Approach to evaluation of cholestasis in neonates and young infants

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Literature review current through: Feb 2021. | **This topic last updated:** Jan 20, 2021.

INTRODUCTION

Neonatal cholestasis is generally defined as conjugated hyperbilirubinemia that occurs in the newborn period or shortly thereafter. Cholestasis results from diminished bile formation and/or excretion, which can be caused by a number of disorders. Neonatal cholestasis lasting more than two weeks affects approximately 1 in 2500 births (excluding infants with intestinal failure-associated liver disease), but estimates vary depending on the definition used to define cholestasis [1,2].

This topic review provides an approach to patients with neonatal cholestasis. The pathogenesis and management of neonatal unconjugated hyperbilirubinemia and common causes of neonatal cholestasis are discussed separately. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology" and "Unconjugated hyperbilirubinemia in term and late preterm infants: Management" and "Causes of cholestasis in neonates and young infants".)

DEFINITIONS

- **Cholestasis** – Cholestasis is defined as an impairment in the excretion of bile, which can be caused by defects in intrahepatic production of bile, transmembrane transport of bile, or mechanical obstruction to bile flow. The biochemical features of cholestasis reflect the retention of components of bile in the serum (eg, bilirubin, bile acids, and/or cholesterol). The pattern and severity of each of these abnormalities vary with the underlying disorder.

Elevated conjugated bilirubin is the predominant characteristic in most of the causes of neonatal cholestasis.

- **Conjugated hyperbilirubinemia** – The terms "conjugated bilirubin" and "direct bilirubin" are often used interchangeably because conjugated bilirubin can be estimated by the "direct" reaction with a diazo reagent (van den Bergh reaction). However, direct-reacting bilirubin includes both the conjugated bilirubin and the delta fraction, which represents bilirubin covalently bound to albumin [3]. (See "Clinical aspects of serum bilirubin determination", section on 'Measurement of serum bilirubin'.)

  In a jaundiced infant, a threshold for initiating a clinical evaluation is conjugated or direct bilirubin >1.0 mg/dL (17.1 micromol/L) [4]. (See "Biliary atresia", section on 'Laboratory studies'.)

  The threshold is somewhat higher, usually a serum direct bilirubin greater than 2.0 mg/dL (34.2 micromol/L), for defining clinically significant hyperbilirubinemia in infants with intestinal failure-associated liver disease (also known as parenteral nutrition-associated liver disease). (See "Intestinal failure-associated liver disease in infants", section on 'Definitions'.)

- **Neonatal cholestasis** – The term "neonatal cholestasis" is often used to refer to cholestatic liver disease that is present at birth and/or develops within the first few months of life, rather than referring strictly to the neonatal period (the first 28 days of life). In clinical practice, these disorders usually become apparent within the first three months of life, which is the critical period for identifying infants with biliary atresia (table 1). However, similar diagnostic considerations apply for infants whose cholestasis is identified after three months of age. Although the cholestasis caused by these disorders is persistent, infants should be evaluated as soon as the conjugated hyperbilirubinemia is identified to avoid delay in diagnosis.

OVERVIEW

Any infant noted to be jaundiced at the two-week well-child visit should be evaluated for cholestasis (ie, conjugated hyperbilirubinemia) [4]. This is because physiologic jaundice (characterized by unconjugated hyperbilirubinemia) resolves by 14 days of age in at least 85 percent of infants [5,6]. Although most infants who are still jaundiced at two weeks of age have benign causes (breastfeeding, breast milk, or hemolytic jaundice), a few will have biliary atresia or other diseases that require prompt diagnosis and treatment to optimize outcomes. Initiating

evaluation at the two-week visit is important because some of these infants may not have another health care visit until they are two months old. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology" and "Biliary atresia", section on 'Evaluation'.)

This approach results in screening between 60 and 375 healthy infants to detect one case of neonatal cholestasis [4]. To reduce the screening burden, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) suggests the following approach in jaundiced infants who are most likely to have breast milk jaundice because they are exclusively or near-exclusively breastfed: The evaluation for cholestasis may be delayed until three weeks of age in such infants if they have a normal physical examination, no history of dark urine or light stools, and can be reliably monitored [4].

Initial screening — The first step in evaluating a jaundiced infant for possible cholestasis is to measure the serum concentrations of both total and conjugated bilirubin.

- If the infant has **unconjugated** hyperbilirubinemia (>2 mg/dL [34.2 micromol/L] at two weeks of age), this is often caused by breast milk jaundice, but other causes also should be considered, particularly if the total bilirubin is markedly elevated. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology" and "Evaluation of jaundice caused by unconjugated hyperbilirubinemia in children".)

- If the infant has **conjugated** hyperbilirubinemia, causes of cholestatic jaundice should be investigated promptly, as discussed in the remainder of this topic. Conjugated hyperbilirubinemia is defined as a serum conjugated bilirubin concentration greater than 1.0 mg/dL (17.1 micromol/L) if the total bilirubin is <5.0 mg/dL (85.5 micromol/L), or greater than 20 percent of the total bilirubin if the total bilirubin is >5.0 mg/dL (85.5 micromol/L).

Stages of evaluation — The evaluation of an infant with conjugated hyperbilirubinemia is complex because many disorders can present with neonatal cholestasis (table 1), and distinguishing among these disorders is difficult because of the lack of specific diagnostic tests. However, relatively few diagnoses account for the majority of cases (table 2) [7]. In term infants, the most common causes of neonatal cholestasis are biliary atresia (25 to 40 percent) and an array of rare genetic disorders (25 percent collectively) [4]. In **premature** infants, cholestasis more frequently results from total parenteral nutrition or sepsis. The causes of neonatal cholestasis are discussed elsewhere. (See "Causes of cholestasis in neonates and young infants" and "Biliary atresia".)

Evaluation should be undertaken in a staged approach [8]:

- The initial step is rapid diagnosis and early initiation of therapy of treatable disorders:

- Biliary atresia must be identified early and differentiated from other causes of neonatal cholestasis because early surgical intervention (ie, before two months of age) results in a better outcome. Important steps in making this diagnosis are performing ultrasonography and liver biopsy. (See "Biliary atresia", section on 'Evaluation'.)

- Conditions such as sepsis, hypothyroidism, panhypopituitarism, and inborn errors of metabolism (eg, galactosemia) must be recognized and treated promptly to avoid significant progression of the illness. For infants in whom these disorders are excluded, consultation with a pediatric gastroenterologist is warranted [4]. (See 'Laboratory studies' below.)

- Additional testing is directed at the diagnosis of specific conditions, such as PI testing for alpha-1 antitrypsin deficiency and sweat and/or gene testing for cystic fibrosis, and at potential complications of liver disease such as coagulopathy.

HISTORY

A wide variety of disorders may cause neonatal cholestasis, as outlined in the table (table 1) and detailed in a separate topic review. (See "Causes of cholestasis in neonates and young infants".)

Aspects of the history that may be helpful in narrowing the differential diagnosis are summarized in the table (table 3) [4].

PHYSICAL EXAMINATION

Specific components of the physical examination may be useful in narrowing the differential diagnosis and are outlined in the table (table 4). Key features include [4]:

- Infants with biliary atresia are generally well-appearing, except for jaundice, and stools are often acholic (examples of stool colors here). Infants who present late (>90 days of age) with biliary atresia may have features of advanced liver disease including failure to thrive, ascites, and hepatosplenomegaly.

- By contrast, infants who are ill-appearing or failing to thrive are more likely to have infection or metabolic disease.

LABORATORY STUDIES

Laboratory studies can help assess the extent of hepatobiliary dysfunction and may identify an etiology. Staged laboratory evaluation is presented in the table (table 5). These tests usually should be performed simultaneously with the imaging evaluation described below.

Initial tests — The initial laboratory evaluation should include:

- Comprehensive metabolic panel:
  - Total and conjugated bilirubin – To evaluate for conjugated hyperbilirubinemia (cholestasis) versus unconjugated hyperbilirubinemia.
  - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) – To assess liver cell injury.
  - Serum alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP) – These tests may provide supportive evidence for biliary obstruction. Furthermore, several genetic/metabolic disorders can be divided into high- and low-GGTP categories. For example, GGTP is typically elevated in biliary atresia and Alagille syndrome, while a normal to low GGTP is seen in most forms of progressive familial intrahepatic cholestasis, bile acid synthetic disorders, and arthrogryposis-renal dysfunction-cholestasis syndrome. (See "Causes of cholestasis in neonates and young infants".)
  - Total protein and albumin.
  - The comprehensive metabolic panel includes electrolytes, bicarbonate, and glucose, as an initial screen for metabolic disease.
- Complete blood count with differential.
- Prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) – To further evaluate hepatocellular function and/or vitamin K deficiency.

Other laboratory tests — Additional tests may be appropriate to evaluate for systemic illness or specific causes of liver disease. Selection of these tests will vary based on the clinical presentation (table 5).

IMAGING STUDIES

Several imaging studies can assist in establishing the cause of the neonatal cholestasis. Most patients should be evaluated with abdominal ultrasonography. Hepatobiliary scintigraphy may be of use in some cases. It is important to complete these studies expeditiously since outcomes

after Kasai portoenterostomy are improved with earlier intervention. Many patients will also require liver biopsy to establish the diagnosis. (See 'Additional tests' below and "Biliary atresia", section on 'Evaluation'.)

Ultrasonography — We suggest abdominal ultrasonography as the initial test because it is noninvasive, easily available, and can identify structural abnormalities of the hepatobiliary tract and abdominal organs [4]. The main utility of this test is to exclude other anatomic causes of cholestasis (ie, choledochal cyst). However, certain findings may suggest the diagnosis of biliary atresia, including absent (or nonvisualized) gallbladder and the presence of the triangular cord sign (triangular or band-like periportal echogenic density >3 mm in thickness) [9,10]. Ultrasound may also identify situs abnormalities, polysplenia, or vascular anomalies that could be associated with biliary atresia.

Scintigraphy — Hepatobiliary scintigraphy (sometimes known as a "HIDA scan") is an optional second step performed at institutions where this test is readily available, provided that it does not delay subsequent diagnostic steps. It provides useful information about biliary obstruction. However, the test is associated with substantial numbers of false-positive results and occasional false-negative results (ie, excretion of tracer into the bowel despite biliary atresia) [4,11]. As a result, scintigraphy should be used only for supportive information and not to independently confirm or exclude the diagnosis of biliary atresia.

The test is performed by administering a technetium-labeled iminodiacetic acid analog intravenously and monitoring uptake by the liver and subsequent excretion into the biliary tree and intestine. Infants with biliary atresia usually have normal uptake of the isotope but absent excretion into the bile and intestine, whereas those with neonatal hepatitis typically have delayed uptake but appropriate excretion [8]. Thus, if scintigraphy demonstrates patency of the biliary tract, biliary atresia is unlikely, except in very young infants [4]. However, nonvisualization of the gallbladder or lack of excretion can occur in patients without biliary atresia [12]. The test depends upon adequate hepatocellular function, and pretreatment for five days with phenobarbital (5 mg/kg per day) increases the accuracy of this test by enhancing isotope excretion [13]. However, in most cases, we do not use phenobarbital, because it will delay diagnosis and does not obviate the need for liver biopsy. (See "Biliary atresia", section on 'Hepatobiliary scintigraphy'.)

The sensitivity of scintigraphy in detecting biliary obstruction is approximately 99 percent, and the specificity ranges from 69 to 72 percent [14]. This range reflects variations in use by different centers [4].

ADDITIONAL TESTS

Liver biopsy — If the initial laboratory evaluation and imaging does not identify a specific diagnosis, we recommend performing a percutaneous liver biopsy, particularly when there is a clinical suspicion of biliary atresia or other causes of biliary tract obstruction [4]. The results can help to support the diagnosis of biliary atresia before moving on to an open cholangiogram, or help to differentiate this disorder from intrahepatic causes of cholestasis that might not require surgical exploration [4,15]. The biopsy should be interpreted by a pathologist with expertise in pediatric liver disease. If the results are equivocal and biopsy was performed when the infant was <6 weeks of age, repeat biopsy may be necessary. (See "Biliary atresia", section on 'Liver biopsy'.)

Cholangiogram

Open cholangiogram — If the above steps in the evaluation support the diagnosis of biliary atresia, the infant should be taken to the operating room. The first step is an intraoperative cholangiogram, which is the gold standard in the diagnosis of biliary atresia. If the intraoperative cholangiogram demonstrates biliary obstruction (ie, if the contrast does not fill the biliary tree or reach the intestine), the surgeon should perform a hepatoportoenterostomy (Kasai procedure). (See "Biliary atresia", section on 'Cholangiogram'.)

Endoscopic retrograde cholangiopancreatography — Endoscopic retrograde cholangiopancreatography (ERCP) is an alternative technique available at a few select tertiary care centers [4]. It involves endoscopic intubation of the biliary and pancreatic ducts through the ampulla of Vater with a small catheter and injection of contrast material to facilitate radiologic visualization of the ductal systems. (See "Endoscopic retrograde cholangiopancreatography (ERCP) for biliary disease in children".)

ERCP appears to be a sensitive and specific means of detecting biliary obstruction [4,16-21]. However, its utility in neonates is limited by the availability of appropriately-sized endoscopes [21], the need for deep sedation or general anesthesia in most cases [4], and the lack of validation. In select circumstances, ERCP can clarify the etiology of neonatal cholestasis and obviate the need for laparotomy.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pediatric liver disease"

and "Society guideline links: Neonatal jaundice".)

SUMMARY AND RECOMMENDATIONS

- Any infant who is noted to be jaundiced at two weeks of age should be evaluated for cholestasis by measuring total serum bilirubin and conjugated (or direct) bilirubin. The laboratory evaluation of breastfed infants who have a normal physical examination, have normally colored stools and urine, and can be closely monitored may be delayed until they are three weeks of age. (See 'Overview' above.)

- In a jaundiced infant, a threshold for initiating a clinical evaluation is conjugated or direct bilirubin >1.0 mg/dL (17.1 micromol/L). (See 'Definitions' above.)

- Causes of cholestasis in neonates and young infants include several types of biliary obstruction, hepatic or systemic infection, metabolic diseases, and toxic or alloimmune insults (table 1). Biliary atresia and neonatal hepatitis account for most cases of cholestasis in term infants. In premature infants, cholestasis more frequently results from total parenteral nutrition or sepsis. (See 'Stages of evaluation' above and "Causes of cholestasis in neonates and young infants".)

- The evaluation of cholestatic jaundice in infants after two weeks of age should be undertaken in a staged approach, guided by a focused history (table 3), physical examination (table 4), and laboratory evaluation (table 5). (See 'Stages of evaluation' above.)

    - The initial step is rapid diagnosis and early initiation of therapy of treatable disorders (eg, sepsis, hypothyroidism, inborn errors of metabolism). (See 'Laboratory studies' above.)

    - The next step is to distinguish biliary atresia from other causes of neonatal cholestasis because early surgical intervention for biliary atresia before 60 days of age results in improved outcomes. Key steps are ultrasonography and liver biopsy. (See 'Imaging studies' above and 'Liver biopsy' above.)

    - Additional testing is directed at the diagnosis of specific conditions and evaluation of associated complications (eg, coagulopathy).

- If jaundice fails to resolve in an infant in whom a treatable condition is diagnosed (eg, urinary tract infection or galactosemia) and treated, further evaluation should be performed.

- In the evaluation of an infant with cholestasis of unknown etiology, ultrasonography of the liver is almost always included and liver biopsy is often indicated. (See 'Ultrasonography' above and 'Liver biopsy' above.)

- Hepatobiliary scintigraphy provides supportive information about biliary obstruction and can be performed if the test is readily available and does not delay subsequent diagnostic steps. However, the test is associated with substantial numbers of both false-positive and false-negative results, so it should not be used solely to either confirm or exclude the diagnosis of biliary atresia. (See 'Scintigraphy' above.)

- Endoscopic retrograde cholangiopancreatography (ERCP) is not routinely recommended. However, if expertise in neonatal ERCP is available, this procedure can be used to detect extrahepatic obstruction, including biliary atresia or cholelithiasis. (See 'Endoscopic retrograde cholangiopancreatography' above.)

ACKNOWLEDGMENT

The editorial staff at UpToDate would like to acknowledge Robert J Shulman, MD, and Stephanie H Abrams, MD, MS, who contributed to an earlier version of this topic review.

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GRAPHICS

Causes of neonatal cholestasis

Obstruction
Biliary atresia[¶]
Biliary cysts
Inspissated bile/mucous plug
Cholelithiasis or biliary sludge
Tumors/masses (intrinsic and extrinsic to the bile duct)
Neonatal sclerosing cholangitis
Spontaneous perforation of the bile ducts
Infection[¶]
Viral
Adenovirus, cytomegalovirus, echovirus, enterovirus, herpes simplex virus, HIV, parvovirus B19, rubella
Bacterial
Urinary tract infection, sepsis, syphilis
Protozoal
Toxoplasma
Genetic/metabolic disorders
Inherited cholestatic disorders
Alagille syndrome[¶Δ] (MIM #118450)
Alpha-1 antitrypsin deficiency (PI*Z homozygotes or PI*SZ heterozygotes)[¶] (MIM #613490)
ARC syndrome (arthrogryposis-renal dysfunction-cholestasis) (MIM #208085)
Cystic fibrosis (MIM #219700)
Progressive familial intrahepatic cholestasis (types 1 to 5)[¶◊] (MIM #211600, MIM #601847, MIM #602347, MIM #615878, MIM #617049)
MYO5B mutations (with or without congenital diarrhea due to microvillus inclusion disease)[1] (MIM #251850)
NISCH syndrome (neonatal ichthyosis sclerosing cholangitis) (MIM #607626)
Dubin-Johnson syndrome[§] (MIM #237500)
Disorders of carbohydrate metabolism
Galactosemia[¶] (MIM #230400)
Fructosemia (MIM #229600)
Glycogen storage disease type IV (MIM #232500)
Disorders of amino acid metabolism
Tyrosinemia (type 1)[¶] (MIM #276700)
Disorders of lipid metabolism
Wolman (MIM #278000), Niemann-Pick type C (MIM #257220), Gaucher type 2 (MIM #230900)
Disorders of bile acid synthesis
Bile acid synthesis defects (types 1 to 6) (MIM #607765, MIM #235555, MIM #613812, MIM #214950, MIM #616278, MIM #617308)
Cerebrotendinous xanthomatosis (MIM #213700)
Amidation defects (*BAAT* or *SLC27A5* gene mutations)

Zellweger spectrum disorders◊ (MIM #214100 and others)
Smith-Lemli-Opitz syndrome◊ (MIM #270400)
Mitochondrial disorders¥
Urea cycle defect
Citrin deficiency (type II) (MIM #605814)
Congenital disorders of glycosylation
Phosphomannomutase 2 deficiency (MIM #212065)
Phosphoglucomutase 1 deficiency (MIM #614921)
Mannosephosphate isomerase deficiency (MIM #602579)
Alloimmune
Gestational alloimmune liver disease
Toxic
Intestinal failure-associated liver disease (parenteral nutrition)¶
Drugs
Miscellaneous
"Idiopathic" neonatal hepatitis
Nonsyndromic paucity of the interlobular bile ducts
Shock/hypoperfusion
Intestinal obstruction
Hypothyroidism
Hypopituitarism (eg, in septo-optic dysplasia)

¶ More common disorders causing neonatal cholestasis.
Δ Alagille syndrome is also known as syndromic paucity of the interlobular bile ducts, or arteriohepatic dysplasia.
◊ These disorders are classified as secondary bile acid metabolic defects.
§ Presentation of Dubin-Johnson syndrome in neonates and young infants is rare but has been reported.[2]
¥ For mitochondrial hepatopathies, refer to UpToDate table and content on acute liver failure in infants and children.

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Graphic 64995 Version 11.0

Most common causes of neonatal cholestasis

Diagnosis	Proportion of young infants with conjugated hyperbilirubinemia
Extrahepatic biliary atresia	25% (range 2 to 55%)
Idiopathic neonatal hepatitis	25% (range 4 to 45%)
Infectious hepatitis (eg, cytomegalovirus)	11% (range 3 to 38%)
Parenteral nutrition-associated	6% (range 7 to 30%)
Metabolic disease (eg, galactosemia, tyrosinemia)	4%
Alpha-1 antitrypsin deficiency	4%
Alagille syndrome	1%
Progressive familial intrahepatic cholestasis	1%

The percentages shown here are based upon a systematic review of 17 studies encompassing 1692 infants. Most but not all of the studies were from resource-rich countries. The proportion of infants in each category varied substantially across the studies, likely due to differences in infectious diseases in the population as well as the methods used to make the diagnoses.

Data from: Gottesman LE, Del Vecchio MT, Aronoff SC. Etiologies of conjugated hyperbilirubinemia in infancy: A systematic review of 1692 subjects. BMC Pediatrics 2015; 15:192.

Graphic 79511 Version 7.0

Important elements of the clinical history for evaluating a neonate or young infant with cholestatic liver disease

Finding	Implications
Birth history	
Prenatal ultrasonography and results	Evaluate for choledochal cyst or bowel anomalies.
Birth weight and gestational age	Infants with biliary atresia typically have normal prenatal history and normal birth weight. Many genetic and metabolic causes of neonatal liver disease are associated with poor fetal growth.
Newborn screen results	Disorders on the newborn screen that can present with cholestasis include cystic fibrosis, galactosemia, tyrosinemia or other disorders of amino acid metabolism, and disorders of fatty acid oxidation or organic acid metabolism*.
Isoimmune hemolysis	In infants with severe ABO incompatibility, conjugated hyperbilirubinemia occasionally persists until 2 weeks of age¶.
Maternal infections (TORCH)	Among the TORCH infections, herpes simplex virus infection and syphilis are particularly likely to be associated with liver injury in the neonate.
Complications of pregnancy	Intrahepatic cholestasis of pregnancy in the mother (which may manifest as pruritus without jaundice) suggests the possibility of PFIC in the infant.
	Acute fatty liver of pregnancy in the mother suggests the possibility of a fatty acid oxidation defect in the infant.
Family history	
Consanguinity	Increases the risk of an autosomal recessive disorderΔ.
History of similar problems in the family	Suggests a heritable disorder, particularly those with dominant or codominant inheritance◊.
Stool characteristics	
Stool color	Persistent acholic (clay-colored) stools are a sign of cholestasis, which could be the result of biliary obstruction (eg, biliary atresia) or other causes§.
Stooling pattern	Delayed stooling may occur in cystic fibrosis or hypothyroidism; diarrhea may occur in infection, metabolic disease, or PFIC.
Diet and gastrointestinal symptoms	
Dietary history	Galactosemia is only expressed if the infant is consuming breastmilk or a cow's milk-based formula (contains lactose, which is hydrolyzed to galactose).
Weight gain	Severe cholestasis, genetic disease, or metabolic disease may cause failure to thrive.
Vomiting	May occur in metabolic disease, bowel obstruction, and pyloric stenosis.
Other symptoms	
Urine color	Dark urine suggests hyperbilirubinemia.
Excessive bleeding (eg, after circumcision)	May indicate coagulopathy (eg, due to vitamin K deficiency or poor hepatocellular function).
Infant's behavior	Irritability may indicate metabolic disease or sepsis; lethargy may indicate metabolic disease, sepsis, hypothyroidism, or panhypopituitarism.
Neonatal infection	Infections, particularly urinary tract infections, may be associated with transient cholestasis.

PFIC: progressive familial intrahepatic cholestasis; TORCH: toxoplasmosis, other (syphilis), rubella, cytomegalovirus, herpes simplex virus.

* All states in the United States routinely perform newborn screening for cystic fibrosis, galactosemia, and several fatty acid and organic acid disorders. Most states also include screening for tyrosinemia. Details are available at the National Newborn Screening and Global Resource Center.

¶ Isoimmune hemolysis causes a hyperbilirubinemia that is predominantly unconjugated but may have a significant conjugated component due to immaturity of the liver and enterohepatic circulation.

Δ Disorders with an autosomal recessive pattern of inheritance include cystic fibrosis, alpha-1 antitrypsin deficiency, galactosemia, tyrosinemia, and PFIC.

◊ Disorders with dominant or codominant inheritance include Alagille syndrome.

§ Stool color cards provide examples of normal and abnormal infant stool colors. An example is available at: http://www.perinatalservicesbc.ca/Documents/Screening/BiliaryAtresia/StoolColourCard_English.pdf.

Graphic 111411 Version 3.0

Important elements of the physical examination for evaluating a neonate or young infant with cholestatic liver disease

Finding	Implications
Vital signs	Infants with biliary atresia typically have normal vital signs. Abnormal vital signs are more likely in infants with an underlying infectious or metabolic disease.
General health and vigor	Infants with biliary atresia typically appear well; ill appearance may indicate infection or metabolic disease.
Growth parameters	Infants with biliary atresia typically have normal growth initially but poor weight gain as cholestasis progresses.
Facies and appearance	Infants with Alagille syndrome may have a characteristic facial appearance with a broad nasal bridge, triangular facies, and deep-set eyes. This and other facial malformations or dysmorphism should prompt further evaluation for genetic disorders, such as cleft lip or palate (Hardikar syndrome), or other syndromic features.
Ophthalmologic examination	Cataracts suggest congenital infection or galactosemia, macular cherry red spot suggests Niemann-Pick, posterior embryotoxon suggests Alagille syndrome, and optic nerve hypoplasia suggests septo-optic dysplasia.
Cardiac examination	Congenital heart disease may be present in patients with biliary atresia or Alagille syndrome.
Abdominal examination	
Ascites	Suggests portal hypertension*.
Abdominal wall veins	Prominent abdominal wall veins suggest portal hypertension*.
Liver size	Hepatomegaly suggests a storage disorder. Hepatomegaly may also be present in biliary atresia or other cholestatic disorders.
Liver consistency	Firm liver texture suggests fibrosis and may be present in biliary atresia.
Spleen	Splenomegaly suggests portal hypertension or storage disorder*.
Skin	Bruising or petechiae suggest coagulopathy or thrombocytopenia. Jaundice confirms hyperbilirubinemia (which may be either conjugated or unconjugated).
Urine	Dark urine suggests hyperbilirubinemia.
Stool	Acholic (very pale) stools suggest absent bile flow¶.

* Portal hypertension is unusual at the time of diagnosis in biliary atresia, unless the presentation is late.
¶ Stool color cards provide examples of normal and abnormal infant stool colors. An example is available at: http://www.perinatalservicesbc.ca/Documents/Screening/BiliaryAtresia/StoolColourCard_English.pdf.

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Laboratory testing for evaluating a neonate or young infant with suspected cholestatic liver disease

Finding	Implications
Initial tests for all infants	
▪ Comprehensive metabolic panel	
• Total and conjugated bilirubin	To evaluate for conjugated hyperbilirubinemia (cholestasis) versus unconjugated hyperbilirubinemia.
• ALT and AST	To assess for hepatocyte injury.
• Alkaline phosphatase and GGTP	To assess for biliary injury. Furthermore, several genetic/metabolic disorders can be divided into high- and low-GGTP categories*.
• Total protein and albumin	To assess hepatocyte function. Low albumin suggests poor nutrition, renal losses, or poor hepatic synthetic function.
• Electrolytes, bicarbonate, glucose	To assess for metabolic disease. Abnormalities in these results are often seen in infants with metabolic disease.
▪ CBC with differential	To assess for infection and/or splenic sequestration. Elevated WBC is suggestive of infection. Low WBC and platelet count could indicate portal hypertension (with splenic sequestration).
▪ PT/INR and PTT	To assess hepatocyte function and/or vitamin K deficiency. Abnormal results indicate impaired liver synthetic function and/or vitamin K deficiency.
Additional tests to evaluate for systemic illness of specific liver diseases ¶	
▪ Urinalysis and urine culture	Appropriate for most infants with cholestasis to exclude urinary tract infection and to evaluate possible renal involvement.
▪ Blood culture	If clinical presentation suggests sepsis.
▪ Urine-reducing substances	Screen for galactosemia (in infants ingesting lactose)[Δ].
▪ Serum bile acids	Elevations are diagnostic of cholestasis. Serum bile acids will be low in infants with bile acid synthetic disorders.
▪ Alpha-1 antitrypsin concentration	Low levels suggest alpha-1 antitrypsin deficiency. Normal levels do not exclude alpha-1 antitrypsin deficiency, because this is an acute phase reactant.
• Protease inhibitor phenotype (PI type)	The primary alleles associated with liver disease are PI*ZZ homozygosity or PI*SZ heterozygosity.
▪ TSH, T4	Screen for congenital hypothyroidism (primary or central).
▪ Urine bile acid analysis by FAB-MS	Screen for inborn errors of bile acid metabolism (BASD), which may present with low-GGT cholestasis[◊].
▪ Metabolic testing	If a metabolic disorder is suspected, initial screening includes plasma amino acids, urine organic acids, acylcarnitine profile, ammonia, lactate:pyruvate ratio.
▪ Genetic testing	Genetic testing is rapidly evolving with the availability of new technologies[§].

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGTP: gamma-glutamyl transpeptidase; CBC: complete blood count; WBC: white blood cell count; PT: prothrombin time; INR: international normalized ratio; PTT: partial thromboplastin time; TSH: thyroid-stimulating hormone (thyrotropin); T4: thyroxine; FAB-MS: fast atom bombardment mass spectrometry; GGT: gamma-glutamyl transferase.

* GGTP is disproportionately elevated (compared with AST and ALT) in the most common types of neonatal cholestasis, including biliary atresia and Alagille syndrome, while a normal or low GGTP is seen in most forms of progressive familial intrahepatic cholestasis, BASD, and arthrogryposis-renal dysfunction-cholestasis syndrome.

¶ These tests are selected based upon the clinical presentation and results of initial tests.

Δ Urine-reducing substances is only valid as a screen for galactosemia if the infant is fed breast milk or a cow's milk-based formula (which contains lactose, then hydrolyzed to galactose).
◊ Infants must be off of ursodeoxycholic acid for at least 5 days prior to urine collection for bile acid analysis because the FAB-MS signature of the drug overlaps with some of the abnormal bile acid metabolites seen in BASD.
§ Individual gene sequencing can be done if the clinical presentation suggests a specific diagnosis, such as Alagille syndrome. For screening of multiple genes associated with inherited cholestasis, next-generation sequencing panels are available. Each panel interrogates approximately 20 to 50 genes. Current information is available at GeneTests.org.

Graphic 111409 Version 6.0

Contributor Disclosures

Kathleen M Loomes, MD Grant/Research/Clinical Trial Support: Mirum [Alagille syndrome and PFIC]; Mirum and Albireo [PFIC]. Consultant/Advisory Boards: Mirum and Albireo [PFIC]. **Jessi Erlichman, MPH** Nothing to disclose **Steven A Abrams, MD** Grant/Research/Clinical Trial Support: Perrigo Nutrition [Food insecurity; coronavirus disease 2019]. **Elizabeth B Rand, MD** Nothing to disclose **Alison G Hoppin, MD** Nothing to disclose

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