American Academy of Pediatrics – CA2 Newsletter – May 2017

Peds@CA2 e-News

F. Tania Mitsinikos, MD, FAAP
Clinical Fellow, PGY-6
Division of Gastroenterology
Children's Hospital Los Angeles

Daniel W. Thomas, MD, FAAP
Medical Director of Liver and Intestinal Transplant,
Division of Gastroenterology
Children's Hospital Los Angeles

When Hyperbilirubinemia Isn't Physiologic – A Modern Day Screening Approach

Every pediatrician is well trained to screen and identify neonates with hyperbilirubinemia. The American Academy of Pediatrics (AAP) has established guidelines for screening and management of neonates with hyperbilirubinemia[1]. Fortunately, the incidence of kernicterus, caused by unconjugated hyperbilirubinemia, has declined over the years and is estimated to be near 1 in100,000, but is largely unknown due to lack of definitive epidemiologic studies, particularly in the United States[2,3]. Risk factors for hyperbilirubinemia leading to neurotoxicity include: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, sepsis, acidosis, and albumin <3.0 mg/dL, which differ somewhat from the risk factors for severe hyperbilirubinemia[4]. However, there is a larger group of neonates with conjugated hyperbilirubinemia that need our heightened attention due to long-term morbidity and mortality, which is only briefly touched upon in the AAP recommendations.

Conjugated or direct hyperbilirubinemia in the neonate requires just as much clinical concern as unconjugated or indirect hyperbilirubinemia to prevent serious medical sequelae. After a screening bilirubin has been obtained and is found to be

elevated, a fractionated bilirubin should be checked, as the approach to the infant with elevated conjugated or unconjugated fractions is very different. The AAP recommends that possible causes of jaundice should be sought in an infant receiving phototherapy or whose total serum bilirubin level is rising rapidly, and is not explained by the history and physical examination (i.e. including measurement of direct or conjugated bilirubin). Sick infants and those who are jaundiced at or beyond three weeks of age also should have measurement of total and direct or conjugated bilirubin to identify cholestasis per AAP guidelines[1]. Conjugated hyperbilirubinemia is almost always indicative of intrinsic cholestatic liver disease, and what we as gastroenterologists are most concerned about is evaluation for biliary atresia (BA). Although seemingly rare, its incidence is equivalent to that of childhood leukemia, closer to 1 in 10,000.

BA is a congenital defect of the biliary system resulting from an obliterative necroinflammatory cholangiopathy and eventual absence of the extrahepatic biliary tree that prevents normal bile elimination from the liver. Affected infants universally have acholic stools due to lack of biliary excretion. An abdominal ultrasound is often obtained in infants suspected as having cholestatic liver disease and BA, and while technician dependent, may show a small or absent gallbladder, or common bile duct. Confirmation of BA is made with liver biopsy and intraoperative cholangiogram demonstrating failure of passage of contrast into the duodenum. Identification of these infants at a young age allows earlier intervention. The treatment is surgical in which is a Kasai portoenterostomy (HPE) is performed. Proximal small bowel is used to replace the child's atretic biliary system and is attached to the liver hilum in a roux-en-Y fashion to facilitate bile drainage[5]. Optimal timing of this procedure is before 60 days of life, as outcomes beyond this age are generally poor[5,6]. Not only is timing of surgery important, but in patients who have successful biliary draining surgery, defined as total bilirubin less than 2.0 three months post-operatively, have improved transplant-free survival, reaching 45.6%[7].

If the diagnosis is missed or made late and a Kasai HPE is either not done or the surgery is unsuccessful, end-stage liver disease occurs quite rapidly. Complications of

progressive cholestatic liver disease include ascites and potential respiratory compromise, electrolyte disturbances, gastrointestinal bleeding from varices, poor nutritional intake and absorption resulting in malnutrition, bone disease due to vitamin D deficiency as well as other fat-soluble deficiencies, and infection (particularly ascending cholangitis in patients who have had a Kasai HPE). Management is targeted at each of these complications, using fluid and sodium restriction, diuretics such as furosemide and spironolactone to control fluid excess, esophagogastroduodenoscopy with sclerotherapy or banding to treat and prevent recurrence of variceal bleeding, nutritional support with supplements and, if severe, the use of parenteral nutrition. Highly specialized care is required to manage these medical complications. Liver transplantation remains the only option left for the infants with BA who develop chronic end-stage liver disease. Despite our best efforts, these complications worsen and some infants die awaiting transplantation.

At Children's Hospital Los Angeles (CHLA), we performed 29 liver transplants in 2016, and 18 of those transplants were for biliary atresia. Of those 18 cases, 9 were infants with missed BA referred to CHLA because they either had a late Kasai HPE done or no surgery at all. Why were 50% missed and diagnosed beyond the optimal window for surgical intervention? The answer is certainly not simple and probably multifactorial, including inconsistent access to healthcare resulting in late identification of abnormally jaundiced infants, difficulty getting insurance approval for laboratory testing, and maybe to a lesser extent, lack of awareness of the frequency of the disease and severity if left undiagnosed. In a recent technical report from the AAP on newborn screening for BA, the efficacy of both universal measurement of total and direct or conjugated bilirubin levels and screening for acholic stools were discussed. However, application of universal bilirubin level screening for BA is not yet ready for prime time[8]. But, utilizing the lack of pigmented stool that occurs in BA is a useful and easy screening modality for caregivers to learn and bring worrisome appearing stool colors to the attention of their child's pediatrician.

The use of stool color cards is not a new idea. This has been well described in several Asian countries, like Taiwan and Japan, who have higher reported incidence of BA, 1.48 per 10,000 births recorded in Taiwan[9]. A landmark retrospective cohort study before and after implementation of a stool color card study was published from Taiwan in 2004[9]. Decreased rates of first admission with suspected biliary atresia from 47 to 43 days (p=0.028), decreased median age for patients undergoing a Kasai HPE from 51 to 48 days (p=0.051) with 73.6% of procedures being completed <60 days of age, as well as reduced rates of late referrals from 9.5% to 4.9% were demonstrated[9]. Not only did this decrease the age that BA was diagnosed and treated, but this lead to reduced mortality as well[10]. Stool color cards have been implemented in Japan because of these results. In 2012, a Japanese nationwide effort was made by adding a stool color card in the discharge handbook for new mothers[6].

Challenges that occurred with caregivers in these studies were incorrect identification of the infant's stool color. Eliminating caregiver stool color interpretation and utilization of modern (and mobile) technology could allow for improved identification of acholic stools. The development of the PoopMD App is a medical mobile application that is available on Apple or Android cellular phones utilizing the device's camera and the application's color recognition software. Rather than the added cost of a card to be printed, using this technology which is already available may improve its use as well as decrease cost, particularly when 56% of American adults own smartphones and utilize medical information through these devices[11]. The application was developed in a joint project at Johns Hopkins University and HCB Health in Austin, Texas. This pilot study focuses on the accuracy of the application in differentiating photographs of stool as acholic or normal. There were over 6 pediatricians that evaluated 45 photographs, for which 27 were identified as normal stools and 7 as true acholic stools, and the remaining 11 were discarded, as they were deemed indeterminate amongst reviewers. These 34 photographs were then used as the gold standard set of images for both acholic and normally pigmented stools. The sensitivity of PoopMD under these circumstances was 100% with no false negatives and the specificity was 89% with 3

images falsely labeled as indeterminate and no images falsely labeled as acholic[11]. The interface of the application is user friendly with capability of contacting the pediatrician and emailing the photograph of the stool (Image 1). We hope recommendation of this free application to caregivers prior to discharge from the hospital and at subsequent outpatient follow up will identify infants with acholic stools for earlier laboratory testing and timely referral.

Mobile cell phone applications such as this, not just stool color cards may be efficacious from a medical standpoint, but is this a cost effective approach? While the PoopMD application is still new, cost-effective analysis has been done for the stool color card by Mogul et al at Johns Hopkins. They compared two different strategies. Strategy A was no stool color screening while strategy B used nationwide screening with the stool color developed by the Taiwan Health Bureau as referenced above. The 20-year cost of strategy A was $142,479,725 with 3702 life-years, 74 deaths, and 158 liver transplants. Strategy B cost was $133,893,563, with 3731.7 life-years, 71 deaths, and 147 liver transplants[WS1] [12]. It was concluded that there was 97% probability that screening with stool color cards would be cost saving and increase life-years gained.

Given that the mobile phone application is already developed and free for use by parents, it could be part of our screening tool armamentarium to aid in early identification of acholic stools, and thus earlier referrals for prompt diagnosis and intervention to improve outcomes for infants found to have BA. The use of universal total and direct or conjugated bilirubin levels to screen for such cholestatic disorders as BA may eventually be proven to be cost-effective.

Images:

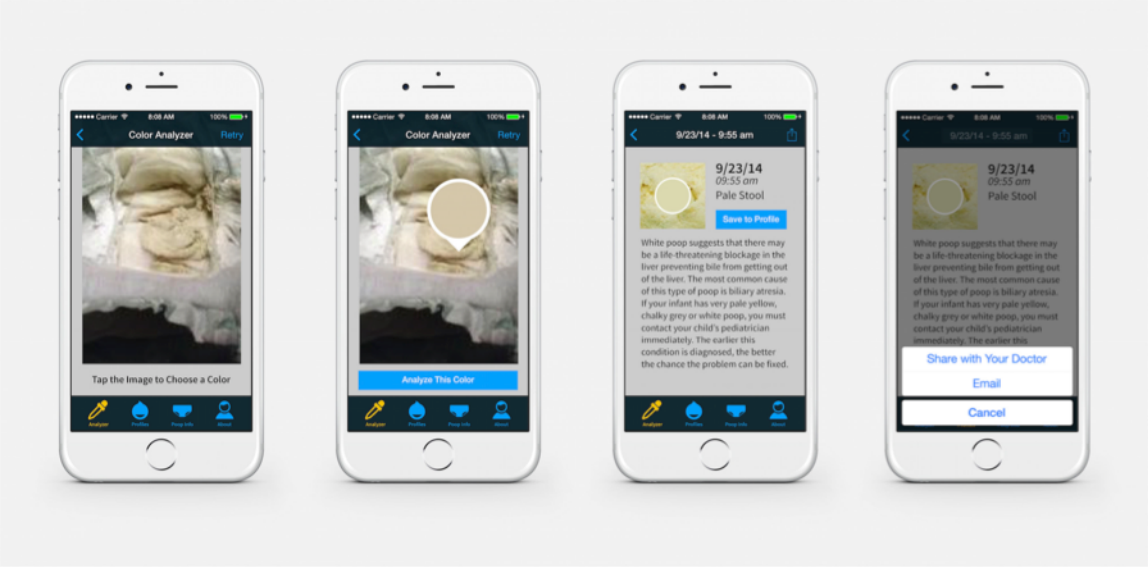

Image 1: Screenshots from PoopMD, taken from referenced article.

References:

1. Hyperbilirubinemia AAoPSo. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297-316.
2. Ebbesen F, Andersson C, Verder H, et al. Extreme hyperbilirubinaemia in term and near-term infants in Denmark. *Acta Paediatr.* 2005;94(1):59-64.
3. Manning D, Todd P, Maxwell M, Jane Platt M. Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland. *Arch Dis Child Fetal Neonatal Ed.* 2007;92(5):F342-346.
4. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. *Pediatrics.* 2009;124(4):1193-1198.
5. Ohi R. Biliary atresia. A surgical perspective. *Clin Liver Dis.* 2000;4(4):779-804.
6. Nio M, Wada M, Sasaki H, Tanaka H. Effects of age at Kasai portoenterostomy on the surgical outcome: a review of the literature. *Surg Today.* 2015;45(7):813-818.
7. Superina R, Magee JC, Brandt ML, et al. The anatomic pattern of biliary atresia identified at time of Kasai hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. *Ann Surg.* 2011;254(4):577-585.
8. Wang KS, Surgery So, Newborn CoFa, Network CLDR. Newborn Screening for Biliary Atresia. *Pediatrics.* 2015;136(6):e1663-1669.
9. Tseng JJ, Lai MS, Lin MC, Fu YC. Stool color card screening for biliary atresia. *Pediatrics.* 2011;128(5):e1209-1215.
10. Lee M, Chen SC, Yang HY, Huang JH, Yeung CY, Lee HC. Infant Stool Color Card

Screening Helps Reduce the Hospitalization Rate and Mortality of Biliary Atresia: A 14-Year Nationwide Cohort Study in Taiwan. *Medicine (Baltimore).* 2016;95(12):e3166.
11. Franciscovich A, Vaidya D, Doyle J, et al. PoopMD, a Mobile Health Application, Accurately Identifies Infant Acholic Stools. *PLoS One.* 2015;10(7):e0132270.
12. Mogul D, Zhou M, Intihar P, Schwarz K, Frick K. Cost-effective analysis of screening for biliary atresia with the stool color card. *J Pediatr Gastroenterol Nutr.* 2015;60(1):91-98.