intubation with gentle ventilation should be initiated in an infant with congenital diaphragmatic hernia and respiratory distress. Bag-mask ventilation can lead to aeration of the thoracic intestinal contents leading to increased respiratory distress. Needle thoracostomy is contraindicated as intestinal perforation may occur.
- [48.3] **C.** Endotracheal intubation with direct suction should be performed in a depressed infant with thick meconium noted at delivery. Bag-mask ventilation or endotracheal intubation without suction may increase the volume of meconium aspirated.
- [48.4] **B.** This infant most likely has a right-sided pneumothorax that should reveal excessive light transmission by transillumination and hyperresonance on the right side. Infants with meconium aspiration and respiratory distress are at increased risk for pneumothorax, especially if significant PEEP is used to maintain adequate oxygenation. This infant is likely to require a chest tube to alleviate the pneumothorax. If the infant has severe respiratory distress or circulatory involvement, emergent needle aspiration may be necessary.

CLINICAL PEARLS

The diagnosis of CDH is often made by prenatal ultrasonography. CDH occurs more commonly on the left side. CDH is associated with congenital heart disease, esophageal atresia, and trisomy 21, trisomy 13, and trisomy 18.

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◆ CASE 49

A 12-month-old boy is brought to the emergency department with a 1-day history of intermittent abdominal pain and vomiting without diarrhea. His family reports that he has become lethargic over the past 2 hours. In the emergency department, the child is quiet and almost lethargic between periods of intense crying and remarkable distress. Upon examination, the right lower quadrant feels devoid of bowel and a sausage-like mass is palpated in the right upper quadrant.

- ◆ What is the most likely diagnosis?
- ◆ What is the best management for this condition?

ANSWERS TO CASE 49: Intussusception

Summary: A 12-month-old boy has intense, episodic abdominal pain and lethargy, accompanied by a sausage-like mass in the right upper quadrant.

◆ **Most likely diagnosis:** Intussusception.

◆ **Best treatment:** Air contrast enema.

Analysis

Objectives

1. Know the presentation of intussusception.
2. Understand the treatment of intussusception.
3. Be familiar with the differential diagnosis of acute abdominal pain in children.

Considerations

In this child with intermittent, severe abdominal pain, a variety of etiologies are possible (Table 49–1). The clues to the appropriate diagnosis in this patient are the sausage-like mass coupled with the episodic nature of the severe pain alternating with periods of relatively little pain. The most important steps in this patient are to determine the etiology of this severe pain and to prevent loss of viable intestine.

APPROACH TO INTUSSUSCEPTION

Definitions

Currant jelly stools: A classic finding for intussusception, stools are red with mucus. Venous stasis causes blood to enter the intes-

Table 49-1
COMMON ETIOLOGIES OF ACUTE ABDOMINAL PAIN
IN INFANTS AND YOUNG CHILDREN

CONDITION	SIGNS AND SYMPTOMS
Abdominal migraines	Recurrent abdominal pain with emesis
Appendicitis	Right lower quadrant pain, abdominal guarding and rebound tenderness
Bacterial enterocolitis	Diarrhea (may be bloody), fever, vomiting
Cholecystitis	Right upper quadrant pain
Diabetes mellitus	History of polydipsia, polyuria, and weight loss
Henoch-Schönlein purpura	Purpuric lesions and joint pain
Hepatitis	Right upper quadrant pain and jaundice
Incarcerated hernia (inguinal)	Inguinal mass, lower abdominal or groin pain, emesis
Intussusception	Colicky abdominal pain and currant jelly stools
Malrotation (with volvulus)	Abdominal distention, bilious vomiting, blood per rectum; usually presents in infancy
Nephrolithiasis	Hematuria, colicky abdominal pain
Pancreatitis	(Severe) epigastric abdominal pain, fever, and persistent vomiting
Pneumonia	Fever, cough, rales on auscultation of the chest
Small-bowel obstruction	Emesis, frequent history of prior abdominal surgery
Streptococcal pharyngitis	Fever, sore throat, headache
Testicular torsion	Testicular pain and edema
Urinary tract infection	Fever, vomiting, and diarrhea in infants; back pain in older children

tinal lumen with resulting ischemia leading to mucus drainage: "currant jelly" stools are formed.

Pneumatosis intestinalis: Air within the intestinal wall noted by radiography.

Clinical Approach

Intussusception is the leading cause of intestinal obstruction in young children beyond the neonatal period, occurring most commonly in healthy children between the ages of **3 months and 6 years**. Eighty percent of cases occur in children younger than 24 months of age. The incidence of intussusception is 1 to 4 cases per 1000 live births, with a male predominance. Seasonal peaks occur in spring and autumn. Although a viral etiology is postulated and an association exists with adenovirus and rotavirus, a clear causal relation remains to be established.

The pathophysiology of intussusception involves a **proximal portion of the gastrointestinal tract telescoping into the adjacent distal portion**. A leading point for the intussusception is identified at times and may include a hypertrophied Peyer patch, an enlarged mesenteric lymph node, a Meckel diverticulum, a polyp, ectopic pancreatic tissue, a lymphoma, a benign tumor, intestinal wall edema such as that found in Henoch-Schönlein purpura or mucus gland hypertrophy of cystic fibrosis. The most common location is ileocolic, followed by ileo-ileocolic, and less frequently, cecocolic or ileoileal.

Following the intussusception, the involved bowel experiences lymphatic and venous obstruction leading to edema and finally to ischemia. Necrosis can occur if the condition goes untreated. With **venous stasis causing blood to enter the lumen and ischemia leading to mucus drainage**, the classic "**currant jelly**" stools are formed. While "currant jelly" stools are virtually diagnostic, the condition, if it occurs, is a late finding and the affected children are often quite sick.

The typical presentation of a patient with intussusception is that of a previously healthy infant or toddler with **vomiting and severe, paroxysmal abdominal pain who is relatively comfortable between episodes**. Emesis is clear initially and progressively becomes bilious.

Early during the course, normal stools are evacuated and later the stools become bloody and may become currant jelly-like. Children may have high fevers and lethargy as presenting symptoms. During episodes of pain caused by peristalsis, the child is visibly distressed, often bringing the knees flexed to the chest, crying loudly, or writhing. Between the paroxysms of pain, the abdomen is soft, may be scaphoid, and is often only mildly tender. In approximately 70% of cases a palpable sausage-like mass can be felt, most commonly in the right upper quadrant at the hepatic flexure.

Ultrasonography is a useful tool for diagnosis, especially in critically ill children who cannot tolerate contrast studies (see below). Plain abdominal radiographs may reveal a mass or nonspecific findings of bowel obstruction or perforation. While a clinical diagnosis can be made in a child with paroxysmal abdominal pain, vomiting, bloody stools, and a palpable sausage-like mass, the **"gold" standard for diagnosis**, and often treatment, is **contrast enema**. Although contrast may be air, water (hydrostatic) or barium, air contrast is usually preferred because complication risk is lower than with other forms of contrast material.

Prior to diagnostic intervention, the patient should receive appropriate fluid resuscitation and have measurements of serum electrolytes and hemoglobin. When the suspicion for intussusception is high, a pediatric surgeon should be consulted. Some surgeons request that a dose of antibiotics be given and that the operating room be on standby prior to the contrast enema in case emergent surgery is needed. If a child has free air in the abdomen or pneumatosis intestinalis on plain radiograph, has peritoneal signs, is critically ill, or fails contrast enema reduction, surgical treatment is required.

Contrast enema results in successful reduction in 30% to 80% of cases; recurrence of the intussusception after contrast reduction is seen in 5% to 10% of cases. The main risk of this procedure is perforation. Approximately 25% of children with intussusception require surgical reduction and some also require resection of nonviable bowel segments.

Children who undergo reduction of their intussusception within 24 hours of onset have a good prognosis. The mortality rate increases after 48 hours of symptoms. If left untreated and spontaneous reduction does not occur, intussusception is usually lethal.

Comprehension Questions

- [49.1] Intussusception is *most* likely to be present in which of the following patients?
- A. A healthy 15-month-old with severe paroxysmal abdominal pain and vomiting
 - B. A 15-year-old sexually active girl with lower abdominal pain
 - C. A 6-hour-old term infant with choking, coughing, and cyanosis
 - D. A 4-day-old premature neonate who is the product of a 33-week gestation and has recently been started on nasogastric feeds and now has abdominal distention, bloody stools, and thrombocytopenia
 - E. A 7-year-old girl with abdominal pain, vomiting, fever, and diarrhea
- [49.2] A 12-month-old boy presents to the emergency department with a 6-hour history of vomiting, colicky abdominal pain, and fever. Upon physical examination a sausage-like mass is palpable in the right upper quadrant of the abdomen. The most appropriate next step in the child's management is to:
- A. Order an abdominal ultrasonograph.
 - B. Order a computerized tomography scan of the abdomen.
 - C. Order a barium swallow with small bowel follow-through.
 - D. Obtain a surgical consultation.
 - E. Order a chest radiograph.
- [49.3] A 9-year-old boy presents with persistent abdominal pain and vomiting for 24 hours. His physical examination is remarkable for abdominal guarding and right lower quadrant rebound tenderness. Of the following, the most likely diagnosis is:
- A. Appendicitis
 - B. Gastroenteritis
 - C. Gastroesophageal reflux

D. Intussusception

E. Pyloric stenosis

[49.4] An 18-month-old male undergoes successful reduction of his intussusception by hydrostatic enema. Eighteen hours following the procedure the child has severe paroxysms of abdominal pain. The next best step in management is to:

A. Administer morphine for pain control.

B. Order a computerized tomography of the abdomen.

C. Order a radiograph of the abdomen.

D. Administer an intravenous fluid bolus

E. Obtain an emergent surgical consultation.

[49.5] A 6-week-old male infant presents with projectile emesis after feeding. Upon physical examination he is found to have an olive-shaped abdominal mass. Which of the following statements is true?

A. He is likely to have a hypochloremic metabolic alkalosis.

B. He is likely to have metabolic acidosis.

C. This condition is more common in female infants.

D. The infant should be restarted on feeds when the vomiting resolves.

E. It is likely that the infant will develop diarrhea.

Answers

[49.1] **A.** The 15-month-old child with paroxysmal abdominal pain is the most likely to have intussusception. In the case of the adolescent female, evaluation for ectopic pregnancy, pelvic inflammatory disease, appendicitis, ovarian torsion, and ruptured ovarian cyst must be considered. In the case of the premature infant, necrotizing enterocolitis is in the differential diagnosis. The 7-year-old girl is much more likely to have gastroenteritis.

[49.2] **D.** A surgical consultation should be obtained.

- [49.3] A. This child most likely has appendicitis.
- [49.4] E. Recurrence of intussusception following successful reduction occurs in 5% of cases.
- [49.5] A. This infant has the features of pyloric stenosis, a condition that is four times more common in males, and more common in children who are first in birth order. Affected infants most commonly present between the third week and second month of life with increasing projectile emesis. Abdominal examination may reveal an olive-shaped mass and visible peristaltic waves. Measurement of serum electrolytes is indicated, as infants are prone to develop hypochloremic metabolic alkalosis. Ultrasonography is useful in confirming the diagnosis.

CLINICAL PEARLS



Classic features of intussusception are fever, colicky abdominal pain, currant jelly stools, and a sausage-like mass in the abdomen.



Classic features of pyloric stenosis include projectile vomiting, an olive-shaped abdominal mass, and a hypochloremic metabolic alkalosis.



Intussusception can be associated with Henoch-Schönlein purpura.

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◆ CASE 50

A 13-year-old female complains that her face and shoulders have “zits everywhere. She has tried over-the-counter benzoyl peroxide products, and has stopped eating chocolate and french fries upon her mother’s advice, yet her skin continues to break out. She has been invited to go to a school dance in 6 weeks and wants to look her very best. She complains that some of her acne lesions are just blackheads, but also notes that others are “deep underground” and painful.

◆ What is the diagnosis?

◆ What is the best treatment for her condition?

ANSWERS TO CASE 50: Acne Vulgaris

Summary: A 13-year-old adolescent girl presents with acne on her face and shoulders.

- ◆ **Most likely diagnosis:** Combination acne.
- ◆ **Best therapy:** Front-line therapy includes antibacterial soap, keratolytic agent (benzoyl peroxide), with the possible addition of a comedolytic agent (tretinoin) or topical antibiotics. Second-line treatment includes the addition of oral antibiotics. Isotretinoin (Accutane) is reserved for severe, resistant nodulocystic acne.

Analysis

Objectives

1. Understand the various types of acne vulgaris.
2. Know the treatments most effective for the various types of acne.
3. Discuss the potential side effects of Accutane.

Considerations

This patient's pubertal hormonal surges are leading to an increase in sebum production from the sebaceous glands. An obstruction of sebum flow leads to rupture of epithelial cells and other contents within the dermis. Inflammation, scarring, and pitting can result.

APPROACH TO ACNE VULGARIS

Definitions

Comedones: Open comedones (blackheads) are formed when melanocytes become compacted in the skin; they are not caused by poor hygiene. Closed comedones are known as "whiteheads."

Cyst: A swollen, often tender, dilated follicle within the dermis.

Inflammatory papule: An inflammatory reaction to sebum, fatty acids, and bacteria that occurs deep within the follicle and appears as a red "bump" under the skin surface.

Pustule: Inflammation and exudate around comedones, occurring in superficial portion of the dermis.

Clinical Approach

The normal pilosebaceous unit is made up of sebaceous glands, a rudimentary hair, and a wide pilary duct lined with stratified squamous epithelial cells. With normal desquamation the epithelial cells are carried up the follicular canal by sebum secreted from the sebaceous glands. Hormonal surges during puberty lead to an increase in sebum production. Proliferation of the bacterium *Propionibacterium acnes* leads to distention of the follicular lining and wall, causing obstruction of sebum flow. The walls reach a maximum capacity and rupture, releasing their contents that act as a foreign body to the surrounding tissue. Neutrophils and liposomal enzymes are released, leading to further inflammation. Scarring and pitting often result.

Acne lesions are categorized as inflammatory or noninflammatory. Noninflammatory lesions consist of open and closed comedones. Inflammatory lesions are characterized by the presence of one of the following types of lesions: papules, pustules, and nodules (or cysts).

The treatment goal of acne is to eliminate comedones, papules, pustules, cysts, and nodules and also to decrease the amount of hyperpigmented scarring (Table 50-1). Improvement in acne may not be noticed for at least a month after therapy is initiated; flare-ups may occur during the course of treatment. Patients should be discouraged from picking or squeezing skin lesions because doing so will increase inflammation and lead to scarring. The affected skin should be gently washed with the hands twice daily with antibacterial soap (e.g., Neutrogena Oil-Free Acne Wash or any inexpensive antibacterial soap) and rinsed well to prevent soap buildup on the skin surface; some recommend avoiding use of scrubbing agents and harsh cloths when washing. Controversy exists among dermatologists regarding the use of alcohol-based drying agents (skin toners) with some feeling that the alcohol

Table 50-1
TREATMENT FOR VARIOUS TYPES OF ACNE

ACNE TYPE	TREATMENT*
Pure comedonal acne	Topical tretinoin or adapalene at night
Mild papular acne	Benzoyl peroxide in the morning and at night
Papulopustular and cystic acne (inflammatory)	Benzoyl peroxide and/or topical antibiotics in the morning and topical tretinoin or adapalene at night
Severe pustulocystic acne	Benzoyl peroxide and oral antibiotics
Severe cystic acne	Oral retinoid (isotretinoin)

*Wash all types with antibacterial soap in the morning and at night.

may stimulate more oil production to counteract the drying effects of alcohol.

First-line management should begin with topical benzoyl peroxide or a comedolytic agent such as tretinoin (Retin-A). The combination of benzoyl peroxide in the morning and tretinoin at night may be effective when either agent alone has failed. The benzoyl peroxide must be washed off prior to application of tretinoin or the retinoid will be rendered ineffective. Benzoyl peroxide is bactericidal and keratolytic, causing follicular desquamation. It is available in over-the-counter preparations, yet these preparations lack uniformity, stability, and efficacy. Although they eliminate bacteria at the skin surface, they do not have a carrier vehicle that allows deep penetration into the follicular orifice. Therefore, prescription preparations (2.5%, 5%, 6%, and 10%) are preferable. A benzoyl peroxide wash is beneficial when a wide distribution of lesions is present (such as on the back) or when adherence to the treatment plan is a problem. The wash can be applied in the shower, left on for a few seconds, and then washed off. Benzoyl peroxide can result in bleaching of clothing; skin to which this agent was recently applied should be dry before fabrics are touched.

Topical tretinoin (Retin-A, Avita), a vitamin A derivative, inhibits the formation of microcomedones and increases cell turnover. Therapy

should begin conservatively (0.025% cream) allowing 3 to 4 weeks for accommodation. Patients should use a mild soap, such as Dove or Caress, and allow the skin to dry 20 to 30 minutes prior to applying the tretinoin. Mild redness and peeling are expected, and patients should avoid exposure to sun and use sunscreens. Adapalene 1% gel (Differin) is a newer formulation of retinoid that causes less irritation, more activity, less photosensitivity, and can be used concomitantly with benzoyl peroxide preparations. Tazarotene (Tazorac gel) is a retinoid that is active against psoriasis. This agent is teratogenic and causes irritation; it is to be used with caution. Some feel that azelaic acid applied twice daily for 4 to 6 months may provide acne relief, especially for those sensitive to other agents and in cold weather.

Topical antibiotics are preferred over systemic antibiotics because of the lower potential for side effects. Topical antibiotics such as erythromycin or clindamycin are applied to affected areas twice daily or in combination with benzoyl peroxide or tretinoin. Oral antibiotics are used when inflammatory and pustular acne does not respond to topical treatment. Tetracycline is the most frequently used oral antibiotic because it is inexpensive and has few side effects.

Isotretinoin (Accutane) is the treatment of choice for severe, resistant nodulocystic acne. A 4-month course often clears a severe case of acne. It is **highly teratogenic** and has many side effects, including cheilitis, conjunctivitis, hypertriglyceridemia, elevated serum cholesterol, blood dyscrasias, elevated liver enzymes, dry eyes and mouth, and photosensitivity. Females should have a negative pregnancy test within 1 week before the drug is initiated and should maintain effective contraception 1 month prior to therapy, during therapy, and 1 month after therapy.

Oral contraceptives (Ortho Tri-Cyclen) are approved for the treatment of acne, and intralesional steroid therapy is sometimes used in unresponsive cases.

Comprehension Questions

- 50.1] A teenager with severe cystic acne started isotretinoin 1 month ago. Initially her acne got worse but now it is starting to improve. However, she is complaining of "not feeling like herself."

She does not want to go to school, cries frequently during the day, and feels rather hopeless about her life. She also feels “achy” all over. What is the best course of action?

- A. Refer to a psychiatrist for evaluation.
- B. Prescribe an antidepressant.
- C. Discontinue the Accutane immediately and refer to a psychiatrist for evaluation.
- D. Decrease the dose of isotretinoin by 20 mg/d to determine if the side effects resolve.
- E. Counsel her that these symptoms will resolve over time.

[50.2] A teenage boy complains of a several-week history of “hard red zits” on his face that are painful and itchy. He has no other areas of breakouts. He works on a farm to make extra money on the weekends. His face has inflammatory papules and pustules in the beard and moustache area. He has mild cervical lymphadenopathy. What is the most likely diagnosis?

- A. Acne vulgaris
- B. Rosacea
- C. Tinea barbae
- D. Eczema
- E. Herpes infection

[50.3] A 7-day-old infant is brought to clinic because he has developed “pimples” on his cheeks and forehead. The infant is breast-feeding well and the parents have no other concerns about him. The skin around the pimples on the face has a red base yet does not appear to be secondarily infected. There are no other areas of breakouts on the body. This infant most likely has:

- A. Atopic dermatitis
- B. Urticaria
- C. Herpes simplex
- D. Neonatal acne
- E. Tinea corporis

[50.4] A 17-year-old girl is prescribed oral tetracycline, topical tretinoin, and topical benzoyl peroxide. She is sexually active and takes oral contraceptives. You counsel her to:

- A. Take the tetracycline with food or milk
- B. Use another form of birth control in addition to oral contraceptives
- C. Get a little sun to help dry her face lesions
- D. Avoid chocolate and fried foods
- E. Avoid sunscreen because it will burn the face

Answers

- [50.1] C. Depression is a rare side effect of isotretinoin, but it can be severe; suicides have been reported. Myalgias and arthralgias have also been reported as side effects. It would be best to stop the drug and have the patient evaluated for depression and potential suicidal tendencies.
- [50.2] C. Tinea barbae is caused by a trichomycosis; it closely resembles tinea capitis. It may be acquired through animal exposure and is more common in farmers. Topical antifungal preparations are ineffective; oral antifungals are required.
- [50.3] D. Approximately 20% of normal neonates develop at least a few comedones within the first month of life. The cause of *neonatal acne* is unknown but has been attributed to placental transfer of maternal androgens, hyperactive adrenal glands, and a hypersensitive neonatal end-organ response to androgenic hormones.
- [50.4] B. Oral antibiotics may decrease the effectiveness of oral contraceptive pills. Tretinoin can lead to photosensitivity; patients should avoid sun exposure or use sunscreen. Diet has not been found to have an effect on acne. Tetracycline should be taken on an empty stomach; milk products bind to the tetracycline.

CLINICAL PEARLS

Acne is a disorder of the sebaceous follicle in which excess sebum, keratinous debris, and bacteria accumulate, producing microcomedones, which, in turn, may become inflamed.

Treatment for acne depends on its severity and may include topical benzoyl peroxide, topical retinoic acid, topical antibiotics, oral antibiotics, and/or oral isotretinoin (Accutane).

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◆ CASE 51

A 3700-g male infant is born at 38 weeks gestation to a 23-year-old gravida 1 mother. The pregnancy was uncomplicated and an ultrasonogram done at 20 weeks' gestation was reportedly normal. The infant is noted shortly after birth to have a dribbling urinary stream and a mass in the lower abdomen. Postnatal ultrasonography reveals bilateral hydronephrosis with bladder wall hypertrophy and an enlarged prostatic portion of the urethra.

- ◆ What is the most likely diagnosis?
- ◆ What is the most appropriate next test?

ANSWERS TO CASE 51: Posterior Urethral Valves

Summary: A term newborn male has evidence of severe urinary obstruction.

◆ **Most likely diagnosis:** Posterior urethral valves (PUV).

◆ **Most appropriate next test:** Renal ultrasonography.

Analysis

Objectives

1. Know the various presentations of patients with PUV.
2. Know the possible long-term sequelae associated with PUV.
3. Be familiar with common abdominal masses in the newborn period.

Considerations

A wide variety of conditions can lead to abdominal masses in the newborn infant (Table 51-1). In this infant's case, however, the dribbling urinary stream provides a clue to the diagnosis of PUV. Ultrasonogra-

Table 51-1
ABDOMINAL MASSES CAUSING DISTENTION

Hepatic enlargement	Renal mass
Cardiac failure, arrhythmias	Multi- or polycystic kidney
Hepatic tumors (mesenchymal hamartoma, hemangioma, hemangioendothelioma, metastatic tumors such as neuroblastoma)	Hydronephrosis (posterior urethral valves, ureterovesical or ureteropelvic junction obstruction)
Metabolic disorders (storage diseases [lysosomal or carbohydrate],	Renal vein thrombosis
	Retroperitoneal masses
	Neuroblastoma

Table 51-1
ABDOMINAL MASSES CAUSING DISTENTION (*Continued*)

tyrosinemia, galactosemia)	Wilms tumor
Beckwith-Wiedemann syndrome	Mesoblastic nephroma
Congenital infections (cytomegalic inclusion disease, syphilis, toxoplasmosis, rubella)	Sacroccygeal teratoma
	Lymphangioma
Pelvic masses	Gastrointestinal masses
Ovarian cyst (follicular, dermoid, teratoma)	Duplication
Hydrocolpos, hydrometrocolpos	Mesenteric cyst
Imperforate hymen	
Vaginal atresia/stenosis	
Cloaca	
Adrenal masses	
Adrenal hemorrhage	
Neuroblastoma	

Source: Adapted from Seashore JH. Distended abdomen. In: McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB, eds. *Oski's pediatrics*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999:323.

phy of the abdomen is an extremely useful and noninvasive tool to aid in the diagnosis of this patient.

APPROACH TO POSTERIOR URETHRAL VALVES

Definitions

Vesicoureteral reflux (VUR): Retrograde urine flow from the bladder into the ureter(s) and, if severe, into the kidney. This condition is more common in females, and may lead to recurrent urinary tract infections and a significant deterioration of renal function. Depending on the degree of reflux, treatment ranges from antibiotic prophylaxis to surgical intervention.

Voiding cystourethrogram (VCUG): A radiographic study in which a catheter is placed in the bladder and contrast is instilled.

Upon voiding, the urethra is visualized and, in cases of vesicoureteral reflux, the ureters are visualized as well.

Clinical Approach

The widespread use of fetal ultrasonography often leads to the prenatal diagnosis of urinary tract obstruction. **Sonographic findings include bilateral hydronephrosis with bladder distention**, and if the obstruction is severe, oligohydramnios. If the oligohydramnios is significant, poor fetal lung development with resultant pulmonary insufficiency and congenital contractures can be seen.

Neonates with PUV may present with a distended bladder, poor or dribbling urinary stream, palpable kidneys, reduced renal function, or urinary tract infection. Older infants may have failure to thrive, renal dysfunction, or urinary tract infection. Older boys may present with symptoms limited to voiding difficulty such as diurnal enuresis or hesitancy.

The diagnosis of PUV is confirmed with a voiding cystourethrogram or perineal ultrasonography. Because of the high incidence of PUV in boys with urinary tract infection, a thorough evaluation of the urinary tract includes both a voiding cystourethrogram and an ultrasonogram.

PUV, the most common cause of severe urinary tract obstruction in male infants, occurs in 1 of every 8000 newborn males. Thirty percent of these patients ultimately have end-stage renal disease or chronic renal insufficiency. Urethral valves are leaflets of tissue located in the lumen of the distal urethra from the prostate to the external sphincter.

In patients with PUV, immediate relief of the obstruction includes bladder catheterization via the urethra with a small feeding tube. If urinary tract infection is suspected, antimicrobial therapy should be initiated. Measurements of serum electrolytes, blood urea nitrogen and creatinine are essential, and any electrolyte abnormalities should be corrected. Hemodynamic status is monitored as sepsis or renal failure can lead to cardiovascular collapse.

After the acute obstruction is relieved, endoscopic transurethral ablation may be performed if the serum creatinine is less than 1.0 mg/dL and size of the urethra permits. If the serum creatinine remains elevated, the urethral lumen is too narrow to allow catheterization, or if the

urinary tract infection does not respond to antibiotic treatment, emergent vesicostomy may be necessary.

Following ablation of the valves, vesicoureteral reflux and persistent post-obstructive hydronephrosis is common. Antibiotic prophylaxis can be useful in decreasing the frequency of urinary tract infections.

Follow-up

After surgical treatment patients require close surveillance of renal function and for possible urinary tract infection. Many patients will have polyuria secondary to diminished ability to concentrate the urine and, thus, are at greater risk for dehydration with routine illnesses such as viral gastroenteritis. Some boys with PUV develop renal tubular acidosis.

Routine care for boys with a history of PUV includes regular monitoring with urinalysis, renal sonography, serum electrolytes, blood pressure, and linear growth. These boys may have prolonged diurnal enuresis and may require urodynamic studies to evaluate their voiding. Renal insufficiency is common and some patients may require renal transplantation. Poor prognostic factors for normal renal development include oligohydramnios, hydronephrosis before 24 weeks' gestation, persistently elevated serum creatinine, bilateral cortical cysts, and diurnal enuresis beyond the age of 5 years.

Comprehension Questions

[51.1] A 3-month-old boy presents to the emergency department with fever without a source. As part of his evaluation for suspected sepsis a urine specimen is collected. Based on initial results of laboratory testing, urinary tract infection is suspected. Which of the following statements is true?

- A. If the urine culture reveals urinary tract infection, renal sonography and a voiding cystourethrogram should be performed.
- B. Only if this infant has a second urinary tract infection, should a voiding cystourethrogram be performed.

- C. Antimicrobial therapy should be initiated after urine culture and sensitivities are obtained.
- D. A renal biopsy should be performed.
- E. Preferred methods of collection for urine culture for this infant include midstream clean-catch and bag urine.

[51.2] An 8-month-old girl presents to the emergency department with fever and vomiting. Her serum white blood cell (WBC) count is elevated and urinalysis has 100 WBC per high-power field (unspun); the urine is positive for nitrates and leukocyte esterase. After urine culture results confirm the diagnosis of urinary tract infection, renal sonography and VCUG reveal that the infant has mild hydronephrosis and grade I vesicoureteral reflux on the right side. Which of the following statements is true?

- A. She will require surgical reimplantation of her right ureter.
- B. After completion of her present antibiotic course, antimicrobial prophylactic therapy is warranted.
- C. VCUG should be performed on a monthly basis.
- D. Subsequent urine specimen must be obtained only by suprapubic aspiration.
- E. Renal arteriography is indicated.

[51.3] A 6-month-old infant male you have never seen before presents to your clinic with an abdominal mass, discovered by his mother during the child's bath. On close physical examination you note the infant to have macroglossia and right-sided hemihypertrophy. This infant is likely to have:

- A. Down syndrome with duodenal atresia
- B. Alagille syndrome and biliary atresia
- C. Beckwith-Wiedemann syndrome with Wilms tumor
- D. Neurofibromatosis and abdominal neurofibromas
- E. Zellweger syndrome and hepatomegaly

[51.4] An 8-year-old boy presents with bedwetting three to four times per week for "as long as he can remember." He has a strong

stream of urine, is continent of urine during the day, and has not had frequent urinary tract infections. His physical examination is normal. Which of the following is the most appropriate next course of action?

- A. Urinalysis and urodynamic studies
- B. Reassurance; he has secondary nocturnal enuresis
- C. Use of enuresis alarm
- D. Desmopressin acetate may be administered every 6 hours to control enuresis
- E. Behavior modification that includes punishment for each wet night and a reward for each dry night

Answers

- [51.1] A. If this infant has a urinary tract infection, evaluation of the urinary tract anatomy and function is necessary. The preferred methods of urine collection include bladder catheterization and suprapubic bladder aspiration. Antimicrobial therapy should be started empirically while awaiting urine culture and sensitivity results.
- [51.2] B. Infants and children with VUR receive prophylactic antimicrobial therapy and close monitoring for infection, with urinalysis and urine culture at 3- to 4-month intervals. VUR is graded from I to V based on the degree of reflux. Higher-grade reflux is less likely to resolve spontaneously and is more likely to result in renal damage.
- [51.3] C. This infant with features of Beckwith-Wiedemann syndrome is at high risk of developing Wilms tumor, hepatoblastoma, and gonadoblastoma.
- [51.4] C. Nocturnal enuresis occurs in 15% of 5-year-old children and has a natural resolution rate of 15% per year. Males are more frequently affected and family history of nocturnal enuresis is

common. Initial evaluation includes thorough history of pattern of wetting, prior urinary tract infections, developmental, social, and emotional history. Physical examination includes palpation for kidneys, neurologic examination, and examination of the back looking for sacral dimple or hairy nevus. The enuresis alarm has a success rate of 70% to 90% and requires parental support and involvement. Pharmacological interventions include nighttime doses of oral imipramine or desmopressin acetate, administered orally or intranasally. Following use of desmopressin acetate, fluid intake is restricted to avoid water intoxication. Behavior modification does not include punishment.

CLINICAL PEARLS

Posterior urethral valves occurs exclusively in males.

Renal ultrasonography and VCUG are important in the evaluation of infants with urinary tract infection.

Boys with PUV are at risk for end-stage renal disease, even following appropriate therapy.

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◆ CASE 52

The mother of a healthy 8-year-old boy is concerned about his school performance. At the last parent-teacher conference, his teacher noted that he is easily distracted and routinely fails to complete both homework assignments and papers in the classroom. His mother states that at home he also has difficulty in completing tasks and fidgets constantly. Although the child is very talkative, it is difficult for him to answer questions clearly. His physical examination is significant only for his inability to sit still.

- ◆ What is the most likely diagnosis?
- ◆ What is the next step in management?

ANSWERS TO CASE 52: Attention Deficit Hyperactivity Disorder

Summary: An 8-year-old boy is easily distracted, and he cannot complete school work or stay on task at home. In addition he has hyperkinetic activity.

- ◆ **Most likely diagnosis:** Attention deficit hyperactivity disorder (ADHD).
- ◆ **Next step in management:** An evaluation for ADHD, which includes information regarding the child's behavior obtained from both the caregiver and from the classroom teacher.

Analysis

Objectives

1. Understand the basic evaluation of the child with symptoms of attention deficit hyperactivity disorder.
2. Know the various treatment options available for this condition.

Considerations

This 8-year-old boy exhibits classic behaviors of ADHD including easy distractibility, inability to focus and complete tasks, and excessive fidgeting (see also Case 40, Absence Seizures). The next step is a complete evaluation for ADHD, which includes obtaining information regarding the child's behavior from both the caregiver and the classroom teacher. If sufficient information is obtained to suggest the diagnosis of ADHD, the child should undergo developmental and psychological evaluation to assess for coexisting psychiatric conditions or learning disability. After the full evaluation is complete, target outcomes are identified and a comprehensive treatment plan is designed, including behavioral therapy, classroom modification, and possibly medication.

APPROACH TO ATTENTION DEFICIT HYPERACTIVITY DISORDER

Definition

Attention Deficit Hyperactivity Disorder: A condition consisting of developmentally inappropriate inattentiveness, hyperactivity, and impulsivity.

Clinical Approach

The *Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition* (DSM-IV) describes criteria in the categories of inattentiveness and hyperactivity/impulsivity necessary to make the diagnosis of ADHD. It is estimated that ADHD affects 3% to 5% of school-aged children. The risk of finding ADHD in a primary relative of a patient diagnosed with ADHD is 25%; 59% to 81% of monozygotic twin pairs can be diagnosed when one has been identified as having ADHD. The pathophysiology for this condition remains to be elucidated but research suggests that decreased activity of certain brain regions in the frontal lobes may be responsible.

The inattention criteria of ADHD include making careless mistakes, having difficulty paying attention, not listening, not following through on tasks, avoiding sustained mental effort, frequently losing things, easy distractibility, and forgetfulness. The hyperactivity criteria include frequent fidgeting, being out of his/her seat frequently, running and climbing excessively, having difficulty playing quietly, always being "on the go," and often talking excessively. The impulsivity criteria include often blurting out answers, having difficulty waiting for his/her turn, and interrupting or intruding frequently.

The diagnosis of ADHD is subdivided into 3 types: ADHD/I which requires at least 6 of 9 inattention behaviors; ADHD/HI which requires at least 6 of 9 hyperactive/impulsive behaviors, and; ADHD/C which requires at least 6 of 9 in both the inattention and hyperactive/impulsive behaviors. Children must demonstrate symptoms for at least 6 months in two or more settings, and have resultant impairment of function from these behaviors.

Behavioral information is obtained from caregivers and classroom teacher(s). ADHD-specific checklists, such as the Conners Teacher Rating Scale, the Conners Parent Rating Scale, or the Barkley's School Situation Questionnaire, are useful tools to elicit information regarding behaviors of ADHD. Alternatively, information can be surmised via narratives or descriptive interviews.

Psychological and developmental testing is part of the evaluation of a child with ADHD because **coexisting psychological and learning disorders occur frequently**. Common coexisting psychiatric conditions include oppositional-defiant disorder (35.2%), conduct disorder (25.7%), anxiety disorder (25.8%), and depressive disorder (18.2%). An estimated 12% to 60% of children with ADHD have **concurrent learning disorders** and may benefit from special education services.

Management of the child with ADHD includes the implementation of a long-term treatment program in collaboration with caregivers and teachers. The care plan includes setting specific attainable goals such as increasing independence, decreasing disruptive behavior, improving academic performance and task completion, and improving relationships with family members, teachers, and peers. **Behavioral modification techniques** can be used alone or in conjunction with pharmacologic therapy. Positive reinforcement such as providing rewards or privileges and negative consequences such as time-out or withdrawal of privileges are used to reinforce appropriate behavior. Small class size, structured work, stimulating schoolwork, and appropriate seating arrangements can be helpful adjuncts to decrease disruptive behaviors in the classroom. Children with ADHD benefit from learning to improve organizational skills. Medications are often used to assist in the treatment of ADHD, and stimulant medications are generally considered first-line pharmacologic therapy; these agents are effective in decreasing ADHD behaviors and in improving overall function. **Commonly used stimulant medications** include **methylphenidate** and **dextroamphetamine**, which exist in short-, intermediate-, and long-acting forms. Atomoxetine (Strattera) is a non-stimulant, selective nor-epinephrine reuptake inhibitor approved for use in adults, and recently became available for children. Tricyclic antidepressants and bupropion.

often prescribed under the direction of a psychiatrist or neurologist, also decrease behaviors of ADHD.

*Long-term sequela of this condition includes poor peer relationships, poor fine motor control, and increased risk of accidents. Adolescents with ADHD may develop **substance abuse problems** as a comorbid condition, but this comorbidity **does not seem to be related to treatment** of the condition **with stimulant medication**. Approximately 50% of children with ADHD function well in adulthood, but the remaining demonstrate continued symptoms of inattention and impulsivity.*

Comprehension Questions

- [52.1] An 8-year-old boy presents because his mother is concerned that he has ADHD. At home he is always restless, never seems to pay attention, and is always losing things. In the office, the child is cooperative and has a normal examination. The next step in management is to:
- A. Give the child a 2-week trial of stimulant medication.
 - B. Obtain further information from the parents and teachers.
 - C. Send the child for psychological assessment.
 - D. Send the child for psychiatric evaluation.
 - E. Reassure the child's mother that this is age appropriate behavior.
- [52.2] A 7-year-old boy is brought to the office because he frequently appears distracted. His mother notes that he daydreams "all of the time" and when he is daydreaming he does not respond to her. She describes these as short episodes lasting several seconds that occur many times a day. When he is not daydreaming, he is attentive and can complete tasks. His behavior in class is not disruptive. The next step in management is to:
- A. Obtain further information from his parents and teachers by using the Conners rating scales.
 - B. Send the child for an electroencephalogram.

- C. Send the child for psychological assessment.
- D. Reassure the child's mother that this is age-appropriate behavior.
- E. Begin a program of behavioral modification.

[52.3] A 14-year-old child was recently diagnosed with ADHD. His evaluation for coexisting psychiatric disorders is most likely to identify which of the following disorders?

- A. Schizophrenia
- B. Pervasive developmental disorder
- C. Posttraumatic stress disorder
- D. Oppositional-defiant disorder
- E. Bipolar disorder

[52.4] An 8-year-old boy has completed the initial evaluation for ADHD. Information from his parents and his teachers demonstrated that he meets 7 of the 9 criteria for inattention and also has many impulsive behaviors. The next step in management is to:

- A. Give the child a 2-week trial of stimulant medication.
- B. Arrange for special education placement.
- C. Send the child for a complete psychoeducational assessment.
- D. Send the child for an electroencephalogram.
- E. Reassure the child's mother that this is age appropriate behavior.

Answers

[52.1] **B.** A thorough physical examination (with emphasis on the neurologic component) is completed to identify any soft signs of neurologic conditions. If none are found, this child should receive a complete evaluation for ADHD. A diagnosis is considered if the child has ADHD-specific behaviors in two or more settings. Information is obtained from caregivers and teachers regarding ADHD-specific behaviors.

- [52.2] B. This child does not fit the classic pattern of ADHD. These episodes of "daydreaming," which last several seconds, are consistent with petit mal or absence seizures and initial evaluation for these conditions includes obtaining an electroencephalogram.
- [52.3] D. Common coexisting psychiatric conditions include oppositional-defiant disorder (35.2%), conduct disorder (25.7%), anxiety disorder (25.8%), and depressive disorder (18.2%).
- [52.4] C. Prior to developing a management plan, the child is assessed for coexisting psychiatric and learning disorders (psychoeducational testing). After this is complete, management can include stimulant medication, behavioral modification, and therapy appropriate for coexisting conditions, if applicable.

CLINICAL PEARLS

The diagnosis of ADHD is considered in children who have specific behaviors in two or more settings, such as home and school or work.

Children with ADHD frequently have coexisting psychiatric or learning disorders including oppositional-defiant disorder, conduct disorder, anxiety disorder, and depression.

The most common pharmacologic agents used for ADHD are methylphenidate and dextroamphetamine.

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◆ CASE 53

A previously healthy 12-year-old boy presents to your office with right knee pain of 3 weeks' duration. He is an athletic adolescent playing basketball and running track. He denies any recent trauma. He describes increased pain when he is running or jumping. He has a completely normal physical examination except for mild edema and tenderness over his right tibial tubercle.

- ◆ What is the most likely diagnosis?
- ◆ What is the next step in management?

ANSWERS TO CASE 53: Osgood-Schlatter Disease

Summary: An adolescent male presents with knee pain that increases with activity and tenderness and swelling of his tibial tubercle of the affected knee.

- ◆ **Most likely diagnosis:** Osgood-Schlatter disease.
- ◆ **Next step in management:** For most patients rest after activity, and in severe cases, immobilization of the

Analysis

Objectives

1. Know the presentation and treatment of children with Osgood-Schlatter disease.
2. Be familiar with the differential diagnosis of bone pain and extremity swelling in children.

Considerations

A thorough history is critical to determine whether other signs and symptoms are present in this adolescent with knee pain and swelling. His lack of constitutional signs and symptoms such as fever, redness, fatigue, weight loss, night sweats, bruising, and cough are important clues to the relatively benign nature of this condition. If any of these signs or symptoms are present, evaluation for more serious, potentially life-threatening conditions, such as malignancy (such as leukemia or osteosarcoma), is appropriate.

APPROACH TO OSGOOD-SCHLATTER DISEASE

Definitions

Osgood-Schlatter disease: A condition of painful, inflammation of the tibial tubercle.

Clinical Approach

The **knee pain of Osgood-Schlatter disease** is caused by **inflammation of the tibial tubercle**, an extension of the tibial epiphysis or growth plate. Although ossification centers begin to form in children between the ages of 9 and 13 years, ossification is not completed until the ages of 15 to 17 years. Patients with Osgood-Schlatter disease are usually males who present in late childhood through early adolescence. **Repetitive motions of running and jumping** cause traction and microstress fractures to the developing area, resulting in inflammation and bony changes.

The diagnosis of Osgood-Schlatter disease can be made clinically in an older child or adolescent. The patient complains of **knee pain that increases with exercise**. They usually have no history of trauma to the affected knee. The patient has edema and tenderness of the tibial tuberosity.

Differential diagnosis of knee pain in adolescents includes patellofemoral stress syndrome, patellar tendonitis, iliotibial band friction syndrome, slipped capital femoral epiphysis, trauma, tumor, and septic joint. Patellofemoral stress syndrome, also common in athletes, causes chronic, dull, nonlocalizing knee pain in children and adults. *Jumper's knee* or patellar tendonitis is caused by microscopic injury to the patellar tendon. Most affected patients complain of chronic, anterior knee pain and have tenderness of the inferior portion of the patella. Iliotibial band friction syndrome causes lateral knee pain in runners. **Slipped capital femoral epiphysis (SCFE)** occurs in **adolescents during the growth spurt** and generally leads to a **limp and pain in the groin or thigh**; however, hip pain may be referred to the knee. Examination of a patient with SCFE reveals limited hip flexion, internal rotation, and abduction. Radiographs of the hip reveal widening of the femoral epiphysis and osteopenia. Patients with SCFE are at great risk for avascular necrosis of the femoral epiphysis and should be evaluated by an orthopedic surgeon.

Initial treatment of Osgood-Schlatter disease consists of **rest** or decreasing the amount of activity. Use of ice after exercise and use of non-steroidal antiinflammatory agents may aid in providing relief. In severe cases, immobilization of the knee and the use of crutches may be required. Symptoms may recur until ossification is complete. Long-term prognosis is excellent.

Comprehension Questions

- [53.1] A 12-year-old boy comes to your office complaining of right knee pain that is worse after he runs. His pain started 1 week after he joined the track team. Upon examination he has tenderness of the tibial tubercle. Which of the following statements is true?
- A. The most likely diagnosis is slipped capital femoral epiphysis.
 - B. Initial therapy consists of immobilization.
 - C. The most likely cause for his pain is a stress fracture.
 - D. Use of a properly fitted orthotic device in his left shoe will allow him to continue running while alleviating his discomfort.
 - E. Decreasing his activity should alleviate the pain.
- [53.2] A 13-year-old boy comes to your office with 1 week of limping and right knee pain. Upon examination, the patient is found to be overweight with diminished ability to flex and internally rotate his right femur. The next step is to:
- A. Instruct the patient to rest and apply ice to the affected area.
 - B. Prescribe daily oral nonsteroidal antiinflammatory agents until the pain is resolved.
 - C. Order a magnetic resonance imaging to evaluate the adolescent's knee and hip.
 - D. Arrange for an orthopedic surgery consultation.
 - E. Prescribe a short course of oral steroids to decrease inflammation and recommend weight loss to avoid recurrence.
- [53.3] A 14-year-old girl presents with right knee pain. She states that the pain has occurred intermittently over the past 2 months and is not associated with exercise. Her mother has questions about sunscreen use, as the patient had severe "sunburn" on her face across her cheeks and nose 3 weeks ago. The patient also notes that she has not been feeling well and is increasingly tired recently. Upon examination her knee appears normal and has

good range of motion and her gait is normal. The next step in management is to:

- A. Prescribe ibuprofen and recommend daily sunscreen use.
- B. Obtain radiographs of the affected knee.
- C. Obtain further history, specifically regarding fever, weight loss, other rashes, and other arthritis.
- D. Recommend the use of a knee immobilizer.
- E. Arrange for an emergent orthopedic consultation for evaluation of possible slipped capital femoral epiphysis.

[53.4] A 15-year-old boy presents with right knee pain. Upon examination he is unable to bear weight on the affected joint. The knee is tender, edematous, warm, erythematous, and has significantly diminished range of motion. The next step in his evaluation is to:

- A. Obtain a thorough history including sexual history.
- B. Prescribe a course of systemic steroids.
- C. Administer intraarticular steroids to decrease inflammation.
- D. Prescribe antiinflammatory agents.
- E. Arrange for an outpatient orthopedic surgery consultation.

Answers

[53.1] **E.** This adolescent's history is consistent with Osgood-Schlatter disease. Initial therapy includes ice after exertion and rest.

[53.2] **D.** The most likely diagnosis is slipped capital femoral epiphysis. The patient is put on bed rest and orthopedic surgery consultation is required.

[53.3] **C.** This patient has complaints of joint pain and malaise and had a facial rash consistent with the malar rash found in systemic lupus erythematosus (SLE). The next step is to obtain a more detailed history of other signs and symptoms of autoimmune disease, medication use (drug-induced SLE), and travel history (tick exposure for Lyme disease).

- [53.4] A. This patient has signs and symptoms of a septic joint. *Neisseria gonorrhea* is a major cause of septic arthritis in sexually active adolescents and young adults. If the diagnosis of septic arthritis is suspected, immediate orthopedic evaluation and intravenous antimicrobial therapy are warranted.

CLINICAL PEARLS

- ◆ Osgood-Schlatter disease is found exclusively in young adolescents prior to closure of the growth plate.
- ◆ Edema and tenderness of the tibial tuberosity are classic features of Osgood-Schlatter disease.
- ◆ Slipped capital femoral epiphysis can cause limping and is most common in overweight adolescents.

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◆ CASE 54

A 2-week-old male infant presents with a “twisted neck.” He was the product of a term gestation with a birth weight of 4550 g, and was born via spontaneous vaginal delivery. The delivery was difficult because of the infant’s size. On physical examination, the infant’s head is tilted toward the right side and the chin is rotated toward the left side. The right sternocleidomastoid muscle has a palpable, firm mass.

◆ What is the most likely diagnosis?

◆ What is the best treatment?

ANSWERS TO CASE 54: Torticollis

Summary: A 2-week-old male, large-for-gestational-age infant with the history of having a difficult delivery and torticollis. Upon examination the infant has a palpable mass in the sternocleidomastoid muscle.

- ◆ **Most likely diagnosis:** Muscular torticollis.
- ◆ **Best treatment:** Initial therapy consists of passive stretching of the sternocleidomastoid muscle.

Analysis

Objectives

1. Understand the common causes of torticollis.
2. Recognize the differences in treatment of torticollis based on the etiology.

Considerations

This 2-week-old infant is large for gestational age and had a difficult delivery because of size. He has torticollis, with his head tilted toward the right and his chin rotated toward the left, owing to decreased range of movement of the right sternocleidomastoid muscle caused by the mass. Large infants with difficult deliveries are at increased risk for this type of muscular torticollis, because of injury to the sternocleidomastoid muscle during delivery.

APPROACH TO TORTICOLLIS

Definitions

Klippel-Feil syndrome: Includes congenital fusion of portions of the cervical vertebrae, restricted neck movement, short neck, and

low hairline. Associated features include Sprengel deformity (see below) and structural urinary tract abnormalities.

Sandifer syndrome: Gastroesophageal reflux, hiatal hernia, and posturing of the head.

Sprengel deformity: Congenital elevation of the scapula.

Clinical Approach

Torticollis is identified in a patient with an obviously **twisted neck, the head tilted toward one side, and the chin tilted toward the opposite side**. Torticollis has many etiologies. The most common cause is of muscular origin as a result of injury and contracture of the sternocleidomastoid muscle. Infants with torticollis present at or soon after birth; they may have had birth trauma and usually have a palpable, firm mass within the affected muscle. Radiography of the cervical spine is generally performed to investigate the presence of possible **vertebral malformations**.

In the absence of congenital cervical spine abnormalities, **initial therapy involves gentle stretching of the sternocleidomastoid muscle** by moving the head toward a neutral position. This stretching is performed by the caregivers with frequent follow up of the infant by the healthcare provider and possibly a physical therapist. If the condition persists beyond the first few months of life, referral to an orthopedic surgeon is indicated. Without intervention, persistent torticollis can lead to facial asymmetry.

Congenital malformations of the cervical vertebrae can cause torticollis. In these infants gentle stretching does not improve the condition and may result in **spinal cord injury**. Radiography demonstrates spinal anomalies such as hemivertebrae or areas of vertebral fusion or subluxation. Klippel-Feil syndrome can present as torticollis and includes congenital fusion of portions of the cervical vertebrae, restricted neck movement, short neck and low hairline, Sprengel deformity, and structural urinary tract abnormalities.

Torticollis occurring beyond infancy requires cautious evaluation. Two of the more common causes of torticollis in this age group are **trauma and inflammation**. Traumatic torticollis can occur following injury to the cervical vertebrae with subsequent fracture or atlanto-occipital, atlantoaxial, or C2-C3 subluxation or injury to the cervical

musculature. These patients will have a history of significant trauma and radiographic evaluation of the cervical spine is essential. In contrast, inflammatory torticollis often follows an upper respiratory illness. These patients will have muscular pain and tenderness and a normal neurologic evaluation. Other inflammatory causes include cervical lymphadenitis, retropharyngeal abscess, cervical vertebral osteomyelitis, rheumatoid arthritis, and upper lobe pneumonia. Children with cervical lymphadenitis are generally febrile and have palpable, tender cervical lymph nodes. Patients with retropharyngeal abscess present with dysphagia or dyspnea and may have drooling or airway stridor secondary to compression.

A variety of neurologic conditions cause torticollis including visual disturbances, dystonic reactions to medications, spinal cord or posterior fossa tumors, syringomyelia, Wilson disease, dystonia musculorum deformans, and spasmodic torticollis. The patient's medication history may reveal a medication such as phenothiazine, haloperidol, and metoclopramide that can cause a dystonic drug reaction. A careful physical examination with particular attention to the neurologic examination may identify subtle findings associated with one of these neurologic causes of torticollis.

Other miscellaneous causes of torticollis include cervical disc calcification, Sandifer syndrome, benign paroxysmal torticollis, bone tumors, soft-tissue tumors, and hysteria.

Comprehension Questions

- [54.1] A 3-month-old male infant presents with intermittent torticollis. He was a term baby with a normal prenatal course and uneventful delivery. He frequently spits up after feeding and has had one episode of pneumonia. The next step in management is to:
- A. Begin gentle stretching of the sternocleidomastoid muscle.
 - B. Evaluate the infant for gastroesophageal reflux.
 - C. Refer the infant for orthopedic evaluation.
 - D. Obtain radiographs of the cervical spine.
 - E. Observe and, if the condition persists, refer the infant for orthopedic evaluation.

- [54.2] A 5-month-old female infant presents to the emergency department with sudden onset of torticollis and with some facial grimacing. The infant has been alert and interactive during this time. The infant has been doing well and gaining weight for the last month after having been prescribed ranitidine and metoclopramide for gastroesophageal reflux disease diagnosed by her primary care physician. Family history is negative for epilepsy. Which of the following statements is true?
- A. The infant most likely is having a partial-complex seizure and needs an immediate electroencephalograph.
 - B. A lumbar puncture for cell count, glucose, and protein is warranted.
 - C. Measurement of serum electrolytes and glucose is unnecessary.
 - D. The infant is most likely having a dystonic reaction to one of her medications.
 - E. A magnetic resonance image (MRI) of the cervical spine is likely to show a congenital abnormality.
- [54.3] A 4-year-old boy presents with torticollis, fever, and a sore throat. He complains of difficulty swallowing but has not been drooling. He denies headache and dyspnea and has continued to be playful. Physical examination reveals edema of the right posterior pharynx. The best next step in management is to:
- A. Examine his cerebrospinal fluid.
 - B. Obtain imaging studies of the airway and soft tissues of the neck.
 - C. Send a throat culture and begin antibiotic therapy based on the results of the culture.
 - D. Begin oral penicillin.
 - E. Prescribe ibuprofen and neck stretching exercises.
- [54.4] A 1-week-old female infant presents with her new adoptive parents. The family complains that the child seems to have a twisted neck. The limited information they can provide includes an unremarkable prenatal history but "delivery was almost a

c-section because the baby was lying sideways.” The infant has been feeding well and has had appropriate urine and stool output for the last 24 hours that the family has had the child. Physical examination is significant for torticollis. Which of the following statements is true?

- A. This infant is at significant risk for aspiration pneumonia.
- B. The parents should immediately begin a regimen of gentle stretching of the neck.
- C. Radiographs of the cervical spine should be obtained.
- D. Immediate orthopedic consultation should be arranged.
- E. Immediate neurologic consultation should be arranged.

Answers

- [54.1] **B.** This infant most likely has gastroesophageal reflux with intermittent torticollis or Sandifer syndrome. The infant has a history of frequently spitting up and has had pneumonia (possibly aspiration), which indicates that the child has gastroesophageal reflux. Infants with Sandifer syndrome have abnormal head posturing associated with reflux. The head movements are thought to occur either in response to pain or in order to protect the airway.
- [54.2] **D.** This infant has sudden onset of the dystonic features of torticollis and facial grimacing. Although it is most likely a dystonic reaction to metoclopramide, initial evaluation for seizures including measurement of serum electrolytes, glucose, and calcium is indicated. Administration of diphenhydramine may rapidly reverse this drug-induced dystonia. An MRI is unlikely to demonstrate a cervical abnormality since the onset of the condition was abrupt. Analysis of the cerebrospinal fluid as a first step is unlikely to result in obtaining an etiology to this type of torticollis.
- [54.3] **B.** This child has signs and symptoms of having a retropharyngeal cellulitis or abscess. Patients with retropharyngeal abscess may have dysphagia, drooling, stiff neck, dyspnea, or airway

stridor. Physical finding include a midline or unilateral swelling which may progress to become a fluctuant mass. Management includes antibiotic therapy and incision and drainage of the abscess. Computerized tomography sometimes is helpful in early identification of abscess formation.

- [54.4] C. This child appears to have had a difficult delivery, making muscular torticollis likely. However, cervical spine abnormalities must be excluded. If radiography of the cervical spine is normal, the parents can begin gentle stretching to move the head in a neutral position. If the condition persists, orthopedic referral is necessary.

CLINICAL PEARLS

Muscular torticollis is most commonly found in infants at or after birth as a result of trauma to the sternomastoid muscle. Sandifer syndrome is characterized by gastroesophageal reflux and posturing of the head. Drug-induced dystonia is most frequently caused by phenothiazine, metoclopramide, and haloperidol.

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◆ CASE 55

A healthy 2-week-old girl presents with yellow discharge from her left eye. Her mother had prenatal care starting at the second month of pregnancy. The prenatal course was uncomplicated and the baby was born by spontaneous vaginal delivery with a birth weight of 3300 g. The baby was discharged within 48 hours of birth. Within the first few days of life, mother noted that the baby had increased tear production in the left eye. During the past 3 days a yellow discharge had been present. Examination of the infant's eyes revealed that red reflexes are present and normal bilaterally, pupils are equal and reactive to light, and the scleral conjunctiva are not injected. A mucopurulent discharge is present on the left side.

◆ What is the most likely diagnosis?

◆ What is the next step in management?

ANSWERS TO CASE 55: Dacryostenosis

Summary: A 2-week-old infant has excessive unilateral tearing which progresses to mucopurulent eye discharge. The scleral conjunctivae are normal.

- ◆ **Most likely diagnosis:** Dacryostenosis (congenital nasolacrimal duct obstruction).
- ◆ **Next step in management:** Initial treatment involves nasolacrimal massage and cleansing of the eyelids. When mucopurulent discharge is present, topical antibiotics are added.

Analysis**Objectives**

1. Know about excessive tearing in the newborn period.
2. Know the differential diagnosis of conjunctivitis in the newborn period.

Considerations

This infant had excessive tear production that later became a mucopurulent discharge. The remainder of her ophthalmologic examination is normal. Of particular note is that the conjunctiva is not inflamed and the cornea is not involved. Initial treatment includes topical antibiotic therapy and nasolacrimal duct massage two to three times daily with warm water eyelid cleansing.

APPROACH TO DACRYOCYSTITIS**Definitions**

Chemosis: Swelling and fluid collection in the membranes lining the eyelids and conjunctiva.

Dacryostenosis: A common condition in neonates and infants caused by narrowing or blockage of the tear duct.

Clinical Approach

The evaluation of a newborn with mucopurulent eye discharge includes examination of the conjunctivae, cornea, and pupils and assessment for the presence of red reflexes. In cases of dacryostenosis, the conjunctiva, cornea, and pupils are normal. Infants with **dacryostenosis** have **increased tearing which can be unilateral or bilateral**.

Dacryostenosis occurs in 2% to 6% of newborns and is caused by a **failure of canalization of the nasolacrimal duct**. Conservative management includes massage of the nasolacrimal duct two to three times daily along with warm water eyelid washes. Gentle massage of the nasolacrimal duct leads to expulsion of the mucoid contents proximal to the obstruction. When the discharge becomes mucopurulent, a short course of topical, ophthalmic antibiotics is given. Ninety-six percent of cases of dacryostenosis resolve spontaneously, generally by 1 year of age. In uncomplicated cases, if spontaneous resolution does not occur by this time, the pediatric ophthalmologist will probe the nasolacrimal duct. If symptoms persist, **nasolacrimal ductal tubes may be placed or reconstructive surgery may be required**. If dacryocystitis occurs systemic antimicrobial therapy is indicated.

Infantile glaucoma occurs in 1 in 100,000 births and has a **classic triad** of features including **tearing, photophobia, and blepharospasm**. Infantile glaucoma may be isolated or may occur with various conditions including congenital rubella, neurofibromatosis type 1, mucopolysaccharidosis I, Lowe oculocerebrorenal syndrome, Sturge-Weber syndrome, Marfan syndrome, and several chromosomal abnormalities. The increased intraocular pressure can lead to expansion of the globe and cornea causing damaged associated with glaucoma.

If conjunctivitis is present (Figure 55-1), appropriate evaluation is critical. Ophthalmia neonatorum or conjunctivitis occurring in infants younger than 4 weeks of age is common, and has multiple etiologies and varying outcomes, from complete resolution to blindness. Physical findings of ophthalmia neonatorum include erythema and chemosis of the conjunctiva, edema of the eyelids, and discharge that may be purulent or serosanguineous. The etiology of the conjunctivitis can be determined from the timing, quality, and quantity of the discharge.



Figure 55-1. Infant with conjunctivitis. (Courtesy of Kathryn H. Musgrove, MD).

Topical erythromycin, tetracycline, or silver nitrate used for prophylaxis of gonococcal ocular infection may cause a chemical conjunctivitis that generally begins between 6 and 12 hours after birth and resolves by 48 hours of life. **Common pathogens for conjunctivitis in the neonatal period include *Neisseria gonorrhea* and *Chlamydia trachomatis*.** The incubation periods differ slightly with gonococcal infection presenting between the second and fifth days of life, and chlamydia-

mal infection becoming apparent between 5 and 14 days of life. At the onset of ocular infection with *Neisseria gonorrhea*, a serosanguineous discharge is present, and later the discharge becomes purulent. Inflammation of the conjunctiva, eyelids, and cornea develops and profound complications include corneal ulceration, iridocyclitis, anterior uveitis, and exophthalmos. Intracranial antimicrobial treatment with ceftriaxone or cefotaxime in combination with frequent saline eye washes is required. With erythrogenic exanthema, inflammation of the facial skin (erythema) is prominent and may be mild or severe. A purulent discharge may be present. A 7-day course of oral erythromycin or clarithromycin therapy. Oral erythromycin given in the usual dose may be toxic in infants with hepatic dysfunction. A baseline or initial serum bilirubin should be obtained prior to use.

Comprehension Questions

- [55.1] A 6-month-old male infant with right-sided dacryostenosis presents with mucopurulent discharge and an indurated, erythematous, tender 1-cm mass on the right side just below his nasal bridge. He has a temperature of 101°F (38.3°C). The next step in therapy is to:
- A. Administer intravenous antibiotic therapy.
 - B. Begin a course of topical antimicrobial treatment.
 - C. Recommend massage and warm compresses to the affected area.
 - D. Incise and drain the area.
 - E. Refer the child for an outpatient ophthalmologic evaluation.
- [55.2] A 12-hour-old male infant presents with bilateral conjunctivitis. The next best step in management is to:
- A. Administer prophylaxis with topical erythromycin.
 - B. Send the eye discharge for culture and start antimicrobial therapy based on culture results.
 - C. Start saline eye washes.
 - D. Begin systemic antibiotic therapy with erythromycin.
 - E. Begin systemic antibiotic therapy with ceftriaxone.

[55.3] A 2-week-old male infant presents to the clinic with his foster mother because he has bilateral purulent eye discharge. His prenatal history is unknown. The examination demonstrates significant tarsal conjunctivitis and eye discharge. Which of the following statements is true?

- A. Initial therapy includes administration of intramuscular ceftriaxone.
- B. The organism most likely to be responsible for this infant's conjunctivitis also causes pneumonia in infants aged 1 to 3 months.
- C. Immediate referral to a pediatric ophthalmologist is warranted.
- D. Warm compresses and gentle massage are first-line therapies.
- E. Topical antimicrobial therapy is preferred.

[55.4] A 4-month-old male infant presents with excessive tearing on the right side. His mother states he becomes irritable in bright light and calms only in a darkened room. On physical examination he appears to have asymmetry of his eyes with the right eye appearing to be larger than the left. Which of the following statements is true?

- A. Warm compresses and gentle massage are first-line therapy.
- B. In most cases, treatment is nonsurgical.
- C. The infant has the classic features of Down syndrome.
- D. Immediate systemic antibiotic therapy will reduce complications.
- E. Immediate referral to a pediatric ophthalmologist is warranted.

Answers

[55.1] A. This infant has dacryocystitis and needs immediate treatment with systemic antibiotics. After initial therapy, surgical

treatment is usually necessary. Topical antimicrobial therapy is inadequate.

- [55.2] B. Conjunctivitis presenting in the first few days of life is most likely caused by chemical irritation. Laboratory evaluation of the eye discharge is performed; treatment usually can be withdrawn and is based upon culture results.
- [55.3] B. A chlamydial infection is the most likely cause of conjunctivitis in this 2-week-old infant. *Chlamydia trachomatis* causes pneumonia in infants, generally between the ages of 1 and 3 months. Infants present with cough, tachypnea, and rales and are afebrile. A complete blood count might show eosinophilia. A 2- to 3-week course of oral erythromycin is given.
- [55.4] E. With the history of excessive tearing and photophobia and examination finding of corneal enlargement, this infant should be evaluated immediately for congenital glaucoma.

CLINICAL PEARLS

Ninety-six percent of infants with dacryostenosis have spontaneous resolution of their symptoms by 1 year of age.

Topical erythromycin, tetracycline, and silver nitrate are effective for prophylaxis against gonococcal eye infection but not chlamydial infection.

Ophthalmologic complications of congenital rubella include glaucoma, cataracts, and retinopathy.

Prophylactic use of oral erythromycin for infants of mothers with untreated chlamydial infection is generally not indicated. The efficacy in this situation has not been established and oral erythromycin use in neonates has been linked to infantile hypertrophic pyloric stenosis.

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◆ CASE 56

A 15-month-old boy is brought in for evaluation because his parents are concerned about his language development. He does not speak any recognizable words, has never made babbling sounds such as “baba” or “dada,” does not follow verbal commands, and does not respond to his name. The child is the product of an uncomplicated full-term vaginal delivery. He has neither been hospitalized nor had frequent illnesses. He sat without support at 6 months and began walking at 12 months. He is active in the examination room, but does not respond to his name nor does he respond to verbal cues from his mother. He is a well-developed, well-nourished child with a seemingly normal physical examination.

◆ **What is the most likely diagnosis?**

◆ **What is the next step?**

ANSWERS TO CASE 56: Severe Hearing Loss

Summary: A 15-month-old otherwise healthy boy has severe language delay. His motor development is normal.

- ◆ **Most likely diagnosis:** Hearing loss.
- ◆ **Next step:** Audiologic evaluation.

Analysis

Objectives

1. Understand the major types of hearing loss.
2. Be aware of common causes of hearing loss.

Considerations

This 15-month-old boy has never made babbling sounds such as “baba” and “dada,” which are the normal precursors to the development of language. Most infants are able to make a string of consonant sounds by 9 months of age. His history and physical examination do not lead to a specific reason for this speech delay, that is, global developmental delay, syndromic features, or history of prematurity with associated morbidity. After a thorough history and physical examination, the child would benefit from a formal audiologic evaluation.

Definitions

Conductive hearing loss (CHL): Hearing loss caused by disorders of the outer ear, such as atresia of the external auditory canal and otitis externa, or disorders of the middle ear, such as otitis media and cholesteatoma.

Retrocochlear (central) hearing loss: Hearing loss caused by deficits in the auditory nerve or central auditory nervous system.

Sensorineural hearing loss (SNHL): Hearing loss caused by disorders of the cochlea such as damage from infection, noise, ototoxic agents, or genetic defects.

APPROACH TO HEARING LOSS

Hearing can be divided into several categories:

- The normal hearing range has a threshold of 0 to 15 decibels (dB)
- Slight hearing loss has a threshold of 16 to 25 dB
- Mild hearing loss in the range of 25 to 30 dB results in the inability to hear some speech sounds
- Moderate hearing loss occurs if the threshold is between 30 and 50 dB and most speech at normal levels cannot be discerned
- Severe hearing loss occurs at the threshold of 50 to 57 dB, while profound hearing loss is defined as greater than 70 dB

One to 2 newborns per 1000 live births will have moderate to profound bilateral sensorineural hearing loss.

SNHL can be congenital or can be acquired at any time during life. Approximately half of the cases of SNHL are a result of genetic factors, with autosomal dominant inheritance accounting for approximately 10% of cases and autosomal recessive inheritance accounting for 38% of cases. The hearing loss may be isolated or may occur in conjunction with other anomalies as part of a syndrome. The most common autosomal dominant syndromes associated with SNHL are **Waardenburg syndrome** (types I and II) and **branchiootorenal syndromes**. **Waardenburg syndrome** consists of **partial albinism (often a white forelock), deafness, lateral displacement of the inner canthi, medial flare of the eyebrows, and a broad nasal bridge and mandible**. **Branchiootorenal syndrome** consists of hearing impairment, preauricular pits, and branchial fistulae. Other entities associated with SNHL include **Alport syndrome** (nephritis and progressive renal failure, neurosensory hearing loss, and ocular abnormalities), **Down syndrome**, **neurofibromatosis**, **Jervell and Lange-Nielsen (prolonged Q-T) syndrome**, and **Hunter-Hurler syndrome**. Ophthalmic abnormalities and malformations of the external auditory system and

metabolic, neurologic and musculoskeletal disorders may be associated with SNHL. Some congenital craniofacial anomalies can result in CHL.

Prenatal cytomegalovirus (CMV) infection is the most common infectious cause of congenital SNHL, but this virus also can cause hearing loss later in infancy and childhood. Toxoplasmosis, rubella, and syphilis also can lead to congenital SNHL. Hence, ongoing hearing evaluations in patients with these infections are important. Postnatal infections commonly associated with SNHL include group B streptococcal sepsis and *Streptococcus pneumoniae* meningitis. Uncommon causes include parvovirus, Lyme disease, and varicella. *Haemophilus influenzae* meningitis, mumps, measles and rubella were common causes of acquired SNHL prior to the availability of current vaccines.

Pharmacologic and other chemical exposures can lead to SNHL. Aminoglycosides, loop diuretics, chemotherapeutic agents (cisplatin), lead, arsenic, and quinine may cause SNHL with either in utero or postnatal exposure. Other causes of SNHL include temporal bone fractures, head trauma, extracorporeal membrane oxygenation (ECMO), radiation, and prolonged exposure to loud noises.

Early diagnosis of hearing impairment can have a significant impact on the development of communication skills. Adequacy of hearing is evaluated during well-child visits by asking parents about their baby's response to sounds and early language development. In the past, formal hearing evaluation of infants was limited to children with known risk factors for hearing loss, but this approach identified only about 50% of children with severe hearing impairment by 14 months of age. The American Academy of Pediatrics (AAP) now formally endorses universal newborn hearing screening via otoacoustic emissions (OAE) or auditory brainstem-evoked responses (ABR). The goal of universal screening is diagnosis of hearing loss prior to 3 months of age and intervention before 6 months of age with the belief that early intervention results in enhanced communication skills and better academic performance. Several states now require universal hearing tests.

Hearing screening can be performed by various methods depending on the child's developmental level and degree of hearing loss. ABR testing uses measurements of electrophysiologic response and does not require cooperation from the patient; it is useful for testing newborns. Although OAE can also be used for testing newborns, OAEs are absent if the threshold for hearing is above 30 to 40 dB. Infants, toddlers, and

young preschool children can be assessed via visual reinforcement audiometry, behavioral audiometry, or play audiometry; these methods reveal information specific to each ear. In cooperative children air conduction audiometry can be performed using headphones and pure tones between 250 to 8000 Hz. The same sounds are presented via oscillator, usually on the mastoid, thus evaluating bone conduction as well.

After the type and degree of hearing loss have been determined, a treatment plan is established. For instance, middle ear effusion may be treated medically or require surgical intervention and hearing aids may be useful for patients with ear malformations. All infants and children with SNHL require careful evaluation in conjunction with an audiologist and speech pathologist. Patients with mild to moderate hearing loss can benefit from hearing aids, which can be fitted in infants as young as 2 months of age. With severe and profound hearing loss, conventional therapy includes a combination of hearing aids, sign language, and lip reading, in addition to appropriate educational surroundings. Cochlear implantation is a surgical treatment option that has recently been approved for selected children older than age 2 years.

Comprehension Questions

[56.1] A mother brings her 26-month-old son to the clinic because she is concerned about his hearing. She notes that over the past few weeks, she has had to speak more loudly for him to respond. He has greater than a 50-word vocabulary and can put 2 to 3 words together to form short sentences. Three weeks prior to this examination, the child had an upper respiratory infection. Which of the following is the best next step in treatment?

- A. Order ABR testing for the child.
- B. Perform otoscopy with insufflation
- C. Send the child for a complete audiologic evaluation.
- D. Perform hearing screening in the office.
- E. Explain to the child's mother that 2-year-old children often do not respond to their parents.

[56.2] A 4-month-old boy presents for a well-child visit. On physical examination he has a white forelock, a broad mandible, and lateral

displacement of the inner canthi. His mother also has a white forelock. Which of the following statements about this child is true?

- A. This child is at risk for conductive hearing loss (CHL) and requires an audiologic evaluation.
- B. This child is not at risk for hearing loss if his mother has normal hearing.
- C. This child is at risk for sensorineural hearing loss (SNHL) and requires an audiologic evaluation.
- D. The inheritance pattern of this disorder is X-linked recessive.
- E. This child should have ongoing office hearing screening with referral for formal hearing if abnormalities are detected.

[56.3] Which of the following groups of children are at an especially high risk of hearing loss?

- A. A full-term, large-for-gestational-age infant male born to a mother with gestational diabetes
- B. An appropriate for gestational age (AGA) infant who is the product of a 34-week pregnancy who had Apgar scores of 7 at 1 minute and 8 at 5 minutes
- C. A full-term 3300-g birth weight infant born by repeat cesarean section who had a peak total bilirubin of 18 mg/dL at 72 hours of life
- D. A full-term AGA infant receiving cefotaxime and ampicillin for 48 hours after having an evaluation for suspected sepsis
- E. A full-term AGA infant born by cesarean section for placental abruption with Apgar scores of 3 at 1 minute and 5 at 5 minutes

[56.4] Which of the following would be the expected language development of a normal 24-month-old child?

- A. The child's speech is 90% understandable.
- B. The child has a 10-word vocabulary and does not combine words.
- C. The child has a 50-word vocabulary and combines 2 words to make a sentence.

- D. The child uses pronouns appropriately.
- E. The child has a 200-word vocabulary and combines 4 to 5 words to make a sentence.

Answers

- [56.1] **B.** This child has normal speech development and was recently noted to have a possible hearing deficit. With the history of recent upper respiratory tract infection, this child is at risk for otitis media with effusion, and as such, for conductive hearing loss. Otoscopy with insufflation (gently blowing air into the ear canal to determine movement of the tympanic membrane) is helpful for qualitative evaluation of middle ear effusions. Tympanometry is a reliable, quantitative tool for assessing middle ear effusions. If the child does not have conductive hearing loss, further evaluation is indicated.
- [56.2] **C.** This child has features of Waardenburg syndrome which includes partial albinism, often a white forelock, deafness (SNHL), lateral displacement of the inner canthi, medial flare of the eyebrows, and a broad nasal bridge and mandible. The inheritance pattern of Waardenburg syndrome is autosomal dominant. Children with features of syndromes that are strongly associated with hearing loss require full hearing evaluation.
- [56.3] **E.** Infants born with **Apgar scores of 4 or less at 1 minute and 6 or less at 5 minutes require audiologic evaluation.** Other infants who should have ABR or OAE testing include those with a family history of childhood SNHL; cytomegalovirus, rubella, syphilis, herpes, or toxoplasmosis infection; craniofacial anomalies; birth weight less than 1500 g; hyperbilirubinemia at a level requiring exchange transfusion; bacterial meningitis; mechanical ventilation for greater than 5 days; and stigmata of syndrome associated with hearing loss, especially those with renal abnormalities.
- [56.4] **C.** At the age of 24 months, the average child will have a vocabulary of about 50 words and be able to put 2 words together

to form a sentence. Expected language development for a 12-month-old child includes a vocabulary of 2 to 4 words in addition to appropriately saying "mama" and "dada." By 36 months, a child should have a vocabulary of 250 words, produce at least 3-word sentences, and be able to use pronouns.

CLINICAL PEARLS

CMV is the most common infectious cause of congenital SNHL. Antiviral therapy and loop diuretics may cause SNHL. Children with syndromes associated with renal abnormalities have a higher incidence of hearing loss. The American Academy of Pediatrics recommends universal hearing screening at birth.

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CASE 57

A previously healthy 3-year-old boy presents with sudden onset of rash. His mother notes that he had been playing at the park when she first noticed small red spots and a large purple area on his skin. He has had no fever, upper respiratory tract symptoms, nor diarrhea. He is taking no medications. Three weeks previously, he had a mild febrile illness that resolved without intervention after 48 hours. Upon physical examination, the child is playful and cooperative, but has multiple petechiae and purpuric lesions on his upper and lower extremities and his trunk. He has neither adenopathy nor splenomegaly. His white blood cell count and his hemoglobin are normal, but his platelet count is $29,000/\text{mm}^3$.

◆ What is the most likely diagnosis?

◆ What is the next step in management?

ANSWERS TO CASE 57: Idiopathic Thrombocytopenic Purpura (ITP)

Summary: A previously healthy 3-year-old boy develops thrombocytopenia with petechiae and purpuric lesions. He is well-appearing, but has a history of recent febrile illness. His white blood cell count and hemoglobin are normal.

- ◆ **The most likely diagnosis:** Idiopathic (also known as Immune) thrombocytopenic purpura.
- ◆ **The next step in management:** Evaluation of his peripheral blood smear.

Analysis

Objectives

1. Know the most common causes for thrombocytopenia in children.
2. Understand the natural history of idiopathic thrombocytopenic purpura.

Considerations

This 3-year-old boy has purpuric lesions and petechiae secondary to his thrombocytopenia. He lacks systemic signs of illness that would be present in patients with disseminated intravascular coagulation or hemolytic-uremic syndrome. Because his hemoglobin and white blood cell counts are normal, bone marrow infiltration is less likely to be the cause of his thrombocytopenia. A peripheral blood smear should be examined with attention to any immature white blood cells and red cell morphology. Children with ITP have a normal peripheral blood smear without evidence of leukemic or microangiopathic processes. This child has a platelet count $>20,000/\text{mm}^3$ and lacks signs or symptoms of active bleeding; therefore, the next step is close observation.

APPROACH TO THROMBOCYTOPENIA

Definitions

Hemolytic-uremic syndrome (HUS): A clinical syndrome that consists of nephropathy, thrombocytopenia, and microangiopathic hemolytic anemia. It is associated with *Escherichia coli* 0157:H7, *Shigella*, and *Salmonella*. A prodrome of bloody diarrhea is common.

Henoch-Schönlein purpura (HSP): A clinical syndrome of small vessel vasculitis in young children. Children with HSP may have dermatologic, renal, gastrointestinal, and joint involvement (petechial/purpuric rash, arthritis, nephritis, nephrosis, abdominal pain, gastrointestinal bleeding, and intussusception).

Idiopathic (immune) thrombocytopenic purpura: A condition of increased platelet destruction by circulating antiplatelet antibodies, most frequently glycoprotein anti-IIb/IIIa.

Clinical Approach

Acute ITP is the most common cause of thrombocytopenia in an otherwise well child usually aged 2 to 5 years. Although the evidence suggests an immunologic etiology that may be triggered by a preceding viral illness (e.g., varicella, cytomegalovirus, Epstein-Barr virus), the specific pathophysiologic mechanism has not been elucidated. Acute ITP occurs most commonly in young children with an equal predilection in males and females. Children present with the acute onset of petechiae and purpura, and often have a history of a viral illness 1 to 4 weeks previously. Bleeding from the gingivae and other mucous membranes may occur. Findings on physical examination include the presence of petechiae and purpura, especially in areas of trauma. If the child has significant lymphadenopathy or organomegaly, other causes for thrombocytopenia must be considered.

Laboratory findings in ITP include thrombocytopenia, which can be severe ($<20,000/\text{mm}^3$), but the platelet size is normal or increased. The white blood cell count is normal as is the hemoglobin and hematocrit

(unless excessive bleeding has occurred). Measurements of prothrombin time (PT) and activated partial thromboplastin time (aPTT) are normal. The peripheral blood smear may reveal eosinophilia or atypical lymphocytes; however, immature white blood cells and abnormal red cell morphology are absent. In most cases of acute ITP, bone marrow aspiration is no longer considered necessary. If the peripheral blood smear is concerning, the white blood cell count is significantly increased or diminished, or adenopathy or organomegaly are present, evaluation of the bone marrow aids in proper diagnosis. **The bone marrow biopsy in a patient with ITP usually reveals an increased number of megakaryocytes.**

Within 1 month of presentation, more than half of untreated children have complete resolution of their thrombocytopenia and up to another 30% resolve by 6 months. If the thrombocytopenia persists beyond 6 months, it is considered chronic ITP.

The most serious complication of ITP is intracranial hemorrhage, which occurs in fewer than 1% of affected children. Treatment is considered for specific cases; that is, patients with severe thrombocytopenia ($<20,000/\text{mm}^3$) and extensive mucosal bleeding (these patients are considered at higher risk for intracranial hemorrhage); patients with severe complications (such as massive gastrointestinal [GI] bleeds); and patients without a protective environment. **Treatment for ITP is controversial;** no data demonstrate an improved clinical outcome with any treatment modality. Treatment is aimed at decreasing platelet destruction include intravenous immunoglobulin (IVIG) given once daily for 1 to 2 days, a 2- to 3-week course of systemic corticosteroids, or intravenous anti-D therapy. **Platelet transfusions may be useful to temporarily increase platelet counts in cases of serious bleeding or as prophylaxis prior to emergent surgery. Splenectomy may be considered in children with serious complications not responding to other therapies. After splenectomy patients are at great risk for sepsis with encapsulated organisms and require pneumococcal vaccine and penicillin prophylaxis.**

Ten percent to 20% of patients with ITP have thrombocytopenia that lasts more than 6 months and are considered to have chronic disease. **Chronic ITP** occurs more commonly in older children and adolescents and has a female predominance; it may be part of other autoimmune

disease or may occur with infection such as human immunodeficiency virus or Epstein-Barr virus. The treatment options listed above for acute ITP are available for patients with chronic ITP; the goal of therapy remains the prevention of serious complications of thrombocytopenia.

Many pharmacologic agents may cause thrombocytopenia by immune mediated responses. Medications that more commonly cause drug-induced thrombocytopenia include penicillins, trimethoprim-sulfamethoxazole, digoxin, quinine, quinidine, cimetidine, benzodiazepine, and heparin. Measles-mumps-rubella vaccine (MMR) is associated with thrombocytopenia and is used with caution in patients with a history of ITP. A thorough history, including exposure to these agents is obtained when evaluating a patient with ITP.

Comprehension Questions

- [57.1] A 2-year-old girl presents with new onset rash. She was well until 2 weeks prior when she had fever and upper respiratory symptoms that resolved without treatment. She has not had fever since and has continued to be playful and active. Upon examination she has petechiae on her upper and lower extremities and trunk. Her platelet count is $25,000/\text{mm}^3$. Her white blood cell count and hemoglobin are normal. Which of the following is the best next step in management?
- A. Obtain a review of the peripheral blood smear.
 - B. Administer intravenous immunoglobulin.
 - C. Send a blood culture and begin empiric antimicrobial therapy.
 - D. Order a platelet transfusion.
 - E. Arrange for bone marrow biopsy.
- [57.2] A 14-year-old girl presents with a rash on her arms and legs. She was diagnosed with a urinary tract infection 4 days ago, which is being treated with trimethoprim-sulfamethoxazole. She denies fever, vomiting, diarrhea, headache, and dysuria.

Her examination is remarkable for multiple petechiae on her upper and lower extremities. Her white blood cell count and hemoglobin are normal and her platelet count is $35,000/\text{mm}^3$. The next step in management is to:

- A. Send blood for antinuclear antibody (ANA).
- B. Send a repeat urinalysis.
- C. Discontinue the trimethoprim-sulfamethoxazole.
- D. Obtain HIV testing.
- E. Administer intravenous immunoglobulin.

[57.3] A 7-year-old boy presents with a rash on his lower extremities and right knee pain. He has had a low-grade fever, abdominal pain, and has felt tired. Upon physical examination he has a nontoxic appearance and has palpable petechiae on his lower extremities and buttocks. His right knee is edematous, erythematous, and warm. He is able to bear weight on his right leg, but the range of motion of his right knee is limited by the edema. The next step in treatment is to:

- A. Begin a course of systemic corticosteroids.
- B. Begin empiric antimicrobial therapy for sepsis.
- C. Obtain a urinalysis and provide supportive care.
- D. Perform aspiration of the synovial fluid in his right knee.
- E. Administer intravenous immunoglobulin.

[57.4] A 3-year-old boy is brought to the emergency department with pallor, lethargy, and decreased urine output. He was well until the preceding week, when he had symptoms of fever, vomiting and bloody diarrhea that have since resolved. Upon physical examination the child is lethargic, and has hepatosplenomegaly and scattered petechiae. Urinalysis reveals hematuria and proteinuria. Which of the following statements about this child's condition is true?

- A. A complete blood count is likely to reveal thrombocytosis.
- B. Initial therapy includes systemic corticosteroids.
- C. Empiric antimicrobial therapy for sepsis should be initiated.

- D. An emergent oncology consultation for probable leukemia should be arranged.
- E. The serum creatinine is likely to be elevated.

Answers

- [57.1] A. This child has classic features of ITP: isolated thrombocytopenia in a well-appearing child. A thorough physical examination and peripheral blood smear are necessary. If the child does not have lymphadenopathy or organomegaly and the peripheral blood smear is normal, initial management includes close observation and a protective environment.
- [57.2] C. This patient's thrombocytopenia may be a result of the use of trimethoprim-sulfamethoxazole. The medication should be discontinued and her platelet count should be monitored. If she has continued thrombocytopenia after the medication is discontinued, she may have ITP and must also be followed for possible chronic ITP. Chronic ITP occurs in older children with a female predominance and may be associated with systemic lupus erythematosus or with chronic infections.
- [57.3] C. This child has signs and symptoms of Henoch-Schönlein purpura. HSP is a vasculitis of the small vessels and may have renal, gastrointestinal, joint and dermatologic involvement. Initial therapy consists of hydration and pain control. With renal involvement, urinalysis reveals red blood cells, white blood cells, casts or protein. As gastrointestinal complications include hemorrhage, obstruction, and intussusception, complaints of abdominal pain requires careful evaluation.
- [57.4] E. This child has features of hemolytic-uremic syndrome, which frequently follows a bout of gastroenteritis; it has been associated with *Escherichia coli* 0157:H7, *Shigella*, and *Salmonella*. Patients present with pallor, lethargy, and decreased urine output; some may have hepatosplenomegaly, petechiae, and edema. Hematologic laboratory findings include hemolytic anemia and thrombocytopenia; peripheral blood smear reveals

helmet cells, burr cells, and fragmented red blood cells. Acute renal failure of HUS is manifested by hematuria, proteinuria, and elevated serum creatinine. Management is largely supportive with careful monitoring of renal and hematologic parameters. With significant renal disease, peritoneal dialysis may be required.

CLINICAL PEARLS

ITP is the most common cause for acute thrombocytopenia in an otherwise well child, usually occurring between the ages of 2 and 5 years.

Approximately 70% to 80% of children with ITP have spontaneous resolution within 6 months.

Hemolytic-uremic syndrome is a clinical syndrome that consists of nephropathy, thrombocytopenia, and microangiopathic hemolytic anemia, and is associated with *Escherichia coli* O157:H7, *Shigella*, and *Salmonella*.

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◆ CASE 58

A 2-year-old boy presents with inability to walk for the past 2 days. His mother states he fell from the bed on to a carpeted floor 2 days ago. He lives with his mother, his 15-month-old sister, and his 3-month-old brother. On physical examination the child is apprehensive and has pain on palpation of the right thigh. Radiograph of the right lower extremity reveals a femur fracture.

- ◆ What is the most likely diagnosis?
- ◆ What is the next step in the management of this child?

ANSWERS TO CASE 58: Child Abuse

Summary: A 2-year-old boy presents with a 2-day history of inability to walk. The only noted trauma is a fall from the bed. A metaphyseal femur fracture is present.

◆ **Most likely diagnosis:** Physical abuse.

◆ **Next step:** Obtain a skeletal survey.

Analysis

Objectives

1. Understand the importance of reporting suspected child maltreatment.
2. Recognize that if significant inconsistencies exist between the physical injury and the given history of trauma, child abuse must be suspected.

Considerations

The only history for trauma for this 2-year-old boy is a fall from a bed onto a carpeted floor. It is unlikely that such a significant injury as a femur fracture would arise from a common, insignificant fall; **the history appears incongruent with the injury.** An added concern is the mother's delay in seeking medical care for 2 days from the onset of the child's inability to walk. All cases of suspected abuse must be reported to children's protective service agency or law enforcement. Thus, the next step in the evaluation of this child is to obtain a complete skeletal survey to assess for other bony injuries, and to report this child's possible child abuse case to children's protective services.

Definitions

Children's protective services: Local governmental agency responsible for investigating suspected cases of child maltreatment.

Munchausen syndrome by proxy: A form of abuse in which the caretaker falsifies symptoms or inflicts injury upon a child to necessitate medical intervention.

Shaken baby syndrome: Brain injury believed to result from violent shaking of the infant. Infants may present with seizures, respiratory arrest, a bulging fontanelle, or irritability. Intracranial injury is evident with radiographic evaluation (computerized tomography [CT] or magnetic resonance image [MRI]) and retinal hemorrhages may be visualized on funduscopy. Infants with shaken baby syndrome often present with a clinical picture similar to that of a septic infant.

Clinical Approach

Child maltreatment is a serious problem with approximately 1 million substantiated cases per year in the United States. Forms of child maltreatment include neglect, physical abuse, sexual abuse, and emotional abuse, and children often suffer from more than one type of abuse. **Neglect is the most common form of child maltreatment** and consists of failure to provide adequate nutrition, shelter, supervision, or medical care. Physical abuse accounts for approximately 25% of cases and occurs when excessive physical injury is inflicted by the caregiver. Although debate continues regarding the definition of "appropriate" corporal punishment, physical abuse is considered if marks (e.g., bruising, lacerations, burns, or fractures) result from the event. Sexual abuse is reported to occur in 9% of substantiated maltreatment cases (see Case 12 for more information).

Munchausen syndrome by proxy is a less-common form of child abuse, in which the caretaker falsifies symptoms or inflicts injury upon a child to necessitate medical intervention. Affected children are often hospitalized repeatedly with undiagnosed or vague conditions. The hospitalization is remarkable for a caretaker who takes great interest in the medical staff and interventions. Cases of Munchausen syndrome by proxy may range from the caregiver fabricating symptoms to actual poisoning or suffocating the child.

Reporting cases of child maltreatment to children's protective services has been mandated since the 1960s, and since that time, public and medical awareness has slowly increased. In all states,

health care providers who suspect physical abuse are legally required to report suspected abuse to children's protective services or to law enforcement.

Medical evaluation of suspected cases of child maltreatment includes obtaining a medical history and assessment of the family, conducting a physical examination, obtaining appropriate diagnostic testing, and where possible interviewing the child and the family. Routine medical history includes information regarding illnesses, hospitalizations, injuries, and pertinent family history. A complete developmental history is essential to help determine whether the description of the events given by the family is a plausible explanation for injuries found (e.g., a 10-month-old child would be unable to climb into a bathtub, turn on the water, and give himself second-degree burns only to the buttocks). Documentation of who lives in the home and who provides care for the child should be included in the medical record.

A complete physical examination is performed with attention to any skin lesions. Body charts are useful tools to assist in diagramming visible injuries and photographic images can further demonstrate the injuries. **In abused children younger than age 3 years, a complete skeletal survey (skull, chest, spine, and limbs) assists in obtaining evidence of prior trauma.** Recent fractures may not be detectable for 1 to 2 weeks after the injury; bones scans may be necessary as they usually demonstrate fractures within 24 to 48 hours of injury. Children with **bruising on examination** often are evaluated with a **platelet count and coagulation studies** to eliminate hematologic disorders as a cause of their physical findings.

While bruises and lacerations are common physical indicators of abuse, they also occur commonly by accidental injury in nonabused children. **Accidental bruises are usually found over bony areas such as the knees, shins, elbows, and forehead,** and are appropriate to the child's age. Bruises to the abdomen, buttocks, thighs, and inner arms occur less frequently in cases of accidental trauma. The color of the bruise evolves from a blue-brown color during the first few days following injury to a yellow-green color at about a week following injury and finally to a light brown color as the hematoma resolves. Bruises with bleeding deep in to the tissues may heal and demonstrate color changes at a slower rate. **Characteristic injury patterns** consistent with child abuse include **loop marks**, which resemble a

looped cord, bruises in the shape of a belt buckle, handprints, bite marks, and circumferential cord marks around the neck from strangulation.

In cases of extensive bruising, the differential diagnosis includes hemophilia, Henoch-Schönlein purpura (or other vasculitis), and disseminated intravascular coagulation (DIC). Patterned injury can result from folk medicine practices such as cupping in which a heated cup is applied to the skin leaving a circular injury or coin rubbing which leaves linear red marks on the back. A thorough history, a complete physical examination, and a few screening tests can help eliminate these diagnostic considerations.

Burn injuries may take the shape of the insulting object, such as a steam iron or curling iron. **Immersion into burning water will leave a smooth border to the burn.** Cigarette burns are circular and may be difficult to differentiate from impetigo.

Skeletal injuries that are concerning for abuse include injury to the metaphyses of the long bones, rib fractures, complex skull fractures, and multiple fractures, especially if they are in various stages of healing. Spiral or oblique fractures of the long bones were once considered diagnostic of child abuse; however these fractures occasionally may result from unintentional injury with a rotating force. Nursemaid's elbow or subluxation of the radial head occurs commonly as an accidental injury when a toddler falls while walking and holding an adult's hand (dislocation of the elbow occurs as the limb is pulled and twisted). Conditions that cause increased susceptibility to bony injury include osteogenesis imperfecta, scurvy, cortical hyperostosis, and Menkes kinky hair disease; these are rare conditions in pediatrics.

Comprehension Questions

- [58.1] A 2-year-old boy presents 4 hours after injury to his left arm. His mother states that while they were walking, he tried to run into the street. She held his left hand tightly and he fell. Since that time the child has not moved his arm. On physical examination the child is holding his left arm close to his body with the elbow flexed and the forearm in pronation. The left elbow is

neither erythematous nor edematous. The child cries when the elbow is touched. The next step is to:

- A. Obtain a radiograph of the left elbow.
- B. Order a skeletal survey.
- C. Place the left arm in a sling.
- D. Supinate the child's forearm while applying pressure over the radial head.
- E. Apply traction to the forearm while increasing the degree of pronation.

[58.2] A 15-year-old girl presents with nasal congestion and cough for 2 days. Upon auscultation of her back, multiple circular ecchymoses are noted (Figure 58-1). The most likely etiology for this child's condition is:



Figure 58-1. Picture of child's back. (Courtesy of Dr. Sheela Lahoti, MD)

- A. Cupping
- B. Physical abuse
- C. Disseminated intravascular coagulation (DIC)
- D. Henoch-Schönlein purpura
- E. Coining

[58.3] Which of the following describes the most common form of child maltreatment?

- A. Sexual abuse
- B. Physical abuse
- C. Neglect
- D. Emotional abuse
- E. Munchausen syndrome by proxy

[58.4] A 4-month-old girl presents with extreme fussiness. Upon examination she appears to have pain on palpation of the right leg and her sclerae are notable for their bluish color. Radiograph reveals fracture of the right femur. The child's parents deny any severe trauma. The child's mother states that she had multiple fractures as a child. Family history is also likely to include:

- A. Blindness
- B. Hearing loss
- C. Tall stature
- D. Renal disease
- E. Aortic aneurysm

Answers

[58.1] **D.** This child has the history consistent with an injury involving traction on an outstretched arm. The elbow is not swollen and the arm is being held in a flexed and pronated position. It is most likely that the child has suffered subluxation of the radial head or "nursemaid's elbow." Initial therapy includes

applying pressure over the radial head while supinating the arm in order to relieve the subluxation. If treatment is not delayed, the child will generally begin using the arm soon after the maneuver.

- [58.2] A. This adolescent has multiple perfectly circular lesions on her back which are consistent with cupping. When asked how these marks on her back were made, she gave the history of cupping. Injuries from physical abuse would be unlikely to have exactly the same appearance with each mark that was left. Patients with DIC will have significant systemic manifestation of illness, and the pattern of ecchymoses would not be multiple lesions of the exact size and shape. Coining causes the formation of erythematous lines.
- [58.3] C. The most common form of child maltreatment is neglect (the failure to provide adequate nutrition, shelter, supervision, or health care).
- [58.4] B. This infant has features of osteogenesis imperfecta which is an autosomal dominant genetic disorder. Features include long bone fractures and vertebral injury with minimal trauma, short stature, deafness, and blue sclerae. Four types of osteogenesis imperfecta exist: type I is mild; type II is lethal (in utero or within the first year of life); type III is the most severe; and type IV is moderately severe.

CLINICAL PEARLS

All cases of suspected child maltreatment must be reported to a Children's Protective Services agency or law enforcement. If the history of trauma does not fit the injury pattern found on the patient, child abuse is suspected. If the child's development is not consistent with the history of injury, child abuse is suspected.

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◆ CASE 59

A 7-month-old boy with respiratory difficulty is brought to the emergency department at 3 A.M. He appears moderately distressed with nasal flaring, and use of accessory neck and chest muscles with every breath. His mother reports that several family members have had "colds" over the past week. The infant first developed cough and coryza 5 days previously, and the cough has become "barky." She reports that his immunizations are current and that he has had no previous illness. On further physical examination, the infant has an axillary temperature of 100.4°F (38°C), a respiratory rate of 55 breaths per minute, and a heart rate of 140 beats per minute. Auscultation of the chest reveals inspiratory stridor and coarse expiratory breath sounds. His examination is otherwise unremarkable.

- ◆ What is the next step in management of this patient?
- ◆ What is the most likely diagnosis?

ANSWERS TO CASE 59: Croup

Summary: Following a 5-day prodrome of coryza and worsening cough, a 7-month-old boy develops moderate respiratory distress characterized by tachypnea, nasal flaring, accessory respiratory muscle use, inspiratory stridor, and coarse expiratory breath sounds. He has no significant past medical history, and reportedly his immunizations are current. Several household members have upper respiratory symptoms.

- ◆ **Most likely diagnosis:** Croup (laryngotracheitis or laryngotracheobronchitis).
- ◆ **Next step in management:** Aerosolized racemic epinephrine and administration of corticosteroids often result in improvement of symptoms. Supportive measures including oxygen and parenteral fluids may be indicated. The child should be monitored closely for possible further decompensation requiring endotracheal intubation.

Analysis**Objectives**

1. Recognize the presenting signs and symptoms of acute upper airway obstruction in a child.
2. Know the differential diagnosis for upper airway obstruction in a child.
3. Know the principles of acute management of upper airway obstruction in a child.

Considerations

Tachypnea, nasal flaring, and the use of accessory muscles are symptoms common to many acute respiratory conditions. The infant in this case additionally has inspiratory stridor and coarse expiratory sounds,

suggesting a disorder that involves both the upper and lower airways. The history of a 5-day prodrome of coryza and worsening cough, as well as cold symptoms in several household members, makes a viral infection the most likely etiology. This infant's history and physical symptoms are most consistent with a diagnosis of croup. Varying degrees of laryngeal obstruction secondary to croup result in the characteristic hoarseness, a "barky" ("croupy") cough, and inspiratory stridor. As in this case, many children with croup present at night when symptoms typically worsen.

Cool mist, hot steam, and other aerosolized therapies historically have been used for patients with croup in an attempt to relieve laryngeal spasm, although the evidence to support their effectiveness is lacking. Moderately and severely affected children deserve a trial of racemic epinephrine, which reduces in size blood vessels in the airway, thereby reducing swelling and improving symptoms. For a moderately ill child such as the one in this case, consideration should also be given to administration of a corticosteroid, either via aerosol (budesonide), or orally (dexamethasone). Dexamethasone can also be administered parenterally. Potentially irritating procedures such as the use of a tongue blade or needle-sticks should be avoided initially unless absolutely necessary, as agitation and crying aggravate the respiratory symptoms.

APPROACH TO SUSPECTED CROUP

Definitions

Croup (laryngotracheobronchitis): A clinical syndrome characterized by a "barky" ("croupy") cough, hoarseness, and inspiratory stridor. The cause is usually a viral infection, and it generally involves the trachea, larynx, and bronchi in varying degrees.

Stridor: A high-pitched musical sound that results from partial airway obstruction. The obstruction may be supraglottic (i.e., above the vocal cords), glottic, and/or subglottic (i.e., below the vocal cords).

Clinical Approach

Croup is one of the most common causes of respiratory distress in young children, particularly in the winter months. A variety of viral infections have been implicated. The **most common culprits are parainfluenza viruses**, but influenza, measles, respiratory syncytial virus, herpes simplex and adenovirus can also cause the disorder. **Croup that occurs in the summer is most often caused by enteroviruses or parainfluenza type 3.** *Mycoplasma pneumoniae* has also been isolated in a small number of cases of croup. Diphtheria was once a common cause, but now is rarely seen due to widespread vaccination. **Nasal washings for respiratory syncytial virus (RSV) and influenzae** may assist in the diagnosis.

Hoarseness, a "barky" cough, and inspiratory stridor help to distinguish croup from asthma, bronchiolitis, and other causes of respiratory distress in young children. Peritonsillar or retropharyngeal abscesses occasionally are mistaken for croup; neck radiographs reveal a mass in children who have an abscess, while children with croup will demonstrate airway narrowing. **Epiglottitis** is identified by its characteristic clinical signs: **drooling, a preference to sit in a tripod or upright position, muffled vocalizations, inspiratory stridor, and absence of cough.** The distinction between epiglottitis and other forms of upper airway obstruction is crucial, as children with epiglottitis require immediate expert care because of the high risk for sudden complete airway obstruction. Fortunately, this is a rare condition owing to widespread vaccination of children with *Haemophilus influenzae* type B vaccine. **Noninfectious etiologies** that can mimic croup include **foreign-body aspiration, tracheomalacia, extrinsic airway compression** (such as from a hematoma or tumor), and **intraluminal obstruction** (as a result of a tumor or cyst).

The term "spasmodic croup" is used to describe the syndrome of sudden nighttime onset of hoarseness, "barky" cough, and inspiratory stridor in an afebrile child. Children with spasmodic croup have no or only mild daytime symptoms. Viral infections, respiratory allergies, and gastroesophageal reflux are implicated as etiologies of this disorder. Like the purely viral variety, spasmodic croup is relieved by racemic epinephrine and steroids. Recurrent episodes of spasmodic croup may require an evaluation for anatomic problems such as gastroesophageal reflux.

For children who have only mild symptoms from croup, symptomatic management may be sufficient. Humidified air and oxygen historically have been used to relieve laryngeal spasm in croup, but the effectiveness of these treatments has not been conclusively demonstrated. More severely affected children require aerosolized epinephrine and steroids in an emergency department, and many children require hospitalization for further management until the airway swelling subsides. Tracheal intubation is required for a small number of patients with croup.

Most children with croup recover completely. Occasional complications of croup include otitis media, pneumonia, and bacterial superinfection. Bacterial tracheitis usually is the result of secondary infection with coagulase-positive staphylococci in a child with viral laryngotracheitis. These children present with severe croup-like symptoms, and require tracheal intubation and initial management in an intensive care unit. Severe hypoxia and death have been reported in children with bacterial tracheitis.

Comprehension Questions

- [59.1] A 2-year-old child presents to the emergency department with the complaint of sudden onset of inspiratory stridor, tachypnea, and chest retractions. He had been playing with his 6-year-old brother before this episode. He is afebrile. Apart from the stridor, his lung sounds are clear, and his physical examination is otherwise normal. A chest radiograph reveals no abnormalities. What is the next best step in management of this child?
- A. Administer aerosolized racemic epinephrine.
 - B. Administer oral dexamethasone.
 - C. Evaluate the airway with bronchoscopy.
 - D. Administer parenteral antibiotics.
 - E. Perform nasotracheal intubation.
- [59.2] A 14-month-old girl presents to the emergency department with a 6-hour history of fever to 102.6°F (39.2°C) and an increasingly ill appearance. She appears very anxious and does not want to leave her mother's arms, but she gives only a faint cry when approached. Her respiratory rate is 70 breaths per minute,

with chest retractions and inspiratory stridor. A spot of moisture is noted on the shoulder of the mother's blouse. What is the next most appropriate step in management of this child?

- A. Perform a complete physical examination with particular emphasis on examination of the mouth and upper airway.
- B. Secure the airway in the emergency department with an endotracheal tube.
- C. Secure the airway in the operating room via tracheal intubation or tracheostomy.
- D. Administer aerosolized racemic epinephrine and budesonide (nebulized steroids).
- E. Obtain blood, urine, and cerebrospinal cultures and begin parenteral antibiotics.

[59.3] A 5-month-old boy with mild upper respiratory symptoms but no fever is brought to his pediatric clinic following an episode of stridor and increased effort of breathing that occurred the previous night. He was well prior to this episode. Apart from some mild rhinorrhea, his physical examination is normal. The most likely etiology is:

- A. A combination of viral, atopic, and possible gastroesophageal reflux components.
- B. Foreign-body aspiration.
- C. Tracheomalacia.
- D. Extraluminal compression of the trachea by a tumor.
- E. *Streptococcus pyogenes* pharyngitis.

[59.4] A 2-year-old boy with a 3-day history of upper respiratory congestion and cough now has inspiratory stridor, a respiratory rate of 50 breaths per minute, chest retractions, and a fever of 101°F (38.3°C). The therapies most likely to ameliorate his current symptoms are:

- A. Pseudoephedrine and dextromethorphan
- B. Albuterol and cromolyn
- C. Ampicillin and gentamicin

- D. Cool mist and herbs
- E. Aerosolized racemic epinephrine, and budesonide or dexamethasone

Answers

- [59.1] C. Children younger than age 3 years commonly put nonfood objects into their mouths. In this child with **no cough**, fever, or cold symptoms, a history of sudden onset of stridor, and no ill contacts, foreign-body aspiration is a strong diagnostic possibility. Many objects (e.g., an older sibling's plastic toy) are radiolucent and thus will not be visible on radiographs. Bronchoscopy is both diagnostic and therapeutic in these cases. Alternatively, inspiratory and expiratory routine chest radiographs can be helpful: a normal inspiratory film with unilateral hyperexpansion on the expiratory film may indicate air trapping on the hyperinflated side as a consequence of obstruction of a bronchus.
- [59.2] C. This child's clinical picture is most consistent with epiglottitis. This is a medical emergency. She must be kept calm and immediately transported to an operating room where the airway can be examined and secured by a surgeon who is skilled in both tracheal intubation and tracheostomy. An attempt at visualizing the pharynx may lead to complete airway obstruction. Clinicians who care for children must remember that even though epiglottitis is now rare due to routine vaccination against *Haemophilus influenzae* type B, it is occasionally seen in hypoimmunized children, or as a result of infection with *Streptococcus pyogenes*, *S. pneumoniae*, or *Staphylococcus aureus*.
- [59.3] A. Children with spasmodic croup appear well during the daytime, but develop stridor and difficulty breathing at night. The cause is thought to be multifactorial. Foreign-body aspiration is less likely in a nonambulatory infant than in an older child. Infants with mild tracheomalacia may have stridor only intermittently (e.g., with crying), but the condition is first noted in early infancy. A tumor compressing the trachea would be expected to

cause persistent, not intermittent, stridor. Children with streptococcal laryngitis have fever and throat pain, but generally do not present with a significant history of stridor.

- [59.4] E. Aerosolized epinephrine and steroids are the only therapies that significantly improve symptoms of croup. Systemic and nebulized steroids also reduce hospital admissions, length of hospital stay, and hospital reattendance.

CLINICAL PEARLS

Croup is characterized by hoarseness, inspiratory stridor, and a "barky" cough. It is often preceded by a prodrome of upper respiratory symptoms.

The most important entities to consider in the differential diagnosis of croup are epiglottitis, bacterial tracheitis, and foreign body aspiration. Epiglottitis and bacterial tracheitis require stabilization in a calm environment by an expert skilled in immediate airway management.

Aerosolized epinephrine, systemic steroids, and aerosolized steroids are effective therapies for the management of moderate and severe cases of croup. However, most children with croup have mild symptoms that can be safely managed at home.

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◆ CASE 60

A 3-year-old boy presents for his second visit to the pediatric clinic. Two days ago he was brought in with a 4-day history of fever spiking to 104°F (40°C). His physical examination at that time was remarkable for an enlarged but nonsuppurative right anterior cervical lymph node, injection of the oropharynx, and dry, cracked lips. His right tympanic membrane was dull but nonerythematous. He drank 4 ounces of an electrolyte solution in clinic, and was sent home with a prescription for amoxicillin for a presumed streptococcal pharyngitis. Today, after taking antibiotics for 2 days, he has persistent fever. The physical findings noted previously are still present, and he also now has bilateral conjunctivitis, a maculopapular truncal rash, and edema of the hands and feet.

- ◆ What is the most likely diagnosis?
- ◆ What is the best diagnostic test for this disorder?
- ◆ What is the treatment for this condition?

ANSWERS TO CASE 60: Kawasaki Disease

Summary: A 3-year-old boy with high-spiking fevers of 6 days duration. An enlarged anterior cervical lymph node, pharyngeal erythema, and dry, cracked lips were noted on day 4 of his illness. He developed bilateral conjunctivitis, a truncal rash, and edema of the hands and feet by day 6. His condition has not improved despite two days of therapy with amoxicillin.

- ◆ **Most likely diagnosis:** Kawasaki disease (also known as mucocutaneous lymph node syndrome).
- ◆ **Best diagnostic test:** No laboratory study is diagnostic for Kawasaki disease. Echocardiography is the most useful test to monitor the development of coronary aneurysms, which are the most serious potential complication of this disease. The findings of elevated acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), normocytic anemia, and thrombocytosis, support the diagnosis.
- ◆ **Treatment:** Early initiation of anti-inflammatory therapy with high-dose intravenous immunoglobulin (IVIG) and aspirin reduces the risk of development of coronary complications.

Analysis**Objectives**

1. Know the diagnostic criteria for Kawasaki disease.
2. Recognize the importance of early diagnosis and treatment for the prevention of coronary complications.
3. Be familiar with other diagnostic possibilities for the constellation of symptoms found in Kawasaki disease.

Considerations

Diagnosing Kawasaki disease can be difficult in the first few days of illness, when only a few of the classic clinical findings may be present. Streptococcal pharyngitis was perhaps the initial presumptive diagnosis at the first visit, but this child's unilateral lymphadenopathy and the absence of palatal petechiae and pharyngeal exudate are not entirely consistent with "strep throat." A negative streptococcal antigen test ("rapid strep test") or throat culture would have been helpful, although a small number of persons are chronic carriers of group A streptococcus. Furthermore, the clinical course of acute streptococcal pharyngitis is shorter than that of Kawasaki disease. This child's diagnosis became more obvious on the sixth day of illness, when he manifested additional clinical signs although other possible conditions, such as rickettsial infection, measles, drug hypersensitivity reactions, and leptospirosis must still be excluded.

APPROACH TO FEVER AND RASH

Definitions

Polymorphous rash: An exanthem that may take various forms among affected individuals, such as maculopapular, erythema multiforme, or scarlatiniform.

Strawberry tongue: Erythema of the tongue with prominent papillae.

Thrombocytosis: Elevation of the platelet count above $450,000/\text{mm}^3$. In Kawasaki disease, this usually occurs after the tenth day of illness, and may last for a few weeks.

Clinical Approach

Kawasaki disease was first described in Japan, in 1967, by Dr. Tomisaku Kawasaki. The incidence is highest among Asians, although it has been reported worldwide. It occurs most frequently in children

younger than 5 years of age. The etiology is unknown, although epidemiologic evidence most strongly suggests an infectious origin.

The diagnosis of Kawasaki disease is based on the demonstration of characteristic signs (see Table 60-1), although atypical cases of children with fewer signs who later develop coronary artery disease are recognized. Atypical disease occurs most frequently in infants, and this group is most likely to develop coronary complications. Although no single laboratory test can establish the diagnosis, certain laboratory findings are characteristic. The erythrocyte sedimentation rate (ESR) and C-reactive protein are elevated, and a normocytic anemia is common. The platelet count is normal during the first week of illness, but often rises above normal after the tenth day. Sterile pyuria, cerebrospinal fluid pleocytosis, and mild elevation of hepatic transaminases may also be seen. Echocardiography is performed at the time of diagnosis, and again usually 2 to 3 weeks later, to identify abnormalities of the coronary arteries.

The diagnosis of Kawasaki disease also depends on exclusion of other possible conditions. **A defervescence after initiation of penicillin therapy is characteristic of streptococcal infection but not Kawasaki disease.** Documentation of measles vaccination virtually excludes this possibility of rubeola. A low erythrocyte sedimentation rate may suggest a noninfectious process, such as a drug eruption (e.g., Stevens-Johnson syndrome). **Hepatosplenomegaly in association with persistent fever, lymphadenopathy and a salmon-colored rash**

Table 60-1
DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE

Fever lasting for at least 5 days in the child without evidence of other more likely pathology, plus the presence of at least four of the following five signs:

1. Bilateral conjunctivitis, generally nonpurulent
2. Oropharyngeal mucosal changes including pharyngeal injection, injection or fissuring of the lips, and strawberry tongue
3. Edema or erythema of the hands or feet in the acute phase; periungual desquamation in the subacute phase.
4. Polymorphous rash that is primarily truncal
5. Cervical lymphopathy of 1.5 cm or greater, usually unilateral

is characteristic of **systemic-onset juvenile rheumatoid arthritis**. Hypotension, renal involvement, elevated creatinine phosphokinase level, and a focus of staphylococcal infection are features of toxic shock syndrome.

Successful treatment of Kawasaki disease depends on **rapid initiation** of antiinflammatory therapy consisting of **high-dose aspirin and intravenous immunoglobulin (IVIG)**. Rapid defervescence generally occurs with this regimen. Aspirin therapy is later reduced from antiinflammatory to antithrombotic doses, and is usually continued until 6 to 8 weeks after onset of disease, when the ESR normalizes. Children who develop **coronary artery disease** require **prolonged antithrombotic therapy**.

Death as a consequence of Kawasaki disease is rare and is caused by **myocardial infarction** or, less commonly, **aneurysm rupture**. Risk factors for development of coronary aneurysms include male gender, prolonged fever for more than 10 days, age younger than 12 months, low serum albumin or hemoglobin, early cardiac findings (e.g., mitral regurgitation or pericardial effusion), and thrombocytosis. Mild coronary artery dilation often resolves within 6 to 8 weeks of disease onset.

Comprehension Questions

- [60.1] A 12-month-old child comes to the office for a routine well-child examination. He was hospitalized 3 months prior for Kawasaki disease, and was taken off aspirin therapy 6 weeks prior to this visit. His most recent echocardiogram was normal. For this patient, special consideration should be paid to:
- A. His developmental assessment
 - B. The abdominal examination
 - C. Live-vaccine administration
 - D. Serum hemoglobin evaluation
 - E. Assessment of possible lead toxicity
- [60.2] A 15-month-old child is on long-term aspirin therapy for coronary artery abnormalities that resulted from Kawasaki disease. In addition to his routine vaccinations, he should receive a:

- A. Pneumococcal vaccine
- B. Influenza vaccine
- C. Meningococcal vaccine
- D. Oral polio vaccine
- E. Varicella vaccine

[60.3] A 5-month-old infant develops 3 days of high fever, a maculopapular diaper rash, and swollen, red lips. He is also very irritable. His white blood cell count is $15,000 \text{ cells/mm}^3$ with a predominance of neutrophils and immature forms, and he has a mild normocytic anemia. The urinalysis is normal, but the cerebrospinal fluid shows a pleocytosis with a negative gram stain. After 24 hours of parenteral ceftriaxone, the child continues to have high fever, and he develops edema of the feet. Subsequent management of this child should include:

- A. Nystatin for the diaper rash
- B. Repeat of the spinal tap
- C. Addition of vancomycin to the antibiotic regimen
- D. Consultation with a pediatric cardiologist and initiation of IVIG infusions and oral high-dose aspirin
- E. Continuing current management and follow the culture results

[60.4] Which of the following children with Kawasaki disease is at greatest risk for the development of coronary artery disease?

- A. A 5-year-old boy with 6 days of high fever, sterile pyuria, a truncal rash, and strawberry tongue
- B. A 3-year-old girl with 5 days of high fever and cerebrospinal fluid pleocytosis
- C. A 2-year-old girl with 5 days of high fever and an initial ESR of 80
- D. A 1-year-old boy with 6 days of high fever, a maculopapular diaper rash, and mildly elevated hepatic transaminases
- E. A 6-month-old boy with 11 days of high fever and a small pericardial effusion on initial echocardiogram

Answers

- [60.1] **C.** Live-virus vaccines (measles-mumps-rubella and varicella vaccines) should be delayed for 11 months following administration of high-dose IVIG because of its potential to interfere with the immune response. The measles vaccine, typically given at the 12-month visit, may be given if the child's risk of exposure is high, but reimmunization will be required unless serologic testing indicates adequate antibody titers.
- [60.2] **B.** Children on prolonged aspirin therapy should receive the influenza vaccine because of the increased risk of Reye syndrome in those who become infected with the disease and take aspirin.
- [60.3] **D.** This child's initial presentation is consistent with, but not diagnostic of, Kawasaki disease (see Table 60-1). His persistent fever and development of peripheral extremity edema increase the possibility of this diagnosis, and should prompt further investigation and treatment.
- [60.4] **E.** Risk factors for development of coronary aneurysms include male sex, prolonged fever for more than 10 days, age younger than 12 months, low serum albumin or hemoglobin, early cardiac findings (e.g., mitral regurgitation or pericardial effusion), and thrombocytosis.

CLINICAL PEARLS

The diagnosis of Kawasaki disease is based on clinical criteria, and should be suspected in a young child with a combination of high fever of greater than 5 days duration, oropharyngeal changes, conjunctivitis, changes in the extremities, rash, and cervical adenopathy.

The most important complication of Kawasaki disease is coronary artery disease. A pediatric cardiologist is usually involved in the care of these children.

Early recognition and initiation of therapy for Kawasaki disease is key to preventing potential coronary complications.

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Listing of Cases

Listing by Case Number

Listing by Disorder (Alphabetical)

LISTING BY CASE NUMBER

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44	Atopic dermatitis	455
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34	Bacterial meningitis	357
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58	Child abuse	577
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13	Acute otitis media	147
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38	Pinworm (<i>Enterobius vermicularis</i>)	397
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29	Acute poststreptococcal glomerulonephritis	307
30	Precocious puberty	315
7	Rickets	84
35	<i>Salmonella/Shigella</i> (bacterial enteritis)	367
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