Neonatal Cholestasis: Opportunities To Increase Early Detection

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ABSTRACT

OBJECTIVE: To describe primary care management of early and prolonged jaundice in otherwise-healthy term infants to identify opportunities to increase early diagnosis of cholestasis.
METHODS: Community-based pediatricians in St Louis, Missouri completed a mailed, anonymous, 29-item survey to assess practice demographics, timing of routine newborn office visits, and the management of early and prolonged neonatal jaundice.
RESULTS: A total of 108 of 230 (47%) of eligible physicians responded (mean years in practice, 15.3, SD, 9.4). More respondents were very familiar with national guidelines for management of early (49%) than prolonged (16%) neonatal jaundice. Eighty-six percent reported all newborns were checked with transcutaneous bilirubin before hospital discharge. For transcutaneous bilirubin results at 48 hours of 7, 10, 12 and 15 mg/dL, 1%, 26%, 70%, and 74% of respondents, respectively, would order a fractionated bilirubin. Although the first routine visit usually occurred in the first week after discharge, 25% of physicians reported the 2nd visit was routinely scheduled after 4 weeks of age. Ninety-four percent reported they would obtain a fractionated bilirubin for infants jaundiced beyond 4 weeks of age. If cholestasis was identified at 6 weeks of age, 32% would obtain additional testing without referral to a subspecialist.
CONCLUSIONS: Management of early and prolonged neonatal jaundice is variable. Current practices appear to miss opportunities for early diagnosis of cholestasis and referral that are unlikely to be addressed without redesigning systems of care.

KEYWORDS: biliary atresia; cholestasis; hyperbilirubinemia; kernicterus

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WHAT'S NEW

Care for neonatal jaundice varied greatly. Opportunities for earlier detection of infants with cholestasis include routine follow-up visits at 3 to 4 weeks of age to facilitate testing for conjugated bilirubin for those with prolonged jaundice and immediate subspecialty referral with no additional testing for patients with documented cholestasis.

IN THE UNITED States 60% to 80% of newborns will develop jaundice in the first week of life.[1,2] Most neonatal jaundice is benign and quickly resolves without sequelae, but for those rare cases with underlying liver disease, early identification and treatment can improve outcomes. Biliary atresia (BA), the most common cause of neonatal biliary obstruction and cholestasis, occurs in 1:10,000 to 1:14,000 live births, causes severe liver injury, and, if untreated, causes death by the age of 2 years.[3] Although the pathogenesis of BA is unclear, early diagnosis and surgical treatment may forestall liver transplantation and improve survival.[4–9] Children with rarer causes of cholestasis such as alpha-1-antitrypsin deficiency, Alagille's syndrome, and progressive familial intrahepatic cholestasis also benefit from early diagnosis to prevent complications, most importantly malnutrition and fat-soluble vitamin deficiencies associated with blindness (vitamin A), rickets (vitamin D), central and peripheral neuropathy (vitamin E), and coagulopathy (vitamin K).[10–12] Unfortunately, the diagnosis of cholestasis is often delayed and the benefits of early intervention are not realized.[13] Despite evidence that surgical intervention before 45 days of age improves outcomes,[6,8] the average age at diagnosis of BA in the United States is about 60 days.[4,14–16]

Identifying infants with cholestasis among those with neonatal jaundice is difficult. Initially, newborns with cholestasis are likely to have mild jaundice and are otherwise well.[17] Also, typical measures of total bilirubin that are used to identify hyperbilirubinemia (transcutaneous bilirubin [TcB] or total serum bilirubin [TSB]) do not distinguish those with cholestasis. In 2004, the American Academy of Pediatrics (AAP) published recommendations for the management of early and prolonged neonatal jaundice in otherwise healthy term and near-term infants, with an update with clarifications in 2009.[18,19] The main focus of the guidelines is to reduce the frequency of severe neonatal hyperbilirubinemia and acute bilirubin encephalopathy, thereby preventing kernicterus (estimated incidence, 1:100,000 live births).[18,19]

Universal predischarge screening of all infants with TcB or TSB is recommended with risk assessment for the

development of severe hyperbilirubinemia with phototherapy or exchange transfusion treatment for infants at high risk.[19] For those assessed to be at low risk for severe hyperbilirubinemia follow-up should be timed according to "age at discharge and concerns other than jaundice (eg, breastfeeding)."[19] At follow-up, those with jaundice at or beyond 3 weeks of age should have a fractionated (direct or conjugated) bilirubin measured to assess for cholestasis and underlying liver disease.[18]

Compliance with the guideline recommendations is not known, and their effectiveness in preventing kernicterus remains controversial.[19–24] More detailed guidelines for the management of cholestatic jaundice in infants that recommend a fractionated test for bilirubin at 2 to 3 weeks of age were developed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.[13] Although endorsed by the AAP, these guidelines were not published in a general pediatric journal.

Little is known about current management of neonatal jaundice in the community setting. We sought to describe current practice and to identify opportunities to increase the early identification of infants with cholestatic liver disease within the context of routine management of the common clinical problem of neonatal jaundice. The objective of this study was to describe management by office-based general pediatricians of neonatal jaundice in otherwise healthy term infants.

Design and Methods

We developed and implemented a survey to assess how community pediatricians routinely diagnose and manage jaundice in a newborn and prolonged neonatal jaundice. The study was approved by the Washington University Human Research Protection Office.

Study Population

Eligible physician subjects were office-based general pediatricians who were affiliated with St. Louis Children's Hospital or Washington University Department of Pediatrics. All eligible physicians were mailed a written invitation to participate in the survey, together with the self-administered questionnaire. Because the questionnaire was anonymous, physicians indicated their participation (yes or no) by returning a postcard separate from the questionnaire. Up to 2 additional mailings were sent to those who did not return the postcard.[25]

Study Instrument

The survey was developed by the authors on the basis of the literature and their collective experience in primary and subspecialty care. Survey items were further refined after 2 rounds of pilot testing to increase usability. Items assessed the physician's usual practice regarding the frequency of newborn office visits and the diagnosis and management of neonatal jaundice in the first 6 weeks of life for a healthy term infant. The 29-item survey took approximately 10 minutes to complete and is available in the Appendix (www.academicpedsjnl.com)

Respondents indicated their level of familiarity (very, somewhat, not familiar) with AAP recommendations for management of early and prolonged neonatal jaundice and provided demographic information. They indicated which newborns would routinely get a TcB and a total serum bilirubin before being discharged from the hospital and whether they would routinely order a fractionated bilirubin for all infants with jaundice who were ≥4 weeks old. Participants chose from a list of possible options to indicate their next step in the management of a jaundiced term newborn without any risk factors for severe hyperbilirubinemia with an initial TcB of 7 mg/dL, 10 mg/dL, 12 mg/dL, and 15 mg/dL measured at 48 hours of age. Testing options included no additional testing, repeat TcB, obtain TSB, or obtain bilirubin panel, including direct or conjugated bilirubin, and the treatment option was phototherapy.

In a series of 3 sequential questions describing a developing clinical scenario, respondents selected options from a list (testing with TcB, TSB, or fractionated bilirubin; treatment with phototherapy; primary care follow-up and referral to gastroenterology) to indicate their management of a full term breastfed male infant (otherwise healthy, feeding and voiding well) who had scleral icterus and a TSB of 6 mg/dL at 36 hours. At 4 weeks the infant's jaundice remained but had not worsened. He continued to breastfeed and was gaining weight appropriately and looked well. At 6 weeks, he had a TSB of 6 mg/dL and a conjugated bilirubin of 3 mg/dL.

Data Analysis

Continuous variables are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical data as percent. We used the χ^2 test to test our hypothesis that management in accordance with guideline recommendations would be more likely for physicians who reported they were very familiar with the guidelines. A probability of $P \leq .05$ (2-tailed) was used to establish statistical significance. All statistical analyses were done using STATA 9.0 (Stata Corp.2001. *Stata Statistical Software*: Release 9.0 College Station, TX: Stata Corporation).

Results

Study Population

Between June 24, 2009, and October 27, 2009, surveys were mailed to 230 eligible pediatricians. One hundred eight (47%) pediatricians completed the survey (Table 1). Participants were similar with respect to gender, practice type, and practice location to those (n = 23) who returned a postcard to indicate they would not participate (data not shown), and for age and gender to the sample of pediatricians who completed the AAP Socioeconomic survey in 2010 (www.aap.org/research/periodicsurvey/ps43soci.htm).

Participants were experienced pediatricians (mean years in practice 15.3, SD 9.4) most of whom worked in suburban practices. The median number of newborns seen per year was 100 (IQR 60−150). Respondents reported being "very familiar" with current AAP recommendations for