Neonatal Cholestasis

Erin Lane, MD, Karen F. Murray, MD*

KEYWORDS

• Neonatal cholestasis • Neonatal liver disease • Biliary atresia • Jaundice
• Cholestasis

KEY POINTS

- The initial evaluation of a jaundiced infant should always include measuring serum conjugated (or direct) and unconjugated (or indirect) bilirubin levels.
- Jaundice in an infant that is of very early onset (less than 24 hours of age), persistent beyond 14 days of life, or of new-onset is abnormal and should be investigated.
- Conjugated hyperbilirubinemia in an infant (direct bilirubin levels >1.0 mg/dL or >17 μmol/L, or >15% of total bilirubin) is never normal and indicates hepatobiliary abnormality.
- Infants with cholestasis should be evaluated promptly for potentially life-threatening and treatable causes whereby timing of intervention directly impacts clinical outcomes.

INTRODUCTION

Jaundice in the neonate is common, usually secondary to unconjugated or indirect hyperbilirubinemia, and is most typically not dangerous to the infant. However, even in the setting of the well-appearing neonate, jaundice should be investigated if it is of very early onset (less than 24 hours of life), prolonged beyond 14 days of life, of new-onset, or at high levels. In these settings, it is critical to evaluate for potentially life-threatening causes, such as infection or evolving hepatobiliary dysfunction, and determine if urgent therapeutic intervention is required. Conjugated hyperbilirubinemia warrants expedient evaluation as timing of invention in some cases directly impacts clinical outcomes.

Bile is primarily composed of bile acids, bilirubin, and fats, is formed in the liver, and is secreted into the canaliculus. From the canaliculus, bile flows into biliary ducts from where it is ultimately secreted into the intestine after transient storage within the gallbladder. Disruption of this process at any level results in cholestasis. Cholestasis is the end result of obstruction of the normal excretion of bile from the liver, resulting in the abnormal accumulation of bile salts, bilirubin, and lipids in liver and the blood. Although cholestasis is not synonymous with conjugated hyperbilirubinemia, the abnormal retention of bilirubin, elevated serum levels in cholestasis, low cost, and

Division of Gastroenterology, Seattle Children's Hospital, 4800 Sand Point Way Northeast, M/S OB 9.620, PO Box 50020, Seattle, WA 98115, USA
* Corresponding author.
E-mail address: Karen.murray@seattlechildrens.org

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wide availability of testing make serum-conjugated bilirubin the most clinically useful marker of cholestasis.

Clinically, cholestasis in the infant may present as jaundice, pruritus, fat-soluble vitamin deficiency, or may evolve during or following acute liver failure. Functional or anatomic biliary obstruction is often heralded by the presence of acholic stools. Although cholestasis is frequently the primary presenting symptom of neonatal hepatobiliary disease, it also commonly represents the final common pathway of any disease that affects the neonatal liver. As such, cholestasis is often classified by origin and is designated as either (1) biliary, referring to structural abnormalities and obstruction of extrahepatic or intrahepatic bile ducts; or (2) hepatocellular, resulting from impairment in bile transport, genetic or metabolic abnormalities, and infection.

This review presents an approach to the evaluation of the jaundiced infant. The authors discuss the most common causes, disease-specific evaluation, and clinical management of neonatal cholestasis. In addition, general concepts of supportive care for infants with cholestasis are reviewed.

EVALUATION OF THE JAUNDICED INFANT

Jaundice in the infant is usually clinically evident when the total serum bilirubin level exceeds 2.5 to 3.0 mg/dL (42–51 μmol/L) and is seen as scleral icterus or yellowing of the oral mucosa. However, visual estimates of serum bilirubin levels are inadequate and not precise,[1] and hence, levels should be determined when concern for elevation is raised. Although jaundice in neonates is common and can be physiologic, the continued presence of jaundice at 2 weeks of age should alert providers to the possibility of a pathologic process. A thorough examination and history evaluating for the possibility acute life-threatening conditions such as sepsis are paramount. In addition, clinical evaluation should survey for stigmata of hepatobiliary disease that may be heralded by the presence of dark urine or acholic stools or examination findings of hepatosplenomegaly and ascites. If the infant is exclusively breastfed and is well, the evaluation of serum bilirubin levels may be delayed up to 1 week (until 3 weeks of age) after repeat clinical evaluation.[2] However, if the infant is ill appearing, is formula fed, or carries any additional “red flags” such as poor growth or dysmorphic features, the provider should obtain total and fractionated (direct and indirect) serum bilirubin levels.[2] Conjugated hyperbilirubinemia in an infant (direct bilirubin levels >1.0 mg/dL or >17 μmol/L, or >15% of total bilirubin) is never normal and indicates hepatobiliary abnormality. The identification of elevated unconjugated hyperbilirubinemia warrants a different approach to management and is beyond the scope of this review.

If conjugated hyperbilirubinemia is identified, referral to a pediatric hepatologist is mandatory because timely identification of treatable causes of cholestasis can improve clinical outcomes. Secondary laboratory evaluations after cholestasis is identified may include serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, prothrombin time and international normalized ratio (INR), and albumin levels. The initial diagnostic imagining should include an abdominal ultrasound (US), which can identify congenital anatomic or obstructive causes of cholestasis, including choledochal cysts and gallstones, and screen for vascular anomalies and evidence of portal hypertension such as splenomegaly. Liver biopsy often provides critical information to the diagnostic evaluation of neonates with cholestasis.

An algorithmic approach to the evaluation of the cholestatic infant is summarized in Fig. 1. Specific causes of neonatal cholestasis are reviewed in the text and tabulated in Table 1.