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Duchenne Muscular Dystrophy

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Author Disclosure
Dr Biggar did not disclose any financial relationships relevant to this article.

Objectives After completing this article, readers should be able to:

1. Describe the pathogenesis of Duchenne muscular dystrophy (DMD).
2. Describe the natural history and late complications of DMD.
3. List the laboratory investigations available to diagnose muscle disorders.
4. Discuss the management for DMD.

Case History

MD was born following a normal pregnancy and delivery. His parents were nonconsanguineous, and the family history was unremarkable. He had a 6-year-old brother who was well. MD walked when he was 18 months old, 6 months later than his brother. He was a toe-walker and had large calves. He never ran as well as his brother, and he could not hop on one foot. By 4 years of age, he had difficulty climbing stairs at home and the ladder at the neighborhood playground. His pelvic girdle muscles were weak, he walked with a rocking, side-to-side, waddling gait (Trendelenburg), and he developed lumbar lordosis. He fell more frequently for no apparent reason. His parents became concerned and sought medical advice.

Laboratory testing revealed a serum creatine kinase value 50 times greater than normal. On genetic testing, Duchenne muscular dystrophy (DMD) was diagnosed. His weakness progressed. To get up after falling, he would have to use his hands to climb up his legs to stand.

In the first grade, his academic performance was judged to be delayed. His teachers noticed that his concentration was poor; he had difficulty staying on task. He scored higher on his verbal intelligence quotient than on his performance intelligence quotient. He also was teased by other children at recess. His parents elected to have him repeat the first grade. He required an educational assistant for classroom activities. He also displayed some obsessive-compulsive behaviors.

When he was 10 years old, walking became more difficult, and he required a wheelchair for ambulation. His weight gain became excessive as he lost ambulation. He could, however, dress and feed himself. He developed a scoliosis of 35 degrees and required surgery to stabilize his spine when he was 14 years old. By age 16 years, he could not feed, toilet, or dress himself. Not surprisingly, he was clinically depressed.

The boy's sleep pattern became disturbed, and at age 17 years, he developed symptoms of nighttime hypoventilation. These symptoms included a restless sleep pattern that required him to be turned in bed every hour, gave him morning headaches, reduced his school performance, and caused him to fall asleep in school during the afternoon. His cough became weaker, and he had difficulty clearing respiratory secretions. He required three hospitalizations for pneumonia. At 19 years of age, he developed a severe pneumonia, declined a tracheostomy, and died. At autopsy, a severe dilation of the left ventricle of his heart was discovered.

Pathogenesis

DMD is caused by a mutation of the X-linked gene that encodes for the protein dystrophin. Dystrophin is a large, 427-kDa protein that bridges the inner surface of the muscle sarcolemma to the protein F-actin. The gene, also very large, is located on the short arm of the X chromosome. Most genetic mutations involve deletions; less often, point mutations and duplications are seen. Without dystrophin, the glycoprotein structure of the muscle sarcolemma is less stable. Membrane instability leads to muscle damage, with the initiation of an inflammatory cascade contributing further to muscle damage, necrosis, and

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fibrosis. Proximal muscles are involved first. Skeletal and cardiac muscle are affected primarily.

Clinical Features

The term muscular dystrophy refers to those inherited disorders of skeletal muscle that have no central or peripheral nervous system involvement. Classification of the muscular dystrophies has been difficult. Most, but not all, are associated with progressive muscle weakness, and children who have congenital muscular dystrophy (CMD) may show periods of improvement.

The CMDs are a subset of the muscular dystrophies that usually are diagnosed when a child presents with early-onset muscle weakness, delayed development, and contractures. Currently, there are two classifications of CMD: syndromic when other organs (brain, eye) are involved and nonsyndromic when only muscles are involved. The other large group of muscular dystrophies includes the limb girdle muscular dystrophies.

A muscle biopsy may not always be diagnostic. However, with the newer techniques for genetic analysis, including polymerase chain reaction testing, computer-assisted laser densitometry, and immunohistochemical probes, understanding of the muscular dystrophies is growing. Current classifications probably will change over time as new genetic and clinical information is catalogued. For the present, however, the primary criteria for disease classification include phenotype, muscle pathology, and genetic analysis. The most common type of muscular dystrophy is DMD.

DMD is an X-linked recessive disorder affecting primarily skeletal and cardiac muscle. The incidence is 1 in 3,300 liveborn males. Boys who have DMD exhibit a progressive and predictable loss of muscle function. The muscles are affected at birth, but clinical symptoms of proximal muscle weakness usually manifest between 3 and 5 years of age. The boys may walk later than their siblings, but most are walking by 18 months of age. Toe-walking is common. Running, jumping, and hopping are awkward and difficult, if not impossible. Muscle weakness often is apparent when the boys are observed playing with their siblings or other children.

As the pelvic muscles weaken further, affected boys develop a lumbar lordosis and a Trendelenburg gait. They fall more often and have difficulty rising. To raise themselves up, they get into a knee-elbow position, extend their elbows and knees, bring their hands and feet as close together as possible, and place one hand at a time on their knees. They then place their hands on their thighs and move proximally in alternating steps (“climb-

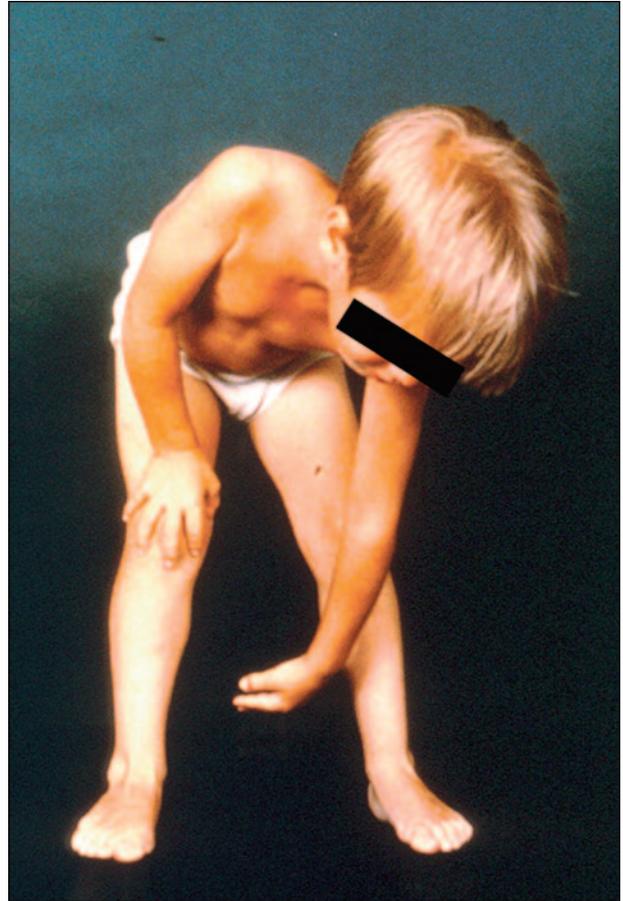


Figure. A boy who has DMD exhibits the Gower maneuver, in which he uses his hands to push off his thighs to rise up from the floor.

ing up their legs”) to become erect. This is known as the Gower maneuver (Figure).

Boys who have DMD are at increased risk for certain cognitive concerns. Dystrophin is present in the brain, but its function is unknown. Their motor and language development may be delayed. Many affected boys tend to be creative and artistic. Parents may report that their son is easily frustrated, easily distracted, has a poor attention span, and is immature. These boys may be afraid of new situations and have some features of obsessive-compulsive behavior. Unlike their muscle weakness, which is progressive, their cognitive skills do not deteriorate over time. They frequently require extra help for academic work.

Muscle weakness continues, with the legs affected earlier than the arms. The boys begin to use wheelchairs full time between 8 and 12 years of age, most by 10 years. Approximately 3 to 4 years after losing ambulation, 90%

of the boys develop a spinal curvature of greater than 20 degrees. Surgery is required to stabilize the spine. Joint contractures develop initially in the lower extremities, with the feet assuming the typical equinovarus position. Upper extremity function declines in the mid-teens, and the boys lose the ability to feed and care for themselves. This impairment frequently occurs after spinal surgery. Pulmonary function begins to deteriorate between 9 and 11 years of age. The forced vital capacity declines by 5% to 10% per year, their cough becomes weaker, and the ability to clear respiratory tract secretions is impaired. Pneumonia is common. Nocturnal assisted ventilation frequently is required in their mid-to-late teens. Improved pulmonary care and aggressive treatment of pulmonary infections have improved life expectancy.

Electrocardiographic and echocardiographic changes are present in more than 50% of boys who have DMD. They usually are free of cardiac symptoms (fatigue and reduced exercise tolerance) because they use a wheelchair

The most spectacular elevation of serum creatine kinase (50 to 100 times normal) occurs in Duchenne muscular dystrophy.

full time and do not exercise vigorously. Some boys experience tachycardia and are aware of their hearts beating. They usually die in their late-teens to mid-twenties—75% from respiratory causes and approximately 25% from severe left ventricular failure.

Laboratory Tests

Laboratory investigations of muscle are performed primarily via four methods: biochemical analysis, electromyography, DNA analysis, and histologic examination. Several muscle enzymes are released from the sarcoplasm when muscle fibers are damaged. Creatine kinase (CK) is measured most commonly. Isoenzymes of CK are found in different tissues, including the brain, but not in hepatocytes. The normal serum concentration of CK varies with age, sex, and physical activity. After significant and prolonged physical activity, the serum concentration of CK may be elevated 5 to 10 times that of normal. Other causes of an elevated serum CK value include trauma, inflammatory muscle disorders from a variety of causes (bacterial, viral, and immunologic), idiopathic myositis, rheumatoid arthritis, spinal muscular atrophy, and mus-

cular dystrophies. The most spectacular elevation of serum CK (50 to 100 times normal) occurs in DMD. It is elevated at birth before there is clinical evidence of muscle weakness.

Other muscle enzymes whose concentrations are elevated in the blood include aspartate aminotransferase, alanine aminotransferase, and lactic dehydrogenase, which also are found in hepatocytes. When concentrations of these enzymes are elevated in serum, they may be misinterpreted as having a hepatic origin and indicating abnormal liver function. An elevated gamma-glutamyl transferase value helps to differentiate a hepatic source from a muscle source because it is not found in muscle. CK is the most useful marker of muscle disease.

Electromyography is the recording of muscle electrical activity by an electrode, both surface and needle. With needle electrodes, electrical activity is measured on insertion, at rest, and during muscle contraction. At rest, healthy muscle usually is electrically silent. Spontaneous activity, as would be seen with muscle fasciculations and fibrillations, usually reflects neurogenic causes or myopathic disorders such as congenital myotonia. Electromyographic changes in DMD are nonspecific and of little use in establishing the diagnosis.

The molecular techniques for complimenting the diagnosis of muscular disorders have advanced significantly in the past few years. Approximately two thirds of boys who have DMD have gene deletions; an additional 5% to 10% have a duplication within the DMD gene. If a mutation is not detected by direct analysis, a linkage analysis might be required to assess the carrier risk. These advances have reduced the number of boys requiring a muscle biopsy for diagnosis and have greatly facilitated carrier detection for genetic counseling. The remaining 10% to 20% of boys require a muscle biopsy to confirm the clinical and biochemical suspicion of DMD. Mothers of isolated cases of DMD/Becker muscular dystrophy (BMD) where there is no family history have a recurrence risk of approximately 10% due to a germline mosaicism. BMD is a milder allelic form of DMD.

A muscle biopsy is a very useful diagnostic tool but less so if the CK concentration and electromyography results are normal. The biopsy can be either a needle biopsy or an open biopsy. Histopathology and histochemistry are the two techniques used most commonly. Electron microscopy is most useful in diagnosing mitochondrial disorders of muscle, and findings may be normal early in

the course of disease or when the muscle changes are not present in all muscles. Sampling errors also can occur late in the course of disease when the typical histopathologic changes no longer are seen.

The histologic changes in DMD depend somewhat on the muscle selected and the age of the boy. When the boys are very young, the histologic changes are minimal and include some focal areas of inflammation and muscle degeneration or regeneration. With time, muscle fibers are replaced with fibrous and fatty tissue along with inflammatory cells. Dystrophin, as assessed by immunohistochemical staining, is absent or nearly absent.

Management

Rehabilitation

Management must be multidisciplinary to accommodate the patient's complex and changing needs over time. Initially, around the time of diagnosis, genetic counseling and psychosocial support for the boy and family members are important. Referral usually is made to a pediatric rehabilitation program for ongoing management. Early rehabilitation goals focus on promoting mobility and maintaining good ankle positioning through physical therapy and orthotic devices. Moderate activities such as swimming and biking are encouraged. Excessively strenuous activities and fatigue should be avoided.

Obesity is common and can have a major impact on such areas as quality of life, life expectancy, and burden of care. Some boys who are thin and weigh less than the 10th percentile may require extra calories, but excessive weight gain often becomes apparent for many boys between 7 and 10 years of age. This frequently is the time when physical activity is declining and replaced with boredom, increased television viewing, and playing of electronic games. Inappropriate food intake also is common. Nutritional management is most important and frequently requires alterations in the eating habits of all family members.

Some centers advocate the use of surgical tendon lengthening to prolong ambulation. Night splints for the feet and ankles may provide an effective passive stretch to maintain a good range of motion at the ankles and reduce the tendency to toe-walk. Some centers advocate the use of long leg braces or calipers to prolong ambulation. However, some feel that these are heavy and cumbersome and do not really facilitate a functional gait. Some boys say that they are afraid of falling when they are standing in the long leg braces.

Corticosteroids

Despite recent advances in our understanding of the molecular and genetic aspects of DMD, very few treatments exist. Corticosteroids delay the very predictable and relentless progression of muscle weakness; their mechanism of action is unknown. Two corticosteroids, prednisone and deflazacort, seem to be equally effective and the most effective when administered daily. Prednisone can delay the progression of muscle weakness, but it often is associated with significant adverse effects. Weight gain can be particularly problematic.

Deflazacort is an oxazolone derivative of prednisone. It can preserve muscle function as well as prednisone but often without the tendency for excessive weight gain encountered in most boys treated with daily prednisone. We have used a regime of daily deflazacort for more than a decade. The long-term benefits are significant and include improved ambulation, preservation of pulmonary and cardiac function, a significant reduction in the incidence of scoliosis, and maintenance of arm function required for feeding and self-care. There may be adverse effects, but they usually are acceptable. The boys' appetites may increase, requiring strict dietary control. Their height may be reduced, but that could be considered a benefit because less work is required of the short person for activities such as walking and climbing stairs. Fifty percent of the boys develop asymptomatic posterior, subcapsular cataracts that do not impair their vision and do not require treatment.

Boys who have DMD develop osteopenia of immobility and have an increased risk for developing fractures. In our experience, many boys who have DMD and have been treated with deflazacort have reduced bone mineral density but not a significantly greater incidence of long bone fractures. We recommend daily vitamin D and calcium supplementation. When fractures do occur, the period of immobilization should be as short as possible. When possible, this can be achieved by surgical stabilization rather than casting and 4 to 6 weeks of immobilization. We have not seen hypertension, glucosuria, or an increased susceptibility to infection or gastric ulcers in affected boys. We normally continue the steroids after the boys stop ambulating.

Longer-term studies are needed to determine the duration of deflazacort benefits. Our findings to date indicate that deflazacort has had a significant impact on the natural history of this progressive and fatal muscle disease, improved the quality of life for the boys and their families, and reduced the burden of care in the second decade.

School Issues

Many boys who have DMD have significant learning issues. Their schools must accommodate both physical and learning needs. The family, the school, and the rehabilitation team need to communicate with each other and work together. Some suggestions for the school environment include seating the child near the door and allowing “free” bathroom privileges. The desk may need to accommodate a wheelchair. Learning to read should not be pushed if the child is not ready. He may have difficulty understanding complex, multi-stepped tasks, and his frustration may interfere with learning. Computer skills should be encouraged early. Enjoyable activities should be found for the child and emphasized. These children may need assistance with classroom and bathroom activities. The teacher should be encouraged to learn about DMD and approaches that might facilitate and strengthen school experiences.

As independent ambulation becomes more compromised, rehabilitation issues shift to mobility equipment and accessibility for the home and school. The rehabilitation team now expands to include expertise from cardiology, pulmonology, orthopedics, gastroenterology, and nutrition colleagues. Transportation needs to be accommodated. The occupational therapist assumes a more active role for many issues, including accessibility, activities of daily living, communication and writing aids, and feeding and swallowing. Spinal alignment requires close monitoring, along with a medical focus on pulmonary and cardiac function.

The entire family needs support as major decisions are being contemplated, major costs are incurred, and major changes are occurring. Psychosocial support for family members is very important. Support groups and reliable muscular dystrophy-oriented Web sites can provide information about management, research, and education. Two such sites are www.parentprojectmd.org and www.mdausa.org.

Future Treatments

Although only corticosteroids offer any therapeutic benefit today, the future holds real promise. Much can be learned from dystrophin-deficient animal models, including the mouse, dog, and cat. With specific exon deletions being identified in the DMD gene, opportuni-

ties for gene repair or gene “patching” are being pursued. For boys whose genetic defect is not a deletion but a stop codon, attempts to “jump this point mutation” and create some read-through of the dystrophin gene are being pursued with compounds that include the aminoglycoside gentamicin and PTC 124.

Another therapeutic approach rests with gene transfer rather than gene repair. Genetic material can be transferred several ways. These include giving the isolated DNA, usually packaged in some type of transport “vehicle,” such as an adenovirus or adeno-associated virus, to the host. Other sources of genetic material include myoblasts and stem cells. Although important progress is being made in genetic transfer, clinical trials are still in the future.

Finally, pharmaceuticals (in addition to corticosteroids) directed at the various facets of the pathologic cascade (eg, inflammation, fibrosis, membrane damage) leading to muscle death may offer some relief or attenuation of this progressive and fatal disease of skeletal and cardiac muscle.

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. For children who have DMD, the absence of dystrophin primarily affects normal physiology within the:
 - A. Anterior horn cell.
 - B. Muscle cell membrane.
 - C. Muscle cell mitochondria.
 - D. Muscle-nerve junction.
 - E. Peripheral nerve.
2. An 11-year-old boy who has DMD is now using an electric wheelchair as his primary method of mobility. Over the next 5 years, the likelihood of him developing a significant spinal curvature is *closest* to:
 - A. 10%.
 - B. 30%.
 - C. 50%.
 - D. 70%.
 - E. 90%.
3. Many laboratory approaches have been described to diagnose DMD. The *most* systematic order for this assessment is:
 - A. Molecular testing, muscle biopsy, muscle enzyme.
 - B. Molecular testing, muscle enzyme, muscle biopsy.
 - C. Muscle biopsy, muscle enzyme, molecular testing.
 - D. Muscle enzyme, molecular testing, muscle biopsy.
 - E. Muscle enzyme, muscle biopsy, molecular testing.
4. Corticosteroids represent one of the few treatments for DMD, although their mechanism of action is unknown. Adverse effects of this intervention include the risk of increased:
 - A. Intraocular pressure.
 - B. Linear growth.
 - C. Osteopenia.
 - D. Scoliosis.
 - E. Susceptibility to infection.
5. For mothers of children who have DMD in whom molecular testing results are negative and there is no family history of similar disorders, the recurrence risk is approximately:
 - A. 0%.
 - B. 10%.
 - C. 25%.
 - D. 50%.
 - E. 100%.

Care of the Well Newborn

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Author Disclosure
Drs Stellwagen and Boies did not disclose any financial relationships relevant to this article.

Objectives After completing this article, readers should be able to:

1. Describe the purpose of the prenatal visit.
2. Recognize the significance of common abnormalities found on prenatal ultrasonography.
3. Discuss the importance of growth and maturity assessment as well as the careful examination of the newborn.
4. Delineate prevention strategies for hepatitis B, syphilis, and group B streptococcal infections.
5. Explain the basics of car seat safety and sudden infant death syndrome prevention in the newborn unit.
6. List the basic tenets of providing breastfeeding support for the breastfeeding mother and infant.
7. Explain appropriate outpatient follow-up for the healthy newborn.

Introduction

Recent advances in obstetrics and pediatrics have brought about numerous changes in the care of the healthy newborn and have led to a re-evaluation of old routines, a commitment to helping mothers breastfeed their infants exclusively, and improvements in infant medical care and safety. In this article, we review the care of the newborn, including issues of antenatal testing, the prenatal visit, delivery, care on the postpartum/newborn unit, discharge from the hospital, and the first outpatient visit, emphasizing contemporary practices.

Prenatal Visit

The most important focus of the prenatal visit is to begin a positive relationship with the parents. In addition, data can be recorded about pertinent medical and psychosocial history and potential high-risk situations, and basic education of the family regarding their newborn can begin. The clinician needs to address the following:

- The mother's medical and pregnancy history, including any history of depression and use of medication, tobacco, or other substances
- Maternal and paternal family medical history, including ethnicity, history of atopy, diabetes, neonatal jaundice, and children who have birth defects or serious illness
- Social history, including parental employment, education, planned maternity/paternity leave, and the individuals who will be the support system for the expectant parents
- Feeding plan and discussion of current breastfeeding recommendations
- Anticipatory guidance

Abbreviations

AAP:	American Academy of Pediatrics
CDC:	Centers for Disease Control and Prevention
GBS:	group B <i>Streptococcus</i>
HBV:	hepatitis B virus
HIV:	human immunodeficiency virus
IUGR:	intrauterine growth restriction
LGA:	large for gestational age
SGA:	small for gestational age
SIDS:	sudden infant death syndrome
US:	ultrasonography
VCUG:	voiding cystourethrography

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- Routine office procedures, including office hours, other clinicians in the office, telephone triage, and after-hours routines

Hospital Care of the Newborn

Maternal History

At the time of the first postnatal examination, a history of the mother should be elicited and her obstetric chart reviewed, including:

- Pregnancy-related health issues
- Blood type, Rh antigen, red blood cell antibody status, and infant blood type, if known
- Prenatal laboratory values: hepatitis B, syphilis, rubella, group B *Streptococcus* (GBS) culture, glucose tolerance test, purified protein derivative, human immunodeficiency virus (HIV), hepatitis C (if obtained), sexually transmitted disease screening, and drug screening

The most important focus of the prenatal visit is to begin a positive relationship with the parents.

- Antenatal testing results, including triple screen, antenatal ultrasonography (US) reports, and chromosome analysis
- Medications
- Lactation history and history of breast abnormalities or surgery
- Family/social history, if not obtained prenatally

Antenatal US Findings

Clinicians need to know the postnatal management of infants who exhibit common abnormal findings on US.

Choroid plexus cysts are seen commonly on US prior to 24 weeks' gestation. If not associated with other anomalies, they are unlikely to be of any significance. There is no need for follow-up assessment if results of the baby's physical examination are normal.

Echogenic intracardiac focus is a bright spot near the papillary muscle of the left ventricle. There is a correlation with trisomy 21, but it is a normal finding in most cases. If the antenatal karyotype was normal or the baby does not have clinical findings suggestive of Down syndrome, the family can be reassured that the baby needs no further testing.

Echogenic bowel may be a marker for aneuploidy, cystic fibrosis, congenital infections, or rare intestinal disorders. However, most infants who exhibit this finding are normal. The mother may have undergone fetal karyotype, cystic fibrosis, and cytomegalovirus testing before delivery. If the baby appears normal on physical examination and if the antenatal testing results were negative, the baby needs no further testing. The primary care practitioner should be aware of the finding in case other signs arise in the future.

Mild enlargement or asymmetry of the cerebral ventricles may have more significance. Often the obstetric service performs serial US, karyotype, and cytomegalovirus and toxoplasmosis testing. In addition to a physical examination, we recommend performing a cranial US after delivery to document the brain anatomy and the size and concordance of the ventricles. An infant who has abnormal findings on physical examination or US should be referred for consultation. These findings, when mild, often represent normal variation. However, children whose ventricles are enlarged or asymmetric may be at risk for neurodevelopmental problems.

Hydronephrosis is found on fetal US in as many as 4.5% of pregnancies. Many affected infants have some abnormality found on postnatal evaluation. Generally accepted criteria for fetal hydronephrosis are greater than 4 mm renal pelvic dilation in the antero-posterior diameter in the second trimester and greater than 7 mm dilation in the third trimester. Infants who meet these criteria should undergo postnatal renal US. Caliectasis, which refers to dilation of the calyces, may be more significant and warrants postnatal evaluation even if the fetus does not reach the previously noted thresholds for size. Opinions differ about the necessity of performing voiding cystourethrography (VCUG). Normal renal US findings do not rule out vesicoureteral reflux. Recent studies confirm that 10% to 30% of newborns who have antenatal hydronephrosis have vesicoureteral reflux and are at risk of renal scarring from urinary tract infection. (1) Depending on the assessment of patient compliance with follow-up, the renal US and VCUG may be performed during the newborn stay or later as an outpatient. If results of the full evaluation are normal, but it was performed in the days after delivery, a repeat US at 2 to 3 months of age may be prudent to assure that mild hydronephrosis was not missed. Infants who are not yet evaluated or have been found to have abnormalities should

be discharged on prophylactic antibiotics. Infants who are known to have bladder outlet obstruction, cystic kidneys, high grades of hydronephrosis, or reflux require prompt urologic referral. Those who have mild hydronephrosis or low-grade reflux can be seen by a urologist after hospital discharge.

Delivery

Understanding the impact that labor and delivery have on the baby as well as the metabolic and physiologic adaptation involved in the transition to extrauterine life is important. The clinician should be aware of fetal and maternal risk factors for neonatal depression. Antenatal evaluations such as nonstress tests and other assessments of fetal well-being, which may provide information about the adequacy of the intrauterine environment and uteroplacental function, should be reviewed. A biophysical profile includes results of a reactive nonstress test and assessments of fetal breathing, heart rate, tone, and amniotic fluid levels (fluid levels reflect fetal urinary output and, thus, renal perfusion).

Approximately 10% of infants require some form of resuscitation; 20% of such infants require aggressive intervention. Because resuscitation may be an infrequent event, preparation of staff and equipment is paramount. Physicians should familiarize themselves with their hospital's delivery suite, equipment, and staffing. The American Academy of Pediatrics (AAP) and the American Heart Association's Neonatal Resuscitation Program is an excellent standard for neonatal care in the delivery room (<http://www.aap.org/nrp/nrpm.html>).

Most infants begin effective respirations following delivery and should establish regular respirations by 1 minute of age. An infant who has primary apnea and fails to respond to stimulation generally responds to bag and mask ventilation. The clinician must be familiar with the bag and mask that he or she will be using, know how to obtain a good seal with the mask, and be able to judge the infant's response to ventilation. Periodic practice sessions with a mannequin or mock codes may help maintain skills. Vigorous babies who are delivered through meconium do not require intubation. Common errors in delivery room resuscitation include overly vigorous stimulation of an infant who has apnea and inappropriate or premature use of gastric suctioning.

Keeping the baby warm after delivery and during resuscitation minimizes heat loss. Newborns are at risk of heat loss due to their large surface area-to-body mass ratio. Cold stress can lead to depletion of important stores of the infant's fat and glycogen. A radiant warmer that has a servocontrolled mechanism should be available

in the delivery area for babies who need resuscitation. Healthy infants should be dried, covered with dry linen, and kept warm. Placing infants skin-to-skin with the mother immediately after delivery may promote bonding and breastfeeding success while keeping the baby warm. (2)

The Apgar score (a table can be found in *Guidelines for Perinatal Care* (3)) has been used for many years to assess an infant's transition to extrauterine life. The 1-minute Apgar score reflects the infant's intrauterine environment and tolerance of the delivery process. The 5-minute score reflects the success of the infant's transition. The scores can provide information about the initial status of the baby and the response to interventions as well as help predict neonatal survival. However, Apgar scores should not be used to make decisions about the initiation or method of resuscitation. Cord blood gases may provide more useful information about the baby's physiologic status and the magnitude of any preceding hypoxic-ischemic insult. Infants who have 5-minute Apgar scores of less than 7 are at risk for suboptimal transition and may require close observation. Infants whose 5-minute Apgar scores are 3 or less need very careful subsequent monitoring and observation, often requiring intensive care. The ability of the infant to maintain his or her temperature and sustain a normal heart and respiratory rate generally indicates a successful transition.

After Delivery

Placing the healthy newborn skin-to-skin on the mother's chest immediately after birth may facilitate breastfeeding by encouraging latch-on during the baby's early alert period. (3) Infants often root and find the breast with minimal assistance. Vitamin K and erythromycin administration, as well as weighing and measuring the baby, can be delayed for 1 hour to allow this important mother-child interaction.

Nursing Routines

The infant's vital signs, including temperature, respiratory rate, heart rate, and pain assessment, should be monitored frequently in the first hours after birth until stable (and then per hospital routine). Blood pressure does not need to be assessed routinely in healthy babies. Blood pressure measurements are needed when infants are not transitioning well (blood pressure norms vary with gestational age). Parents should be instructed in skin and cord care. Studies that have evaluated cord care practices have not documented superiority of any one method. The recent trend of dry cord care without the application of antimicrobial agents has not led to in-

creased infection rates in newborns delivered in developed countries. (4)

Soon after birth, infants at risk for specific problems such as infection, hypoglycemia, HIV, or hepatitis B and those exposed to maternal medications should be identified because they may need additional screening. Medical problems diagnosed prenatally should be brought to the attention of the supervising clinician. The infant should be weighed daily and the percent weight loss from birth recorded on the bedside chart. Healthy infants may lose 2% to 3% of their birthweight daily for the first 2 to 3 postnatal days. When breastfeeding is optimal, the infant's weight loss begins to plateau after 48 to 72 hours, and an infant whose weight is more than 7% to 8% below birthweight should be evaluated. Excessive loss may indicate feeding problems such as inadequate milk or colostrum supply or poor milk transfer. Hospital routines that involve initial feeding of newborns with formula should be avoided in the absence of medical indications. Sterile water or glucose water should be avoided in newborns because of the risk of hyponatremia.

First Examination

Before examining the infant, the clinician should review the baby's gestational age, growth parameters, and vital signs. Starting with the best obstetric dates, the examination of the baby can aid in assigning a correct gestational age.

A tool such as the new Ballard score (a figure of which can be found in *Guidelines for Perinatal Care* (3)) can be used to assess maturity. A preterm infant is defined as one whose gestation is fewer than 37 weeks, a term infant as one whose gestation is between 37 and 41 6/7 weeks, and a postterm infant as one whose gestation is 42 weeks or greater. Near-term refers to infants whose gestations are 35 to 37 6/7 weeks.

The weight, length, and head circumference should be plotted on standardized growth curves (available at <http://www.cdc.gov/growthcharts>). Infants whose birthweights are less than 2,500 g are referred to as being of low birthweight. Infants whose birthweights are below the 10th percentile are referred to as being small for gestational age (SGA). Babies can be small because they are preterm or constitutionally small or because they have experienced inadequate prenatal growth. Infants whose birthweights are greater than the 90th percentile are considered large for gestational age (LGA) and may be at risk for hypoglycemia and birth trauma (clavicular frac-

ture, scalp hematoma, brachial plexus injury). Intrauterine growth restriction (IUGR) refers to a baby who does not follow the expected prenatal growth pattern. The prenatal history, placental examination, or infant examination may explain the cause of the poor growth. Additional laboratory tests may be needed. Such small or poorly grown babies are at higher risk for problems related to poor reserve and increased metabolic requirements, including problematic transition, poor feeding, hypothermia, hypovolemia, and hypoglycemia. Postterm babies also may experience IUGR and be at risk for similar problems as well as for meconium aspiration and pulmonary hypertension.

Performance of the infant's first physical examination in the presence of the parents allows the clinician to assess the infant's transition and evaluate for abnormalities while highlighting the strengths of the healthy newborn and providing family-centered care. The examination should take place in a quiet area with good lighting and the necessary instruments to examine the newborn from

Approximately 10% of infants require some form of resuscitation; 20% of such infants require aggressive intervention.

head to toe. As the baby is examined, the clinician should narrate the findings to engage the parents' interest. Performing the less invasive aspects of the examination first, before fully undressing the baby, makes the examination easier. During the examination, the clinician also can assess the quality of the infant-parent interaction; the developmental strengths of the infant; and the infant's posture, tone, color, and state. A direct ophthalmoscope should be used to visualize the retinal red reflex and a bright light to inspect the palate. Time should be taken to calm the baby so the assessment of heart, lungs, abdomen, and hips is optimal. The baby may have undergone a stressful birth process that could result in injuries, bruising, or physical signs of stress.

The gestational age of the infant should be confirmed as predicted by dates. Preterm infants may have abundant vernix, decreased subcutaneous fat, pink thin skin, decreased tone, and immature reflexes. A normally developing term infant should be pink and chubby, alert and able to fixate visually, and have normal muscle tone and

Table 1. Near-term Order Set

- Lactation evaluation within 24 hours of delivery
- Mother to pump breasts every 3 hours after nursing unless infant nurses vigorously
- Infant put to breast at least every 3 hours; observe latching-on three times per day
- Consider supplement after nursing with expressed breast milk (or formula if needed) if weight loss is more than 3% per day, the infant is feeding poorly, or weight is less than 2,500 g
- Keep baby skin-to-skin or well bundled
- Take temperature every 3 hours prior to feeding

reflexes. Postterm infants may have decreased subcutaneous tissue, dry or peeling skin, and wrinkled skin or sparse hair, reflecting their malnutrition. Babies who experience IUGR may lack subcutaneous fat and have an alert, wide-eyed, or anxious appearance.

Care of Near-term Infants

The care of the healthy near-term infant (born between 35 and 37 6/7 weeks' gestation) deserves special consideration because these babies often appear robust but may have physiologic vulnerabilities. Such infants, even if weighing more than 3,000 g, are physiologically immature and may not feed well. They are prone to hypothermia, hypoglycemia, jaundice, kernicterus, dehydration, breastfeeding problems, and an increased rate of readmission. (5) Preterm infants have a greater daily fluid requirement per kilogram of body weight and often require more calories per kilogram per day than do term infants. Insensible water loss is increased with prematurity, phototherapy, and the use of radiant warmers. Infants born at fewer than 37 weeks' gestation at our hospital are monitored for 12 hours in the transitional unit and transferred to couplet care when their vital signs are stable. With lactation assistance, maternal breast pumping, and judicious use of supplementation, these babies breastfeed well. We have a specific written order set for the near-term infant that addresses their physiologic vulnerabilities (Table 1). Clinicians should consider keeping these infants (with their mothers) in the hospital until they are feeding well and gaining weight. Infants fewer than 37 weeks' gestation need a car seat test prior to discharge, which involves a 1- to 2-hour observation of heart rate, respirations, and oxygen saturation while in the car seat. (6)

Table 2. Evaluation of Delayed Voiding or Stooling

Delay in voiding (more than 24 hours after birth)

- Repeat examination of abdomen and genitalia
- Assess for adequacy of feeding
- Catheterize baby to see if urine is present
- Obtain urinalysis
- Check blood urea nitrogen and creatinine levels
- Order renal ultrasonography
- If baby begins to void spontaneously and is observed to have no further problem, evaluation need not be completed
- If baby continues not to void, urology referral may be needed

Delay in stooling

- Repeat examination of abdomen and rectum
- Assess for adequacy of feeding
- If no stool at 48 hours, order barium enema to evaluate for Hirschsprung disease
- Order surgical consultation for rectal biopsy
- Observe for signs of intestinal obstruction, hydration, and feeding until a diagnosis is established

Breastfeeding

Policy makers, scientists, and parents increasingly have recognized that breastfeeding is the optimal method of infant feeding. Pediatricians need the knowledge and skills to help mothers make informed decisions and assist them with breastfeeding. To that end, we encourage all clinicians to review the recently published AAP policy statement on breastfeeding and the use of human milk. (2) Key points of the statement include:

- Recommend human milk for all infants except where contraindicated
- Educate and support both parents about the importance of breastfeeding and strategies for dealing with common problems that may arise
- Put healthy infants skin-to-skin after delivery and have them remain there at least until the first feeding is accomplished (longer if possible)
- Avoid procedures that may interfere with breastfeeding
- Avoid supplements of water or formula unless a medical indication exists
- Avoid using pacifiers during the initiation of breastfeeding
- Encourage mothers to feed the infant whenever he or she demonstrates interest in feeding or suckling, at least 8 to 12 times a day

- Conduct a formal evaluation of breastfeeding twice daily while in the hospital
- Provide close follow-up in the days following hospital discharge
- Know that exclusive breastfeeding for 6 months provides optimal infant nutrition
- Have mother and infant sleep in proximity to one another
- Should either mother or infant need hospitalization, make every effort to maintain breastfeeding or provide human milk for the infant

Norms of Renal and Gastrointestinal Function

Most infants void by 12 hours of age and pass stool by 48 hours. If either function is delayed, such delay must be evaluated prior to discharge. Clinical evaluation of a healthy infant who has delays in voiding or stooling is shown in Table 2.

Routine Screening and Testing

Blood glucose screening should be performed on infants at risk for hypoglycemia, including infants of diabetic mothers, low-birthweight infants (<2,500 g), SGA infants (<10th percentile for weight), LGA infants (>90th percentile for weight), infants experiencing hypothermia, and infants who have signs of hypoglycemia or sepsis. Such infants may require additional therapy and testing if their blood glucose levels are not maintained in the normal range with routine feeding.

Hearing screening of all newborns is the standard of care across the United States. Some 1 to 3 per 1,000 newborns have bilateral hearing loss. Multiple studies have confirmed the long-term benefit of early identification of the hearing-impaired infant. Each hospital should develop a plan for screening infant hearing. Either otoacoustic emission or auditory brainstem response screening provides efficient noninvasive screening of newborns; both methods are associated with low rates of follow-up testing. Clinicians should understand the basics of infant hearing screening and follow-up for hearing-impaired infants.

Newborn metabolic/genetic screening should be performed on every newborn according to the newborn screening program mandated in each state. Tandem mass spectrometry technology allows expanded screening for many inborn errors of metabolism, but is not yet standard in all states. There is evidence that this new method

ensures earlier diagnosis of affected infants and may decrease morbidity and parental stress related to the infant's diagnosis. (7) The infant's clinician is responsible for appropriate testing, follow-up of abnormal test results, coordination of care with the subspecialist if the child is found to have a disorder, and maintenance of accurate records. As with all chronic disorders, pediatric clinicians should assist the family by explaining the disease or test results and referring them to the appropriate community services.

The clinician must understand current prevention strategies for hepatitis B virus (HBV) transmission. The AAP Committee on Infectious Diseases and the Centers for Disease Control and Prevention (CDC) have created guidelines to prevent transmission of HBV from mother to infant. Current guidelines recommend screening all pregnant women, vaccinating all newborns, administering hepatitis B immune globulin and vaccine to all infants born to HBV surface antigen-positive mothers, and determining HBV serologies on high-risk infants at 9 to 15 months of age.

GBS infection has been a leading cause of neonatal morbidity and mortality since the 1970s. Strategies to

Healthy infants may lose 2% to 3% of their birthweight daily for the first 2 to 3 postnatal days.

prevent transmission of GBS from mother to infant have reduced the incidence of early-onset GBS disease from 1.7 per 1,000 live births in 1993 to 0.6 per 1,000 live births in 1998. The recently published CDC guidelines for prevention of perinatal GBS disease recommend that: 1) all pregnant women be screened for GBS at 35 to 37 weeks' gestation, 2) these results be available to the baby's clinician, 3) all GBS-positive mothers receive intrapartum antibiotic prophylaxis, 4) the asymptomatic infant of a GBS-positive mother who received appropriate intrapartum antibiotic prophylaxis generally not receive sepsis evaluation or treatment, 5) the infant of a GBS-positive mother who did not receive proper intrapartum antibiotic prophylaxis receive a sepsis evaluation and possibly further evaluation or treatment, and 6) infants undergo a full diagnostic evaluation and treatment if the mother is suspected of having chorioamnionitis.

Mothers generally are tested serologically for syphilis

Table 3. Ten Key Elements in Preventing Severe Hyperbilirubinemia (8)

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin or transcutaneous bilirubin of infants who exhibit jaundice in the first 24 hours after birth.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels relative to the infant's age in hours.
6. Recognize that infants born at fewer than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Assess all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

early in pregnancy, and the American College of Obstetrics and Gynecology recommends a repeat test at delivery. Protocols for management of mothers and infants who have positive syphilis test results should address the diagnosis and treatment of infants who have congenital syphilis or those born to the inadequately treated mother as well as follow-up for the infant who has a passively acquired positive syphilis blood test.

Vitamin K administration after delivery reduces the risk of hemorrhagic disease in the newborn. Concerns about increased risk of malignancy from vitamin K injection are unfounded. Skeptical parents can be referred to the AAP policy statements of 1999 and 2003. Reviewing package inserts with families also may allay fears of additives or preservatives.

Erythromycin eye ointment for the prevention of ophthalmic gonorrhea is recommended.

Common Problems

Recent concerns about kernicterus have led to the recommendation that newborns receive specific care to prevent severe hyperbilirubinemia. There are several risk factors for excessive production or decreased elimination

Table 4. Safe Sleep Instructions

- Always have baby sleep on the back (supine)
- Place the baby on a firm mattress in a safe sleep environment
- Avoid loose bedding, pillows, and blanket rolls and use proper sleep clothing
- Avoid overheating
- Avoid waterbeds, soft mattresses, and sofas
- Avoid cigarette smoke exposure
- Avoid nonparent adults, children, or pets in the bed
- Encourage breastfeeding
- Discuss risks and benefits of cosleeping

of bilirubin that may lead to hyperbilirubinemia. The increase in breastfeeding rates, the multiethnic population in the United States, and early discharge of newborns all have contributed to the increase in babies who have significant hyperbilirubinemia. The recent AAP policy for the prevention of hyperbilirubinemia outlines 10 key elements (Table 3). (8) We recommend that each newborn unit develop a policy that addresses these key points. The AAP Web site provides answers in English and Spanish to frequently asked questions that can be used for parent education (www.aap.org).

Developmental dysplasia of the hip refers to the presence of an unstable, subluxated, dislocated, or malformed hip. The incidence is approximately 11.5 per 1,000 infants, but infants who have risk factors have a much higher rate. The AAP practice parameter of April 2000 provides an excellent review of the problem. (9) The standard of care is for all infants to have repeated hip examinations until they are walking well. Pediatric clinicians should document each hip examination in the medical record. Newborns who have positive Ortolani or Barlow signs need orthopedic referral; infants who have equivocal signs may be re-examined in 2 weeks and referred if the signs persist. Those who have risk factors, such as breech presentation or a positive family history, should undergo screening hip ultrasonography at 4 to 6 weeks of age, even if the physical examination results are normal.

Pain assessment and management is important. Every newborn unit should have a procedure to assess and document pain in the newborn. Offering newborns the breast, sucrose solution, or non-nutritive sucking is recommended for infants undergoing painful procedures. When a newborn male is being circumcised, adequate analgesia in the form of a regional nerve block or topical anesthetic cream should be used for pain reduction.

Deformational plagiocephaly and brachycephaly are

becoming increasingly common. The causes are many, with excessive time on the back, use of infant positioning devices, and the presence of torticollis all probably contributing. Infants who are born with a head turn preference and are not given adequate “tummy time” may quickly develop positional cranial flattening. The excessive use of infant seats, car seats, and “travel system” strollers probably also contribute. (10) Parents should be instructed how to prevent plagiocephaly, reminding them always to place the baby in a supine position for sleep. Recommendations include altering the baby’s head position and body orientation when putting him or her to sleep, placing the baby prone when awake as much as possible during the day, minimizing the use of infant seats, using the car seat primarily in the car, and using front carriers and slings when the baby can support his or her head.

Safety

Prevention of sudden infant death syndrome (SIDS) begins in the newborn unit. The supine sleeping position has reduced the rate of SIDS by almost 50% in the last 12 years. Infant sleep position used by the hospital staff influences how parents position their babies. We recommend providing written materials about the other aspects of infant care that may affect the risk of SIDS (Table 4). Free educational materials can be obtained by contacting the National Institute of Child Health and Human Development Back to Sleep Campaign (phone: 800-505-CRIB (2742), www.nichd.gov/SIDS).

Car seat safety counseling should be provided by clinicians caring for newborns. The AAP has published recommendations for the safe transportation of newborns at hospital discharge: (11)

- Families should be informed of particular car seat laws in their state
- Maternity units should have provision for educating parents about car seat safety; Safe Ride News (www.saferidenews.com) and the National Highway Traffic Safety Association (www.nhtsa.gov) both provide up-to-date patient educational materials
- Every newborn should be discharged in a properly fitting car seat, and “hands-on” teaching should be part of the instruction provided to parents
- Infants younger than 37 weeks’ gestation require car seat safety testing before discharge

- The newborn unit may want to have free car seats and beds available for donation to indigent families or preterm infants who fail the car seat test, respectively

Discharge

Most infants are ready for discharge at 48 hours after a vaginal delivery and 72 to 96 hours after a cesarean section delivery. The infant is medically ready for discharge when he or she has stable vital signs for at least 12 hours, appears healthy and has normal results on physical examination, has stoolled and voided, is feeding well (or will be sent home after additional lactation evaluation with a feeding plan in place), has completed all screening tests, and has appropriate follow-up care planned. Additionally, parent education should be completed and competency demonstrated.

The care of the healthy near-term infant deserves special consideration because these babies often appear robust but may have physiologic vulnerabilities.

Early discharge prior to 48 hours may be appropriate for selected well infants. (12) Early discharge should only occur after a vaginal delivery; when the antepartum, delivery, and postpartum course are uncomplicated for both mother and baby; when the baby is term and appropriate for gestational age; and when the baby has been evaluated for jaundice. The family should be assessed for risk factors and prompt medical follow-up assured. Early discharge can benefit the family, improving bonding and attachment while minimizing iatrogenic risks. Complications of early discharge include delayed detection of treatable medical conditions, hyperbilirubinemia, poor feeding, early termination of breastfeeding, or hospital readmission.

The clinician must arrange for an outpatient visit within 2 to 3 days of discharge or determine that a mechanism is in place for parents to make the appointment. If a mother is discharged before her infant, every effort should be made to allow the mother to stay on the postpartum unit with her baby.

Outpatient Visits

As noted previously, the first outpatient visit must occur several days after hospital discharge to evaluate for hyper-

bilirubinemia, dehydration, and general well-being. The 2-week newborn visit no longer is viewed as an appropriate first outpatient appointment. We encourage the mother to bring her spouse or support person to the visit. The clinician should review pertinent aspects of the maternal history, newborn hospital course, and interim feeding and elimination and perform a physical examination. The 4- to 5-day-old infant who is consuming an adequate amount of human milk should have 6 to 8 voids and yellow, seedy stools daily; have lost no more than 7% to 8% of birthweight; and be satisfied after 20 to 30 minutes of nursing. The clinician should observe a feeding at the breast if the mother reports a problem with breastfeeding or if the infant has lost excessive weight. The infant who is not gaining weight may need to be supplemented with pumped human milk or formula, but every effort should be made to address the underlying breastfeeding problem.

Infants who have problems such as hip dysplasia, hearing screen failures, or abnormal antenatal testing results may need additional follow-up or referrals to a specialist.

Subsequent Visits

Many newborns, even those doing relatively well, benefit from a second outpatient visit about 1 week after the first to ascertain that appropriate weight gain (ie, at least 1 oz/d) and return to birthweight have been achieved. Office visits may occur every 2 to 3 days if adjustments are being made to feeding routines until the infant is gaining weight consistently. Other topics to cover include vitamin D supplementation, a review of metabolic/genetic screening results, and assessment of maternal mental health. High-risk situations, as in the case of a single mother, a teen parent, or a mother who has had limited or no prenatal care, should prompt specific questions about infant safety.

Postpartum Depression

During the weeks after delivery, the pediatric clinician is in an excellent position to screen for postpartum depression. Although 50% to 80% of all mothers experience “baby blues” during the first 2 weeks postpartum, 10% of mothers experience postpartum depression. “Baby blues” are characterized by heightened emotions and tearfulness and usually resolve by the third week after delivery. The mother may be assessed for depression with a standardized screening tool such as the Edinburgh Postnatal Depression Scale (<http://www.dbpeds.org>). Inquiring about the mother’s ability to eat, sleep when given a chance, and experience pleasure usually reveals depressive symptoms, if present. The pediatrician should refer the mother to her obstetrician or a psychiatric care

clinician when postpartum depression is suspected. If the mother is deemed at risk to injure herself or her infant or appears to be exhibiting psychotic symptoms, an emergent referral is mandated. It should be noted that most antidepressants are compatible with breastfeeding.

Conclusion

The mission of pediatric clinicians in caring for well newborns is to ensure the physical health and well-being of the child while supporting and educating the family during this critical time.

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. The infant must make many adaptations from the intrauterine to the extrauterine environment. A healthy newborn should be expected to establish regular respirations by:
 - A. 30 seconds.
 - B. 1 minute.
 - C. 2 minutes.
 - D. 3 minutes.
 - E. 4 minutes.

7. At a delivery, the attending pediatrician needs to be concerned about excessive heat loss in a newborn. The *most* likely reason for such heat loss in a newly delivered infant is:
 - A. Group B streptococcal sepsis.
 - B. Low Apgar score.
 - C. Maternal narcotics administered shortly before delivery.
 - D. Oligohydramnios.
 - E. The newborn's large surface area-to-body mass ratio.

8. First voiding by a newborn is an important function to document. *Most* newborns void by:
 - A. 3 hours.
 - B. 6 hours.
 - C. 9 hours.
 - D. 12 hours.
 - E. 15 hours.

9. For a number of reasons, pediatricians continue to receive pressure to permit a newborn to be discharged early after delivery. Early discharge now is considered to be before the age of:
 - A. 48 hours.
 - B. 72 hours.
 - C. 96 hours.
 - D. 120 hours.
 - E. 144 hours.

Group A Streptococcal Infections

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to this article.

Objectives After completing this article, readers should be able to:

1. Discuss the differential diagnosis of pediatric acute pharyngitis and the epidemiology and transmission of group A *Streptococcus* (GAS) pharyngitis.
2. Delineate the rationale for and the treatment regimens of GAS pharyngitis as well as the complications of GAS pharyngitis.
3. Know the carrier state of GAS.
4. Describe the clinical criteria for rheumatic fever and streptococcal toxic shock syndrome.

Introduction

Group A *Streptococcus* (GAS) causes the widest range of syndromes of any bacterium, including simple skin infections and pharyngitis, severe suppurative infections, the toxin-mediated streptococcal toxic shock syndrome (STSS), and immune-mediated illnesses such as acute rheumatic fever and acute glomerulonephritis. Specific manifestations of GAS infections represent the complex interplay of bacterial virulence factors and host immunogenetic factors.

Pharyngitis

GAS accounts for about 15% to 30% of acute pharyngitis cases in children. Children ages 5 to 11 years have the highest incidence of GAS pharyngitis, although it occurs among all age groups. The major rationale for accurate diagnosis and treatment of GAS pharyngitis is the prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). In temperate climates, GAS pharyngitis is more common during the winter and early spring months. The incubation period for streptococcal pharyngitis is short (2 to 5 days). Transmission occurs with close contact via inhalation of organisms in large droplets or by direct contact with respiratory secretions.

GAS is only one of the causes of acute pharyngitis; others are listed in Table 1. One of the most crucial decisions in evaluating a patient who has pharyngitis is whether to perform a rapid antigen test or bacterial culture of the throat for GAS. The clinician must keep in mind three important principles. First, accurate detection and treatment of GAS pharyngitis are needed to prevent ARF and other complications. Second, unnecessarily performing these tests in patients who present with typical viral upper respiratory tract symptoms (eg, rhinorrhea, cough, hoarseness) can result in the misdiagnosis of GAS pharyngitis in asymptomatic chronic GAS carriers who have an intercurrent viral illness. GAS pharyngeal carriers generally do not progress to invasive or immunologic sequelae and, therefore, do not require treatment with antimicrobials. Third, the phenomenon of the GAS carrier state negates the conclusion that a positive rapid GAS antigen test (or throat culture) result in a patient who has acute pharyngitis always means that the patient has GAS pharyngitis. Indeed, this is not always the case, but because it is difficult to prove a timely alternative diagnosis, antibiotic treatment usually is administered when test results are positive and the clinical findings are consistent with GAS infection. These three principles should remind

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Table 1. Non-Group A Streptococcal Causes of Pharyngitis

Bacteria	Viruses
Beta-hemolytic streptococci: groups C, G	Epstein-Barr
<i>Corynebacterium diphtheriae</i>	Adenovirus
<i>Arcanobacterium haemolyticum</i>	Enterovirus
<i>Neisseria gonorrhoeae</i>	Herpes simplex
<i>Chlamydophila pneumoniae</i>	Influenza
<i>Chlamydia trachomatis</i>	Parainfluenza
<i>Mycoplasma pneumoniae</i>	Rhinovirus
<i>Francisella tularensis</i>	Coronavirus
<i>Coxiella burnetii</i>	Respiratory syncytial
<i>Yersinia enterocolitica</i>	
<i>Yersinia pestis</i>	

the physician to obtain throat swabs only from patients whose symptoms are consistent with GAS pharyngitis.

Because pharyngitis accompanied by rhinitis, stridor, hoarseness, conjunctivitis, cough, or diarrhea is highly likely to have a viral etiology, a bacterial throat culture generally is unnecessary when these symptoms are present. Symptoms such as an abrupt onset of fever, throat pain, headache, abdominal pain, and dysphagia and signs such as exudative pharyngitis, palatal petechiae, uvulitis, and tender anterior cervical nodes suggest GAS pharyngitis. In addition, the absence of rhinitis, hoarseness, conjunctivitis, and cough is more suggestive of GAS pharyngitis. Patients who have symptoms for longer than 4 to 5 days are unlikely to have GAS pharyngitis, a self-limited illness that usually lasts 3 to 5 days even without therapy. An erythematous, diffuse, sandpapery exanthema combination known as scarlet fever sometimes accompanies GAS pharyngitis, as well as other streptococcal illnesses, and is caused by streptococcal pyrogenic exotoxins (A, B, C). The rash usually is concentrated in flexor skin creases (Pastia lines), blanches with pressure, and generally spares the circumoral region. Signs and symptoms suggestive of GAS pharyngitis are listed in Table 2.

Patients who have a constellation of signs and symptoms suggestive of GAS pharyngitis should be tested for infection by obtaining a throat

swab of the posterior pharynx. Relying solely on a clinical impression to decide if treatment is warranted results in the gross overdiagnosis of GAS pharyngitis and is discouraged. Because children younger than 3 years of age develop classic GAS pharyngitis infrequently and almost never develop acute rheumatic fever, documentation and treatment of GAS in this age group is optional.

Pharyngeal Complications of GAS Pharyngitis

GAS pharyngitis is a self-limited illness, generally not lasting more than 3 to 5 days, even in the absence of treatment. If a patient has not responded to treatment, complications or a nonstreptococcal illness must be considered. GAS pharyngitis can be complicated by peritonsillar cellulitis and subsequent abscess formation, usually occurring at the superior pole of the tonsil. Patients who have parapharyngeal abscesses usually are adolescents and present with severe sore throat, muffled voice, dysphagia, difficulty opening the jaw fully, and drooling, although some may appear well. In these instances, the posterior pharynx should be inspected for deviation of the uvula and unilateral bulging of the peritonsillar area. Gentle palpation of the peritonsillar area may reveal fluctuance.

Retropharyngeal abscess (abscess formation between the posterior pharyngeal wall and prevertebral fascia) also may complicate GAS pharyngitis. Affected children present with symptoms similar to those of GAS pharyngitis plus reluctance to move the neck. It usually occurs in younger children, and affected patients also may present with hyperextension of the neck. A lateral radiograph may help identify a retropharyngeal mass by demonstrating increased dimension of the retropharyngeal space at the level of C2 (normally 3 to 6 mm). Contrast-enhanced computed tomography is more precise than plain radiog-

Table 2. Clinical Signs and Symptoms Suggestive of GAS Pharyngitis

Symptoms	Signs*
Abrupt onset of fever, throat pain, dysphagia	Exudative pharyngitis
Headache	Palatal petechiae
Abdominal pain without diarrhea	Uvulitis
Absence of cough, hoarseness, rhinitis	Tender anterior cervical lymph nodes
Symptoms occurring for fewer than 5 days	Scarlet fever exanthem

*Viruses also cause exudative pharyngitis, lymphadenopathy

Table 3. Criteria for Streptococcal Toxic Shock Syndrome

Hypotension or shock plus at least two of the following:

- Renal impairment
- Disseminated intravascular coagulation
- Hepatic abnormalities
- Acute respiratory distress syndrome
- Scarletiform rash
- Soft-tissue necrosis

A definite case has hypotension, at least two of the above criteria, and isolation of GAS from a sterile body site

A probable case has hypotension and at least two of the above criteria and isolation of GAS from a nonsterile body site

raphy in showing posterior pharyngeal structures and abscess formation.

STSS

GAS and *Staphylococcus aureus* strains that produce superantigens or toxins that trigger massive cytokine release have been demonstrated to cause TSS. STSS often is accompanied by focal infection such as cellulitis or necrotizing fasciitis. Patients who have STSS and necrotizing fasciitis have a high rate of mortality. Defining characteristics of classic STSS include hypotension or shock plus at least two of the following six criteria: scarlatiniform rash, hepatic abnormalities, renal abnormalities, disseminated intravascular coagulation, respiratory distress syndrome, or extensive soft-tissue necrosis (necrotizing fasciitis). These disorders must occur in the absence of other explanations or other positive bacterial cultures (Table 3).

Nonsuppurative Poststreptococcal Diseases

ARF and poststreptococcal glomerulonephritis (PSGN) both follow acute GAS infection after an asymptomatic latent period; they virtually never occur in the same patient. ARF follows pharyngeal infection only; PSGN can follow either skin or pharyngeal infection. A full discussion of these illnesses is beyond the scope of this article, but they are discussed briefly.

Rheumatic heart disease remains the leading cause of acquired heart disease worldwide in children. The pathogenesis of ARF is not understood clearly, and no animal model exists, but it appears to be an immune response to GAS antigen(s) that cross-react with human tissue through molecular mimicry. The latent period following GAS pharyngitis is usually 2 to 4 weeks. Clinical criteria

Table 4. Jones Criteria for Diagnosis of Rheumatic Fever

Diagnosis requires one major and two minor or two major criteria along with supporting evidence of recent GAS infection

Major Criteria

- Carditis
- Polyarthritits
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor Criteria

- Arthralgia
- Fever
- Elevated acute-phase reactants
- Prolonged PR interval

Supporting Evidence of Recent GAS Infection

- Rising or elevated antistreptococcal antibody titers or positive throat culture or rapid antigen test

for ARF were developed by T. Duckett Jones in 1944, and the revised Jones criteria are still used to aid in diagnosis today (Table 4). Diagnosis requires supporting evidence of an antecedent GAS infection. In addition, two major criteria or one major criterion and two minor criteria are required. GAS infection can be documented by a positive throat culture or rapid antigen test or by an elevated or rising streptococcal antibody titer. Major criteria include carditis, polyarthritits, chorea, erythema marginatum, and subcutaneous nodules. Arthritis occurs in approximately 75% of affected patients, is usually migratory, and involves the larger joints. Carditis may involve any or all of the myocardium, pericardium, and endocardium. If carditis is present, valvulitis resulting in a cardiac murmur almost always is found. Echocardiographic evidence of valvular insufficiency without the presence of a cardiac murmur does not fulfill this criterion.

Erythema marginatum is a rare, serpiginous, macular, transitory rash seen in 4% of ARF patients. Subcutaneous nodules rarely occur and develop on the extensor surface of tendons. Sydenham chorea, sometimes called St. Vitus dance, is manifested by incoordination, an uncontrolled movement disorder, and facial grimacing that disappears in sleep and is exacerbated by stress. Because the latent period for the development of chorea extends for months (mean of approximately 5 mo) after the initial infection, titers of antistreptococcal antibodies are not always elevated at the time of its occurrence. Minor manifestations

of ARF include arthralgia, fever, elevated acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein), and prolonged PR interval on electrocardiography.

PSGN was described first in the early 19th century as hematuria following scarlet fever. The renal disease results from deposition of immune complexes in the glomerulus. PSGN usually follows about 10 days after GAS pharyngitis or about 3 to 4 weeks after GAS skin infection. Common findings include hematuria, edema, hypertension, and oliguria. Total hemolytic complement levels and C3 almost always are decreased in the initial illness, although C4 values usually are normal. Most children have a favorable prognosis.

Diagnosis

Because throat culture requires 24 to 48 hours for GAS diagnosis, rapid antigen detection systems for identification of GAS have been developed. Standard rapid antigen tests generally have very high specificity (95% to 98%), but their sensitivity varies from 70% to 90%. Sensitivity varies with inoculum quantity and technical expertise in processing and interpreting the sample. GAS pharyngitis, therefore, can be diagnosed presumptively with a positive standard rapid antigen test for GAS (confirmatory testing by culture is not needed), but a negative test result generally should be confirmed by a throat culture. Highly sensitive rapid antigen detection systems have been developed by using optical immunoassay technology. Rapid antigen tests using this technology have been shown in some studies to be as sensitive as the throat culture when performed in the office setting; some experts suggest that a confirmatory throat culture is not needed if a high-sensitivity rapid antigen test result is negative. This recommendation, however, remains controversial. Therefore, if physicians wish to rely on a high-sensitivity rapid antigen test alone, they should consider confirming the reliability of the assay in comparative studies with throat culture among their own patients before using this test without backup cultures in daily practice.

Throat culture has long served as the gold standard for diagnosis of GAS pharyngitis and has a 90% to 95% sensitivity for identifying GAS in the nasopharynx. Proper specimen collection is important to increase culture sensitivity. It is optimal to rub both tonsils and the posterior pharyngeal wall with a cotton- or synthetic

fiber-tipped swab. Specimens should be inoculated promptly or placed in transport media, then inoculated onto 5% sheep blood agar and incubated in an aerobic chamber with 5% to 10% carbon dioxide at 37°C for at least 24 hours. If no beta-hemolytic organisms grow after 24 hours, the plate should be reincubated for another 24 hours at room temperature. On microscopy, GAS appear as gram-positive cocci in pairs and chains. On blood agar, they form small gray-white colonies with a zone of beta-hemolysis (a clear rim that surrounds the colonies). Other beta-hemolytic streptococci include groups B (*S agalactiae*), C, G, and F. Beta-hemolytic organisms should be confirmed as group A *Streptococcus* by latex agglutination, inhibition of growth around a bacitracin disc, or other techniques. Bacterial throat culture also may be useful in detecting *Neisseria gonorrhoeae* in the sexually active patient who has acute pharyngitis. GAS may remain part of resident oropharyngeal flora,

Because pharyngitis accompanied by rhinitis, stridor, hoarseness, conjunctivitis, cough, or diarrhea is highly likely to have a viral etiology, a bacterial throat culture generally is unnecessary when these symptoms are present.

resulting in chronic colonization, with the patient becoming a chronic carrier. Therefore, growth on routine culture in such a patient does not prove acute streptococcal pharyngitis or identify the cause of pneumonia, otitis media, sinusitis, or meningitis.

Serologic testing for acute GAS pharyngitis generally is not useful in acute infection because antistreptococcal antibodies increase only weeks after infection. Antibodies against streptolysin O, deoxyribonuclease B, hyaluronidase, and streptokinase are used to confirm a recent (but not current) GAS infection for those in whom the likelihood of culturing GAS is poor but confirmation of a recent GAS illness is needed, such as in suspected ARF or PSGN.

Treatment

Pharyngitis

Accurate diagnosis and treatment of acute GAS pharyngitis reduces suppurative complications (such as retro-

Table 5. Recommended Antimicrobial Drugs for GAS Pharyngitis

	Medication	Pediatric Dosage	Adult Dosage	Duration
First-line Therapy	Penicillin VK	≤27 kg (60 lb): 400,000 U (250 mg) bid or tid >27 kg (60 lb): 800,000 U (500 mg) bid or tid	500 mg tid	10 d
	Intramuscular penicillin G benzathine	≤27 kg (60 lb): 600,000 U >27 kg: 1.2 million U single dose OR 900,000 U benzathine penicillin G + 300,000 U procaine penicillin	1.2 million U	Single dose
	Amoxicillin	Once daily regimen*: 50 mg/kg qd (maximum 750 mg) 20 to 40 mg/kg divided bid–qid 40 mg/kg per day divided bid–qid (maximum 1 g/d)	Once daily regimen: 750 qd 500 mg bid 500 mg bid	10 d
Drugs for Penicillin-allergic Patients	Erythromycin estolate [†]	7.5 mg/kg per dose bid	250 mg bid	10 d
	Erythromycin ethylsuccinate [†]	25 to 50 mg/kg per day divided bid	500 mg bid	10 d
	Clarithromycin	10 to 20 mg/kg per day divided tid	150 mg tid	10 d
	Cephalexin	12 mg/kg per day qd × 5 d (not to exceed adult dose)	500 mg qd × 1 d, then 250 mg qd × 4 d	5 d
	Azithromycin			

*This regimen appears to be effective but is not yet approved by the United States Food and Drug Administration or recommended by the American Academy of Pediatrics.

[†]First-line therapy.

pharyngeal or peritonsillar abscesses), decreases transmission of GAS, and to a limited degree, shortens the duration of pharyngeal symptoms. In addition, therapy markedly reduces the risk of ARF. However, therapy has not been shown to reduce the risk of acute PSGN. Prevention of ARF is most effective if therapy is initiated within 9 days of the onset of symptoms. Although GAS pharyngitis is self-limited, appropriate treatment resolves symptoms about 1 day earlier than observation.

GAS remains universally sensitive to penicillin, which is the first-line therapy for GAS pharyngitis (as recommended by the American Academy of Pediatrics, the American Heart Association, and the Infectious Diseases Society of America) because of its narrow spectrum, low cost, and proven efficacy (Table 5). A clinical isolate of GAS that is resistant to penicillin or a cephalosporin in vitro has never been documented. Parenteral therapy can be administered if needed to ensure compliance; a single intramuscular dose of benzathine penicillin G is bactericidal for up to 28 days. However, parenteral penicillin is a painful injection and is associated with more potentially serious allergic reactions than oral therapy. Therefore, many clinicians prefer to use oral penicillin V, which must be continued for 10 days to ensure eradication of GAS. Twice-daily regimens of 500 mg in adults and children weighing 60 lb (27 kg) or 250-mg doses in smaller children achieve similar cure rates for GAS pharyngitis as thrice-daily dosing.

An alternative medication used primarily because of its increased palatability and greater associated compliance is amoxicillin. Previously published and ongoing studies show that once-daily amoxicillin at 50 mg/kg (up to 750 mg once daily) in children and adults who have GAS pharyngitis results in bacteriologic cure rates equal to those achieved with thrice-daily penicillin dosing. Although once-daily amoxicillin treatment for GAS pharyngitis is not approved by the United States Food and Drug Administration, it appears to be an excellent alternative to penicillin.

For individuals who are allergic to penicillin, the drug of choice is erythromycin; other macrolide antibiotics, such as clarithromycin and azithromycin, are acceptable (although more costly) alternatives. Azithromycin, administered at a higher dose of 12 mg/kg, often is chosen because of once-daily dosing and a treatment course of only 5 days that provides 10 days of antimicrobial activity. In areas of the world that have heavy macrolide use, a direct relationship has been shown between overall macrolide usage and GAS macrolide resistance rates. In 2000 to 2001, a high rate of macrolide-resistant GAS (up to 48%) was described in Pittsburgh, Pennsylvania, rais-

ing concerns about possibly increasing United States macrolide resistance rates. However, ongoing nationwide surveillance has not confirmed this high rate of resistance in other parts of the country. Studies indicate a nationwide macrolide resistance rate of approximately 4% to 6% from 2000 to 2004. First-generation cephalosporins may be used for patients who are penicillin-allergic if there is no history of immediate severe hypersensitivity to the penicillins, but these agents have broader antimicrobial activity than is necessary and are more expensive. Clindamycin may be used if other antibiotics are not an option. Tetracyclines and sulfonamides should *not* be used to treat GAS pharyngitis because they are ineffective in eradicating the organism.

Patients who have streptococcal pharyngitis are considered to be noncontagious 24 hours after initiation of treatment. In the United States, it is unnecessary to reculture the posterior pharynx routinely following GAS pharyngitis because the incidence of ARF remains low in almost all areas. Clinical treatment failure of GAS pharyngitis is rare. If a patient returns for evaluation of recurrent symptoms compatible with GAS pharyngitis and has a positive throat culture within a few weeks of treatment, the possibilities of the chronic pharyngeal carrier state with intercurrent viral pharyngitis, noncompliance with medication, or a new infection with a different strain of GAS should be considered. Recurrent pharyngitis caused by the same GAS strain is uncommon.

Peritonsillar/Retropharyngeal Abscess

Deep oropharyngeal abscesses require incision and drainage and immediate consultation with an otolaryngologist. Adequate suction is needed to drain the pus that is released. Because of occasional mixed flora with oropharyngeal anaerobes or *S aureus*, ampicillin-sulbactam with or without added clindamycin is used empirically until culture results are obtained. Emergency tonsillectomy occasionally is needed for peritonsillar abscess. Needle aspiration often can be performed for peritonsillar abscess; retropharyngeal abscesses usually require surgical drainage.

STSS

Treatment of STSS requires appropriate antibiotic treatment, including penicillin and clindamycin, which is used

for its antitoxin effects. Some experts also recommend intravenous immune globulin, which neutralizes toxins, to ameliorate disease severity. In addition, supportive care is needed, including aggressive fluid management and urgent debridement of any foci of necrotic tissue.

ARF and PSGN

Treatment of ARF involves: 1) antimicrobials to eradicate GAS from the nasopharynx followed by long-term prophylactic antimicrobials to prevent further intercurrent GAS illness, 2) anti-inflammatory treatment, and 3) supportive care. Initial treatment can be intramuscular benzathine penicillin or 10 days of oral penicillin or erythromycin. Anti-inflammatory medications usually include salicylate, but this agent may need to be replaced with corticosteroids initially in those who have significant carditis with cardiomegaly or congestive heart failure. PSGN treatment primarily involves supportive care to control hypertension, oliguria, and renal failure.

Conclusion

GAS causes a wide variety of clinical syndromes. Knowledge of the epidemiology and clinical presentations of these illnesses will aid the clinician in recognizing and treating GAS infections and their complications.

Suggested Reading

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- Chesney PJ. Clinical aspects and spectrum of illness of toxic shock syndrome: overview. *Rev Infect Dis*. 1989;11S1:S1–S7
- Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. *JAMA*. 1993;269:390–391
- Gerber MA, Tanz RR, Kabat W, et al. Optical immunoassay test for group A beta-hemolytic streptococcal pharyngitis. *JAMA*. 1997;277:899–903
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PIR Quiz

Quiz also available online at www.pedsinreview.org.

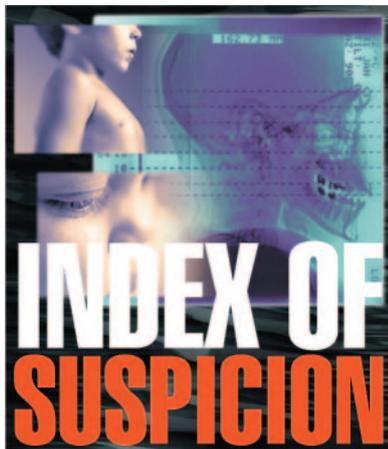
10. The *primary* rationale for diagnosing and treating group A beta-hemolytic streptococcal (GAS) pharyngitis is prevention of:
 - A. Acute glomerulonephritis.
 - B. Acute rheumatic fever.
 - C. Otitis media.
 - D. Prolonged colonization.
 - E. Toxin-mediated shock syndrome.

11. A previously healthy 5-year-old girl developed a sore throat 2 days ago, copious clear rhinorrhea yesterday, and slight hoarseness this morning. The sore throat makes her uncomfortable, but she is breathing normally and is taking fluids well. Her mother calls in the evening for advice. Of the following, the *most* appropriate recommendation is to:
 - A. Call in a prescription for penicillin.
 - B. Direct her immediately to an after-hours clinic.
 - C. Order a throat swab at a local laboratory.
 - D. Provide reassurance and analgesia.
 - E. Schedule an office visit in the morning.

12. A previously healthy 5-year-old girl presents to your office with a 12-hour history of sore throat accompanied by fever, headache, and abdominal pain. Physical examination reveals only erythema of the soft palate without petechiae and slightly enlarged and tender cervical lymph nodes. Results of the standard GAS rapid antigen test are negative. Of the following, the *most* appropriate next step is:
 - A. A 5-day course of azithromycin.
 - B. A mononucleosis spot test.
 - C. A throat culture for GAS.
 - D. Reassurance and analgesia.
 - E. Treatment with 10 days of penicillin.

13. A previously healthy 5-year-old girl has a 12-hour history of sore throat and fever without other symptoms. In your office, a standard GAS rapid antigen test turns quickly positive. She is not allergic to beta-lactam antibiotics but is a picky medicine-taker. She weighs 25 kg. Of the following, the *preferred* therapy is:
 - A. Amoxicillin 750 mg once daily for 10 days.
 - B. Azithromycin 300 mg once daily for 10 days.
 - C. Clindamycin 125 mg three times daily for 10 days.
 - D. Erythromycin estolate 250 mg twice daily for 10 days.
 - E. Penicillin VK 250 mg twice daily for 5 days.

14. Following the recommendations of the American Academy of Pediatrics, you have begun treatment of documented GAS pharyngitis in a 5-year-old girl. A resident asks you about the need for follow-up after completion of therapy. The *most* appropriate response is that:
 - A. Eradication of GAS must be documented by culture.
 - B. Examination for new heart murmurs is essential.
 - C. Inspection of skin and joints is mandatory.
 - D. Recurrence of sore throat warrants re-evaluation.
 - E. Urinalysis to rule out hematuria is recommended.



The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Nazarian at LFredN@aol.com.

Author Disclosure

Drs Rudra, Park, Wehbe-Hijazi, Alfaifi, Alrifai, Nazer, Srinivasan, and Kamat did not disclose any financial relationships relevant to these cases.

To view *Suggested Reading lists* for these cases, visit pedsinreview.org and click on *Index of Suspicion*.

Frequently Used Abbreviations

ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CBC:	complete blood count
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
ECG:	electrocardiography
ED:	emergency department
EEG:	electroencephalography
ESR:	erythrocyte sedimentation rate
GI:	gastrointestinal
GU:	genitourinary
Hct:	hematocrit
Hgb:	hemoglobin
MRI:	magnetic resonance imaging
WBC:	white blood cell

Case 1 Presentation

Introduction

A 7-week-old girl of Middle Eastern descent is admitted to the hospital for a cough of 10 days' duration that is worsening and has produced post-tussive emesis for the last 7 days. An episode of perioral cyanosis lasting less than 1 minute was noted 5 minutes after a feeding. There has been no fever, rhinorrhea, emesis, or diarrhea. The baby was born at term without perinatal complications.

Three days into her illness, the child's pediatrician had placed her on nebulized bronchodilator therapy for presumed viral bronchiolitis. Re-evaluation on the day of admission shows no improvement. A chest radiograph reveals marked cardiomegaly with clear lung fields.

The physical examination reveals a well-nourished baby who looks alert but manifests slightly decreased activity. Her heart rate is 130 beats/min, respiratory rate is 35 breaths/min, blood pressure is 85/45 mm Hg, and pulse oximetry saturation is 100% in room air. The child's length is at the 95th percentile, and her weight and head circumference are at the 75th percentile. Auscultation reveals scattered end-expiratory wheezes, more prominent at the bases, but no grunting, retractions, or nasal flaring. A soft grade I/VI systolic flow murmur that does not radiate is audible at the left sternal border. Both heart sounds are normal. The baby appears well perfused and has normal femoral pulses. The rest of her physical findings are normal.

CBC, electrolyte levels, and liver function tests all yield normal results. Further laboratory studies reveal the diagnosis.

Case 2 Presentation

A 7-year-old-girl who has type 1 diabetes mellitus is admitted to the

hospital with a 1-month history of intermittent weakness of her lower extremities associated with pain in her feet and lower legs. The weakness is worse in the morning, when she is unable to walk. She has no associated numbness, and her weakness is not related to activity, food, or cold.

The physical examination reveals an alert, oriented girl who has normal cardiovascular, pulmonary, and abdominal findings. The neurologic examination shows intact cranial nerves. She has good tone and strength levels of 5/5 in her arms and 4/5 in her legs, with preserved sensation and deep tendon reflexes throughout. She is able to bear weight with help but cannot take any independent steps. Laboratory tests to determine the cause of her muscle weakness show a normal CBC and chemistry panel, thyroid-stimulating hormone level of 0.97 U/L (normal, 0.35 to 5.5 U/L), free thyroxine of 15.6 pmol/L (normal, 11.5 to 22.7 pmol/L), creatine kinase of 66 U/L, ESR of 40 mm/hr, and ECG that shows a corrected QT interval of 0.44.

Case 3 Presentation

A 4-year-old Arabic boy has experienced leg pain for the past 2 months. He localizes the pain to the middle of his right thigh, sometimes extending to his knee. He is able to run and play, but pain recurs at the end of vigorous play, is worse at the end of the day, and often wakes him at night. It is relieved by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). There is no history of trauma, redness, swelling, fever, weight loss, or rashes. The patient has had no similar complaints in the past. There is no family history of bone or joint diseases. He was born in the United States but has lived in Lebanon for the past year.

On physical examination, the boy's temperature is 99.1°F (37.3°C), pulse is 108 beats/min, respiratory rate is 28 breaths/min, and blood pressure is 103/68 mm Hg. He localizes pain to the middle of his right thigh, but there is no tenderness, swelling, or erythema in that area. There is full range of motion at both the right hip and knee joints, and strength is 5/5.

Laboratory values include a WBC count of $8.5 \times 10^3/\text{dL}$ ($8.5 \times 10^9/\text{L}$), Hgb level of 13.3 g/dL (133 g/L), platelet count of $455 \times 10^3/\text{dL}$ ($455 \times 10^9/\text{L}$), ESR of 22 mm/hr, and C-reactive protein level of 2.85 mg/dL. An imaging test reveals the diagnosis.

Case 1 Discussion

An ECG revealed tall QRS complexes with inverted T waves consistent with a strain pattern indicative of left ventricular hypertrophy (Fig. 1). The PR interval was slightly shortened at 80 msec. An echocardiogram revealed moderate-to-severe hypertrophic cardiomyopathy affecting both ventricles. Diastolic dysfunction was moderate to severe.

The clinical picture clearly indicated a hypertrophic cardiomyopathy. Viral titers for coxsackievirus, enterovirus, and Epstein-Barr virus were negative. Carnitine levels were normal. Based on the ECG and echocardiographic results, suspicion was high for Pompe disease. A skin biopsy for fibroblast culture and a blood assay for acid alpha-glucosidase activity revealed diminished activity, thus confirming the diagnosis.

The Disorder

Pompe disease belongs to a group of inborn errors of metabolism referred to as glycogen storage diseases.

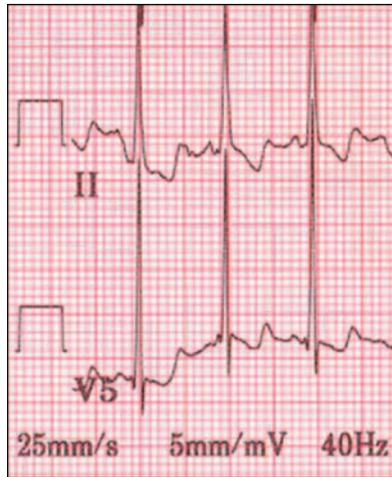


Figure 1. ECG tracing for a child who has Pompe disease reveals high-voltage QRS complexes with shortened PR intervals.

These diseases are caused by a deficiency or absence of one of the enzymes involved in glycogen metabolism that results in the accumulation of glycogen in tissues. Glycogen storage diseases are classified numerically based on the chronologic order in which the enzyme was discovered. Pompe disease is a type II glycogen storage disease.

The enzyme defect in Pompe disease involves lysosomal acid alpha-glucosidase or acid maltase. This enzyme is responsible for the degradation of glycogen in lysosomes, technically making Pompe disease a lysosomal storage disease. The incidence of Pompe disease is 1 in 40,000 live births; it is transmitted in an autosomal recessive pattern. The gene locus for the enzyme has been localized to chromosome 17q25.2. No ethnic predilection exists.

The range of phenotypic expression is wide, varying in age of onset and organ involvement, but all variations involve a myopathy. The infantile form is the most severe. It is associated with cardiomegaly and hypotonia, with death occurring usually before the age of 2 years. Af-

ected children typically appear normal at birth but soon develop generalized muscle weakness, feeding difficulties, macroglossia, hepatomegaly, and progressively worsening heart failure due to hypertrophic cardiomyopathy. The classic ECG finding consists of high-voltage QRS complexes with a shortened PR interval (Fig. 1). Death usually results from cardiorespiratory failure or from aspiration pneumonia.

The juvenile-onset form usually presents in adolescence but can manifest as early as age 1 year with delayed motor development or difficulty walking. Affected children develop oromotor dysfunction and swallowing difficulties. Death may occur before the second decade from cardiorespiratory failure. The degree of cardiomegaly is variable, but overt cardiac failure unusual. An adult form also presents as a slowly progressive myopathy.

A Misleading Sign

This case shows that not all wheezing should be assumed to be a result of acute bronchiolitis. Wheezing occasionally is heard in patients who have congestive heart failure. In hypertrophic cardiomyopathic states, the reduction in ventricular compliance and relaxation leads to elevated diastolic and end-diastolic pressures, which cause elevated left atrial pressure and volume and increased pulmonary venous and pulmonary capillary pressure. If the latter exceeds the plasma oncotic pressure, interstitial lung fluid develops initially, followed by alveolar edema. The clinical counterparts are moist rales and, occasionally, wheezing. Marked cardiomegaly, as in this case, can cause wheezing by extrinsic pressure on airways.

Differential Diagnosis

Given the unique and acute constellation of findings, the differential diagnosis of infantile Pompe disease is limited. However, valuable time can be lost between the onset of symptoms and consideration of the diagnosis. Most infants survive only a few months beyond the time of diagnosis, necessitating the need for a rapid diagnosis so supportive therapy can be started. Diagnosing this condition requires considerable suspicion and awareness of the disease on the part of pediatricians and specialists. In older children, signs and symptoms can be insidious and attenuated, thus delaying the diagnosis.

Diseases that have been mistaken for infantile Pompe disease because they cause either hypotonia or cardiomyopathy include Werdnig-Hoffman disease, hypothyroidism, myocarditis, endocardial fibroelastosis, Krabbe disease, congenital muscular dystrophy, and respiratory chain disorders. Few, if any, diseases are associated with both hypotonia and cardiomyopathy in infancy. Werdnig-Hoffman disease, a type of spinal muscular atrophy (SMA), presents with hypotonia but also can be associated with structural congenital heart defects, but not cardiomyopathy. Type III SMA is associated with hypotonia and dilated cardiomyopathy but presents in adolescence. Congenital hypothyroidism is associated with hypotonia but not (usually) cardiomyopathy. The presence of hypotonia along with cardiomegaly virtually confirms the diagnosis of Pompe disease. Diseases that can mimic some of the symptoms of the juvenile form include poliomyelitis, limb-girdle muscular dystrophy, Becker muscular dystrophy, and myasthenia gravis.

Laboratory Findings

Laboratory findings consist of elevated creatine kinase, AST, and

lactate dehydrogenase levels. Chest radiography reveals massive cardiomegaly and often provides the first clue that the child has Pompe disease. Echocardiography and electrocardiography are used to assess the degree and severity of cardiac involvement. Echocardiography demonstrates hypertrophic cardiomyopathy with thickening of both ventricles and the interventricular septum. ECG findings are as mentioned previously. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen. The definitive diagnosis is established by testing for the absence or reduced levels of acid alpha-glucosidase in muscle, cultured skin fibroblasts, or blood. Skin biopsy is preferred.

Therapy

No definitive treatment exists for Pompe disease. A high-protein diet may be beneficial in the juvenile and adult forms. Nocturnal ventilatory support for patients who have late-onset disease improves the quality of life and can be beneficial during the phase of respiratory decompensation. Recent clinical trials involving enzyme replacement therapy with recombinant acid alpha-glucosidase have shown a decrease in cardiomegaly and improved cardiac and skeletal muscle function, with increased survival. These trials offer some hope in the treatment of an otherwise devastating disease.

Lessons for the Clinician

Pompe disease is a rare but devastating disease that has a unique constellation of signs and symptoms. Diagnosis requires a high degree of suspicion; a timely diagnosis can help ensure that the child receives proper supportive therapy. This case also illustrates how an uncommon disease such as Pompe disease can present with common symptoms such as

coughing or wheezing. (*Harish S. Rudra, DO, Jin H. Park, MD, Inova Fairfax Hospital for Children, Falls Church, Va.*)

Case 2 Discussion

Because of the unusual manifestations of the child's muscle weakness involving only the lower extremity, with no cranial nerve involvement, no relationship to activity, worsening of weakness on school days, and improvement during holidays and weekends, in addition to a recent history of school difficulty, a diagnosis of conversion disorder was entertained.

A simple test strongly supported that diagnosis; 1 mL of intravenous normal saline was administered to the child after it was explained to her that this could cure her illness. Shortly after the injection, the child stood up alone and walked unassisted back and forth in the hallway. Psychiatric consultation identified school as a major stressor in the patient's life. The presence of type 1 diabetes, with its daily testing and insulin injections, was identified as a vulnerability that might have triggered the conversion reaction.

Physical therapy was initiated and the parents advised about the nature of the problem. Strategies were offered to alleviate the stressors in the child's life. The family also was advised to shift attention from the child's symptoms and to focus on recovery. The girl responded well to treatment, and follow-up showed better coping abilities and amelioration of her muscle weakness.

The Condition

Conversion disorder should be suspected when a patient's symptoms do not fit into the framework of known medical illnesses or when appropriate evaluation reveals no or-

ganic disease or plausible pathophysiological explanation. Conversion disorders in children do not indicate a major psychiatric disorder but represent the child's subconscious plea for help in situations in which he or she cannot cope. These situations can arise from a variety of stressors, such as struggles in school, family disharmony, and sexual and physical abuse. Symptoms are referable to the CNS in 65% of children who have conversion disorders. The most usual presentations are episodic loss of awareness, such as pseudoseizures and syncope; motor dysfunction, including gait disturbances and paresis; sensory abnormalities, primarily pain and numbness; and disorders of the special senses.

Diagnosis

Once the diagnosis of conversion disorder is suspected in a child who has persistent and debilitating symptoms, a sensible evaluation plan should be created. In severe cases, hospitalization may be warranted. During the evaluation, focused investigation and testing should be pursued to be reasonably certain that there is no medically treatable cause. Psychiatric evaluation instituted simultaneously should concentrate on five main areas: 1) the levels of stress or anxiety in the child and family, 2) any special predisposing vulnerabilities in the child that might lower the threshold for coping with stress and anxiety (eg, learning disabilities, peer pressures, problems of body image, chronic illness, and family disharmony or conflict), 3) a possible temporal relationship between a specific stress and the onset of symptoms, 4) role models from whom the symptoms might have been learned, and 5) evidence of primary or secondary gain from the symptom.

Differential Diagnosis

The differential diagnosis of a child presenting with intermittent muscle weakness includes familial periodic paralysis (hypokalemic or normokalemic); metabolic myopathies, including myophosphorylase deficiency and mitochondrial deficiency; limb-girdle muscular dystrophy; myasthenia gravis; and endocrinopathies such as thyroid disorders and adrenal disorders. Delineation of the clinical pattern and laboratory testing should allow the clinician to determine if any of these disorders is present. If no other disorder fits and if significant stress is evident, a psychosomatic cause should be considered.

Treatment

Once the evaluation has been completed, a treatment plan is presented to the parents and the child. The first step is to explain that the symptom is real but that no organic disease has been demonstrated. Anxiety or stress has led to the symptom, and this element must be understood and relieved for the child to get better. The treatment must be tailored to the problem, with set goals and the provision of positive feedback as goals are achieved. In addition to measures aimed at understanding and relieving stress, treatment for a patient complaining of weakness might involve "graded" physical therapy.

Removing the secondary gain achieved by the symptom is essential for recovery and to eliminate perpetuation of the symptom. Examples of secondary gain include missed school days and increased parental attention because of the symptom. It is essential that the treatment provide "escape with honor" and that the regimen give some control to the child. After discharge, continued psychotherapy should be aimed at allowing the child to give up the sick role and

cope with future stress and anxiety more productively.

Prognosis

Except for children who have pseudoseizures, most children who have a conversion disorder have no underlying major mood disorder or psychiatric illness. Major mood disorders have been identified in 32% of children who have pseudoseizures. A history of sexual abuse is common in patients who have conversion disorders.

Because children are still in the formative stages of personality development, the adult diagnosis "hysterical personality," now called "histrionic personality disorder," is questionable when applied to children who have conversion disorder. Histrionic personality disorder comprises a constellation of traits, including dependency, immaturity, egocentricity, attention-seeking behavior, and manipulation. With timely intervention, the child who has a conversion disorder will develop better coping abilities and give up the sick role, thus aborting perpetuation of the symptom and progression to an adult histrionic personality disorder.

Further Observations

This patient had a chronic illness and had become aware of its power to influence the adults in her world. Another example of this effect is that pseudoseizures are common in children who have true epilepsy.

Clinical testing should be judicious because the tests themselves promote anxiety and confirm and reinforce the power and seriousness of the symptom. The child herself is deceived about the source of her symptoms, and families of children who have conversion disorders tend to have conversion symptoms, reinforcing the impressionable child's

symptomatology. The clinician must be firm in the diagnosis of conversion and resist his or her own anxiety, which tends to produce the need to do more testing. The simple test employing intravenous saline was an effective diagnostic tool in this case, but it is important that clinicians undertake such procedures with sensitivity to avoid their being perceived by the patient as a trick, potentially undermining trust.

The use of physical therapy was a face-saving treatment for the patient and more likely to be acceptable to patient and parents than a purely psychiatric approach, which can be counterproductive if instituted at the wrong time. Similarly, early hospitalization can raise the stakes ominously. Sometimes, psychotherapy will be acceptable if the reason given for recommending such treatment is “to help you cope with the stress of being ill for so long.”

Lessons for the Clinician

Conversion disorder represents a child’s expression of a difficult or stressful situation through a physical symptom. The pediatrician, being familiar with the child and parents, should be able to gain the trust of the child and identify stressors and difficulties in the child’s life. Psychiatric referral and sometimes hospitalization are crucial for the recovery of children whose symptoms are prolonged and unresponsive to counseling by the pediatrician. (*Najla Wehbe-Hijazi, MD, Mohammed Al-faifi, MD, Muhammad Alrifai, MD, King Abdul Aziz Medical City for National Guard, Riyadh, Saudi Arabia*)

Case 3 Discussion

A plain radiograph of the right hip and femur showed an approximately



Figure 2. Plain radiograph showing lytic lesion with a sclerotic rim in the metaphysis of the proximal right femur.

1-cm, focal, lytic lesion with sclerotic margins at the interior cortex of the proximal right femoral diaphysis (Fig. 2). There was no evidence of periosteal reaction, associated soft-tissue mass, or pathologic fracture. The soft tissue was unremarkable. The visualized hip and pelvis were within normal limits. Findings were believed to be consistent with osteoid osteoma, and the CT scan made that diagnosis more certain (Fig. 3). Histologic examination of a specimen obtained by CT-guided biopsy of the lesion confirmed the diagnosis of osteoid osteoma.

The Condition

Osteoid osteoma is a common benign bone tumor. Most patients are

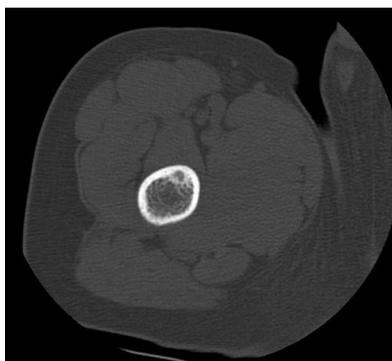


Figure 3. CT scan showing the same lesion in the femur on a cross-sectional view.

5 to 20 years old. The most common sites of involvement are the proximal femur and tibia, but any bone can be involved, including the posterior elements of the spine. Pain is the symptom that causes the patient to seek care.

The physical examination may reveal tenderness to touch or pressure. Patients also may have disuse atrophy, painful scoliosis, or limb-length discrepancy.

Differential Diagnosis

Leg pain in childhood has many causes, ranging from benign conditions requiring no treatment to malignant tumors necessitating immediate intervention. This boy’s history was inconsistent with “growing pains,” a controversial term diagnosed only by exclusion of other disorders. “Growing pains” usually are bilateral, intermittent, worse in the evening, not present the next morning, and associated with normal physical and laboratory findings.

The differential diagnosis of leg pain includes infections (septic arthritis, osteomyelitis), malignancies not primarily derived from bone (leukemia, neuroblastoma), and primary malignant and benign bone tumors.

This patient’s history was consistent with his diagnosis. Patients who have osteoid osteoma classically present with gradually increasing sharp focal pain that is worse at the end of the day or at night. Pain from osteoid osteomas located in bones of the leg usually is not related to activity, which helps differentiate this condition from a stress fracture, and the pain responds dramatically to NSAIDs, including aspirin. Constitutional symptoms usually are absent.

A normal CBC and peripheral smear along with the radiologic findings made leukemia unlikely. This

child's age is younger than the age range for primary bone tumors, which also may cause leg pain but usually present in the second decade of life.

Evaluation

When evaluating a child who has leg pain, the clinician should start with the history and physical examination. Initial investigations include a CBC, ESR, and radiographs. A radiograph of the normal side is recommended for comparison.

Osteoid osteoma generally can be diagnosed by clinical presentation and radiologic appearance. It usually appears as a small spherical or oval lytic lesion surrounded by soft-tissue edema and reactive bone formation on plain radiographs. Most osteoid osteomas are cortical or periosteal, but 20% arise within the marrow. Osteoid osteoma is visualized better by CT than by MRI. CT is used for precise localization of the lesion and as a guide for percutaneous biopsy and ablation. A biopsy confirms the diagnosis when the history, clinical examination, location, or radiographic findings are nonclassical or suspicious of any other etiologies. Most patients do not require a biopsy

because the CT so often is diagnostic.

Small lytic lesions can be caused by infections, benign neoplasms of the bone, and leukemia. Benign neoplasms include osteoid osteoma, periosteal chondroma, chondroblastoma, eosinophilic granuloma, hemangioma, and intracortical osteosarcoma. The most common of these lesions is osteoid osteoma. Given the history of relief with NSAIDs, physical findings, small size of the lesion, and location in the diaphysis, osteoid osteoma was the most likely diagnosis in this patient. Orthopedic surgeons elected to perform a biopsy due to a second lesion that appeared on further evaluation. Biopsy provided confirmation of the diagnosis and ruled out other conditions.

Management and Prognosis

Osteoid osteoma is a benign bone tumor that does not progress or have malignant potential. Some lesions may regress spontaneously. The primary goal of treatment is pain control with medications, usually NSAIDs. However, if pain is not controlled by medications alone or the patient has complications of osteoid osteoma, such as neuropathy, synovitis, growth disturbances, or

scoliosis, the lesion should be removed surgically or by radiofrequency ablation. Surgical options include en bloc excision, curettage, or CT-guided removal. However, radiofrequency ablation, when possible, is a less invasive, effective treatment that may avoid complications of an open procedure. A relative contraindication to radiofrequency ablation is an osteoid osteoma adjacent to vital structures such as the spinal cord, which may be damaged by heat from the procedure.

Lessons for the Clinician

Leg pain in children is due most often to a benign condition. However, if the pain is persistent, unilateral, interferes with daily activities or sleep, or is associated with systemic manifestations, the clinician should start appropriate investigations. A history, physical examination, CBC, ESR, and radiographs are good initial components of the evaluation. Leg pain, although common in children, may be a symptom of a severe underlying disease. (*Dena Nazer, MD, Lakshmi Srinivasan, MD, Deepak Kamat, MD, Children's Hospital of Michigan/Wayne State University, Detroit, Mich.*)

In Brief

Secondary Amenorrhea

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Author Disclosure

Dr Bloomfield did not disclose any financial relationships relevant to this In Brief.

Menstrual Cycle Abnormalities: Diagnosis and Management. Iglesias E, Coupey S. *Adolescent Medicine: State of the Art Reviews*. 1999;10:255–273

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The Female Athlete Triad: Disordered Eating, Amenorrhea, Osteoporosis. Yeager KK, Agostini R, Nattiv A, Drinkwater B. *Med Sci Sports Exerc*. 1993;25:775–777

Secondary amenorrhea, the cessation of previously normal menstruation, should be considered in any female who has a gynecologic age of at least 24 months and has not menstruated for three or more consecutive cycles. The gynecologic age, the time in months since menarche, is the best indicator that a normal ovulatory pattern should have been established; regular monthly cycles are not reliably present until 2 years after menarche. The underlying causes of secondary amenorrhea can be understood from a review of the normal menstrual cycle.

The menstrual cycle is regulated by interplay within the hypothalamic-pituitary-ovarian axis. In normal ovula-

tion, gonadotropin-releasing hormone (GnRH) starts the cycle by initiating the release of follicle-stimulating hormone (FSH) from the anterior pituitary gland. FSH promotes the maturation of an ovarian follicle, which is released at midcycle after a surge of luteinizing hormone (LH). The estrogen produced by the follicle supports the proliferative phase of the endometrium; the progesterone produced by the corpus luteum causes the endometrium to differentiate and stabilize. Approximately 14 days after ovulation, if the ovum is not fertilized, the rapid decline of the levels of estrogen and progesterone results in regression of the endometrium, with menstruation following.

Most commonly, secondary amenorrhea results from some disruption of the hypothalamic-pituitary-ovarian axis. The disrupting agent can range from a neoplasm, such as a craniopharyngioma or pituitary adenoma, to physical or emotional stress, which can induce a functional hypothalamic state in which reduced secretion of GnRH produces levels of LH and FSH that are too low to stimulate ovulation.

Female athletes are at risk for secondary amenorrhea from the loss of pulsatile LH release, directly related to reduced energy intake from dieting coupled with high energy expenditure from exercise. In addition, with reduced adipose tissue, athletes have lower levels of leptin, which normally helps trigger the secretion of GnRH. The triad of a disordered eating pattern, amenorrhea, and osteoporosis among female athletes is now well recognized, particularly among young women who compete in sports where leanness is emphasized, such as gymnastics, ballet dancing, figure skating, and long-

distance running. The eating disorder, which can range from decreased food intake to vomiting and laxative abuse, most often is not severe enough to meet the criteria for anorexia nervosa. Still, it may have adverse consequences, leading, in time, to menstrual dysfunction and osteoporosis from hypoestrogenism. With appropriate weight gain, menses resume, and the loss of bone mineral density reverses.

Secondary amenorrhea can be an early signal of anorexia nervosa, occurring before weight loss becomes dramatic. Typically, menses ceases when body weight falls to 85% of the ideal for age and height, the result of hypothalamic dysfunction related to the weight loss itself and exacerbated by excessive exercise and stress. Interestingly, a patient who has moderate weight loss from a chronic illness such as inflammatory bowel disease is more likely to maintain menstruation than is an adolescent who has an eating disorder and has lost the same amount of weight. With a prevalence of 1 per 300 among 15- to 19-year-old adolescent women, anorexia nervosa is an important consideration in any patient who has secondary amenorrhea. Treatment centers on restoring and maintaining a normal body weight, at which time menses resumes. With longstanding anorexia and amenorrhea, hypoestrogenism and consequent osteopenia are risks. In this select group, hormone replacement therapy may be an option.

Although derangements of the hypothalamus and pituitary are the most common causes of secondary amenorrhea, most often related to emotional or physical stress, malfunction of the ovary also can interfere with normal menstruation. In functional ovarian hy-

perandrogenism, elevated ovarian androgen and an elevated LH/FSH ratio contribute to chronic anovulation. Also known as polycystic ovary syndrome, this common condition can be associated with hirsutism and evidence of hyperinsulinism, in particular with acanthosis nigricans. Pelvic ultrasonography may reveal polycystic ovaries, hence the syndrome's original name. Management involves oral contraceptives, which decrease GnRH production by negative feedback to the hypothalamus, ultimately reducing stimulation

of the ovaries, resulting in a decrease in production of ovarian androgens. Hyperandrogenism also can result from late-onset congenital adrenal hyperplasia (21-hydroxylase deficiency) and from ovarian or adrenal tumors.

Failure of normal ovarian function, with consequent amenorrhea, also can result from an autoimmune process, often associated with thyroid dysfunction and diabetes mellitus. Patients who have ovarian failure have low levels of estradiol and elevated FSH levels from the absence of normal negative

feedback. Amenorrhea from ovarian failure also can be seen in survivors of cancer as an effect of chemotherapy. The treatment of choice for ovarian failure is hormone replacement with oral contraceptives.

Stress-related conditions are the most common cause of secondary amenorrhea, followed in frequency among adolescent girls by pregnancy, and its possibility certainly needs to be considered. Finally, illicit drugs can cause secondary amenorrhea, and their use should be ruled out.

In Brief

Escherichia coli

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Author Disclosure

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Escherichia coli O157:H7. Tarr P, Neill M. *Gastroenterol Clin North Am.* 2001;30:735–751

Escherichia coli are gram-negative bacilli in the *Enterobacteriaceae* family.

Most of the many known strains of *E coli* are beneficial, colonizing the intestines of healthy humans and suppressing growth of pathogenic bacteria. However, at least five different pathotypes of diarrhea-producing *E coli* have been identified. Clinically, the disease caused by each pathotype is distinctive.

Enterotoxigenic *E coli* (ETEC) causes a self-limited illness, usually lasting fewer than 5 days. The organism colonizes the small intestine, where it releases an enterotoxin. Symptoms, usually of moderate severity, include nonbloody, watery diarrhea and abdominal cramps. On routine stool cultures, *E coli* organisms are read as "normal flora," so specific testing is required to diagnose ETEC. The most common cause of traveler's diarrhea, ETEC also is an increasingly recognized cause of food-borne illness in the United States. With the self-limited duration of its symptoms, ETEC infection generally does not require antibiotic therapy.

Enteroinvasive *E coli* (EIEC) infection often is associated with fever. The or-

ganism invades the colonic mucosa, where it induces a local inflammatory response. Diarrhea can be bloody, but is usually watery and without blood or mucus. The incidence of EIEC in developed countries is believed to be low, but occasional food-borne outbreaks have been identified.

Shiga toxin-producing *E coli* (STEC), formerly known as enterohemorrhagic *E coli* (EHEC) or verotoxin-producing *E coli*, is the only pathotype commonly responsible for diarrhea in children in the United States, and it can cause a hemorrhagic colitis with systemic complications. Both the hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) have been associated with STEC infection, with HUS more common among children and TTP among adults. In particular, *E coli* O157:H7 has emerged as the most virulent member of this pathotype, responsible both for outbreaks and for sporadic cases of diarrhea in North America. Typically, illness with *E coli* O157:H7 begins with 24 to 48 hours of nonbloody diarrhea that often, but not

always, is followed by frankly bloody stools. Severe cramping abdominal pain, nausea, and vomiting are typical. Fever, most often low-grade, is reported in only about one third of patients.

Annually, *E coli* O157:H7 infects about 75,000 people in the United States and causes about 60 deaths. Transmission is usually through food or water contaminated with animal or human feces, but person-to-person transmission also has been documented in households, nurseries, and hospitals. Healthy cattle are the primary recognized animal reservoir. Outbreaks have been linked to undercooked ground beef, unpasteurized milk and apple cider, raw vegetables, salad dressing, salami, yogurt, and water. Transmission also has been reported in persons swimming in a fecally contaminated lake as well as among visitors to dairy farms and petting zoos, where children have direct contact with the animals.

Infection with *E coli* O157:H7 is most common in the summer months. The incubation period for most *E coli* strains is from 10 hours to 6 days. For *E coli* O157:H7, it usually is 3 to 5 days, but can be as long as 8 days. The infectious dose of *E coli* O157:H7 is low; ground beef patties that have fewer than 700 organisms each have been associated with illness.

The illness caused by *E coli* O157:H7 typically is biphasic, beginning with localized intestinal disease, in which the pathogen attaches to the small-bowel mucosa, invades mucosal cells, and disrupts the microvillus brush border. The result is a secretory diarrhea. The second, systemic phase depends on production of a potent cytotoxin, the same toxin produced by *Shigella dysenteriae* type 1: shiga-toxin, also known

as verocytotoxin or verotoxin. Absorbed into the systemic circulation, the toxin enhances thrombin formation, impairs fibrinolysis, and compromises blood flow to the kidneys, brain, and other organs, potentially resulting in HUS or TTP.

HUS is characterized by thrombocytopenia, hemolytic anemia, and nephropathy. Although it can have other causes, HUS among children most often results from infection with STEC, most commonly O157:H7. Approximately 10% of children younger than 10 years of age who are infected with *E coli* O157:H7 develop HUS, with a mortality rate of about 3% to 5%.

If *E coli* O157:H7 infection is suspected, specific testing must be requested. Clinical laboratories can screen for the organism by using MacConkey (SMAC) agar base with sorbitol. Most *E coli* strains rapidly ferment sorbitol, but O157 strains do not. Positive isolates should be forwarded to public health laboratories for confirmation and serotyping. Methods for definitive identification include DNA probes, polymerase chain reaction, and enzyme immunoassay. Shiga-toxin may be tested by using rapid diagnostic kits.

Treatment of *E coli* O157:H7 infection is supportive and involves correcting and maintaining fluid and electrolyte balance. Retrospective data suggest that antimicrobial agents may be harmful, possibly increasing the likelihood of HUS, perhaps by causing the release of shiga-toxin from injured bacteria in the intestine, making the toxin more available for absorption. The use of antimotility agents also is discouraged because they may delay clearance of the organism and lengthen the time of toxin absorption.

In view of the seriousness of human infection caused by *E coli* and the limited therapeutic options, preventing transmission is vital. Education and legislation should promote safe food preparation and food-handling practices. In child care centers, the most important prevention measure is supervised hand washing. Physicians can help prevent *E coli* O157:H7 infection by counseling families about the risk of eating undercooked ground beef and drinking unpasteurized milk and juice. Early reporting of cases to local health departments allows for earlier identification of the source of infection and more effective control of outbreaks.

Comment: An issue related to *E coli* that pediatricians commonly face is traveler's diarrhea: to offer prophylaxis or not? Several antibiotics, particularly ciprofloxacin and trimethoprim/sulfamethoxazole, are effective in preventing traveler's diarrhea, but evidence suggests that early treatment once symptoms have begun is a reasonable alternative to prophylaxis. Early treatment rapidly reduces the severity of diarrhea, and in an age when the emergence of drug-resistant pathogens has become a major problem throughout the world, widespread use of broad-spectrum antimicrobials as prophylaxis for travelers would surely lead to burgeoning resistance among coliforms. The best prophylaxis is good advice: stick to bottled beverages and bottled or boiled water, don't forget that ice is water, and avoid salads and fruits.

Henry M. Adam, MD
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In Brief

Vulvovaginitis

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Author Disclosure

Drs Kokotos and Adam did not disclose any financial relationships relevant to this In Brief.

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Vulvovaginitis is an inflammation of the vulva and vaginal tissues. The usual symptoms are discharge, discomfort, pain or pruritus, vulvar irritation, or burning on urination. With infants and young children, the parent may report a discharge on the diaper or panties, an abnormal vaginal odor, or redness of the vulva. The epidemiology and presentation of vulvovaginitis differ in prepubescent and adolescent girls. In childhood, the infection begins in the vulva, with secondary spread to the

vagina; in adolescence, particularly after the onset of sexual intercourse, vaginal involvement is primary.

Young girls are particularly susceptible to vulvovaginitis. The genital area is close to the rectum, and without the labial fat pads and pubic hair that come with maturity, the vulva of a young child is unprotected. Vulvar skin is thin and particularly sensitive to trauma from scratching or rubbing or to exposure to irritants such as harsh soaps or bubble baths. The vaginal mucosa of young girls also is thin and relatively atrophic, and the vaginal cavity, with its neutral pH, warmth, and moisture, makes an excellent environment for bacterial growth. Children tend to have poor hygiene after urination and defecation, allowing pathogens to contaminate the vulva. Inadequate hand washing, especially after playing in dirt or sand, can add to irritation or bacterial contamination of the vulva. Tight-fitting clothing, nonabsorbent underpants, and obesity also can contribute to vulvar irritation. Other risk factors for vulvovaginitis are an intravaginal foreign body and sexual abuse.

The first step in any evaluation is to take a history, which should be obtained from both the parent and from the child, if she is old enough. An adolescent should be interviewed alone. The history should include questions about itching, discharge (color, quantity, odor, consistency, and duration), dysuria, and redness as well as about perineal hygiene, exposure to irritants such as bubble baths and soaps, and the use of medications, either topically or systemically. Anal pruritus and any allergies or recent infection in the child or family can be relevant, as, obviously, is sexual activity in an adolescent. As

uncomfortable as the subject is, sexual abuse must be considered and the pertinent questions asked.

The physical examination should look for evidence of chronic illness or dermatologic disease. In children, the perineum and vulvar introitus can be inspected while the child is in the frog-leg (supine) position or knee-chest position. The labia can be retracted gently to allow visualization of the vagina. Any abnormality of the hymen should be documented if sexual abuse is suspected. If there is significant discharge, specimens should be collected with a sterile, saline-moistened swab for wet mount preparation, Gram stain, and culture. If sexual abuse is a consideration, appropriate cultures should be collected for forensic evidence. A saline-moistened calcium alginate swab is smaller and more comfortable for a prepubescent girl than a cotton-tipped swab. For a sexually active adolescent, a complete pelvic examination with speculum should be performed. When bleeding or malodorous discharge raises concern about a foreign body, an examination under anesthesia may be necessary if adequate visualization is not otherwise possible. If night-time pruritus suggests pinworms, the family can be instructed to apply the sticky side of adhesive tape to the perianal area to collect eggs for microscopic inspection.

Some 25% to 75% of vulvovaginitis in a pediatric practice is nonspecific, resulting from poor hygiene, improper wiping, vaginal voiding, tight panties, or irritation from bubble bath or harsh soap. Typically, the associated discharge is scanty, nonpurulent, mucoid, and nonodorous. Treatment involves improving hygiene with appropriate

hand washing, wiping from front to back, using loose cotton underpants and avoiding nylon tights or tightly fitting clothing, and eliminating chemical irritants. Sitz baths and bland emollients may offer symptomatic relief.

Bacterial vulvovaginitis most commonly results from poor hygiene in young girls and may be due to respiratory or enteric organisms. Among adolescents or prepubescent girls who have been abused, sexually transmitted organisms must be considered. Group A beta-hemolytic *Streptococcus* is the most common cause of infections among respiratory pathogens, usually presenting with an abrupt onset of a seropurulent discharge, pruritus, dysuria, and erythema and tenderness of the vulva. *S pneumoniae* and *Neisseria meningitidis* also have been associated with vulvovaginitis. *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Haemophilus influenzae* can be normal flora, but also may cause active infection. *Shigella* sp are the most common of the enteric pathogens causing vulvovaginitis, with a mucopurulent bloody discharge often accompanied by diarrhea either in the patient or her family. Both *Escherichia coli* and *Yersinia enterocolitica* also have been associated with vulvovaginal infection. Treatment of bacterial infection consists of an appropriate antibiotic.

Candidal vulvovaginitis is common in the adolescent years and does occur, although less frequently, in prepubescent girls, often secondarily to a predisposing factor such as a recent course of antibiotics, diabetes mellitus, an immunodeficiency, or wearing of diapers. Usually, the patient complains of a nonodorous white discharge, pruritus, and dysuria. Physical findings typically are erythema and edema of the vulva and vaginal mucosa, with an adherent white discharge and, in severe cases, fissures and excoriations. In infants and

young girls, an erythematous perineal rash with satellite lesions is common. The classically described "cottage cheese" discharge actually is an unusual finding. The diagnosis can be confirmed by a wet mount preparation, to which 10% potassium hydroxide is applied, that shows characteristic pseudohyphae. Treatment consists of topical and, in severe or complicated cases, oral antifungal preparations.

For a young girl who has malodorous purulent discharge, especially if it is blood-tinged, a foreign body is the most common cause, usually toilet paper unintentionally placed in the vagina. Among adolescents, the most common foreign body is a forgotten tampon, which may cause a very malodorous discharge and vaginal ulcerations. Removal of a foreign body from a young girl may require sedation.

Pinworms (*Enterobius vermicularis*) are a common cause of perirectal and vulvar pruritus in children. Mature pinworms lay eggs at night around the anus and vulva. The diagnosis can be made by seeing the 1/2-inch long white, threadlike worms in the perianal region at night or by touching transparent adhesive tape to the perianal region to look for microscopic eggs. Treatment is 100 mg of oral mebendazole, repeated 2 weeks later to kill worms that may have hatched after the initial dose. Bedding and clothing should be laundered.

Trichomonas vaginalis, a protozoan, is an uncommon cause of vulvovaginitis in children or adolescents unless they have been sexually abused or are sexually active. The presenting complaint is vaginal discharge, dysuria, and vulvar pruritus. The discharge typically is malodorous and may be yellow-green or frothy. Erythema of the genitals sometimes is accompanied by punctate hemorrhages of the vagina and cervix. The diagnosis is made by microscopic examination of a wet-mount preparation

disclosing motile, flagellated, tear-shaped organisms. Because trichomonal infection is sexually transmitted, its presence should raise concern about other sexually transmitted diseases. Metronidazole is the treatment of choice.

Both herpes simplex virus-1 and -2 can cause genital disease. Although perinatal transmission has been described as a cause of childhood genital herpes, infection occurs primarily through sexual contact and, in prepubescent girls, should raise concern about abuse. Patients complain of vaginal itching, dysuria, and local pain. Grouped vesicles on an erythematous base, with pain and erosions, are the typical physical finding. Viral culture confirms the diagnosis. Treatment is with oral acyclovir; sitz baths and topical emollients may be used for symptomatic relief.

Vulvovaginitis is common in pediatric practice. The differences in cause and presentation between prepubescent and adolescent girls should guide the evaluation. Diagnosis may lead to a specific therapy, but many times, especially with young children, the problem is nonspecific and related to poor hygiene or chemical irritants. Treatment must include education.

Comment: Just a reminder that human immunodeficiency virus (HIV) is a sexually transmitted infection, and when sexual abuse is considered in a child who has vulvovaginitis, HIV testing should be included in addition to appropriate cultures and serology for syphilis. Obviously, any adolescent who has sexually transmitted vaginitis also should be offered testing for HIV infection.

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Editor, In Brief

In Brief

Egg-based Vaccines

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Author Disclosure

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Safe Administration of the Measles Vaccine to Children Allergic to Eggs. James JM, Burks AW, Roberson PK, Sampson HA. *N Engl J Med.* 1995;332:1262-1266

Safe Administration of Influenza Vaccine to Patients With Egg Allergy. James JM, Zeiger RS, Lester MR, et al. *J Pediatr.* 1998;133:6240-6248

Immunization of Egg-allergic Individuals With Egg- or Chicken-derived Vaccines. Kelso JM, Yuniginger JW. *Immunol Allergy Clin North Am.* 2003;23:635-648

Prevalence of Anti-gelatin IgE Antibodies in People With Anaphylaxis After Measles-Mumps-Rubella Vaccine in the United States. Pool V, Braun MM, Kelso JM, et al. *Pediatrics.* 2002;110:e71

Egg-containing vaccines present potential risks to children who have an egg allergy. Such vaccines include influenza, measles-mumps-rubella (MMR), rabies, and yellow fever vaccines. Influenza and MMR frequently create concerns due to their recommended administration to all children younger than age 2 years, a period of life when egg allergy is most common. It is important when considering the risk for anaphylaxis to understand both the production methods for these vaccines and the patient's clinical history.

Inactivated influenza vaccine is grown in the chorioallantoic fluid or ovalbumin of chick embryos. Three influenza vaccines are used in the United States: split virion (Flushield[®], Wyeth-Ayerst) and purified subvirion using zonal centrifugation (Fluogen[®], Parke-Davis; Fluvirin[®], Powderject Vaccines). The allergenicity of influenza vaccines varies with methods of preparation, with whole virus from red cell eluates (not available in the United States) containing more chick egg protein than centrifuged or chemically precipitated vaccines. Recent studies have shown more than a 30-fold variability in the amount of egg protein present in lots of these vaccines. Therefore, the risk of anaphylaxis for the individual patient is difficult to determine.

A large multicenter study demonstrated the safety of administering graded doses of influenza vaccine to egg-allergic children. The children initially received one-tenth of the recommended dose of vaccine, followed 30 minutes later by nine-tenths of the dose. None of the children had allergic reactions. The authors, however, cautioned that vaccines containing larger amounts of egg protein could cause serious reactions.

It is important to obtain an allergy history prior to administering influenza vaccine. The decision on whether to give the vaccine to a child who has a known history of egg allergy should be based on the severity of allergy (local reaction, urticaria, or anaphylaxis) and the clinical indication. Does the child have asthma or another chronic disease for which influenza vaccine would be protective? Is the child at high risk for influenza in crowded housing or child care? If the decision is made that the

child would greatly benefit from the vaccine, it can be administered by graded procedure in a location where epinephrine and oxygen are available. However, influenza vaccine should be withheld from any child who has a history of anaphylaxis to eggs. The recently developed live, attenuated intranasal influenza vaccine (FluMist[®], Medimmune Vaccines) also contains small amounts of egg proteins, and there are no reports to date on the safety of its administration to patients who have egg allergy.

Unlike influenza vaccine, the measles component of MMR is grown in chick fibroblast cultures that do not contain egg antigens. Concern developed over the administration of MMR to egg-allergic children after scattered case reports described generalized allergic urticaria and angioedema following MMR vaccination. However, hundreds of reports have described no reaction to MMR in children who have egg allergy. In fact, anaphylactic reactions to MMR vaccine have occurred in children who do not have this allergy. Multiple studies have shown that many anaphylactic reactions to MMR and other vaccines have been due to gelatin or neomycin allergy.

To summarize current data, most egg-allergic children can be vaccinated routinely with MMR as a whole dose. Even though the vaccine may contain picogram or nanogram quantities of egg protein, there is little evidence to suggest that this amount is sufficient to be allergenic. Other vaccine components are responsible for most anaphylactic reactions to MMR. Cross-reactivity reactions also may occur in children who are allergic to chicken or feathers, and these reactions cannot be

predicted by using skin tests. The American Academy of Pediatrics *Red Book*, therefore, states that children who have egg allergy routinely may be given MMR. As with the administration of any vaccine, epinephrine should be readily available at the clinical site because anaphylaxis is a rare, unpredictable complication.

Yellow fever vaccine presents the greatest potential risk for allergic reactions because it is grown in chick embryos that are homogenized. It contains about 10-fold the amount of egg pro-

tein as does influenza vaccine. All children requiring yellow fever vaccination should be referred to an allergist. The rabies vaccine presents very little risk to egg-allergic individuals. Of the three available rabies vaccines, only one is grown in chick fibroblasts and contains picogram amounts of egg protein.

Comment: Many vaccine constituents have the potential for hypersensitivity reactions. Fortunately, such reactions are rare, although clinicians must be prepared for this possibility. The *Red*

Book outlines the four types of hypersensitivity reactions related to vaccine constituents: 1) allergy to egg-related antigens; 2) mercury or thimerosal sensitivity; 3) antimicrobial-induced allergy (eg, streptomycin, neomycin, polymyxin B); and 4) hypersensitivity to other vaccine components, including stabilizers (eg, gelatin), yeast protein, and the infectious agent.

Tina L. Cheng, MD, MPH
Associate Editor

Clarification

A reader wrote: “While phenacetin can lead to hemolysis in patients who have G6PD deficiency, its metabolite acetaminophen is relatively safer to use. Reports in the literature are few and limited to acetaminophen overdose in patients who have severe G6PD deficiency.”

Our response:

The reader’s observation was discussed with the author and our hematology consultants, who point out that there is a great variation in the degree of enzyme deficiency from one form of G6PD deficiency to another. Acetaminophen should not cause trouble in less severely afflicted individuals, but could enhance hemolysis in those who are severely affected, particularly those who have a low level of enzyme and experience chronic hemolysis.—LFN

International Travel with Children: Tips for Physicians and Families

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Author Disclosure

Dr Ferguson did not disclose any financial relationships relevant to this article. Dr Yetman is a member of the Speakers' Bureau for Ross Products Division, Abbott Laboratories.

Introduction

For a variety of political and economic reasons, opportunities for childhood travel outside the United States have increased dramatically. Expatriation of employees and their families to global markets, deployment of families who have children for military or humanitarian aid purposes, foreign adoption, return of recent immigrants for visits to their countries of origin, and increased ease of leisure travel in areas previously “off the beaten path” have contributed to opportunities for international travel with children.

Often, the first source of information for families that include children who are considering international travel is their pediatrician or other primary care practitioner. The practitioner may be asked to help plan for anticipated and unanticipated health-care needs abroad, to provide information about the prevention of infectious diseases and other health problems specific to certain destinations, and to assist in planning for routine health care in areas where politics and health-care funding are different from those in the United States. Additionally, the health-care practitioner may see patients who recently have traveled abroad, who have immigrated to this country, or who are here for a prolonged stay. A pediatrician's familiarity with the resources available and current recommendations about international travel allows for helpful guidance to the family.

Types of International Travel and Available Resources

International travel with children is likely to fall into two general categories: 1) short-term travel for leisure or adoption and 2) expatriation for parental career purposes (which may last for months or years). For the leisure traveler, *Lonely Planet Travel Guides* or a local travel agent can offer suggestions for lodging and dining. For the expatriate, the family's sponsoring organization often is invaluable, providing names of other expatriated employees and perhaps providing for a visit prior to travel so housing, schooling, and health care can be arranged. International groups for expatriates (eg, Federation of American Women's Clubs Overseas) are abundant, often offer Web sites and orientations in host countries for American families that have children (www.aca.ch), and frequently are a source of much useful information.

For both groups of international travelers, the Centers for Disease Control and Prevention (CDC) Web site (www.cdc.gov) is invaluable to the physician and family. This Web site provides up-to-date information about travel hazards, immunization recommendations, and precautions for specific travel destinations (such as malaria prophylaxis). The United States State Department (http://travel.state.gov/travel/tips/regional/regional_1178.html) can provide information about areas to be avoided because of civil unrest. Table 1 lists many helpful Web sites. For those practitioners and families who are not facile with or who do not have access to the Internet, contacting the local or state health department by phone is an alternative.

Pretrip Planning

Gathering Documents and Arranging for Medical Care

As a part of the travel planning process, parents should gather necessary documentation, such as copies of birth certificates and passports, childhood immunization records, and a list of medicines with their *generic* names (medications often are marketed under different trade names in different countries). If the travel is likely to be for an extended period of time, complete duplicate copies of the child's medical and dental records may be necessary

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Table 1. Web Site Resources for Practitioners and Parents

American Academy of Pediatrics, Fellowship Directory	www.aap.org
American Board of Pediatrics	www.abp.org
American Red Cross First Aid Handbook	www.redcross.org
American Citizens Abroad	www.aca.ch
Association of Tropical Medicine and Hygiene	www.astmh.org/clinics/clinindex.html
Association of Americans Resident Overseas	www.aaro.org
Centers for Disease Control and Prevention	www.cdc.gov/travel/camerica.htm
Federation of American Women's Clubs Overseas	www.fawco.org
International and Continental Pediatric Societies	www.il-st-acad-sci.org/health/pedssocs_i.html
International Association for Medical Assistance to Travelers	www.iamat.org
International Diabetes Foundation	www.idf.org
International Pediatric Association	www.ipa-world.org
International Society for Travel Medicine	www.istm.org
Lonely Planet Publications	www.lonelyplanet.com
Travel Clinic Directory, American Society of Tropical Medicine and Hygiene	www.astmh.org/publications/clinics.cfm
Travel Medicine Providers	www.tripprep.com/scripts/main/topframe.set.asp?DocID=tmp
United States Department of State: "Services and Information for American Citizens Abroad"	http://travel.state.gov/travel/tips/regional/regional_1178.html
Virtual Hospital	www.vh.org
World Health Organization: general travel, vaccines, immunizations, and biologicals	www.who.org

and should be packed in both carry-on and checked luggage, in the event that immediate availability en route is required.

Children who have chronic medical conditions, especially those whose medical conditions may be exacerbated by stress or unfamiliar activity, should have ready access to a pediatrician or family physician on arrival in the host country. A new clinician should be identified prior to departure with the help of the child's regular physician. Sources of international health care include the International Pediatric Association (www.ipa-world.org), the list of American Academy of Pediatrics fellows overseas (AAP Fellowship Directory), the American Board of Pediatrics Online Directory (www.abp.org), and the Primary Care Internet Guide (www.uib.no/isf/guide/family.htm). Subspecialty care can be arranged through contacts with domestic subspecialists, through international subspecialty societies (http://www.il-st-acad-sci.org/health/pedssocs_i.html), or by contacting pediatric departments of medical schools in the host country. Online resources for individuals traveling with specific disabilities (eg, Virtual Hospital [www.vh.org] and others) also may be useful.

An appointment at a travel medicine clinic or an international adoption clinic, depending on the circumstances, may be recommended to review travel destination needs, especially for families traveling to developing

areas. Many children's hospitals have Web sites that can be accessed for these types of clinics, and lists are available from the CDC Web site and the Institute of Travel Medicine (www.istm.org). Parents adopting children from outside the United States should consider the services of an adoption clinic specializing in such care, which may be able to provide useful planning information, especially regarding risk for infectious diseases. The CDC Web site also provides information about the legal requirements for documenting the health and vaccination status of children adopted outside the United States.

Although parents may have many questions about endemic and epidemic diseases in the host country (especially for preventable and treatable ones such as malaria), the leading causes of death outside the United States are due to illnesses for which American children are routinely immunized, including *Haemophilus influenzae* type b, measles, pneumococcal disease, and chickenpox. It is imperative to ensure that a soon-to-be-traveling child's United States immunization status is current. Equally important is accessing destination-specific information for additional immunization or prophylaxis measures. Specifically, the parent and physician should seek information about malaria, cholera, dengue fever, typhoid, and other tropical diseases from the CDC (www.cdc.gov), travel medicine clinics, or country-specific publications or Web sites.

Special attention must be paid to patterns of malarial drug sensitivity and to ensuring that palatable formulations of medications, such as chloroquine and mefloquine, are obtained well in advance of departure. The CDC Web site provides a list of specific medication recommendations for malaria prophylaxis in children based on age and underlying medical condition (www.cdc.gov/travel/mal_kids_pub.htm); they recommend that medications for children *always* be purchased in the United States. For small children, it may be necessary to contact a compounding pharmacy for a syrup preparation well in advance of travel.

Teenagers and college-age young adults often travel independently or with school or community groups. Parents of these travelers can plan in advance to assist their children should emergency needs arise. They should ask their domestic physicians for references for pediatric care in a foreign country before travel begins. Parents may wish to consider an appointment with a travel medicine clinic prior to departure to ensure that immunization and prophylaxis arrangements for their child have been met (see references). Ideally, parents also should ensure that their own travel documents (passports and visas), immunization requirements, and medical needs are current in the unlikely event they are required to travel to the child's destination to arrange or assist with urgent issues. Parents can ensure that letters with contact information for the child's domestic pediatrician and a description of the child's medical needs, including full details about the medical condition of children who regularly take medication or have ongoing medical needs, are in the hands of the traveling chaperones.

Teens traveling to the United States as exchange students or working as au pairs usually carry their medical forms and immunization documents with them, but host families may want to interview the teens or contact their parents on arrival to the United States to review any special needs. A "get-acquainted visit" with a physician may be a good idea for teens staying for more than a few weeks; the university health service where they are enrolled or the resources available to au pairs and exchange students via the sponsoring agency can be referenced.

Packing for the Trip

Most parents are accustomed to packing "comfort" items for their children (toys, games, snacks, and juice boxes); including these items for the initial portion of the trip can make the travel easier. Some items taken for granted in the United States or Western Europe (eg, disposable diapers, prepackaged baby wipes) may be difficult to procure or exorbitantly expensive in rural or

less-developed areas; alternatives for these types of items should be considered.

Medications and medical supplies such as asthma inhalers, insulin syringes, and glucometer strips can be divided between carry-on luggage and packed bags. Some items typically recommended for a first aid kit may *not* be carried on aircraft due to airline safety regulations; these items must be packed in checked baggage (Table 2). A signed letter from each family member's physician describing the diagnosis and need for each medication may expedite immigration and customs queries. Some durable medical equipment could be subject to confiscation or payment of a "duty" in host country currency if importation for profit is suspected, even if the item is accompanied by a physician's statement.

Most airlines supply oxygen on their aircraft, but they must be notified prior to passenger arrival; a written letter or prescription from the child's health-care practitioner can be required. The patient's own oxygen canister may be carried in the cargo compartment, but it must be empty. (1) Parents traveling with children who require oxygen must arrange for replacement canisters in advance from one of the many companies that provide this service worldwide (www.oxygentravel.com).

Families traveling to industrialized countries in which medical supplies are readily available require only a complete standard first aid kit, as recommended by the American Red Cross. (2) Families anticipating prolonged stays in rural areas or in developing countries should consider additional items, such as water purification tablets (3) and perhaps antibiotics to be used judiciously under prediscussed circumstances. The family pediatrician may want to discuss with families who will be living in areas more than 1 day's travel from medical care the possible need for treating skin infections not responding to local care and associated with fever, dysentery not improving with oral rehydration, or signs and symptoms of pneumonia or urinary tract infection. Depending on the destination, parents may want to take a copy of the *American Red Cross First Aid Book* or other health and first aid references (see Suggested Reading).

The need to adjust for varying electrical sources in various countries is commonly known, but planning for this is critical for parents of children who use equipment such as apnea monitors or nebulizers. Most parents are aware of the need to have both a voltage converter and a plug adaptor, and kits containing various types can be purchased at many department stores, as well as online from travel supply companies. In some cases, alternative

Table 2. Contents of an Expanded First Aid Kit*

- Sterile gauze in individual packages
- Elastic bandages
- Antiseptics (povidone-iodine, hydrogen peroxide)
- Scissors, tweezers, medicine spoon and cup
- Disposable plastic razor[†]
- Utility or pocket knife[†]
- Digital thermometer (replace battery yearly)
- Sealed wet wipes (replace every 6 months)
- Soap
- Clean washcloth
- Sunscreen
- Nonaerosol insect repellent
- Hydrocortisone 1% cream
- Antibiotic ointment
- Decongestant (topical and oral)
- Bismuth subsalicylate (eg, Pepto-Bismo[®]) (for use in those older than age 16 years for prevention or treatment of traveler's diarrhea)
- Acetaminophen and ibuprofen
- Antihistamine (diphenhydramine)
- Cefixime, ciprofloxacin, or other temperature-stable antibiotics for *Salmonella* and *Shigella* infections
- Antibiotics (azithromycin or cephalexin capsules) for skin infections
- Waterproof ground cover or plastic trash bags
- Tongue depressors
- Sling
- Band-aids
- Blanket
- Saline nose wash
- Mosquito netting and poles
- Sterile cotton tip applicators
- Sanitary napkins
- Twist-activated heat pack
- Blue ice
- Bottled water
- Oral rehydration salts in powder form
- Sports drink (powder or liquid)
- Flashlight and transistor radio
- Extra batteries
- Separate copies of passports, birth certificates, insurance cards, and calling card/credit numbers
- Coins for use in phone in host country
- Crackers or other nonperishable snack
- Water purification tablets (halazone or iodine compound) with use instructions
- Splint material (heavy cardboard, length of PVC pipe, balsa wood)
- Sealable sandwich bags with lock strips

*Items can be adjusted by families for specific needs and travel destinations.

[†]Check with the airline for current restrictions.

Adapted from Ferguson LE, Parks DK, Yetman RJ. Health care issues for families traveling internationally with children. *J Pediatr Health Care.* 2002;16:51-59.

medications can be used (eg, an appropriately used metered dose inhaler with spacer and mask for most asthma patients has been shown to provide at least as good, if not better, delivery of medication than does a nebulizer). (4)(5) In other instances (eg, children who have cystic fibrosis and may require a nebulizer for some medications), specialized equipment is required. Some medical devices (home ventilators and apnea monitors) require significant knowledge to change settings or download information, and parents must ensure that they are knowledgeable about the equipment and sources of repair.

Emergency medical care and evacuation, including the insurance coverage for such eventualities, should be discussed prior to an extended stay for families in a foreign country. Parents should check with their health insurance carriers and may want to consider additional coverage. Information about health insurance available to expatriates may be found from the American Citizens Abroad (www.aca.ch) or Associations of Americans Resident Overseas (www.aaro.org). Commercial airlines have strict rules about the medical conditions of those

who fly. Commercial medical evacuation flight services can be found throughout the world, and the United States State Department may be a resource for emergency evacuation or acute needs for care from a rural area.

The Trip Amenities in the Host Country

Parents should understand that “American-style” motels conveniently located along travel routes and continuous service restaurants where children are universally welcome are not always the norm in other countries; plans for meals and accommodations before embarking on any road trip outside the United States should be considered. Information from the United States State Department should be incorporated into such travel plans.

Although most industrialized cities throughout the world have modern water treatment facilities, these modern systems may be supplemented in some regions by rooftop cisterns or garden wells that may not be satisfactory. Posted signs usually advise as to the water's potability. If in doubt, parents should insist that their children

drink and brush their teeth with only bottled water and not allow them to drink or play with bath water. Water purification tablets may be used 30 minutes prior to ingestion, but parents should be aware that they may confer a bitter taste to water. (3)

Infectious diarrhea is known to be a significant cause of morbidity and mortality worldwide and is the primary cause of traveler's diarrhea. In some regions, most of the native population may be carriers of *Salmonella* sp, *Shigella* sp, or enterotoxigenic *Escherichia coli*. Education of parents includes routes of transmission of these organisms as well as ensuring proper food handling, storage, and refrigeration (which may be inadequate in nonindustrialized locales). Parents should be warned against buying any consumables from street vendors. Rather, families should be directed to use supermarkets (where available) for snacks; generally safe foods for children to consume include packaged cereal, bread, pasta, canned and bottled food and juices, and pasteurized dairy products. They should not provide raw, uncooked food for their children unless they can wash it themselves. Salad bars and cold buffets are especially suspect; fruits and vegetables that cannot be peeled (such as berries) should be avoided. (6) Families should be encouraged to provide only cooked food that is served at the table steaming hot (7) and to be aware that eating in private homes may be a concern if household help has not been trained in sanitation precautions.

A high priority for public health entities in the United States has been vigilance about environmental concerns such as lead poisoning and air quality. In some cases, these concerns may have been addressed to a lesser degree by public health entities in other countries. Leaded gasoline continues to be produced and used in many parts of the world, especially in rural areas, although most countries (including Thailand, Indonesia, India, and Mexico) have begun phase-out programs. High levels of lead continue to be found in paint, folk remedies, over-the-counter medicines, and cosmetics in Latin America and the Middle East in particular; avoidance of these products is crucial. Annual lead testing may be indicated in children returning from those regions. Measurement of serum lead levels may be especially germane for couples adopting children from China, Mexico, and Russia; pediatricians caring for immigrant children from these areas should be on the alert and may choose to provide screening on arrival to the United States.

Children who have significant food allergy may be at special risk during international travel. Although the European Union has strict food labeling guidelines that

are equal to or exceed those found in the United States, parents of children who have peanut, milk, shellfish, or other allergies that result in urticarial reactions or anaphylaxis will want to review the food labeling laws specific to the country they plan to visit. EpiPen® and Epi Pen Jr® (Dey LP, Napa, Calif) are important components of that family's first aid kit, and the parent should investigate availability of these items abroad via purchase or mail order.

Air pollution is a significant concern worldwide; Mexico City and large cities in India are particularly notable for high degrees of pollution, which can be a problem for children who have chronic respiratory diseases. Organophosphate pesticides continue to be used throughout the world, especially in malaria-bearing mosquito areas. Exposure to and proper storage of these chemicals is of concern; parents should be diligent in washing fruits and vegetables to eliminate this toxin.

American children accustomed to living in more northern latitudes may require special anticipatory guidance about using sunscreens or sun block when traveling to tropical or subtropical locales. Unscented PABA (para-aminobenzoic acid) preparations that have an SPF of 15 to 30 are recommended and should be used frequently; supplies should be replenished by mail order or on annual home visits as needed.

Rabies vaccination of household pets in developing countries is low compared with American and European standards. A dog bite in the United States is almost never a cause for concern, although public health laws allow for observation of the animal. A bite by an animal in a developing country, however, should be treated as a risk for rabies, and inoculation with rabies immune globulin and rabies vaccine should be undertaken as soon as possible. For those families exploring caves or forests in Africa, Asia, and Latin America, strong consideration should be given to pre-exposure rabies prophylaxis because the availability of vaccine for postexposure prophylaxis may be limited in these areas (www.cdc.gov).

Accessing Health Care Abroad

Many United States parents are aware of differences in the structure of health-care services in foreign countries. As a part of trip planning, parents can be reminded of the need to learn how to use the host country's private versus public health facilities and how to access general versus specialty care (see resources for finding physicians discussed earlier). Parents may be unaware that pediatricians often serve as consultants rather than primary community-based physicians. Conversely, many parents of children traveling overseas may be surprised to learn

that in contrast to those medical services in the public domain in the United States (such as immunization clinics, school nurses, and school-based screening programs for vision, hearing, scoliosis), health screenings and immunizations are not necessarily required for school entry abroad, but rather are left to the discretion of the parents. Especially in developing countries, some immunizations may be unavailable due to cost, and they will need to be administered on home visits to the United States.

Families who immigrated to the United States and who anticipate moving back to the country of origin or who are planning an extended vacation to their homeland may want to consult a United States pediatrician to determine which vaccines are available in the home or host country and to obtain information on the country's vaccine administration schedule. The World Health Organization Web site contains vaccine summaries listed by country. The parent and pediatrician may consider expediting inoculation for those vaccines not available in the foreign country if safety and efficacy are reasonable. In discussing with their pediatrician their planning for extended stays in countries where tuberculosis is an endemic problem, families may question why bacillus Calmette-Guérin is not usually provided in the United States (due to low incidence of tuberculosis disease and presence of mechanisms for risk-based screening) but may be recommended in those countries.

Increasingly, parents in the United States are familiar with complementary and alternative remedies, but the extent to which these modalities of treatment for children are used abroad may surprise them. The practitioner can caution parents about the use of these agents and provide families with one of the pediatric references for safe use of herbs and other remedies. Prior to travel, the pediatrician can remind parents that safe immunization and acupuncture practices necessitate needle precautions; parents may opt to avoid any injections or needle usage in some settings.

Although a discussion of obstetric care is beyond the scope of this article, Americans will be surprised at the huge variance in customs and facilities worldwide. In some areas, the family must provide for all newborn needs in a hospital setting, including diapers and blankets; in other settings, the availability of doulas along with midwives in homelike birth centers may feel more supportive than some birth centers in the United States. The availability of neonatal intensive care and attitudes toward resuscitating very low-birthweight infants vary widely and should be explored prior to undertaking a pregnancy abroad.

Accessing Mental Health Care and Therapy for Developmental Disabilities

Attitudes and beliefs with regard to mental illness, learning disabilities, mental retardation, speech delay, and attention-deficit disorders are extremely variable throughout the world. Even in Western Europe and other industrialized countries, cultural attitudes and health-care financing practices often do not provide for widespread psychiatric, psychological, psychopharmaceutical, or occupational therapy. Educational disabilities may not be provided for either in foreign schools or even in American schools abroad. Alternatively, some therapies such as physical therapy may be available in hospitals abroad just as they are here. Arranging for continuation of the therapeutic program for a child receiving such services may require significant preplanning with an academic or tertiary care center, frequent trips home, or a decision to cease therapy during expatriation.

Parents can be reassured that ophthalmologic care and basic dental care usually are widely available and are of a professional standard in most industrialized countries. Invasive dental procedures may be risky in those environs where needle hygiene has been an issue, and the parent should look for qualified professionals who are certified by a dental certification system in the host country. Carrying a prescription for eyeglasses or contacts or a duplicate set is helpful for those who have vision needs. The availability of contact lens solution may be an issue in developing areas, and supplies may need to be replenished from the United States by mail order.

Special needs, such as for children who have diabetes or those who may need transfusions (sickle cell disease or hemophilia), may be met by engaging the services of a pediatrician in a travel medicine clinic abroad. These clinics can be identified via the International Association for Medical Assistance to Travelers (www.iamat.org) or the International Society for Travel Medicine (www.istm.org). Blood cannot be transported internationally in an emergency (www.who.org). Transfusions should be avoided wherever possible when traveling because the safety of the blood supply varies by country. European Union member countries and South Africa have certified safe blood supplies, but other areas, including India and Pakistan, have yet to achieve this level of certification. Synthetic blood products and volume expanders are preferable in an emergency pending evacuation to Europe or the United States. Diabetic medications may pose a problem in some countries (due to availability of synthetic insulin, cost, and prescribing practices). Contacting the International Diabetes Foundation (www.idf.org) prior to departure for information or looking

online for host country academic centers that have diabetes clinics is advisable.

Back in the United States

When children are returning from extended travel abroad, a health-care visit promptly on return may be helpful. During the weeks and months after travel, the physician should note arising symptoms that may be attributable to exposures during travel. Practitioners should consider diseases endemic to the area from which the child came. Gastrointestinal complaints that may mimic viral gastroenteritis may be due to hepatitis or a parasite, and appropriate studies may be indicated if resolution is not prompt and spontaneous. Fever and anemia should prompt the ordering of a complete blood count for children who have come from malaria-endemic areas, but the clinician also must order a “malaria” prep or “thick smear” to improve sensitivity of the testing for malaria antigen.

The pediatrician should update the traveling child’s problem list to include any incidents abroad and note, for example, “travel to Africa” for future reference. Immunizations received abroad, if any, should be documented in the record.

Conclusion

Just as we often speak of a “global economy” and “global communications,” children who travel internationally have led us into the era of the “global pediatrician.” The pediatrician is uniquely qualified to consider the needs of the child during these trips. A pediatrician’s familiarity with the anticipated and unanticipated needs of a family

during international travel can help make the travel safe and incident-free.

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