Conjugated Hyperbilirubinemia in Children

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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.

Abbreviations

AIH:	autoimmune hepatitis
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
A1AT:	alpha-1 antitrypsin
BA:	biliary atresia
BRIC:	benign recurrent intrahepatic cholestasis
BSEP:	bile salt excretory protein
CDC:	choledochal cyst
ERCP:	endoscopic retrograde cholangiopancreatography
GGT:	gamma glutamyltransferase
MCT:	medium chain triglycerides
MRCP:	magnetic resonance cholangiopancreatography
PFIC:	progressive familial intrahepatic cholestasis
PN:	parenteral nutrition
PSC:	primary sclerosing cholangitis

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

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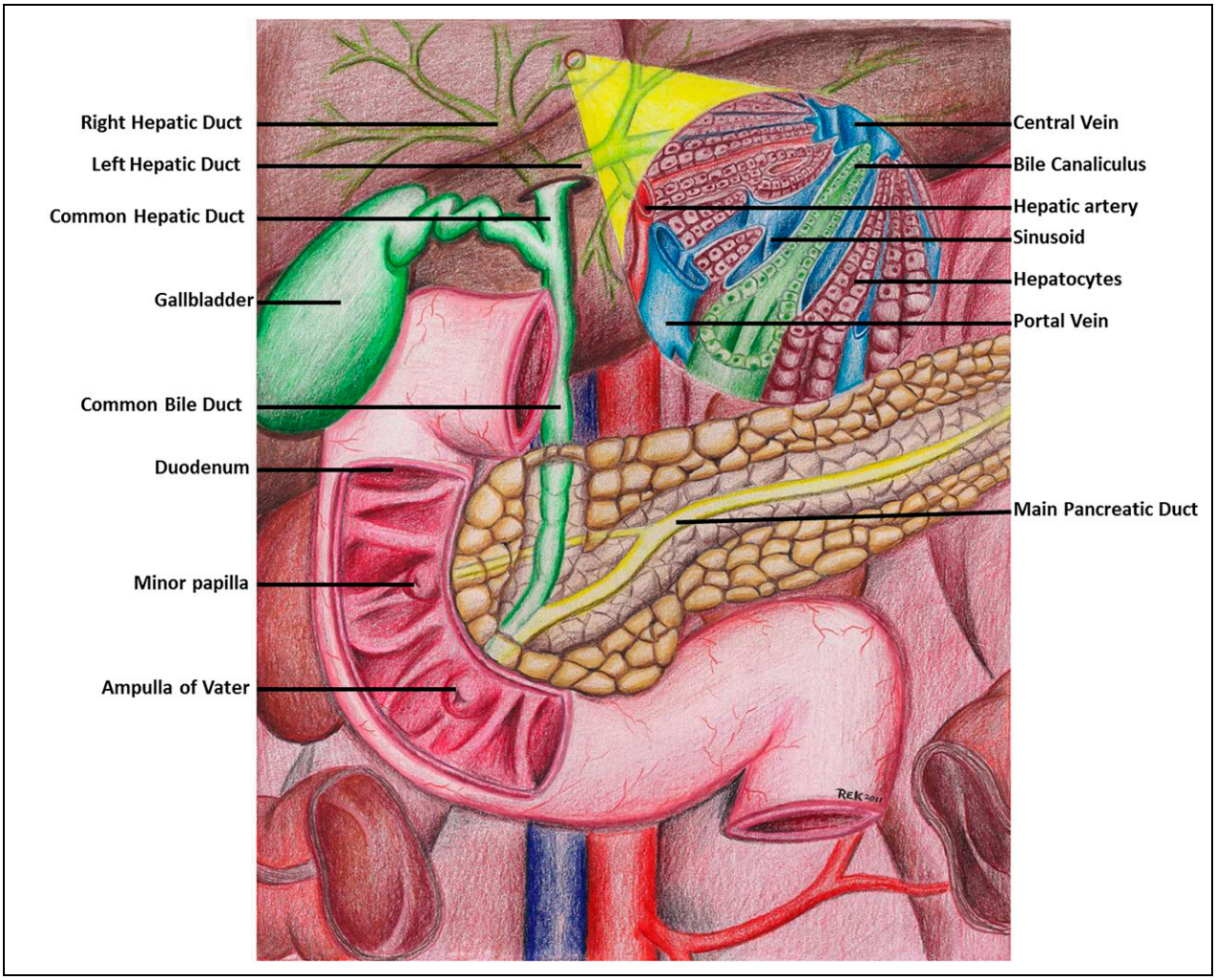

Figure 1. Biliary drainage with magnification of portal triad. (Courtesy of Robert E. Kramer, MD.)

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.

Expedient 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. (2)

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. (3) There are two

Table. Differential Diagnosis of Neonatal Cholestasis

- Congenital infection
  - Cytomegalovirus
  - Toxoplasmosis
  - Rubella
  - Herpes simplex virus
  - Syphilis
  - HIV
- Acquired infection
  - Urinary tract infection
  - Sepsis
- Metabolic
  - Alpha-1 antitrypsin deficiency
  - Cystic fibrosis
  - Galactosemia
  - Tyrosinemia
  - Defects in bile acid synthesis
  - Inborn errors of carbohydrate, fat, protein metabolism
- Obstructive
  - Biliary atresia
  - Choledochal cyst
  - Inspissated bile syndrome
  - Spontaneous perforation of bile duct
- Cholestatic syndromes
  - Alagille syndrome
  - Progressive familial intrahepatic cholestasis
- Endocrinopathy
  - Hypothyroidism
  - Hypopituitarism
- Drug or toxin induced
  - Parenteral nutrition
  - Drugs
- Systemic disorder
  - Shock
  - Congenital heart disease/heart failure

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.

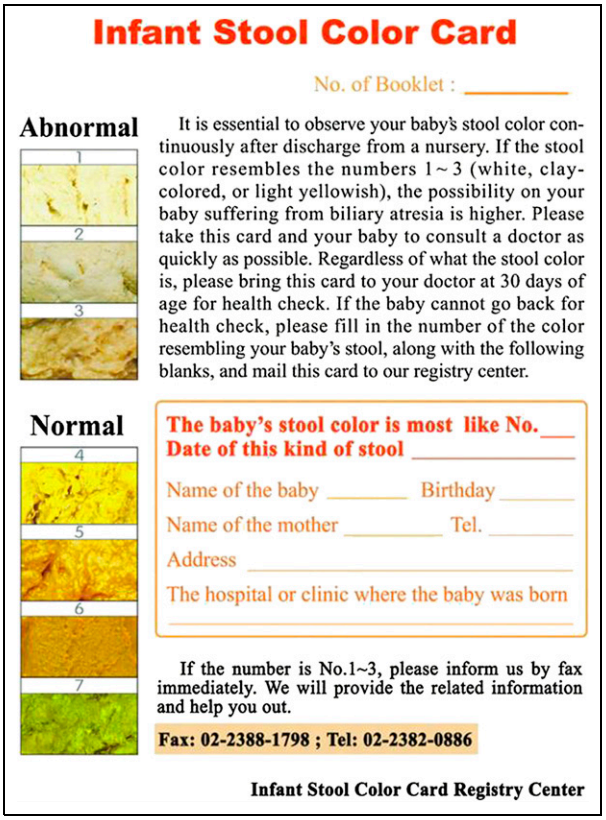

Figure 2. English version of Infant Stool Color Card. Distributed universally to parents of newborns in Taiwan. (Reprinted with permission from Chen SM, Chang MH, Du JC, et al. Screening for biliary atresia by infant stool color card in Taiwan. *Pediatrics*. 2006;117(4):1147–1154.)

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

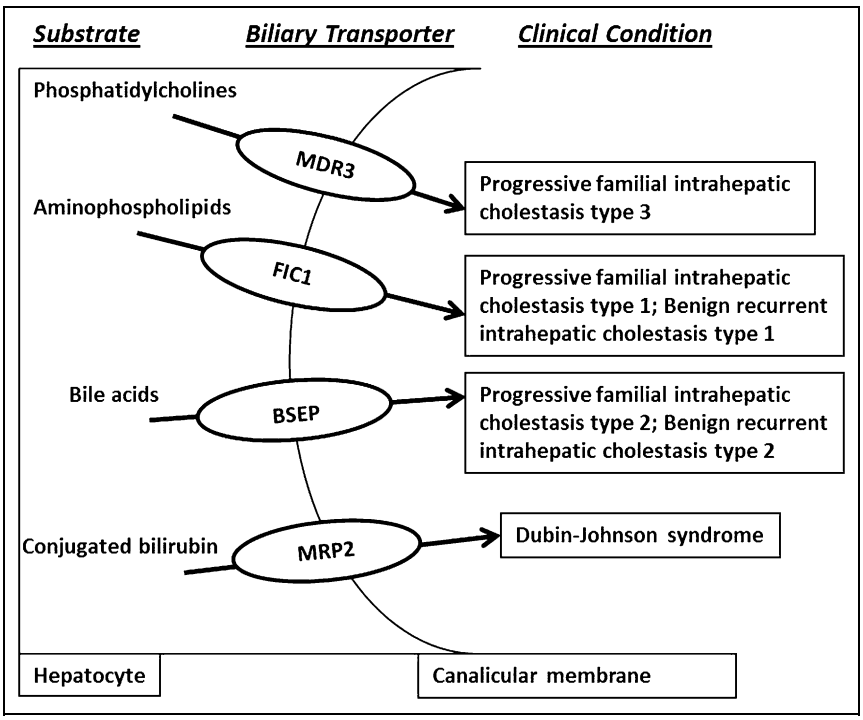

Figure 3. Canalicular membrane surface proteins, their substrates, and known associations with pediatric disease. (For a recent review, see Wagner M, Zollner G, Trauner M. New molecular insights into the mechanisms of cholestasis. *J Hepatol*. 2009;51:565–580.)

within hepatocytes. This mutation produces the clinical phenotype of cholestasis and pruritis 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. Pruritis, 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 medusae, 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.

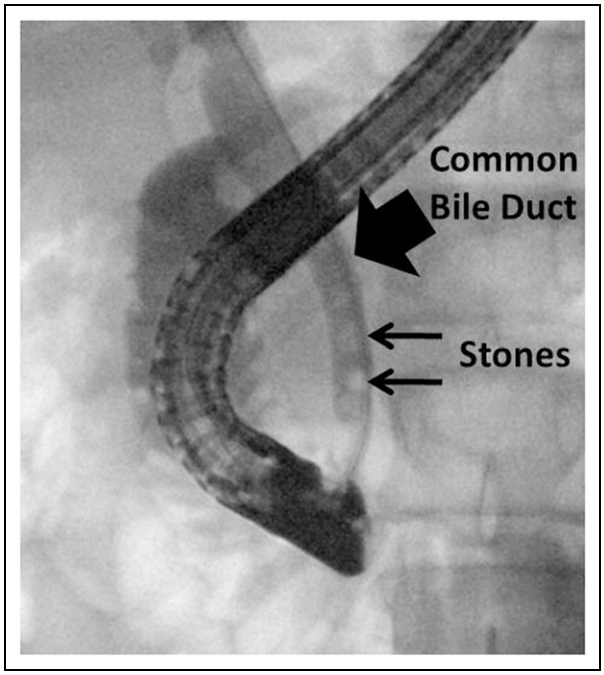

Figure 4. Contrast imaging of common bile duct via endoscopic retrograde cholangiopancreatography (ERCP) in a 12-year-old girl who has right upper quadrant abdominal pain and conjugated hyperbilirubinemia. Arrows show filling defects in the lumen of a dilated common bile duct, representing multiple gallstones in the common bile duct.

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 hepatis 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 in addition to conjugated hyperbilirubinemia 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, influenza virus, parvovirus, members of the enterovirus family, herpes simplex virus, and varicella virus also can lead to hepatic involvement, usually in the context of other clinical symptoms typical of the individual virus.

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 is 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 stricturing 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.

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.

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Suggested Reading

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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.

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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 1-1 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 prosthetic 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.

Conjugated Hyperbilirubinemia in Children

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