

Neonatal Cholestasis: A Primer of Selected Etiologies

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ABSTRACT

Cholestasis refers to impairment in formation or excretion of bile. This can be due to defects in intrahepatic production of bile, defects in the transmembrane transport of bile, or mechanical obstruction to bile flow. Clinical features of cholestasis reflect the retention of components of bile (bilirubin, bile acids, cholesterol) in the body. In the neonatal period, hyperbilirubinemia can be categorized as either unconjugated (and often benign) hyperbilirubinemia, or conjugated hyperbilirubinemia due to cholestasis. It is for this reason that the first laboratory evaluation in a patient with jaundice, dark urine, and/or acholic stool is a fractionated bilirubin. This article serves as a practical primer for pediatric and neonatology trainees and covers common causes of neonatal cholestasis, as well as the diagnostic work-up and treatment. Causes that are discussed include biliary atresia, idiopathic neonatal hepatitis, gestational alloimmune liver disease, metabolic and genetic diseases, total parenteral nutrition cholestasis, and congenital infection. [*Pediatr Ann.* 2018;47(11):e433-e439.]

Neonatal cholestasis refers to impairment in formation or excretion of bile. This can be due to defects in intrahepatic production of bile, defects in the transmembrane transport of bile, or mechanical obstruction to bile flow. Clinical features of cholestasis reflect the retention of components of bile (bilirubin, bile acids, cholesterol) in the

body. Conjugated hyperbilirubinemia in the neonate is defined as direct bilirubin >1 mg/dL or >20% of total bilirubin.¹

This article is a primer for pediatric and neonatology trainees and covers the common causes of cholestasis. An incomplete list of causes is shown in **Table 1**. Together, biliary atresia (BA) and idiopathic neonatal hepatitis comprise about one-half of all cases of neonatal cholestasis. Other causes discussed in this article include gestational alloimmune liver disease (GALD), metabolic and genetic diseases, intestinal failure associated liver disease (IFALD; also known as total parenteral nutrition [TPN] cholestasis), and congenital infection.^{2,3}

DIAGNOSTIC WORK-UP

Visual determinations of bilirubin levels are largely inaccurate, even among

experienced providers. If the infant appears icteric before the week-2 visit, the first step is to test for fractionated bilirubin level. If the 2-week-old infant is breast-fed and without dark urine or acholic stool (implying breast-milk jaundice), the provider may reevaluate the infant 1 week later. If jaundice persists, laboratory evaluation is recommended.

Details about the onset of jaundice, presence of dark urine or acholic stool, feeding history (eg, intake of soy formula), and timing of the first bowel movement (as delayed passage of meconium can signal cystic fibrosis) may be helpful.

Family history may be significant for consanguinity or history of siblings with neonatal cholestasis (suggesting a genetic cause), history of prior fetal losses (suggesting GALD), or maternal infection during pregnancy (indicating TORCH [Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes] infection).

On physical examination, providers should note firm hepatomegaly (seen in BA) and/or splenomegaly (may suggest storage or hematologic disorders). Extrahepatic signs of cholestatic disease may include dysmorphic features and poor growth, as well as dermatologic, neurologic, or cardiac abnormalities.¹

Suggested laboratory evaluation is outlined in **Table 2**.

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TABLE 1.

Selected Causes of Neonatal Cholestasis

Extrahepatic obstruction
Biliary atresia
Biliary cysts
Inspissated bile/mucous plug
Cholelithiasis
Tumors/masses
Neonatal sclerosing cholangitis
Idiopathic neonatal hepatitis
Metabolic/genetic disease
Galactosemia, tyrosinemia, Wolman disease, Niemann-Pick disease type C, Gaucher disease, BASDs (primary and secondary), A1AT, citrin deficiency, congenital disorders of glycosylation, PFIC, ALGS, ARC syndrome, cystic fibrosis
Mitochondrial disorders
Infection
UTI, sepsis, adenovirus, CMV, enterovirus, HSV, HIV, parvovirus B19, rubella, toxoplasma
Endocrine
Hypopituitarism
Hypothyroidism
Toxic
Drugs
Total parenteral nutrition
Alloimmune
Gestational alloimmune liver disease
Miscellaneous
Shock/hypoperfusion
Intestinal obstruction

Abbreviations: A1AT, alpha-1-antitrypsin; ALGS, alagille syndrome; ARC, arthrogryposis-renal dysfunction-cholestasis; BASDs, bile acid synthesis disorders; CMV, cytomegalovirus; HSV, herpes simplex virus; PFIC, progressive familial intrahepatic cholestasis; UTI, urinary tract infection.

Adapted from Gotze et al.²

BILIARY ATRESIA

BA is a progressive idiopathic fibro-obliterative disease of the biliary tree and the most common indication for liver transplantation in children. It must be diagnosed promptly, as surgical intervention before age 2 months results in better outcomes.¹

Types

BA is divided into three types. BA without any other anomalies accounts for about 80% of cases and is known as the “perinatal” form.⁴ Biliary atresia splenic malformation, or the “embryonal” form, consists of BA with laterality malformations such as asplenia/polysplenia, malrotation, and cardiac anomalies. The third type is BA in association with congenital malformations that are not laterality defects, such as genitourinary or gastrointestinal anomalies.⁴

Signs/Symptoms

Infants with BA are generally healthy at birth and develop progressive jaundice within 2 months. They present with signs of cholestasis including acholic stools, dark urine, hepatomegaly, and, in some cases, congenital anomalies.

Diagnosis

Evaluation should be completed as quickly as possible. Laboratory examination reveals hyperbilirubinemia, mild-to-moderate transaminitis, and a disproportionately elevated gamma-glutamyl transferase (GGT).

Abdominal ultrasound may show an abnormal gallbladder and/or common bile duct. Additional findings, such as polysplenia/asplenia or heterotaxy, may increase the suspicion for BA. A hepatobiliary iminodiacetic acid (HIDA) scan may show absent tracer excretion into the bile and intestine. Pretreatment with phenobarbital for 3 to 5 days enhances tracer excretion; however, this may delay diagnosis, and given the low specificity (70%) of HIDA scans,¹ it does not obviate the need for liver biopsy.

Liver biopsy in BA may show bile duct proliferation, fibrosis, and inflammation. These findings may be nonspecific and result in a false-negative diagnosis if done too early.

Definitive diagnosis is made by intraoperative cholangiogram. If cholangiogram confirms BA, the surgeon should immediately perform a hepatoportoenterostomy (HPE), also known as the Kasai procedure.¹

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Treatment

HPE attempts to restore bile flow from the liver to the proximal small bowel. If jaundice clears by 3 months post-HPE, the 10-year transplant-free survival rates are 75% to 90%; if jaundice persists, the 3-year transplant-free survival rate is only 20%.⁵

Success rates for HPE vary widely. Important prognostic factors include younger age at time of HPE, expertise of surgical center (>5 HPE/year), and total bilirubin of <2 mg/dL by age 3 months.⁵

At least 80% of BA patients have undergone transplantation by age 20 years, often despite receiving optimal medical management. Prognosis is generally good, with 1-year survival around 90%.⁵

IDIOPATHIC NEONATAL HEPATITIS

Idiopathic neonatal hepatitis is defined by prolonged conjugated hyperbilirubinemia with associated signs and symptoms of cholestasis, but without an obvious etiology after complete evaluation. Characteristic findings on liver biopsy are nonspecific, with multinucleated giant cells and variable amount of inflammation. Cholestasis may take months to resolve, and treatment is supportive.⁶

GESTATIONAL ALLOIMMUNE LIVER DISEASE

In infants with GALD, alloimmune disease leads to intrahepatic and extrahepatic iron accumulation resulting in hepatic failure. Transplacental passage of maternal immunoglobulin G activates the fetal complement cascade, and formation of the C5b-9 membrane attack complex leads to hepatocyte injury.⁷ Recurrence rate of GALD in pregnancies is close to 90%, and GALD is the cause of many third trimester fetal losses.⁸

TABLE 2.

Suggested Laboratory Evaluations for Neonatal Cholestasis

Tests	Purpose
Initial tests	
Fractionated bilirubin	Distinguishes cholestasis from benign unconjugated hyperbilirubinemia
ALT, AST	Assess severity of liver disease; elevated AST without increase in other liver function tests may suggest hematologic or muscular process
GGT	Assess severity of liver disease; GGT is generally elevated in cholestasis (eg, BA, ALGS, PFIC3) but low levels can be seen in some conditions (eg, PFIC1, PFIC2, BASD)
PT/PTT	Assess severity of liver disease; severe coagulopathy out of proportion to liver injury may indicate GALD or metabolic disease
Glucose, albumin	Assess severity of liver disease and nutritional status
Electrolytes	Identify metabolic derangements and renal involvement
CBC with differential	Identify infection or splenic sequestration
Newborn screen	Screen for diseases presenting with cholestasis (eg, hypothyroidism, galactosemia, tyrosinemia, CF)
Culture of blood, urine, or other fluids	Identify infection
Targeted tests	
Echocardiogram	Identify cardiac anomalies (may be present in BA and ALGS)
Thyroid function tests, cortisol	Identify hypopituitarism
Plasma amino acids	Screen for disorders of amino acid metabolism or urea cycle disorders
Urine reducing substances	Screen for galactosemia
Urine organic acids and succinylacetone	Screen for tyrosinemia and other organic acidemias
PCR for CMV and HSV	Identify viral infection
Urine bile acids	Diagnose BASD
RBC GALT activity	Diagnose galactosemia
Genetic testing	Identify inherited disorders that are not clinically defined
Imaging	
Abdominal ultrasound	Assess visible obstructions of the biliary tree (eg, biliary cysts, cholelithiasis), abnormal gall bladder or common bile duct morphology, anatomic abnormalities (eg, heterotaxy, midline liver, polysplenia)
HIDA scan	May identify lack of biliary tract patency (limited by low specificity)
Invasive studies	
Liver biopsy	Bile duct proliferation, bile plugs, and fibrosis suggest BA, but other causes of cholestasis can also be identified
Intraoperative cholangiogram	Gold standard to diagnose biliary atresia
Oral mucosa biopsy	Identify extrahepatic siderosis (pathognomonic for GALD)

Abbreviations: ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, biliary atresia; BASD, bile acid synthesis disorder; CBC, complete blood count; CF, cystic fibrosis; CMV, cytomegalovirus; GALD, gestational alloimmune liver disease; GALT, galactose-1-phosphate uridyl transferase; GGT, gamma glutamyltransferase; HIDA, hepatobiliary iminodiacetic acid; HSV, herpes simplex virus; PCR, polymerase chain reaction; PFIC, progressive familial intrahepatic cholestasis; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell.

Adapted from Fawaz et al.¹

Signs/Symptoms

Infants present with signs of severe liver failure, including hyperbilirubinemia (total bilirubin often

>30 mg/dL), coagulopathy, hypoglycemia, hypoalbuminemia, and edema. Notably, transaminases are often normal.⁸

Diagnosis

Diagnosis is made by identifying extrahepatic siderosis by oral mucosa biopsy. T2-weighted magnetic reso-

nance imaging (MRI) shows abnormalities in iron-laden tissues, specifically the pancreas, thyroid, and myocardium. Many liver diseases cause hepatic siderosis; therefore, this finding cannot be used for differentiation. Interestingly, the spleen, bone marrow, and lymph nodes appear normal, as GALD spares the reticuloendothelial system from siderosis.

When suspicion for GALD is high and both mucosal biopsy and MRI are negative, a liver biopsy for C5b-9 complex staining may be performed.

Treatment

Treatment for GALD is double-volume exchange transfusion and intravenous immunoglobulin (IVIG) therapy. Outcomes for untreated infants are poor, with only 17% survival for those who do not receive liver transplantation. Liver transplant can be curative but is difficult in this age group.⁹

For pregnant women who have had a previous infant with GALD, prenatal treatment with high-dose IVIG has been shown to reduce severity of GALD in the infant.¹⁰

GALACTOSEMIA

Altered metabolism of galactose caused by deficiency in any one of three specific enzymes results in galactosemia (Figure 1).

Deficiency of galactose-1-phosphate uridyl transferase (GALT) is the most common and severe form. Many variants result in partial GALT activity (often 15%-25% of normal), most commonly the Duarte variant.¹¹

If galactokinase (GALK) is deficient, the only clinical consequence is cataracts.¹² Uridine diphosphate galactose-4-epimerase (GALE) deficiency is often localized to the red blood cells, and patients have no symptoms. However, if generalized, GALE deficiency presents as classic galactosemia.¹³

Signs/Symptoms

Within days of introducing breast-milk or lactose-containing formula, infants may have jaundice, failure to thrive, lethargy, and sepsis. The main cause of early mortality is sepsis caused by *Escherichia coli*. Less frequent findings are hypotonia, seizures, encephalopathy, and coagulopathy. Galactitol deposition in the lens of the eye can cause cataracts.¹⁴

Laboratory Findings

Every state in the United States includes galactosemia on the newborn screen; however, infants may become symptomatic prior to receiving the results. Initial laboratory evaluation may show hyperbilirubinemia, transaminitis, and coagulopathy. Renal tubular acidosis, increased plasma amino acids, and increased plasma/urine galactitol levels may be seen. A positive test for urine-reducing substances (indicating galactosuria) is neither sensitive nor specific for galactosemia, and the reducing substance must be differentiated from glucosuria.

If there is suspicion for galactosemia or if the newborn screen is positive, the infant should immediately be switched to a soy formula. False-negative screens may occur in infants who fed poorly or were fed lactose-free formula before the sample was drawn.

Diagnosis

The definitive diagnosis for galactosemia is made by quantitative erythrocyte GALT activity. Measuring quantitative GALT activity identifies variants with partial enzyme activity. Unfortunately, red blood cell transfusion can affect this value for as long as 3 months.¹⁵ If GALT activity is normal, consider GALK or GALE deficiency.

Increased erythrocyte galactose-1-P concentration can be used for diagnosis, as the concentration will not be affected by red blood cell transfusion; however,

it cannot accurately distinguish between partial and complete GALT deficiency.¹⁵

Treatment

Initial therapy is supportive and consists of intravenous hydration, antibiotics if indicated, and treatment of coagulopathy. The infant should be switched to a lactose-free formula, as definitive treatment for GALT and generalized GALE deficiency is discontinuing galactose intake. In the Duarte variant, many agree that dietary restriction is not necessary, although there is not yet a standard of care.¹⁶ In GALK deficiency, dietary restriction is necessary to prevent cataracts.¹⁷

Follow-Up

Early treatment resolves most symptoms, but neuropsychological problems and premature ovarian failure can occur despite adequate dietary management. For those with classic galactosemia, annual neurodevelopment assessment (including ophthalmology examination, motor function, and cognitive function) should be performed, as neurodevelopmental delay can occur even with dietary compliance. Most female infants with galactosemia become infertile; pubertal development and fertility in male infants are normal.¹⁸

BILE ACID SYNTHESIS DISORDERS

Bile acid synthesis disorders (BASDs) are rare but treatable causes of cholestasis. Bile acids in the liver promote bile flow, help absorb fat and fat-soluble vitamins, and assist with cholesterol degradation. Primary BASDs are caused by defective synthesis of two main bile acids: cholic acid and chenodeoxycholic acid. This results in accumulation of abnormal bile acids, cholesterol, and other metabolites, causing intrahepatic and extrahepatic damage.¹⁹

Disorders involved in the transport of bile acids are considered secondary BASDs. These include progressive fa-

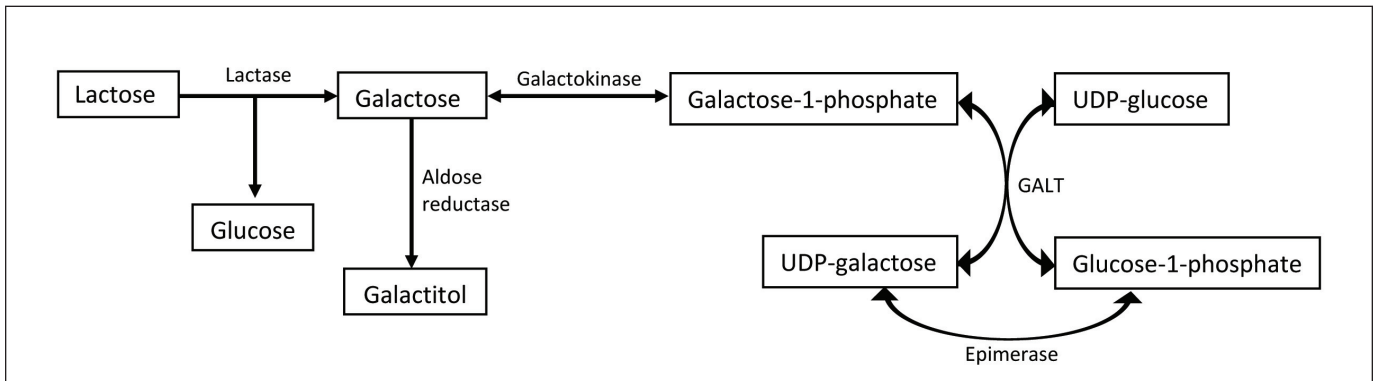


Figure 1. Galactose metabolism. GALT, galactose-1-phosphate uridyl transferase; UDP, uridine diphosphate. Adapted from Berry.¹⁴

mild intrahepatic cholestasis, Smith-Lemli-Optiz syndrome, and Zellweger spectrum disorders.

Signs/Symptoms

Signs of fat-soluble vitamin malabsorption and cholestasis will be present. Infants will have direct hyperbilirubinemia, transaminitis, and normal GGT.

Diagnosis

Diagnosis is made by analysis of urinary bile acids with mass spectrometry.

Treatment

Treatment is with the administration of either cholic acid or chenodeoxycholic acid, depending on the type of BASD. Ursodeoxycholic acid may provide short-term benefit. If left untreated, BASDs may progress to cirrhosis, end stage liver disease, and neurologic disease.¹⁹

TYROSINEMIA

Tyrosinemia is caused by defective tyrosine metabolism (**Figure 2**). Deficiency of fumarylacetoacetate hydrolase leads to build up of tyrosine, as well as toxic metabolites such as succinylacetone, which cause dam-

age to the liver, kidney, and peripheral nerves.

Signs/Symptoms

Renal tubular acidosis and coagulopathy disproportionate to the degree of liver disease are common. Mild cholestasis and increased alpha-fetoprotein, plasma tyrosine, and plasma/urine succinylacetone may be present. Urine organic acids may be positive, reflecting tyrosine metabolites.

Diagnosis

Diagnosis is by confirmation of characteristic biochemical findings or genetic testing.

Treatment

Although dietary modification results in decreased tyrosine levels, this does not stop the production of succinylacetone, so infants remain at risk for liver and renal disease, hepatocellular carcinoma, and neurologic abnormalities. Treatment is with nitisinone, which prevents formation of succinylacetone. Liver transplantation is needed in severe cases.²⁰

ALPHA-1-ANTITRYPSIN DEFICIENCY

Alpha-1-antitrypsin (A1AT) is the most common genetic cause of liver

disease in the neonate. A1AT is a protease inhibitor produced in the liver that inhibits neutrophil elastase from breaking down elastin in the pulmonary alveoli. In alpha-1-antitrypsin deficiency (A1ATD), a genetic defect modifies A1AT so that it is produced but cannot be secreted, and it then accumulates in the liver.

Signs/Symptoms

Infants presenting with A1ATD have signs of liver dysfunction, including hepatomegaly, transaminitis, ascites, and coagulopathy.

Diagnosis

Phenotyping by isoelectric focusing is the gold standard; when this is not available, genotyping provides definitive diagnosis. One phenotype, PiZZ, is responsible for nearly all A1ATD patients with both emphysema and liver disease.

Treatment

Adults with emphysema may be treated with intravenous A1AT (augmentation therapy). Unfortunately, there is no approved treatment for A1ATD-associated cholestatic disease other than supportive care and liver transplantation.²¹

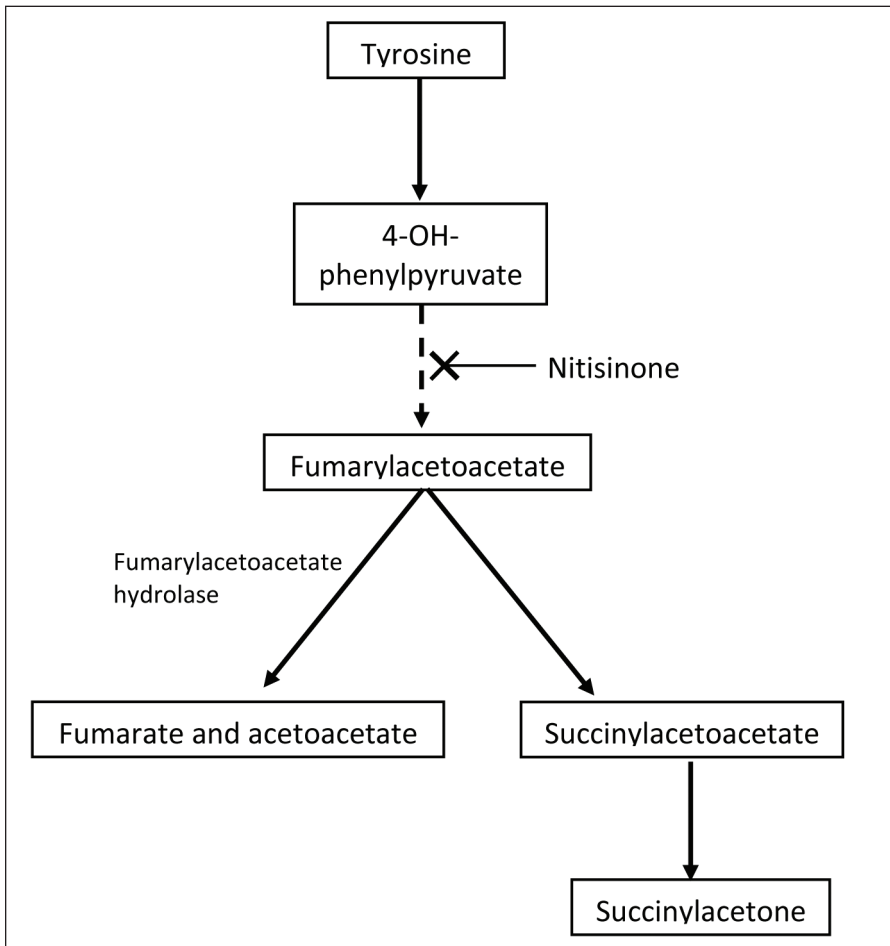


Figure 2. Tyrosine metabolism. Adapted from De Laet et al.²⁰

ALAGILLE SYNDROME

The paucity of interlobular bile ducts in Alagille syndrome results in chronic cholestasis. Mutations in the Jagged1 gene (*JAG1*) or deletions on chromosome 20p12 can be identified in 70% of Alagille syndrome patients.²²

Signs/Symptoms

Associated abnormalities in Alagille syndrome include cardiac anomalies (most commonly peripheral pulmonary stenosis), butterfly vertebrae, eye findings (most commonly posterior embryotoxon), and dysmorphic facies. Short stature, developmental delay, and systemic and intracranial vascular malformations may be present.

Diagnosis

Laboratory studies show hyperbilirubinemia, variably elevated transaminases, and disproportionally increased GGT. Diagnosis remains challenging as there are many causes of bile duct paucity; therefore, liver biopsy is not a requirement for diagnosis. In those with characteristic clinical features, genetic testing is recommended.

Treatment

Treatment is supportive. For patients with severe refractory pruritus or growth failure, biliary diversion may be indicated. End stage liver disease develops in about 20% of patients, for whom liver transplant is the only option.²²

INTESTINAL FAILURE ASSOCIATED LIVER DISEASE

Infants on TPN for prolonged periods are at risk for developing cholestasis. Risk of IFALD is compounded by prematurity, immaturity of the newborn liver, damage from infections (specifically necrotizing enterocolitis and central line infections), and disruption of enterohepatic circulation due to continuous TPN and/or lack of enteral feeds.

Signs/Symptoms

Infants with advanced IFLAD may show signs of portal hypertension, thrombocytopenia, and esophageal varices.

Diagnosis

Severity of liver failure can be evaluated by fractionated bilirubin, prothrombin time/partial thromboplastin time, and albumin.

Treatment

Cyclic TPN (ie, given for <24 hours per day), when compared with continuous infusion, may result in decreased transaminases, conjugated bilirubin, and fat deposition in the liver. For infants on long-term TPN, manganese and copper content should be reduced as these metals may rise to toxic levels. Initiating enteral feedings as early as possible, even at trophic amounts, is essential to stimulating bile flow and intestinal motility.²³

INFECTIONS

In one large systematic review of neonatal cholestasis, infection was identified as the cause in 11.5% of infants; one-third of these infants had cytomegalovirus (CMV).³ CMV affects 1% to 2% of newborns. Although most of those infected are asymptomatic, 5% to 10% have symptoms such as cholestasis, microcephaly, periventricular calcifications, chorioretinitis, and deafness.¹

Other common infectious causes of cholestasis include congenital syphilis,

urinary tract infection caused by *E. coli*, and both bacterial and viral sepsis. Less frequent causes are rubella, toxoplasmosis, and herpes simplex virus.³

The pathogenesis of infection-induced cholestasis is multifactorial and likely due to increased hemolysis, hepatocellular injury caused by circulating endotoxins, and side effects of antimicrobial treatment.²⁴ It has been reported that *E. coli* increases red blood cell fragility more than other organisms, and this may be why *E. coli* in particular causes neonatal cholestasis.²⁵ Interestingly, in one study of infants with sepsis with hepatobiliary dysfunction, cholestasis was more common in babies who survived. This suggests that bilirubin, a known antioxidant, may be a protective mechanism that allows infants to cope with increased oxidative stress.²⁶

Although signs and symptoms should guide laboratory investigations, many providers have a low threshold to consider infectious causes for neonatal cholestasis. Work-up may include serologic, hematologic, and urine studies, as well as radiographic imaging.

CONCLUSION

This article serves as a basic introduction to neonatal cholestasis for trainees, but it is not comprehensive. Neonatal cholestasis can be due to a variety of diseases resulting in impairment in formation or excretion of bile, and there are many rare conditions not described here. A simple fractionated bilirubin test can differentiate cholestasis from the more common unconjugated hyperbilirubinemia. In addition, patient history, physical examination, and specific laboratory investigations can assist with diagnosis and prompt treatment of what may be a rare and fatal disease.

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