

Jaundice: Newborn to Age 2 Months

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Education Gap

Neonatal jaundice is a common clinical sign that indicates hyperbilirubinemia. Clinicians should become familiar with the differential diagnoses of hyperbilirubinemia in newborns and young infants and the importance of early referral of all patients with cholestatic jaundice to a pediatric gastroenterologist or hepatologist.

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

1. Recognize jaundice as a sign of hyperbilirubinemia and identify risk factors for neonatal jaundice.
2. Explain bilirubin metabolism.
3. Define hyperbilirubinemia and differentiate between the types of hyperbilirubinemia in newborns and young infants.
4. Explain the broad differential diagnoses of neonatal jaundice.
5. Recognize the importance of screening and postdischarge follow-up to prevent severe unconjugated hyperbilirubinemia.
6. Describe the management of neonatal jaundice, including cholestasis.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BA	biliary atresia
BUGT	bilirubin uridine diphosphate-glucuronosyltransferase
GALD	gestational alloimmune liver disease
GGT	γ -glutamyl transpeptidase
G6PD	glucose-6-phosphate dehydrogenase
Ig	immunoglobulin
IVIg	intravenous Ig
MCT	medium-chain triglyceride
MR	magnetic resonance
MRCP	MR cholangiopancreatography
PFIC	progressive familial intrahepatic cholestasis
PN	parenteral nutrition
PT	prothrombin time
TORCH	toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes simplex

The term *jaundice*, derived from the French word *jaune*, meaning yellow, is a yellowish discoloration of the skin, sclerae, and mucous membranes that is caused by tissue deposition of pigmented bilirubin. Jaundice is also known as *icterus*, from the ancient Greek word *ikteros*, signifying jaundice. Jaundice is a common clinical sign in newborns, especially during the first 2 weeks after birth. The first description of neonatal jaundice and bilirubin staining of the newborn brain goes back to the eighteenth century. The finding of jaundice on physical examination is an indicator of hyperbilirubinemia. This differs from carotene-emia, which can also manifest as a pale yellow-red skin color and is caused by a high level of carotene in the blood.

Older children and adults have a normal total serum bilirubin level less than 1.5 mg/dL (26 μ mol/L), with the conjugated fraction accounting for less than 5%. (1) Hyperbilirubinemia is defined as a total serum bilirubin level greater than 1.5 mg/dL (26 μ mol/L). In newborns, serum bilirubin universally exceeds this level for physiological reasons during the transitional period after birth. Jaundice becomes evident when the total serum bilirubin level reaches 5 mg/dL (86 μ mol/L). More than 60% of healthy newborns develop

neonatal jaundice and receive diagnoses of neonatal hyperbilirubinemia during the first week after birth. (2) In a more recent study, neonatal jaundice affected 84% of neonates born at least 35 weeks of gestation. (3) Jaundice usually begins on the face and progresses in a cephalocaudate fashion, for unknown reasons. The total bilirubin level roughly correlates with progression of jaundice (face, 4–8 mg/dL [68–137 $\mu\text{mol/L}$]; upper trunk, 5–12 mg/dL [86–205 $\mu\text{mol/L}$]; lower trunk, 8–16 mg/dL [137–274 $\mu\text{mol/L}$]; soles of the feet, >15 mg/dL [>257 $\mu\text{mol/L}$]). (4)

It is important to understand the metabolism of bilirubin to be able to identify the factors that lead to hyperbilirubinemia in the newborn (Fig 1). Bilirubin is the end product of heme degradation. (1)(5) Heme is produced by the breakdown of hemoglobin (70%–80%) and other hemoproteins (20%–30%). The conversion from heme to bilirubin occurs mainly in the reticuloendothelial system of the spleen, liver, and bone marrow. Heme is first converted to biliverdin by the microsomal enzyme heme oxygenase and then to unconjugated bilirubin by the cytosolic enzyme biliverdin reductase. (6) The unconjugated bilirubin is tightly bound to serum albumin and transported to the liver for conjugation and clearance. Once inside the hepatocyte, unconjugated bilirubin binds to a cytosolic binding protein and is then conjugated with glucuronic acids in the endoplasmic reticulum by the enzyme bilirubin uridine diphosphate-glucuronosyltransferase (BUGT) to form bilirubin mono- and diglucuronides, known as *conjugated bilirubin*. (7) The conjugated bilirubin is then excreted into the bile through the

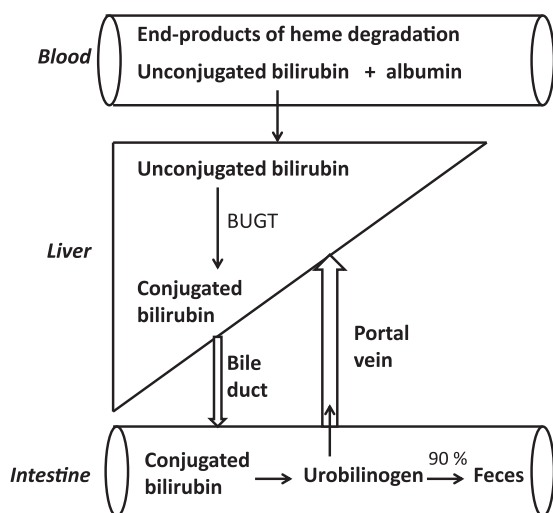


Figure 1. Diagram of bilirubin metabolism. BUGT=bilirubin uridine diphosphate-glucuronosyltransferase.

canalicular membrane, a process mediated by an adenosine triphosphate-dependent transporter system. This excreted bilirubin is further metabolized by intestinal bacterial flora to form urobilinoids, which are then eliminated in the feces. The conjugated bilirubin can also be deconjugated by bacterial or tissue β -glucuronidase converting back to unconjugated bilirubin, which is reabsorbed in the intestine, a process known as enterohepatic circulation. (8)

Jaundice is quantified by measuring transcutaneous and/or serum bilirubin levels. The transcutaneous bilirubin measurement is a quick and noninvasive tool to measure total bilirubin levels in newborns, and it can be used in the initial screening and follow-up. (9) This measurement has generally correlated well with the serum bilirubin level in both term and preterm newborns. (10)(11) However, clinicians should be aware that there are discrepancies between transcutaneous and serum bilirubin measurements, especially in African-American newborns. (12) When in doubt, clinicians should confirm the result by obtaining a serum bilirubin level. Serum bilirubin is conventionally measured in the clinical laboratory as total and direct bilirubin levels. Indirect bilirubin is calculated as the difference between the total bilirubin level and the direct bilirubin fraction. The terms “indirect” and “direct” are used interchangeably with unconjugated and conjugated bilirubin, respectively. Hyperbilirubinemia is classified as unconjugated or indirect and conjugated or direct hyperbilirubinemia. Neonatal unconjugated hyperbilirubinemia is often transient and benign; less frequently, it can be a manifestation of an underlying disorder. Furthermore, severe unconjugated hyperbilirubinemia can cause acute bilirubin encephalopathy and chronic irreversible neurological damage (kernicterus). Conjugated hyperbilirubinemia or cholestasis, on the other hand, is always pathologic and refers to a direct bilirubin level greater than 2 mg/dL (34 $\mu\text{mol/L}$) or greater than 20% of the total bilirubin level. The term *neonatal cholestasis* is defined as cholestasis or conjugated hyperbilirubinemia occurring within the first 3 months after birth.

Unconjugated and conjugated hyperbilirubinemia in newborns and young infants differ in their etiologic origins and management approaches. A brief list of the differential diagnoses of jaundice in newborns and young infants is presented in the Table.

UNCONJUGATED HYPERBILIRUBINEMIA

It is important to distinguish between benign transient neonatal jaundice and pathologic jaundice caused by underlying conditions on the basis of the newborn’s age, risk factors,

TABLE. Differential Diagnosis of Jaundice in Newborns and Young Infants

Unconjugated hyperbilirubinemia
Increased production of bilirubin:
<ul style="list-style-type: none"> • Physiological jaundice • Hemolysis: ABO or Rh incompatibility, erythrocyte membrane or enzyme defects, disseminated intravascular coagulopathy • Polycythemia • Cephalohematoma
Decreased hepatocellular uptake or conjugation:
<ul style="list-style-type: none"> • Physiological jaundice • Prematurity • Congenital hypothyroidism • Breast milk jaundice • Drugs • Gilbert syndrome and Crigler-Najjar syndrome
Conjugated hyperbilirubinemia
Obstruction of biliary system:
<ul style="list-style-type: none"> • Biliary atresia • Choledochal cyst • Alagille syndrome
Defect of bile acid synthesis or transport:
<ul style="list-style-type: none"> • Bile acid synthesis defect • PFIC-1, BESP defect, MDR3 defect
Metabolic liver diseases and systemic conditions:
<ul style="list-style-type: none"> • Gestational alloimmune liver disease • Metabolic liver disease: tyrosinemia, α_1-antitrypsin deficiency, galactosemia, mitochondrial hepatopathies • Infection: TORCH, sepsis, UTI • Acute liver injury: ischemia, hypoxia, acidosis • Parenteral nutrition-associated cholestasis

PFIC-1=progressive familial intrahepatic cholestasis-1; TORCH=toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes simplex; UTI=urinary tract infection.

and laboratory findings. It is also important to monitor the development of severe hyperbilirubinemia, which could potentially lead to acute and chronic bilirubin encephalopathy (kernicterus). Risk factors for severe hyperbilirubinemia include prematurity, maternal diabetes, race (Asians and Native Americans), male sex, trisomy 21, cephalohematoma,

oxytocin induction, breastfeeding, delayed passage of meconium, and a history of siblings who had neonatal jaundice. (3)(13) All term or near-term newborns are screened by using an hour-specific total serum or transcutaneous bilirubin nomogram (Fig 2). (14) This tool allows physicians to identify newborns at low (<40th percentile), intermediate (40th–95th percentiles), or high (>95th percentile for age) risk for developing severe hyperbilirubinemia and potential kernicterus. The nomogram is not designed for infants with hemolysis or other illness that requires intensive care.

Mild, unconjugated hyperbilirubinemia, also known as *physiological jaundice*, is common in the first few days after birth. It develops in newborns who are otherwise healthy, without any underlying conditions, and their total serum bilirubin levels rarely exceed 12 mg/dL (205 μ mol/L). Multiple factors can lead to physiological jaundice, including (a) increased bilirubin production from breakdown of red blood cells, which have a higher concentration and shorter lifespan at birth; (b) relatively low BUGT enzyme activity, so more bilirubin monoglucuronides than bilirubin diglucuronides are excreted into the bile; the bilirubin monoglucuronides are easily deconjugated and reabsorbed in the intestine; (15) and (c) lack of intestinal bacterial flora at birth to metabolize bilirubin to nonabsorbable urobilinoids. This type of jaundice typically does not appear in the first 24 hours after birth. It develops between the second and fourth days after birth, reaches its peak between the fourth and fifth days, and resolves within the first 2 weeks after birth. During the first week after birth, physiological jaundice often overlaps with breastfeeding jaundice, a phenomenon of indirect hyperbilirubinemia in breastfed infants caused mainly by inadequate breast milk intake and dehydration. (16)(17) In contrast, breast milk jaundice typically develops after the first week after birth and lasts longer than breastfeeding jaundice. The mechanism of breast milk jaundice is thought to be inhibition of BUGT enzyme activity and increased enterohepatic circulation caused by compounds in breast milk. (16) More recent data from Japan showed a variation in the gene encoding BUGT as a genetic basis of breast milk jaundice. (18) Breastfeeding interruption is no longer recommended for breast milk jaundice because of its low specificity as a diagnostic procedure. (19)

Nonphysiological jaundice should always be considered in the differential diagnosis of neonatal jaundice. Features such as early onset of jaundice, rapid progression, persistent jaundice beyond 2 weeks after birth, or association with other signs or symptoms suggest a pathologic process. In general, pathologic, unconjugated hyperbilirubinemia results from excessive production and/or abnormal hepatic

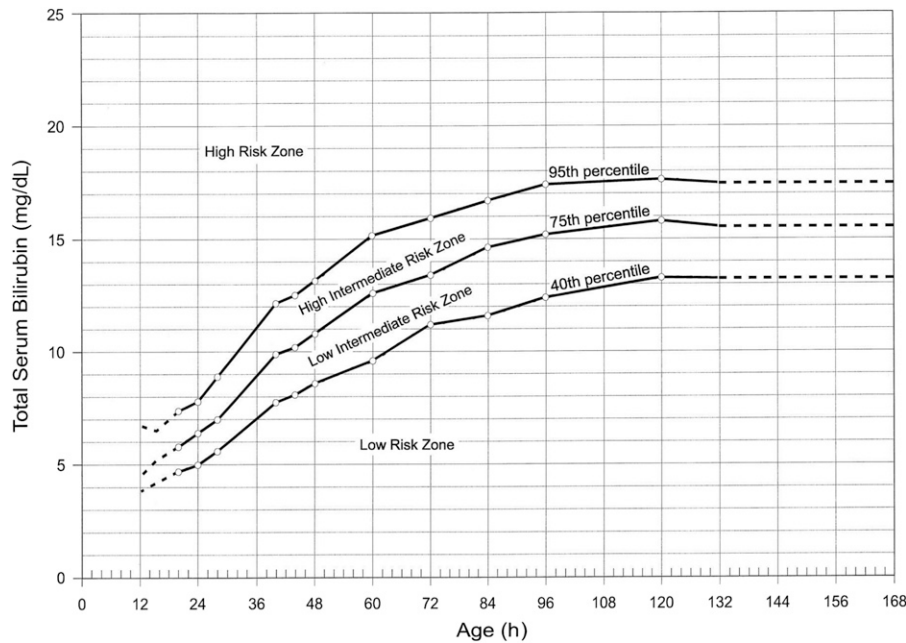


Figure 2. Serum bilirubin nomogram shows the risk designation for term and near-term well newborns on the basis of their hour-specific serum bilirubin values (14).

clearance of bilirubin. To screen newborns for pathologic jaundice, the initial diagnostic tests should include a total and direct bilirubin level, complete blood cell count, reticulocyte count, blood grouping, and Coombs test. Laboratory findings to support the diagnosis of hemolysis include anemia, a positive direct Coombs test result, a high reticulocyte count, an increased unconjugated bilirubin level, and presence of fragmented red blood cells on the blood smear. Severe, unconjugated hyperbilirubinemia can lead to acute or chronic bilirubin encephalopathy. Under normal circumstances, unconjugated bilirubin is hydrophobic and is albumin-bound. When an excessive amount of unconjugated bilirubin is produced, the unbound bilirubin can cross the brain-blood barrier, resulting in brain toxicity. Affected infants can present with symptoms such as lethargy, hypotonia, and decreased suck, known as *acute bilirubin encephalopathy*. This process can be reversible if treated promptly. However, it may progress to kernicterus, an irreversible brain damage with cerebral palsy, sensorineural hearing loss, posturing, arching, and seizures. (20)(21)

Hemolysis can cause rapid and excessive bilirubin production, which can result in neonatal jaundice. This type of hyperbilirubinemia usually starts within the first 24 hours after birth and often requires intensive phototherapy and exchange transfusion to prevent kernicterus. Hemolysis is often seen in association with immune-mediated maternal-fetal blood type incompatibility or non-immune-mediated

conditions such as hemoglobinopathies, erythrocyte membrane defects, and enzyme deficiencies. ABO and Rh incompatibility are the two most common types of immune-mediated maternal-fetal blood type incompatibility that can lead to hemolysis in the newborn. ABO incompatibility occurs in approximately 15% of all pregnancies but results in hemolytic disease in only 3% of newborns, with less than 0.1% of infants needing exchange transfusion. (22) Hemolysis secondary to ABO incompatibility is usually seen in newborns with blood type A or B who are born to mothers with blood type O who have anti-A or anti-B immunoglobulin (Ig) G antibodies, which can pass through the placenta. Hemolytic disease in maternal-fetal Rh (D) antigen incompatibility can also develop after an Rh-negative mother has become sensitized after exposure to Rh-positive fetal blood during a previous pregnancy. Rh incompatibility is less common, but it is usually more severe than ABO incompatibility. (23) In the United States, the prevalence of the Rh-negative genotype is approximately 15% in white subjects, 5% in African-American subjects, and less than 1% in Asian subjects. (24) Rh incompatibility occurs in approximately 1.06 per 1,000 live births. (25) These neonates usually present with jaundice in the first hours after birth, anemia, and hepatosplenomegaly. In severe cases, neonates may be born with fetal hydrops as the result of intrauterine fetal hemolysis. The prophylactic use of anti-D γ -globulin (RhoGAM; Kedrion Biopharma, Fort Lee, NJ) in Rh-negative mothers has significantly

decreased the incidence of hemolytic disease of the newborn to less than 0.11% of Rh-negative pregnancies. (26)(27)(28)

Non-immune-mediated causes of hemolysis that can lead to neonatal jaundice and unconjugated hyperbilirubinemia include hemoglobinopathies, erythrocyte membrane defects, enzyme deficiencies, polycythemia, and cephalohematoma. Hemoglobinopathies such as α -thalassemia should be suspected in newborns with jaundice and a moderate hypochromic, microcytic, hemolytic anemia. (29) Hereditary spherocytosis, a red blood cell membrane defect, should be suspected if there is a positive family history, and the diagnosis can be confirmed with an osmotic fragility test. Erythrocyte enzyme defects, such as glucose-6-phosphate dehydrogenase (G6PD) or pyruvate kinase deficiency, may cause hemolysis in the newborn period. (29)(30) A newborn screening for G6PD deficiency is available; however, routine screening for this condition occurs in only a few states. G6PD deficiency is X-linked. Severe neonatal hyperbilirubinemia with potential kernicterus may develop in the presence of oxidant stressors, such as infections. All newborns with G6PD deficiency should be closely monitored for the development of severe jaundice before and after discharge. Neonatal polycythemia can lead to increased bilirubin production due to an absolute increase in red blood cell mass. It occurs in 0.5% to 1.5% of newborns and results in unconjugated hyperbilirubinemia in 22% to 33% of affected babies. (31) Cephalohematomas can result in increased bilirubin production from rapid breakdown of red blood cells in the extravascular space.

Decreased hepatocellular uptake or conjugation of bilirubin is another mechanism that can lead to unconjugated hyperbilirubinemia. Drugs such as aspirin, cephalosporins, and sulfonamides can impair bilirubin transport by altering bilirubin-albumin binding. (32) Rifampin has been shown to competitively inhibit hepatocellular uptake of bilirubin. (33) In a number of clinical conditions, such as physiological jaundice, breast milk jaundice, and congenital hypothyroidism, unconjugated hyperbilirubinemia is at least in part associated with decreased conjugation of bilirubin, as a result of decreased or delayed maturation of BUGT enzyme activity. (15)(34)

Gilbert and Crigler-Najjar syndromes are 2 types of familial unconjugated hyperbilirubinemia caused by a number of mutations in the gene encoding for BUGT. (35) Gilbert syndrome is a common inherited condition characterized by mild, unconjugated hyperbilirubinemia and caused by a reduced level of expression of the gene. This is a benign condition that affects 7% of the general population. It is inherited as an autosomal dominant trait, although an autosomal recessive pattern has also been described. Gilbert syndrome is usually diagnosed during or after adolescence;

however, it can present as transient neonatal hyperbilirubinemia. Genetic testing is available to diagnose Gilbert syndrome. Crigler-Najjar syndrome is a rare familial form of unconjugated hyperbilirubinemia inherited as autosomal recessive disease, and it is caused by either absent (type I) or decreased (type II) BUGT enzyme activity. Crigler-Najjar syndrome type I manifests with severe nonhemolytic jaundice in the first hours after birth. In Crigler-Najjar syndrome type II, jaundice is usually less severe. The main risk of this condition is kernicterus. Clinical suspicion and DNA sequencing for known mutations can help establish the diagnosis. Patients with Crigler-Najjar syndrome type I require long-term phototherapy or liver transplantation to prevent kernicterus. Unconjugated hyperbilirubinemia may improve with the use of phenobarbital in patients with Crigler-Najjar syndrome type II but not type I.

CONJUGATED HYPERBILIRUBINEMIA

Conjugated hyperbilirubinemia, also known as *cholestasis*, is always pathologic. It is caused by impaired bile formation in the liver and/or interrupted bile flow in the intra- or extrahepatic biliary system. (36) Physicians need to identify the cause of cholestasis, whether it is a primary liver condition, such as intrahepatic diseases and extrahepatic biliary obstruction, or a systemic condition that affects the liver. Full-term newborns with prolonged jaundice beyond 2 weeks after birth require detailed clinical evaluation to determine the type of hyperbilirubinemia and to identify underlying etiologic origins. The incidence of neonatal cholestatic jaundice is 1 in 2,500 live births. (37)(38) Various conditions are associated with cholestatic jaundice, including primary hepatobiliary disorders, genetic or metabolic diseases, ischemic injury to the liver, infections, and drug toxicity. (39) The most common cause of neonatal cholestasis is biliary atresia (35%–41%). Other conditions are progressive familial intrahepatic cholestasis (10%), preterm birth (10%), metabolic and endocrinologic disorders (9%–17%), Alagille syndrome (2%–6%), infectious diseases (1%–9%), mitochondrial hepatopathy (2%), biliary sludge (2%), and idiopathic cases, including idiopathic neonatal hepatitis (13%–30%). (40) As more and more specific etiologic origins of neonatal cholestasis have been identified, the percentage of idiopathic cases has decreased significantly in recent years.

Biliary atresia (BA) is an ascending inflammatory process of both the intra- and extrahepatic bile ducts that can lead to progressive obliterative scarring and result in biliary cirrhosis. (41) It occurs in 1 in 6,000 to 18,000 live births. In some cases, it may be part of a syndrome associated with other congenital malformations, such as polysplenia, double

spleens, or asplenia, known as *BA splenic malformation syndrome*. (42) Other malformations in this syndromic BA include situs inversus, cardiac defects, intestinal malrotation, or anomalies of the portal vein and hepatic artery. Affected neonates typically present around 2 to 4 weeks of age with cholestasis and acholic stools; however, in an early stage, the stools may still have some bile pigment. These newborns need prompt referral and evaluation for BA, since the prognosis is better with early diagnosis and timely surgery. (43) Abdominal ultrasonography is a useful screening tool. The absence of the gallbladder or the appearance of the “triangular cord” sign (echogenic cord of fibrous tissue) at the hilar region is suggestive of BA. (44) However, the presence of a gallbladder at ultrasonography does not exclude this condition, since a small number of patients with BA may have an atretic gallbladder. A percutaneous liver biopsy is often performed to further evaluate patients with suspected BA. The typical histopathologic features are bile duct proliferation, portal inflammation, bile plugs, and fibrosis. When the diagnosis of BA is highly suspected, patients undergo a laparotomy with an intraoperative cholangiogram to confirm the diagnosis. Once the diagnosis is confirmed, the surgeon will then perform a hepatoportoenterostomy (Kasai procedure). The success rate of the procedure in reestablishing bile flow is significant when performed before 8 weeks after birth, which underscores the importance of early diagnosis of BA.

Choledochal cysts are rare congenital anomalies of the biliary tract characterized by cystic dilation of the intra- and/or extrahepatic biliary tree. They are categorized into 5 different types, based on the location of the cystic lesions. (45) Choledochal cysts may be detected at any age, with 18% of cases diagnosed during infancy. (46) These cystic changes of the bile ducts can be detected at ultrasonography and can be further characterized with magnetic resonance (MR) cholangiopancreatography (MRCP).

Alagille syndrome, also known as *arteriohepatic dysplasia*, is inherited as an autosomal dominant condition with variable penetrance. Alagille syndrome occurs in 1 in 70,000 live births, and almost all patients have a mutation in the *JAG1* gene. Cholestatic jaundice is usually present during the newborn period or early infancy. This condition is characterized by paucity of the intrahepatic bile ducts at liver histologic examination, peripheral pulmonary stenosis, butterfly vertebrae, peculiar faces, growth retardation, and posterior embryotoxon of the eye, which is a prominent, centrally positioned Schwalbe ring of eyes (a circular bundle of sclera at the level of termination of the deep trabeculae). (47)

Gestational alloimmune liver disease (GALD, previously known as *neonatal hemochromatosis*) is a rare, idiopathic syndrome characterized by liver disease of antenatal onset and

excess iron deposition in extrahepatic sites. (48)(49) Neonates with GALD are usually born preterm with intrauterine growth retardation. In most cases, signs and symptoms of neonatal liver failure are present at birth or develop soon after birth. GALD should be suspected in every case of neonatal liver failure. Typical clinical features are hypoglycemia, hypoalbuminemia, profound coagulopathy, and cholestatic jaundice. The laboratory screening test includes serum iron, ferritin, and transferrin levels, as well as transferrin saturation. The diagnosis of GALD is established on the basis of the presence of extrahepatic siderosis. The buccal punch biopsy is often used to identify iron deposition in salivary glands. T2-weighted MR imaging can also be used to document siderosis in the liver and pancreas. The treatment for GALD is intravenous Ig (IVIg) and exchange transfusion. In some cases, patients may need liver transplantation.

Defects of bile acid synthesis and transport have become increasingly recognized in recent years owing to advancing molecular techniques that can be used to discover specific gene mutations for specific defects. (38) Patients with these conditions develop progressive liver disease with cholestatic jaundice during the newborn period or early infancy. Bile acid synthesis defects are rare autosomal recessive disorders for which specific enzyme defects lead to primary failure to synthesize bile acids. (50) Patients with this condition have undetectable serum bile acid level. Quantitative measurement of the serum bile acid level can be used to screen for the bile acid synthesis defect and differentiate it from all other cholestatic conditions in which the bile acid level is always high. Progressive familial intrahepatic cholestasis (PFIC) has been identified as a distinct group of conditions involving intrahepatic cholestasis due to bile acid transport defects, leading to impairment of bile formation. (51) Three types of PFIC have been identified, including PFIC-1, also known as *Byler disease* (defect at the protein level is not yet identified), PFIC-2 (bile salt export pump defect), and PFIC-3 (multidrug-resistant protein defect). (52)(53)(54) Physicians should suspect PFIC-1 or PFIC-2 in patients with the unique laboratory finding of a normal or low γ -glutamyl transpeptidase (GGT) value in the setting of cholestasis. Progression to cirrhosis and liver failure in early infancy is common, especially in patients with PFIC-1 and PFIC-2.

Metabolic liver diseases usually present during infancy and should always be considered in a differential diagnosis of a newborn or young infant with cholestasis, especially when presenting with hypoglycemia, hyperammonemia, and/or lactic acidosis. (55) Tyrosinemia type 1, also known as *hepatorenal tyrosinemia*, is a rare disorder that can affect the liver, kidneys, and peripheral nerves. (56) It is caused by deficiency of fumarylacetoacetate hydrolase, an enzyme involved in tyrosine degradation. This results in tissue

accumulation of tyrosine and other intermediate metabolites. The clinical presentation can range from severe liver disease or acute liver failure in early infancy to chronic liver disease later in life. The striking laboratory finding is a markedly increased α -fetoprotein level. The presence of succinylacetone in urine or blood is pathognomonic for this condition. Early diagnosis is important, since specific medical therapy can delay progression of the liver disease.

α_1 -antitrypsin deficiency is a relatively common genetic disorder, with the homozygous PiZZ phenotype found in 1 in 1,600 to 2,000 live births. Only 10% of patients with α_1 -antitrypsin deficiency will develop clinical signs and symptoms of liver disease. (57) This condition is the most common inherited cause of neonatal liver disease. (58) Injury to the liver is thought to be related to the toxic effect of retained mutant α_1 -antitrypsin PiZZ molecule in the endoplasmic reticulum of hepatocytes. Patients typically present with cholestatic jaundice in the first few months after birth, and the diagnosis is established by identifying a serum α_1 -antitrypsin PiZZ phenotype. The treatment of α_1 -antitrypsin deficiency-associated liver disease is largely supportive, and liver transplantation should be considered in patients who develop liver failure from this condition.

Galactosemia is an inborn error of galactose metabolism. It is inherited as an autosomal recessive trait, and its estimated occurrence is 1 in 60,000 live births. The classic transferase-deficiency galactosemia can affect multiple organs, including the liver, kidneys, brain, eyes, intestines, and gonads. The hepatocellular damage in galactosemia is caused by accumulation of toxic metabolites of both galactose-1-phosphate and galactitol. The clinical presentation of this condition varies from mild liver disease to acute liver failure in the neonatal period. Major signs and symptoms are hepatomegaly, jaundice, vomiting, cataract, liver dysfunction, and *Escherichia coli* sepsis. (59) The newborn screening can be used identify most of the patients with galactosemia. Patients with this condition should be treated by avoidance of formulas that contain galactose and lactose. Breast milk also contains lactose, so breastfeeding is contraindicated in patients with galactosemia.

Primary mitochondrial hepatopathies are caused by a variety of defects, including mitochondrial DNA depletion, respiratory chain defects, fatty acid oxidation defects, and mitochondrial membrane enzyme defects. (60) In addition to signs and symptoms of liver disease, these patients often have various degrees of neuromuscular involvement and may have marked lactic acidosis. Symptoms usually develop within the first few months after birth.

Congenital "TORCH" infections, including toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella,

cytomegalovirus, and herpes simplex, have been associated with neonatal cholestasis. Infants with TORCH infections often have low birth weight, hepatosplenomegaly, and cutaneous manifestations, as well as ophthalmologic and central nervous system involvement. Common laboratory findings include anemia, thrombocytopenia, increased transaminase levels, and conjugated hyperbilirubinemia. The diagnosis is based on viral culture results, serologic titers, imaging studies, and ophthalmologic examination findings. Newborns who receive a diagnosis of sepsis can present with cholestatic jaundice and hepatocellular dysfunction. (61) The most frequent bacterial organisms associated with conjugated hyperbilirubinemia in neonatal sepsis are *E coli*, group B *Streptococcus*, and *Listeria monocytogenes*. Conjugated hyperbilirubinemia may also develop in newborns and young infants with urinary tract infections.

Conditions that alter the systemic circulation, such as cardiopulmonary arrest, birth asphyxia, hypoxia, shock, and severe metabolic acidosis, may cause an acute ischemic insult to the liver that can lead to hepatocyte damage. Newborns are more susceptible to this type of injury, and these patients may develop rapid and marked increase of serum transaminase levels and direct hyperbilirubinemia within 24 to 48 hours after the initial insult. In most cases, the liver chemistry test will normalize once the initial insult is corrected, although a small number of patients may progress to acute liver failure.

Cholestatic jaundice is one of the major complications associated with prolonged course (longer than 2 weeks) of parenteral nutrition (PN). (62) There is a strong association between the lipid content of PN and cholestasis, although many factors are thought to contribute to PN-associated cholestasis, including lack of enteral feedings, immaturity of the hepatobiliary system, and sepsis. The incidence of PN-associated cholestasis has declined in recent years because of decreased dosing of intravenous lipids and increasing use of fish oil-based lipid emulsion. Intravenous lipid restriction is currently recommended for infants who have developed PN-associated cholestasis. (63) Cholestasis and abnormalities in liver chemistry test results usually resolve within 4 to 6 months after discontinuation of PN in most infants. In severe cases, progression to end-stage liver disease may occur.

EVALUATION

The initial step in the evaluation of an infant with jaundice should focus on distinguishing between unconjugated and conjugated hyperbilirubinemia. This differentiation will help in selecting appropriate laboratory tests and imaging studies. A detailed history is essential when evaluating a newborn

with jaundice, as the information obtained may help the clinician identify a possible etiologic origin. The prenatal care history, maternal blood test results, and birth history will help identify potential risk factors. A family history is also important and should include information such as neonatal jaundice, chronic liver diseases, hemolysis, or metabolic diseases. In addition, the newborn screening result should be reviewed as part of the initial evaluation, since a panel of different metabolic diseases is included in the test. In newborns with unconjugated hyperbilirubinemia, the initial screening should focus on identifying any underlying pathologic conditions, such as hemolytic diseases. In newborns with conjugated hyperbilirubinemia, the initial diagnostic assessment should include liver tests, coagulation profile, and complete abdominal ultrasonographic examination.

In general, newborns with jaundice due to unconjugated hyperbilirubinemia usually present with a bright yellow-colored skin, while patients with jaundice due to conjugated hyperbilirubinemia present with a dark yellow-greenish-colored skin. Patients should undergo a complete physical examination, with special attention given to the general appearance, growth, and development; signs of cardiovascular dysfunction; neurological involvement; and organomegaly. A careful abdominal examination should be performed to identify the presence of an enlarged liver or spleen, intra-abdominal masses, or ascites. The size and character of the liver should be carefully determined. The liver in newborns and infants is a large organ relative to body size and may be palpable on examination. The enlarged liver is usually palpable more than 2 cm below the right costal margin. The consistency and character of the liver edge may help determine the stage of the underlying liver disease. An end-stage cirrhotic liver may have a hard and irregular edge; however, its edge is not always palpable. Splenomegaly in a patient with underlying liver disease is suggestive of portal hypertension, especially in the presence of ascites and thrombocytopenia. Other physical findings may indicate a particular etiologic origin, such as a skin rash for congenital cytomegalovirus infection, or characteristic facial features of Alagille syndrome, although it may be too early to see in a newborn. The stool color is the most important clinical observation in an infant with jaundice. Infants with pale or acholic stools require an urgent referral to evaluate the presence of BA or other biliary obstructive conditions.

The initial diagnostic screening should focus on a complete blood cell count, reticulocyte count, Coombs test, liver testing, and coagulation profile. Thrombocytopenia is typically seen in patients with hypersplenism and portal hypertension. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are markers of hepatocellular

injury. (64) Compared to AST, ALT is a more specific indicator of hepatocyte injury, as AST may be increased in other conditions, such as hemolysis and myocardial or skeletal muscle injuries. A determination of normal creatinine phosphokinase level will ensure that the ALT and AST increases are not due to muscle diseases. In general, a rapid, marked increase in AST and ALT level occurs in acute ischemia and hypoxia-induced hepatic necrosis. (65) A declining AST and ALT level usually indicates hepatocyte recovery. However, if seen in association with worsening liver synthetic function in the course of acute liver failure, this may be an ominous sign of massive hepatic necrosis, with few viable hepatocytes remaining to further release these enzymes. (66) AST and ALT levels are less useful in patients with chronic end-stage liver disease, since they can be normal or only slightly increased in the presence of cirrhosis. Normal GGT values in newborns may be 5 to 8 times greater than those in adults. (67) In most hepatobiliary diseases, both GGT and alkaline phosphatase levels are increased, with the exception of a normal or low GGT value in PFIC-1 and PFIC-2.

The prothrombin time (PT) and serum albumin level are used to evaluate the hepatic synthetic function. An abnormal PT results from an impaired hepatic synthesis of coagulation factors I, II, V, VII, and X and/or deficiency of vitamin K. Parenteral administration of vitamin K generally normalizes a prolonged PT in patients with vitamin K deficiency related to cholestasis, but not in patients with impaired hepatic synthetic function. An increased PT not corrected by vitamin K suggests the possibility of acute or chronic liver failure. Hypoalbuminemia may be seen in patients with acute and chronic liver diseases. In early stages of acute liver failure, the serum albumin level may remain normal, since albumin has a long half-life of approximately 21 days.

On the basis of the gathered clinical information and results of the initial tests, further evaluation for conjugated hyperbilirubinemia, including imaging studies and disease-specific tests, may be warranted, depending on clinical suspicion. Additional studies may include serum bile acids, amino acids, blood and urine cultures, TORCH, toxin and/or drug screening, α_1 -antitrypsin phenotype, urine succinylacetone, and PFIC genetic testing.

Ultrasonography is a useful initial imaging study in the assessment of the intra- and extrahepatobiliary system in newborns with cholestatic jaundice. (68) This simple, non-invasive study may provide information suggestive of the etiologic origin of jaundice, such as BA, choledochal cysts, gallstones, or biliary sludge. A hepatobiliary iminodiacetic acid scan may also serve as an additional diagnostic tool to assess the bile duct patency. To enhance the scan result,

patients require prior treatment with 5 mg/kg of phenobarbital per day for 5 days. The hepatobiliary iminodiacetic acid scan has been used in differentiating BA from other causes of neonatal cholestasis; however, its use is limited because of low specificity. (69) MRCP can be used to further identify abnormalities of the intra- and extrahepatic system, and T2-weighted MR imaging may help in diagnosing GALD by demonstrating siderosis in the extrahepatic tissue, such as the pancreas. Endoscopic retrograde cholangiopancreatography provides information similar to MRCP; however, it is a technically challenging procedure to perform in small infants and should be reserved for patients who need a possible therapeutic intervention, such as biliary irrigation and sphincterotomy for sludge or stones. (70) Both MRCP and endoscopic retrograde cholangiopancreatography will require general anesthesia in neonates and infants.

Liver biopsy is an invaluable diagnostic tool in the evaluation of infants with cholestatic jaundice. It should be considered in patients with persistent cholestasis and abnormal liver chemistry tests, especially when conventional laboratory and imaging studies do not lead to a specific diagnosis. A biopsy provides information on the histology and architecture of the liver and often demonstrates a possible specific diagnosis. Percutaneous liver biopsy is commonly performed in early infancy, between 4 and 6 weeks after birth, to ensure that there are no delays in the surgical intervention if the diagnosis of BA is suspected. In infants with acute liver failure, a percutaneous liver biopsy is relatively contraindicated because of a high risk of bleeding. When needed, a transjugular liver biopsy should be performed by an interventional radiologist.

MANAGEMENT

Newborns with jaundice should have bilirubin levels closely monitored before and after discharge from the hospital to prevent potentially serious complications of hyperbilirubinemia. The practice guideline published by the American Academy of Pediatrics (AAP) in 2004 recommended that all neonates born at at least 35 weeks of gestation be assessed before discharge for the risk of severe hyperbilirubinemia by using clinical risk factors and/or bilirubin measurements. (20) This guideline provides a framework in detecting and managing neonatal hyperbilirubinemia to prevent kernicterus. In a 2009 update, the AAP suggested combined universal screening of serum and/or transcutaneous bilirubin measurements with clinical risk factors as a predischarge assessment. (71)(72) Any infant discharged before the age of 72 hours should be examined within 2 days of discharge. Phototherapy or exchange

transfusion is considered for newborns with severe hyperbilirubinemia. The decision to initiate phototherapy is based on the newborn's age, risk factors, and total serum bilirubin levels, as indicated on the bilirubin nomogram (Fig 2). The initiation of phototherapy is usually warranted when the serum bilirubin level is in the high-risk zone. Phototherapy can be used to convert unconjugated bilirubin to less toxic water-soluble photoisomers that are excreted in the bile and urine. Phototherapy has no effect on conjugated bilirubin and is not indicated in patients with cholestatic jaundice. When used in these patients, phototherapy can lead to the development of gray-brown-colored skin, giving an appearance known as *bronze neonates*. IVIg has been shown to reduce the need for exchange transfusions in ABO and Rh hemolytic diseases. The AAP guideline recommends administration of IVIg (0.5–1.0 g/kg over 2 hours) if the total serum bilirubin level is increasing despite intensive phototherapy or if the total serum bilirubin level is within 2 to 3 mg/dL (34–51 $\mu\text{mol/L}$) of the exchange level. If necessary, this dose can be repeated in 12 hours. Exchange transfusion is reserved for newborns in whom total serum bilirubin levels do not decrease with intensive phototherapy and the level reaches 25 mg/dL (428 $\mu\text{mol/L}$) or higher at any time. This is a medical emergency, and the infant should be admitted immediately. In newborns with breastfeeding jaundice, the feeding frequency should be increased, and supplementation with infant formula or donor human milk from human milk banks should be considered to provide a higher caloric intake and to stimulate stool production, therefore decreasing bilirubin reabsorption.

The treatment of patients with conjugated hyperbilirubinemia should focus on correcting the underlying conditions and optimizing nutrition. Malabsorption of fat and fat-soluble vitamins is a common complication in infants with cholestasis. Bile acids are important molecules for the solubilization of dietary lipids prior to absorption, and patients with cholestasis have impaired bile excretion that can result in decreased availability of bile acids in the intestine. Unlike long-chain triglycerides, which require bile acid micelles for solubilization, medium-chain triglycerides (MCTs) are relatively water soluble and are directly absorbed into the portal system. For this reason, a diet that contains high levels of MCTs should be used to promote growth in infants with cholestasis. Infant formulas with a relatively high MCT concentration, such as Alimentum (Abbott, Lake Forest, Illinois) and Pregestimil (MeadJohnson, Ramsey, New Jersey), are frequently used in cholestatic infants. Enfaport (MeadJohnson, Ramsey, New Jersey) is a new, specialized formula that has a high MCT content but contains sufficient essential fatty acids to avoid essential

fatty acid deficiency. Supplementation of fat-soluble vitamins A, D, E, and K is essential. Serum vitamin levels should be routinely monitored, since these patients may still have biochemical evidence of fat-soluble vitamin deficiency despite supplementation. Ursodeoxycholic acid (ursodiol) is commonly used for intrahepatic cholestasis, but it is contraindicated for extrahepatic biliary obstruction.

Pediatric liver transplantation is now an accepted therapy for many life-threatening liver diseases. (73) Whole-liver, split-liver, or living-donor transplantation has been successful in infants. Indications for liver transplantation in infants may include neonatal and infant liver failure caused by GALD, metabolic liver diseases, and bile acid synthesis or transport defects. Early referral to a liver transplant center is key to improve the outcome of these patients.

Summary

1. On the basis of moderate research and American Academy of Pediatrics guidelines, universal screening with bilirubin measurements, combined with risk factor assessment, can improve outcomes of newborns with unconjugated hyperbilirubinemia. The bilirubin nomogram results can guide clinicians in determining low-, intermediate-, and high-risk zones of hyperbilirubinemia according to postnatal age in hours.

2. On the basis of strong research, prompt diagnosis and proper management of severe, unconjugated hyperbilirubinemia are critical to prevent acute bilirubin encephalopathy and kernicterus.
3. On the basis of moderate research, there are differences in the presentation and management of breastfeeding and breast milk jaundice.
4. On the basis of strong research, biliary atresia is the most common cause of cholestasis in infants younger than 2 months of age. The stool color is an important part of the initial evaluation in infants with cholestasis, and pale or acholic stool is highly suspicious for biliary atresia or other biliary obstruction. Early referral to a subspecialist is important to improve outcome.
5. On the basis of moderate research and consensus, gestational alloimmune liver disease (GALD) is a rare neonatal condition with early onset of cholestasis during the first week after birth. Intravenous immunoglobulin should be given as soon as possible in newborns with suspected GALD to decrease the risk of mortality.
6. On the basis of strong research, malabsorption of fat and fat-soluble vitamins is common in patients with cholestasis. It is essential to provide supplementation with medium-chain triglyceride oil and fat-soluble vitamins and to closely monitor serum vitamin levels.

References for this article are at <http://pedsinreview.aappublications.org/content/38/11/499>.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

- Chapter 170: Jaundice - <https://pediatriccare.solutions.aap.org/chapter.aspx?sectionid=108725307&bookid=1626>

Point-of-Care Quick Reference

- Jaundice - <https://pediatriccare.solutions.aap.org/content.aspx?gbosid=165445>

Parent Resources from the AAP at HealthyChildren.org

- Jaundice in Newborns: Parent FAQs: <https://www.healthychildren.org/English/ages-stages/baby/Pages/Jaundice.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

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1. Upon making morning rounds in the newborn nursery, the pediatric intern presents to you a male newborn admitted the previous evening. He was born at 36 3/7 weeks' gestation via vacuum-assisted delivery. He is now 16 hours old. Physical examination shows facial features consistent with trisomy 21 and bilateral cephalohematomas, but no cardiac murmur. He has demonstrated mature breastfeeding skills. His bilirubin level is 5.6 mg/dL. In explaining to the intern the pathophysiology of this patient's jaundice, which of the following is the most accurate statement regarding bilirubin metabolism at the cellular level?
 - A. Bilirubin that reaches the intestine typically does not undergo further metabolism.
 - B. Conjugation of bilirubin in the newborn is initiated in the serum.
 - C. Intestinal β -glucuronidase and bacteria play an important role in enterohepatic circulation.
 - D. Once conjugated, bilirubin is excreted into the bile via an adenosine diphosphate-mediated process.
 - E. Unconjugated bilirubin is conjugated with glucuronic acids via hepatic β -glucuronidase.
2. A gravida 1, para 1 mother with gestational diabetes delivers a 4-kg male neonate via cesarean section at 39 weeks' gestation. The newborn is breastfeeding inadequately, with poor latch. Upon routine evaluation of vital signs, the charge nurse in the newborn nursery notes jaundice on physical examination at 6 hours of age. She notifies the attending pediatrician of this finding. You order a total and direct bilirubin level, complete blood count, reticulocyte count, blood group, and Coombs test. Which of the following laboratory test results is most likely suggestive of hemolysis as a cause for hyperbilirubinemia in this patient?
 - A. Elevated conjugated bilirubin level.
 - B. Fragmented red blood cells on a peripheral smear.
 - C. Hematocrit level of 55%.
 - D. Negative direct Coombs test result.
 - E. Normal to low reticulocyte count.
3. Six hours after birth, a male newborn appears jaundiced. The baby is the product of a full-term pregnancy and a spontaneous vaginal delivery in a 24-year-old gravida 1, para 0 mom, who is rapid plasma reagin nonreactive, group B *Streptococcus* negative, hepatitis B surface antigen negative, and rubella immune and who received prenatal care. The baby is breastfeeding well. Physical examination findings are only significant for jaundice and scleral icterus. There are no dysmorphic features, no cephalohematoma, and no hepatosplenomegaly. Chemistry panel findings are clinically significant for severe unconjugated hyperbilirubinemia. The direct Coombs test result is negative. Reticulocyte count and smear findings are normal. You start a workup on this patient to rule out Crigler-Najjar syndrome type I. DNA sequencing for known mutations is ordered, and results are pending. In confirming the diagnosis of Crigler-Najjar syndrome type I, which of the following is most likely to be consistent with this diagnosis?
 - A. Absent bilirubin uridine diphosphate-glucuronosyltransferase enzyme activity.
 - B. Autosomal dominant inheritance.
 - C. Immediate response to treatment with phenobarbital.
 - D. Low risk for kernicterus.
 - E. Presence of hemolytic jaundice.

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4. A mother brings her 3-week-old daughter to the emergency department (ED) for evaluation of a "greenish" color of her skin. She has been eating poorly over the previous 36 hours. She has not produced stools during this time. The newborn was delivered at 41 weeks' gestation, without complications. She was discharged at 48 hours of age. In the ED, her conjugated bilirubin level was found to be 11.4 mg/dL (194.99 μ mol/L). Which of the following is most accurate when establishing a diagnosis of biliary atresia in this patient?
- A. A hepatopertoenterostomy (Kasai procedure) is most effective for reestablishing adequate bile flow if performed prior to 12 weeks of age.
 - B. Biliary atresia may be a part of the BA splenic malformation, which includes situs inversus, cardiac defects, and urologic and mesenteric abnormalities.
 - C. Presence of the gallbladder at ultrasonography does not exclude the diagnosis of biliary atresia, since a small percentage of infants with biliary atresia may have an atretic gallbladder.
 - D. The pathophysiology of biliary atresia includes only the extrahepatic bile ducts, with resulting scarring and biliary cirrhosis.
 - E. Typical histopathologic findings in biliary atresia include bile duct fibrosis and vascular proliferation.
5. A formerly premature infant born at 26 weeks' gestation, who is now 96 days old, is a patient in the neonatal intensive care unit. She was intubated shortly after birth after a failed trial of nasal continuous positive airway pressure, was treated with indomethacin for a patent ductus arteriosus, and developed medical necrotizing enterocolitis at 4 weeks of age. She required a prolonged course of parenteral nutrition and subsequently has cholestasis with an elevated conjugated bilirubin level of 5.8 mg/dL (99.20 μ mol/L). Which of the following should be taken into consideration when designing appropriate management and nutritional regimens for this infant with cholestasis?
- A. Adequate vitamin supplementation, specifically vitamins A, D, E, and K, and routine testing of vitamin levels.
 - B. Infants with cholestasis typically have enhanced availability of bile acids in the intestine.
 - C. A diet low in medium-chain triglycerides (MCTs) is indicated, since MCTs require bile acid micelles to aid in solubility in the intestine.
 - D. The formula Enfaport contains a high percentage of MCTs but lacks the essential fatty acids necessary for proper growth.
 - E. Ursodeoxycholic acid is typically used in the management of extrahepatic biliary atresia but is contraindicated in intrahepatic biliary atresia.