Peri-Operative Factors Predicting the Outcome of Hepatic Porto-Enterostomy in Infants with Biliary Atresia

SURASAK SANGKHATHAT, MD*, SAKDA PATRAPINYOKUL, MD*,
KAMOLNATE TADTAYATHIKOM, MD*, SEKSIT OSATAKUL, MD**

Abstract

Introduction : Without hepatic transplantation, hepatic porto-enterostomy is the only definitive surgical therapy for infants with biliary atresia. Unfortunately, clearance of jaundice by the procedure is not promising. Pre-operative data that may predict the outcome is of great value in the selection of surgical candidates. Early post-operative determinants of outcome also help in follow-up planning.

Objective : To determine peri-operative factors influencing jaundice clearance after hepatic porto-enterostomy in infants with biliary atresia

Patients and Method : Clinical and laboratory data of pediatric patients undergoing hepatic porto-enterostomy in Songklanagarind Hospital from 1988 to 2001 were reviewed regarding age at operation, clinical presentation, gross pathology of bile duct atresia, liver function profiles and changes after the procedure, liver pathology and post-operative ascending cholangitis. Univariate comparison followed by multivariate logistic regression analysis was analyzed against the clearance of jaundice. Statistical analysis was aided by the Stata 7.0 program. Statistical significance was set at p-value less than 0.05.

Results : There were 62 infants operated on during the thirteen-year period. Four cases of operative death and a case lost to follow-up before the second post-operative month was excluded. The median age at the operation was 78 days (34-326 days). Twenty-four cases (42.1%) presented with signs of portal hypertension. After the operation, 19 cases (33.4%) were jaundice free, 6 cases (10.5%) had fair clearance and 32 cases (56.1%) had a poor result. Univariate analysis revealed an association between age at surgery and jaundice clearance. Post-operative stool color and decline of total bilirubin level at one month after surgery were significantly correlated with the outcome ($p < 0.01$). Cholangitis within the first post-operative month significantly had an adverse effect on the short-term survival probability. Multivariate analysis showed an independent association of jaundice clearance with age at surgery and type of bile duct atresia.

Conclusion : Age of the infants younger than 60 days and type I of bile duct atresia were the key determinants of successful hepatic porto-enterostomy. Early cholangitis was an accelerator of progressive cirrhosis. Stool color and bilirubin level at one month after surgery can be used as predictors of jaundice clearance.

Key word : Biliary Atresia, Hepatic Porto-Enterostomy, Kasai's Operation, Ascending Cholangitis

SANGKHATHAT S, PATRAPINYOKUL S, TADTAYATHIKOM K, OSATAKUL S
J Med Assoc Thai 2003; 86: 224-231

* Pediatric Surgery Unit, Department of Surgery,
** Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand.

Without liver transplantation, Kasai's hepatic porto-enterostomy (HPE) is the only surgical treatment available for infants with biliary atresia. Unfortunately, success of the operation is not promising. Recent series reported a ten-year actuarial survival with native liver at 13.0 per cent-27.3 per cent[1-4]. Among developed countries where liver transplantation is available, HPE is accepted not only for its potentially curative role but also as a palliative procedure, while waiting for transplantation[2,5]. However, with limited resources, a liver transplant is hardly possible in Thailand. Instead of palliation, HPE may prolong suffering in some cases. Selection of an appropriate surgical candidate is then essential.

Various prognosticating factors have been reported to correlate with HPE outcome. Early data emphasized the age at surgery and type of biliary atresia[6]. Recent studies found the importance of institute experience and negative influence of cholangitis[2,7-9]. The objective of the present study was to review the experience of a regional tertiary-care center in HPE and to determine the factors influencing the treatment outcome.

MATERIAL AND METHOD

Medical records of pediatric patients who underwent HPE at Songklanagarind Hospital from the establishment of the pediatric surgical unit from 1988 to 2001 were retrieved and reviewed. Data was extracted, regarding clinical presentations, age at surgery, types of bile duct atresia, and the evidence of early post-operative ascending cholangitis. Follow-up was by clinical visit or personal contact with the patient's family.

Definitions

Duration of jaundice means the period in days between the onset of jaundice and the operation. Types of bile duct atresia were defined according to the Japanese classification[6] with some modification as I = isolated obliteration of the distal duct, II = isolated obliteration of the proximal duct, and III = total atresia of the extrahepatic bile duct. (Fig. 1) HPE in Songklanagarind Hospital was performed in hepaticojejunostomy fashion without an external biliary conduit. Steroids or prophylaxis antibiotics were not routinely given. Post-operative stool color was recorded as 'yellow' or 'pale'. Results were stratified into three categories according to the lowest post-operative total bilirubin (TB) level: 'Good clearance' meant that TB was less than 2 mg%, 'Fair clearance' meant TB was 2-5 mg%, and 'Poor clearance' meant that TB level persisted more than 5 mg% thorough the follow-up period. Regarding short-term outcome analysis, good and fair results were grouped together as improved outcome, for comparison with poor outcome. Survival analysis was carried out using a Kaplan-Meier life table and log-rank test.

Statistics

The chi square test or student-*t*-test, where appropriate, were used for univariate comparisons.

	Type I Isolated obliteration of the distal duct 7.14%
	Type II Isolated obliteration of the proximal duct 17.7%
	Type III Total atresia of the extrahepatic bile duct 72.6% IIIa Preserved gallbladder 24.2% IIIb Atretic gallbladder 48.4%

Fig. 1. Types of gross pathology of bile duct atresia (n = 62).

Only variables with a tendency to correlate with the poor outcome were brought to multivariate analysis. Variables having a p-value < 0.2 in univariate analysis were then included in multivariate logistic regression models, which were refined by stepwise exclusion guided by the change in log-likelihood of consecutive models. The p-value for significance in the likelihood ratio test was set at 0.05. Data processing was aided by the Stata program version 7.0 (Stata Corporation, USA) All deaths within 30 days of surgery were considered operative mortality. Cases lost to follow-up within the second post-operative month were excluded from outcome analysis.

RESULTS

Demographic data

Sixty-two infants underwent primary HPE in the 13-year period of review. There were 32 male and 30 female patients. The average weight at surgery was 4908.8 (± 1156.7) grams and the median age was 78 (34-326) days. Fourteen cases were reported dead, with the median to death from HPE 11.9 months. Among the rest, 24 cases were lost to follow-up and 19 cases were proven alive by either a regular visit or a letter. Median follow-up of the survivors was 48 months. Cases with poor outcomes were lost to follow-up significantly more than those with improved result (87.5% compared to 31.6%, $p < 0.01$).

Clinical presentation

Presenting symptoms were jaundice (100%), pale stool (87%), and dark urine (67.7%). History of neonatal jaundice that had not resolved within one post-natal week could be traced in 30 cases (48.4%). Hepatomegaly presented in 56 cases (90.3%) and 27 patients (43.5%) manifested one or more clinical signs of portal hypertension (splenomegaly, ascites). Umbilical hernia and inguinal hernia were recorded in 9.7 per cent and 4.8 per cent, respectively. Unusual co-presentation included scalp hematoma, lower gastrointestinal bleeding and steatorrhea. Associated con-

genital anomalies were detected in 6 cases (9.7%), hydrocephalus in 2 cases, and one each of congenital cardiac defect, cutaneous hemangioma, hemoglobinopathy, and microcephaly. The median pre-operative serum TB was 12.2 (range 7.7-44.1) mg%. Median serum alkaline phosphatase level was 576 (range 224-1,290) mg%. Cytomegalovirus serology was positive in 11 cases (17.7%). Hepatitis-B viral antigen was detected in 2 infants and there was one case of congenital syphilis.

The gross bile duct pathology was type III in 45 cases (72.6%), (IIIa = 15, IIIb = 30), type II in 11 cases (17.7%), type I in 4 cases (6.5%) and not clearly recorded in two cases (3.2%). Associated biliary tract anomalies were described in 6 cases, 3 cases of common bile duct cysts, 2 anomalous hepatic arteries and 1 malposition of a gallbladder.

Hepatic-porto-enterostomy (HPE) results

There were 62 infants operated on during the thirteen-year period. Only 19 infants were operated on within the 'golden period' of 60 days, while 22 cases received the surgical treatment after 90 days. Four cases of operative death and a case lost to follow-up before the second post-operative month were excluded from analysis. Good clearance was achieved in 19 cases (33.4%), fair clearance in 6 cases (10.5%) and poor clearance in 32 cases (56.1%) (Fig. 2). Except one case who underwent HPE at the age of 265 days, all cases with correctable type biliary atresia (type C) achieved good jaundice clearance in the long-term (34-88 months). Among good clearance, biliary cirrhosis developed later and the jaundice worsened in 7 cases (12.3%). Cholangitis occurred in 26 patients (45.6%) within one month of HPE and 43 patients (75.4%) within 3 months. Only one re-operation was performed for a case with initial good clearance that developed cessation of bile flow and a recurrent bout of cholangitis at 26 months. The 5-year and 10-year actuarial survival rates were 20.0 per cent and 13.3 per cent, respectively.

Histopathology

Bile duct histopathology confirmed atresia in all patients. Biliary cirrhosis was reported in 33 specimens (57.9%). Bile ductules were detected in 25 of 38 specimens of portal tissue examined.

Factors analysis

Univariate analysis demonstrated the association of sex and age at surgery to the achievement of bile flow, while the other pre-operative factors showed no relationship. The jaundice duration and age at surgery showed co-linearity, but only the latter was included in the multivariate analysis model. Peri-operative transfusions tended to have a negative influence on the treatment outcome (Table 1).

Considering post-operative factors, the histopathology of biliary cirrhosis had no correlation with HPE success when the presence of bile ductule showed

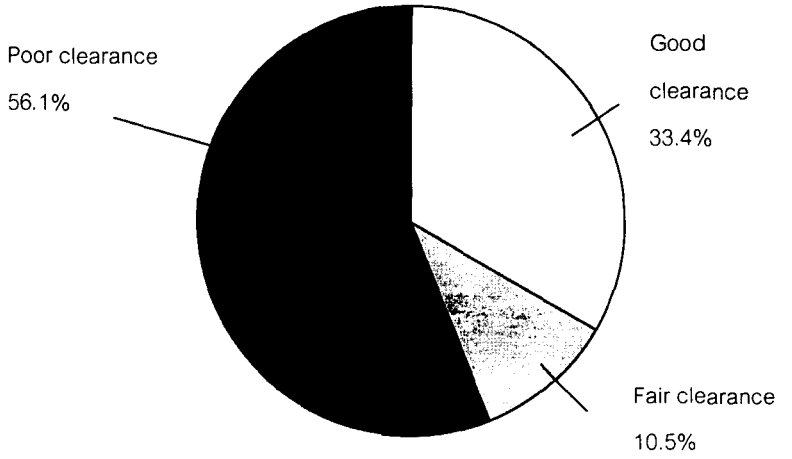

Fig. 2. Result of hepatic porto-enterostomy in terms of jaundice clearance.

Table 1. Univariate analysis of peri-operative variable.

Factors	No. (cases)	No. jaundice improved	%	P-value
Sex				0.129**
Male	30	16	53.3	
Female	27	9	33.3	
Age at surgery				0.014**
0-60 days	18	13	72.2	
61-90 days	19	6	31.6	
> 90 days	20	6	30.0	
Jaundice duration				
0-60 days	30	18	60.0	
61-90 days	13	4	30.8	
> 90 days	14	3	21.4	
Associated anomalies	7	3	42.8	0.954
Type of biliary atresia (n = 56)				0.178**
Type A or B	52	21	40.4	
Type C	4	3	75.0	
Initial bilirubin				0.395
≤ 12 mg%	28	14	50.0	
> 12 mg%	29	11	37.9	
Signs of portal hypertension	24	9	37.5	0.409
Peri-operative transfusion (n = 55)	39	14	35.9	0.071**
Histopathology				
Biliary cirrhosis (n = 53)	30	14	46.7	0.817
Presence of bile ductule (n = 35)	23	13	56.5	0.201**
Post-operative stool color				< 0.01
Yellow	25	20	80	
Pale	32	5	15.6	
Post-operative cholangitis	25	6	24.0	0.008
End of first month decline of bilirubin				< 0.01
> 50% of initial TB	12	10	83.3	
25-50% of initial TB	13	7	53.8	
< 25% or increase	22	3	13.6	

* number of complete data sets for analysis = 57, unless stated otherwise

** selected for multivariate analysis

possible association (p-value 0.20). By linear regression, decline of TB levels at one month were associated with ultimate clearance (p-value < 0.01). Post-operative stool color was also significantly associated with the outcome. Cholangitis within one month post-HPE showed a negative influence on the short-term survival.

Stepwise exclusion revealed statistically significant independent associations with jaundice clearance of TB level at one month and evidence of cholangitis within the first month. However, considering only variables that could be used as predictors, logistic regression was repeated, excluding those two variables. Finally, age at surgery and type of bile duct atresia were shown to be significant independent predictors of jaundice improvement after HPE (Table 2).

Log-rank test of the 3-year and 4-year failure rates between the groups with and without early cholangitis showed statistically significant difference. (Fig. 3) However, the survival probability curves coalesce after the fifth post-operative year when the difference began to loss its significance.

DISCUSSION

Before the introduction of HPE (Kasai's operation) in 1959[10], survival of infants with biliary atresia was never longer than 2 years. The operation gained worldwide acceptance as the only hope available, although the results were not promising. A large report of short-term outcome from Juntendo University, Japan showed 40-59 per cent jaundice free[11], whereas, series from Western institutes showed comparable short-term achievement at 36-

Table 2. Result of the final model of logistic regression analysis.

Factors	Odds ratio	95% Confidence interval	P-value
Age at diagnosis	0.30	0.13-0.68	< 0.01
Type of biliary atresia (Type C)	0.06	0.00-0.75	0.03

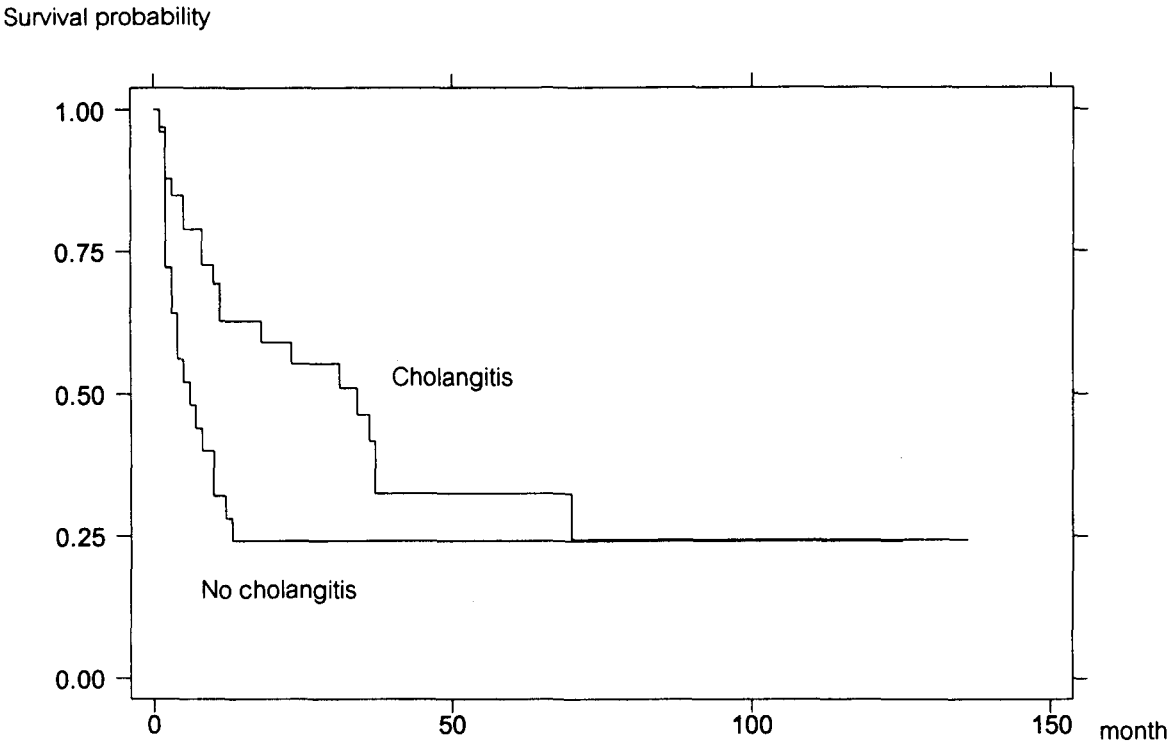

Fig. 3. Survival probability comparison between cases with and without early post-operative cholangitis.

55 per cent[4,7,12]. Of these short-term successes, about half survived more than ten years with their native livers. The rest were either rescued by hepatic transplantation or succumbed to progressive cirrhosis.

Sixty-nine new patients with biliary atresia were reported in a national survey of the Association of Pediatric Surgery of Thailand in 2001. Based on this figure, not fewer than 30 cases that fail HPE will require transplantation each year. However, the availability of hepatic transplantation in Thailand is limited by economic constraints and a shortage of donors. The palliative role of HPE is then seen as an endless road and only curative outcome is warranted. Identification of an appropriate surgical candidate who has a good chance to benefit from HPE needs reliable pre-operative prognosticating factors. Also, on the other hand, early identification of a potential failure case is valuable for follow-up planning.

Age at surgery was found in various series to have an influence on the outcome[2,6,11]. Our data support the importance of early operation in this group of patients. Our analysis showed that 'duration of jaundice' was also significantly correlated with the clearance of jaundice with almost the same likelihood ratio as 'age at surgery' History of persistent neonatal jaundice had no significant association with the poor result. Recent histopathological studies have demonstrated a close correlation between the age of the patient and the degree of hepatic fibrosis[13]. How-

ever, there was also contradictory evidence regarding the association between age at surgery and long-term survival(4,5,7).

Gross pathology of bile duct atresia is another factor demonstrated by the presented data to be associated with the outcome. All patients with isolated obliteration of the distal duct had long-term cirrhotic-free survival, with the exception of one case who underwent surgery at the age of nine months. This finding was also found in other large series(2,14).

Considering post-operative variables, the stool color and the initial decline of total bilirubin appeared to correlate well with HPE outcome. This is consistent with recent studies(12) and supports the values of these parameters in the identification of cases at risk of surgical failure, which are likely to have cirrhosis and be lost to follow-up.

Ascending cholangitis has a significant association with poor outcome. However, it remains debatable whether the infection itself is a negative factor or a result of poor bile flow. A clinical study, focusing on bacterial cholangitis from Taiwan reported a higher incidence in the group with poorer bile flow (8). The same study also showed significant reduction in survival probability in infants with cholangitis, regardless of the operative outcome. In a comprehensive histopathological study from Germany, cholangitis was mentioned as a 'secondary influence' to the progression of hepatic fibrosis(9). The study also found that the incidence of cholangitis was independent of the initial severity of hepatic pathology. The presented survival probability curves between the groups with and without cholangitis coalesce after the sixth post-operative year. The phenomenon may be explained that ascending cholangitis is not a key determiner of long-term survival, but it does play a role in accelerating the severity of hepatic fibrosis.

SUMMARY

The authors reviewed the outcome of HPE over a thirteen-year period at Songklanagarind Hospital. Age at surgery and type of biliary atresia were important factors predicting the result of the operation. Post-operative stool color and the initial decline of bilirubin level correlated well with the outcome. Ascending cholangitis within the first post-operative month showed a negative correlation with the clearance of jaundice.

ACKNOWLEDGEMENT

The authors wish to thank Miss Apiradee Lim, from the Epidemiology Unit, for her suggestions in data analysis. Review of medical records was performed with the permission of the Research Committee, Faculty of Medicine, Prince of Songkla University.

(Received for publication on September 6, 2002)

REFERENCES

1. Valayer J. Conventional treatment of biliary atresia: Long-term results. J Pediatr Surg 1996; 31; 1546-51.
2. Chardot C. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986-1996. Hepatology 1999; 30: 606-11.
3. Okazaki T, Kobayashi H, Yamataka A, et al. Long-term post-surgical outcome of biliary atresia. J Pediatr Surg 1999; 34: 312-5.
4. Carceller A, Blanchard H, Alvarez F, et al. Past and future of biliary atresia. J Pediatr Surg 2000; 35: 717-20.
5. Davenport M, Karkar N, Mieli-Vergani G, et al. Biliary atresia: The King's College Hospital experience (1974-1995). J Pediatr Surg 1997; 32: 479-85.
6. Nio M, Ohi R. Biliary atresia. Semin Pediatr Surg 2000; 9: 177-86.
7. Mckieman PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. Lancet 2000; 355: 25-9.
8. Wu ET, Chen HL, Ni YH, et al. Bacterial cholangitis in patients with biliary atresia: Impact on short-term outcome. Pediatr Surg Int 2001; 17: 390-5.
9. Lunzmann K, Schweizer P. The influence of cholangitis on the prognosis of extrahepatic biliary atresia. Eur J Pediatr Surg 1999; 9: 19-23.
10. Kasai M, Suzuki S. A new operation for "non-correctable" biliary atresia: Hepatic porto-enterostomy. Shujusu 1959; 13: 733-9.
11. Miyano T, Kobayashi H, Chen SC, Okazaki T. Biliary atresia - Post Kasai prognosis. Asian J Surg.

1999; 22: 125-30.
12. Yanchar NL, Shapiro AMJ, Sigalet DL. Is early response to porto-enterostomy predictive of long-term outcome for patients with biliary atresia? J Pediatr Surg 1996; 31: 774-8.
13. Schweizer P, Lunzmann K. Extrahepatic bile duct atresia: How efficient is the hepaticporto-enterostomy? Eur J Pediatr Surg 1998; 8: 150-4.
14. Altman RP, Lilly JR, Greenfield J, et al. A multivariable risk factor analysis of the porto-enterostomy (Kasai) procedure for biliary atresia. Ann Surg 1997; 226: 348-55.

ปัจจัยทางคลินิกซึ่งสัมพันธ์กับผลการผ่าตัดรักษาทารกที่มีท่อน้ำดีตีบโดยวิธี hepatic porto–enterostomy

สุรศักดิ์ สังขทัต ณ อยุธยา, พบ, ศักดา ภัทรภิญโญกุล, พบ*,*
กมลเนตร ตัณยาธิคม, พบ, เสกสิต โอสถากุล, พบ***

ได้รวบรวมข้อมูลผู้ป่วยทารกซึ่งป่วยด้วยโรคท่อน้ำดีตีบและเข้ารับการผ่าตัด hepatic porto–enterostomy (HPE) ในโรงพยาบาลสงขลานครินทร์ ระหว่างปีพุทธศักราช 2531 ถึง 2543 และวิเคราะห์หาปัจจัยซึ่งมีความสัมพันธ์ต่อความสำเร็จในการระบายน้ำดีรวมทั้งโอกาสรอดชีพในระยะยาวของผู้ป่วยเหล่านี้โดยวิธีวิเคราะห์แบบเอกปัจจัยและพหุปัจจัย

ผลการศึกษาพบมีผู้ป่วยเข้ารับการผ่าตัดทั้งสิ้น 62 ราย มัธยฐานอายุขณะผ่าตัด 78 วัน ผู้ป่วยตายในระยะ 1 เดือนหลังผ่าตัด 4 ราย ผู้ป่วยมิได้กลับมาเพื่อติดตามผลการรักษา 1 ราย รวมคัดออก 5 ราย เหลือจำนวน 57 รายเพื่อนำมาวิเคราะห์ ผลการผ่าตัดในแง่การลดภาวะดีซ่าน ร้อยละ 33.4 หายเหลือง ร้อยละ 10.5 ค่าบิลิรูบินลดลงต่ำกว่า 5 มก.% แต่ไม่หายเหลือง ร้อยละ 56.1 ภาวะดีซ่านเลวลงหรือดีขึ้นเพียงน้อย การวิเคราะห์แบบ univariate พบความสัมพันธ์ระหว่างอายุขณะผ่าตัดและลักษณะทางพยาธิวิทยามหภาคของท่อน้ำดีตีบกับความสำเร็จของการผ่าตัดอย่างมีนัยสำคัญ เมื่อวิเคราะห์ปัจจัยหลังผ่าตัดพบว่าการติดเชื้อในท่อน้ำดีมีความสัมพันธ์กับอัตราชีพรอดในระยะ 4 ปีแรก สีของอุจจาระและค่าบิลิรูบินที่ระยะ 1 เดือนหลังผ่าตัดสัมพันธ์กับผลการลดระดับดีซ่าน อัตราชีพรอดในระยะ 5 ปีและ 10 ปีเท่ากับร้อยละ 20.0 และ 13.3 ตามลำดับ

คำสำคัญ : ท่อน้ำดีตีบ, บิลิรูบิน, การติดเชื้อในท่อน้ำดี, กุมารศัลยศาสตร์

สุรศักดิ์ สังขทัต ณ อยุธยา, ศักดา ภัทรภิญโญกุล,
กมลเนตร ตัณยาธิคม, เสกสิต โอสถากุล
จดหมายเหตุทางแพทย์ ฯ 2546; 86: 224–231

* หน่วยกุมารศัลยศาสตร์, ภาควิชาศัลยศาสตร์,
** ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์, สงขลา 90110