Conjugated Hyperbilirubinemia in the Neonate and Young Infant

Anna K. Weiss, MD, MSc and Parag V. Vora, MD, MBA

Abstract: Cholestatic jaundice in the first few weeks of life may herald potentially life-threatening pathology. It is therefore incumbent upon the pediatric practitioner to have a high index of suspicion for severe disease when investigating jaundice in a young infant. This article outlines the epidemiology, pathophysiology, differential diagnosis, and diagnostic workup for both the most common and the most severe causes of cholestasis in the neonatal period.

Key Words: jaundice, neonate, cholestasis, hyperbilirubinemia, biliary atresia, clinical practice guideline

(*Pediatr Emer Care* 2018;34: 280–285)

TARGET AUDIENCE

This CME activity is intended for all pediatric practitioners.

LEARNING OBJECTIVES

After completion of this CME article, the reader should be better able to:

1. Define pathologic jaundice in the neonate and describe the steps needed to evaluate a cholestatic infant.
2. Enumerate the most common and the most serious causes of conjugated hyperbilirubinemia in the neonatal period.
3. Promptly recognize infants with biliary atresia, and appropriately intervene.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) defines neonatal cholestasis as an elevation in serum conjugated bilirubin that is present in the newborn period, or that appears within the first few months of life.[1] Cholestatic jaundice is a rare condition—affecting approximately 1 in 2500 births—but its presence in a neonate is always pathologic and must be promptly investigated.[2,3] Biliary atresia (BA) is the most common cause of cholestasis in young infants, and is amenable to surgical intervention if detected early (ideally within the first 45 days of life).[4–8] Other causes of neonatal cholestasis—including inborn errors of metabolism and perinatal infections—also require prompt diagnosis and treatment to avoid poor outcomes.[1] Because clinical jaundice from benign etiologies (eg, physiologic jaundice and breast milk jaundice) is common in neonates, pediatricians must have a high index of suspicion for cholestasis so that the best possible outcome can be attained for the infant suffering from a potentially life-threatening underlying condition.

Assistant Professor of Clinical Pediatrics (Weiss), Perelman School of Medicine at the University of Pennsylvania; Attending Physician (Weiss), Division of Emergency Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA; and Attending Physician (Vora), Pediatric Emergency Medicine, Envision Physician Services, Capital Health Medical Center, Pennington, NJ.

The authors, faculty, and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations pertaining to this educational activity.

Reprints: Anna Weiss, MD, MSc, Division of Emergency Medicine, The Children's Hospital of Philadelphia, 3501 Civic Center Boulevard, Philadelphia, PA 19104 (e-mail: weissak@email.chop.edu).

CME Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 0749-5161

DEFINITIONS

Cholestasis is defined as a defect in either formation or excretion of bile, with a resulting increase in the serum of retained biliary components (bilirubin, bile acids, or cholesterol). Most causes of neonatal cholestasis will manifest biochemically as an increase in serum conjugated bilirubin. Although the terms "conjugated bilirubin" and "direct bilirubin" are often used interchangeably, the latter is a proxy measure for the former (by demonstrating a proportion of "direct" reaction with a diazo reagent) and tends to overestimate the concentration of conjugated bilirubin in the serum.[9] Therefore, a true conjugated bilirubin ought to be obtained whenever possible when evaluating a jaundiced infant. Conjugated hyperbilirubinemia in a neonate is defined as serum conjugated bilirubin concentration greater than 1.0 mg/dL if the total serum bilirubin is less than 5.0 mg/dL, or a conjugated bilirubin greater than 20% of the total serum bilirubin if the total is greater than 5.0 mg/dL. An elevated conjugated bilirubin is always abnormal and should prompt the pediatric practitioner to investigate further.[1] Although infants with cholestasis may appear clinically jaundiced and may occasionally present with acholic stools, these subjective measures have been shown to be unreliable indicators of hyperbilirubinemia severity, and ought not to be used to guide laboratory screening.[10,11]

PATHOPHYSIOLOGY

The presence of conjugated hyperbilirubinemia in the neonatal period heralds an impairment in bile formation and/or excretion. In the physiologic state, a complex system of basolateral membrane transporters brings bile components from the serum into hepatocytes where they are used in the formation of bile via a multistep synthetic pathway. A different set of membrane transporters secretes formed bile across the apical hepatocellular surface into the bile canaliculus where it then flows into bile ducts of increasing diameter until it enters the gall bladder.[12,13] An impairment in any of these steps will lead to cholestasis and to an elevation in serum conjugated bilirubin. Defects can present anywhere along the pathway, from the molecular level (eg, single-gene mutations of membrane-transporter molecules or exposure to hepatocellular toxins) to the level of mechanical obstruction (eg, BA or gallstones).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal cholestasis can be divided into 2 primary categories: obstructive causes, and causes resulting from hepatocellular injury or genetic alteration (Table 1).

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Most Common Etiologies of Cholestasis in the Neonatal Period

Obstructive Causes of Cholestasis	Nonobstructive or Hepatocellular Causes of Cholestasis
BA	Idiopathic neonatal hepatitis
Alagille syndrome	Infection
Choledochal cyst	Viral infection (especially, CMV, HIV)
Gallstones, biliary sludge, or inspissated bile	Bacterial infection (especially, UTI, syphilis)
Neonatal sclerosing cholangitis	Sepsis
Congenital hepatic fibrosis	Genetic, metabolic, endocrinologic disorders
	PFIC
	α_1-Antitrypsin deficiency
	Tyrosinemia
	Galactosemia
	Hypothyroidism
	Cystic fibrosis
	Panhypopituitarism
	Toxic
	Medication exposure
	Prolonged parenteral nutrition

Adapted from Fawaz et al.[1]

CMV indicates cytomegalovirus; PFIC, progressive familial intrahepatic cholestasis; UTI, urinary tract infection.

Biliary Obstruction

Biliary Atresia

The most common cause of biliary obstruction in infants is BA, an idiopathic condition that accounts for 30% to 50% of all cases of neonatal cholestasis and that affects 1 in 10,000 to 19,000 infants in North America and Europe.[14–19] Biliary atresia is characterized by destruction of intrahepatic and extrahepatic bile ducts that leads to progressive cholestasis and to end-stage liver disease by 6 to 9 months of age. Prognosis for children with BA relates directly to prompt detection and early surgical intervention with Kasai portoenterostomy (KPE), a procedure that reestablishes biliary flow into the intestine.[4] Despite evidence that outcomes for KPE are best if the procedure is performed before 45 to 60 days of life, late detection and referral of infants with BA continues to be a problem.[6–8,20,21] Even after restoration of biliary flow, BA remains a progressive disease marked by continued hepatocellular destruction. For this reason, BA is the most common reason for liver transplant in the pediatric population.[22–25] Because infants with BA can be extremely well appearing in the early neonatal period, pediatric practitioners must maintain a high index of suspicion for screening and detection of children with this condition.

Alagille Syndrome

Alagille syndrome is the most common cause of familial intrahepatic obstructive cholestasis with an estimated incidence of 1 in 30,000.[26] It is caused by an autosomal dominant mutation in either the *JAG1* or the NOTCH2 genes, which leads to a paucity of interlobar bile ducts and which is associated with a host of clinical features, including the following: chronic cholestasis, cardiac and vascular anomalies, butterfly vertebrae, ophthalmologic abnormalities, distinct facial differences, and renal abnormalities.[26–28]

Other Obstructive Causes

Other causes of biliary obstruction include biliary cysts (formerly termed choledochal cysts), gallstones or biliary sludge, neonatal sclerosing cholangitis, congenital hepatic fibrosis, obstructive tumors, and inspissated bile (also known as bile plug syndrome—most commonly seen in patients with cystic fibrosis).

Nonobstructive Causes of Cholestasis

Infection

Many of the most common vertically-acquired infections, including cytomegalovirus, toxoplasmosis, rubella, herpes, syphilis, and HIV can all result in cholestasis and conjugated hyperbilirubinemia in the neonatal period. Bacterial infections acquired after birth—including sepsis and urinary tract infections—can also present with cholestasis and should be high on the differential for a jaundiced neonate, especially in the setting of temperature abnormalities.[29,30]

Metabolic and Genetic

A multitude of genetic and metabolic disorders cause defects that lead to intrahepatic cholestasis. Metabolic conditions that present with elevations in conjugated bilirubin include galactosemia, tyrosinemia, citrin deficiency, α_1-antitrypsin deficiency, and disorders of lipid metabolism, including Niemann-Pick and Gaucher diseases, and the Zellweger spectrum of disorders.[12–14,19,27] At the hepatocellular level, mutations affecting the regulation of bile acid formation result in a host of individually described bile acid synthesis disorders. Mutations that lead to defects in storage and membrane transport of bile lead to a multitude of other conditions, including the Dubin-Johnson and Rotor syndromes, and the group of conditions known collectively as progressive familial intrahepatic cholestasis.[1,12–14]

Toxic

Exposure to exogenous toxins in the neonatal period can also lead to hepatocellular injury that presents as cholestasis. Among the most common toxic causes of hepatocyte damage are medications metabolized by the cytochrome p450 system and chronic exposure to total parenteral nutrition.[1,3,14]

DIAGNOSTIC EVALUATION

The Cholestasis Guideline Committee of NASPGHAN recommends that any infant noted to be clinically jaundiced at 2 weeks of age be evaluated for cholestasis.[1] The timing of this evaluation is especially important, because most infants may not have any further evaluation until the 2-month well visit, at which point the window for successful intervention upon many severe causes of cholestasis will have closed. The evaluation of neonatal cholestasis involves a multistepped approach aimed first at rapidly identifying and intervening upon treatable pathology. Disorders like BA that are amenable to surgical intervention must be identified early, and conditions such as sepsis and inborn errors of metabolism must be recognized and treated quickly to minimize disease progression. In addition to laboratory work, a thorough evaluation of the jaundiced infant includes family and gestational history, a complete physical examination with attention to detection of hepatomegaly, and inspection of stool.[1] Because clinicians' visual estimation of jaundice severity is known to be unreliable,

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

providers should have a low threshold to screen infants for cholestasis at the 2-week well visit.[11]

Laboratory Evaluation

The first step in establishing the presence of neonatal cholestasis is laboratory confirmation of conjugated hyperbilirubinemia. Initial laboratory work includes conjugated and total serum bilirubin levels, as well as complete blood count with differential. A blood type and Rh (of both neonate and mother) as well as a direct antiglobulin (Coombs) test on the neonate may be helpful in determining whether hemolytic disease is contributing to elevations in unconjugated (and hence, total) bilirubin. As noted previously, a conjugated bilirubin greater than 1.0 mg/dL in a child with a total bilirubin less than or equal to 5.0 mg/dL is always pathologic and warrants further investigation.[1]

Once the diagnosis of cholestasis is confirmed by the total and conjugated bilirubin, evaluation of serum and liver chemistries—including aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase—is recommended. Alkaline phosphatase levels are of less utility in the neonate given the large variation in normal levels among young infants.[1] Liver function should also be evaluated by measuring prothrombin time and partial thromboplastin time, as well as glucose, albumin, cholesterol, ammonia, and α_1-antitrypsin. Where available, the results of the infant's newborn screen should be reviewed, because in many states, newborn testing panels include assays for galactosemia, hypothyroidism, tyrosinemia, and cystic fibrosis.[1] Bacterial cultures of blood, urine, and other body fluids should be obtained in those patients in which infection remains a concern, and viral assays should be collected in those infants with known risk factors for vertical transmission of viral hepatitis. Upon completion of this initial lab work, consultation with a pediatric gastroenterologist is recommended to determine a plan for additional targeted laboratory evaluation (eg, genetic testing and enzyme function assays), depending on the suspected etiology of the infant's cholestasis.

Imaging

Fasting ultrasound of the liver and biliary tree should be performed in all infants with conjugated hyperbilirubinemia to evaluate for anatomic causes of cholestasis, with a particular focus on prompt detection of BA. Although measurement standards have been developed for the sonographic evaluation of patients with suspected BA, a normal ultrasound result does not definitively rule out the condition.[1] In cases where a normal-appearing ultrasound is accompanied by an otherwise concerning clinical presentation, additional imaging studies can be used to aid in the diagnosis, including hepatobiliary scintigraphy, endoscopic retrograde cholangiopancreatography, and magnetic resonance cholangiopancreatography. Endoscopic retrograde cholangiopancreatography has excellent positive and negative predictive values, but requires expertise and experience, as well as specific equipment that is not available at many centers.[31] Magnetic resonance cholangiopancreatography has been shown to have excellent sensitivity (~99%) for BA, but relatively low specificity, and is thus primarily helpful as an exclusionary test.[32]

In addition to BA, other anatomic causes of cholestasis such as choledochal cysts can be detected on ultrasound. It is important to note that BA and choledochal cysts can co-occur, making exclusion of BA important even in cases where a cyst is detected on initial imaging.[33] In cases requiring imaging beyond initial ultrasound, guidance should be sought from a pediatric gastroenterologist to determine the best study for the patient.

Histopathologic Diagnosis

Percutaneous Biopsy

Liver biopsy remains central to the evaluation of cholestatic jaundice, and the correct diagnosis can be made in 90% to 95% of cases by an experienced pathologist.[34] A standardized system for interpreting the liver biopsies of cholestatic infants has shown to have a high level of sensitivity for the diagnosis of obstruction and of BA.[35] A biopsy may also reveal histological features that can help predict the successful outcome of a KPE and may thus assist the treatment team in determining whether to operate.

Intraoperative Cholangiogram

Intraoperative cholangiography and histological examination of the biliary duct are the criterion standard for the diagnosis of BA in particular and are often performed as a confirmatory test just before initiation of KPE in the operating room.[1]

MANAGEMENT

Management of the cholestatic infant should include close monitoring of stool color, because increasingly acholic stools are suggestive of progressive biliary obstruction and are particularly concerning for BA. All infants with cholestasis should receive supplementation of fat-soluble vitamins (A, D, E, and K).[36] High-calorie enteral/oral hyperalimentation with an increased medium-chain triglyceride fraction is also recommended, especially for those patients in which BA remains a concern, because medium-chain triglycerides do not require bile for absorption.[36] Ursodeoxycholic acid can also assist in ameliorating cholestasis by reducing bile flow and has also been theorized to displace toxic bile acids from hepatocytes. Rifampin can be used to treat pruritus, although its mechanism is unknown. Antihistamines have been shown to be of little utility in treating the pruritus of cholestasis.[37] Further initial management should be directed toward the suspected etiology of the infant's cholestasis and should be performed in conjunction with a pediatric gastroenterologist and with any other appropriate specialists (eg, infectious diseases, genetics, and endocrinology).

PROGNOSIS

The prognosis for infants found to have conjugated hyperbilirubinemia is determined primarily by the underlying etiology of the neonate's cholestasis. Timeliness of diagnosis is essential to ensuring the best prognosis—both in instances in which there is a concern for BA and in cases where other treatable pathology is suspected. For patients with BA, this is difficult because diagnosis is often delayed given that the timeline of normal physiologic jaundice and breastfeeding jaundice are often confounders. Infants with conjugated hyperbilirubinemia as the result of infection or of inborn errors of metabolism, for example, can be extremely ill-appearing upon presentation to care, but can have excellent outcomes if their underlying disease state is rapidly diagnosed and treated.

As noted earlier in this article, KPE procedures performed within the first 2 months of life for infants with BA have a significantly greater chance of success (~70%) in reestablishing biliary flow compared with those performed after 3 months (<25%); nevertheless, late referrals continue to hinder the achievement of good outcomes.[1,4,6,16,18,23,38] Even in cases where bile flow is restored, BA remains a progressive disease with 70% to 80% of patients afflicted infants developing hepatic fibrosis, portal hypertension, and cirrhosis, and approximately 50% of patients requiring liver transplantation before age 2 years.[16,37]

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

REFERENCES

1. Fawaz R, Baumann U, Ekong U, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2016;64:154–168.
2. Dick MC, Mowat AP. Hepatitis syndrome in infancy—an epidemiological survey with 10 year follow up. *Arch Dis Child*. 1985;60:512–516.
3. Balistreri WF. Neonatal cholestasis. *J Pediatr*. 1985;106:171–184.
4. Chardot C, Carton M, Spire-Bendelac N, et al. Is the Kasai operation still indicated in children older than 3 months diagnosed with biliary atresia? *J Pediatr*. 2001;138:224–228.
5. Serinet MO, Wildhaber BE, Broue P, et al. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. *Pediatrics*. 2009;123:1280–1286.
6. Mieli-Vergani G, Howard ER, Portman B, et al. Late referral for biliary atresia—missed opportunities for effective surgery. *Lancet*. 1989;1:421–423.
7. Altman RP, Lilly JR, Greenfeld J, et al. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. *Ann Surg*. 1997;226:348–353; discussion 353–345.
8. Mowat AP, Davidson LL, Dick MC. Earlier identification of biliary atresia and hepatobiliary disease: selective screening in the third week of life. *Arch Dis Child*. 1995;72:90–92.
9. Davis AR, Rosenthal P, Escobar GJ, et al. Interpreting conjugated bilirubin levels in newborns. *J Pediatr*. 2011;158:562–565.e561.
10. Bakshi B, Sutcliffe A, Akindolie M, et al. How reliably can paediatric professionals identify pale stool from cholestatic newborns? *Arch Dis Child Fetal Neonatal Ed*. 2012;97:F385–F387.
11. Moyer VA, Ahn C, Sneed S. Accuracy of clinical judgment in neonatal jaundice. *Arch Pediatr Adolesc Med*. 2000;154:391–394.
12. Trauner M, Meier PJ, Boyer JL. Molecular pathogenesis of cholestasis. *N Engl J Med*. 1998;339:1217–1227.
13. Wagner M, Zollner G, Trauner M. New molecular insights into the mechanisms of cholestasis. *J Hepatol*. 2009;51:565–580.
14. Gottesman LE, Del Vecchio MT, Aronoff SC. Etiologies of conjugated hyperbilirubinemia in infancy: a systematic review of 1692 subjects. *BMC Pediatr*. 2015;15:192.
15. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet*. 2009;374: 1704–1713.
16. Hartley J, Harnden A, Kelly D. Biliary atresia. *BMJ*. 2010;340:c2383.
17. Yoon PW, Bresee JS, Olney RS, et al. Epidemiology of biliary atresia: a population-based study. *Pediatrics*. 1997;99:376–382.
18. McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet*. 2000;355:25–29.
19. Danks DM, Campbell PE, Jack I, et al. Studies of the aetiology of neonatal hepatitis and biliary atresia. *Arch Dis Child*. 1977; 52:360–367.
20. Hussein M, Howard ER, Mieli-Vergani G, et al. Jaundice at 14 days of age: exclude biliary atresia. *Arch Dis Child*. 1991;66:1177–1179.
21. Wadhwani SI, Turmelle YP, Nagy R, et al. Prolonged neonatal jaundice and the diagnosis of biliary atresia: a single-center analysis of trends in age at diagnosis and outcomes. *Pediatrics*. 2008;121:e1438–e1440.
22. Schwarz KB, Haber BH, Rosenthal P, et al. Extrahepatic anomalies in infants with biliary atresia: results of a large prospective North American multicenter study. *Hepatology*. 2013;58:1724–1731.
23. Shneider BL, Brown MB, Haber B, et al. A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000. *J Pediatr*. 2006;148:467–474.
24. Sokol RJ, Shepherd RW, Superina R, et al. Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop. *Hepatology*. 2007;46:566–581.
25. Sundaram SS, Mack CL, Feldman AG, et al. Biliary atresia: indications and timing of liver transplantation and optimization of pre-transplant care. *Liver Transpl*. 2017;23:99–109.
26. Kamath BM, Bason L, Piccoli DA, et al. Consequences of JAG1 mutations. *J Med Genet*. 2003;40:891–895.
27. Hartley JL, Gissen P, Kelly DA. Alagille syndrome and other hereditary causes of cholestasis. *Clin Liver Dis*. 2013;17:279–300.
28. Kamath BM, Spinner NB, Emerick KM, et al. Vascular anomalies in Alagille syndrome: a significant cause of morbidity and mortality. *Circulation*. 2004;109:1354–1358.
29. Rooney JC, Hill DJ, Danks DM. Jaundice associated with bacterial infection in the newborn. *Am J Dis Child*. 1971;122:39–41.
30. Seeler RA, Hahn K. Jaundice in urinary tract infection in infancy. *Am J Dis Child*. 1969;118:553–558.
31. Chardot C. Endoscopic retrograde cholangiopancreatography in patients with neonatal cholestasis: an additional diagnostic tool for selected indications. *J Pediatr Gastroenterol Nutr*. 2009;49:380–381.
32. Liu B, Cai J, Xu Y, et al. Three-dimensional magnetic resonance cholangiopancreatography for the diagnosis of biliary atresia in infants and neonates. *PLoS One*. 2014;9:e88268.
33. Caponcelli E, Knisely AS, Davenport M. Cystic biliary atresia: an etiologic and prognostic subgroup. *J Pediatr Surg*. 2008;43:1619–1624.
34. Morotti RA, Jain D. Pediatric cholestatic disorders: approach to pathologic diagnosis. *Surg Pathol Clin*. 2013;6:205–225.
35. Russo P, Magee JC, Boitnott J, et al. Design and validation of the biliary atresia research consortium histologic assessment system for cholestasis in infancy. *Clin Gastroenterol Hepatol*. 2011;9: 357–362.e2.
36. Fischler B, Lamireau T. Cholestasis in the newborn and infant. *Clin Res Hepatol Gastroenterol*. 2014;38:263–267.
37. Brumbaugh D, Mack C. Conjugated hyperbilirubinemia in children. *Pediatr Rev*. 2012;33:291–302.
38. Balistreri WF, Bezerra JA. Whatever happened to "neonatal hepatitis"? *Clin Liver Dis*. 2006;10:27–53, v.

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.