Province-wide Biliary Atresia Home Screening Program in British Columbia: Evaluation of First 2 Years

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ABSTRACT

Background and Objectives: Biliary atresia (BA), a rare newborn liver disease, is the leading cause of liver-related death in children. Early disease recognition and timely surgical Kasai hepatoportoenterostomy (KP) offers long-term survival without liver transplant. Universal BA screening in Taiwan using infant stool color cards (ISCCs) has proven effectiveness. We report our experience with infant stool color card (ISCC) BA screening in a province-wide program in British Columbia (BC). The objective of this study is to assess program performance and cost from launch April 1, 2014 to March 31, 2016.

Methods: ISCCs distributed to families upon maternity ward discharge. Parents were instructed to monitor their infant's stool color for 1 month and contacted the screening center with concerns. The number of live births, ISCC distribution, BA cases, and costs were recorded. Cases with Program screen success had both acholic stool recognition (ISCC screen success) and timely referral for BA.

Results: All 126 maternity units received ISCCs. Of 87,583 live births there were 6 BA cases. Of the 5 cases with ISCC Screen Success 3 had Program Screen Success. The median KP age in the program screen success and failure groups was 49 (42–52) and 116 (49–184) days, respectively. Program sensitivity was 50%, specificity 99%, positive predictive value 4%, and negative predictive value 99%. A random sample of 1054 charts at BC Children's Hospital found an ISCC distribution rate of 94%. After a phase-in period, the annual program cost was $30,033.82, and the ISCC cost per birth was $0.68.

Conclusions: The screening program has high specificity and distribution with low cost. Successful program case identification had earlier age at KP. Program modifications aim to improve sensitivity. Longer-term studies will determine program impact on health outcomes.

Key Words: cost-effectiveness, neonatal cholestasis, newborn screening, stool color card

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What Is Known

- Biliary atresia is a leading cause of newborn liver disease and the major indication for pediatric liver transplantation.
- Delayed disease recognition and late surgical intervention (Kasai hepatoportoenterostomy) (>90 days of age) has worse outcome.
- Universal biliary atresia screening using infant stool color cards in Taiwan and elsewhere has proven effectiveness.

What Is New

- This is the first report of large-scale infant stool color card biliary atresia screening in a North American setting.
- The infant stool color card had high distribution rate at low cost.
- Successful screening led to earlier infant age at Kasai hepatoportoenterostomy.
- Program performance was comparable to reports from elsewhere.

Biliary atresia (BA) is a leading cause of liver failure and major indication for liver transplantation in the pediatric population. This rare but severe pediatric liver disease, affecting 1:19,000 live births in Canada, manifests in the first weeks of life with persistent jaundice, due to a conjugated hyperbilirubinemia, and pale (acholic) stools (1). Standard treatment for BA is an initial hepatic portoenterostomy (Kasai hepatoportoenterostomy [KP]) to re-establish bile flow, alleviate the obstructive jaundice and preserve the native liver. Early liver transplantation is reserved for those cases with failure of the initial KP. Without surgical intervention all infants with BA will die by 3 years of age (1,2).

The most important prognostic factor for a successful KP outcome is the infant's age at the time of the KP (2). The older the infant age, the less likely for the KP to be successful, rendering the infant in urgent need of liver transplantation to ensure survival. In Canada, the 10-year post KP native liver survival was 49% in infants undergoing KP at age <30 days compared to 15% for those having their KP at age >90 days (1).

Delays in timely BA detection and intervention, with poor native liver survival, have been reported worldwide (1–4). The current median age of KP is 64 days in Canada and ~20% of BA cases in Canada have KP at >90 days of age (3). Detecting BA is challenging because physiologic jaundice in newborns is common and icteric newborns are often not recognized to have liver disease.

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Acholic stools are extremely sensitive indicator for BA (5); however, routine stool color screening is not widely practiced as a standard of newborn care among health care professionals and parents are not educated about abnormal stool colors (6). Following the introduction of a universal BA screening program in Taiwan using an infant stool color card (ISCC), no infant had a KP at >90 days of age and the 5 year post KP native liver survival has improved from 37% to 64% (7,8).

We recently reported that introduction of a BA screening program in Canada using ISCC would be feasible and cost-effective (9,10). In 2014, a provincial wide BA home screening program using ISCC was introduced in British Columbia under the auspices of the Ministry of Health and Perinatal Services BC. We report our first 2-year experience with the program including its performance and cost.

METHODS

Infant Stool Color Card

A province-wide universal screening program for BA using an ISCC given to families at maternity discharge was launched in April 1, 2014. British Columbia (BC) is the most western province of Canada having a population of 4.6 million (*gov.bc.ca*) and 126 maternity units. Initially the ISCC included 6 photos of stools (3 normal and 3 abnormal). In June 2015, the card was revised to include 9 stool photos (3 normal and 6 abnormal) (Supplementary Fig. 1, http://links.lww.com/MPG/B384). The ISCC photos were identical to the ones used and validated in Taiwan (courtesy of Professor Mei-Hwei Chang). A toll free telephone number and a dedicated e-mail address were provided on the ISCC and families were instructed to contact the BA screening center with any concerns. A statement was added on the revised ISCC in June 2015 that instructed physicians to order a bilirubin test for infants jaundiced at >2 weeks of age. An online ISCC reminder tool to remind parents to check their newborn's stool daily for 1 month was also available to families by having them sign up online or by using their smartphones to scan a QR code on the ISCC. The printed card with accurate colors was distributed in English, but versions of the ISCC in 12 languages were available online (*www.perinatalservicesbc.ca*).

Card Distribution

Before the official start of the program, all maternity ward nurses and practicing midwives across the province were provided with educational seminars about the screening program either directly on the maternity ward or via webinars. Maternity ward nurses and midwives used a scripted education instruction sheet to uniformly explain the screening process to the families. The parents were instructed to monitor their infant's stool color daily for the first month of life, to compare the stool color with photos of normal and abnormal stool color on the ISCC and to directly contact the screening center by a toll free number or e-mail if an abnormal stool color was detected. In BC, all maternity care providers are mandated to complete a newborn discharge checklist when babies are discharged home from the maternity ward. An ISCC check box to confirm that the family received both the ISCC and program education was introduced into the discharge checklist when the program was launched. The roll out of these new newborn discharge checklists was fully completed within 12 months.

Study Population

All live neonates born in British Columbia between April 1, 2014 and March 31, 2016 discharged from maternity wards were included in our evaluation. Babies admitted to neonatal intensive care units (NICUs) were excluded from the screening program as NICUs have intensive monitoring and parental screening of stool color using the ISCC was felt to be unnecessary.

Data Collection and Statistical Analysis

The number of provincial live births and program costs were calculated using data from Perinatal Services BC. The BA phone line was monitored for ISCC phone calls from families. Frequency of calls and reasons for contacting the center were recorded. Patient follow-up from each phone call was documented. All BA patients in BC are referred and followed at BC Children's Hospital (BCCH). The number of BA cases detected since the launch of the program and the age of KP were recorded. Registration rates for the online ISCC reminder tool were also recorded. Card distribution was assessed by examining the number of ISCCs re-ordered by maternity units at each provincial hospital or birthing center relative to the number of births at each of these sites. Also, BCCH charts from four 2-week periods were randomly selected between July 2015 and June 2016 to determine ISCC distribution rates based on nurse sign-off of the ISCC check box on the newborn discharge checklist. The ISCC was considered successful (ISCC screen success) if acholic stools were identified by the families in a BA case. The BA screening program was considered successful (Program screen success) if both acholic stools were identified and case referral was in a timely manner leading to KP before 90 days of age. Analyses of sensitivity, specificity, positive predictive value, negative predictive value, and false-positive rate of ISCC and the screening program performance were performed.

Ethical Approval

This study was approved by the University of British Columbia's Research Ethics Board.

RESULTS

Detection of Biliary Atresia using the ISCC

There were 87,583 live births through the study period (43,932 during the first year) and 6 cases of BA were identified (1:14,597 live births). ISCC screen success was demonstrated in 5 cases. Among these 5 cases, 3 had program screen success: 1 family contacted the call center directly and the other 2 visited their physician; all were then referred for assessment in a timely manner, making all 3 of these program screen successes (Table 1). Three cases were program screen failures. In 2 of these cases the families had correctly identified acholic stools (the remaining 2 of 5 ISCC screen success) and sought immediate consultation with their primary care physician without contacting the screening center. They were, however, given reassurance by the treating MD and no further timely action was taken. This led to late referral and delayed diagnosis (program screen failure). In the third case with program screen failure the family had frequently visited their physician primarily concerned about their infant being jaundiced but felt that the stool color was only intermittently abnormal (ISCC screen failure), and no referral or laboratory tests were done (program screen failure). Given the experiences in the first year of screening, the ISCC was modified in June 2015 to include 9 stool colors and a statement was added to the card to instruct physicians to order a bilirubin test for newborns with jaundice who presented with parental concerns about their infant's stool color (Supplementary Fig. 1, http://links.lww.com/MPG/B384, front of card). The median age of KP in the program screening success and failure groups was 49 (42–52) and 116 days (49–184), respectively.

TABLE 1. Screening details of the 6 biliary atresia cases

Case no.	Age at KP (days)	ISCC successful (Y/N)	BA screening program successful? (Y/N)	Other details
1	49	Y	Y	
2	52	Y	Y	
3	42	Y	Y	
4	184	Y	N	Acholic stools detected early by parents, seen by GP but no tests were done until late referral
5	107	Y	N	Acholic stools detected early by parents, seen by GP but no tests were done until late referral
6	116	N	N	Abnormal stool color not consistently recognized by the Family. Seen by MD for jaundice but no tests done until late referral

BA = biliary atresia; GP = general practitioner; ISCC = infant stool color card; KP = Kasai hepatoportoenterostomy; MD = medical doctor.

One false-positive case had a KP at 79 days due to uncertain diagnosis, despite careful post-referral subspecialty evaluation. He presented on day of life (DOL) 58 with high gamma-glutamyl transpeptidase cholestasis and acholic stools. An abdominal ultrasound demonstrated normal-sized liver and gallbladder presence without intra or extraheptic bile duct dilation. The kidneys were normal. A CXR and L/S spine film were unremarkable. Thorough cardiac assessment including echocardiogram did not identify a cardiac lesion. Posterior embryotoxin was seen on ophthalmological exam. Liver biopsy on DOL 60 was limited in sample size (only 7 portal tracts) and non-conclusive, without definitive diagnosis for large duct obstruction or duct paucity. On DOL 71, hepatobiliary scintigraphy was non-excreting. With ongoing concern for BA, the decision was taken for an intraoperative cholangiogram on DOL 79. The gallbladder contained clear non-bilious fluid. Injection of contrast rapidly drained to the intestine, but there was no visualization of the common hepatic duct or intrahepatic biliary tree despite clamping of the common bile duct. Given these findings and the surgical assessment of the extrahepatic biliary system, a KP was performed. Although the preoperative and intraoperative findings were suggestive of BA, the diagnosis of Alagille syndrome (AGS) was eventually confirmed only after the KP, when a larger sample of liver tissue established duct paucity and genetic testing identified a novel JAG1 mutation. This case, despite having acholic stools recognized by the parents and a timely referral, was classified as a false positive in view of the ultimate diagnosis of AGS.

Calls to the Biliary Atresia Screening Center

The BA screening center received 75 parent phone calls during the study period, which averaged 3 calls per month. All calls were responded to by a single pediatric hepatologist (R.A.S.). Only 1 call had a confirmed diagnosis of BA. Of the 74 calls with a false-positive ISCC for BA, 9 calls were for cases >6 months of age, 25 calls had normal stool color or other non-related stool issues, and 29 had transient acholic stool that resolved by the phone call follow-up without requiring a physician visit or laboratory studies. Two cases had identifiable causes (one with UTI and the other with hypothyroidism). No cause was identified in 9 cases.

Card and Biliary Atresia Screening Program Performance

The sensitivity of the BA screening program was 50%, specificity 99%, PPV 4%, and NPV 99%. The false-positive rate was 0.09%. The ISCC successfully detected acholic stools in 5/6 BA cases (sensitivity 83%, specificity 99%, PPV 6%, NPV 99%); however, challenges with next steps in the referral process led to delayed diagnosis in 2 further cases (Table 2).

Online Infant Stool Color Card Reminder Tool

The online ISCC reminder tool had an overall registration rate of 40 participants in the 2 years. Registrations occurred in 4 languages other than English (Chinese, Japanese, Spanish, and Punjabi). All registered via the website. Fifty eight percent subscribed to text reminders, the remaining to e-mail reminders.

Card Distribution

All 126 maternity units across the province of BC received ISCCs. Eight sites did not reorder sufficient number of ISCCs based on their number of births, accounting for 2% of the provincial births (1751 births may not have received an ISCC). A total of 1054 BCCH charts were randomly selected for review (Supplementary Fig. 2, http://links.lww.com/MPG/B385). Of the charts that did not contain a discharge sheet, 53 were babies discharged from the NICU. Of the remaining 991 charts, 94% had the ISCC signed off as a maternity discharge checklist item. Of the 63 charts without the ISCC item checked off, 27 charts were missing multiple checked off items on the maternity discharge checklist. Other reasons for an incomplete ISCC maternity discharge checklist included early discharge, parental decline and unclear documentation. There was, however, no obvious reason for 2.4% of the discharges without the ISCC item checked off on the maternity discharge checklist.

Program Costs

The program set-up and operational costs during the first year (2014/2015) were $80,154.63. Operational costs during the second year were $30,033.82 (Table 3). The initial ISCC card printing, pre-program education and the development of the reminder tool accounted for the additional cost of $50,120.81 for the program launch in its inaugural first year. After the program start up, the ISCC cost per birth, including ongoing administrative

TABLE 2. Screening program performance

	Biliary atresia	Not biliary atresia	Total
Program positive	3	75	78
Program negative	3	87502	87505
Total	6	87577	87583

TABLE 3. Program costs for the study period

Expense	Fiscal year 2014/2015	Fiscal year 2015/2016	Total
Infant stool color card			
Card printing	$24,000.00	$13,453.06	$37,453.06
Card translation	$6608.33	$2274.00	$8882.33
Toll-free phone line	$600.00	$600.00	$1200.00
Total	$31,208.33	$16,327	$47,535.39
Reminder tool (QR code)			
Development	$6481.75	$256.25	6718.00
Annual subscription	$464.55	$670.51	1135.06
Total	$6946.30	$906.76	$7853.06
Administrative			
Secretarial and other personnel	$12,000.00	$12,000.00	$24,000.00
Educational program	$30,000.00		$30,000.00
Webinars (nursing education)		$800.00	$800.00
Total	$42,000	$12,800	$54,800
Grand total	$80,154.63	$30,033.82	$110,188.45
ISCC cost per birth	$1.82	$0.68	$1.25

expense for secretary and medical advisory as well as continuing nurse education costs was $0.68.

DISCUSSION

Newborn screening for rare orphan disease, including conditions with incidence rates similar to BA (ie PKU), are currently in place in most jurisdictions throughout the Western World. The overriding goal of these programs is early disease identification to enable timely and effective treatment to improve and optimize patient outcome. Late referral and delayed diagnosis remains a global concern for BA. Although timely surgical intervention with a KP at <60 days of age has proven benefit, there is not an accurate and convenient screening laboratory test for ''early'' BA detection that can be incorporated into routine neonatal screening regimens. Screening methods such as serum bile acids or urine bilirubin have been considered for BA, but these lack adequate sensitivity and have poor specificity (6,11). Newborn serum conjugated bilirubin concentration may have utility as a screening test for BA but further prospective studies using larger sample size are necessary (12). A conjugated bilirubin-screening test would require special procurement methods and standardization of normative values across different laboratories (13). More recently, smartphone applications to detect abnormal stool color have been developed, but their universal accessibility and efficacy have not been yet fully evaluated (14).

BA screening using ISCC has been implemented in European and South American countries (15,16). ISCC screening has been reported to be highly feasible, effective, and cost-effective in both Taiwan and Japan (7,8,17,18) The Taiwanese national ISCC BA screening program, in place since 2004, has eliminated late BA referrals after 90 days of age with improved 5-year native liver survival (8). In the Tochigi Prefecture of Japan, where the stool color card was first developed and introduced in 1994 by Matsui, the native liver 5 and 10 year survival rates increased by >20% during 1994–2011 compared with other Japanese jurisdictions without an ISCC screening program (18).

This is the first report of a BA home screening province-wide program using ISSC in a North American setting. The BC incidence of BA is 1:14,497 live births, almost 1.5 times as high as the reported Canadian national incidence (1:19,000). This is expected given the higher incidence of BA among Asian communities (1:7000–9000) and the larger Asian population living in BC (16%) compared with the other Canadian provinces (0.07) (*www.statcan.gc.ca*) (1,7,18).

The BC home screening program is family centered and uniquely designed. It is the parents who perform the screening at home and, unlike several other screening programs, there is no requirement to submit biological specimens. Our study found the screening program to have both high specificity (99%) and NPV (99%) in keeping with the rates reported from Taiwan and Japan. (18,19,20). It is important to distinguish between ISCC screen and program screen success. In our study, despite ISCC screen success in 5 of the 6 BA cases, in 2 of these 5 cases there was program screen failure, with delayed referral and late treatment at the tertiary care center. After our first year of operation, several modifications were made to the ISCC to improve the program screen success. These included a broader picture selection of abnormal stool color (from 3 to 6 photos) and a more detailed instruction to health care providers regarding the recommended next steps in the follow-up for the cases of acholic stool identified by the family that included bilirubin testing (Supplementary Fig. 1, http://links.lww.com/MPG/B384). It is noteworthy that several years ago we implemented a provincial wide policy that requires all laboratories in British Columbia to automatically test for both total and fractionated bilirubin whenever a serum bilirubin test is requisitioned for a child between 7 days and 1 year of age.

Importantly, the stool color pictures used in our ISCC have been previously validated for screening in the Taiwan program. Pictures depicting stool color for BA screening, for example, the recent smart phone application PoopMD (PoopMD+©Beneufit Inc. [https://itunes.apple.com/us/app/poopmd/id1082065820?mt=8]), and the screening app released in China using numeric color model as a parameter for acholic stool, require large scale study to ensure their screening efficacy (21). An additional concern is that some smartphone manufacturers and models provide better color accuracy than others. (*www.displaymate.com/Color_Accuracy_ShootOut_1.htm*). Several studies have examined the ability of the lay public or health care professionals to recognize abnormal newborn stool color. Bakshi found that pediatric nurses and physicians were able to identify 63% of stool photos suspicious for BA (6). A Dutch study had similar findings, with 61% of young health care doctors and 36% of general practitioners recognizing acholic stool (22). We found that the ISCC performed well with 86% of the cases successfully identified.

The majority of the 74 cases who contacted the study center with a false-positive ISCC had transient stool color change and were easily managed with phone follow-up by experienced medical personnel at the screening center. This screening strategy is relevant to the potential cost-effectiveness of the program as these cases did not incur the additional expense of laboratory investigations or physician visits. Since the online ISCC reminder tool had an overall low registration rate, a QR tool is not a necessary program expense. The per birth cost of the program in the second year, including administrative secretarial and medical advisory costs, ongoing nurse education (webinar) expenses and after the program implementation costs were expended, was $0.68. We anticipate that in the long term, the screening program will be inexpensive and highly cost-effective.

The potential to identify other newborn cholestatic liver disease is a secondary outcome of the screening program. During our 2-year screening period, a newborn with treatable urinary tract infection and another with thyroid disease were found. One of our cases with presumed BA was eventually found to carry a novel JAG1 mutation for AGS. BA and AGS may be indistinguishable and pose diagnostic challenge for neonatal cholestasis. AGS can

share biochemical, imaging, histological, and operative cholangiogram features with BA (23). Although genetic testing may help to differentiate the diseases, the results often take several weeks (>4 weeks) to return at a time when further delay in BA diagnosis and surgical intervention may compromise outcome. Dedic et al (24) reported JAG1 mutation in 5 patients presenting initially as BA. Similar to our case, each of these patients had some clinical features but did not meet the diagnostic criteria for AGS during the initial hospital evaluation for neonatal cholestasis. Kosaka et al (25) recently identified JAG1 mutations in 9 of 102 patients with BA. Although these cases had no phenotypic features of AGS, their prognosis was worse suggesting that *JAG1* gene abnormality in BA may be an aggravating factor for disease progression (25). Similarly, others have recognized that KP performed in children with AGS have worse outcome with a significantly larger number of liver transplants and higher mortality (26). These studies underscore the diagnostic difficulty for a rare subgroup of neonates with obstructive jaundice suggestive of BA who have clinical characteristics that overlap but are not diagnostic for AGS. It is anticipated that with the advent of modern clinical genetic techniques and advanced rapid sequencing methods that offer robust and timely results, the current approach to the assessment and classification of these complex cases will be more definitive.

We recognize several limitations to this study. The short duration and small number of BA cases did not allow for an assessment of the overall impact of the screening program on longer-term health outcomes including the 2 or 5 year native liver survival. It also precluded a detailed analysis of cost-effectiveness. The actual rates of the card distribution to the families and the card utilization could not be fully ascertained because of the current constraints of the Ministry of Health database regarding privacy and confidentiality policies.

In summary, this is a first report of our 2-year experience with the BC BA home screening program. The program is feasible with high specificity. Use of the ISCC by families correctly identified acholic stools in all but one of the BA cases. Modifications to the stool color card have now been instituted to increase the screening program sensitivity. Further assessment of the program in the next 5 years will provide important information regarding patient outcomes and cost effectiveness.

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