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Pediatrics 2006;117;1147-1154
DOI: 10.1542/peds.2005-1267

ARTICLE

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. We aimed to detect biliary atresia (BA) in early infancy to prevent additional liver damage because of the delay of referral and surgical treatment and to investigate the incidence rate of BA in Taiwan.

METHODS. A pilot study to screen the stool color in infants for the early diagnosis of BA was undertaken from March 2002 to December 2003. We had designed an "infant stool color card" with 7 numbers of different color pictures and attached it to the child health booklet. Parents were then asked to observe their infant's stool color by using this card. The medical staff would check the number that the parents chose according to their infant's stool color at 1 month of age during the health checkup and then send the card back to the stool color card registry center.

RESULTS. The average return rate was ~65.2% (78 184 infants). A total of 29 infants were diagnosed as having BA, and 26 were screened out by stool color card before 60 days of age. The sensitivity, specificity, and positive predictive value were 89.7%, 99.9%, and 28.6%, respectively. Seventeen (58.6%) infants with BA received a Kasai operation within 60-day age period. The estimated incidence of BA in screened newborns was 3.7 of 10 000.

CONCLUSIONS. The stool color card was a simple, efficient, and applicable mass screening method for early diagnosis and management of BA. The program can also help in estimating the incidence and creating a registry of these patients.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-1267

doi:10.1542/peds.2005-1267

Key Words
biliary atresia, infant stool color card, incidence, Kasai operation

Abbreviations
BA— biliary atresia
NH—neonatal hepatitis

Accepted for publication Sep 1, 2005

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BILIARY ATRESIA (BA) is one of the most common causes of cholestasis in infants <3 months of age and the most frequent hepatic cause of death in early childhood.[1] The average lifespan for infants with untreated BA is ~2 years.[2] In 1968, Kasai introduced an effective surgical treatment for BA, and the "Kasai procedure" has become the current standard surgical approach. The 10-year survival rate for the patients treated before the age of 60 days versus those treated after the age of 91 days were reported to be 57% vs 13%.[3] The success of the Kasai operation is correlated with the age at surgery. However, a significant number of affected infants were still referred beyond 60 days.[4]

To get effective bile drainage after surgery and improve the prognosis of infants with BA, early identification and prompt intervention is very important. According to the study of Lai et al,[5] 95.2% of infants with BA had persistent pale-pigmented or even clay-colored stool in early infancy. Therefore, careful observation of stool color may help identify infants who need additional assessment to exclude the possibility of BA. In 1994, Matsui and Ishikawa[1] reported on a study using an infant stool color card to increase the efficacy of the 1-month health check in identifying BA in Japan. Inspired by their experience, we conducted a pilot study using a stool color card, which uses a series of stool pictures of Taiwanese infants, for the early screening of BA since March 2002. For enhancing the awareness of the public and for assisting families or medical personnel in identifying infants with BA, we established an "infant stool color card registry system" in Taiwan. Here we report the efficacy of the stool color card for early screening of BA and the incidence rate of BA in Taiwan.

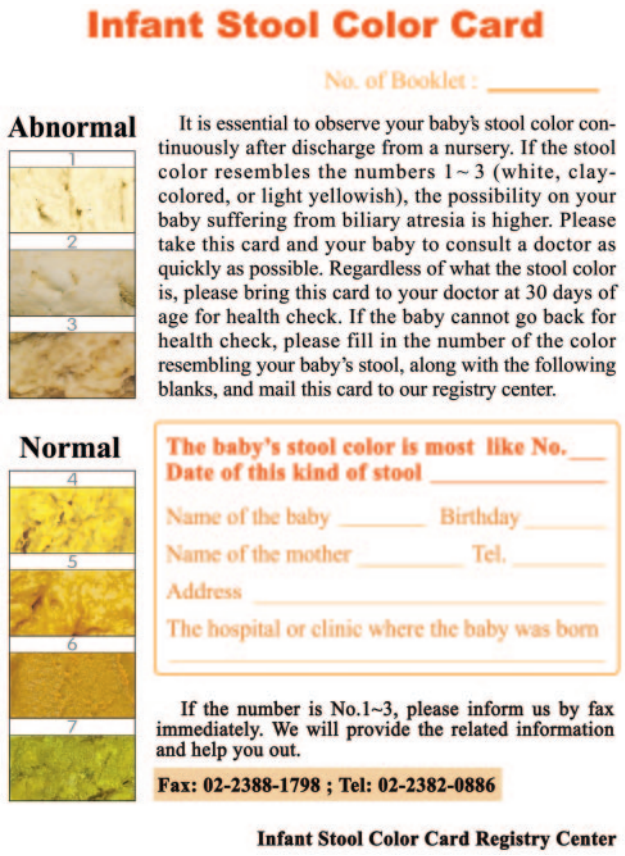

FIGURE 1
English version of the infant stool color card (first edition). The notice for parents on this card reads: "It is essential to observe your infant's stool color continuously after discharge from a nursery. If the stool color resembles the numbers 1–3 (white, clay-colored, or light yellowish), the possibility of your infant suffering from biliary atresia is higher. Please take this card and your infant to consult a doctor as quickly as possible. Regardless of what the stool color is, please bring this card to your doctor at 30 days of age for health check. If the infant cannot go back for health check, please fill in the number of the color resembling your infant's stool, along with the following blanks, and mail this card to our registry center. If the number is 1–3, please inform us by fax immediately. We will provide the related information and help you out."

METHODS

Subjects

The subjects were all newborns from our collaborating hospitals and clinics covering the northern, central, southern, and eastern parts of Taiwan from March 2002 to December 2003. In 2002, a total of 49 hospitals and clinics in Northern and Central Taiwan, including Taipei city, Taipei county, Taichung city, Taichung county, and Changhua county, were enrolled, with 47 180 newborns included in this study. In 2003, the range of cooperation extended to Southern and Eastern Taiwan, including Tainan city, Tainan county, and Hualien county. A total of 96 hospitals and 72 793 newborns were included.

Infant Stool Color Card

To enhance the understanding and practical use for the families and medical staff in recognizing the stool color as normal or abnormal, we designed an infant stool color card, which imprints 7 numbers of different stool color pictures form Taiwanese infants (Fig 1). This design was inspired from the report of Matsui et al.[1] Three of the pictures (Nos. 1–3) on the stool color card are labeled as abnormal (clay colored to light yellowish), whereas the 4 other colors (Nos. 4–7) are normal (yellow to greenish). In addition, during the second year, to study the influence of the labeling of "normal" and "abnormal" color to the parent, we designed the second edition of the stool color card, which delete the labeling of normal and abnormal colors. It was applied in the same initial 49 hospitals and clinics as that in first year. The results of the first edition stool color card in the first year and the second edition in the second year in the same 49 hospitals were then compared.

Screening Method

In Taiwan, the parents obtain a "child health booklet" for every newborn, which is used for recording the schedule of vaccination and health check. The medical

staff in our collaborating hospitals and clinics put the stool color card and information sheet within the child health booklet when the newborn is discharged. At the same time, the parents were asked to observe the stool color of their infant in accordance with this card and to take it back to the hospitals or clinics at 1 month of age for health check. The doctors would check the number of the picture chosen by the parents according to their infant's stool color. If the number was 4–7 (normal), the card would be collected by the medical staff and sent to our stool color card registry center. If the number was 1–3 (abnormal), the card would be forwarded to the stool color card registry center by fax or telephone within 24 hours, and we would contact the parents to provide related information.

If the infant could not go back for a health check at 1 month of age, the parents were asked to mail this card to the registry center directly (Fig 2). The consulting telephone and fax numbers were printed on our stool color card, and parents could inform us regardless of the infant's age if acholic stools were found. Furthermore, we contacted the pediatric gastroenterologists in the medical center in 4 in areas (north, middle, south, and east) of Taiwan to serve as the core doctors for promotion work and case referral. Once these doctors found the infant with acholic stool referred from the clinics or local hospitals, they could inform the stool color card registry center instantly regardless of the infant's age. Each abnormal case would be followed-up until a definite diagnosis was made. We continued to follow up the clinical course and postoperation outcome in each infant with BA. We also provided consultation and related information for the clinics and hospitals, including posters and CD-ROMs. The jaundice-free or successful Kasai operation was defined as the postoperative value of total serum bilirubin <34 μmol/L (2.0 mg/dL) with normal stool color. The pediatric gastroenterologists of the whole of Taiwan were contacted periodically. BA patients who were born in the participating hospitals or clinics but who failed to be screened out by the infant stool card would finally be reported by the pediatric gastroenterologists. Operation at centers not participating the study did not affect the reporting.

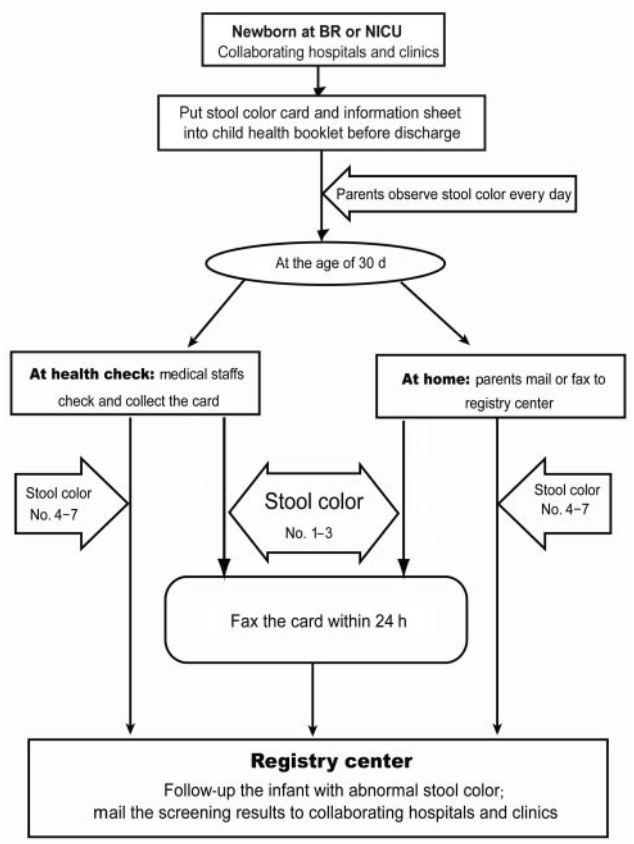

FIGURE 2
Algorithm of infant stool color screening and registry process in Taiwan. BR indicates infant room.

Statistical Analysis

χ^2 test and Fisher's exact test for categorical variables and Student's t test for continuous variables were used. A P value of $<.05$ was considered statistically significant.

RESULTS

Return Rates of Stool Color Card and Reported Cases

During the 1-year and 10-month study period, the total number of live births in the collaborating hospitals was 119 973. The total number of stool color cards collected among these infants was 78 184, with an overall average return rate of 65.2%. In the first 10 months, the return rate was 62.3% and went up to 67.0% on the second year. There were 94 infants with abnormal stool color (Nos. 1–3), and 91 of them were screened out before 60 days of age. Twenty-nine (30.9%) of the 94 infants were identified as having BA. Neonatal hepatitis (NH) was found in 8 infants (8.5%), and progressive familial intrahepatic cholestasis, choledochal cyst, and benign hepatic hemangioma, each in 1 infant, were diagnosed later. The remaining 54 infants with transient pale-colored stool turned out to be normal after >3 months of follow-up (Table 1). Three infants with abnormal stool color were discovered beyond 60 days of age, because pale-colored stools were noted later.

Incidence of BA

A total of 29 infants with BA were detected by stool color card during the study period. Another infant with BA, whose stool color card was not sent to the hospital, clinic, or registry center, was diagnosed and registered later by the medical personnel. Therefore, a total of 30 cases of BA were diagnosed during the study period. Fifteen of them were male, and the male/female ratio was 1.07:1. Four infants (13.8%) were premature. Twenty-three (79.3%) infants had BA alone, 2 infants

TABLE 1 **Underlying Causes of Pale-Colored Stool in 94 Infants Screened out by Infant Stool Color Card**

Diagnosis	No. of Cases
BA	29
Screened out before 60 d of age	26
Screened out after 60 d of age	3
Associated anomalies	
Isolated	23
Umbilical hernia	2
Congenital intestinal atresia	2
ASD type II	2
NH	8
PFIC	1
Choledochal cyst	1
Hepatic hemangioma	1
Normal	54
Total	94

ASD indicates atrial septal defect; PFIC, progressive familial intrahepatic cholestasis.

had umbilical hernia, and 2 infants had atrial septal defect type II. Two were monozygotic twins (6.9%) affected with BA in combination with congenital intestinal atresia that, respectively, involved the duodenum and the jejunum. Both of them underwent laparotomy and resection of the atresic bowel within the first week of life. Their stools were at first normally colored until 3 weeks of life. Laboratory studies showed cholestatic jaundice, and BA was suspected. Another laparotomy and a Kasai portoenterostomy were performed on both. According to our data, the incidence rate of BA in the screened newborns is 3.7 of 10 000 (29 of 78 184; 95% confidence interval: 0.00024–0.00051).

Reliability of the Infant Stool Color Card

We further analyzed the clinical course of 29 infants with BA detected by stool color card registry. Twenty-three (79.3%) infants and 26 (89.7%) infants were found to have pale-colored stool (Nos. 1–3) before 30 and 60 days of age, respectively. For the detection of BA before 60 days, the sensitivity of this card was 89.7% (26 of 29) and the specificity was 99.9% (78 090 of 78 155). The positive and negative predictive values for BA were 28.6% and 99.9%, respectively (Table 2). The comparison of the return rate and reliability among the first edition (labeled) and second edition (unlabeled) stool color cards in the same 49 hospitals that participated this study since the first year of the study is shown in Table 3.

TABLE 2 **Results of Screening for BA Before 60 Days of Age by Infant Stool Color Card**

Stool Color	BA		Total
	Yes	No	
Nos. 1–3	26	65	91
Nos. 4–7	3	78 090	78 093
Total	29	78 155	78 184

TABLE 3 **Comparison Between the First and Second Edition of Infant Stool Color Card**

Variable	First Edition (Labeled)	Second Edition (Unlabeled)
Live births, *n*	47 180	54 413
Collected stool color card, *n*	29 412	37 632
Return rate, %	62.3	69.2
Stool color Nos. 1–3, *n*[a]	31	40
BA[b]	15	9
Detection of BA before 60 d of age[c]	13	8
Reliability of method (before 60 d of age)		
Sensitivity, %	86.7	88.8
Specificity, %	99.9	99.9
Positive predictive value, %	41.9	20.0
Negative predictive value, %	99.9	99.9
Diagnostic accuracy, %[d]	99.9	99.9

The color pictures of the infant stool color card applying to 49 hospitals and clinics in 2002 (first edition) were distinctly labeled as normal (Nos. 1–3) or abnormal (Nos. 4–7). In 2003, we designed another stool color card without foregoing labeling and applied it to the same initial 49 collaborating hospitals and clinics. Another 47 hospitals and clinics that joined the 2003 stool color card study were not included in this comparison.

[a] $P = .97$, first versus second edition, in number of stool color Nos. 1–3 among infants for whom their stool color card was sent back.

[b] $P = .022$, first versus second edition, in number of BA among infant with stool color Nos. 1–3.

[c] $P = .045$, first versus second edition, in number of BA detecting before 60 days of age among infants with stool color Nos. 1–3.

[d] The proportion of infants with or without BA was correctly identified by the stool color card.

Kasai Operation

All of the 29 affected infants were found to have abnormal stool color before 90 days of age and received Kasai hepatic portoenterostomy, except 1. This female infant was impressed as NH syndrome, although the diagnosis of BA was confirmed later when the patient was undergoing liver transplantation at 19 months of age because of end-stage liver disease. The age at Kasai operation among these 28 infants was 64.8 ± 38.9 days (mean ± SD; range: 23–186).

A successful Kasai operation was defined as jaundice-free with postoperative bilirubin levels <34 μmol/L. The mean age at Kasai operation was 50.5 ± 16.7 days (mean ± SD; range: 23–83) in infants with successful operation and 94.8 ± 54.6 days (mean ± SD; range: 31–186) in the failure group ($P < .05$). Three of these infants received surgery beyond 91 days of age. One was initially considered as NH according to a first liver biopsy report at 42 days of age. She was diagnosed as having BA according to a reevaluation at 147 days of age, including liver biopsy and Tc-99m diisopropyl iminodiacetic acid (DISIDA) scan, and received a corrective operation at 153 days of age. Another was diagnosed as having BA at 47 days of age, but his parents refused the surgical intervention for their infant until the age of 145 days. The other was impressed as progressive familial intrahepatic cholestasis at 87 days of age after a series of work-ups and received Kasai operation at 186 days of age. Except for the 3 above-mentioned cases, the average time for work-up between the day of admission and

actual surgery was 8.2 ± 5.0 days (mean ± SD; range: 1–21). Furthermore, 17 (58.6%) infants received Kasai operation before 60 days of age. Twenty-three (79.3%) affected infants were detected to have abnormal stool color before 30 days of age, and 17 (73.9%) of them performed prompt operation before 60 days of age. Another 6 infants were diagnosed as having NH ($n = 5$) or total parenteral nutrition-associated cholestasis ($n = 1$) before the age of 60 days according to the clinical presentation and initial work-up.

Nineteen (67.9%) of the 28 infants became jaundice-free (with bilirubin <34 μmol/L) after the Kasai operation. The jaundice-free rate after Kasai operation in those operated before 60 days of age were 82.4% (14 of 17) but dropped to 45.5% (5 of 11) in those operated later than 60 days of age ($P = .095$). Although 62.5% (5 of 8) of those operated at the age of 61–90 days still became jaundice-free, 3 infants that underwent the Kasai operation beyond 91 days of age did not experience restored bile drainage and remained icteric (Table 4).

Follow-up of the BA Patients

Up to June 2004, the mean duration of follow-up was 12.8 ± 6.5 months (mean ± SD; range: 4–25), and 9 (32.1%) of the 28 infants with BA who have received Kasai operation did not get jaundice-free postoperatively. Five of them had undergone liver transplantation at a young age (10.4 ± 3.9 months of age; range: 5–18). One girl died at the age of 23 months without receiving liver transplantation. Three other infants had persistent jaundice and pale-colored stool (Fig 3).

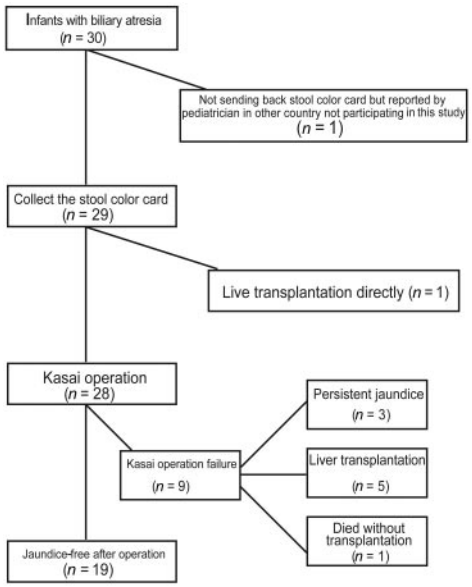

FIGURE 3
Flow diagram of this study showing the outcome of all 30 infants with BA born during the study period. The mean duration of follow-up was 12.8 ± 6.5 months (range: 4–25 months).

DISCUSSION

BA is an obliterative cholangiopathy of unknown etiology.[6] Kasai operation is the primary surgical therapy for BA even in the era of liver transplantation.[7,8] However, the success of the Kasai operation is correlated with the age at surgery, and a significant number of affected infants are still referred at a delayed age of 60 days.[4,9] In our data, the age at operation in the successful Kasai operation group was significantly younger compared with the failure group, and the results again highlighted the importance of surgery before 60 days of age. The affected infants may present with pigmented stools after birth, and a prolonged jaundice maybe easily misinterpreted as physiological or breast milk jaundice. As a result, they were often referred too late to obtain the optimal benefit from surgical treatment via the Kasai procedure.

The failure of bile flow restoration can lead to the cirrhotic changes of the liver and even a life-threatening intracranial hemorrhage because of vitamin K deficiency.[10] For the recent decade, the practice of mass screening for BA has been attempted. The "yellow alert," an educational program for health visitors and parents, was launched in the United Kingdom in 1993. They expected all infants who remain jaundiced after 14 days of age to be tested for conjugated hyperbilirubinemia and referred for a specialist investigation.[11] The use of serum bile acid and urine bile acid for the screening of BA has been reported also.[12,13] However, these methods have not been put into practice extensively.

Our previous study showed that persistent clay-colored stool is valuable in the differential diagnosis of cholestasis with a high sensitivity for BA (95.2%).[5] However, the clinical identification of stool color is often perplexing for both the parents and the physicians. The discrepancy of color recognition significantly contributed to the delay of the detection of BA. Matsui et al[14] conducted a mass screening for BA and collected data from 17 641 infants from January 1994 to January 1995. To increase the efficacy of detecting BA, they had attempted to deliver a series of color picture cards for detecting normal and acholic stools to be used by moth-

TABLE 4 **Outcome of 29 Infants With BA Screened out by Infant Stool Color Card According to Age at Kasai Operation**

Age at Surgery	No. of Cases (%)	Jaundice-Free After Kasai Operation *n* (%)[a]
Receiving Kasai operation	28 (96.6)	19 (67.9)
<60 d	17 (58.6)	14 (82.4)[b]
≥60 d	11 (37.9)	5 (45.5)[b]
60–90 d	8 (27.6)	5 (62.5)
≥91 d	3 (10.3)	0 (0)
Without Kasai operation, *n* (%)	1 (3.4)	

[a] Total serum bilirubin < 34 μmol/L (2.0 mg/dL).
[b] $P = .095$ (Fisher's exact test), <60 vs ≥60 days.

ers. From the above experiences, we began to map out our screening project by designing our own infant stool color card in Taiwan and established the registry system to increase the cognition of parents and medical staff for the early detection of infants with BA. Moreover, we longed to set up an effective path of referral by promoting this card.

Maki et al[15] reported a study of screening in Tochigi prefecture from August 1994 to July 1997. A total of 87.2% of 58 396 infants was collected during the 3-year period. The sensitivity and specificity of their method are 80% and 99.9%, respectively, and the positive predictive value is 22.9%. In this study, the screening case numbers (119 973) had exceeded one-fourth of live births during the study period in Taiwan. In contrast to the situation of Japan, our study contained 8 different areas in the whole country at the same time under limited resources. We selected areas in the north, middle, south, and east Taiwan as the starting points of promotion to educate the public and the medical personnel extensively. It was contributed to the future nationwide promotion as well. Analyzing the reliability of stool color card, the sensitivity, the specificity, and positive predictive values were 89.7%, 99.9%, and 28.6%, respectively. Thus, we believe that our method can be used as an efficient and applicable tool for a mass screening of BA. Currently, additional effort to promote the application of the stool color card is needed to increase the return rate of the stool color card.

Moreover, we proved that the stool color card was able to increase the numbers of infants with BA undergoing Kasai operation within 60 days of age and enhance the efficacy of operation simultaneously. According to the study of Lin et al[16] from 1976 to 1989 in Taiwan, only 23.3% of 60 infants with BA were operated before 60 days of age, and the success rate of the Kasai operation was 38.3% in this series. Comparing the data of Lin et al[16] with our data, $P = .0002$ and .01, respectively (17 of 28 [58.6] vs 14 of 60 [23.3%]; 19 of 28 [67.8%] vs 23 of 60 [38.3%]). In Japan, the report of the Japanese Biliary Atresia Registry between 1989 and 1999 proved that 505 (43%) patients underwent operation at the age of ≤60 days, and there was no remarkable change in the trend of the age at operation since 1990. The rate of disappearance of jaundice was ~59% to 61% in infants operated before the age of 60 days, and 48% to 61% in the whole series.[9] In our study, more than two thirds (67.9%) of cases were able to become jaundice-free postoperatively, and it reached 82% in those operated before 60 day of age. Yet, as many as 26.1% of affected infants still did not receive the Kasai operation within 60 days of age, although a pale-colored stool had been found before the age of 30 days. By establishing a screening and registry system, each infant with pale-colored stool could be referred to a pediatric gastroenterological specialist promptly to prevent the delay of diagnosis. In addition, the average time for work-up in our study was 8 days. The work-up should be achieved as soon as possible and should not exceed 1 week, especially in those beyond 50 days of age. For this reason, we considered it essential to use an efficient and reliable evaluation for cholestatic infants, not only to shorten the interval between referral and surgery but also to avoid unnecessary laparotomy. A 3-day protocol, originally used by Chang et al,[17] is a fast and feasible method for detecting an infant with BA in early infancy. This comprehensive protocol showed an accuracy of 96.8% in the differential diagnosis of BA from NH.[5]

Comparing the statistical results of the first and second edition stool color cards, the latter showed a better return rate, because it was applied on the second year of promotion. The label with normal and abnormal did not cause a low return rate of abnormal cases (Nos. 1–3; $P = .97$), nor did it affect the parents in making a faithful choice according to the infant's stool color. Nevertheless, there were significant differences between the 2 editions in terms of the number of BA and detection of BA before 60 days of age among abnormal cases ($P = .022$ and .045). In statistical analysis, the sensitivity and specificity were good in both editions. However, the first edition had a better positive predictive value in detecting infants with BA. A few parents in Taiwan did not agree to surgery for their infant in infancy so far. These affected infants might be given herbal medication therapy or folkloric support. Hence, most of them missed the optimal timing for corrective operation and thereby have a poorer prognosis. To educate the parents about the difference between normal and abnormal stool color and the necessity of early surgery for infants with BA, we designed the labeled stool color card with the labeling of normal and abnormal stool color in our country.

Following up the clinical course of the affected infants, 6 infants received liver transplantation before 18 months of age. Five of them had undergone Kasai operation previously but failed to achieve good bile drainage. On the United Network for Organ Sharing waiting list, the numbers of patients awaiting liver transplantation between 0 and 5 years of age were more than twofold of that between 6 and 10 years of age.[18] Undoubtedly, a successful Kasai operation enabled many to lower the need for organs and the risk of undergoing transplantation. There was also the benefit of reduced risk of posttransplant lymphoproliferative disease. Newell et al[19] reported that the risk of posttransplant lymphoproliferative disease was highest in recipients who were <5 years of age. Overall, there is an estimated 60 to 90 cases of BA annually in Taiwan. It would be a critical issue for the family and the community to detect the disease as early as possible. The medical expenditure in the affected infants would be a heavy load to the global budget payment system under the National Health In-

surance, if the diagnosis is delayed and surgery is unsuccessful.

On the basis of the above reasons and the encouragement of preliminary benefits, we believe that the stool color card is a simple, efficient, and applicable mass screening method for the early diagnosis of BA. Hence, it is worthy of extensive application. In 2004, we began a nationwide promotion of early screening by stool color card. A revised stool color card has been included in the child health booklet, and the national infant stool color card registry system has been established. We anticipate that >80% of infants with BA can be identified within 50 days after birth and receive Kasai operation within 60 days of age. In the meantime, we will continue analyzing the cost benefit of our stool color card and exploring the epidemiology of BA in Taiwan.

APPENDIX Summary of 29 Registered Infants With BA From March 2002 to December 2003 (With Follow-up to June 2004)

Case	Gender	Stool Color No.	Age With Abnormal Stool, d	Age at Kasai Operation, d	Jaundice-Free After Kasai Operation
1	F	3	41	71	Yes
2	M	3	9	40	No[a]
3	F	2	<30	31	No[a]
4	F	2	<30	57	Yes
5	M	~2–3	24	24	Yes
6	F	2	<30	83	Yes
7	M	3	<30	47	Yes
8	F	3	<30	153	No[a]
9	M	3	<30	47	Yes
10	M	~2–3	<30	59	Yes
11	M	3	7	53	Yes
12	F	5	60	71	No[b]
13	M	~2–3	23	36	Yes
14	M	2	42	63	Yes
15	F	4	70	90	No[a]
16	F	2	7	23	Yes
17	F	~2–3	30	46	Yes
18	F	~2–3	24	52	No[a]
19[c]	F	3	2	—	—
20	M	1	21	145	No
21	M	~2–3	25	41	Yes
22	M	3	50	73	Yes
23	M	~2–3	19	63	Yes
24	M	3	<30	50	Yes
25	F	3	30	52	Yes
26	F	3	27	85	No
27	F	3	15	48	Yes
28	M	3	60	186	No
29	M	2	<14	23	Yes

[a] Had received liver transplantation.
[b] Died.
[c] Underwent liver transplantation directly.

ACKNOWLEDGMENTS

This project is supported by a grant of the Bureau of Health Promotion, Department of Health, Taiwan, Republic of China.

The Taiwan Infant Stool Color Card Study Group includes Shu-Fen Wu (China Medical University Hospital), Yu-Cheng Lin (Far Eastern Memorial Hospital), Lung-Huang Lin (Cathay General Hospital), Ya-Huei Tasi (Taipei Hospital, Department of Health, Taiwan, Republic of China), Wen-Terng Lin (En Chu Kong Hospital), Chun-Hsien Yu (Taipei City Hospital, Branch for Women and Children), Shiun-Bin Fang (Taiwan Adventist Hospital), Ching-Fing Huang (Tri-Service General Hospital), Hui-Wen Chen (Chang Gung Memorial Hospital, Department of Taipei Pediatrics), Ming-Hua Chen (Taipei City Hospital, Yang Ming Branch), Wn-Hsin Wen (Caridnal Tien Hospital Yung Ho Branch), Ming-Tzong Cheng (Changhua Christian Hospital), Yu-Kung Chou (Kuang Tien General Hospital), and Te-Jen Chen (Chi Mei Hospital).

We are sincerely grateful to Dr Mao-Meng Tiao, Dr I-Fei Huang, and Shu-Fen Lau for assistance in conducting this project.

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Screening for Biliary Atresia by Infant Stool Color Card in Taiwan

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Pediatrics 2006;117;1147-1154
DOI: 10.1542/peds.2005-1267