SPECIAL ARTICLE

Growth Failure and Outcomes in Infants with Biliary Atresia: A Report from the Biliary Atresia Research Consortium

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Malnutrition is a significant clinical problem in infants with biliary atresia. The natural history of poor growth and its potential association with early transplantation or death in children with biliary atresia was determined. Serial weight- and length-for-age z-scores were computed as part of a retrospective study of 100 infants who underwent hepatoportoenterostomy (HPE) for biliary atresia at 9 U.S. pediatric centers between 1997 and 2000. Poor outcome was defined as transplantation or death by 24 months of age (n = 46) and good outcome was defined as survival with native liver at 24 months of age with total serum bilirubin less than 6 mg/dL (n = 54). Growth velocity was significantly slower in the poor outcome group compared to the good outcome group ($P < 0.001$ for both weight and length). Mean weight z-scores were significantly lower by 6 months after HPE in the poor outcome group (-2.1 ± 1.4) compared to the good outcome group (-1.2 ± 1.4) ($P < 0.001$). In a subgroup with total bilirubin between 2 and 6 mg/dL at 3 months after HPE (n = 28), the weight z-scores at 3 months after HPE were significantly lower in the poor outcome group (-2.0 ± 1.2) compared to the good outcome group (-1.0 ± 1.2) ($P = 0.04$) despite similar bilirubin concentrations. _Conclusion:_ Growth failure after HPE was associated with transplantation or death by 24 months of age. The combination of intermediate bilirubin concentrations and poor mean weight z-scores 3 months after HPE was also associated with poor clinical outcome. (HEPATOLOGY 2007;46:1632-1638.)

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Biliary atresia is a neonatal cholangiopathy of unknown etiology that affects 1 in 8,000 to 18,000 newborns.[1,2] It is the most frequent indication for liver transplantation in children accounting for almost 50% of pediatric liver transplants in the United States.[1,2] Early surgery with hepatoportoenterostomy (HPE) to relieve extrahepatic biliary obstruction and restore bile flow is critical. Despite surgery, however, progressive hepatic fibrosis often ensues and liver transplantation is eventually necessary in 70%-80% of patients. At least half of infants with biliary atresia are likely to undergo liver transplantation within the first 2 years of life.[3-5]

The evaluation of outcomes in infants with biliary atresia after HPE has been one focus of the Biliary Atresia Research Consortium (BARC), which was formed in

2002 as a National Institutes of Health (NIH)-supported network of 9 pediatric clinical centers and a data coordinating center. BARC has previously reported that survival to 24 months of age with native liver in children with biliary atresia was predicted by lower serum total bilirubin concentrations (<2 mg/dL compared to >6 mg/dL) at 3 months after HPE. [6] However, less than half of the entire cohort who required transplantation or died had a total serum bilirubin >6 mg/dL at 3 months after HPE. Clearly, other factors that predict rapid progression to end-stage liver disease need to be identified.

Malnutrition is a significant clinical problem in children with biliary atresia[7-16] particularly during the first year of life and indeed has been shown to increase mortality risk once a patient has been listed for liver transplantation. Recognition of this risk is best illustrated by the inclusion of growth failure as a parameter in the Pediatric End-Stage Liver Disease (PELD) scoring system used to rank candidates awaiting liver transplantation in the United States.[7] It has been proposed that maintaining optimal nutritional status in young biliary atresia patients might improve outcomes before and after liver transplantation.[13-15]

The aims of this study were to evaluate growth in infants with biliary atresia and to determine growth patterns over the first 2 years of life that were associated with an increased risk for early liver transplantation or death. This study is unique because it is the first multicenter assessment of growth after HPE in a large cohort of infants with biliary atresia in the United States.

Patients and Methods

Study Population and Design. A comprehensive review of medical records was performed at the 9 BARC clinical centers to identify all children who underwent HPE for biliary atresia between January 1, 1997 and December 31, 2000.[6] All children with biliary atresia who were followed for at least two years or until liver transplantation or death before 2 years of age were included. Children who did not undergo HPE were not included. A survival analysis of this cohort has been previously published.[6] This study was approved by the Institutional Review Boards with a waiver of consent at each of the BARC clinical centers and the data coordinating center.

Data Collection. Information was extracted from medical records by trained clinical research coordinators at the following time points: the time of initial evaluation at the BARC center, the time of HPE, discharge from the hospital after HPE, the first out-patient visit after HPE, and the visits closest to 3 and 6 months after HPE, 12, 18 and 24 months of age, and the final visit before death or first liver transplantation if before age 2 years. Data (including demographics, weight and length measurements, use of supplemental nutrition, and laboratory results) were recorded from chart review at each of the time points. Case report forms utilized in this study are available on the BARC website (http://www.barcnetwork.org).

Growth Assessment. Weight-for-age and length-for-age data for each gender were used to develop z-scores which were calculated by using a SAS program based on the 2000 Center for Disease Control growth charts (http://www.cdc.gov/growthcharts/).

Definitions of Outcome Variables. Good outcome was defined as alive with native liver and total serum bilirubin <6.0 mg/dL at 24 months of age.[6] Poor outcome was defined as either liver transplantation or death before 24 months of age. Four infants who had their native liver but had total bilirubin >6.0 mg/dL at 24 months of age were considered to have an indeterminate outcome and were not included in the analysis. Biliary atresia splenic malformation (BASM) syndrome was defined as a macroscopic splenic malformation (*e.g.,* polysplenia or asplenia) together with another major congenital malformation in biliary atresia infants.

Data Analysis. All analyses were performed on the age-adjusted z-scores instead of actual weight or length measurements. Mean weight z-scores and length z-scores at each of the nine measurement time points were compared using two-tailed Student *t*-tests with unequal variances (the Behrens-Fisher test). To capture the non-linear trajectory of the growth curves, a semi-parametric stochastic mixed model (SPMM)[17] was used. This model fits the population mean curve flexibly with a smoothing spline which can capture any kind of trajectory. The model also adjusts for the within-subject correlation and uses time after HPE calculated from the exact ages at the time of each measurement. To test whether the growth curves differed between the good outcome and poor outcomes groups, we assumed that the difference between the mean population curves of the two groups was a linear function and tested whether this linear function was different from zero.

In addition, a special feature of the data of subjects with poor outcomes, a so-called informative dropout problem, requires adjustment of the standard analysis. This is caused by the fact that sicker subjects tend to have poorer growth and earlier liver transplantation or death. Because the growth measurements in the poor outcome group were not accessible after liver transplantation or death, subjects with poorer growth tended to have fewer weight and length measurements. To correct the potential underestimation of growth failure of the poor outcome group introduced by this informative dropout problem,

Table 1. Characteristics of Infants with Biliary Atresia in the Good Outcome (n = 54) and Poor Outcome (n = 46) Groups

Characteristic	Good Outcome	Poor Outcome	P
Age at presentation (days)	49 ± 24 (n = 50)	55 ± 30 (n = 45)	NS
Age at hepatoportoenterostomy (days)	56 ± 23 (n = 52)	64 ± 27 (n = 46)	NS
Weight z-score at presentation	−0.81 ± 1.4 (n = 45)	−0.70 ± 1.0 (n = 44)	NS
Length z-score at presentation	−0.69 ± 1.69 (n = 38)	−0.57 ± 1.61 (n = 32)	NS
BASM	2	9	P = 0.02

Mean ± SD

Table 2. Weight for Age Z-Scores: Comparison Between the Good and Poor Outcome Patients

	Good Outcome		Poor Outcome		
	N	Weight Z-Score	N	Weight Z-Score	P
Presentation	45	−0.81 ± 1.4	44	−0.71 ± 1.0	NS
HPE	40	−1.08 ± 1.3	38	−0.73 ± 0.9	NS
Discharge	33	−1.40 ± 1.3	36	−1.26 ± 1.0	NS
1st visit after HPE	43	−1.39 ± 1.3	33	−1.37 ± 1.2	NS
3 months after HPE	41	−1.37 ± 1.3	37	−1.55 ± 1.3	NS
6 months after HPE	40	−1.22 ± 1.4	26	−2.10 ± 1.4	0.01
12 months of age	45	−0.92 ± 1.5	19	−1.76 ± 1.4	0.04
18 months of age	41	−0.49 ± 1.2	9	−1.67 ± 1.3	0.01
24 months of age	46	−0.01 ± 1.2			

Mean ± SD

Abbreviation: HPE, hepatoportoenterostomy

we trimmed the data of this group by using the following procedure: (1) determine the time of transplant or death in the poor outcome group and arrange them in increasing order; (2) match the first subject to the last subject on this list, and the second with the second to the last, until 23 pairs of subjects were identified; and (3) in each of these pairs for the subject with longer survival time, delete any measurements after the transplant or death of the subject's match with the shorter survival time. The results obtained from the trimmed data were similar to those found with the original data except that the estimated difference between groups increases more rapidly; this occurs because the growth curve for the poor outcome group is no longer improved by survivor bias. Both the original and trimmed data are presented in the figures.
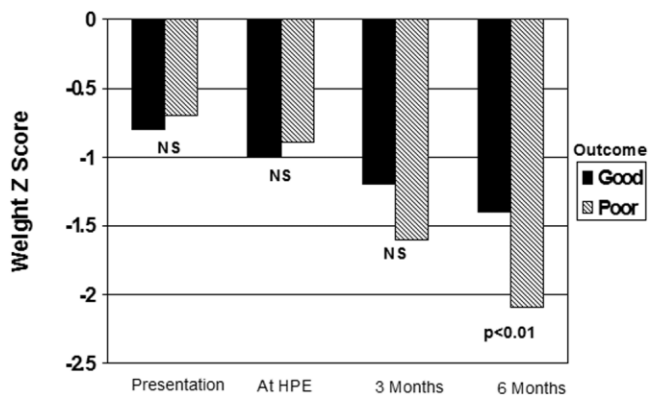

Fig. 1. Mean weight-for-age z-scores in infants with biliary atresia in the good and poor outcome groups at presentation, at HPE, 3 months after HPE and at 6 months after HPE. Dark bars represent the good outcome group and hatched bars represent poor outcome group. A significant difference in mean weight z-scores was seen at 6 months after HPE between the good and poor outcome groups (P < 0.01). HPE, hepatoportoenterostomy.

Weight z-scores were also analyzed in a subgroup of patients according to three strata of total serum bilirubin concentrations that were established *a priori* as previously reported:[6] (a) less than 2.0 mg/dL, (b) 2.0 to 6.0 mg/dL, and (c) greater than 6.0 mg/dL.

Results

Patient Characteristics. One hundred patients who underwent HPE for biliary atresia with known outcomes as reported previously[6] were identified. The good and poor outcome groups were comparable for age at presentation, age at HPE, weight z-score at presentation, and length z-score at presentation (Table 1). The mean age at presentation was 53 (±28) days. Fifty-nine percent were females, 63 were non-Hispanic white, 15 were African American, 10 were Hispanic white and 9 were Asian. Eleven had BASM; 2 in the good outcome group and 9 in the poor outcome group. Forty-six percent of infants had a poor outcome (42 transplanted and 4 deaths). The 4 deaths occurred prior to transplantation and were attributable to complications of congenital heart disease.

Table 3. Length for Age z-Scores: Comparison Between the Good and Poor Outcome Patients

	Good Outcome		Poor Outcome		
	N	Length z-Score	N	Length z-Score	P
Presentation	38	−0.69 ± 1.7	32	−0.57 ± 1.6	NS
HPE	18	−0.76 ± 1.8	17	0.02 ± 1.2	NS
1st visit after HPE	40	−0.99 ± 1.4	25	−0.89 ± 1.6	NS
3 months after HPE	39	−1.09 ± 1.3	30	−0.71 ± 1.1	NS
6 months after HPE	39	−1.13 ± 1.4	25	−1.36 ± 1.4	NS
12 months of age	41	−0.73 ± 1.5	18	−1.14 ± 1.3	NS
18 months of age	40	−0.62 ± 1.2	9	−1.54 ± 1.0	0.04
24 months of age	42	−0.59 ± 1.1			

Mean ± SD

Abbreviation: HPE, hepatoportoenterostomy
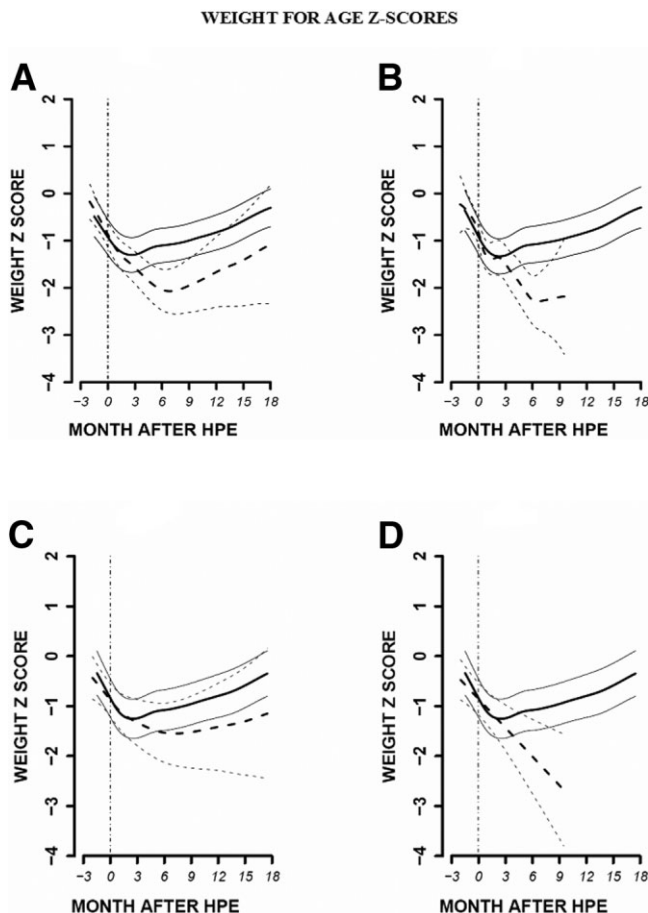
WEIGHT FOR AGE Z-SCORES

Fig. 2.   Weight for age z-scores in infants with biliary atresia comparing good and poor outcome groups on each graph. (A) Original data for all 100 subjects; (B) Trimmed data for all 100 subjects; (C) Original data for only subjects without BASM or ascites; (D) Trimmed data for only subjects without BASM or ascites. Good outcome group is represented by solid lines and poor outcome group is represented by dashed lines. The dotted vertical line on each graph represents time of HPE. The 2 outer lines are the 95% confidence intervals. Among the 100 subjects, the number of children followed (with measurements) at HPE were 52 (good outcome) and 46 (poor outcome), at 6 months after HPE 48 and 32, at 12 months after HPE 47 and 13 and at 18 months after HPE 45 and 4, respectively. Analysis on the complete dataset (n = 100) shows a significant difference in the shape of the growth curves between the good and poor outcome group (P < 0.0001). Excluding children with BASM and ascites, the significant difference remains (P = 0.0001). HPE, hepatoportoenterostomy.

Average Z-Scores and Growth Curves in the Good and Poor Outcome Groups. Average z-scores were compared between the good and poor outcome group at initial presentation, at HPE, and at each follow-up time. At initial presentation, mean weight and length z-scores for the entire cohort were less than zero (-0.8 ± 1.2, and -0.6 ± 1.7, respectively). During the first 3 months after HPE the weight and length z-scores declined in both the good and poor outcomes groups. At 6 months after HPE, there was a significant difference in mean weight z-scores between the good outcome group (-1.2 ± 1.4) and the

poor outcome group (-2.1 ± 1.4; $P < 0.01$) (Fig. 1). A significant difference in mean weight z-scores between the 2 groups persisted beyond the first year of life (Table 2). The mean length z-scores in the poor outcome group declined over time (Table 3). In the good outcome group, length and weight z-scores returned to scores similar to those at presentation between 12 and 18 months of age.

The growth curves over time after HPE for both the good and poor outcome groups were fitted using the SPMM longitudinal model (Figs. 2 and 3): the shapes of the growth curves differ between the two groups for both weight and length (each $P < 0.0001$). Although the av-

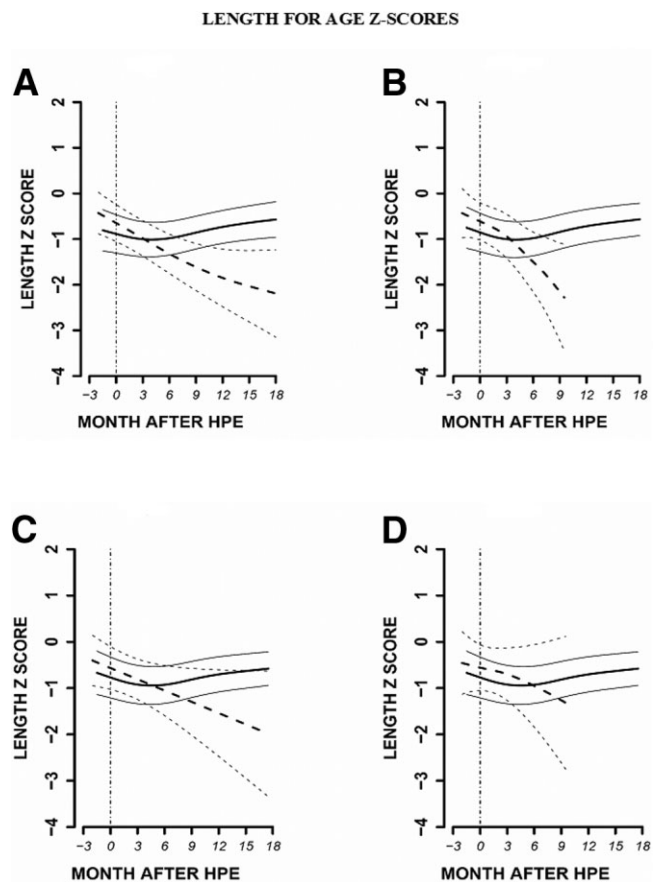## LENGTH FOR AGE Z-SCORES

Fig. 3.   Length for age z-scores in infants with biliary atresia comparing good and poor outcome groups on each graph. (A) Original data for all 100 subjects; (B) Trimmed data for all 100 subjects; (C) Original data for only subjects without BASM or ascites. (D) Trimmed data for only subjects without BASM or ascites. The good outcome group is represented by solid lines and poor outcome group is represented by dashed lines. The dotted vertical line on each graph represents time of HPE. The 2 outer lines are the 95% confidence intervals. Among the 100 subjects, the number of children followed (with measurements) at HPE were 51 (good outcome) and 46 (poor outcome), at 6 months after HPE 47 and 30, at 12 months after HPE 47 and 12, and at 18 months after HPE 44 and 4, respectively. Analysis on the complete dataset (n = 100) shows a significant difference in the shape of the growth curves between the good and poor outcome group (P < 0.0001). Excluding children with BASM and ascites, the significant difference remains (P < 0.0001). HPE, hepatoportoenterostomy.

erage weight and length z-scores were similar in the good and poor outcome group at the time of HPE, the weight and length z-scores in the good outcome group started to improve by 3 months after HPE while the weight and length z-scores in the poor outcome group continued to decline. The difference in both weight and length growth velocity between the 2 groups was apparent by 6 months after HPE. The mean weight z-score by 6 months after HPE of the good outcome group was better than the poor outcome group, and by 9 months after HPE (at approximately one year of age) the mean length z-score of the good outcome group was better than the poor outcome group. These findings persist even when children with BASM or who develop ascites are excluded from the study population (Fig. 2C,D and 3C,D), suggesting that neither of these factors alone is responsible for the findings.

Because of the influence of ascites and/or splenomegaly on weight, the probability of developing these complications were assessed in both the good and poor outcome groups. At 12 months of age the probability of ascites and/or splenomegaly in the poor outcome group was 0.63 (n = 12/19) compared to 0.20 (n = 10/50, P = 0.012) in the good outcome group.

Although there was a trend towards lower weight and length growth curves in the group with BASM compared to those without, the differences were not statistically significant (data not shown).

Average z-Scores and Growth Curves in a Subgroup of Patients with Total Serum Bilirubin 2-6 mg/dL at 3 months After HPE. Among the 100 patients with known outcomes, 84 had a total serum bilirubin
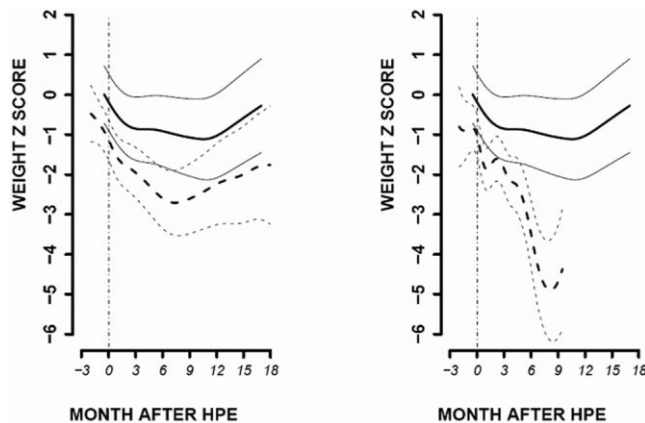
Fig. 5. Weight-for-age z-scores in subgroup (n = 28) with total bilirubin between 2 and 6 mg/dl at 3 months after HPE; a comparison of the good and poor outcome groups on each graph. The original data are shown on the left graph and trimmed data are shown on the right graph. The good outcome group is represented by solid lines and poor outcome group is represented by dashed lines. The dotted vertical line on each graph represents time of HPE. The 2 outer lines are the 95% confidence intervals. The number of children followed (with measurements) at HPE were 10 (good outcome) and 18 (poor outcome), at 6 months after HPE 10 and 15, at 12 months after HPE 10 and 7, and at 18 months after HPE 8 and 2, respectively. There was a significant difference in the shape of the growth curves between the good and poor outcome group (P < 0.05). HPE, hepatoportoenterostomy.

concentration reported at the 3 month visit after HPE. Among these 84 patients, 38 had bilirubin <2 mg/dL, 28 had total bilirubin between 2 and 6 mg/dL, and 18 had total bilirubin >6mg/dL. In the subgroup with bilirubin concentrations of 2 to 6 mg/dL at 3 months after HPE, 10/28 (36%) infants had a good outcome and 18/28 (64%) had a poor outcome. The poor outcome group had significantly lower weight z-scores at 3 months after HPE (−2.0 ± 1.2) compared to the good outcome group (−1.0 ± 1.2) (P = 0.04) (Fig. 4). This difference widened at 6 months after HPE (−2.5 ± 1.4 in the poor outcome group compared to −0.9 ± 1.8 in the good outcome group; P = 0.02). Growth curves for this subgroup were also fitted using the SPMM model (Fig. 5). In the infants with total bilirubin concentrations between 2 and 6 mg/dL at 3 months after HPE, the weight z-scores over time (Fig. 5) were significantly worse in the poor outcome group (P < 0.05). Given the small numbers of children in this subgroup, we are not able to meaningfully evaluate the potential impact of BASM or ascites on these findings.

Nutritional Supplementation. Nutritional supplementation was defined as nasogastric tube feedings or total parenteral nutrition. Supplementation was given to both the good (17/54; 31.5%) and poor outcome (22/46; 47.8%) (P = 0.11) groups at varying times and durations. Among those in the good outcome group who received
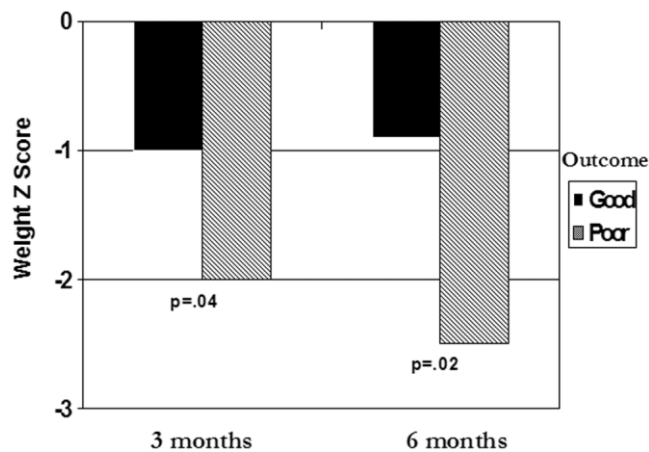

Fig. 4. Mean weight-for-age z-scores at 3 and 6 months after HPE in the subgroup with total bilirubin concentrations between 2 and 6 mg/dl at 3 months after HPE. Dark bars represent the good outcome group and hatched bars represent poor outcome group. A significant difference in mean weight z-scores were seen between the good and poor outcome groups at 3 months (P = 0.04) and 6 months (P = 0.02) after HPE. HPE, hepatoportoenterostomy.

nutritional supplementation, 14/17 (82%) were receiving nutritional supplementation at time of HPE and/or discharge from HPE. In the poor outcome group, only 8/22 (36%) received nutritional supplementation at the time of HPE and/or discharge, which is significantly less than in the good outcome group ($P < 0.01$). In another 8/22 patients who subsequently received nutritional supplementation in the poor outcome group, supplementation was not initiated until the time period just preceding liver transplantation or death. Data were not available regarding the percentage of total calories received from supplementation and no determination could be made regarding potential benefits of supplementation.

Discussion

A major finding in this study is that infants with biliary atresia who ultimately required liver transplantation or died had poorer growth after HPE compared to those who survived with their native liver at 24 months of age. On average, the infants had suboptimal growth at the time of initial presentation. The infants who had their native liver at 24 months of age had an initial decline in growth after HPE followed by improvement. The mean weight and length z-scores in the good outcome group did not return to values similar to those seen at presentation until they were over 1 year of age. In those infants destined to early transplantation or death, their growth continued to decline relative to the good outcome group. Differences between the two groups in mean weight z-scores occurred before differences in mean length z-scores. Although BASM patients had worse survival with native liver after HPE, the growth data did not change significantly when BASM patients were excluded from our analyses. In contrast to other investigations, this study was not limited by cross-sectional evaluation of single growth measurements but is unique in that weight and length measurements were obtained during disease progression and correlated with clinical outcome.

A difference in weight and length growth velocity between the 2 groups was apparent as early as 6 months after HPE for both weight and length. Furthermore, in a subgroup of infants with intermediate total bilirubin concentrations (between 2 and 6 mg/dL at 3 months after HPE), a significantly lower mean weight z-score became apparent as early as 3 months after HPE in the group who were transplanted or died. The true difference in weight-for-age z-scores is most likely underestimated because patients in the poor outcome group were more likely to develop ascites and/or splenomegaly which could increase weight-for-age z-scores. Indeed, an increase in weight-for-age z-scores was seen on the growth curves in the poor outcome group over time yet a significant difference in the z-scores

remained between the 2 groups. It is likely that linear growth is a better indicator of nutritional status than weight in this population.

It is interesting to note that although there was no significant difference in the number of patients in each group who received nutritional supplementation, the majority of patients in the good outcome group received supplementation at the time of HPE and/or discharge. In over 1/3 of the patients in the poor outcome group, nutritional supplementation was not initiated until the time just preceding transplantation or death. Although it is tempting to speculate that early nutritional supplementation may have made a difference for the good outcome group, data regarding the amount and duration of supplementation were not available and therefore conclusions regarding the impact of nutritional supplementation cannot be made.

Several studies support our findings that growth failure is a risk factor for poor outcome in infants with biliary atresia and end stage liver disease.[12,13,18] Growth failure was found to be an independent risk factor for pre-transplant mortality, post- transplant mortality, and even graft failure in 755 patients with biliary atresia listed for liver transplantation and enrolled in the Studies in Pediatric Liver Transplantation (SPLIT).[12] Most of the patients who died while on the liver transplant waiting list had height or weight deficits. Growth failure was found to be an important factor associated with death or moving to the intensive care unit in a multi-center cohort of SPLIT patients[7], the majority of whom had biliary atresia. Growth failure, defined as height or weight <2 standard deviations, was associated with increased morbidity and mortality.

The retrospective nature of this study precluded an accurate assessment of the optimal timing, amount and duration of supplemental feedings that could potentially reverse growth failure in biliary atresia. Improved growth velocity may reflect improvement in the disease state but does not occur in the absence of adequate energy and nutrient intake. Chin et al.[14,15] and Holt et al.[16] have demonstrated that improved growth could be accomplished with supplemental feedings. Chin et al.[14] in a randomized crossover trial of 19 children with end stage liver disease, mostly with biliary atresia, showed improvements in weight and height during specialized enteral feedings, with no significant change on the standard formula. The use of nasogastric tubes did not alter the rate of variceal bleeding in another study.[15] In an observational study of 33 patients (median age 0.6 years) with biliary atresia and failure to thrive, Holt et al.[16] reported improved weight and length z-scores after receiving nasogastric supplemental feedings for a median duration of 3.7 months. Although these studies were short term and effect

on outcomes were unclear, they indicate that malnutrition can be reversed in the majority of biliary atresia patients with aggressive nutritional rehabilitation.

In summary, poor growth over the first two years after HPE in infants with biliary atresia is associated with an increased need for liver transplantation or death by 24 months of age. The combination of intermediate total bilirubin concentrations and poor growth at 3 months after HPE increases the risk of transplantation or death. Poor growth and nutritional deficiencies may be an important potentially reversible risk factor for early need for liver transplantation or death. Studies are needed to determine whether early aggressive nutritional support after HPE can improve growth and prolong survival with the native liver.

APPENDIX: THE BILIARY ATRESIA RESEARCH CONSORTIUM

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Children's Memorial Hospital, Chicago: Peter Whitington, M.D., Susan Kelly, R.N.

Johns Hopkins School of Medicine: Kathleen Schwarz, M.D., Patricia DeRusso, M.D., Michele Walton, RN

The Mount Sinai School of Medicine, New York City: Benjamin Shneider, M.D., Jae Johnson

Texas Children's Hospital and Baylor College of Medicine: Saul Karpen, M.D., Ph.D.

University of California, San Francisco: Philip Rosentahl, M.D., Julie Lustig

University of Colorado School of Medicine and The Children's Hospital, Denver: Ronald J. Sokol, M.D., Michael R. Narkewicz, M.D., Cara L. Mack, M.D., Judith O'Connor, M.D., Frederick Karrer, M.D., Elizabeth Esterl, R.N., Susan Brantz, R.N.

Washington University School of Medicine, St. Louis: Ross W. Shepherd, M.D., FRACP, Rosemary Nagy

University of Michigan, Ann Arbor (Data Coordinating Center): John Magee, M.D., Morton B. Brown, Ph.D., Jeffrey M. Gonzalez, Wen Liang, Margaret Stewart Steiner, Linda Vandell, Wen Ye

NIH/NIDDK: Edward Doo, M.D., Patricia Robuck, Ph.D., MPH, Jay Hoofnagle, M.D.

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