Total Serum Bilirubin within 3 Months of Hepatoportoenterostomy Predicts Short-Term Outcomes in Biliary Atresia

Benjamin L. Shneider, MD[1], John C. Magee, MD[2], Saul J. Karpen, MD, PhD[3], Elizabeth B. Rand, MD[4], Michael R. Narkewicz, MD[5], Lee M. Bass, MD[6], Kathleen Schwarz, MD[7], Peter F. Whitington, MD[6], Jorge A. Bezerra, MD[8], Nanda Kerkar, MD[9], Barbara Haber, MD[10], Philip Rosenthal, MD[11], Yumirle P. Turmelle, MD[12], Jean P. Molleston, MD[13], Karen F. Murray, MD[14], Vicky L. Ng, MD[15], Kasper S. Wang, MD[16], Rene Romero, MD[17], Robert H. Squires, MD[18], Ronen Arnon, MD[19], Averell H. Sherker, MD[20], Jeffrey Moore, MS[21], Wen Ye, PhD[21], and Ronald J. Sokol, MD[5], on behalf of the Childhood Liver Disease Research Network (ChiLDReN)*

Objectives To prospectively assess the value of serum total bilirubin (TB) within 3 months of hepatoportoenterostomy (HPE) in infants with biliary atresia as a biomarker predictive of clinical sequelae of liver disease in the first 2 years of life.

Study design Infants with biliary atresia undergoing HPE between June 2004 and January 2011 were enrolled in a prospective, multicenter study. Complications were monitored until 2 years of age or the earliest of liver transplantation (LT), death, or study withdrawal. TB below 2 mg/dL (34.2 μM) at any time in the first 3 months (TB <2.0, all others TB ≥2) after HPE was examined as a biomarker, using Kaplan-Meier survival and logistic regression.

Results Fifty percent (68/137) of infants had TB <2.0 in the first 3 months after HPE. Transplant-free survival at 2 years was significantly higher in the TB <2.0 group vs TB ≥2 (86% vs 20%, $P < .0001$). Infants with TB ≥2 had diminished weight gain ($P < .0001$), greater probability of developing ascites (OR 6.4, 95% CI 2.9-14.1, $P < .0001$), hypoalbuminemia (OR 7.6, 95% CI 3.2-17.7, $P < .0001$), coagulopathy (OR 10.8, 95% CI 3.1-38.2, $P = .0002$), LT (OR 12.4, 95% CI 5.3-28.7, $P < .0001$), or LT or death (OR 16.8, 95% CI 7.2-39.2, $P < .0001$).

Conclusions Infants whose TB does not fall below 2.0 mg/dL within 3 months of HPE were at high risk for early disease progression, suggesting they should be considered for LT in a timely fashion. Interventions increasing the likelihood of achieving TB <2.0 mg/dL within 3 months of HPE may enhance early outcomes. *(J Pediatr 2016;170:211-7)*.

Trial registration ClinicalTrials.gov: NCT00061828 and NCT00294684.

Although biliary atresia (BA) is a rare disorder occurring between 1 in 8000 and 1 in 18 000 live births, nearly one-half of affected children will require liver transplantation (LT) within the first 2 years of life. An additional 20%-30% will require LT in childhood and adolescence. Consequently, BA is the leading indication for LT in childhood, accounting for nearly 35% of pediatric LT (based upon Organ Procurement and Transplantation Network data as of February 16, 2015[1]). The underlying cause(s) and mechanisms of progression of this fibroinflammatory obliterative cholangiopathy are unknown. The sole intervention that has been shown to affect survival with native liver is the hepatoportoenterostomy (HPE), commonly referred to as the Kasai procedure since it was

AUC	Area under the curve
BA	Biliary atresia
ChiLDReN	Childhood Liver Disease Research Network
HPE	Hepatoportoenterostomy
LT	Liver transplantation
PROBE	Prospective Database of Infants with Cholestasis
ROC	Receiver operating characteristic
START	Steroids in Biliary Atresia Randomized Trial
TB	Total bilirubin

From the [1]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Baylor College of Medicine, Houston, TX; [2]University of Michigan Medical School, Ann Arbor, MI; [3]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Emory University School of Medicine/Children's Healthcare of Atlanta, Atlanta, GA; [4]Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA; [5]Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO; [6]Pediatrics Division of Gastroenterology, Hepatology, and Nutrition, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [7]Johns Hopkins School of Medicine, Baltimore, MD; [8]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [9]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Los Angeles, University of Southern California, Los Angeles, CA; [10]Merck Sharp and Dohme Corp, Merck Research Laboratories, North Wales, PA; [11]Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Francisco Benioff Children's Hospital, San Francisco, CA; [12]Washington University School of Medicine, St. Louis, MO; [13]Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Indiana University School of Medicine, Indianapolis, IN; [14]Division of Gastroenterology and Hepatology, Department of Pediatrics, University of Washington and Seattle Children's, Seattle, WA; [15]The Hospital for Sick Children, Toronto, Ontario, Canada; [16]Division of Pediatric Surgery, Children's Hospital, Los Angeles, CA; [17]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Emory University, Atlanta, GA; [18]Children's Hospital of Pittsburgh, Pittsburgh, PA; [19]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Mount Sinai Medical Center, New York, NY; [20]Liver Diseases Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; and [21]Department of Biostatistics, University of Michigan, Ann Arbor, MI

*List of additional members of ChiLDReN is available at www.jpeds.com (**Appendix 1**).

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first described by Morio Kasai.[2] In cases where the HPE is ineffective in restoring bile flow, there is rapid progression to biliary cirrhosis, liver failure, and death by 2-3 years of age.[3] Though LT is an excellent option to restore health, prediction of the need for and determining the optimal timing of LT are challenging. Predictors of outcomes in BA have been identified largely through single center studies or retrospective multicenter analyses.[4-21] Despite BA becoming the focus of increased research activity in the past decade, prospective multicenter studies of clinical outcomes are limited.

This study reports findings of the Prospective Database of Infants with Cholestasis (PROBE) study undertaken by the 16 member institutions and investigators of the National Institutes of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health-supported Childhood Liver Disease Research Network (ChiLDReN; formerly the Biliary Atresia Research Consortium). PROBE was designed to acquire longitudinal, prospective clinical and laboratory data in a standardized fashion at defined time points to enable definitive studies of natural history of cholestatic liver diseases in infants and early childhood. Here, we focus on the analysis of the outcomes of children with BA over the first 24 months of life and the laboratory and clinical markers that predict these near-term outcomes. We hypothesized that serum levels of total bilirubin (TB) in the first 3 months after HPE (as an indicator of successful bile drainage post-HPE) would be predictive of 2-year outcomes in children with BA.

Methods

Study participants included subjects enrolled in PROBE (Clinicaltrials.gov: NCT00061828), more than 2 years before the data cutoff date (ie, who had the potential for at least 2 years of follow-up). Informed consent was obtained from parents or guardians, and the protocol was carried out under institutional review board approval. Inclusion criteria for enrollment in PROBE included presentation prior to 180 days of age with cholestasis defined as serum direct or conjugated bilirubin greater than or equal to 2.0 mg/dL and greater than 20% of TB. Infants who had undergone previous hepatobiliary surgery with dissection or excision of biliary tissue before presentation at a ChiLDReN site were not eligible for PROBE. The study population for this report was further restricted to subjects with BA who underwent HPE. After September 1, 2005, PROBE participants with BA who underwent HPE were eligible to be co-enrolled in a prospective, randomized double-blinded, placebo-controlled trial of corticosteroid therapy after HPE for BA (Steroids in Biliary Atresia Randomized Trial [START]; Clinicaltrials.gov: NCT00294684). Participants co-enrolled in START (n = 135) were excluded from this analysis because they were the focus of a separate report.[22] Corticosteroids were not typically employed as adjunctive therapy to HPE outside of START.

Data prospectively collected by study research coordinators and clinical investigators were entered into a centralized database at the data coordinating center. Baseline data included demographics, medical and family history, and laboratory studies. Follow-up visits for data collection occurred at 1, 2, 3, and 6 months after HPE and at 12, 18, and 24 months of age.

Data Analyses

Descriptive data were summarized as the mean and SD for continuous variables and as percentages for categorical variables. In addition to the descriptive analysis of baseline variables, we evaluated the fidelity of TB as a marker of clinical outcomes at 3 months up to 2 years of age following surgical drainage. Outcomes of interest included survival with native liver and complications of advancing liver disease, including manifestations of portal hypertension. Response to HPE was dichotomized into 2 groups based upon TB levels in the first 3 months after HPE. TB <2.0 mg/dL (TB <2) was defined by any TB less than 2.0 mg/dL (34.2 μM) within the first 3 months post HPE, and TB $\geq$2.0 was defined as never achieving a TB less than 2.0 mg/dL in the first 3 months post-HPE.

Logistic regression was used to model the probability that a specific clinical event occurred at least once in the period beginning 3 months after HPE as a function of the TB dichotomy described above. The clinical end points of interest were development of ascites (deemed clinically significant and/or requiring ongoing diuretic therapy), variceal hemorrhage (gastrointestinal bleed confirmed on endoscopy), thrombocytopenia (platelet count <150 000 $\times$ 10^9/L), splenomegaly (spleen palpable more than 2 cm below the costal margin), hypoalbuminemia (serum albumin <3.0 gm/dL), hyponatremia (serum sodium <130 mmol/L), coagulopathy (international normalized ratio >1.5), weight-for-age z-scores (failure to thrive defined as a z-score < −2.5), height-for-age z-scores, mid-arm circumference z-scores, receiving a LT, and death. The number and proportion for each TB group is reported, as well as an OR, *P* value, and 95% CI. In addition, 2-year Kaplan-Meier survival curves were generated to examine the time course for these clinical outcomes for each TB group, starting at HPE. To determine the relationship of successful HPE drainage in the first 3 months with each outcome, in all the above analyses, participants who had experienced the outcome of interest or underwent transplant or died before 3 months after HPE were excluded from the analysis cohort. An event was defined as the first occurrence of the clinical end point, with subjects censored at the earlier of transplant or death (except for the transplant or death analysis, where this would be considered the end point), loss to follow-up, or the end of the data collection period (January 1, 2013).

To compare the mean time trajectories of weight z-score and height z-score between the 2 TB groups, we used a joint model of longitudinal and survival data with penalized B-splines[23,24] to adjust for potential bias because of informative dropout caused by LT.[25] In addition, the same method was used to estimate the mean trajectories of TB in the 2 TB groups. This joint model corrects the bias caused by informative dropout