Screening for biliary atresia: it's in the cards

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Biliary atresia (BA) is a serious pediatric liver disease. It is the leading cause of cholestasis in newborns, the most frequent reason for cirrhosis and liver-related death in infants and children, and the foremost indication for liver transplantation in the pediatric population. The condition, of unknown pathogenesis, arises from a rapidly progressive sclerosing injury of large bile ducts that results in the complete blockage of bile flow.[1] While not an inherited condition, BA occurs in 1:19 000 live births in Canada (similar to rates reported in France [1:20 000] but less frequently than in Asia [1:9460]) and manifests exclusively in the first weeks of life with jaundice and pale (acholic) stools.[2] In contrast to the approximately two-thirds of newborns with benign jaundice due to unconjugated hyperbilirubinemia, BA results in an obstructive-type jaundice with conjugated hyperbilirubinemia. The current standard of care for BA involves sequential surgical treatment with an initial hepatic portoenterostomy (Kasai procedure [KP]), in which the obstructed extrahepatic bile duct is resected and a loop of bowel is brought to the porta of the liver to restore bile flow, followed by liver transplantation for those cases that progress to liver failure. Infants who do not receive the initial KP or for whom the KP fails to re-establish bile flow require semiurgent liver transplantation and have a worse prognosis. Left untreated, all infants with BA will die by 3 years of age.

Problem of late referral

The most important prognostic factor for a successful KP is the age of the infant at the time of the procedure. The best outcomes are achieved when the KP is performed at or before 30 days of age.[2] In a large Canadian cohort study (N = 349), the worst outcomes were in patients who underwent KP at older than 90 days of age, with a high likelihood of KP failure and need for liver transplant. Only 14% of BA cases who received the operation after 90 days of age still had native liver survival by 4 years of age.[2] Late referral, delayed diagnosis, and untimely surgery for BA are worldwide problems.[2] In Canada, the median age at BA referral to a tertiary centre was 59 days, and about 20% of Canadian BA patients were identified after 90 days of age (late referral).[2]

This article has been peer reviewed.
Can Fam Physician 2017;63:424-5

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Many factors contribute to late referral and delayed KP.[3] The cardinal clinical features of BA are jaundice and pale stools. However, jaundice in neonates is often considered inconsequential and no further investigations are pursued. Moreover, the assessment of stool colour is not routine to "well-baby" care, and monitoring for pale stools, especially in infants with jaundice, is not standard practice for health care providers or parents. In general, there is a poor understanding among health care providers of the importance of early identification of BA. Although the Canadian Paediatric Society recommends total and conjugated (direct) bilirubin testing in all neonates with jaundice beyond 2 weeks of age, this is rarely done. In most jurisdictions, ordering a test for total bilirubin does not automatically trigger a test for conjugated bilirubin. Therefore, any physician managing a newborn with prolonged jaundice who requisitions a serum total bilirubin test or uses transcutaneous bilirubin measurement will not identify BA cases with conjugated hyperbilirubinemia. Additionally, the well-baby visit schedule in Canada is not uniform across jurisdictions and often infants are seen at 2 and then 8 weeks of age, at which time the "window of opportunity" for early BA case identification has nearly passed.

Screening for BA using infant stool colour cards

Efforts have been made worldwide to facilitate earlier diagnosis and more timely KP in order to improve outcomes.[4,5] Attempts to develop a BA diagnostic biochemical test have been hampered by the lack of a known disease-specific serum or urine biomarker. Recently, Taiwan introduced a universal infant stool colour card screening program for BA, with proven success.[6,7] The rate of KP surgery at earlier than 60 days increased from 47% to 74%, and no case underwent KP at later than 90 days.[6] Since the introduction of the screening program, there has been a remarkable increase in the success of the KP (61%), and the 3-year native liver survival rate is 62%.[7] This is well above the current Canadian 4-year native liver survival rate of 39%.[2]

A recent project funded by the Canadian Institutes of Health Research involving more than 9000 families showed that, in Canada, introduction of a BA stool colour card screening program would be feasible and highly cost effective, and that such a program would be used by families.[8,9] Based on these studies, a BA home screening program was implemented throughout British Columbia (BC) in July 2014. The program is managed by Perinatal Services BC and is designed such that the parents of each

newborn are issued a stool colour card when they are discharged from the maternity ward, or at home by their midwives, with instructions to monitor their infant's stool colour every day for the first month of life. The stool card has 6 pictures depicting shades of abnormal (pale) stool colour and 3 pictures depicting shades of normal stool colour. If parents notice an abnormal stool colour, they are instructed to call the screening centre using a toll-free number. Perinatal Services BC expedites telephone follow-up with a pediatric hepatologist who then decides whether any further evaluation is required.

Additionally, in BC and Alberta, a policy has been implemented that requires all laboratories to automatically test for both total and fractionated (conjugated or direct) bilirubin whenever a serum bilirubin test is requisitioned for a child between 7 days and 1 year of age. If the result finds the conjugated bilirubin fraction is above 20% of the total bilirubin, the following flagged message will appear: "Conjugated hyperbilirubinemia in infants is considered pathologic when conjugated bilirubin is greater than 20 percent of total bilirubin. Prompt evaluation is necessary, especially to assess biliary atresia."

How can you help?

If parents present to your office with concern that their infant's stool colour is pale, or the infant has prolonged jaundice beyond 2 weeks of age, it is recommended that a serum total and conjugated bilirubin test is requisitioned. For further information about the home BA screening program, please go to **www.perinatalservicesbc.ca** and click on the screening programs link.

Biliary atresia is the most important and serious pediatric liver disease. Early diagnosis before 2 months of age yields the best outcomes. Careful assessment of newborn infants for persistent jaundice and pale stool colour in the first month of life is key to timely case identification. A test for serum bilirubin including the conjugated fraction is recommended should there be any concern. More information about the new BA home screening program introduced in BC using infant stool colour cards is available from **www.perinatalservicesbc.ca**.

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Competing interests
None declared

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References

1. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet* 2009;374(9702):1704-13.
2. Schreiber RA, Barker CC, Roberts EA, Martin SR, Alvarez F, Smith L, et al. Biliary atresia: the Canadian experience. *J Pediatr* 2007;151(6):659-65.
3. Chitsaz E, Schreiber RA, Collet JP, Kaczorowski J. Biliary atresia: the timing needs a changin'. *Can J Public Health* 2009;100(6):475-7.
4. Sokol RJ. Biliary atresia screening: why, when and how? *Pediatrics* 2009;123(5):e951-2.
5. Benchimol EI, Walsh CM, Ling SC. Early diagnosis of neonatal cholestatic jaundice. Test at 2 weeks. *Can Fam Physician* 2009;55:1184-92.
6. Hsiao CH, Chang MH, Chen HL, Lee HC, Wu TC, Lin CC, et al. Universal screening for biliary atresia using an infant stool color card in Taiwan. *Hepatol* 2008;47(4):1233-40.
7. Lien TH, Chang MH, Wu JF, Chen HL, Lee HC, Chen AC, et al. Effects of the infant stool color card screening program on 5-year outcome of biliary atresia in Taiwan. *Hepatol* 2011;53(1):202-8. Epub 2010 Dec 7.
8. Schreiber RA, Masucci L, Kaczorowski J, Collet JP, Lutley P, Espinosa V, et al. Home-based screening for biliary atresia using infant stool colour cards: a large-scale prospective cohort study and cost-effectiveness analysis. *J Med Screen* 2014;21(3):126-32. Epub 2014 Jul 9.
9. Morinville V, Ahmed N, Ibberson C, Kovacs L, Kaczorowski J, Bryan S, et al. Home-based screening for biliary atresia using infant stool color cards in Canada: Quebec feasibility study. *J Pediatr Gastroenterol Nutr* 2016;62(4):536-41.