An 11½-year-old girl presents to the clinic with a 6-week history of left leg pain. She is an active participant in gymnastics, and, although she has fallen a few times during practice, she denies any significant trauma. Recently, she has limited her participation in training because her leg pain has increased significantly. However, the pain does not restrict her walking. She denies other limb or joint pain, night sweats, joint swelling, fever, rash, anorexia, weight loss, or recent illness. Her past medical history is unremarkable.

The patient is a well-appearing girl. Vital signs are normal. The only significant finding upon physical examination is point tenderness over the anterior aspect of the proximal left tibia. There is no swelling, warmth, or erythema of the left leg or knee. There is no active or passive restriction of range of motion of all joints. The remainder of the physical examination is normal. Laboratory examination reveals a normal complete blood cell count and erythrocyte sedimentation rate and normal levels of C-reactive protein, electrolytes, blood urea nitrogen, creatinine, and liver enzymes. Urinalysis yields unremarkable results.

Radiography of the left leg reveals an abnormality that may be associated with her pain (Fig 1).

Figure 1. Radiographs of the left knee demonstrate a radiolucent oval lesion with sharp borders within the proximal tibia.
Diagnosis: Bone Cyst of Proximal Tibia
Radiography reveals a radiolucent oval lesion; it is most likely a unicameral bone cyst (UBC). There is no evidence of a fracture. The patient is referred to a pediatric orthopedist for further evaluation.

Discussion
Described by Virchow in 1876, a UBC (also known as a simple bone cyst, solitary bone cyst, or juvenile bone cyst) is a benign fluid-filled cavity found primarily in the metaphyseal region of the long bones, especially in skeletally immature children. This type of cyst tends to expand and weaken the bone, thereby predisposing it to a pathologic fracture. (1)(2) UBCs appear more frequently in males than in females (2:5:1), and occur primarily in patients under age 20 years (85%), with a peak incidence at age 10 years. (1)(3) This lesion accounts for 3% of biopsied bone tumors. Typical cyst locations include the humerus, femur, tibia, and fibula. (2)(3) Less common locations include the calcaneus (2%-3% of cases), (2) distal radius, (4) and spine. (5)

Etiology and Pathogenesis
The cause of formation of a UBC is unclear, but theories include venous obstruction, development of an intrasosseous syncytial cyst, dysplastic bone formation in response to trauma, and localized failure of ossification during a period of rapid growth. (1)(2)(3) The fluid within the cyst contains oxygen-free radical scavengers, prostaglandins, interleukin-1, and proteolytic enzymes that cause bone resorption, thereby contributing to the formation and growth of the cyst. (1) Microscopic examination of the cyst walls reveals primarily fibrous tissue with occasional giant cells. (1)(2)

Clinical and Radiologic Features
The UBC usually is asymptomatic and is detected often by incidental radiographic imaging of a limb for reasons not related to the cyst, such as minor trauma or limp. Any associated pain may be due to a pathologic fracture through the cyst or to microfractures not yet detected by radiograph.

On radiograph, the bone cyst appears as a round or ovoid lucent lesion with an overlying thin, expanded cortical bone. Occasionally, when there is a fracture, a fragment of the cyst wall appears within the fluid cavity, evident as a “fallen leaf” radiographic sign. (1)(2) Computed tomography and magnetic resonance imaging will show the lesion to be fluid filled with a thin enhancing wall, but are often not necessary for diagnosis due to the characteristic appearance of UBC on plain radiographs. Sometimes a few septations are present. (2)

Seventy-five percent of patients who have UBC present with a pathologic fracture. (6) Although the proximal metaphysis is the classic location of most UBCs, there have been reports of epiphyseal involvement. Ovadia and associates (7) reported eight children with a median age at diagnosis of 8.4 years having bone cysts crossing the growth plate. All children had more than two pathologic fractures; seven patients had growth disturbance without functional impairment.

A UBC is defined as active if the cyst has increased in length or width by 25% in serial radiologic studies, if the patient has functional pain, if pathologic fractures appear without resolution of the cyst, or if the cyst is associated with cortical thinning (impending fracture). (6) In addition, a cyst is considered active if it has close proximity to the epiphyseal plate, and is considered latent if it is >0.5 cm distal from the physis. (6) Wilkins states that it is radiographically difficult to assess the current stage (growth versus involution) of the cyst at the time of diagnosis, a status that has implications regarding treatment and possible complications. (1)

Differential Diagnosis
The differential diagnosis for UBC includes an aneurysmal bone cyst, which is a benign osteolytic bone neoplasm characterized by expansive hemorrhagic, lobulated tissue arising in bone, and fibrous dysplasia, which is a benign disorder characterized by presence of intramedullary fibro-osseous tissue that arises in the diaphysis. (6)

Treatment
Conservative management with close outpatient follow-up is the treatment of choice for the asymptomatic, physically active child who has a small cyst with thickened walls (asymptomatic UBC), because chances are good that the cyst is in its involutorial stage and will soon disappear. (1)(3) However, if there is increased risk for a pathologic fracture through the thin cortex, treatment should occur to prevent fracture and possible complications, such as residual skeletal deformity. (1)(3) Sites of particular concern are lesions in the proximal femur and the dominant throwing arm of athletes, due to the high stresses at these locations and an elevated risk of pathologic fracture. If presentation involves a pathologic fracture, fracture treatment occurs first, reserving...
treatment of the cyst for those that persist after fracture healing.

Treatment options are (1) percutaneous aspiration and local corticosteroid or autogenous bone marrow injection and (2) open curettage and bone grafting (autografting, allografting, or use of an artificial bone substitute such as calcium sulfate). A new modified procedure consisting of minimally invasive curettage, ethanol cauterization, disruption of the cystic boundary, insertion of a synthetic calcium sulfate bone graft substitute, and placement of a cannulated screw to provide drainage has been described recently. This operative procedure showed the highest radiographic healing rate in comparison with the other methods discussed. (3) Donaldson, in a review of treatment options, states that corticosteroid injection is the only evidence-based treatment for UBCs, but treatment strategies that include opening the medullary canal, disrupting the cyst wall, and filling the lytic defect with a bone substitute may be preferable; however, evidence is still lacking. (8)

Successful healing of a UBC after surgical intervention as judged by radiograph ranges from 29% to 100%. Complications include physeal injury and cyst recurrence. Children who received instrumentation as part of their treatment eventually require implant removal. (3) Long-term clinical and radiographic follow-up is recommended, because recurrence of UBC has been reported in 18% to 88% of patients at 6 months to 7 years after the initial

Figure 2. Axial and sagittal computed tomographic sections of left leg confirming UBC morphology.

Figure 3. Histology of UBC. The cyst wall is composed of fibrous membrane (black arrow) bordered by bony trabeculae. Fibrin-like material and a few osteoclast-like giant cells are present within the cyst (red arrow).

Figure 4. Left leg radiograph confirming surgical filling of UBC.
treatment. (3) Subsequent fracture after surgery is another complication and can affect a child’s quality of life adversely; a child may avoid physical activities for fear of causing a fracture. (1)

Patient Course
Based on the clinical examination and the radiographic picture, the diagnosis of UBC was established and the patient was asked to restrict physical activities. She returned 3 months later complaining of pain, even without physical effort. Computed tomography demonstrated a hypodense lesion with a sclerotic border measuring $22 \times 52 \times 21$ mm located in the metaphysis (Fig 2). A repeat radiograph of the leg showed a slight increase in the cyst’s size without evidence of an obvious pathologic fracture. The patient underwent cyst curettage with bone grafting. Pathologic examination confirmed the diagnosis of UBC, showing that the wall of the cyst was composed of fibrous membranes bordered by the bony trabeculae. Fibrin-like material and a few osteoclast-like giant cells were seen focally as well (Fig 3). The postoperative period was uneventful. Two years later, the patient no longer has leg pain and has returned to full physical activities. A follow-up radiograph confirmed filling of the cavity without complications (Fig 4).

Summary
- Unicameral bone cysts (UBCs) in children usually are asymptomatic. Most UBCs are discovered when a radiograph is performed on a child who has had accidental trauma to a limb.
- Symptomatic cysts typically present with pain, often the result of pathologic fracture through a large cyst or occult stress fracture within the thinned cortex around the cyst.
- Simple radiography is the best method for detecting such cysts, which typically are located within the long bone (femur, tibia, fibula, humerus), but can appear elsewhere.

- Cysts typically appear in the proximal metaphysis, but some involve the epiphysis and growth plate, thereby affecting bone growth.
- If clinically necessary to confirm the diagnosis, computed tomography or magnetic resonance imaging can delineate the cyst better or demonstrate an occult fracture.
- For the asymptomatic UBC, close follow-up is the recommended course of action. However, surgical intervention by corticosteroid or autogenous bone marrow injection or open curettage with bone grafting is recommended if the cyst is symptomatic, carries an increased risk for pathologic fracture (weight-bearing bone or dominant arm of a throwing athlete), or shows signs of an impending pathologic fracture.
- Clinical and radiographic follow-up is recommended after surgical intervention, because UBC recurrence after initial surgery is reported to occur in 18% to 88% of patients.

References

Suggested Reading
Conjugated Hyperbilirubinemia in Children

Drs Brumbaugh and Mack have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Education Gaps

1. Awareness of telltale signs and performance of appropriate diagnostic testing can help clinicians identify neonatal cholestasis in time to ameliorate its potentially catastrophic outcomes.

2. The success of the Kasai procedure to restore bile flow is directly related to patient age: at less than 60 days after birth, two-thirds of patients benefit from the procedure; however, at 90 days after birth, chances for bile drainage diminish markedly.

Objectives

After completing this article, readers should be able to:

1. Understand the metabolism of bilirubin, the differences between conjugated and unconjugated bilirubin, and the relationship of conjugated hyperbilirubinemia to cholestasis.

2. Delineate the causes of cholestasis in the newborn and know how to evaluate the cholestatic neonate.

3. Manage the infant who has prolonged cholestasis.

4. Understand the causes of conjugated hyperbilirubinemia in the older child and adolescent and know how to assess children who have conjugated hyperbilirubinemia.

Introduction

Central to human digestive health are both the production of bile by hepatocytes and cholangiocytes in the liver and the excretion of bile through the biliary tree. By volume, conjugated bilirubin is a relatively small component of bile, the yellowish-green liquid that also contains cholesterol, phospholipids, organic anions, metabolized drugs, xenobiotics, and bile acids. In most cases, the elevation of serum-conjugated bilirubin is a biochemical manifestation of cholestasis, which is the pathologic reduction in bile formation or flow.

Complex mechanisms exist for the transport of bile components from serum into hepatocytes across the basolateral cell surface, for the trafficking of bile components through the hepatocyte, and finally for movement of these bile components across the apical cell surface into the bile canaliculus, which is the smallest branch of the biliary tree. From the bile canaliculus, bile then flows into the extrahepatic biliary tree, including the common bile duct, before entering the duodenum at the ampulla of Vater (Fig 1). Isolated gene defects in proteins responsible for trafficking bile components can lead to cholestatic diseases.

Diagnosis

Unconjugated bilirubin is the product of heme breakdown, and this molecule, poorly soluble in water, is carried in the circulation principally as a water-soluble complex joined with albumin. Unconjugated bilirubin is then taken up into hepatocytes, where a glucuronic acid moiety is added, rendering the conjugated bilirubin water soluble. Conjugated

Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>AIH</td>
<td>autoimmune hepatitis</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>AST</td>
<td>aspartate aminotransferase</td>
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<td>A1AT</td>
<td>alpha 1 antitrypsin</td>
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<tr>
<td>BA</td>
<td>biliary atresia</td>
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<tr>
<td>BRIC</td>
<td>benign recurrent intrahepatic cholestasis</td>
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<tr>
<td>BSEP</td>
<td>bile salt excretory protein</td>
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<tr>
<td>CDC</td>
<td>choledochal cyst</td>
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<tr>
<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
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<tr>
<td>GGT</td>
<td>gamma glutamyltransferase</td>
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<tr>
<td>MCT</td>
<td>medium chain triglycerides</td>
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<tr>
<td>MRCP</td>
<td>magnetic resonance cholangiopancreatography</td>
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<tr>
<td>PFIC</td>
<td>progressive familial intrahepatic cholestasis</td>
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<tr>
<td>PN</td>
<td>parenteral nutrition</td>
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<td>PSC</td>
<td>primary sclerosing cholangitis</td>
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hyperbilirubinemia is defined biochemically as a conjugated bilirubin level of >2 mg/dL and >20% of the total bilirubin. There are two commonly used laboratory techniques to estimate the level of conjugated bilirubin. The first uses spectrophotometry to measure directly conjugated bilirubin. The laboratory may also estimate a “direct” bilirubin, which reflects not just conjugated bilirubin but also delta-bilirubin, which is the complex of conjugated bilirubin and albumin. Hence, the “direct” bilirubin will tend to overestimate the true level of conjugated hyperbilirubinemia, and in neonates is less specific for the presence of underlying hepatobiliary disease. (1)

With the exception of Rotor and Dubin-Johnson syndromes, discussed later in this article, the elevation of serum-conjugated bilirubin reflects cholestasis. The presence of cholestasis may be a manifestation of generalized hepatocellular injury, may reflect obstruction to bile flow at any level of the biliary tree, or may be caused by a specific problem with bile transport into the canaliculus. Systemic disease leading to hypoxia or poor circulatory flow also can impair bile formation and lead to cholestasis.

**Recognition of the Cholestatic Newborn**

Owing to immaturity of the excretory capability of the liver, the newborn is particularly prone to the development of cholestasis. The challenge for the primary care clinician is prompt recognition of the cholestatic infant. Observation of stool color is a necessary component of the initial assessment, because acholic stools represent significant cholestasis. Furthermore, hepatomegaly, with or without splenomegaly, often is identified in the setting of cholestasis.
In the early neonatal period, jaundice caused by physiologic unconjugated hyperbilirubinemia or human milk jaundice is impossible to distinguish from jaundice caused by cholestasis based on physical appearance alone. Indeed, physiologic unconjugated hyperbilirubinemia and cholestasis can coexist in early infancy. A critical time point for establishing the diagnosis of cholestasis is at the 2-week well-child visit. Persistent jaundice at 2 weeks after birth should alert the care provider to the possibility of cholestasis. The diagnosis is made by obtaining a conjugated bilirubin level or “direct” bilirubin fraction, whichever is available locally. If the infant appears well otherwise, a second option is to see the infant back in 1 week. If the jaundice persists at 3 weeks after birth, laboratory evaluation is mandatory.

Expeditious recognition of cholestasis is of great importance in the neonatal period because early intervention may improve outcome. For instance, in the case of hypopituitarism, in which jaundice may be the presenting symptom, early diagnosis may prevent catastrophic hypoglycemia. Antimicrobial therapy in the cholestatic infant who has an occult Gram-negative urinary tract infection may prevent bacteremia and sepsis. Avoidance of extended fasting in an infant born with an underlying metabolic disorder could prevent severe episodes of hypoglycemia and acidosis. Diagnosis of biliary atresia (BA) before 60 days of age leads to earlier surgical intervention and improved long-term outcome.

Initial Approach to the Cholestatic Infant
In addition to conjugated hyperbilirubinemia, the serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels typically are elevated to a variable degree, but are not specific for the cause of cholestasis. The gamma glutamyltransferase (GGT) level usually is elevated in cholestasis. Normal or low GGT levels in the setting of cholestasis have been associated with bile acid synthesis defects, some cases of hypopituitarism, and progressive familial intrahepatic cholestasis types 1 and 2 (PFIC1, PFIC2).

Abnormalities in hepatic synthetic function, such as a prolonged prothrombin time, elevated ammonia level, low serum albumin concentration, or hypoglycemia, suggest advanced hepatic injury and should prompt immediate referral to a pediatric tertiary care facility. A urinalysis and urine culture will assess for urinary tract infection, and the presence of reducing substances in the urine suggests galactosemia.

Newborn screens should be reviewed for the diagnosis of cystic fibrosis, hypothyroidism, galactosemia, and other inborn errors of metabolism, all of which can present with neonatal cholestasis. Because of the broad differential diagnosis for neonatal cholestasis, ultimately the diagnosis and treatment of the cholestatic infant should be accomplished in a center with expertise in pediatric gastroenterology and hepatology. Recent advances in molecular diagnostic techniques have led to targeted approaches to the identification of genetic mutations that may cause neonatal cholestasis. A chip-based resequencing method allowed for identification of suspected causative gene mutations in 27% of subjects in a cohort of infants who have unexplained cholestasis.

### Differential Diagnosis of Neonatal Cholestasis
The following should be considered in the differential diagnosis of neonatal cholestasis (Table).

#### Extrahepatic Biliary Obstruction
BA is the most common cause of neonatal cholestasis, accounting for ~40% to 50% of all cases. There are two
forms of BA. The embryonic form of BA, which is associated with other congenital anomalies such as heterotaxy syndrome and polysplenia, accounts for ~15% to 20% of BA.

The acquired form of BA is far more common (~85%); the etiology of this disease is unclear. The pathophysiology of acquired BA is that of a brisk inflammatory response involving both the intra- and extrahepatic bile ducts. The ducts are destroyed gradually and replaced with fibrous scar tissue. The lumen of the bile duct is eventually obliterated, and normal bile flow is impaired, leading to cholestasis.

Infants who have acquired BA typically are asymptomatic at birth and develop jaundice in the first weeks after birth. Typically, they feed well and thrive. As the bile flow diminishes, the stool color loses its normal pigmentation and becomes acholic, or clay-colored. The finding of acholic stools in the setting of a jaundiced newborn should prompt expedient evaluation for BA. Light-colored stools may not be appreciated by the inexperienced parent, and the stool should be examined by the primary care provider to assess pigmentation.

In Taiwan, which has one of the highest incidences of BA in the world, a universal screening program provides parents with a stool color card on discharge from the newborn nursery (Fig 2). At 1 month of age, the parents return the stool card to their provider after marking the picture of the stool color that most closely resembles the infant’s stool. The universal screening program has led to improvement of early detection of infants who have BA, which has resulted in dramatic improvement in surgical outcomes. (4)

Evaluation for BA includes abdominal ultrasonography to rule out other anatomic abnormalities of the common bile duct, such as choledochal cyst (CDC), and to identify anomalies associated with the embryonic form of BA. A liver biopsy often is performed, and histopathologic findings consistent with BA include bile ductular proliferation, portal tract inflammation and fibrosis, and bile plugs within the lumen of bile ducts. The gold standard in confirming the diagnosis of BA is the intraoperative cholangiogram, which shows obstruction of flow within a segment or the entirety of the extrahepatic bile duct.

A Kasai portoenterostomy is then performed in an attempt to reestablish bile flow. This operation entails excision of the fibrous bile duct followed by anastomosis of a loop of jejunum to the base of the liver in a Roux-en-Y fashion. The success of this surgery, which is the restoration of bile flow to intestine, is directly related to the age of the patient. Early Kasai procedure, defined as <60 days after birth, leads to initial biliary flow in approximately two-thirds of patients; if performed after 90 days after birth the chance of bile drainage is markedly diminished.

Even after restoration of bile flow with the Kasai operation, BA continues to be a progressive disease in most patients, with ongoing inflammatory injury to the intrahepatic bile ducts; 70% to 80% of patients who have BA will develop fibrosis, portal hypertension, and cirrhosis. BA continues to be the most common reason for liver transplantation in pediatric patients. A recent nationwide study reported that ~50% of patients who have BA will require liver transplantation in the first 2 years after birth, with an overall incidence of liver transplantation of ~80% in childhood. The progressive nature of this disease has led investigators to define BA as a chronic inflammatory disorder of the biliary tract.

Other causes of extrahepatic biliary obstruction include CDC and spontaneous perforation of the common bile duct. These anatomic abnormalities can be diagnosed with abdominal ultrasonography. CDC may present with jaundice, acholic stools, and a palpable mass. Spontaneous perforation of the bile duct is a rare entity that usually occurs in the neonatal period. Infants present with jaundice,
poor weight gain, ascites, acholic stools, and vomiting. Ultrasonography typically reveals ascites and fluid around the gallbladder. Bile-stained ascitic fluid is a hallmark finding. The treatment of both of these conditions involves surgical intervention.

Stagnant flow of bile leading to cholestasis is seen often in the setting of intestinal disease and parenteral nutrition (PN) in the neonate. Precipitation of cholesterol and calcium salts within bile can result in the formation of sludge. Bile sludge can be detected by ultrasonography. When sludge builds up and leads to biliary obstruction and the development of cholestasis, the patient is said to have inspissated bile syndrome. Inspissated bile can be managed conservatively with ursodeoxycholic acid, a bile salt that acts as a choleretic agent to promote bile flow. Because inspissated bile syndrome can mimic biliary atresia, the diagnosis sometimes is made at the time of intrahepatic cholangiogram, and saline flushes of the biliary tree by the surgeon can provide the definitive therapy. The use of third-generation cephalosporin antibiotics, in particular ceftriaxone, has been associated with the formation of bile sludge in newborns.

**Infections**

Neonatal cytomegalovirus infection, vertically acquired from the mother, is the most common congenital infectious cause of neonatal cholestasis. Any of the conditions formerly identified as the “TORCH” family of infections (toxoplasmosis, rubella, cytomegalovirus, herpesvirus, syphilis) can lead to a similar pattern of cholestasis and growth restriction. Acquired infections after birth can lead to cholestasis, in particular Gram-negative infections associated with urinary tract infections and sepsis, because hepatic bile flow is very sensitive to circulating endotoxins.

**Genetic Disorders**

Alagille syndrome is an autosomal dominant mutation of the Jagged 1 gene on chromosome 20. There is variable penetrance of this mutation, which can lead to abnormalities of the liver (cholestasis), heart (peripheral pulmonary stenosis), skeletal system (butterfly vertebrae), kidneys, and eyes (posterior embryotoxin).

The characteristic finding on liver histology is paucity of bile ducts. The clinical course of liver disease in infants who have alagille syndrome is highly variable, with some children experiencing a gradual improvement in cholestasis in childhood, whereas others progress to cirrhosis, requiring liver transplantation in childhood. Infants born with Trisomy 21 also are at increased risk for development of a paucity of intrahepatic bile ducts; however, this situation usually is very mild, with resolution of cholestasis in infancy. Cystic fibrosis is another genetic disorder that can present with neonatal cholestasis and often is associated with meconium plug syndrome. Early diagnosis is aided by the availability in all 50 states of newborn screening for cystic fibrosis by measurement of immunoreactive trypsinogen levels.

Along the apical surface of the hepatocyte, there are specific transporter proteins that are responsible for traffic of bile components into the bile canaliculus (Fig 3). (5) Defects in these proteins are associated with cholestatic disease. For instance, a mutation in the gene coding for bile salt excretory protein (BSEP) interferes with bile salt trafficking into the canaliculus, leading to reduced bile flow and the toxic accumulation of hydrophobic bile acids.
within hepatocytes. This mutation produces the clinical phenotype of cholestasis and pruritus in the first year after birth, a condition known as PFIC2.

A defect in the gene coding for FIC1, another canalicular surface protein, produces the clinical phenotype PFIC1, which, in addition to cholestasis, can present with diarrhea and growth failure. Pruritus, a dominant clinical feature of both PFIC1 and PFIC2, typically is not problematic until after 6 months of age.

PFIC3 is a syndrome caused by a defect in the gene coding for the transporter MDR3, which is responsible for phosphatidylcholine secretion into the bile canaliculus. The onset of cholestasis is variable in PFIC3 but typically occurs later than in PFIC1 and PFIC2. In contrast to PFIC1 and PFIC2, which are featured by a GGT level in the low or normal range, the GGT in PFIC3 is elevated.

**Metabolic Disorders**

A range of metabolic diseases can present initially as cholestasis in the newborn period and are associated with gene mutations in most cases (thus, these diseases could also fall under the category of genetic disorders). Persistent jaundice in the newborn period is one of the earliest potential clinical manifestations of alpha-1 antitrypsin (A1AT) deficiency, a defect in the “ATZ” molecule that results in abnormal accumulation of A1AT in the endoplasmic reticulum of hepatocytes. The abnormal retention of A1AT within the hepatocyte leads to abnormal bile formation and secretion.

Inborn errors of metabolism, which include disorders of fatty acid oxidation, tyrosinemia, and galactosemia, among others, can present in the neonatal period with a spectrum of liver disease that includes cholestasis. Finally, bile acid synthesis defects often present with neonatal cholestasis. As the production of bile acids from cholesterol and their subsequent export into the canaliculus are the rate-limiting steps in bile flow, defects in a number of enzymatic steps within this pathway result in abnormal bile acid synthesis and cholestasis. Bile acid synthesis defects generally can be treated effectively by oral bile acid supplementation.

**Endocrinopathies**

Congenital endocrinopathies must be considered in the differential diagnosis of neonatal conjugated hyperbilirubinemia. Neonatal cholestasis is a well-recognized manifestation of congenital hypothyroidism. Congenital panhypopituitarism is manifested by deficiencies in cortisol, growth hormone, and thyroid hormone. These hormones have been shown to promote bile formation or secretion and chronic deficiencies lead to cholestasis. Other clinical findings associated with panhypopituitarism include optic nerve hypoplasia, septo-optic dysplasia, and, in male patients, microphallus. In contrast to most of the cholestatic diseases, which lead to an elevation in serum GGT concentrations, the GGT level in hypopituitarism typically is normal. Hypoglycemia can complicate prolonged fasts in these infants.

**Drug Hepatotoxicity**

Dependent on the maturity of the neonate, there is variability in the activity of members of the drug-metabolizing cytochrome P450 family in the newborn period. Thus, the newborn infant may be particularly susceptible to drug-induced hepatotoxicity, which can take a predominantly cholestatic form. The most common drug-induced liver injury is caused by PN, used in the newborn period for a variety of indications. The liver injury caused by PN is multifactorial, but in particular the phytosterol present in soy-based lipid formulations is a known antagonist of the nuclear receptor FXR, which is a regulator of the BSEP, an essential protein involved in bile acid transport. (6)

Initial experience using fish oil–based sources of intravenous lipids has been promising, but larger clinical trials in neonates have not yet been performed. There are case reports of neonatal cholestasis associated with maternal use of prescribed medications (carbamazepine) and illicit drugs (methamphetamine). Postnatal infant exposure to antimicrobial agents, particularly ceftriaxone, fluconazole, and micafungin, has been associated with the development of cholestasis.

**Management of the Infant Who Has Prolonged Cholestasis**

Failure to thrive is found commonly in infants who have chronic cholestatic conditions. The cause of poor weight gain is multifactorial. Reduced bile flow to the intestine results in poor solubilization of dietary fats in mixed micelles, leading to fat malabsorption and steatorrhea. Medium-chain triglycerides (MCT) do not require bile for intestinal absorption and thus are preferred in infants who have cholestasis. Several commercially available formulas have high levels of MCT as their fat source, and there are supplements containing exclusively MCT that can be used for delivery of additional calories.

Infants who have chronic liver disease may have an increased baseline caloric need coupled with demands for additional calories for catch-up growth. Unfortunately, many of these infants are anorexic, justifying the use of nasogastric feeds for caloric delivery. Fat-soluble vitamin deficiencies are pervasive in infants who have chronic cholestasis and should be managed aggressively with frequent monitoring.
of serum vitamin levels and use of oral fat-soluble vitamin supplements.

Ursodeoxycholic acid is a hydrophilic bile acid that is useful in managing many cholestatic conditions. This bile acid has two purported benefits. First, it can stimulate bile flow and reduce cholestasis; second, it may displace more-toxic bile acids from the hepatocyte, thus potentially lessening the hepatocyte injury associated with cholestasis. For severe pruritis seen in cholestasis, which is caused by the deposition of bile acids in the skin, oral antihistamines provide no benefit. Ursodeoxycholic acid can be helpful, and the oral antibiotic rifampin often is added for refractory pruritis. The action of this agent in reducing itching is still incompletely understood; but rifampin has been shown to provide dramatic relief for affected infants.

Approach to the Child and Adolescent Who Has Conjugated Hyperbilirubinemia

Outside of infancy, conjugated hyperbilirubinemia is a much less common laboratory finding. Depending on the cause of the hyperbilirubinemia, clinical manifestations will vary and can include scleral icterus, jaundice, fatigue, pruritis, abdominal pain, and nausea. Chronicity of disease can be assessed by the history, keeping in mind that in the setting of hepatobiliary disease, a nonspecific symptom, such as fatigue, may be present months before the development of more objective symptoms of cholestasis, such as jaundice and pruritis.

The physical examination should include assessment of liver size and texture. A firm, nodular liver suggests chronic hepatobiliary disease and the development of cirrhosis. Physical stigmata of portal hypertension and cirrhosis include splenomegaly, ascites, palmar erythema, caput medusa, and spider angioma. Normal metabolism of the steroid intermediate androstenedione to testosterone typically occurs in the liver. In end-stage liver disease, more androstenedione is eventually converted to estradiol, leading to the development of gynecomastia in male patients.

In female adolescents, secondary amenorrhea may result from chronic liver disease.

Initial laboratory assessment will include the measurement of serum aminotransferases (AST, ALT), GGT, and bilirubin (including conjugated, or direct bilirubin), as well as performing tests of liver synthetic function, including prothrombin time and serum albumin level. Patients who have poor liver synthetic function, manifested as an elevated prothrombin time or low serum albumin level, should be referred urgently to a center with expertise in pediatric hepatology.

If the physical examination and initial laboratory findings do not support chronic liver disease, but there is an elevated direct bilirubin fraction, consider a defect in the canalicular transport of bilirubin. (7) Dubin-Johnson syndrome is a defect in the anion transporter gene ABCC2, inherited in an autosomal recessive fashion, which leads to elevation both of unconjugated and conjugated bilirubin levels. Rotor syndrome has a similar presentation to that of Dubin-Johnson syndrome, but the underlying genetic defect is unknown. These syndromes involve problems in the storage/excretion of conjugated bilirubin and present with normal aminotransferase levels and the absence of pruritis. The principal clinical objective is to distinguish these benign conditions from the serious hepatobiliary diseases discussed later in this article.

The initial evaluation of a child or adolescent who has conjugated hyperbilirubinemia should include abdominal ultrasonography to assess for obstruction of the biliary tree. Typical symptoms reported with biliary obstruction include jaundice, abdominal pain (reliably reported as right upper quadrant or epigastric pain in older children and adolescents), nausea, and vomiting. A more acute presentation is seen when biliary obstruction is accompanied by cholangitis, which is a bacterial infection of the biliary tree caused by stasis of bile upstream from the obstruction. Patients afflicted with cholangitis usually will have fever and leukocytosis and can develop bacterial sepsis.

Gallstone Disease

The most common cause of biliary obstruction in older children and adolescents is gallstone disease (termed cholelithiasis). Little is known about the epidemiology of gallstone disease in pediatrics. The pigmented stone is the most commonly identified type of gallstone in children; however, overweight adolescent girls are at particular risk of developing cholesterol stones. Identified risk factors for the development of gallstones in children include hemolytic disease, existing hepatobiliary disease, cystic fibrosis, Crohn disease, chronic PN exposure, and obesity. If a gallstone becomes lodged within the common bile duct (termed choledocholithiasis), obstructive jaundice will result and anticipated laboratory findings include elevations in conjugated bilirubin, alkaline phosphatase, and GGT. AST and ALT levels may or may not be elevated. Should the gallstone impact distally at the junction of the common bile duct and pancreatic duct, the patient may be symptomatic with both obstructive jaundice and pancreatitis.

Plain abdominal radiographs and computed tomography are poor tests for the detection of gallstones because most stones are not calcified and therefore will not be visible using these techniques. Ultrasonography is highly sensitive and specific for the detection of gallstones >1.5 mm in diameter within the lumen of the gallbladder; however,
the sensitivity drops off substantially for the detection of gallstones within the common bile duct. The common bile duct will dilate in the setting of obstruction, and the diameter of the bile duct is readily measured by the ultrasonographer. The combination of a dilated common bile duct with clinical and laboratory evidence of obstructive jaundice is highly suspicious for a common bile duct stone.

Many of these common bile duct stones will pass spontaneously, resulting in both clinical improvement in the patient and a decrease in the conjugated bilirubin level. If symptoms persist, however, intervention is required urgently because patients are at risk for development of cholangitis and bile duct perforation. Endoscopic retrograde cholangiopancreatography (ERCP) is the methodology of choice for the investigation and treatment of common bile duct stones. ERCP can visualize the presence of the stone (Fig 4), and then deploy a balloon catheter to sweep the stone out of the common bile duct. Typically, a sphincterotomy of the ampulla of Vater is performed to enlarge the opening of the common duct and allow for passage of the stone. Regardless of whether or not a patient passes a common duct stone spontaneously or requires therapeutic intervention, all patients who have symptomatic gallstone disease will require surgical cholecystectomy when clinically stable.

**Choledochal Cyst**

A CDC is a congenital anomaly of the biliary tract characterized by cystic dilatation of some portion of the biliary tree. CDCs can present in the newborn period as conjugated hyperbilirubinemia and a palpable abdominal mass. Outside of the neonatal period, the classic triad of symptoms includes fever, right upper quadrant abdominal pain, and jaundice, symptoms that may be easily confused with gallstone disease. Stones and sludge can form in the dilated biliary tree, leading to obstruction and the development of cholangitis as well as pancreatitis. There are several anatomic subtypes of choledochal cyst, with the most common being type I, which represents cystic dilatation of the common bile duct.

The diagnosis of CDC is made most often with abdominal ultrasonography, which demonstrates a cystic mass near the porta hepatitis that is in continuity with the biliary tree. For better anatomic definition and classification of the CDC, as well as for surgical planning, a more robust radiographic test often is desired. Previously, ERCP was the preferred method for visualization of the CDC; however, because of the risk of post-ERCP pancreatitis as well as exposure to ionizing radiation, magnetic resonance cholangiopancreatography (MRCP) has replaced ERCP as the gold standard for characterization of CDCs. CDC is considered to be a premalignant state with a significant lifetime risk of developing cholangiocarcinoma. Thus, for management of both acute biliary symptoms and for cancer prevention, the treatment for a CDC is surgical excision and Roux-en-Y choledochojejunostomy.

**Other Causes of Obstructive Jaundice**

In the setting of the acute onset of jaundice and fever, hydrops of the gallbladder should be suspected if abdominal ultrasonography demonstrates a distended gallbladder without stones and with normal extrahepatic bile ducts. Hydrops of the gallbladder in children is associated with Kawasaki disease as well as with acute streptococcal and staphylococcal infections.

Tumors of the liver and biliary tract may present initially with jaundice, but jaundice rarely is an isolated finding and more often is accompanied by abdominal pain and an abdominal mass. The possibility of tumor reinforces the importance of the initial abdominal ultrasonography, which will suggest a mass, leading to subsequent computed tomography or magnetic resonance imaging to evaluate the lesion further. Hepatic sinusoidal obstruction syndrome, previously referred to as hepatic veno-occlusive disease, is seen in both children and adults receiving treatment...
for cancer, particularly hematologic malignancy. Through mechanisms that are not fully understood, the development of microthrombi in hepatic sinusoids leads to hepatic dysfunction that often is severe. Patients present with jaundice, hepatomegaly, ascites, and laboratory evidence of hepatic synthetic dysfunction and elevation of aminotransferase levels. Diagnosis is suggested by abdominal ultrasonography with Doppler measurement, which shows a decrease or reversal of portal venous blood flow.

**Infectious Hepatitis**

The acute onset of jaundice, typically associated with right upper quadrant pain, hepatomegaly, nausea, and malaise, with variable fever, is suggestive of an infectious hepatitis. Elevation of AST and ALT levels, usually at least 2 to 3 times the upper limit of normal, is always seen in an infectious hepatitis, although the degree of hyperbilirubinemia can be variable. A broad range of viral agents can lead to infectious hepatitis. The incidence of hepatitis A infection in the United States has plummeted drastically since the universal implementation of vaccination. Both hepatitis B and hepatitis C can cause jaundice at the time of acute infection, and thus it is important to measure serologic markers for hepatitis A, B, and C viruses in any child or adolescent who have hepatitis. Epstein-Barr virus and cytomegalovirus both can cause hepatitis and cholestasis in the context of a mononucleosislike illness. Adenovirus, in-
tomavirus both can cause hepatitis and cholestasis in adolescents who have hepatitis.

**Autoimmune Disease of the Liver and Biliary System**

Autoimmune hepatitis (AIH) is characterized by a chronic active hepatitis and non–organ-specific autoantibodies. (8) Without treatment, this chronic hepatitis progresses to cirrhosis and end-stage liver disease over time. AIH can present at any age in children and adults, although the incidence increases with age during childhood and adolescence. AIH is more common in girls, and the spectrum of clinical presentation is wide. AIH can present insidiously as fatigue, malaise, and recurrent fevers or fulminantly as acute liver failure. Depending on the chronicity of disease, physical findings of portal hypertension may be present at diagnosis. Typically, there is elevation of AST and ALT levels, although with considerable variation in the degree of elevation. Conjugated hyperbilirubinemia, a low albumin level, and an elevated prothrombin time indicate extensive chronic disease. The serum immunoglobulin G (IgG) level usually is elevated, and 90% of patients will test positive for at least one of the associated autoantibodies: antinuclear antibody (ANA), anti–smooth muscle antibody (ASMA), and anti-liver, kidney microsomal antibody (LKM).

Two distinct subtypes of AIH have been described and can be distinguished by serologic autoantibody tests. The first, AIH type I, is the most common, includes 80% of all patients who have AIH, and is characterized by positive ANA or ASMA or both. AIH type 2 is more prevalent in younger children and characterized by anti-LKM positivity. Children who have AIH type 2 are more likely to present with acute hepatic failure. AIH can be associated with the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, one of the polyglandular autoimmune syndromes characterized by mucocutaneous candidiasis, hypothyroidism, and adrenal insufficiency.

Liver biopsy remains the gold standard in the diagnosis of AIH. Histologic features include a dense inflammatory infiltrate in the liver, consisting of mononuclear and plasma cells, that begins in the portal areas and extends beyond the limiting plate into the parenchyma of the liver. Piecemeal necrosis of hepatocytes also is observed frequently. The treatment of AIH involves the use of immunosuppressive agents. Conventionally, remission (defined as the normalization of AST and ALT levels) is induced by using corticosteroids with a taper over several months. Corticosteroid-sparing agents, in particular the immunomodulator azathioprine, are given long term to maintain remission of AIH.

Primary sclerosing cholangitis (PSC) is a progressive, autoimmune-mediated disease targeting both the intra-and extrahepatic bile ducts, resulting in significant scarring of the biliary tree. Patients present with laboratory evidence of bile duct injury, having elevations of GGT and alkaline phosphatase levels. AST, ALT, and conjugated bilirubin concentration may be elevated as well. Imaging of bile ducts, either with MRCP or ERCP, shows evidence of strictureing and dilation of affected portions of the biliary tree. PSC usually is associated with inflammatory bowel disease, particularly ulcerative colitis, and can progress slowly to cirrhosis. Several features distinguish PSC in children from adult disease. (9) In a subgroup of children who have PSC, there is elevation of IgG levels, autoantibody titers, and histologic features on liver biopsy similar to AIH, known as “overlap syndrome.” These children may favorably respond to immunosuppressive therapy. However, for most children and adults with PSC, there is a disconcerting lack of immunomodulatory therapies that can reverse the course of PSC.
Drug- and Toxin-Induced Cholestasis

Drug hepatotoxicity can manifest in many forms, ranging from a systemic drug hypersensitivity syndrome to isolated cholestasis. Although some forms of hepatotoxicity are predictable, most are idiosyncratic owing to genetic variability in drug metabolism, making it difficult to understand the pathogenesis of hepatotoxicity in a given patient. (10) Some drug-induced cholestasis can present as an isolated elevation of conjugated bilirubin; however, often there is a mixed hepatitic-cholestatic reaction with elevation of aminotransferases and conjugated bilirubin. Commonly used medications in pediatrics that potentially can present with cholestatic liver injury include amoxicillin/clavulanic acid, oral contraceptives, and erythromycin. In any patient who has cholestasis of unknown origin, it is critical to obtain a comprehensive medication history that includes recreational use of drugs. Ecstasy, in particular, has been associated with hepatotoxicity and the development of jaundice. Use in adolescents of anabolic steroids for bodybuilding has been reported to cause cholestasis. Questioning also should be directed at therapies that are not regulated by the Food and Drug Administration, such as nutritional supplements and homeopathic treatments, because hepatotoxic metabolites of these substances have been described.

Wilson Disease

Wilson disease is caused by an autosomal recessive inherited defect in the ATP7B gene, which codes for a hepatocyte protein responsible for trafficking of copper into bile. (11) If the liver cannot excrete copper, the metal accumulates in the liver, brain, kidneys, and eyes. Copper toxicity then produces the end-organ dysfunction seen in Wilson disease. Wilson disease rarely presents before 5 years of age, but its age of presentation and clinical manifestations vary. With age, the likelihood of liver involvement at presentation decreases, whereas the likelihood of neuropsychiatric disease increases. The spectrum of the hepatic presentation of Wilson disease includes an acute syndrome with nausea, fatigue, and elevated aminotransferases, mimicking infectious hepatitis. Long-standing liver injury may present with jaundice and conjugated hyperbilirubinemia. Other common hepatic presentations of Wilson disease include chronic hepatitis, cirrhosis with portal hypertension, and fulminant hepatic failure. A clue to Wilson disease in the laboratory evaluation is a low alkaline phosphatase level in the setting of elevation of serum aminotransferase and conjugated bilirubin levels.

Wilson disease also can affect the kidneys, manifesting as proximal tubular dysfunction with urinary loss of uric acid and subsequent low serum uric acid levels. Wilson disease affects the hematologic system, leading in some patients to a direct antibody test (Coombs)-negative hemolytic anemia. Because of the varied presentation of this disease, a high degree of suspicion for Wilson disease must be kept in every school-age child or adolescent presenting with any type of hepatic injury.

The practitioner must rely on interpretation of a number of diagnostic studies in the evaluation for Wilson disease. The sensitivity and specificity of these tests can vary depending on the clinical presentation. Diagnostic tests include measurement of serum ceruloplasmin, which is typically low (<20 mg/dL), and ophthalmologic examination for Kayser-Fleischer rings, which are the corneal deposition of copper seen on slit-lamp examination. Kayser-Fleischer rings are present in 95% of patients who manifest a neuropsychiatric presentation but are seen less frequently in patients who have a hepatic presentation of disease. Serum copper level is a poor screening test for Wilson disease, but a quantitative 24-hour urine copper measure of >40 μg is suggestive of the disorder. Liver tissue can be sent for quantitative copper measurement, and genetic testing is available. Prompt diagnosis of Wilson disease is important because the institution of copper chelation therapy can halt progression of the disease, which is uniformly fatal if untreated.

Benign Recurrent Intrahepatic Cholestasis

Autosomal recessive mutations in canalicular transport proteins FIC1 and BSEP produce the phenotypes PFIC1 and PFIC2, respectively, which typically present in infancy or childhood and may progress to liver failure early in life. Less severe mutations in these genes can produce the disease known as benign recurrent intrahepatic cholestasis (BRIC). Importantly, BRIC does not lead to progressive liver disease, cirrhosis, or hepatic dysfunction. BRIC is an episodic disorder and presents in the first or second decade after birth with pruritis, often severe, and jaundice. Episodes may be precipitated by viral illnesses and typically are heralded by the onset of pruritis, followed weeks later by the development of jaundice. Nausea and steatorrhea also may be present. Laboratory tests of liver function reveal normal or mildly elevated serum AST and ALT, with elevation of both conjugated bilirubin and alkaline phosphatase. The GGT concentration typically is normal or mildly elevated. The prothrombin time may be mildly prolonged because of vitamin K malabsorption and deficiency in the setting of cholestasis. Episodes can last weeks to months, and patients are completely well with normal liver testing in the intermediary periods. Treatment is directed toward relief of pruritis, typically with ursodeoxycholic acid and rifampin, and correction of any fat-soluble vitamin deficiencies.
With the initial episode of pruritis and jaundice, anatomic and histologic tests may be required to distinguish BRIC from PSC and other causes of intrahepatic cholestasis. Detailed imaging of the biliary tree, with either ERCP or MRCP, will be normal. During an episode, the dominant histologic finding in the liver is centrilobular cholestasis. Hepatic lobular or portal inflammation is an unusual finding in the liver. In contrast to other inflammatory diseases of the liver, such as AIH and PSC, liver histology in BRIC will return to normal in asymptomatic periods.

References

Suggested Reading

Summary
- A variety of anatomic, infectious, autoimmune, and metabolic diseases can lead to conjugated hyperbilirubinemia, both in the newborn period and later in childhood.
- The pediatric practitioner is most likely to encounter conjugated hyperbilirubinemia in the neonatal period.
- It is crucial to maintain a high degree of suspicion for cholestasis in the persistently jaundiced newborn. The goal is recognition of conjugated hyperbilirubinemia between 2 and 4 weeks after birth, allowing for the prompt identification and management of infants who have biliary atresia, which remains the most common cause of neonatal cholestasis.

PIR Quiz
This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take Pediatrics in Review quizzes and claim credit online only. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements
Per the 2010 revision of the American Medical Association (AMA) Physician’s Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for AMA PRA Category 1 Credit™. To successfully complete 2012 Pediatrics in Review articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 Pediatrics in Review, AMA PRA Category 1 Credit™ can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.
1. A 3-month-old boy is jaundiced and is found to have conjugated hyperbilirubinemia; however, his gamma glutamyltransferase level is in the low normal range. Which of the following conditions is most likely to be present?
   - A. Alpha-1 antitrypsin deficiency
   - B. Biliary atresia
   - C. Cystic fibrosis
   - D. Progressive familial intrahepatic cholestasis
   - E. Rubella infection

2. A 14-year-old girl presents with a history of intermittent right upper quadrant pain over the last 2 months. Her laboratory evaluation reveals a direct bilirubin of 2.3 mg/dL. Of the following, what is the most appropriate next study?
   - A. Abdominal ultrasonography
   - B. Endoscopic retrograde cholangiopancreatography
   - C. Hepatobiliary iminodiacetic acid scan
   - D. Liver biopsy
   - E. Targeted mutation analysis of the uridine diphosphate glucuronosyltransferase 1A1 gene to assess for Gilbert syndrome

3. You are examining a jaundiced 1-month-old girl and hear a heart murmur consistent with peripheral pulmonic stenosis. A blood test reveals conjugated hyperbilirubinemia, causing you to suspect this condition:
   - A. Alagille syndrome
   - B. Biliary atresia
   - C. Cystic fibrosis
   - D. Hypothyroidism
   - E. Progressive familial intrahepatic cholestasis

4. A toddler who has chronic cholestasis has pruritus that is refractory to ursodeoxycholic acid. Which of the following medications may be helpful in reducing symptoms?
   - A. Amoxicillin
   - B. Diphenhydramine
   - C. Ondansetron
   - D. Rifampin
   - E. Sulfisoxazole

5. A 5-week-old boy has been found to have biliary atresia. His parents are hesitant to authorize surgery and prefer “to see how he progresses. If he does not do well, he can always have surgery later.” Which of the following statements regarding Kasai portoenterostomy is true:
   - A. Age at the time of the Kasai procedure is not associated with surgical outcome.
   - B. Approximately 50% of children with biliary atresia have spontaneous resolution of their disease and do not require a Kasai procedure.
   - C. The Kasai procedure involves insertion of an artificial bile duct.
   - D. The Kasai procedure is curative and most patients do not require follow-up of their liver disease.
   - E. The Kasai procedure, when performed at <60 days after birth, is associated with better outcome.
Juvenile Idiopathic Arthritis

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Beth S. Gottlieb, MD, MS*

Educational Gap
Juvenile idiopathic arthritis affects around 294,000 children in the United States. In 2001, a new classification of the disorder and its subtypes was created. Current therapies, including the use of biologic medications, have improved the prognosis of this condition significantly.

Objectives After completing this article, readers should be able to:
1. Understand the pathophysiology of juvenile idiopathic arthritis (JIA).
2. Recognize the clinical features of the different types of JIA.
3. Be aware of the complications of JIA.
4. Know the treatment of JIA.

Introduction
Juvenile idiopathic arthritis (JIA) is a broad term used to describe several different forms of chronic arthritis in children. All forms are characterized by joint pain and inflammation. The older term, juvenile rheumatoid arthritis, has been replaced by JIA to distinguish childhood arthritis from adult-onset rheumatoid arthritis and to emphasize the fact that arthritis in childhood is a distinct disease. JIA also includes more subtypes of arthritis than did juvenile rheumatoid arthritis.

JIA is the most common rheumatologic disease in children and is one of the more frequent chronic diseases of childhood. The etiology is not completely understood but is known to be multifactorial, with both genetic and environmental factors playing key roles. Without appropriate and early aggressive treatment, JIA may result in significant morbidity, such as leg-length discrepancy, joint contractures, permanent joint destruction, or blindness from chronic uveitis.

Definition
Arthritis is defined as joint effusion alone or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased warmth in one or more joints. JIA is broadly defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. JIA is a diagnosis of exclusion. A number of conditions, such as infections, malignancy, trauma, reactive arthritis, and connective tissue diseases such as systemic lupus erythematosus (SLE), must be excluded before a diagnosis of JIA can be made (1) (Table 1).

JIA is subdivided into seven distinct subtypes in the classification scheme established by the International League of Associations for Rheumatology in 2001 (Table 2). The subtypes differ according to the number of joints involved, pattern of specific serologic markers, and systemic manifestations present during the first 6 months of disease. These categories were established to reflect similarities and differences among the different subtypes so as to facilitate communication among physicians worldwide, to facilitate research, and to aid in understanding prognosis and therapy. (2)

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
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<tr>
<td>ANA:</td>
<td>antinuclear antibody</td>
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<td>ARF:</td>
<td>acute rheumatic fever</td>
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<td>AS:</td>
<td>ankylosing spondylitis</td>
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<td>IBD:</td>
<td>inflammatory bowel disease</td>
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<td>IL:</td>
<td>interleukin</td>
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<td>IV:</td>
<td>intravenous</td>
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<td>JIA:</td>
<td>juvenile idiopathic arthritis</td>
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<td>MAS:</td>
<td>macrophage activation syndrome</td>
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<tr>
<td>NSAID:</td>
<td>nonsteroidal anti-inflammatory drug</td>
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<tr>
<td>RF:</td>
<td>rheumatoid factor</td>
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<tr>
<td>SLE:</td>
<td>systemic lupus erythematosus</td>
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<td>TNF:</td>
<td>tumor necrosis factor</td>
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Epidemiology

It has been estimated that JIA affects ~294,000 children between the ages of 0 and 17 years in the United States. The incidence and prevalence of JIA vary worldwide. This difference likely reflects specific genetic (eg, HLA antigen alleles) and environmental factors in a given geographic area. The incidence rate has been estimated as 4 to 14 cases per 100,000 children per year, and the prevalence rates have been reported as 1.6 to 86.0 cases per 100,000 children. JIA tends to occur more frequently in children of European ancestry, with the lowest incidence rates reported among Japanese and Filipino children.

In white populations with European ancestries, oligoarticular JIA is the most common subtype. In children of African American descent, however, JIA tends to occur at an older age and is associated with a higher rate of rheumatoid factor (RF)-positive polyarticular JIA and a lower risk of uveitis.

Different subtypes of JIA vary with respect to age and gender distributions (Table 2). Oligoarticular JIA, for example, occurs more frequently in girls, with a peak incidence in children between 2 and 4 years of age. Polyarticular JIA also occurs more frequently in girls and has a biphasic age of onset; the first peak is from 1 to 4 years of age and the second peak occurs at 6 to 12 years of age.

Pathogenesis

The cause of JIA is not well understood, but is believed to be influenced by both genetic and environmental factors. Twin and family studies strongly support a genetic basis of JIA; concordance rates in monozygotic twins range between 25% and 40%, and siblings of those affected by JIA have a prevalence of JIA that is 15- to 30-fold higher than the general population.

Strong evidence has been reported for the role of HLA class I and II alleles in the pathogenesis of different JIA subtypes. HLA-B27 has been associated with the development of inflammation of the axial skeleton with hip involvement, and often is positive in patients who have enthesitis-related arthritis. HLA-A2 is associated with early-onset JIA. The class II antigens (HLA-DRB1*08, 11, and 13 and DPB1*02) are associated with oligoarticular JIA. HLA-DRB1*08 is also associated with RF-negative poly JIA.

Clinical features of systemic-onset JIA mostly resemble autoinflammatory syndromes, such as familial Mediterranean fever, and there is a lack of an association between systemic-onset JIA and HLA genes. As a result, many conclude that systemic-onset JIA should be considered a separate entity, distinct from the other JIA subtypes. (4)

Cell-mediated and humoral immunity play a role in the pathogenesis of JIA. T cells release proinflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and IL-1, which are found in high levels in patients who have polyarticular JIA and systemic-onset JIA. Evidence for the role of T cells in JIA comes from studies that show oligoclonal expansion of T cells and a high percentage of activated T cells in the synovium of patients who have JIA.

Table 1. Differential Diagnosis of Arthritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>Reactive</td>
<td>Poststreptococcal rheumatic fever, serum sickness, &quot;Reiter syndrome&quot;</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Juvenile idiopathic arthritis, inflammatory bowel disease, sarcoidosis</td>
</tr>
<tr>
<td>Infection</td>
<td>Septic joint, postinfectious: toxic synovitis, viral (eg, EBV, parvovirus), Lyme disease, osteomyelitis, sacroiliitis, bacterial discitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Systemic lupus erythematosus, Henoch-Schönlein purpura, serum sickness, dermatomyositis, mixed connective tissue disease, progressive systemic sclerosis, periodic fever syndromes, psoriasis, Kawasaki disease, Behçet disease</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Leukemia, neuroblastoma, malignant bone tumors (eg, osteosarcoma, Ewing sarcoma, rhabdosarcoma)</td>
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<tr>
<td>Benign bone tumors</td>
<td>Osteoid osteoma, osteoblastoma</td>
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<tr>
<td>Immunodeficiency</td>
<td>Common variable immunodeficiency</td>
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<td>Trauma</td>
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Table 2. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Frequency (% of all JIA)</th>
<th>Age of Onset</th>
<th>Sex Ratio</th>
<th>Susceptibility Alleles</th>
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<tr>
<td>Systemic onset juvenile idiopathic arthritis (JIA)</td>
<td>Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily (&quot;quotidian&quot;) for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, (4) serositis</td>
<td>4%–17%</td>
<td>Childhood</td>
<td>F=M</td>
<td>HLA-DRB1*11</td>
</tr>
<tr>
<td>Oligo JIA</td>
<td>Arthritis affecting one to four joints during the first 6 months of disease</td>
<td>27%–56%</td>
<td>Early childhood; peak at 2–4 years</td>
<td>F&gt;&gt;M</td>
<td>HLA-DRB1<em>08, HLA-DRB1</em>11, HLA-DQA1<em>04, HLA-DQA1</em>05, HLA-DQB1*04, HLA-A2 (early onset)</td>
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<tr>
<td>• Persistent</td>
<td>Affects no more than four joints throughout the disease course</td>
<td></td>
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<tr>
<td>• Extended</td>
<td>Affects more than four joints after the first 6 months of disease</td>
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<tr>
<td>Polyarthritis (RF-negative)</td>
<td>Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are negative</td>
<td>11%–28%</td>
<td>Biphasic distribution; early peak at 2–4 years and later peak at 6–12 years</td>
<td>F&gt;&gt;M</td>
<td>HLA-DRB1*0801</td>
</tr>
<tr>
<td>Polyarthritis (RF-positive)</td>
<td>Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are positive on at least two occasions that are 3 months apart</td>
<td>2%–7%</td>
<td>Late childhood or adolescence</td>
<td>F&gt;&gt;M</td>
<td>HLAB1*04, HLA-DR4</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, (3) family history of psoriasis in a first-degree relative</td>
<td>2%–11%</td>
<td>Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years</td>
<td>F&gt;M</td>
<td>HLA-B27, IL23R (new association)</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>Arthritis or enthesitis with at least two of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B27 antigen, (3) onset of arthritis in a male &gt;6 years old, (4) acute anterior uveitis, (5) family history in a first-degree relative of HLA-B27-associated disease</td>
<td>3%–11%</td>
<td>Late childhood or adolescence</td>
<td>M&gt;&gt;F</td>
<td>HLA-B27, ERAP1 (new association)</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>Arthritis that fulfills criteria in no category or in two or more of the above categories</td>
<td>11%–21%</td>
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Recently, inflamed joints in patients who have JIA have been shown to have high levels of IL-17–producing T cells; IL-17 induces the production of other interleukins and matrix metalloproteinases that are all involved in joint damage. The role of humoral immunity in JIA pathogenesis is supported by the increased level of autoantibodies, such as antinuclear antibodies (ANAs) and immunoglobulins, by complement activation, and by the presence of circulating immune complexes. (5) Other possible factors that have been implicated in the pathogenesis of JIA include immunologic dysregulation, psychological stress, trauma, hormonal abnormalities, and infectious triggers.

**Clinical Features**

JIA is divided into seven subtypes defined by clinical features during the first 6 months of disease. The International League of Associations for Rheumatology classification of JIA includes the following subtypes: (1) Systemic-onset arthritis, (2) oligoarticular arthritis, (3) polyarticular RF-positive arthritis, (4) polyarticular RF-negative arthritis, (5) psoriatic arthritis, (6) Enthesitis-related arthritis, and (7) undifferentiated arthritis, or “other.” Each subtype varies with respect to clinical presentation, pathogenesis, treatment outcomes, and prognosis. All subtypes of JIA, however, share common symptoms, such as morning stiffness or “gelling phenomenon” (stiffness after a joint remains in one position for a prolonged period) that improves throughout the day, limp, swollen joints, limitation of activities because of pain, and periods characterized by disease remission interspersed with disease flares.

There is no diagnostic test for JIA; therefore, other causes of arthritis must be excluded carefully before the diagnosis is made.

**Systemic-Onset JIA**

Systemic-onset JIA is distinct compared with the other subtypes in that it is characterized by the presence of high-spiking fevers of at least 2 weeks’ duration in addition to arthritis. The disease affects 10% to 15% of children who have JIA, and tends to affect boys and girls equally, with a peak age of onset between 1 and 5 years. Early in the disease course, patients can present with fatigue and anemia. The fever in systemic JIA is characterized by temperatures $>39^\circ C$ that occur daily or twice daily, with a rapid return to baseline or below baseline (quotidian pattern). Fever spikes usually occur in the late afternoon or evening. Children often appear ill during febrile periods and look well when the fever subsides.

The rash in systemic JIA is described typically as an evanescent, salmon-colored macular rash that accompanies febrile periods (Fig 1). The rash generally is nonpruritic and occurs most commonly on the trunk and proximal extremities, including the axilla and inguinal areas. (2) Other extra-articular manifestations that can be seen in systemic JIA include hepatosplenomegaly, lymphadenopathy, pulmonary disease, such as interstitial fibrosis, and serositis, such as pericarditis. The febrile period and other systemic features may precede the onset of arthritis by weeks to months. A definite diagnosis of JIA, however, cannot be made until arthritis is detected on physical examination. (6)

Laboratory abnormalities typically observed in systemic JIA include anemia, leukocytosis, thrombocytosis, elevated liver enzymes, and acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and ferritin. ANA titer is usually negative and is not helpful in making the diagnosis.

Complications of systemic JIA include infection from immunosuppressive therapy, growth disturbances, osteoporosis, cardiac disease, amyloidosis (rare in North America compared with other parts of the world), and macrophage-activation syndrome (MAS) (Table 3). MAS occurs in about 5% to 8% of children who have systemic JIA and is characterized by persistent fever, pancytopenia, hepatosplenomegaly, liver dysfunction, coagulopathy, and neurologic symptoms. Bone marrow examination
in patients who have MAS reveals phagocytosis of hematopoietic cells by macrophages. (2) Triggers of MAS include viral infections and certain changes in medications. Laboratory abnormalities include pancytopenia, prolongation of the prothrombin time and partial thromboplastin time, and elevated levels of D-dimer, triglycerides, and ferritin. Contrary to what would be expected, the erythrocyte sedimentation rate typically falls in MAS because of the low fibrinogen levels resulting from a consumption coagulopathy and hepatic dysfunction. Because MAS carries a significant mortality rate of approximately 20% to 30%, early recognition and treatment of MAS with corticosteroids or cyclosporine is important to prevent multisystem organ failure. (6)

Oligoarticular JIA

Oligoarticular JIA is defined as arthritis that affects four or fewer joints in the first 6 months of disease. This subtype accounts for ~50% of cases of chronic arthritis in children and can be subdivided further into persistent oligoarthritis (affecting four or fewer joints throughout the disease course) or extended oligoarthritis (affecting more than four joints after the first 6 months of disease). The peak age of onset is between 2 and 4 years, with a female-to-male ratio of ~3:1.

Children who have oligoarticular JIA generally are well appearing and typically present with arthritis that affects the lower extremities (Fig 2). In 30% to 50% of cases, one joint is affected at presentation, with the knee being the most commonly affected joint (~89%). (2) The hip joint is affected rarely in oligoarticular JIA. The typical presentation is that of a child who presents with a limp and is found to have a warm and swollen joint that is not very painful or tender. The pain tends to be worse in the morning or after being in one position for an extended period of time (the “gelling phenomenon”).

Growth disturbance may result from prolonged arthritis in a joint, resulting from increased blood flow to the

The prognosis of systemic JIA depends on the severity of the arthritis. Most systemic symptoms resolve over months to years, and mortality, which is <0.3% in North America, is associated mainly with MAS and infections secondary to immune suppression. (6)

### Table 3. Macrophage Activation Syndrome

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Bruising, purpura, mucosal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enlarged lymph nodes, enlarged liver and spleen</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Elevated: AST, ALT, PT, PTT, fibrin degradation products, ferritin, triglycerides</td>
</tr>
<tr>
<td></td>
<td>Decreased: white blood cell and platelet counts, erythrocyte sedimentation rate, fibrinogen, clotting factors</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Active phagocytosis by macrophages and histiocytes</td>
</tr>
<tr>
<td>Treatment</td>
<td>Intravenous glucocorticoid, cyclosporine</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = prothrombin time; PTT = partial thromboplastin.


Figure 2. Swollen right knee in a patient with oligoarticular juvenile idiopathic arthritis. (Courtesy of Charles H. Spencer [http://www.rheumatlas.org].)
growth plate at sites of inflammation, which leads to overgrowth. This complication is most common with knee arthritis and it leads to a leg length discrepancy. Later in the disease course, growth disturbances can result also from growth plate damage or premature fusion of the epiphyseal plates, leading to undergrowth of an affected extremity. (6)

One of the most serious complications of JIA is iritis. Approximately 15% to 20% of children who have oligoarticular JIA are found to have iritis. The iritis tends to be a chronic, anterior, nongranulomatous inflammation affecting the iris and ciliary body and often is asymptomatic. This complication tends to occur in girls affected with oligoarticular JIA at a young age who have positive ANA titers. Appropriate ophthalmologic screening evaluation is imperative in all children who have JIA, especially those who have oligoarticular JIA and are ANA-positive (Table 4). If left untreated, complications include corneal clouding, cataracts, band keratopathy, synchiae, glaucoma, and visual loss (Fig 3). The outcome depends on early diagnosis and treatment. (2)

The differential diagnosis of a child with oligoarthritis includes trauma, septic arthritis, Lyme disease, postinfectious arthritis, and malignancy. In a child who presents with features of an infectious illness, synovial fluid analysis and cultures are important to distinguish inflammatory from infectious processes. In a septic joint, for example, there usually are more than 100,000 white blood cells/mm³, with 90% being polymorphonuclear neutrophils. Lyme arthritis can occur weeks to months after the initial infection, and children typically will present with acute onset of a large, swollen joint, typically the knee.

In children who have oligoarticular JIA, laboratory evaluation may be normal or indicate a mild increase in inflammatory markers. Tests for RF often are negative, and tests for ANA may be positive in low titers in 70% to 80% of children who have oligoarthritis, especially girls and those who have iritis. (2)

Among children who have JIA, those with oligoarthritis have the best prognosis. Children who develop a more complicated disease, characterized by joint space narrowing, bone erosions, and flexion contractures, are more likely to be those who have a polyarticular course.

### Polyarticular JIA

Children affected by arthritis in five or more joints during the first 6 months of disease are diagnosed as having polyarticular JIA. Polyarticular JIA can be either RF-positive (seropositive) or RF-negative (seronegative). RF-positive disease affects approximately 5% to 10% of patients who have JIA and mainly affects girls in late childhood or early adolescence. Seropositive patients tend to develop an arthritis similar to adult rheumatoid arthritis, having a more aggressive disease course. There tends to be symmetric, small joint involvement of both the hands and feet and the cervical spine and temporomandibular joints also may be affected (Fig 4). Rheumatoid nodules and a more severe erosive disease characterized by joint deformities (ie, Boutonnière and Swan neck contractures) also may occur in patients who are RF-positive. (1) Patients with RF-negative arthritis tend to have involvement of fewer joints and have a better overall functional outcome.

Children who have polyarticular JIA may present with morning stiffness, joint swelling, and limited range of motion of the affected joints. In addition, they also may experience fatigue, growth disturbances, elevated inflammatory markers, and anemia of chronic disease. Iritis may develop, although less frequently than in patients who have oligoarticular disease.

The differential diagnosis of patients presenting with polyarthritis includes infection, malignancy, and other collagen vascular diseases such as SLE. Polyarthritis in an adolescent girl could be an initial manifestation of SLE; serologic tests for lupus must be sent.

<table>
<thead>
<tr>
<th>Juvenile Idiopathic Arthritis (JIA) Subtype</th>
<th>Risk of Iritis</th>
<th>Examination Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarticular or polyarticular, onset &lt;7 years of age and antinuclear factor + regardless of age</td>
<td>High risk</td>
<td>Every 3–4 months</td>
</tr>
<tr>
<td>Oligoarticular or polyarticular and antinuclear antibody (–) regardless of age</td>
<td>Medium risk</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Onset &gt;7 years of age regardless of antinuclear antibody status</td>
<td>Medium risk</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Systemic onset JIA</td>
<td>Low risk</td>
<td>Every 12 months</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis
Juvenile psoriatic arthritis is characterized as an asymmetric arthritis that can affect both large and small joints and typically has an onset in mid childhood. The condition is defined more specifically by the presence of arthritis and the typical psoriatic rash, or any two of the following if the rash is absent: family history of psoriasis in a first-degree relative, dactylitis (diffuse swelling of fingers extending beyond the joint margin), and nail pitting (Fig 5). Children who have psoriatic arthritis may develop iritis and should therefore undergo slit-lamp evaluations every 6 months. These children also may be found to be ANA-positive and HLA-B27–positive, especially when there is inflammation of the axial skeleton. (1)

Enthesitis-Related Arthritis
Children affected by enthesitis-related arthritis generally are boys >8 years of age. This type of arthritis is characterized by the presence of enthesitis, or inflammation at the sites of tendon insertions onto bone. Most patients afflicted with this type of arthritis are HLA-B27–positive. Patients typically complain of pain, stiffness, and loss of mobility of the lower back, and can present with arthritis in lower extremity joints. Unlike other JIA subtypes, the sacroiliac joints can be involved at presentation. Children with this subtype may experience anterior or acute iritis, which is characterized by injected, erythematous conjunctiva, photophobia, and pain. Many patients who have this type of arthritis have a positive family history of an HLA-B27–related disease, such as IBD, psoriasis, or ankylosing spondylitis (AS). (2)

Patients who have enthesitis-related arthritis may develop AS, reactive arthritis, or IBD-associated arthritis. Children who have AS typically present with limitation and pain of the lumbar spine and may have evidence of sacroiliac joint inflammation on imaging. AS is most common in boys, with a male-to-female ratio of 7:1, and 90% of patients are found to be positive for HLA-B27. Reactive arthritis often occurs after a genitourinary or gastrointestinal infection and often is associated with conjunctivitis and urethritis. Patients who have IBD may present initially with an asymmetric arthritis involving joints of the lower extremities. Flares of IBD also may be associated with episodic arthritis. (1)

Undifferentiated Arthritis
Children diagnosed as having an undifferentiated arthritis generally do not meet inclusion criteria for any other category, or they may meet criteria for more than one. (2)
Complications
One of the more common and devastating complications associated with JIA is iridocyclitis, a form of chronic anterior uveitis. The condition occurs in approximately 15% to 20% of patients who have JIA and can lead to permanent blindness. (6) It is critical that children who have JIA be screened routinely for iritis because the uveitis can be diagnosed early in the course only with a slit lamp examination by an ophthalmologist. The frequency of required examinations is determined by the child’s age and his or her ANA status. Children <6 years of age who have a positive ANA titer are at highest risk and require evaluation every 3 to 4 months (Table 4). Only the systemic subtype has a minimal risk of iritis and therefore does not require routine screening.

Growth disturbances (ie, leg length discrepancy) must be considered and monitored in growing children who have chronic arthritis. Prolonged arthritis affecting a knee can result in accelerated growth of the affected leg. Prolonged arthritis in ankles or feet and wrists or hands usually results in local growth retardation. Arthritis of the temporomandibular joint can be particularly devastating because of the growth plate’s close proximity to the joint space, resulting in micrognathia.

Osteopenia and osteoporosis, persistent joint damage, and persistent arthritis leading to significant disability and functional limitations are other complications of prolonged uncontrolled arthritis. Psychosocial factors, such as anxiety and school absenteeism, also can occur in children who have a more prolonged disease course. (1)

Treatment
Treatment of JIA relies on a multidisciplinary approach that includes physical and occupational therapy, pharmacologic therapy, and psychosocial interventions. The goal is to implement therapy early in the disease course to prevent the morbidity associated with JIA, such as pain, joint limitation, contractures, and growth disturbances. There is no cure for JIA at present, but current therapies, including the use of biologic medications, have improved the prognosis of this condition significantly. (7) Readers should be aware that some of the drugs used to treat JIA have not been approved by the Food and Drug Administration (FDA) for that indication, including methotrexate, infliximab, anakinra, rituximab, and axiLAB. Clinicians can check the current approval status at the time they are considering the use of any specific agent.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment for patients who have JIA. The most commonly used NSAIDs in children include ibuprofen, naproxen, and indomethacin. NSAIDs may be sufficient to control cases of mild arthritis. Most children tolerate NSAIDs well, but a few develop adverse effects, such as abdominal pain; hematologic, renal, hepatic, and neurologic adverse effects can occur also. Pseudoporphyria cutanea tarda, a rash manifested by small blisters in fair-skinned children occurring after sun exposure, may occur with naproxen. Cox-2 inhibitors, such as celecoxib, occasionally are used in patients who have severe gastrointestinal complaints. In children who have IBD, traditional NSAIDs should be avoided because these can cause a flare in the bowel symptoms. Cox-2 inhibitors would be the choice in this condition.

Intra-articular corticosteroid injections may be very effective in controlling arthritis in patients who have limited disease, such as persistent oligoarthritis. Triamcinolone hexacetonide is used commonly and may lead to rapid resolution of inflammation that may last for a prolonged time and replace the need for oral therapy. Oral or intravenous (IV) corticosteroids are used mainly for systemic manifestations of JIA and, in some cases, for severe polyarthritis.

Patients may be given low doses of prednisone to obtain symptomatic relief of pain and stiffness while waiting for a second-line agent to become effective. High-dose solumedrol or a “pulse” (30 mg/kg with a maximum of 1 g) may be given in systemic-onset JIA that is refractory to oral corticosteroids or to gain control over the disease rapidly with fewer adverse effects than high-dose oral corticosteroids. Adverse effects of corticosteroids are seen most commonly at higher dosages (eg, >20 mg/d) and include immunosuppression, adrenal suppression, increased appetite and weight gain, acne, mood changes, osteoporosis, and avascular necrosis, cataracts and increased intraocular pressures, cushingoid features, and diabetes. (2)

Disease-modifying antirheumatic drugs are agents that slow the radiologic progression of disease and are required by two-thirds of children. These agents include sulfasalazine, azathioprine, hydroxychloroquine, leflunomide, cyclosporin, and methotrexate. Methotrexate, a folate antagonist, is the disease-modifying antirheumatic drug most commonly prescribed in children who have more aggressive arthritis. Methotrexate is given once weekly in either the oral or subcutaneous route. The effects of this medication generally are seen within 6 to 12 weeks. Adverse effects mainly include gastrointestinal manifestations, such as oral ulcers, abdominal pain, nausea, decreased appetite, and hepatic dysfunction (ie, elevation of liver enzymes). Folic acid can be administered to decrease these gastrointestinal side effects.

Pulmonary toxicity is a known adverse effect that rarely occurs in children. There is an increased risk of
immunosuppression while on methotrexate and patients should not receive any live virus vaccines such as measles, mumps, rubella, varicella, and intranasal flu vaccines. A child taking methotrexate who develops a fever or is unwell should be examined by the pediatrician and have studies sent (complete blood count, blood and urine cultures) to exclude an underlying bacterial infection. An increased risk of lymphoproliferative malignancies also is reported in children who take methotrexate, but this effect has not been proven clearly. Blood counts and liver enzymes are monitored every 4 to 8 weeks while a child is taking methotrexate. The treatment period is not defined clearly, but generally, a child is treated with methotrexate for at least 1 year after achieving disease remission. Overall, methotrexate is a very safe and effective drug and is now considered a “gold-standard” therapy for children who have JIA. (2)(8)

Use of biologic agents has improved the morbidity associated with JIA significantly. Biologic drugs are medications, such as monoclonal antibodies, soluble cytokine receptors, and receptor antagonists, that target specific proteins involved in the inflammatory cascade. All biologics are given through the IV or subcutaneous route. All of these agents carry a risk of immunosuppression and cytopenias; therefore, a child taking a biologic agent must be followed closely with detailed physical examinations and laboratory studies.

As with methotrexate, a child taking a biologic who develops a fever or appears unwell even without a fever (biologics such as anti-TNFs can block the febrile response despite active infection) must be examined and have blood work to exclude a serious bacterial infection. Biologics should not be given while a child is acutely ill. Also, children on biologics should not be given live vaccines. Reactivation of tuberculosis is another potential complication, and patients are screened for tuberculosis before the start of therapy and then yearly while on these medications. (8)

Elevated levels of TNF-α are found in patients who have JIA. Etanercept, infliximab, and adalimumab are biologic agents that block TNF-α. Etanercept is a soluble TNF receptor that binds and inhibits TNF-α and was approved by the FDA in 1999 for the treatment of JIA in children >2 years of age. The drug has been shown to be highly effective in patients who have extended oligoarthritis or polyarticular JIA who were not responsive to treatment with NSAIDs or methotrexate. In addition to the risk of immunosuppression, headache, upper respiratory tract infections, and injection site reactions are other common adverse effects.

Infliximab, a chimeric monoclonal antibody to TNF-α that is given through the IV route, has been shown to be efficacious in the treatment of JIA and uveitis. Adalimumab, a humanized monoclonal antibody to TNF, was the second biologic agent to be approved by the FDA in 2008 for moderate to severe JIA in children >4 years of age. Unlike etanercept, which is given once weekly, adalimumab is given once every 2 weeks and has been shown to be effective in patients who have polyarticular JIA.

Elevated levels of IL-1 and IL-6 are found in the sera and synovial fluid of patients who have JIA. These levels are particularly elevated in children who have systemic-onset JIA. Recently, anakinra, an anti-IL-1 receptor antagonist, and tocilizumab, an anti-IL-6 monoclonal antibody, which is now approved by the FDA, have demonstrated promising results in the treatment of patients who have systemic JIA. Abatacept, a recombinant fusion protein that down-regulates T-cell stimulation, was approved by the FDA in 2008 for moderate to severe polyarticular JIA in children >6 years old. Other therapies, such as rituximab (an anti-CD20 B-cell–depleting monoclonal antibody) and rilonacept (an IL-1 blocking agent), are being studied for the treatment of JIA. The duration of treatment with biologics is at least for 1 year after disease remission is achieved. (2)(7)(8)

Treatment of uveitis depends largely on the ophthalmologist’s recommendations. Typically, dilating agents and topical corticosteroids are used first. If inflammation persists or the patient is unable to taper off corticosteroid ophthalmic drops, often methotrexate is started. Infliximab and adalimumab also have been found to be quite beneficial in the treatment of uveitis. (9)

**Autologous Stem Cell Transplantation**

Patients who have JIA that is refractory to the previously described medical interventions may undergo autologous stem cell transplantation. Autologous stem cell transplantation involves using immunosuppression to remove autoreactive lymphocytes followed by stem cell transplantation. This procedure would be considered only for a small subset of patients who have JIA that is refractory to all other treatments. (7)

**Other Considerations**

Other treatment considerations must include physical therapy and occupational therapy to improve mobility of affected joints and maintain muscle strength. Monitoring physical and psychological functioning must be assessed routinely, and counseling or psychotherapy offered when needed. Leg-length discrepancies may require treatment if they become significant and orthopedic referrals should be made when appropriate.

**Prognosis**

Approximately 50% of children who have JIA continue to have active disease into adulthood. In patients who have
active disease into adulthood, there can be significant disability, such as joint deformity, growth abnormalities, visual disturbance caused by uveitis, functional limitations because of pain, and so forth. Factors affecting disease outcome include disease duration, presence of polyarticular disease, and use of systemic corticosteroid treatment. The mortality rate in JIA based on reports from the United States and Canada is 0.29 per 100 patients, and most deaths occur in patients who have systemic JIA. (1)

Summary

• Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood.
• JIA is a chronic disease that is associated with periods of disease flares and periods of disease inactivity.
• Early, aggressive treatment with nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injections, or methotrexate, has significantly improved the outcome of most children who have JIA.
• Biologics have been shown to be both safe and effective for the treatment of more aggressive forms of arthritis and for uveitis. Long-term safety data of biologics is still uncertain.
• In the near future, it is hoped that genetic testing will allow earlier diagnosis of JIA as well as help predict the disease course of children who have JIA. Genetic analysis also may allow physicians to target therapies more effectively.
• It is hoped that development of more specific therapies will decrease overall immunosuppression and other associated toxicities.

References


PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online only. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician’s Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal–based CME activities that are certified for AMA PRA Category 1 Credit™. To successfully complete 2012 *Pediatrics in Review* articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. You are evaluating a 10-year-old girl for joint pain that has been present for ~2 months. She has no fever but complains of pain and swelling in her hands and feet, which is worse in the morning. On physical examination, she has evidence of symmetric swelling of all proximal interphalangeal joints in her hands and feet and pain over her temporomandibular joint. The remainder of the examination is normal. Which of the following is the most likely diagnosis?
   A. Enthesitis-related arthritis
   B. Oligoarticular juvenile idiopathic arthritis (JIA)
   C. Polyarticular JIA
   D. Psoriatic arthritis
   E. Systemic-onset JIA

2. After determining the diagnosis in the patient mentioned above, you decide to initiate therapy for her arthritis. Which of the following medications is the most appropriate first medication to begin?
   A. Celecoxib
   B. Infliximab
   C. Methotrexate
   D. Naproxen
   E. Prednisone

3. Which of the following statements regarding JIA is true?
   A. African American children more often have systemic-onset JIA than other subtypes.
   B. Association with HLA-B27 positivity is typical in enthesitis-related arthritis.
   C. Oligoarthritis occurs most commonly in adolescents.
   D. Polyarthritis occurs most commonly in male subjects.
   E. Psoriatic arthritis is not associated with ophthalmologic disease.

4. Which of the following patients who have JIA is most likely to develop iritis?
   A. A 15-year-old boy who has enthesitis-related arthritis, antinuclear antibody (ANA)-negative
   B. A 3-year-old girl who has oligoarticular subtype, ANA-negative
   C. A 6-year-old girl who has oligoarticular subtype, ANA-positive
   D. A 12-year-old girl who has polyarticular subtype, ANA-positive
   E. A 5-year-old boy who has systemic onset subtype, ANA-negative

5. A 7-year-old girl has developed a limp and complains of pain in her right knee, which is warm and swollen. Although she is afebrile in the office, her parents say she had a fever at home. You suspect oligoarticular JIA but have concerns about infection. Which of the following tests would give you a definitive answer?
   A. ANA
   B. Erythrocyte sedimentation rate
   C. Rheumatoid factor
   D. Synovial fluid analysis
   E. White blood cell count
Sudden Infant Death Syndrome: An Update

Rachel Y. Moon, MD,*
Linda Fu, MD, MSc†

Educational Gap

- Although the rate of sudden infant death syndrome (SIDs) deaths has remained constant—approximately 2,300 infants annually—since 2001, many deaths that previously would have been classified as SIDS now are attributed to other sleep-related causes.
- The American Academy of Pediatrics Task Force on SIDS recently published a new Policy Statement and Technical Report providing evidence-based guidance on the other causes of sleep-related infant deaths, such as soft bedding, prone sleep position, and bed sharing.

Objectives

After completing this article, readers should be able to:

1. Discuss possible etiologic mechanisms for sudden infant death syndrome (SIDS).
2. Identify the risk factors for SIDS.
3. Discuss the American Academy of Pediatrics SIDS Task Force recommendations and underlying rationale.
4. Discuss the most common reasons for nonadherence with SIDS risk reduction recommendations.

Introduction

In 2007, Pediatrics in Review published a review article on sudden infant death syndrome (SIDS). (1) This article uses that article as a reference and provides an update on the topic.

What We Knew Then

Definition

SIDS is defined as a sudden unexplained death before 1 year of age. The death usually occurs in a previously healthy infant, and the cause of death remains unexplained despite a thorough case investigation, including a complete autopsy, death scene investigation, and review of the clinical history.

Epidemiology

In the United States, ~2,300 infants die of SIDS each year. Despite the success of the Back to Sleep campaign, which is associated with a steady decline in deaths from SIDS from the beginning of the campaign in 1994 up to 2000, SIDS remains the third leading cause of death in infancy and the most common cause of death between 1 month and 1 year of age. Since 2001, the SIDS rate has remained constant. In addition, the rate of other sudden unexpected infant deaths, such as suffocation, asphyxia, and other ill-defined or unspecified causes of death,
has risen. Many deaths that previously would have been classified as SIDS are now being classified as having resulted from these other causes of death (see later in this article).

Risk factors for SIDS have been identified through epidemiologic studies. SIDS is more likely to occur in male infants, at a 3:2 ratio. Other risk factors include prone and side sleeping position, maternal smoking during pregnancy, environmental tobacco smoke, overheating, soft bedding, inadequate prenatal care, young maternal age, prematurity or low birth weight, and African American or American Indian/Alaska Native heritage.

Pathophysiology
SIDS is a polygenic, multifactorial condition, with genetic, environmental, and behavioral/sociocultural factors as contributors. Failure of arousal mechanisms likely plays an important role in the final pathway to death. Serotonin receptor abnormalities have been found throughout the ventral medulla in victims of SIDS, possibly representing a network dysfunction that affects arousal and cardiorespiratory responses. In addition, several studies have demonstrated polymorphisms in the promoter region of a serotonin transporter protein gene known as 5-HTT, with alleles that increase promoter effectiveness (resulting in reduced serotonin concentrations at nerve endings), which are found more often in infants who have died of SIDS.

Polymorphisms also have been found in other genes that may be pertinent in SIDS, such as SCN5A, a sodium channel gene that is related to a prolonged QT interval, and genes affecting autonomic nervous system development. Thus, it appears that certain infants may have a genetic predisposition to SIDS, which becomes manifest when the infant experiences some type of environmental challenge, such as prone positioning or tobacco exposure.

Risk Reduction
SIDS risk reduction strategies have focused on eliminating risk factors that are associated with SIDS in epidemiologic studies:
1. Back to sleep for every sleep.
2. Use a firm sleep surface.
3. Keep soft objects and loose bedding out of the crib.
5. Room sharing without bed sharing is recommended.
6. Consider offering a pacifier at nap time and bedtime.
7. Avoid overheating.
8. Do not use home cardiorespiratory monitors as a strategy to reduce the risk of SIDS.

What We Have Learned Since Then
Epidemiology
As mentioned, there have been increases in other causes of sudden and unexpected infant death. Largely because of advances and improved training in death scene investigation, many deaths that previously would have been classified as SIDS are now being classified as the result of other causes of sleep-related infant death. In the past 20 years, much of the decline in SIDS rates may be explained by increasing rates of these other causes of death (Fig 1). In particular, the infant mortality rate from accidental suffocation and strangulation in bed (ASSB) has quadrupled in recent years. ASSB and ill-defined or unspecified deaths are associated particularly with soft bedding, prone sleep position, and bed sharing.

There continue to be racial and ethnic disparities, not only for SIDS, but for ASSB and ill-defined or unspecified deaths. For all three conditions, non-Hispanic black infants and American Indian/Alaska Native infants have much higher mortality rates than other infants of other racial and ethnic groups. SIDS rates for non-Hispanic black infants (99/100,000 live births [LBs]) and American Indian/Alaska Native infants (112/100,000 LBs) are twice as high as those of non-Hispanic white infants (55/100,000 LBs) and almost four times those of Asian/Pacific Islander and Hispanic infants. ASSB rates for non-Hispanic black infants (32.4/100,000 LBs) and American Indian/Alaska Native infants (44.0/100,000 LBs) are more than double those of non-Hispanic white infants (12.9/100,000 LBs). Rates of infant death from ill-defined or unspecified causes for non-Hispanic black infants (47.3/100,000 LBs) and American Indian/Alaska Native infants (64.9/100,000 LBs) are also more than double those of non-Hispanic white infants (21.1/100,000 LBs).

Figure 1. Proportion of sleep-related infant deaths in the United States, 1995 to 2005. Data source: Linked birth/infant death records 1995–2005 on CDC WONDER online database. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Vital Statistics.
Risk Reduction
The American Academy of Pediatrics (AAP) Task Force on SIDS recently published an updated policy statement (2) and technical report. (3) The reader is referred to these documents for additional details.

SLEEP POSITION. The prone position places infants at high risk for SIDS (odds ratio [OR] 2.3–13.1). The side position places infants at similarly high risk for SIDS, and indeed the population-attributable risk for the side sleep position is higher than that for the prone position. Recent studies have demonstrated the possible mechanisms by which the prone position places infants at higher risk for SIDS. There is evidence suggesting that prone sleeping results in altered autonomic control of the infant cardiovascular system during sleep, particularly at 2 to 3 months of age, and may result in decreased cerebral oxygenation. These data may provide more impetus for parents and caregivers to place infants in the supine position, because many are still reluctant to do so.

One common reason for the reluctance is fear that the infant will choke or aspirate while in the supine position; this concern is particularly true when the infant has been diagnosed with gastroesophageal reflux. It may be helpful to explain to parents that the infant’s airway protective mechanisms (including the gag reflex, which is often misinterpreted as choking or aspiration) will prevent aspiration. Indeed, multiple studies in different countries have demonstrated no increased incidence of aspiration since the change to supine sleeping. Even infants with gastroesophageal reflux should be placed supine for sleep.

Parents and caregivers also will use nonsupine sleep positions if they perceive that the infant is uncomfortable or does not sleep well while supine. Infants are less likely to arouse when they are in the prone position; however, frequent awakenings in an infant should not be interpreted as being abnormal or undesirable. On the contrary, sleeping for sustained periods should be interpreted as being undesirable, because the ability to arouse from sleep is an important protective response.

BED SHARING. The AAP recommends that infants share a room with their parents without bed sharing. This arrangement has been shown to be safer than both bed sharing (when the infant sleeps on the same surface as another person) and solitary sleeping (when the infant sleeps in a separate room from the parent), and decreases the risk of SIDS by ~50%. In addition, adult beds are not designed for infant safety, and many accidental infant deaths attributable to suffocation, entrapment, asphyxia, and ill-defined or unspecified cause occur when the infant is bed sharing with another person. Infants are at highest risk of SIDS or accidental death while bed sharing during the first 3 months of life and if they are born prematurely or with low birth weight. In recent years, there has been increased concern about bed sharing among public health officials because of rising rates of infant deaths occurring during bed sharing.

The AAP believes that currently there is insufficient evidence to recommend any bed-sharing situation as safe, particularly because not all risks associated with bed sharing (such as parental fatigue) can be controlled. Specific bed-sharing situations are especially hazardous. These situations include:

- When the infant is <2 to 3 months of age, regardless of whether or not parents are smokers
- When one or both parents are smokers
- When the infant is placed on sofas, armchairs, or waterbeds (extremely soft surfaces)
- When pillows or blankets are present
- When there are multiple bed sharers (ie, other than the parents)
- When the person bed sharing with the infant is not a parent
- When the person bed sharing with the infant has consumed alcohol, medications, or illicit drugs that can affect arousal

There is currently insufficient evidence to determine whether the risk of bed sharing is increased when the adult bed sharer is obese.

There are several common reasons that induce parents to bed share with their infants. For some parents, bed sharing is the only option because of space or financial reasons. For these parents, often there are local organizations through which free or low-cost cribs or portable cribs can be obtained. For others, bed sharing facilitates feeding (both breast and formula feeding) and bonding. In addition, many parents bed share because they believe that they can best monitor and keep the infant safe that way. For some parents, the safety concerns are primarily environmental dangers, such as vermin, stray gunfire, or random kidnappings. For others, it is the belief that parental vigilance at all times will keep the infant safe, and bed sharing is viewed as a strategy to maintain vigilance while sleeping, thus keeping the infant safe.

Some parents choose to bed share specifically if they are aware that their infant’s sleep behavior or environment is unsafe; for example, if the infant sleeps in the prone position. It may be helpful for clinicians to recommend room sharing without bed sharing as an option that will allow parental vigilance and easy access for feeding, bonding with, and monitoring the infant without exposing the infant to the risks associated with bed sharing.
CRIB AND BEDDING ACCESSORIES. Blankets, pillows, and other soft bedding can increase the risk of SIDS and suffocation. It is dangerous to place pillows, quilts, comforters, sheepskins, and other soft surfaces under, on top of, or close to the infant. These practices increase SIDS risk up to 21-fold, particularly when the infant is placed prone in the presence of soft bedding. Use of soft bedding also has been associated with accidental suffocation deaths. Therefore, the AAP recommends that infants sleep on a firm surface, without any soft or loose bedding in the area. Infant sleep clothing can be used in place of blankets.

Parents and caregivers frequently place blankets and pillows under, on, or close to the sleeping infant. The most frequently cited reasons for use of blankets and pillows are the perceptions that these items will make the infant sleep more comfortably (ie, the infant will fall asleep more quickly or will sleep for a more sustained period of time, or that the infant will not be cold while asleep) or will keep the infant safe from injury or falls. Pillows in particular are used to create a barrier to prevent falls or to cushion injury if the infant moves.

A qualitative study found that, although mothers were aware of the need for a firm sleep surface, they believed that they were following that recommendation if they placed padding (blankets or a pillow) in between a mattress and sheet, as long as the sheet was pulled tautly over the padding. (4) Crib bumper pads or similar products generally are used because of the perception that they will protect the infant from injury (eg, limb entrapment between crib slats or head injury from hitting railings) and for esthetic reasons; however, there have been recent concerns about infant deaths from suffocation, entrapment, and strangulation associated with bumper pads. In addition, studies indicate that bumper pad use prevents only minor injuries. A recent study of crib injuries concluded that the risk of suffocation or strangulation far outweighed the potential benefits of preventing minor injury with bumper pad use. (5)

Parents frequently use wedges and positioning devices that are marketed as products that will decrease the risk of SIDS or gastroesophageal reflex. There is no evidence suggesting that these devices are effective against SIDS, suffocation, or gastroesophageal reflux; however, there have been reports of deaths from suffocation and entrapment associated with these devices. These devices therefore are not recommended.

It is important for providers to counsel parents and caregivers about the importance of eliminating soft bedding from the infant’s sleep area. Because of the common misperception that these products will keep their infants safe, parents may unknowingly place their infants at higher risk for SIDS and accidental death when they use products such as blankets, pillows, bumper pads, and positioners.

BREASTFEEDING. Recent reports, including a meta-analysis, (6) demonstrate a protective effect of breastfeeding (nursing or pumped human milk) against SIDS, with an approximate halving of the risk when the baby is breastfed; the protective effect is even stronger when the infant is exclusively breastfed. Possible reasons for this protective effect include decreased infectious diseases (which are associated with increased risk of SIDS) and overall immune benefits. In addition, physiologic studies demonstrate that breastfed infants are more easily aroused from sleep than formula-fed infants.

Infants can be brought into the adult bed for feeding; however, after feeding, when the mother is ready to go back to sleep, the infant should be returned to his or her own sleep area (ie, crib or bassinet). In addition, because of the extremely high risk of SIDS associated with sofas and armchairs, mothers who are likely to fall asleep while nursing should not nurse on a sofa or armchair.

PACIFIERS. Multiple studies, including two meta-analyses, have found pacifier use to be associated with a decreased risk of SIDS (adjusted OR 0.39–0.48). (7)(8) The mechanism of action is unknown, but it is theorized that pacifier use may alter arousal thresholds or autonomic responses during sleep; however, the decreased risk of SIDS persists even when (as frequently occurs) the pacifier falls out of the infant’s mouth after falling asleep. A recent study has demonstrated that pacifier use may positively modify the effect of adverse risk factors, such as prone positioning. (9) The AAP recommends that pacifier use be encouraged as a SIDS risk reduction strategy.

Many parents are concerned about the possible negative effect of pacifier use on breastfeeding success. Randomized clinical trials have not shown pacifier use to result in shortened breastfeeding duration, if the pacifier has been introduced after 2 to 4 weeks of age. Pacifiers can be used for breastfed infants, but they should not be introduced until breastfeeding has been well established.

ROOM VENTILATION AND FANS. One US study found that the use of a fan decreased the risk of SIDS (adjusted OR 0.28; 95% confidence interval, 0.10–0.77). (10) This study, however, was limited by having a small sample of fan users and by questions about the accuracy of parental recall. Furthermore, although one other study has demonstrated a decreased risk of SIDS if the room is well ventilated, no other studies have confirmed these findings. Therefore, there is currently no recommendation for or against fan use as a SIDS risk reduction strategy.
SWADDLING. Swaddling, or wrapping the infant in a light blanket, has been used in many cultures to calm infants and promote sleep. There has been recent interest in swaddling as a way to promote supine positioning and potentially reduce the risk of SIDS. Studies investigating the relationship between SIDS and swaddling have found an increased risk of SIDS if the infant is swaddled and placed in a nonsupine position. One study found a decreased risk of SIDS if the infant was swaddled and placed in the supine position; (11) another study found a 31-fold increase in SIDS risk when swaddled, but this study did not stratify by the sleep position in which the infant was placed. (12)

Physiologic studies have demonstrated that, in general, swaddling decreases startling, increases sleep duration, and decreases spontaneous awakenings; however, studies have been less definitive about the effects of swaddling on arousal. There is some concern that swaddling may have detrimental consequences. For example, tight swaddling (which some believe to be important if the swaddling is to have a calming effect) can reduce the infant’s functional residual lung capacity and can exacerbate hip dysplasia if the hips are kept in extension and adduction. Conversely, loosely applied swaddling could result in head covering and, in some cases, strangulation if the swaddle comes undone.

The AAP has not made any recommendations for or against swaddling as a SIDS risk reduction strategy. If swaddling is to be practiced, however, care must be taken so that the swaddle is not so tight as to adversely affect respirations or exacerbate hip dysplasia, but not so loose as to create a head covering, suffocation, or strangulation risk. Furthermore, swaddled infants should never be placed in the side or prone sleep positions.

IMMUNIZATIONS. Concern has been expressed that there is an increased risk of SIDS immediately after immunizations are given. Although there is a temporal relationship between immunizations and SIDS (the incidence of SIDS is highest between 2 and 4 months of age), no data suggest a causal relationship between immunization and SIDS. In fact, several large case-control studies have demonstrated a protective effect of immunizations on SIDS. A recent meta-analysis found that immunization decreased the risk of SIDS by 46%. (13)

Education and Health Messages

Although the 1994 Back to Sleep campaign was successful initially in changing sleep position for many infants, ~25% of infants continue to sleep in the nonsupine position. It is clear that the current health messages do not resonate with some parents and caregivers. It is critical for clinicians and other health professionals to understand and address some of the barriers that parents perceive about adopting safe sleep recommendations.

For many parents, the link between safe sleep recommendations and SIDS lacks plausibility. Because SIDS is defined as death from an unknown cause, many parents do not understand how any specific behavior can protect against an entity for which the cause is unknown. In addition, many parents believe that SIDS is a random and unpreventable occurrence (“God’s will”) and that parental actions do not influence the ultimate outcome.

Education for parents and caregivers must go beyond distribution of the guidelines. Parents generally welcome detailed explanations about the recommendations, with attention to rationale for the recommendations and addressing of parent concerns. Indeed, educational interventions for parents, caregivers, child care providers, and health professionals are effective in altering practices with regard to sleep position and sleep environment, particularly when the interventions address caregiver concerns and misconceptions about safe sleep recommendations. For instance, education about sleep position should address concerns about aspiration, choking, and infant comfort. Education about room sharing without bed sharing should address concerns about infant safety and parental vigilance.

Health messaging is more effective if the messages are consistent. When parents and caregivers hear or see practices contrary to safe sleep recommendations, they infer that the recommendations are not important. It is critical that physicians, nurses, and other health professionals provide consistent messages.

In addition, media messages are influential in individual decisions regarding sleep position and sleep environment, including use of soft bedding and infant sleep location. One study found that 36% of pictures of sleeping infants and 64% of pictures of infant sleep environments in magazines targeted toward childbearing women portrayed unsafe sleep positions and sleep environments. (14) Media and advertising messages contrary to safe sleep recommendations may create misinformation about safe sleep practices.

Summary

Based on strong research evidence:

- All infants should be placed in the supine position for every sleep. (15)
- Tobacco exposure pre- (16)(17)(18)(19)(20) and postnatally (21)(22) should be avoided.
- Room sharing without bed sharing is recommended. (23)(24)(25)
• It is recommended that blankets, pillows, and other soft bedding be removed from the infant sleep area. (26)(27)
• Overheating should be avoided. (11)(28)(29)(30)
• Breastfeeding should be encouraged for SIDS risk reduction. (6)
• Pacifier use should be encouraged for SIDS risk reduction. (7)(8)
• Immunizations should be encouraged for SIDS risk reduction. (13)
• The evidence for fan use or swaddling as strategies to reduce the risk of SIDS is inconclusive.

References
PIR Quiz
This quiz is available online at http://www.pedsinreview.aappublications.org. Note: Since January 2012, learners can take Pediatrics in Review quizzes and claim credit online only. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements
Per the 2010 revision of the American Medical Association (AMA) Physician’s Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for AMA PRA Category 1 Credit™. To successfully complete 2012 Pediatrics in Review articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 Pediatrics in Review, AMA PRA Category 1 Credit™ can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. Of the following, an epidemiologic risk factor associated with sudden infant death syndrome (SIDS) is:
   A. Caucasian race
   B. Female gender
   C. Paternal alcohol use
   D. Post-term gestation
   E. Prone sleeping position

2. Abnormalities in the receptor for which of the following neuropeptides have been identified in the brainstem of some infants with sudden infant death syndrome:
   A. Acetylcholine
   B. Epinephrine
   C. Galanin
   D. Serotonin
   E. Vasoactive intestinal peptide

3. An intervention recommended by the authors to reduce the risk of infant SIDS is:
   A. Avoiding the use of pacifiers before bedtime
   B. Home cardiorespiratory monitoring
   C. Positioning the infant on the side
   D. Sleeping in the same room as the infant
   E. Swaddling the infant in a soft blanket

4. The American Academy of Pediatrics Task Force on SIDS has recommended against parents sleeping in the same bed as their infants. According to the article, which of the following factors makes bed sharing especially hazardous?
   A. Absence of blankets
   B. Firm bed
   C. Infant age <3 months
   D. Maternal age <20 years
   E. Only 1 person sharing the bed with the infant

5. A mother of a 1-month-old infant comes in for a well-child visit. As you review the infant’s immunization schedule, she tells you that one of her friends’ children died of SIDS 48 hours after the infant received her 4-month diphtheria, pertussis, and tetanus vaccine. Of the following, which piece of information most accurately reflects current knowledge about immunizations and SIDS?
   A. Infants who receive immunizations have a lower risk of SIDS.
   B. Infants who receive immunizations have the same risk of SIDS as infants who are not immunized.
   C. Infants who receive immunizations may have a slightly higher risk of SIDS, but the benefit of the immunization far outweighs the risk.
   D. Only the 2-month diphtheria, pertussis, and tetanus vaccine has been associated with a slightly increased risk of SIDS.
   E. Infants at risk of SIDS should have their Haemophilus influenzae vaccine series postponed until 12 months.
Risk of Thrombophilia

Leonardo R. Brandao, MD, MSc,* George B. Segel, MD†

Question
A 17-year-old girl meets with you to discuss her use of oral contraceptives (OCPs) that contain estrogen. In the family history focusing on evidence of thrombophilia, you find that the patient’s father died of a pulmonary embolus after disembarking from a transatlantic airplane flight. The patient and her mother want to know if she should use OCPs. The girl is leaving for college, and there is concern for an unwanted pregnancy on the one hand and the risk of thrombosis on the other. How should you advise her?

Answer
In this case, the family history provides a vital piece of information in assessing risk of thrombosis for this patient using OCPs. The current guidelines of the American College of Obstetrics and Gynecology do not recommend laboratory testing for thrombophilia if a careful family history is unrevealing. (1) In view of the father’s pulmonary embolus and demise, a consideration of inherited abnormalities that may predispose to a thrombus and acquired conditions that may provoke a thrombus is warranted. The father’s long airplane ride, particularly if it was in the coach section with limited mobility, is a risk factor for a lower extremity or pelvic thrombus and consequent pulmonary embolus, although at least one-third to one-half of the adult patients who experience pulmonary emboli do not have an identifiable source of the embolization. (2) The thrombotic risk would be heightened if he had an underlying malignancy or inflammatory disease, but there was no history of either of these conditions.

If the immobilization of the airplane ride were coupled with an inherited thrombophilic condition, such as factor V Leiden (5% of the population), the risk would be more than additive. In the scenario presented, we have no information about an underlying thrombophilic mutation; but the population frequency of such abnormalities makes it reasonable to explore this possibility in this young woman in view of her positive family history, because such a mutation would increase her risk of a thrombus if she used OCPs.

An established thrombophilia panel includes genetic and plasma-based testing, (3)(4)(5) as follows:
- Inherited genetic factors: (1) Factor V Leiden, a single point mutation in coagulation factor V present in 5% of whites, rendering it resistant to inhibition by activated protein C. (2) Prothrombin G20210A mutation, a second inherited thrombophilic condition that occurs in ~2% of the population. This mutation represents an abnormally regulated gene for the production of coagulation factor II that may result in high, prothrombotic levels of prothrombin. (3) Diminished amounts of natural anticoagulants: proteins C, S, or antithrombin.
- Acquired prothrombotic factors: anticardiolipin antibody, lupus anticoagulant antibody, and heightened factor VIII levels. Although seen in inflammatory states, these

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factors may occur in the absence of an underlying condition.

- Other elements of a comprehensive thrombophilia panel include consideration of high fasting plasma levels of lipoprotein (a) or homocysteine, and high circulating levels of factors IX and XI, but the impact of these factors on the development of thromboembolism is not certain.

The results of plasma-derived coagulation tests performed in children should be compared with their respective age-appropriate values. (6) Furthermore, each thrombophilic factor noted presents a different risk for the development of a thrombus. (7)

The routine testing of children for both acquired and inherited conditions is controversial, given the low prevalence of thrombotic events, the even lower prevalence of unprovoked events, and the variable presence of external risk factors (eg, limited mobility, central lines, estrogen-containing OCP medications). Thrombophilia testing to determine the duration of anticoagulation in children or to prevent venous thromboembolism or life-threatening events in adolescent patients being considered for oral contraception has not been recommended in the absence of a family or patient history of thrombosis. (8)(9)

The patient in the case described should have a complete evaluation for a thrombophilic factor. If a risk factor is identified, estrogen-containing OCPs should not be used. If an abnormality is detected, it would be beneficial to take a multidisciplinary approach, involving a pediatric hematologist and a gynecologist, to consider the different contraceptive methods that are compatible with the results of the thrombophilia investigation. (10) Current data do not indicate any heightened risk of thrombosis with the use of progesterone alone as a contraceptive, and numerous barrier methods of contraception are available. Importantly, additional modifiable risk factors such as obesity, inappropriate diet and sedentarism, and exposure to alcohol and tobacco also need to be addressed.

References
The Evolving Ethics of Cochlear
Implants in Children

John D. Lantos, MD

Introduction
A cochlear implant is a small, complex electronic device that can help to provide a sense of sound to a person who is profoundly deaf or severely hard-of-hearing. Implants all have four key components: (1) a microphone, which picks up sound from the environment; (2) a processor, which selects and arranges sounds picked up by the microphone; (3) a transmitter and receiver/stimulator, which converts signals from the processor into electric impulses; and (4) a group of electrodes that sends impulses from the stimulator to different regions of the auditory nerve. After implantation of the device, recipients must undergo an extensive program of speech therapy to learn how to make the implant useful. As of December 2010, ~219,000 people had received implants worldwide, including 71,000 people in the United States, of whom 28,400 were children. (1)

Over the past two decades, doctors, parents, policymakers, and members of the Deaf community have struggled to understand the benefits, risks, and implications of using cochlear implants for children. These struggles were the latest episode in a debate about medical and educational approaches to deafness that have lasted over a century. They also reflected the fact that there were no good long-term outcome data on cochlear implants. Thus, complex issues of clinical and research ethics are intertwined with complex cultural issues and a long history of discrimination and stigmatization of children who are deaf. In this article, I will review the origins of the controversy, discuss its most heated moments, and summarize the current state of the debate.

Origins of the Controversy
Much of the ethical controversy about cochlear implants reflects a debate that has been going on for >100 years about the best way to educate children who are deaf in order to maximize their opportunities in life. Some people, notably Thomas Gallaudet, were of the opinion that children who are deaf all should be taught sign language and educated by teachers who know sign language. This approach became known as “manualism.” Others, notably Alexander Graham Bell and Horace Mann, thought it was preferable to educate children who are deaf to speak and to read lips. This philosophy was known as “oralism.”

Bell, whose wife was deaf, was himself fluent in sign language. He argued that sign language should be discouraged because it would lead to isolation of individuals who are deaf from hearing people. He also feared that more marriages between people who are deaf would result in a perpetuation of deafness. Thus, his program was motivated by eugenic concerns as well as educational considerations. Bell went as far as advocating a ban on marriages between people who are deaf. (2)

Although Bell’s extreme views about marriage never prevailed, his views on the superiority of oralism over signing did prevail in many schools for the deaf. Throughout the early 20th century, many such schools prohibited signing. (3) By the middle of the 20th century, however, oralism had been...
discredited thoroughly. A 1964 report to Congress on deaf education called oralism a “dismal failure.” The report recommended new approaches to the education of children who are deaf. (4) Oralism failed, in part, because lip reading (or “speechreading”) is difficult and never perfect. Only ~30% to 35% of English sounds can be speechread. Words as different as “queen” and “white” look the same on a person’s lips. So do the three words in the sentence, “Buy my pie”. (5) Sign language, by contrast, allows students who are deaf to understand all that is being communicated.

In recent years, this stark exclusivity has all but disappeared. Most educators today prefer methods that combine lip reading, speech, and sign language, and are known collectively as “total communication”. (6) Still, the years during which signing was prohibited in schools for the deaf left deep scars. Signing became a matter of deep pride and cultural identity within the Deaf community. (7) This history explains, in part, the response of many in the Deaf community to cochlear implants. They saw implants as a return to the philosophy of oralism and a rejection of sign language.

**The Controversy Over Cochlear Implants for Children**

In 1957, Djouma and Eyries were the first surgeons to implant an electrode in a patient’s cochlea. (8) Over the next decades, others developed the technology. Between 1965 and 1970, House developed single-electrode cochlear implants and teamed up with 3M to make the first commercial cochlear implants in the United States. These devices were first marketed in 1972, and in 1984 they were approved by the Food and Drug Administration (FDA) for use in adults.

In the mid-1970s, Clarke developed a multielectrode cochlear implant, and first implanted an adult patient with his prototype device in 1978. Multi-channel devices divide the incoming signal into various frequency bands that are then transmitted to various sites of stimulation spanning the inner ear. Low-pitch sounds are sent to one part of the cochlea, high-pitch sounds to another, more closely mimicking the human ear. Because multiple channels provide a more detailed representation of sound, they are thought to allow better speech understanding than do single-channel devices. Clarke’s multichannel device was approved in 1985. Throughout these years, implants were being offered to children, although they were not yet approved by the FDA for use in pediatric populations.

In 1990, the FDA approved the use of cochlear implants for children over age 2 years. This decision led to a firestorm of controversy. The next year, the National Association of the Deaf (NAD) issued a statement deploring the FDA’s approval decision. (9) They argued that cochlear implants for children remained highly experimental. They accused the FDA of “failing to consult formally with organizations of deaf Americans and with deaf leaders and scholars knowledgeable about the acquisition and use of sign communication and English in deaf children, the psychosocial development and education of deaf children, and the social organization and culture of the American Deaf community.” Most controversially, the NAD claimed that deafness “comprises a linguistic and cultural minority,” and that “we should not seek the scientific tools nor use them, if available, to change a child biologically so he or she will belong to the majority rather than the minority – even if we believe that this biological engineering might reduce the burdens the child will bear as a member of a minority.” They recommended a national conference to address the ethical issues surrounding cochlear implants for children.

In 1995, a conference was convened at the National Institutes of Health (NIH) to address some of the issues raised by cochlear implants. Of note, it was not the conference that the NAD had recommended. Instead, the scope was much more limited. According to the organizers, “The conference was convened to summarize current knowledge about the range of benefits and limitations of cochlear implantation that have accrued to date. Such knowledge is an important basis for informed choices for individuals and their families whose philosophy of communication is dedicated to spoken discourse. Issues related to the acquisition of sign language were not addressed directly by the panel, because the focus of the conference was on new information on cochlear implant technology and its use. The panel acknowledges the value and contributions of bilingual and bicultural approaches to deafness”. (10) Conference panelists were drawn from “the fields of otolaryngology, audiology, speech-language pathology, pediatrics, psychology, and education, and including a public representative.” There was no representative from Deaf culture. The goal of the conference was to make recommendations to the NIH and the FDA about cochlear implants. More than 600 people attended.

The conclusions of the consensus conference were as follows: “Cochlear implantation improves communication ability in most adults with severe-to-profound deafness and frequently leads to positive psychological and social benefits as well. Currently, children at least 2 years old and adults with profound deafness are candidates for implantation. Cochlear implant candidacy should be extended to adults with severe hearing impairment and
open-set sentence discrimination that is less than or equal to 30% in the best-aided condition. Access to optimal education and (re)habilitation services is important for adults and is critical for children to maximize the benefits available from cochlear implantation.”

Critics of the NIH conclusions pointed out that there were no rigorous, controlled studies of outcomes for children. In particular, they worried that only surrogate end points and controversial markers of language acquisition were being used. In a review published in 1997, Lane and Grodin noted that “the decision to have the surgery and habilitation may promote delays in the child’s acquisition of ASL [American Sign Language] and therefore may delay the time when that child has any full language at his or her command. Developmental milestones for signed languages are similar to those for spoken languages, and the later the acquisition of ASL, the poorer its mastery on the average. If implanted children become fluent neither in English nor in ASL, their intellectual, social, and psychological development may be compromised”. (11)

In a comprehensive review published in 1998, Lane and Bahan noted that, until long-term outcome studies were done to quantify linguistic, psychosocial, and educational attainments of implanted children, the procedure should be considered innovative or experimental and should be conducted only in carefully designed research protocols. (12) These articles were asking questions that were partly methodological, partly ethical. By asking which outcome measures should be used, they were asking how to define success. Should it be word recognition? School performance? Quality of life? Or something else?

At this point, both sides in the battle seemed to have firm and incompatible positions. On the one hand, the surgeons and audiologists were enamored of the new technology and even, perhaps, a little starry-eyed about the potential benefits. Reports in the mid-1990s often included individual case reports, but no careful studies of series of patients who had received implants. (13) Such individual case reports were usually optimistic, but not scientifically rigorous. Thus, members of the Deaf community remained skeptical and unsure of the efficacy or the implications of this new technology. These critics within the Deaf community seemed to be the voice of reason, calling for careful study and evaluation. But the real-world situation was never really so simple or dichotomous.

Some advocates within the Deaf community, as well as some bioethicists, suggested that even a treatment that would be 100% effective (what is 100% effective?) was undesirable. (14) Some of these critics saw attempts to treat or cure deafness as a genocidal attack on the Deaf community, an extension of the oralist tradition of Bell and others. An article in The Washington Post in 1997 described this group as “a radical segment” who “…call cochlear implants ‘the devil’s work;’ who consider Miss America 1995, the deaf Heather Whitestone, a charlatan because she speaks; who picket oralist deaf schools and stop parents of children with implants in malls, demanding to know why they butcher deaf babies”. (15) In the eyes of this group, cochlear implants were seen as an intervention that was offered not to improve the outcome for individual children but, instead, as an assault on the Deaf community. Given these views, it seemed that there could be no reconciliation in views between the proponents of implants and their opponents.

A Mysterious Attitude Shift

Then, somehow, and rather suddenly, the terms of the controversy seemed to change. The Deaf community softened its opposition. Cochlear implants came to be seen as one acceptable option among many. The reasons for the transition in attitudes are complex.

One explanation for the shift was that it was a response to public pressure on the NAD. This is the view of I. King Jordan, President Emeritus of Gallaudet University: “The NAD position received adverse attention from the media and criticism from moderates in the deaf community and from physicians and allied health professionals who considered cochlear implants an appropriate option”. (16) In response to this adverse attention, the NAD withdrew its controversial position paper. In 2000, they released a new position paper that recognizes cochlear implants as one of multiple options. Note that this change in outlook does not mean that the NAD’s earlier concerns were wrong. The new statement endorsed informed parental choice, recognized that there is diversity within the Deaf community, and supported parents’ right to make the decision that they think best for their child.

The NAD knows that parents love and care deeply about their deaf children. Since the decision to perform implant surgery on the deaf child is made for the child, it is necessary for parents to become educated about cochlear implants—the potential benefits, the risks, and all the issues that they entail. During this critical education process, parents have both the need and the right to receive unbiased information about the pros and cons of cochlear implants and related matters. The NAD knows that parents want to make informed decisions. Parents also would benefit by opportunities to interact with successful deaf and hard of hearing adults, as well as with parents of deaf and hard of hearing children. (17)
Another reason why the debate shifted is that follow-up studies have answered some of the questions that could not be answered in the early days. When cochlear implants first came into use for children, it was not clear whether the implants would cause more harm than good by promising more hearing, and thus more verbal linguistic functioning, than they could deliver. The earliest outcome studies confirmed some of these fears. Many children who received cochlear implants continued to have poor language acquisition and to do poorly in school.

Later studies showed that outcomes were, in fact, variable. Some children who receive implants are able to function well in the hearing world. More often, however, they continue to require special assistance or to use sign language along with spoken language. Thus, many children who have had a cochlear implant still go to school in classrooms for the deaf, or in hearing classrooms but with special services. For many such children, the approach has changed from an either/or, oralism/manualism choice to an approach that stresses bilingualism (that is, the use of both ASL and oral communication) in an approach that is individualized and uses all available technology. (18)

Issues for the Future

Some issues remain contentious. The question of whether parents who are deaf should be able to choose to have a child who is deaf, either through preimplantation genetic diagnosis or through prenatal testing and termination of pregnancy if the child is not deaf, remains as contentious as ever. (19) Some advocates for the deaf (20) and some bioethicists (21) insist that this option should be available to parents who want an infant who is deaf. Others insist that it is unethical, even though understandable, for parents to choose deafness for a child. (22)

Of course, some forms of reproduction are easier to regulate than others. Couples may be denied access to preimplantation genetic diagnosis. But it is difficult to imagine regulations that would prevent two carriers of an autosomal dominant form of deafness from having children together.

Questions have arisen about the cost of cochlear implants and of access to both the technology and the extensive postsurgical habilitation that is necessary. A recent study from Cleveland showed that poor children were just as likely to receive a cochlear implant as children of higher socioeconomic status, but that they had more complications and poorer follow-up care. (23) Such outcomes are not unique to cochlear implants but are true for many medical treatments that require long-term follow-up. Although disparities in access to health care are common throughout medicine and throughout the world, the issues surrounding deafness raise unique issues, because most newborns in the United States are now screened for hearing loss. (24) In general, screening programs should be implemented only if there is access to appropriate treatment for those who test positive. (25)

Summary

- The story of the ethical controversy over cochlear implants is unique in some ways and paradigmatic in others. It is unique in the ways that it was shaped by the history of deafness, and of cultural responses to deafness, in the United States.
- The story is paradigmatic in two ways. First, cochlear implantation was an innovative therapy that was introduced into practice without adequate study. Promising early trials led to FDA approval, although long-term outcome data from rigorous studies were lacking. In this respect, the story of cochlear implants is similar to the history of other innovations that were introduced without rigorous evaluation, innovations such as supplemental oxygen, (26) extracorporeal membrane oxygenation, (27) or corticosteroids for bronchopulmonary dysplasia. (28)
- Cochlear implants also are paradigmatic of a particular type of ethical dilemma in which advocacy groups claim to know better what is best for children than do the children’s parents or doctors. This controversy happened during the Baby Doe debate in the 1980s, when advocacy groups claimed that doctors and parents were conspiring to discriminate against children with disabilities. (29) Ultimately, the US Supreme Court invalidated that interpretation of disability rights. (30) Instead, parents and doctors working together are given discretion to make decisions about what is best for children.
- With regard to cochlear implants for children, the NAD realizes that they are walking a fine line. As one NAD spokesperson said, “We don’t say that hearing parents aren’t qualified to make decisions about their deaf children. We say that they need to have contact with deaf people if they’re going to make educated decisions”. (7) The same could be said for pediatricians.
- There are 4,000 to 8,000 infants born each year in the United States with severe hearing impairment. Their parents will have to make decisions about what is best.
- Pediatricians need to understand the options and be prepared to help parents sort through the complex data and multiple options in order to arrive at the decision that is best for themselves and their child. Understanding the ethical controversy over cochlear implants will help.

To view the references for this article, visit the July issue at http://pedsinreview.aappublications.org and click on “Ethics for the Pediatrician.”
The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

The editors and staff of *Pediatrics in Review* find themselves in the fortunate position of having too many submissions for the Index of Suspicion column. Our publication slots for Index of Suspicion are filled through 2013. Because we do not think it is fair to delay publication longer than that, we have decided not to accept new cases for the present. We will make an announcement in *Pediatrics in Review* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors. We are grateful for your interest in the journal.

Author Disclosure
Drs Stewart, Piteau, Storr, MacKenzie, Hartsell, and Nagappan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Case 1: Limp in a 23-month-old Girl
Case 2: Abnormal Eyelashes in 17-year-old Boy Who Has Congenital Heart Disease
Case 3: Fever, Pharyngitis, and Chest Pain in a 9-year-old Boy

Case 1: Limp in a 23-month-old Girl
A previously healthy 23-month-old girl presents with fever and a limp. She has had fever every other day for the past 2 months. Over the past 2 weeks, she has been favoring her right leg and occasionally complains of leg pain with ambulation. Today’s clinic visit was prompted by an abrupt refusal to bear weight on the left leg. Review of systems is notable for subjective weight loss, chills, and night sweats during the past month. Her immunizations are up to date, and she has no recent travel or exposure history. She takes no medications.

On physical examination, the girl is alert but fussy and has growth parameters within normal limits. She is afebrile; her heart rate is 164 beats per minute, respiratory rate is 28 breaths per minute, and blood pressure while crying is 158/91 mm Hg. Her left lower extremity is held in extension and external rotation; she will not allow abduction of her hip. There is no rash, swelling, or warmth over the hip or knee joints bilaterally. She will not bear any weight on the left leg, but she moves the right leg spontaneously. She has normal results on neurovascular examination. A few scattered ecchymoses are noted on both legs. The results of the remainder of the physical examination are normal.

Laboratory studies reveal a white blood cell count of 5.9 × 10^3/μL, without any immature cells, hemoglobin level of 8 g/dL, and platelets of 60 × 10^3/μL. Her C-reactive protein level is 5.7 mg/dL, and erythrocyte sedimentation rate is 90 mm/h. Radiographs of the lower extremities show demineralization and mottling at the left femoral metaphysis. Additional laboratory and imaging studies reveal the diagnosis.

Case 2: Abnormal Eyelashes in 17-year-old Boy Who Has Congenital Heart Disease
A 17-year-old boy with congenital heart disease (CHD) presents with a fever and fatigue. His past medical history includes a ventricular septal defect (VSD) with aortic regurgitation and distichiasis (double set of eyelashes arising from the meibomian glands) (Fig 1). Despite closure of his VSD, he developed progressive aortic insufficiency requiring multiple surgeries. His eyelashes were removed at 7 years of age because of persistent conjunctival irritation due to the distichiasis. After his last cardiac surgical (Ross) procedure, he developed chronic progressive right-sided pitting edema below the knee to the midfoot, without evidence of thrombosis.

Physical examination reveals a temperature of 37°C, heart rate of 90 beats per minute, and blood pressure of 99/61 mm Hg. The right eye shows two aberrant eyelashes in the upper eyelid. His cardiovascular exam reveals a grade II/VI systolic ejection murmur heard loudest at the pulmonic area. His right leg is edematous, cool, and non-tender. The rest of the physical findings are normal.

His complete blood cell count is normal, and blood cultures are pending. An echocardiogram shows a successful valvular repair and no evidence of endocarditis. Consultation with a specialist provides the explanation for his CHD, distichiasis, and lymphedema.
Case 3  Presentation

A 9-year-old boy presents to the emergency department with 7 days of fever to a height of 103°F (39.5°C) and night sweats. He complains also of sore throat, rhinorrhea, cough, decreased appetite, fatigue, and chest pain, which is sharp and is located above the sternum. Over the week, the rhinorrhea and cough have improved, but the fever, sore throat, and chest pain have worsened. He denies dysphagia, but is spitting frequently. He also notes a change in his voice.

On physical examination, the boy is not in acute distress. His temperature is 103.1°F (39.5°C), respirations are 18 breaths per minute, heart rate is 128 beats per minute, and blood pressure is 113/72 mm Hg. He has mild erythema of the pharynx without exudates. His neck is supple without lymphadenopathy. He has circular desquamation surrounding his anus, 4 cm in diameter, with flaking skin on his scrotum; his palms are desquamating in thick sheets. The remaining findings on examination are normal.

His white blood cell count is 30.7 × 10^3 /µL (87% neutrophils, 9% lymphocytes), hemoglobin level is 11.1 g/dL, platelet count is 411 × 10^3 /µL, sodium level is 129 mEq/L, chloride level is 92 mEq/L, total serum protein concentration is 7.4 g/L, and albumin level is 2.2 g/L. A rapid streptococcal antigen test is positive. Chest radiograph shows an ~5.1 × 6.6 cm homogeneous opacity in the medial aspect of the right upper chest, extending from the level of the superior hilum up toward the apex (Fig 2). An additional imaging study reveals the diagnosis.

**Case 1 Discussion**

Initial radiographs of the left lower extremity were concerning for an infectious or an oncologic process. The girl’s serum lactate dehydrogenase level was 1,627 units/L, serum uric acid level was 6.3 mg/dL, and urine vanillylmandelic acid and homovanillic acid catecholamine levels were 466 mg/g and 316 mg/g, respectively. This pattern was strongly suggestive of an oncologic sympathomimetic process.

Computed tomography (CT) scan of the chest/abdomen/pelvis was obtained, which showed a thoracic paraspinal soft tissue mass with internal calcifications as well as scattered lytic lesions of the inferior sternum, left scapula, L1 and L3 vertebrae, T3 and T4 vertebrae, iliac wings, and proximal femurs, in addition to a hepatic lesion, a pattern suggestive of a metastatic small round blue cell tumor. Bone marrow and tumor biopsy showed a poorly differentiated neuroblastoma with unfavorable histology consistent with a stage 4 neuroblastoma. The results of the blood cultures and tuberculin skin test were negative.

**Differential Diagnosis**

Fever and limp has a broad differential diagnosis, including infection, trauma, and malignancy, as well as inflammatory, orthopedic, and hematologic conditions. A thorough history is essential for discerning which laboratory and imaging studies to pursue. Processes that require immediate treatment should be ruled out first and include septic arthritis and osteomyelitis. Acute onset of limp suggests trauma or infection, whereas presentations with an insidious onset are more suggestive of inflammatory processes, such as rheumatologic and oncologic diseases.

**The Condition**

Embryonal cancers of the peripheral sympathetic nervous system encompass a spectrum of tumors with variable degrees of neural differentiation. Neuroblastomas are undifferentiated, small, round, blue cell tumors; they are the third most common pediatric cancer. Median age at diagnosis is 2 years of age, and 90% of cases are diagnosed by 5 years of age. Neuroblastoma is the most commonly diagnosed tumor in infants, comprising ~34% of neonatal malignancies. The clinical and morphologic spectrum of neuroblastoma is wide. Presentation varies significantly and reflects the site of sympathetic nervous system tissue affected, as well as the degree of tumor invasion.

The most common preliminary site of tumor invasion is the abdomen, either in the adrenals or retroperitoneal sympathetic ganglia. In one-third of cases, neuroblastoma originates from the cervical, thoracic, or pelvic
Lessons for the Clinician

- Many disease entities can present with acute limb pain in childhood.
- The patient’s history and physical examination should help determine appropriate laboratory and radiographic studies.
- Fever, severe pain, and weight loss suggest more serious causes of limb pain that should prompt immediate evaluation.

(Eileen Stewart, MD, Department of Pediatrics, University of New Mexico, Albuquerque, NM)

Case 2 Discussion

Entry of the features of congenital heart disease, distichiasis, and lymphedema into an online genetics database suggested a possible diagnosis of lymphedema-distichiasis syndrome. A clinical geneticist agreed with the diagnosis, and a mutation in the FOXC2 gene confirmed lymphedema-distichiasis syndrome.

The Condition

Lymphedema-distichiasis syndrome classically presents with late-onset lymphedema (typically late childhood or puberty) and distichiasis. The lymphedema occurs exclusively in the lower extremities, often is asymmetric, and can be unilateral; the severity varies among patients, and males usually present earlier than females. Approximately 94% of affected individuals have distichiasis, which can cause photophobia, recurrent conjunctivitis, and corneal irritation. CHD occurs in 7% of patients and may include VSD, atrial septal defect, patent ductus arteriosus, and Tetralogy of Fallot. Other associated features of the syndrome include varicose veins, ptosis, cleft palate, spinal extradural cysts, and other ocular anomalies.

Diagnosis

This diagnosis is made clinically and confirmed by analysis of FOXC2 gene, which reveals a mutation in about 95% of cases. There is clinical variability with no apparent genotype/phenotype correlation. Lymphedema-distichiasis syndrome is inherited in an autosomal dominant manner. There may be no known family history of distichiasis because relatives may not be aware of asymptomatic cases. Alternatively, the condition may be due to a new mutation, found in ~25% of affected patients.

Differential Diagnosis

Lymphedema should be considered as a cause of any peripheral edema that lacks pain or inflammation. Lymphedema can be difficult to differentiate from chronic venous insufficiency because both can have pitting edema (although lymphedema typically is not of the pitting type). Distinguishing features of lymphedema include a unilateral presentation, a squared-off appearance of the foot, and initial pitting edema progressing to non-pitting, brawny edema. In the later stages of lymphedema, the skin becomes hyperkeratotic, hyperpigmented, and papillomatous or verrucous. The Kaposi-Stemmer sign, in which an examiner is unable to pinch a fold of skin at the dorsal base of the second toe, is indicative of lymphedema.

Lymphedema is classified as either primary or secondary. In primary lymphedema, the dysfunction is caused by congenital hypoplasia or aplasia of the lymphatic vessels or by valvular incompetence, and the clinical changes may not become apparent until later in life. Primary lymphedema can be divided into three categories based on the age of onset of the edema. Congenital lymphedema (Milroy disease) manifests from birth to 1 year of age and is due to anaplastic lymphatic channels. The lower-extremity edema...
is bilateral, pitting, and nonpainful. Lymphedema praecox (Meige disease) manifests from age 1 to 35 years and is the most common form of primary lymphedema. This disorder is due to hypoplastic lymphatic channels. The edema is unilateral, more common in the distal extremity, and presents often at puberty. Lymphedema tarda manifests after age 35 years and is thought to be due to a defect in the lymphatic valves. Primary lymphedema also is associated with genetic syndromes, including Turner and Noonan syndromes, as well as with rarer disorders such as lymphedema-distichiasis syndrome.

In secondary lymphedema, there is blockage of the lymphatic system or disruption of the lymphatic drainage because of recurrent attacks of cellulitis or infections with *filariasis*, malignancy, obesity, surgery, or trauma.

**Management**

Once the diagnosis of lymphedema-distichiasis syndrome is made, further evaluation is recommended to establish the extent of the disease. The following steps should be considered (the timing of which will depend on the initial presentation): referral to an ophthalmologist for slit lamp examination, physical examination to identify a cardiac lesion or the complication of cellulitis, echocardiography, isotope lymphoscintigraphy to document the underlying abnormality of the lymphatic system, and referral to a geneticist for counseling.

The goal in managing primary lymphedema is to restore function and prevent deterioration. A multidisciplinary team is necessary for optimal management. Initial treatment includes the use of compression stockings, multilayer bandages, or pneumatic pumps; leg elevation; and skin care and debridement to prevent cellulitis, if needed. In cases of recurrent cellulitis or lymphangitis, long-term antibiotic therapy with penicillin or cephalosporins should be considered.

Some pharmacologic therapies have proven to be effective in treating lymphedema, including benzopyrenes, oral and topical retinoids, and topical emollients and keratolytics. Diuretics are not effective in treating lymphedema. Surgery is reserved for cases resistant to medical therapy. Ophthalmology referral is indicated for the management of the distichiasis, which can be conservative management with lubrication or more definitive surgical management.

This patient’s lymphedema currently is well controlled, his distichiasis is asymptomatic after surgical repair, and his last echocardiography showed normal heart size and function.

**Prognosis**

Lower-extremity lymphedema can progress if uncontrolled and can be a disabling disease with functional, cosmetic, and psychological consequences. The severity of the edema is variable in lymphedema-distichiasis syndrome. A multidisciplinary team approach, in combination with patient education and compliance, can improve outcome. Prognosis depends also on associated comorbidities.

**Lessons for the Clinician**

- A high level of suspicion for a genetic syndrome is required in the presence of a rare anomaly.
- The presence of two major anomalies significantly increases the likelihood of an underlying genetic condition. Especially with respect to the many rare diseases that manifest phenotypic variability, it is important to have a low threshold for considering genetic syndrome.
- Practitioners also should be familiar with Web-based databases and regional clinical genetics resources.

(Shalea Piteau, MD, Michael Storr, MD, Jennifer MacKenzie, MD, Kingston General Hospital, Kingston, Canada)

**Case 3 Discussion**

Contrast-enhanced CT scan of the chest reveals an extensive fluid collection in the posterior mediastinum suggestive of abscess (Fig 3).

**Differential Diagnosis**

The differential diagnosis of the patient’s initial symptoms included pharyngitis, Ludwig angina, tonsillitis, and pneumonia. However, once the mediastinal mass was seen on chest radiograph, the differential broadened to include neoplasm, cystic lesions, vascular abnormalities, or infection. Further differentiation in such a case would be based on the location of the mass within the mediastinum (anterior, middle, or posterior) and almost always would require further evaluation with CT. This patient ultimately was found to have a posterior mediastinal abscess surrounding the esophagus and abutting the trachea.

**Clinical Course and Management**

The patient was admitted and started on intravenous ampicillin/sulbactam...
and vancomycin. The following day, he developed a scarlatiniform rash. Later the same morning, he underwent surgical drainage via dorsal throracotomy. Surgeons discovered a very large abscess that extended from his posterior mediastinum and surrounded his esophagus, trachea, and portions of the aortic arch. There was no intraoperative evidence of extension to the neck. Cultures sent from the abscess grew group A *Streptococcus*. The desquamation of skin from his palms, anal region, and scrotum was due to streptococcal erythrogenic toxin that also caused the scarlatiniform rash. Drains were placed in the abscess space and removed on hospital day 4. He was discharged on hospital day 5 to complete a 14-day course of amoxicillin/clavulanate.

**The Condition**

Descending mediastinitis is a term defined by Estrera et al in 1983 as acute mediastinitis originating from an oropharyngeal infection. (1) The authors developed criteria for diagnosis of mediastinitis that include (1) clinical symptoms of severe oropharyngeal infection, (2) demonstration of characteristic radiographic features of mediastinitis, (3) documentation of mediastinitis at operation or postmortem examination or both, and (4) establishment of a relationship between oropharyngeal infection and development of the mediastinal process. Descending mediastinitis is a rare, but potentially life-threatening complication of infections that spread through the potential spaces formed by fascial planes extending from the head and neck to the thorax.

The initial clinical presentation includes pain, fever, and swelling at the primary site of infection. Early in the development of mediastinitis, initial complaints may include chest pain and odynophagia (painful swallowing). Vocal change may be present. Respiratory distress and stridor are possible when the infection causes airway impingement. As the disease progresses, physical examination findings may include the Hamman sign, a crunching raspy sound heard over the precordium with the heart beat, or crepitus in the supravacularic region. Left unrecognized, mediastinitis may progress to overwhelming sepsis and cardiovascular compromise.

The most common predisposing condition involves extension of a head and neck infection (pharyngitis, tonsillitis, sinusitis, parotitis, epiglottitis, Ludwig angina, and Lemierre syndrome). Oropharyngeal or cervical abscesses, including retropharyngeal abscesses, odontogenic abscesses, and peritonsillar abscesses are all leading causes. Trauma, surgery, or instrumentation may directly translocate bacteria from the oropharynx into the retropharyngeal space. The infection travels down the fascial planes of the neck via adjacent lymph nodes into the superior mediastinum or into the posterior mediastinum if the danger space, the space between the alar and prevertebral fascia, is involved.

Mediastinitis rarely is due to spread from distant sites, although cases secondary to pneumonia, cellulitis, subphrenic abscess, or osteomyelitis of the rib, sternum, clavicle, or vertebrae have been described. The most common organisms implicated in these suppurrative infections include group A streptococci and common anaerobic oropharyngeal flora. Infections due to methicillin-resistant *Staphylococcus aureus* may begin to play a larger role.

**Treatment and Prognosis**

Delayed diagnosis and inadequate treatment have led to a high mortality in acute descending mediastinitis. Because there are few early clinical signs, patients may present in extremis after a rapid progression of their symptoms. Mortality rates range from 15% to 40%. Treatment is initiated with broad-spectrum intravenous antibiotics directed toward the usual causative organisms, but surgery often is the definitive treatment.

**Lessons for the Clinician**

- Descending mediastinitis is a rare but potentially life-threatening complication of head and neck infections that travel down fascial planes to the mediastinum.
- Descending mediastinitis should be suspected when there are symptoms out of proportion to a simple pharyngeal or odontogenic infection or in a patient who has recently undergone surgery or procedures involving the oropharyngeal space.
- Radiography of the chest may be negative early in the course. Early contrast CT scan of the chest is the recommended diagnostic imaging study in the appropriate context.
- Initial therapy with broad-spectrum antibiotics is important, but early surgical intervention may be necessary.

(Angela Harttell, MD, MPH, Suresh Nagappan, MD, Moses Cone Hospital, Greensboro, NC)

**Reference**


To view Suggested Reading lists, for these cases, visit the July issue at [http://pedsinreview.aappublications.org](http://pedsinreview.aappublications.org) and click on “Index of Suspicion.”
In Brief

Colic

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Author Disclosure
Drs Cohen, Albertini, and Serwint have disclosed no financial relationships relevant to this In Brief. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.


If we understood the mechanism of infant colic, life would be so much easier for parents and pediatricians. Being a new parent is difficult, but being the parent of a fussy infant is infinitely more challenging. An estimated 10% to 26% of infants experience colic, which was defined by Wessel in his classic 1954 article as occurring in an otherwise healthy infant who cries for >3 hours per day, >3 days per week, for >3 weeks in duration. Colic begins during the second week of life, peaks at 6 weeks, and resolves between 12 and 16 weeks. It is equally common in both breast- and bottle-fed infants. Although crying is normal for all infants, averaging 2.2 hours per day, those with colic cry excessively, are more difficult to console, have disrupted sleep, and are the source of much parental anxiety. Mothers of colicky infants are at higher risk for postpartum depression and are more likely to stop breastfeeding early. Infants who are excessively fussy are at higher risk for child abuse. There is no racial, socioeconomic, or gender prevalence for colic.

The diagnosis of colic is made by history and is a diagnosis of exclusion. Colicky infants present with episodic periods of inconsolable crying, most often in the late afternoon and evening. These periods of fussiness are not associated with hunger or discomfort, and the infants are otherwise normal. Laboratory tests and imaging are not necessary to make the diagnosis. An organic cause can be found in <5% of infants who present with excessive crying. A complete differential diagnosis of excessive crying that should be considered when contemplating colic is beyond the scope of this article, but includes constipation, gastroesophageal reflux disease, infections, feeding disorders, and less commonly, acute abdominal pain, occult fracture, and maternal drug effects.

Many theories have been proposed for the cause of colic, including gas, gastroesophageal reflux, food allergies, milk-protein intolerance, gut dysmotility, and maternal tension; however, the cause is most likely to be multifactorial. Because the etiology of colic is unknown, many treatments have been advocated, but few have been studied rigorously. First-line therapy includes parental reassurance and behavioral interventions. These interventions can take many forms, including effective swaddling, gentle rocking, and decreased stimulation of the infant. White noise, vibration, and motion can soothe some infants. Cautioning overtired and frustrated parents never to shake their infant and giving them permission to allow the infant to cry are essential components of any treatment plan and can decrease the risk of child abuse. Encouraging parents to access additional caretakers for their child when they are overly tired or stressed is another important part of a treatment plan.

Elimination diets in breastfeeding mothers and formula changes for bottle-fed infants have been advocated for the treatment of colic. Although there is some evidence that the elimination of specific foods from a nursing mother’s diet may help, benefit is not seen in all infants. The mother’s diet would need to be monitored carefully, and the intervention continued only if deemed effective. Soy and lactose-free formulas have not been shown to improve colic and are not recommended for this indication. One small study of protein hydrolysate formula showed moderate improvement in symptoms, but much more study of this intervention is warranted.

Simethicone, considered by many as a mainstay of colic treatment, is a safe but relatively ineffective remedy. In one randomized controlled trial, simethicone was found to be no more effective than placebo in reducing symptoms of colic. Dicyclomine, an anticholinergic drug that was found to be more effective than placebo in decreasing symptoms of colic, has been shown to cause
apnea and seizures, and its use is contraindicated in infants younger than 6 months.

Complementary interventions are receiving more attention for the treatment of colic. These therapies include natural and botanical products, probiotics, and manipulative therapies. A systematic review of these modalities was published in 2011 and found that, with the exception of a few limited studies, available data do not yet support the routine use of any of these therapies.

Although the etiology and thus effective treatment for colic remains elusive, it is a self-limited process with no long-term adverse effects. Parents need to be reassured that they have normal, healthy infants. Presenting parents with simple strategies to calm and soothe their infants, and themselves, until this common but difficult time in their child’s life passes is key.

Comment: If you have ever been in the presence of an infant with colic, you know how difficult it can be. The heart-wrenching cries instill in all of us—parents, family members, and pediatricians alike—the impulse to want to comfort and make the infant feel better. No wonder everyone seeks a cure. But this search can lead to a never-ending cycle of trying medications, dietary manipulations, behavioral strategies, and nutritional and complementary supplements. Helping parents to understand that colic is a self-limited condition and developing strategies to enhance their self-esteem in parenting are critical; however, the more severe the symptoms, the more intense must be the support.

Isn’t it amazing to know that colic has been described since biblical times, but we still do not truly understand its etiology or effective treatments?

Janet R. Serwint, MD
Consulting Editor, In Brief

Marijuana

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Author Disclosure
Drs Neuspiel and Serwint have disclosed no financial relationships relevant to this In Brief. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.


The Role of Schools in Combating Illicit Substance Abuse. Council on School Health and Committee on Substance Abuse. Pediatrics. 2007;120:1379–1384

Marijuana (cannabis), the illicit drug used most frequently in the United States, may be smoked in cigarettes (joints, nails, reefer), pipes (bongs, bowls), or cigars (blunts); mixed with food; or brewed as a tea. Hashish (hash), a potent resin of cannabis, also may be used as a sticky black liquid (hash oil). Other street terms are pot, herb, weed, grass, widow, and ganja.

The 2010 Monitoring the Future study, which assesses adolescent substance use patterns, revealed that admitted lifetime marijuana use among eighth, 10th, and 12th graders in the United States was 17.3%, 33.4%, and 43.8%, respectively; daily use was 1.2%, 3.3%, and 6.1%, respectively. Trends in use have varied in recent decades.

The primary active chemical in marijuana is THC (delta-9-tetrahydrocannabinol). Increased cultivation of sinsemilla made from buds of female cannabis plants has raised mean THC content from 0.7% in the 1970s to 8.5% in 2008, with wide variability in dose. Street marijuana...
apnea and seizures, and its use is contraindicated in infants younger than 6 months.

Complementary interventions are receiving more attention for the treatment of colic. These therapies include natural and botanical products, probiotics, and manipulative therapies. A systematic review of these modalities was published in 2011 and found that, with the exception of a few limited studies, available data do not yet support the routine use of any of these therapies.

Although the etiology and thus effective treatment for colic remains elusive, it is a self-limited process with no long-term adverse effects. Parents need to be reassured that they have normal, healthy infants. Presenting parents with simple strategies to calm and soothe their infants, and themselves, until this common but difficult time in their child’s life passes is key.

Comment: If you have ever been in the presence of an infant with colic, you know how difficult it can be. The heart-wrenching cries instill in all of us—parents, family members, and pediatricians alike—the impulse to want to comfort and make the infant feel better. No wonder everyone seeks a cure. But this search can lead to a never-ending cycle of trying medications, dietary manipulations, behavioral strategies, and nutritional and complementary supplements. Helping parents to understand that colic is a self-limited condition and developing strategies to enhance their self-esteem in parenting are critical; however, the more severe the symptoms, the more intense must be the support.

Isn’t it amazing to know that colic has been described since biblical times, but we still do not truly understand its etiology or effective treatments? Systematic reviews on the topic reveal >1700 articles and abstracts about colic that have been published, yet there are few randomized trials, and those that have been published span multiple treatment options of pharmaceutical, dietary, behavioral, and complementary interventions. Significant methodologic flaws have hampered research in this area, and future studies need to focus on a research agenda to ensure the use of a consistent definition of colic (Wessel criteria), objective outcome measures, and sufficient sample size and power to determine differences. Time will tell, but perhaps colic will be one entity that will remain elusive, and our current strategies of support and reassurance may be the best.

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**Marijuana**

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**The Role of Schools in Combating Illicit Substance Abuse.** Council on School Health and Committee on Substance Abuse. Pediatrics. 2007;120:1379–1384

Marijuana (cannabis), the illicit drug used most frequently in the United States, may be smoked in cigarettes (joints, nails, reefers), pipes (bongs, bowls), or cigars (blunts); mixed with food; or brewed as a tea. Hashish (hash), a potent resin of cannabis, also may be used as a sticky black liquid (hash oil). Other street terms are pot, herb, weed, grass, widow, and ganja.

The 2010 Monitoring the Future study, which assesses adolescent substance use patterns, revealed that admitted lifetime marijuana use among eighth, 10th, and 12th graders in the United States was 17.3%, 33.4%, and 43.8%, respectively; daily use was 1.2%, 3.3%, and 6.1%, respectively. Trends in use have varied in recent decades.

The primary active chemical in marijuana is THC (delta-9-tetrahydrocannabinol). Increased cultivation of sinsemilla made from buds of female cannabis plants has raised mean THC content from 0.7% in the 1970s to 8.5% in 2008, with wide variability in dose. Street marijuana
in brief

Marijuana increases the risk of injury, unwanted and unprotected sex, and other drug use. Recreational doses impair driving as much as blood alcohol concentrations of 0.07% to 0.1%. No deleterious effects of marijuana use on the fetus have been confirmed.

Long-term marijuana use may lead to addiction, with use continuing despite interference with family life, school, work, and recreation. Tolerance may occur after several days of regular use. Withdrawal symptoms after heavy use peak by day 4 and resolve by 2 weeks. These symptoms include irritability, insomnia, malaise, drug craving, diaphoresis, night sweats, gastrointestinal disturbances, and agitation.

Screening for drug use and addictive symptoms is part of comprehensive adolescent care. Anticipatory guidance should include information about marijuana’s addictive potential; injury risk; and possible impairment of learning, socialization, and sexual function. Parents should be encouraged to rehearse strategies to help teenagers avoid drug-using settings. Skills-based interventions in schools have helped increase drug knowledge, decision-making, self-esteem, and peer pressure resistance and have led to reduced marijuana use. Interventions in nonschool settings, motivational interviewing, and some family interventions also may help prevent marijuana use.

Marijuana and its metabolites are detectable in urine by enzyme-multiplied immunoassay technique starting 1 hour after smoking. The urine assay usually remains positive up to 10 days after infrequent use and up to 30 days in heavy users. Some urine tests may detect passive inhalation of second-hand marijuana smoke. False-positive results may occur from ingestion of nonsteroidal anti-inflammatory drugs; false-negative results may follow urine dilution or adulteration. Various urine and saliva tests as well as adulterants to modify the tests are available on the Internet. Care must be taken to avoid contamination, dilution, or substitution when obtaining urine samples for testing.

The American Academy of Pediatrics (AAP) supports voluntary confidential drug testing to ensure that adolescents seek care. Although parents may ask a physician to test their teenagers for evidence of drug use, the AAP states: “Testing adolescents requires their consent unless (1) a patient lacks decision-making capacity; or (2) there are strong medical indications or legal requirements to do so.” Although recent court decisions allow schools to perform random drug tests on middle and high school students participating in extracurricular activities, the AAP has opposed school-based testing unless part of a funded, comprehensive approach to addressing substance abuse.

Comment: Some of the most challenging encounters I have experienced have involved parents asking for drug testing for their adolescent children. Working toward a trusting relationship between the adolescent and parent is critical, and negotiating these situations has been enhanced by the AAP statement on this topic: that the drug-testing procedure should be done with the adolescent’s consent, and positive results should be used as a mechanism to get treatment for the patient, not punishment. Facilitating this dialogue and helping the adolescent patient know that both family and pediatrician have his or her best interests in mind are essential.

Much controversy has arisen over legalizing marijuana use. Those who are opposed worry that access will be easier for children and adolescents and enhance unwanted drug use. Those who are in favor think that the therapeutic potential of pain relief, increase in appetite, and nausea control could be beneficial for select patients with AIDS, cancer, and multiple sclerosis. More research is needed to determine the best way to approach this public health issue in controlling distribution to those who would benefit medically while minimizing risk from recreational use.