A MULTICENTER STUDY OF THE OUTCOME OF BILIARY ATRESIA IN THE UNITED STATES, 1997 TO 2000

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Objective To determine the prognostic factors and optimal approaches to the diagnosis and management of biliary atresia, the leading indication for liver transplantation in children.

Study design A retrospective study was performed of all children who underwent hepatoportoenterostomy (HPE) for biliary atresia between 1997 and 2000 at 9 centers in the United States. Outcome at age 24 months was correlated with demographic and clinical parameters.

Results A total of 104 children underwent HPE; 25% had congenital anomalies, and outcome was worse in those with biliary atresia splenic malformation syndrome. Diagnostic and clinical approaches varied, although specific approaches did not appear to correlate with outcome. The average age at referral was 53 days, and the average age at HPE was 61 days. At age 24 months, 58 children were alive with their native liver, 42 had undergone liver transplantation (37 alive, 5 dead), and 4 had died without undergoing transplantation. Kaplan-Meier analysis of survival without liver transplantation revealed markedly improved survival in children with total bilirubin level < 2 mg/dL at 3 months after HPE (84% vs 16%; $P < .0001$).

Conclusions Outcome in the study centers was equivalent to that reported in other countries. Total bilirubin in early follow-up after HPE was highly predictive of outcome. Efforts to improve bile flow after HPE may lead to improved outcome in children with biliary atresia. *(J Pediatr 2006;148:467-74)*

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Biliary atresia is a disease of unknown etiology characterized by progressive fibro-obliteration and obstruction of the extrahepatic biliary tree. The disease affects 1:8,000 to 1:18,000 live births and presents in the neonatal period with jaundice, acholic stools, and hepatomegaly in an otherwise apparently healthy infant.[1] If biliary atresia is diagnosed within the first 3 months of life, then surgical therapy with hepatoportoenterostomy (HPE) can successfully restore bile flow from the liver into the intestinal tract in 30% to 80% of patients.[1-3]

Several factors have been reported to determine the ultimate success of HPE, including the patient's age at the time of surgery, presence of cirrhosis, surgeon's experience with performing HPE, occurrence of postoperative cholangitis, and perhaps unknown genetic factors.[1-7] However, even with successful HPE, progressive inflammation and fibrosis of the intrahepatic bile ducts develops to varying degrees, leading to biliary cirrhosis and the need for liver transplantation in 70% to 80% of patients.[5,6] The major research challenges include increased understanding of the pathogenesis and etiology of biliary atresia, improved biomarkers to reliably predict outcome and help guide therapy, and more effective means of diagnosis, prevention, and treatment. These considerations led to the formation of the Biliary Atresia Research Consortium (BARC) in 2002. BARC

BARC	Biliary Atresia Research Consortium	HPE	Hepatoportoenterostomy
BASM	Biliary atresia splenic malformation		

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*A list of Consortium institutions and members is available at www.jpeds.com.

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is a National Institutes of Health–supported cooperative network of 9 clinical centers and a data-coordinating center focused on conducting clinical and basic research of the etiology, pathogenesis, diagnosis, and therapy of biliary atresia.[8]

METHODS

A retrospective study was undertaken to analyze the results of a large cohort of patients with biliary atresia from a diverse group of US institutions with expertise in management of children with liver disease. As a first step, BARC embarked on a retrospective study of the clinical presentation and current management of biliary atresia and the surgical results after HPE. This analysis was particularly important because most of the literature on outcome of HPE from the United States are reports from single centers,[6,9] as opposed to nationwide biliary atresia registry data reported for other countries, including France[5] and Japan.[10] To establish a benchmark representing a contemporary national experience with biliary atresia in the United States, BARC conducted a retrospective chart review of clinical data and outcomes for all patients with biliary atresia undergoing HPE between January 1, 1997 and December 31, 2000 at the 9 BARC clinical centers.

All children (n = 104) who underwent HPE for biliary atresia between January 1, 1997 and December 31, 2000 were followed for 2 years or until loss of the native liver as a result of transplantation or death. Among these 104 children, 65 were white, 17 were black, 10 were Hispanic, and 9 were Asian. As in most series of biliary atresia patients, there was a slight preponderance of females (60%). Children with biliary atresia who did not undergo HPE were not included in this study. The study consisted of a comprehensive review of medical records available at each BARC site. Information was extracted from records by trained clinical research coordinators at the following time points: (1) initial evaluation at the BARC center; (2) performance of HPE; (3) discharge from the hospital after HPE; (4) the first postoperative outpatient visit after HPE; the visits closest to (5) 3 months postoperatively, (6) 6 months postoperatively, (7) age 12 months, (8) age 18 months, (9) age 24 months; and (10) the final visit before death or first liver transplantation. Data collected included demographic information, presenting signs and symptoms, diagnostic studies at the time of evaluation for cholestasis, and clinical course after HPE. Growth parameters, laboratory values, medication use, nutritional support, and sentinel events (eg, cholangitis, ascites, variceal hemorrhage) were recorded from chart review at each time point. Definitions of sentinel events and the case report form used in this study are available at the BARC website (http://www.barcnetwork.org/). Biliary atresia splenic malformation (BASM) syndrome was defined as a splenic malformation occurring together with another major malformation in infants diagnosed with biliary atresia. For the purpose of this study, good outcome was defined as alive with native liver and total serum bilirubin level < 6.0 mg/dL at age 24 months; poor outcome was defined as either death or liver transplantation before age 24 months; and indeterminate outcome was defined as alive with native liver but with serum total bilirubin level > 6.0 mg/dL. The study was approved by the Institutional Review Board at each BARC center with a waiver of consent.

Data are presented as percents or as means and standard deviations. Rates are compared using Fisher's exact test. Means are compared using 2-tailed, 2-sample *t*-tests with unequal variances (Behrens-Fisher test).

RESULTS

Associated Congenital Anomalies

Among the 104 patients, 78 (75%) had no congenital anomalies identified, 13 (12.5%) had 1 anomaly, and the remaining 13 (12.5%) had more than 1 anomaly. The most common anomaly was splenic malformation (12 subjects); the second most common was interrupted inferior vena cava (11 subjects). Eleven of the 13 infants with more than 1 anomaly had BASM (1 asplenia, 10 polysplenia). Nine subjects had a cardiac malformation, and 9 had intestinal malrotation. The most common grouping included 7 subjects with an interrupted inferior vena cava, a cardiac anomaly, and either polysplenia (6 subjects) or asplenia (1 subject).

Age at Evaluation and Surgery

The average age at initial evaluation at a BARC center was 53 days, and average age at HPE was 61 days (Table I); 44% of the patients underwent HPE after age 60 days, and 12% underwent HPE after age 90 days (Table II). There were no differences in age at HPE by sex, but there were differences by race and ethnicity (Table I). Non-Hispanic whites were more likely to have undergone HPE by age 60 days compared with other racial/ethnic groups (44 out of 65 non-Hispanic whites underwent HPE at age $\leq$ 60 days vs 15 out of 39 others; $P = .0044$). Infants with more than 1 anomaly were evaluated and underwent HPE earlier than those without anomalies and those with only 1 anomaly (Table I; $P = .04$ and .06, respectively, compared with those without anomalies).

Laboratory Values at Presentation and Diagnostic Testing

Table III reports initial laboratory values for routine liver biochemistry studies. Characteristic elevations in bilirubin (total and direct), alkaline phosphatase, gamma glutamyl transpeptidase, and alanine aminotransferase levels were observed.

The typical steps in diagnostic evaluation varied considerably among the 9 BARC clinical centers. Most commonly, an ultrasound was obtained (87%). The triangular cord sign[11] was not visualized by ultrasound in any subject, and 10% of subjects had a normal gallbladder. Fewer than half of the subjects (43%) underwent hepatobiliary scintigraphy (3 centers used scintigraphy in $< 25\%$ of cases, and 3 centers did so in $> 75\%$ of cases), and only small numbers underwent either endoscopic retrograde cholangiopancreatography (1%)

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