



# Newborn Screening for Biliary Atresia

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Biliary atresia is the most common cause of pediatric end-stage liver disease and the leading indication for pediatric liver transplantation. Affected infants exhibit evidence of biliary obstruction within the first few weeks after birth. Early diagnosis and successful surgical drainage of bile are associated with greater survival with the child's native liver. Unfortunately, because noncholestatic jaundice is extremely common in early infancy, it is difficult to identify the rare infant with cholestatic jaundice who has biliary atresia. Hence, the need for timely diagnosis of this disease warrants a discussion of the feasibility of screening for biliary atresia to improve outcomes. Herein, newborn screening for biliary atresia in the United States is assessed by using criteria established by the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. Published analyses indicate that newborn screening for biliary atresia by using serum bilirubin concentrations or stool color cards is potentially life-saving and cost-effective. Further studies are necessary to evaluate the feasibility, effectiveness, and costs of potential screening strategies for early identification of biliary atresia in the United States.

Biliary atresia is the most common cause of pediatric end-stage liver disease and the leading indication for pediatric liver transplantation.<sup>1</sup> Infants with biliary atresia develop jaundice and pale, acholic stools within the first few weeks after birth, secondary to fibroinflammatory obstruction of the extrahepatic bile ducts that drain bile from the liver into the intestines. Early diagnosis and successful surgical drainage of bile (the Kasai hepatic portoenterostomy) are associated with greater survival with the child's native liver. Lack of effective drainage inevitably results in liver failure within a year and death within 2 years without transplantation. Successful surgical drainage can, in most instances, prevent or delay the need for liver transplantation, which is associated with significant morbidities from requisite lifelong immunosuppression.<sup>2-5</sup> Unfortunately, because noncholestatic jaundice is extremely common in early infancy, it is difficult to identify the rare infant with cholestasis who has biliary atresia. Education regarding the importance of early identification of biliary atresia could be included in professional continuing education programs for primary care physicians. Thus, the need for timely

## abstract

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diagnosis of this disease warrants a discussion of the feasibility of screening for biliary atresia to improve outcomes.

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children, established in 2003, evaluates conditions nominated for inclusion in the Recommended Uniform Screening Panel and subsequently makes recommendations to the secretary of the US Department of Health and Human Services.<sup>6</sup> An external evidence review group informs the Advisory Committee on the direct and indirect evidence used to answer a series of key questions regarding the potential benefit of newborn screening for a condition. The Advisory Committee then grades the evidence in terms of the benefit of screening and feasibility of screening for the condition.<sup>6–8</sup> Herein, these key questions are used to inform a consensus among the authors of this report in the evaluation of newborn screening for biliary atresia in the United States.

Biliary atresia is an idiopathic cholangiopathy presenting with a

#### KEY QUESTION SET 1: DEFINING BILIARY ATRESIA AND THE EXTENT OF DISEASE

- Is there a case definition for biliary atresia that can be uniformly and reliably applied?
- What is the incidence and prevalence of biliary atresia?
- What is the natural history of biliary atresia, including the spectrum of severity and variations by key phenotypic or genotypic characteristics?

series of findings: (1) complete obstruction of extrahepatic bile ducts documented by cholangiography or bile duct histology, (2) proliferation of intrahepatic bile ducts on liver

biopsy, and (3) marked intrahepatic fibrosis at an early age.<sup>4</sup> The reported incidence of biliary atresia ranges from 5 per 100 000 in the Netherlands to 32 per 100 000 live births in French Polynesia.<sup>9</sup> The incidence of biliary atresia is approximately 6.5 to 7.5 per 100 000 live births in the US mainland and 10.1 per 100 000 live births in Hawaii.

The natural history of biliary atresia explains why it is difficult to diagnose. Infants with biliary atresia generally appear healthy as newborns. They do, however, exhibit jaundice at birth or shortly thereafter and may be clinically indistinguishable from infants with nonconjugated or indirect hyperbilirubinemia, such as “physiological jaundice” and “breast milk-associated jaundice.” Conditions causing conjugated or direct hyperbilirubinemia, which are much less common, include infections, such as toxoplasmosis, rubella, cytomegalovirus, herpes, and hepatitis B, and genetic conditions, such as Alagille syndrome,  $\alpha$ -1 antitrypsin deficiency, cystic fibrosis, progressive familial intrahepatic cholestasis, mitochondrial hepatopathies, and bile acid synthesis defects. The diagnosis of biliary atresia should be considered for any infant with an elevated serum conjugated bilirubin concentration and pale or acholic stools. Because nearly half of all newborn infants exhibit jaundice in the early days of life, making a diagnosis other than physiologic jaundice or breast milk-associated jaundice is challenging. Thus, a late-stage diagnosis of biliary atresia is not uncommon.

The treatment of biliary atresia is the hepatic portoenterostomy, as originally described by Kasai in 1959. The operation involves excision of the extrahepatic biliary tree, with reestablishment of bile flow via a Roux-en-Y segment of intestine sewn directly to the liver at the portal

plate.<sup>1</sup> Whereas all infants with biliary atresia not receiving the Kasai operation will need liver transplantation in the first 1 to 2 years of life, infants receiving the Kasai operation gain considerable benefit, and some avoid liver transplantation altogether. Ultimately, however, approximately 80% of all patients with biliary atresia will require liver transplantation by 10 years of age.<sup>1</sup> Patients with successful biliary drainage may develop cirrhosis more slowly, which can delay the need for liver transplantation into childhood or early adult life. This group of patients is generally healthier before the transplantation, has a larger pool of liver donors for the liver transplantation, and has a better postoperative course after liver transplantation. The most significant factor correlating with success of the Kasai operation is the infant’s age at the time of surgery, with younger infants receiving the greatest benefit. The extent of intrahepatic fibrosis at the time of diagnosis is a key pathologic finding that correlates negatively with prognosis with treatment.<sup>1,10</sup> Clinical evidence of cirrhosis at diagnosis (ie, presence of ascites) correlates with poorer outcome after portoenterostomy.<sup>1</sup> Evidence of associated splenic malformations, such as asplenia or polysplenia, also is associated with poorer outcomes.<sup>1,11</sup>

Hence, there is a good case definition of biliary atresia, which is uniformly and reliably applied; the incidence is comparable to other diseases for which screening is performed, such as phenylketonuria and congenital adrenal hyperplasia; and early recognition and treatment contribute to improving transplant-free survival.

Two screening tests have been investigated: serum conjugated or direct bilirubin concentrations and stool color cards. Because the earliest

## KEY QUESTION SET 2: MODALITIES AND POTENTIAL EFFECTIVENESS OF SCREENING FOR BILIARY ATRESIA

- What methods are available to screen newborn infants for biliary atresia?
- What are the accuracy; the ability to distinguish early versus late onset cases; the sensitivity, specificity, and predictive values; the analytic and clinical validity; and the feasibility of implementing these methods for universal screening?
- What are the potential harms or risks of screening for biliary atresia?
- What is known about costs and cost-effectiveness of screening for biliary atresia? What pilot testing has taken place in population studies or clinical groups?

indicator of abnormality in biliary atresia is an increased conjugated bilirubin concentration, this is a logical test to investigate for universal screening, and several studies have found promising results. In 2003, Powell et al<sup>12</sup> studied a large community-based program in the United Kingdom wherein conjugated bilirubin concentrations were measured from blood samples in neonates younger than 28 days. Of 23 415 samples, conjugated bilirubin concentrations exceeded 18  $\mu\text{mol/L}$  (1.05 mg/dL) in 3.8% of samples. The fraction of conjugated bilirubin relative to total bilirubin exceeded 20% in 16% of samples, and 107 samples (0.46%) exceeded both cutoffs. No infant with a normal test result had liver disease. Thus, this test had a sensitivity of 100%, a specificity of 99.59%, and a positive predictive value of 10%, which is low because of the rarity of clinical liver disease in neonates. Ultimately, 11 of 12 infants with abnormal results on repeat testing were diagnosed with liver disease, 2 of whom had biliary atresia. Although the authors concluded that serum conjugated

bilirubin concentration may be an effective marker for neonatal liver disease, the sensitivity and specificity of screening for biliary atresia may not be accurate, given that only 2 infants would be expected to have biliary atresia in the sample size used. Additional larger studies are, therefore, needed to validate these findings.

Harpavat et al<sup>13</sup> retrospectively studied whether elevated conjugated bilirubin concentration can be used as an early screening test for infants with biliary atresia. Of 61 infants with biliary atresia, 34 had had serum direct or conjugated bilirubin concentration measured within 96 hours of life, and all demonstrated elevated concentrations, which increased over the first 96 hours. The authors speculated that an elevated conjugated bilirubin concentration might be present in all infants with biliary atresia in the immediate postnatal period. In subsequent follow-up, the authors have validated this observation by identifying elevated conjugated bilirubin concentration shortly after birth in 32 of 32 infants cared for at their institution who were later diagnosed with biliary atresia (S. Harpavat, MD, PhD, personal communication, 2015). Thus, serum conjugated or direct bilirubin concentration could prove a valuable screening test for biliary atresia. Cutoffs for the upper limit of normal in young infants would need to be verified in each hospital laboratory. The test would also need to be accompanied by an aggressive educational program for health care providers for an understanding of age-related normal values, as the infants in the Harpavat et al<sup>13</sup> study who had an early abnormal conjugated bilirubin concentration did not come to medical attention any sooner than those who did not have neonatal conjugated or direct bilirubin tested. These observations, in conjunction with those of Powell et al,<sup>12</sup> indicate great potential for serum bilirubin determinations as a screening tool for biliary atresia.

The second potential screening test is the use of stool color cards. The first universal national screening program was implemented in Taiwan, where there is a relatively high incidence of biliary atresia (37/100 000 live births) and, therefore, great motivation to identify infants with biliary atresia early.<sup>14</sup> Parents of all newborn infants were given color cards that showed examples of normal and acholic stools and were asked to report the color of their infant's stool to their pediatrician. In this study, cards were returned for 65% of 119 973 infants. Ninety-four of these infants had acholic stools, and 29 (31%) were ultimately diagnosed with biliary atresia, 90% of whom were diagnosed before 60 days of age. In the Taiwanese population, the stool color card screening program had a sensitivity of 89.7%, a specificity of 99.9%, a positive predictive value of 28.6%, and a negative predictive value of 99.9% for identification of biliary atresia.<sup>14</sup> Positive results from the screening led to focused diagnostic evaluations. In subsequent analyses, the authors concluded that implementation of this screening program led to earlier diagnosis and earlier Kasai surgery (66% vs 49% at <60 days of age) and was associated with improved 3-year jaundice-free survival (57% vs 31.5%) compared with a cohort of historical controls.<sup>15</sup> Confounding this correlation, however, was the increased use of prophylactic antibiotic agents, which may have prevented cholangitis and improved outcomes, following the Kasai operation in Taiwan part of the way through the historical control time period. Given these encouraging observations, Argentina<sup>16</sup> and Switzerland<sup>17</sup> implemented similar nationwide stool color card screening and biliary atresia education programs.

Gu et al<sup>18</sup> recently reported the 19-year experience of Tochigi Prefecture in Japan with stool color card screening for biliary atresia. The

authors reported a decrease in the mean age at the time of the Kasai procedure from 70.3 days to 59.7 days. Of the 34 infants in whom biliary atresia was diagnosed during the study period, 26 were identified via screening. Eight infants were not identified via screening at 1-month follow-up for a variety of reasons, including no action taken despite reporting of pale stool, loss to follow-up, and noncompliance with use of the stool color card. These patients underwent the Kasai procedure at a much later age than those who were identified and promptly worked up for biliary atresia ( $77.5 \pm 20.4$  days vs  $54.3 \pm 15.8$  days;  $P = .002$ ). Survival with native liver for the 34 identified infants was better at 5, 10, and 15 years (87.6%, 76.9%, and 48.5%, respectively) compared with historical controls. Through 2010, the stool color card program has since expanded to 16 other administrative divisions in Japan.

Thus, serum conjugated bilirubin concentrations and stool color cards both exhibit reasonable clinical validity as potential screening modalities for biliary atresia. In neither case is there significant clinical risk or harm to the infant undergoing screening. It could be proposed that blood be drawn for serum bilirubin determinations at the same time as for any other blood tests before discharge from the newborn nursery.

Biliary atresia is currently diagnosed by using a number of modalities. Infants with unexplained conjugated hyperbilirubinemia can undergo serologic testing, including antibody titers against infectious diseases, including toxoplasmosis, rubella, cytomegalovirus, herpes, hepatitis B, syphilis, Coxsackie virus, Epstein-Barr virus, varicella-zoster virus, and human parvovirus, all of which can be associated with jaundice. Ultrasonography of the liver can assess for the presence and size of the gallbladder and identify abnormal

### KEY QUESTION SET 3: CURRENT METHODS OF TESTING FOR BILIARY ATRESIA

- What are the current methods and costs of diagnostic testing for biliary atresia and availability and capability of diagnostic centers?
- For treatment, does presymptomatic or early symptomatic treatment improve health outcomes, and if so, more than treatment after symptoms develop?

findings at the porta hepatis, as well as identify a choledochal cyst. Ultrasonography also can determine the presence of ascites, whether 1 or multiple spleens are present, and the echogenicity of the liver, which is potentially reflective of fibrosis. A technetium-labeled hepatobiliary iminodiacetic acid scan can be performed to determine whether bile drains into the gastrointestinal tract. Nonexcretion of radioisotope into the intestines after initial uptake by hepatocytes is consistent with biliary atresia but may also occur in other intrahepatic cholestatic diseases, and, thus, it is a nonspecific finding. Liver biopsy can be performed to assess for pathologic features of biliary atresia percutaneously under conscious sedation or via a laparotomy with a wedge liver biopsy under general anesthesia if there are greater concerns for bleeding given coagulopathy. Liver transient elastography and sonography are currently under investigation to determine extent of fibrosis noninvasively before surgery.<sup>19</sup> Ultimately, the diagnosis of biliary atresia is confirmed and the Kasai procedure is performed after direct intraoperative visual inspection and intraoperative cholangiography performed by a pediatric surgeon. Charges and costs for these tests and procedures vary widely, and there are insufficient data to determine the cost for diagnosis.

Early diagnosis and treatment is optimal for biliary atresia. All infants with biliary atresia initially exhibit jaundice. They eventually excrete acholic stools. As weeks pass and the liver becomes increasingly fibrotic, infants with biliary atresia will exhibit manifestations of portal hypertension with abdominal ascites and spider angiomas. Failure to thrive, fat-soluble vitamin deficiencies, and cachexia also can develop because of profound malabsorption. The Kasai operation is ideally performed before onset of portal hypertension.

Kasai portoenterostomy is well established as the treatment of biliary atresia. Success rates of biliary drainage after the Kasai operation range from 47% in the United States to 65% in Japan.<sup>1,20</sup> Numerous studies have demonstrated that early diagnosis and treatment with the Kasai operation are associated with better survival without liver transplantation. A retrospective analysis of 251 patients at a single center found that 10-year survival without transplantation was highest (73%) if age at time of surgery was <60 days and lowest (11%) if age at

### KEY QUESTION SET 4: EFFECTIVENESS OF TREATMENT OF BILIARY ATRESIA

- What is known about the efficacy and effectiveness of treatment?
- What is the relationship between treatment timing and treatment outcomes?
- Is treatment standardized? What are the potential harms or risks of treatment?

time of surgery was >91 days.<sup>20</sup> Two other cohort studies similarly showed greatest success rates when surgical drainage was performed at <30 or <45 days of age.<sup>21</sup> More recently, a prospective study of 159 infants funded by the National Institutes of Health reported that performance of



the Kasai procedure at <75 days was associated with greater transplant-free survival.<sup>1</sup> Delayed treatment by Kasai procedure is associated not only with progressive liver failure but also with impaired neurodevelopmental outcome and poor nutritional status.<sup>22,23</sup> Although early diagnosis is associated with improved outcomes after Kasai operation, diagnosis at the time of end-stage liver failure may occur.<sup>1</sup> Screening would enhance awareness of biliary atresia within the pediatric community.

Even a successful Kasai operation with reestablished flow of bile does not ensure cessation of fibrogenesis and prevention of end-stage liver failure. However, without a successful Kasai operation, progression to end-stage liver failure is more rapid and inevitable. Postoperatively, ascending cholangitis is a common complication. Lee et al<sup>24</sup> reported that 27 (64%) of 42 patients experienced at least 1 episode of cholangitis after Kasai operation. Most patients in their cohort experienced multiple episodes of cholangitis requiring hospitalization, with an average length of stay of 15 days. Ng et al<sup>25</sup> reported that 17% of 219 patients who retained their native livers at least 5 years after their Kasai operations had experienced an episode of cholangitis in the preceding year.

A screening test algorithm for biliary atresia has 1 clear goal: to identify affected infants early so they can receive an early Kasai operation and associated benefits, without placing an excessive burden on families and the health care system from false-positive results. Both screening options have advantages and disadvantages. Conjugated bilirubin measurements are widely available, easily interpretable, and inexpensive, with clear cutoffs for abnormal values. They do require blood to be drawn, as conjugated bilirubin concentrations are not measured by instruments measuring

#### KEY QUESTION SET 5: IMPLICATIONS OF SCREENING FOR BILIARY ATRESIA

- What incremental costs are associated with the use of the screening test in (state) newborn screening programs for biliary atresia?
- What are the costs of diagnosis and the failure to diagnose in the presymptomatic period?
- What is the availability of treatment and the costs associated with treatment?

transcutaneous bilirubin. This blood can be obtained at the time of heel stick for the state newborn screen or when blood is obtained for total bilirubin measurements before hospital discharge. Ongoing prospective studies will further address problems and solutions with conjugated bilirubin screening.

The stool color card, on the other hand, avoids drawing blood. The cost is very low for essentially a colored postcard (less than \$0.06 per card); however, its interpretation is more subjective and requires pediatricians and parents to work together to address questions about stool color. In addition, stools become acholic over time, so there is no “start” or “stop” time for the screening. Rather, it is a continuous screen, in which stools are monitored for the first few months of life. In some countries, there is a 1-month well-child visit (eg, for administration of hepatitis B virus vaccine) at which time the stool color card results are captured, allowing for early diagnosis of biliary atresia. The lack of a consistent follow-up visit at 1 month in the United States creates a challenge. Finally, a referral process would need to be clearly developed to ensure that all infants with a positive screen undergo the next level of evaluation. Thus, issues under Key Question 5 are continuing to be addressed and vary depending on the screening modality used.

Because biliary atresia is the number 1 cause of pediatric end-stage liver disease and liver transplantation, a disproportionately large fraction of total health care expenditures is spent on this relatively rare but highly morbid disease.<sup>4</sup> It is important to note that this conclusion was based on extrapolations from adult data and, therefore, underestimates the true cost of care related to lifelong immunosuppression after transplantation in the pediatric population. Hence, preventing or delaying liver transplantation through an early diagnosis translates to reduced health care expenditures, as further documented by a series of pediatric studies, 2 of which are briefly summarized in the next paragraph.

Mogul et al<sup>26</sup> modeled the cost-effectiveness of screening using the stool color card in the United States. By using Markov modeling based on the Taiwan Health Bureau findings projected over 20 years, screening with the stool color card was associated with nearly 30 life-years gained, 11 fewer transplants, 3 fewer deaths, and a decrease in total costs of nearly \$9 million. Moreover, the authors concluded that there was a greater than 97% likelihood that screening using stool color cards would result in a gain in life-years and a significant cost savings. Schreiber et al<sup>27</sup> conducted a prospective study in which infant stool color cards were distributed to more than 6000 families in the maternity ward of a Canadian women’s hospital. The authors used a variety of strategies to follow up on the infant stool color, from voluntary return of the cards at 30 days of age to follow-up with family physicians or families by random phone survey. The authors estimated stool color card utilization at 60% to 94%. By using Markov modeling, the authors further estimated the cost of screening in the Canadian population at approximately \$213 000, for a gain of

9.7 life-years. The authors concluded that screening for biliary atresia by using infant stool color cards was not only feasible, but also effective and cost-effective. Although both studies support the cost-effectiveness of stool color card screening for biliary atresia, it should be noted that both studies relied on extrapolations from results in Taiwan, which may or may not be applicable in North America. Thus, further cost-effectiveness analysis based on a North American pilot study using stool color cards is required before concluding a true cost benefit in the United States.

The cost-effectiveness of screening by using serum conjugated bilirubin concentrations has not yet been established. It is worth noting, however, that many newborn nurseries routinely determine serum bilirubin concentrations at birth. As Harpavat et al<sup>13</sup> noted, all infants who had serum bilirubin determinations performed and ultimately were diagnosed with biliary atresia had elevated conjugated bilirubin concentrations. It is, therefore, worth further investigation to determine the cost-effectiveness of conjugated bilirubin determinations during the first few days of life.

It is important to note, however, that there are “hidden” costs associated with screening for biliary atresia using stool color cards. These include the additional time required to explain biliary atresia screening to parents, which, if past is prologue, will likely be added to preventive services without being recognized as increased services by public and private payers. Also, these additional newborn screening interventions will generate increased office visits and phone calls from concerned parents bringing their “color cards” and possibly soiled diapers for follow-up evaluation by the pediatrician. Future research on cost-effectiveness will be required to consider all costs, including those that may be

considered “hidden.” Nonetheless, even though stool color card screening for biliary atresia has not yet been performed in North America, these cost-effectiveness modeling data are encouraging, and there is merit to pursuing pilot testing to confirm these analyses.

## CONCLUSIONS

The natural history of biliary atresia is sufficiently well established. Early diagnosis is clearly associated with better outcomes for infants with biliary atresia. Outcomes after the Kasai operation in the United States could potentially be improved with early diagnosis. Stool color cards distributed to mothers on discharge would not only function as a screening tool but also for educating primary care physicians and parents, engendering awareness that there is an abnormal color to infant stool.

Newborn screening for conjugated hyperbilirubinemia requires additional analysis. The American Academy of Pediatrics already recommends newborn screening for hyperbilirubinemia. Many nurseries, however, use transcutaneous bilirubin measurements in lieu of serum bilirubin determinations, but thus far, only newborn serum conjugated hyperbilirubinemia has been correlated with the eventual diagnosis of biliary atresia, and the utility of newborn serum conjugated bilirubin screening for biliary atresia remains unknown.

At this point, there is not sufficient evidence to conclude with a high degree of certainty that newborn screening would provide significant benefit for biliary atresia. Pilot studies are necessary to evaluate the feasibility, effectiveness, and costs of potential screening strategies for early identification of biliary atresia in the United States.

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## KEY POINTS

- Biliary atresia is a rare disease with high morbidity and mortality for which the natural history is reasonably well understood.
- Early performance of the Kasai portoenterostomy with successful surgical drainage of bile is associated with better outcomes for infants with biliary atresia; therefore, educational programs for pediatricians and other pediatric care providers to increase awareness of biliary atresia may be helpful.
- Published analyses indicate that newborn screening for biliary atresia, either by measuring serum conjugated bilirubin concentrations or using stool color cards, is potentially of sufficient sensitivity and specificity to be cost-effective.
- Further studies are necessary to evaluate the feasibility, effectiveness, and costs of potential screening strategies for early identification of biliary atresia in the United States.

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