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The extent of intestinal failure-associated liver disease in patients referred for intestinal rehabilitation is associated with increased mortality: an analysis of the Pediatric Intestinal Failure Consortium database

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ABSTRACT

Background: The advent of regional multidisciplinary intestinal rehabilitation programs has been associated with improved survival in pediatric intestinal failure. Yet, the optimal timing of referral for intestinal rehabilitation remains unknown. We hypothesized that the degree of intestinal failure-associated liver disease (IFALD) at initiation of intestinal rehabilitation would be associated with overall outcome.

Methods: The multicenter, retrospective Pediatric Intestinal Failure Consortium (PIFCon) database was used to identify all subjects with baseline bilirubin data. Conjugated bilirubin (CBili) was used as a marker for IFALD, and we stratified baseline bilirubin values as CBili<2 mg/dL, CBili 2–4 mg/dL, and CBili>4 mg/dL. The association between baseline CBili and mortality was examined using Cox proportional hazards regression.

Results: Of 272 subjects in the database, 191 (70%) children had baseline bilirubin data collected. 38% and 28% of patients had CBili >4 mg/dL and CBili <2 mg/dL, respectively, at baseline. All-cause mortality was 23%. On univariate analysis, mortality was associated with CBili 2–4 mg/dL, CBili >4 mg/dL, prematurity, race, and small bowel atresia. On regression analysis controlling for age, prematurity, and diagnosis, the risk of mortality was increased by 3-fold for baseline CBili 2–4 mg/dL (HR 3.25 [1.07–9.92], p = 0.04) and 4-fold for baseline CBili >4 mg/dL (HR 4.24 [1.51–11.92], p = 0.006). On secondary analysis, CBili >4 mg/dL at baseline was associated with a lower chance of attaining enteral autonomy.

Conclusion: In children with intestinal failure treated at intestinal rehabilitation programs, more advanced IFALD at referral is associated with increased mortality and decreased prospect of attaining enteral autonomy. Early referral of children with intestinal failure to intestinal rehabilitation programs should be strongly encouraged.

Level of evidence: Treatment Study, Level III.

Long-term outcomes for the child with intestinal failure have improved significantly over the past decade. Many factors have contributed to this improved survival including the use of alternative lipid emulsions, innovative forms of bowel lengthening, and better prevention of sepsis [1–3]. It has been proposed that the evolution of multidisciplinary intestinal failure programs has made the greatest contribution to improved outcomes [4–6]. Such programs emphasize long range care supervised by a team of specialists including pediatric surgeons, gastroenterologists, hepatologists, transplant surgeons, pharmacists, nutritionists, nurses and social workers.

While the role of multidisciplinary specialized care in these patients has been well described, the optimal timing of referral to an intestinal rehabilitation program is controversial. It remains common practice for some infants to be referred only when complications, such as intestinal failure-associated liver disease (IFALD) or line sepsis, arise or at the time of initial hospital discharge. Previous single center data have suggested that early referral may be beneficial when infants with intestinal failure have progressive IFALD [7].

We hypothesized that referral to an intestinal rehabilitation program early in the evolution of liver disease would be associated with improved long-term outcomes in children with intestinal failure. We

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chose to query the multicenter Pediatric Intestinal Failure Consortium (PIFCon) database to evaluate whether the degree of IFALD at the time of enrollment in an intestinal failure center impacted overall patient survival in a large cohort of infants with intestinal failure.

1. Methods

PIFCon was initiated through funding by the National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases in 2006 and consists of 14 centers with established multidisciplinary pediatric intestinal failure programs [8]. A list of participating programs is included in Appendix A. PIFCon performed a multicenter retrospective cohort study that included all infants with intestinal failure who had received prolonged parenteral nutrition (PN) defined as the administration of PN in 60 of 74 consecutive days prior to 12 months of age. Subject study entry took place from January 1, 2000 to December 31, 2004 with study entry at one institution extended to December 31, 2005. Patient data were collected retrospectively to accrue follow-up data for at least 2 years from study entry. Data from the PIFCon database have been analyzed previously [8,9].

After IRB approval (Seattle Children's IRB #15456), the PIFCon database was queried to identify all subjects with baseline serum bilirubin data at time of enrollment. Conjugated bilirubin (CBili) was chosen as a marker for IFALD as it represents an accurate measure of cholestatic liver disease, is not an approximated value like direct bilirubin, and has been previously studied in this population [7]. In addition, the use of direct bilirubin may overestimate conjugated hyperbilirubinemia as the measurement also includes delta bilirubin. In the PIFCon dataset, baseline CBili values were available for 77 (40%) patients. For patients in which both conjugated and total bilirubin were recorded, correlation was high ($r = 0.93$). A robust linear conversion formula from total to substitute-conjugated bilirubin was estimated on the square-root scale where correlation was even higher. By contrast, correlation with direct bilirubin was moderate ($r = 0.56$) and offered almost no additional cases after the incorporation of total bilirubin data. Therefore only conjugated bilirubin and converted-total-bilirubin data were used in the analyses. A separate sensitivity model found that the conjugated bilirubin data generated from this conversion had no statistically significant effect on our survival analysis. Baseline bilirubin data was defined as the first serum bilirubin measurement obtained within 45 days of enrollment into the PIFCon database.

We stratified baseline bilirubin values at enrollment as CBili <2 mg/dL, CBili 2–4 mg/dL, and CBili >4 mg/dL. Association between baseline CBili and mortality was examined using a Cox proportional hazard regression model adjusting for diagnosis, prematurity, race, and clustering by hospital as well as censoring at enteral autonomy. Deaths after intestinal transplant were included in the original analysis, and an ancillary analysis was performed that censored patients at time of intestinal transplantation. A separate Cox proportional hazard regression model was created to examine the association of baseline CBili at enrollment with the overall prospect of attaining enteral autonomy; this model censored at patient death.

A final multivariable analysis was performed to explore the relationship between subjects' CBili over time after enrollment to mortality. This analysis was constructed as a time-varying Cox proportional hazard model and employed additional stratification of conjugated bilirubin values given the increased quantity of bilirubin data available over the follow-up period ($n = 1164$ bilirubin values). Bilirubin values measured within 30 days of patient death were excluded from analysis.

$p < 0.05$ was used for statistical significance. Data analysis was performed using R 3.2 software.

2. Results

Of 272 subjects in the PIFCon database, baseline serum bilirubin data at study entry was recorded in 191 (70%) patients at mean age 63 (range 60–365) days. Baseline bilirubin data consisted of total bilirubin in 114 (60%) subjects and CBili in 77 (40%) subjects. Of children with baseline bilirubin data, 137 (72%) presented with a CBili >2 mg/dL, and 73 subjects (38%) presented with a CBili of 4 mg/dL or greater.

The most common diagnoses in this cohort included gastroschisis (31%), necrotizing enterocolitis (29%), small bowel atresia (13%) and midgut volvulus (13%). Gestational age data demonstrated that 146 (77%) subjects were born at less than 37 weeks, and 78 (41%) subjects were born at 32 weeks or earlier. Forty-three (23%) subjects died during the study period, and enteral autonomy was achieved in 98 (51%) of patients; these data are similar to previously published data from the entire PIFCon cohort [8]. Sixty (31%) patients received an intestinal transplant, and 10 patients died following transplant. Of the post-transplant deaths, 7 patients died within the first 120 days of transplant.

All-cause mortality was directly correlated with the level of CBili at time of enrollment in the intestinal failure program (Fig. 1, $p = 0.003$). On univariate analysis, mortality was associated with earlier gestational age, baseline bilirubin greater than 2 mg/dL, non-white race, and the diagnosis of intestinal atresia (Table 1). On multivariable regression controlling for chronologic age, gestational age, and intestinal failure diagnosis, mortality was independently associated with baseline bilirubin levels between 2 mg/dL and 3.9 mg/dL (HR 3.68 [1.89–7.16], $p < 0.001$) and greater than 4 mg/dL (HR 4.11 [1.78–9.48], $p = 0.001$, Table 2). An additional regression analysis that censored patients at time of intestinal transplantation was also performed; these data demonstrated that mortality was again independently associated with baseline CBili levels of 2–3.9 mg/dL (HR 3.59 [1.24, 10.42], $p = 0.02$) and greater than 4 mg/dL (HR 4.80 [1.55, 14.86], $p = 0.007$).

The multivariable analysis of follow-up CBili data after initiation of intestinal rehabilitation demonstrated a direct relationship between higher bilirubin levels and mortality. After controlling for diagnosis and prematurity, each step-wise increase in CBili during the study period was associated with an increased risk of mortality ($p < 0.05$, Table 3).

In a secondary analysis using enteral autonomy as the outcome variable, a CBili value greater than 4 mg/dL at study entry was associated with a significant reduction in the overall chance of attaining enteral autonomy (HR 0.45 [0.27–0.74], $p < 0.01$). In this analysis, the diagnosis of necrotizing enterocolitis was associated with an increased prospect of achieving enteral autonomy (HR 1.66 [1.03–2.68], $p < 0.05$) as described previously [9].

3. Discussion

The field of pediatric intestinal failure has seen significant progress over the past two decades. Long-term survival is now standard due to clinical advances carried out through regional multidisciplinary intestinal failure programs. Such programs bring together medical and surgical specialists with the goal of safely rehabilitating the intestinal remnant and weaning PN over time. Data have shown that intestinal rehabilitation centers are a driving factor behind the improved outcomes in pediatric intestinal failure care [4–6].

The benefits associated with multidisciplinary, regionalized care in intestinal failure are multiple. Intestinal failure programs have access to and experience with an assortment of treatment options including alternative lipid emulsions to reverse or prevent IFALD, bowel lengthening techniques to increase functional intestinal capacity, ethanol locks to decrease the incidence of central line-associated blood stream infection, and options for transplantation if intestinal rehabilitation is not successful. These treatment options are not readily available or utilized consistently at smaller centers without dedicated clinical programs to treat intestinal failure. In a similar fashion, programs specializing in intestinal failure also have access to research trials investigating the next generation of therapies for this condition [10]. Finally, providers in intestinal rehabilitation centers have experience with the complications of intestinal failure including bacterial overgrowth, central line infections, and IFALD.

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