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Enteral Autonomy, Cirrhosis, and Long Term Transplant-Free Survival in Pediatric Intestinal Failure Patients

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Abstract

Purpose—Patient selection for transplant evaluation in pediatric intestinal failure is predicated on the ability to assess long-term transplant-free survival. In light of trends towards improved survival of intestinal failure patients in recent decades, we sought to determine if the presence of biopsy-proven hepatic cirrhosis or the eventual achievement of enteral autonomy were associated with transplant-free survival.

Methods—After IRB approval, records of all pediatric intestinal failure patients (parenteral nutrition (PN) >90 days) treated at a single intestinal failure center from February 2002 to September 2014 were reviewed. Chi-squared, Mann-Whitney, and log-rank testing were performed as appropriate.

Results—Of 313 patients, 174 eventually weaned off PN. Liver biopsies were available in 126 patients (most common indication was intestinal failure associated liver disease, IFALD), and 23 met histologic criteria for cirrhosis. Transplant-free survival for the whole cohort of 313 patients was 94.7% at 1 year and 89.2% at 5 years. Among patients with liver biopsies, transplant-free survival in cirrhotics vs. non-cirrhotics was 95.5% vs. 94.1% at one year and 95.5% vs. 86.7% at 5 years ($P=0.29$). Transplant-free survival in patients who achieved enteral autonomy compared with patients who remained PN dependent was 98.2% vs. 90.3% at one year and 98.2% vs. 76.9% at 5 years ($P<0.001$). There was no association between cirrhosis and eventual enteral autonomy ($P=0.88$).

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Conclusions—Achieving enteral autonomy was associated with improved transplant-free survival in pediatric intestinal failure patients. There was no association between histopathological diagnosis of cirrhosis and transplant-free survival in the cohort. These data suggest that automatic transplant referral may not be required for histopathological diagnosis of cirrhosis alone, and that ongoing efforts aimed at achievement of enteral autonomy remain paramount in pediatric intestinal failure.

Keywords

intestinal failure; cirrhosis; IFALD; intestinal transplant; multivisceral transplant; parenteral nutrition

1. Introduction

Pediatric intestinal failure is a life threatening condition defined by inadequate intestinal function for the support of normal homeostasis, growth, and development. Reports of severe intestinal failure utilize a definition of parenteral nutrition (PN) support for a minimum of 90 days (1). While parenteral nutrition is a lifesaving therapy for these patients, its complications are associated with significant morbidity and mortality. These include intestinal failure associated liver disease (IFALD), which histologically demonstrates cholestasis, bile duct proliferation, periportal inflammation, and variable amounts of fibrosis (2). Despite resolution of biochemical evidence of cholestasis with current hepatoprotective strategies of PN management, repeat biopsies and explant pathology from pediatric patients undergoing combined liver-intestine transplant can show continued evidence of advanced fibrosis and cirrhosis (3-5).

Over the past several decades, the survival of children with intestinal failure has improved drastically (6-8). Treatment by a multidisciplinary intestinal rehabilitation team is associated with decreased mortality (7, 9). Strategies employed to limit the progression of IFALD include the provision of low dose parenteral lipids (1 g/kg/d), the use of novel parenteral lipid formulations with higher amounts of fish oil, olive oil and medium-chain triglycerides, cycling of PN, maximizing enteral nutrition, the use of ursodeoxycholic acid, and aggressive prevention strategies to minimize central line-associated blood stream infections, including the use of ethanol locks (10). The most efficacious treatment for IFALD is the transition to full enteral nutrition (11).

Previous studies have implicated IFALD as an important predictor of survival in pediatric intestinal failure patients (12). In addition, it has been suggested that cholestatic liver disease and portal hypertension may impair intestinal adaptation in children with short bowel syndrome (13). Since 2002, the number of new pediatric patients waitlisted for combined liver-intestine transplant has declined steadily, particularly in the <1 year age group, and transplant waitlist mortality has also declined (14). A complete understanding of the prognosis of children with cirrhosis secondary to IFALD is essential to inform guidelines for transplantation, but this remains difficult in light of improving overall survival and an evolving understanding of the treatment of IFALD (15). Despite a history of cirrhosis diagnosed on liver biopsy, it is our clinical observation that some patients remain stable for

prolonged periods of time. Cirrhosis and enteral autonomy are important benchmarks in the health profile of patients with severe intestinal failure. This study aims to describe rates of transplant-free survival in patients treated at a multidisciplinary intestinal failure center, and determine whether biopsy proven cirrhosis or enteral autonomy are predictors of survival.

2. Methods

2.1 Study Design

Following IRB approval (protocol #M06-01-0049), the records of all patients evaluated between February 2002 and September 2014 by the Center for Advanced Intestinal Rehabilitation (CAIR), a multidisciplinary intestinal rehabilitation program at Boston Children's Hospital, were evaluated. 313 patients with severe pediatric intestinal failure as defined by the need for PN >90 days and initiation of PN support before 18 years of age were included. Date of birth, PN start date, cause of intestinal failure, and sex were recorded for all patients. For patients with a neonatal cause of intestinal failure, date of birth was used as PN start date. The date of last follow up, PN stop date if applicable, date and type of transplantation, and date and cause of death if applicable were determined. When available, intestinal length, gestational age, and median serum citrulline level were also recorded. If a patient had undergone intestinal lengthening surgery (serial transverse enteroplasty or Bianchi procedure) or bowel resections, the most recent postoperative bowel length was recorded.

Liver biopsy remains the gold standard for assessing the stage of hepatic fibrosis or cirrhosis (16, 17), and therefore only the 126 patients who had liver biopsies reviewed at this institution were included in analysis of cirrhotic vs. non-cirrhotic patients. All liver biopsies were read by experienced pediatric liver pathologists. Biopsies interpreted as being diagnostic of cirrhosis or reported as METAVIR F4 were classified as cirrhotic. Patients whose liver biopsy did not show cirrhosis were classified as non-cirrhotic. If a patient had more than one liver biopsy, the most recent biopsy result was used. The most common indication for liver biopsy was IFALD. 63 biopsies were core needle biopsies obtained during laparotomy, 42 were wedge biopsies, 20 were percutaneous needle biopsies, and one was transjugular. 114 of the 126 biopsies were obtained at this institution; the others were obtained elsewhere and reviewed in consultation by pathologists at this institution. There was a trend towards more percutaneous or transjugular liver biopsies in the cirrhotic compared with the non-cirrhotic group, but this did not reach statistical significance ($P=0.11$).

For the 23 patients with cirrhosis, the INR, albumin, bilirubin, height-for-age z-score, AST, and ALT were recorded as of their most recent follow up. Maximum AST, ALT, and serum bilirubin were also noted. Using these parameters, PELD score as of most recent follow was calculated for each patient.

2.2 Statistical Methods

Data normality was determined using Kolmogorov-Smirnov tests and demographic and clinical characteristics were reported as frequency (percentage) or median (interquartile

range) as appropriate. Categorical data was assessed using a Pearson chi-squared test and a Mann-Whitney *U* test was used to evaluate continuous data. Kaplan-Meier methods to estimate time-to-event distributions were conducted for comparisons with a log rank (Mantel-Cox) test. Transplant-free survival for patients who achieved enteral autonomy was compared to patients who did not achieve enteral autonomy. Likewise, cirrhotic patients were compared to non-cirrhotic patients (given the presence of a liver biopsy). These two comparisons were, similarly, performed to assess total survival. Transplant-free survival was calculated from PN start date to date of last contact, date of transplant, or date of death. Total survival was calculated from PN start date to last contact or date of death. Mortality included all-cause mortality. Statistical analysis was conducted using the Statistical Package for the Social Sciences, SPSS for Windows Version 22.0 (IBM, Armonk, NY).

3. Results

Patient characteristics for the 313 patients with pediatric intestinal failure treated during the study period are shown in Table 1. Cause of intestinal failure was consistent with previously published reports on pediatric intestinal failure (18). PN initiation most commonly occurred in the neonatal period in all groups. Among patients with non-neonatal PN start date, median age at PN initiation was 2.6 years (IQR 0.5-8.9 years). 174 of 313 patients achieved enteral autonomy. Of 126 patients with liver biopsies, 23 met criteria for cirrhosis.

As expected, patients who attained enteral autonomy had a significantly longer residual small bowel length and higher median citrulline than patients who did not achieve enteral autonomy (19). The cause of intestinal failure differed between the two groups, with a higher percentage of necrotizing enterocolitis (NEC) in the enteral autonomy group and more motility disorders in the non-enteral autonomy group. The group that achieved enteral autonomy had a lower gestational age than those who did not at 33 vs. 35 weeks, and more patients had neonatal initiation of PN. Enteral autonomy was achieved in 56% of patients, after a median duration of PN dependence of 9 months (IQR 5.5-17.9). In the cohort of patients with liver biopsies (Table 2), there were no statistically significant differences between the cirrhotic and non-cirrhotic groups with respect to sex, small bowel length, median citrulline, length of follow up, or age at PN initiation. Cirrhotic patients had a lower gestational age than non-cirrhotic patients (30 vs. 34 weeks, $P=0.04$).

Outcomes are reported in Table 3. There were 17 patients who received transplants, all within five years of PN initiation. Eleven patients received both liver and intestine, and three had isolated liver transplant, one of which was from a living related donor. Two of the patients who received isolated liver transplants had ESLD due to cystic fibrosis in addition to IFALD. Two patients received isolated intestinal transplants. One underwent combined intestine and kidney transplantation for short gut syndrome and end stage renal disease, both of which were the result of a devastating postoperative vascular complication after appendectomy. Of the 14 patients whose transplants included liver, nine were performed at this hospital, with explant pathology showing cirrhosis in eight cases and portal to portal bridging fibrosis without nodular regeneration in one case.

There were 18 total deaths, with 15 of those occurring within five years of PN initiation (Table 3). Five occurred post-transplant (3 multivisceral transplant, 1 liver-intestine, 1 isolated intestine). The most common causes of death were sepsis (7 patients) and ESLD (4 patients). None of the patients who died due to complications of ESLD had achieved enteral autonomy.

Figures 1 and 2 show Kaplan-Meier transplant-free survival curves for the comparator groups, with the relevant predicted percentages of transplant-free and overall survival summarized in Table 4, and the number of deaths and transplants for each group listed in Tables 1 and 2. For the whole cohort of 313 patients, transplant-free survival was 94.7% at one year and 89.2% at five years. Overall survival was 97% at one year and 94.4% at five years.

There was a substantial transplant-free and absolute survival advantage in patients who achieved enteral autonomy compared with patients who never weaned from PN. Transplant-free survival in patients who achieved enteral autonomy compared with patients who remained PN dependent was 98.2% vs. 90.3% at one year, and 98.2% vs. 76.9% at five years ($P < 0.001$). Overall survival was 98.2% at one year and five years in the group that achieved enteral autonomy vs. 95.5% and 89.1% at one and five years in the group that did not wean from PN ($P = 0.001$).

Among patients with liver biopsies, there was no difference in transplant-free survival or total survival at one and five years (Table 4). Among patients with liver biopsies, transplant-free survival in cirrhotics vs. non-cirrhotics was 95.5% vs. 94.1% at one year and 95.5% vs. 86.5% at 5 years ($P = 0.29$). Overall survival was 95.5% vs. 97.0% at one year and 95.5% vs. 94.3% at five years ($P = 0.57$). There was no association between cirrhosis and eventual enteral autonomy ($P = 0.88$). Twelve of the cirrhotic patients with biopsy proven cirrhosis achieved enteral autonomy (52%), and none of these patients died. One of the 11 cirrhotic patients who did not achieve enteral autonomy died. None of the 23 patients with a liver biopsy showing histopathological diagnosis of cirrhosis in this study underwent transplant, after a median follow up duration of 7.0 (IQR 4.2-11.7) years.

For the 23 cirrhotic patients, median highest recorded bilirubin was 6.7 (IQR 2.55-11.1), and median total bilirubin as of most recent follow up was 0.5 (IQR 0.3-1.05). Using the most recent available laboratory and growth parameters in this cohort, median PELD was -7 (IQR -8 to 0) as of last follow up, assuming age at transplant listing greater than 1 year. When maximal AST and ALT were examined, median was 190 unit/L (IQR 110-385) and 223 (IQR 149-305) unit/L respectively. Most recent AST and ALT remained mildly elevated, with median AST of 47 (IQR 33-81) unit/L and ALT of 41 (IQR 24-78) unit/L. This compares with the laboratory normal parameters for AST of 2-40 unit/L and 3-30 unit/L for ALT.

4. Discussion

Achievement of enteral autonomy is a critical predictor of survival and transplant-free survival in pediatric patients with intestinal failure. Among patients undergoing liver biopsy

for IFALD, the presence of cirrhosis on liver biopsy is not a determinant of survival, and is not correlated with the likelihood of achieving enteral autonomy. The clinical observation that some pediatric intestinal failure patients with a diagnosis of cirrhosis remain clinically stable for prolonged periods of time is supported by these data, with excellent five year overall and transplant-free survival. However, ESLD continues to be the second most common cause of death, following sepsis. Indications for transplantation in patients with IFALD continue to shift with improving strategies for long term intestinal rehabilitation and with treatments that mitigate the progression of IFALD.

This population represents patients evaluated at a multidisciplinary intestinal rehabilitation center, but may not be representative of all pediatric intestinal failure patients. Patients with early death may not survive to referral. Patients who were born and live locally may have had all of their surgical and medical care at our center, while others were referred after a period of care elsewhere. Patients who do not live locally may receive some of their emergency care, management of other comorbidities, and long term follow up at other centers. The inclusion of only patients with severe intestinal failure (>90 day duration of PN) is a standard definition, and reflects a more severely affected cohort than patients than that described by less stringent definitions of intestinal failure (8). In addition, patients with primary dysmotility disorders and secretory diarrhea may be underrepresented in this sample. The lower gestational age seen in the group that achieved enteral autonomy may reflect the known favorable prognosis for patients with intestinal failure secondary to NEC (18).

Although liver biopsy remains the gold standard for assessment of hepatic fibrosis and cirrhosis, sampling error and inter-observer variability may result in the misclassification of some patients with advanced fibrosis vs. cirrhosis (16). Patients in the non-cirrhotic group had varying degrees of IFALD, and may have gone on to develop cirrhosis after the time of their most recent biopsy.

There was not a statistically significant difference in length of follow up between patients who did and did not attain enteral autonomy, and median duration of follow up for patients who did not attain autonomy was 4.1 years. Some of those patients may have crossed over to the enteral autonomy group with longer follow up. The process of intestinal adaptation and the decreased caloric requirements for growth over time mean that children may achieve enteral independence even after many years on PN (18). The difference in follow up duration may also be attributable to the national and international patient population treated at this center, as many patients opt to transition their care to local providers after they have achieved enteral autonomy.

Consistent with previously published reports on the use of parenteral fish oil for intestinal failure associated liver disease, laboratory evidence of cholestasis generally improved in this cohort (20). Fibrosis, however, may not improve, and for patients who undergo transplant cirrhosis is usually found on explant pathology even in the context of normalized laboratory parameters (3). Previous studies have shown that the majority of patients with a history of pediatric intestinal failure continue to have abnormal liver histology with fibrosis notable on biopsy years after PN is discontinued (21). Ongoing studies to determine the accuracy and

reliability of non-invasive liver evaluation, such as novel imaging studies and stable isotope breath testing (22), will hopefully lead to improved longitudinal assessment of liver disease in pediatric intestinal failure.

5. Conclusion

The ability to wean to full enteral autonomy is a primary predictor of survival in pediatric patients with intestinal failure. Histopathological diagnosis of cirrhosis does not necessarily portend poor intermediate term survival, and is not associated with lower rates of achieving enteral autonomy in patients with IFALD. Thus, in the setting of multidisciplinary intestinal rehabilitation management, the histopathological diagnosis of cirrhosis secondary to IFALD in pediatric intestinal failure patients should not automatically mandate referral for transplant evaluation but should instead be considered within the context of the patient's overall clinical status.

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HANNAH PIPER (Dallas TX): I'm just wondering whether there was any difference in liver function between your groups of cirrhotic versus non-cirrhotics.

BRENNA FULLERTON: We did not look at the biochemical outcomes or in particular outcomes of other complications. We really studied mortality. It is our clinical observation that despite the histopathological diagnosis of cirrhosis especially for patients that do not have any secondary cause of liver dysfunction that they can remain clinically stable for prolonged periods of time.

SHREYAS ROY (Syracuse NY): I have two questions. One is, did you look or stratify at all on the basis of the nutritional status of the patient and whether that predicted achievement of enteral autonomy or whether or not that affected their transplant-free survival? The second question that I had was, multifactorial liver disease – was that included, excluded and how did that play a role in your data set?

BRENNA FULLERTON: For the second question first, multifactorial liver disease was definitely included and was a factor for our patients. There were in fact three patients who underwent liver transplant alone without intestinal transplant two of whom had CF in addition to short bowel syndrome.

I am not sure I fully understand the question about the nutritional status for our patients. For all of our patients, we make every effort to optimize enteral nutrition and maintain normal growth and development. I'm not sure I ...

SHREYAS ROY: (off mike)

BRENNA FULLERTON: We generally keep them on PN for as long as necessary before they attain enteral autonomy without it.

Figure 1. Kaplan-Meier analysis of transplant-free survival for patients who achieved enteral autonomy compared to patients who did not achieve enteral autonomy

Figure 2. Kaplan-Meier analysis of transplant-free survival for cirrhotic patients compared to non-cirrhotic patients

Table 1
Clinical and demographic comparisons of patients who achieved enteral autonomy to patients who did not achieve enteral autonomy

	All intestinal failure patients N= 313	Patients who achieved enteral autonomy N = 174	Patients who did not achieve enteral autonomy N = 139	P value
Male	175 (56)	91 (52)	84 (60)	0.15
Gestational age (weeks)	34 (29-36)	33 (27-35)	35 (32-38)	< 0.001*
Residual small bowel length (cm)	50 (27-76)	60 (36-82)	37 (21-62)	< 0.001*
Median citrulline (umol/L)	17 (11-25)	23 (15-31)	13 (7-17)	< 0.001*
Cause of intestinal failure				< 0.001*
NEC	95 (30)	72 (42)	23 (16)	<0.001*
Gastroschisis	72 (23)	39 (22)	33 (24)	0.78
Intestinal Atresia	52 (17)	33 (19)	19 (14)	0.21
Motility Disorders	39 (12)	9 (5)	30 (21)	<0.001*
Volvulus	33 (11)	14 (8)	19 (14)	0.11
Trauma / Surgical Resection	10 (3)	6 (3)	4 (3)	0.78
Secretory Diarrhea	8 (3)	0 (0)	8 (6)	0.001*
Other	4 (1)	1 (1)	3 (2)	0.22
Duration of follow-up (years)	4.6 (2.4 – 7.9)	5.4 (3.1 – 8.8)	4.1 (1.9 – 6.8)	0.004*
Neonatal PN initiation	261 (83)	160 (92)	101 (73)	< 0.001*
Number of Transplants	17	0	17	†
Number of Deaths	18	3	15	†

NEC = necrotizing enterocolitis, PN = parenteral nutrition. Neonatal PN initiation defined by initiation before 30 days of life. Data are reported as frequency (percentage) or median (interquartile range) as appropriate; P values calculated from a Pearson Chi-Square test or a Mann-Whitney *U* test comparing patients who achieved enteral autonomy to patients who did not achieve enteral autonomy.

† Please refer to Table 4 and Figure 1 for Kaplan-Meier analysis.

Table 2
Clinical and demographic comparisons of cirrhotic patients to non-cirrhotic patients

	All liver biopsy patients N= 126	Cirrhotic patients N = 23	Non- cirrhotic patients N = 103	P value
Male	68 (54)	13 (57)	55 (53)	0.79
Gestational age (weeks)	34 (28 – 36)	30 (26 – 34)	34 (29 – 36)	0.043*
Residual small bowel length (cm)	53 (30 – 91)	38 (20 – 74)	56 (35 – 93)	0.21
Median citrulline (umol/L)	17 (11 – 25)	16 (8 – 27)	17 (12 – 25)	0.90
Cause of intestinal failure				0.20
NEC	44 (35)	13 (57)	31 (30)	0.03*
Gastroschisis	32 (25)	4 (17)	28 (27)	0.28
Intestinal Atresia	17 (14)	2 (9)	15 (15)	0.41
Motility Disorders	16 (13)	1 (4)	15 (15)	0.16
Volvulus	12 (10)	2 (9)	10 (9)	0.58
Trauma / Surgical Resection	2 (1)	1 (4)	1 (1)	0.26
Secretory Diarrhea	3 (2)	0 (0)	3 (3)	0.39
Other	0 (0)	0 (0)	0 (0)	-
Duration of follow-up (years)	5.9 (3.3 – 8.4)	7.0 (4.2 – 11.7)	5.8 (3.1 – 8.0)	0.13
Neonatal PN initiation	107 (85)	21 (91)	86 (83)	0.70
Duration of PN at time of biopsy (months)	6.4 (4.1 – 22.3)	9.5 (6.6 – 33.0)	5.5 (3.7 – 17.9)	0.006*
Patients who attained enteral autonomy	64 (51)	12 (52)	52 (51)	0.88
Number of Transplants	8	0	8	†
Number of Deaths	8	1	7	†

NEC = necrotizing enterocolitis, PN = parenteral nutrition. Neonatal PN initiation defined by initiation before 30 days of life. Data are reported as frequency (percentage) or median (interquartile range) as appropriate; P values calculated from a Pearson Chi-Square test or a Mann-Whitney *U* test comparing cirrhotic patients to non-cirrhotic patients.

† Please refer to Table 4 and Figure 2 for Kaplan-Meier analysis.

Table 3
Characteristics for death and transplant outcomes

Total transplants (n)	17
Type of transplant (n, %)	
Multivisceral	10 (59)
Liver/intestine	1 (6)
Liver	3 (18)
Isolated intestine	2 (12)
Isolated intestine + kidney	1 (6)
Transplants within first 5 years on PN (n)	17
Age at time of transplant (years) (Median [IQR])	1.16 (0.85 – 2.57)
Duration of PN at time of transplant (years) (Median [IQR])	1.16 (0.85 – 1.73)
Total deaths (n)	18
Cause of death (n, %)	
Sepsis	7 (39)
Cardiopulmonary arrest at home	4 (22)
ESLD	4 (22)
Malignancy	1 (6)
Unknown	2 (11)
Deaths within the first 5 years on PN (n)	15
Age at time of death (years) (Median [IQR])	1.51 (0.87 – 4.90)
Duration of PN at time of death (years) (Median [IQR])	1.13 (0.85 – 3.57)
Patients with both death and transplant (n)	5

Table 4
One year and five year transplant-free survival and total survival rates

	All intestinal failure patients N= 313	Patients who achieved enteral autonomy N = 174	Patients who did not achieve enteral autonomy N = 139	Cirrhotic patients [†] N = 23	Non- cirrhotic patients [†] N = 103
1 year transplant-free survival	94.7	98.2	90.3	95.5	94.1
5 year transplant-free survival	89.2	98.2	76.9	95.5	86.5
1 year survival	97.0	98.2	95.5	95.5	97.0
5 year survival	94.4	98.2	89.1	95.5	94.3

Percentages were derived from Kaplan-Meier curves for transplant-free survival and total survival.

[†] Only 126 patients with liver biopsy were included; Data reported as percentages.