CME

Outcomes of Children With Chronic Intestinal Failure: Experience Over 2 Decades at a Tertiary Paediatric Hospital

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ABSTRACT

Background and Aims: The aim of the study was to aid decisions on prognosis and transplantation; this study describes the outcome of children with intestinal failure managed by the multidisciplinary intestinal rehabilitation program at the Royal Children's Hospital, Melbourne.

Methods: Retrospective review of children requiring parenteral nutrition (PN) for >3 months who were assessed for home PN between 1991 and 2011.

Results: A total of 51 children were included. Forty-two (82%) had short bowel syndrome (SBS), 5 (10%) had chronic intestinal pseudo-obstruction syndrome, and 4 (8%) had congenital enteropathies. Median small bowel length for patients with SBS was 45 cm (interquartile range 30–80) or 23.9% of the expected length for age (interquartile range 17.0%–40.6%). Overall survival rate was 84% (43/51). Mortality in children (n = 7) occurred after a median of 13.2 months (range 6.2–29.2) with intestinal failure–associated liver disease (IFALD) being the only predictor ($P = 0.001$). Out of 50 children 21 (42%) had IFALD. Children who were premature ($P = 0.013$), had SBS ($P = 0.038$), and/or frequent sepsis ($P = 0.014$) were more likely to develop IFALD. PN weaning occurred in 27 of 35 (77%) SBS survivors, after a median of 10.8 months (up to 8.2 years), with longer residual small bowel ($P = 0.025$), preservation of the ileocecal valve ($P = 0.013$) and colon ($P = 0.011$) being predictors. None of 5 (0%) patients with chronic intestinal pseudo-obstruction syndrome and 2 of 4 (50%) patients with congenital enteropathies weaned off PN. Overall sepsis rate was 7.3 episodes/1000 line days. Frequency of sepsis and longevity of central lines improved with time as patients grew older (both $P < 0.001$).

Conclusions: Long-term PN with intestinal rehabilitation was effective in treating most children with intestinal failure. Children with severe refractory IFALD may have benefited from intestinal transplantation.

Key Words: central venous catheter, children, intestinal failure, liver disease, parenteral nutrition, short bowel syndrome

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What Is Known

- Chronic intestinal failure in children is a complex clinical problem.
- Parenteral nutrition therapy is associated with potentially life-threatening complications.
- Intestinal rehabilitation strategies enable some children to eventually wean off parenteral nutrition.
- Intestinal transplantation remains a challenging procedure.

What Is New

- Children with intestinal failure have ~85% chance of survival on parenteral nutrition.
- Children with refractory intestinal failure–associated liver disease may benefit from intestinal transplantation.
- Sepsis rate and the longevity of central lines improve with time as children grow older.
- Children with short bowel syndrome who survive the first 3 years of life have a >75% chance of weaning off parenteral nutrition.

Intestinal failure is the inability of the intestine to absorb sufficient fluid and nutrients to support life in adult and growth in children. It results from anatomical or functional loss of a significant proportion of the intestine. Chronic intestinal failure is rare in children with a current prevalence of 9.6 to 16.6 per million that appears to be on the rise (1–3). The burden of the disease and its management on individuals, their families, and the healthcare system is enormous (4,5). Parenteral nutrition (PN) therapy is

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associated with potentially life-threatening complications such as infection and liver disease. Intestinal rehabilitation refers to the implementation of medical and surgical strategies that promote progressive recovery of intestinal function, with the aim of eventually weaning patient from PN. Intestinal transplantation is an option for patients with irreversible intestinal failure. Although the survival of transplant recipients has improved markedly in the past decades, the requirement for significant immunosuppression and the risk of graft rejection remain challenging issues (6). Therefore, for each individual patient, balancing the relative risks versus benefits of intestinal transplantation and long-term PN can be difficult. Data from a multicenter study in Europe suggests that only patients with life-threatening intestinal failure–associated liver disease (IFALD) had improved survival with transplantation when compared to management with home PN. For all other indications, namely frequent sepsis or ultrashort small bowel, the mortality risk was low on home PN and no survival benefit was observed following transplantation (7).

In this context, we conducted a cohort study of patients with chronic intestinal failure managed by the multidisciplinary Clinical Nutrition and Intestinal Rehabilitation Service at the Royal Children's Hospital in the pretransplantation era in Australia, to inform future decisions following the introduction of pediatric intestinal transplantation.

METHODS

The Clinical Nutrition program at the Royal Children's Hospital in Melbourne has provided a centralized home PN service for children in the states of Victoria and Tasmania since 1991. This program commenced in 1991 with a part-time pediatric gastroenterologist and a clinical nurse consultant and has developed to a multidisciplinary team, which is composed of a sessional pediatric gastroenterologist and pediatric gastrointestinal surgeon, part-time general pediatrician, a nurse consultant, a dietitian, and a pharmacist. The aim of the program is to support the provision of home PN and to optimize the long-term outcomes, promote intestinal adaptation and enteral tolerance, and to identify candidates appropriate for consideration for intestinal transplantation. All patients with anticipated PN dependency for at least 3 months when in stable condition were referred for assessment. Each child and family is assessed for suitability of home PN. Patients were discharged on home PN once clinically stable and when training by experienced Clinical Nutrition nurse consultants has been successfully completed, support services in place and if the home environment permitted.

At the Royal Children's Hospital, PN was provided as a combination of an amino acid and glucose solution and lipid emulsion with added micronutrients with administration guided by age-appropriate recommendations from ASPEN and ESPGHAN (8). The lipid emulsion routinely provided over this period was 20% Intralipid (Pharmacia and Upjohn, Milton Keynes, UK) from 1991 to 2010, and 20% ClinOleic (Baxter Healthcare, Maurepas, France) from 2010 to 2015. Omegaven (Fresenius Kabi, Bad Homburg vor der Hohe, Germany) was used from 2008 in select patients with significant IFALD or at high risk of IFALD. Clinical care of central venous access devices (CVADs) was consistent with international guidelines and issummarized in the Royal Children's Hospital's Clinical Practice Guidelines (9) and in the handbook published by our Clinical Nutrition program (10). Before 2012 this, however, did not include ethanol, antibiotic, or other locks.

Study Design

All patients assessed for home PN at the Royal Children's Hospital between January 1991 and February 2011 were identified by audit of medical documentation maintained by the Clinical Nutrition program. In 2012, an Intestinal Transplantation Service was commenced. Inclusion criteria for this study were patients with PN dependency >3 months due to primary gastrointestinal disorders who were assessed for home PN between January 1991 and February 2011. Patients with oncological diseases or established extraintestinal causes of PN dependency were excluded. The estimation of the prevalence of home PN was calculated using regional population data from the Australian Bureau of Statistics for residents aged 0 to 19 years in June each year (11). This study was conducted under the auspice of the Royal Children's Hospital Human Research Ethics Committee (HREC REF. No: 30120 A).

Data collected on each patient include age, sex, details of the etiology, and management of intestinal failure including relevant medical, surgical, and nutritional management and complications, and the final outcome. Outcome data were collected from when a patient first commenced PN through to study closure on February 15, 2011.

Information on gastrointestinal anatomy was sourced from patient medical records, including the length and portion of bowel resected, residual small bowel length, preservation of ileocecal valve, length of the colonic remnant, stoma formation, and gastrostomy or jejunostomy feeding tube insertion. Small bowel length was defined as the length of residual jejunoileal segment measured intraoperatively and recorded in the surgical report. In patients with long-segment Hirschsprung's disease, the colon and small bowel were considered absent up to the level of the transition zone and/or stoma. Normal small bowel length for gestational age was estimated using the formula derived by Struijs et al (12) and was used to convert absolute small bowel length to a percentage of expected small bowel length for gestational age.

Catheter-related bloodstream infection (CRBSI) was defined as the presence of symptoms and/or signs suggestive of sepsis with growth of microorganisms in 1 or more blood cultures taken from CVAD, peripheral line, or peripheral vein in patients with an indwelling venous catheter. The Centre for Disease Control Criteria of Repeat Infection Timeframe was used to distinguish serial reportable infections from single unresolved infection (13).

To assist comparison with the literature, children were considered as having IFALD if they had elevation in conjugated bilirubin to $\geq$34 μmol/L ($\geq$2 mg/dL) persisting for at least 2 months (14). For children whose PN care was transferred from or under joint care with another hospital (thus liver function test results maybe incomplete), liver biopsy findings were also used as evidence for the presence or absence of IFALD.

Statistics

Statistical analyses were performed using Stata (version 11 2009) and data compiled in an Excel database (Microsoft Excel 2010). Normally distributed continuous data were described as mean and standard deviation; non-normally distributed continuous data as median and interquartile range (IQR) and/or range; categorical data as number and percentage (%). Mean was also provided for some non-normally distributed data for comparison with the literature. Predictors for the longevity of CVAD, the rate of CRBSI, the presence of IFALD, and the PN weaning and survival outcomes were analyzed using chi-squared test (or Fisher's exact test) for categorical variables with categorical outcome, 2-sample *t* test for dichotomous variables with normally distributed continuous outcome, Wilcoxon rank-sum test for dichotomous variables with non-normally distributed continuous outcome, or linear regression for continuous variables with continuous outcome. Survival and PN weaning probabilities were calculated using the Kaplan-Meier method. Time to PN weaning and survival time in relation to

TABLE 1. Patient diagnoses, age, and long-term outcome

	Whole cohort	Short bowel syndrome (n = 42)	Chronic intestinal pseudo-obstruction syndrome (n = 5)	Congenital enteropathies (n = 4)
Underlying diagnosis (n)		Gastroschisis 14 NEC 10 Volvulus 7 Atresias 5 Hirschsprung's 4 Other* 2		Intestinal epithelial dysplasia 2 Autoimmune enteropathy 2
GA at birth, wk, median (IQR)	36 (33–38)	35 (31–38)	40 (38–40)	35 (35–37)
Age at PN onset, mo, median (IQR)	0.3 (0.1–2.1)	0.1 (0.1–0.9)	25.2 (0.5–145.4)	3.9 (0.4–17.3)
Died as a child (n)	7	7	0	0
Time from PN onset, median (IQR, range)	13.2 mo (6.2–19.6, 6.2–29.2)	13.2 mo (6.2–19.6, 6.2–29.2)		
Age, median (IQR, range)	13.8 mo (8.3–20.5; 6.3–29.2)	13.8 mo (8.3–20.5; 6.3–29.2)		
Weaned PN (n)	29	27	0	2†
Time from PN onset, median (IQR, range)	10.6 mo (7.2–28.8, 3.3 mo–8.2 y)	10.8 mo (7.7–32.4, 3.5 mo–8.2 y)		3.3 and 4.4 mo, respectively
Continued PN under pediatric care (n)	12	8	2	2‡
Time from PN onset, median (IQR, range)	6.7 y (2.2–10.8, 6.9 mo–12.0 y)	5.4 y (13.6 mo–9.2 y, 6.9 mo–11.3 y)	5.0 and 5.9 y, respectively	both 12.0 y
Continued PN under adult care (n)	2	0	2	0
Time from PN onset	8.0 and 19.1 y, respectively		8.0 and 19.1 y, respectively	
Died as an adult (n)	1	0	1	0
Time from PN onset /age	21.1 y/ 23.2 y		21.1 y/23.2 y	

GA = gestational age; IQR = interquartile range; NEC = necrotizing enterocolitis; PN = parenteral nutrition.
*One secondary to superior mesenteric artery thrombosis, the other due to hyperosmolar nonketotic coma.
†Both had autoimmune enteropathy.
‡Monozygotic twins with intestinal epithelial dysplasia.

different variables were analyzed using log-rank test for categorical variables and Cox proportional hazard regression for continuous variables. A P value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Fifty-one patient (26/51 [51%] females) met the inclusion criteria. The annual prevalence of Victorian children receiving home PN over the study period increased from 0.8 per million population aged 0 to 19 years in 1992 to 8.7 in 2010 ($P < 0.001$) (Supplemental Fig. 1 , Supplemental Digital Content, *http://links.lww.com/MPG/B646*).

Baseline patient characteristics are described in Table 1. The median residual small bowel length in patients with short bowel syndrome (SBS) was 45 cm (IQR 30–80, range 2–192) or 23.9% of the expected small bowel length for age (IQR 17.0%–40.6%, range 1.1%–99.5%). The ileocecal valve was absent in 52% (22/42) of patients with SBS, and 31% (13/42) had half or more of the colon resected. Seven patients with SBS underwent intestinal tapering and/or plication procedures.

During the study period, the 51 children had received a combined total of 58,595 inpatient PN days and home PN days managed by our center. Twenty-six patients (51%) were discharged on home PN and received a total of 36,564 days of home PN during the study period. A total of 634 episodes of rehospitalization occurred while patients were on home PN. Another child was about to be discharged on home PN at study closure. Children received inpatient PN for a median of 7.9 months (IQR 5.7–11.9) before discharged on home PN. Reasons for not having home PN were PN weaning before discharge in 13 children, death in 5, and unsuitable social situation in 6.

Long-term Patient Outcome

Patient outcome at study closure is summarized in Table 1.

There were 8 deaths in total giving an overall survival rate of 84.3% over 20 years. The survival probabilities are illustrated in Figure 1A. Direct causes of death were liver disease in 5 (62.5%), sepsis in 2 (25.0%), and lung disease in 1 (12.5%). The child who died of lung disease died from acute respiratory failure secondary to aspiration. Death in children occurred after a median of 13.2 months and up to 29.2 months. All deaths occurring in children had a diagnosis of SBS who had developed end-stage IFALD. One patient with chronic intestinal pseudo-obstruction syndrome died of complicated sepsis after being transitioned to adult care.

The characteristics of children who survived versus children who died are presented in Table 2. IFALD was a significant predictor of mortality in children. A higher overall CRBSI rate was also associated with mortality in children; however, the association was not statistically significant when analysis was limited to each child's first 2 years of PN therapy. The median small bowel

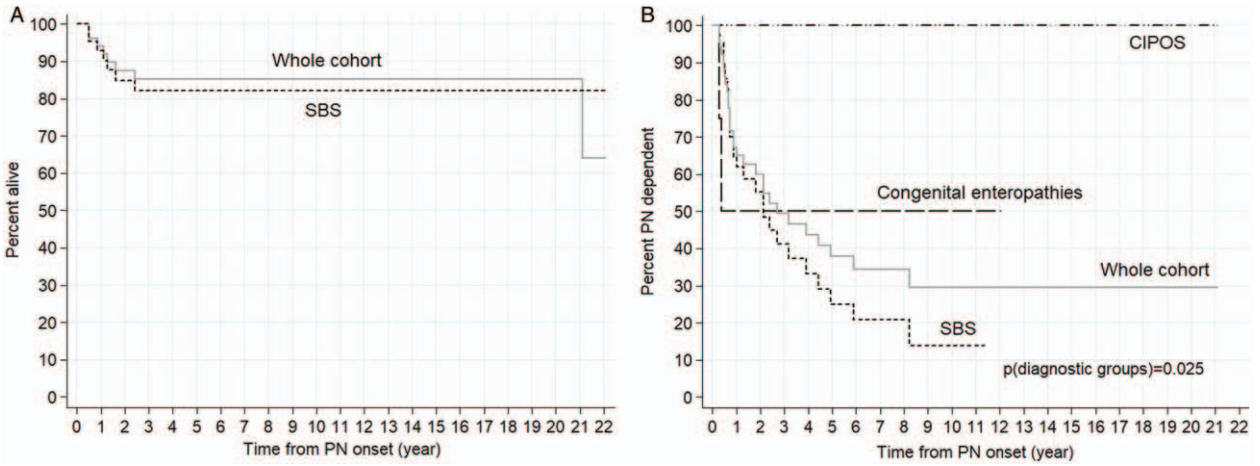

FIGURE 1. Kaplan-Meier curves of (A) survival, whole cohort and SBS; (B) PN-dependency, whole cohort, and by diagnostic groups. CIPOS = chronic intestinal pseudo-obstruction syndrome; PN = parenteral nutrition; SBS = short bowel syndrome.

length for survivors of SBS was 45 cm or 23.9% of the expected length for age, and for nonsurvivors was 35 cm or 30.5% of the expected length for age ($P = 0.960$ for length in cm, $P = 0.244$ for length in %).

At study closure, 29 patients had weaned off PN, resulting in a PN weaning rate of 56.9% over 20 years. Probabilities of PN dependency is illustrated in Figure 1B. Sixty-four percent (27/42) of patients with SBS (77.1% [27/35] of survivors) successfully weaned from PN after a median of 10.8 months and up to 8.2 years. Seventy-eight percent (21/27) of these patients did so by 3 years and 92.6% (25/27) by 5 years. There was a trend toward shorter PN-dependent time in the second decade of the study period, although statistical significance was not reached (Supplemental Fig. 2, Supplemental Digital Content, *http://links.lww.com/MPG/B646*).

Small bowel length, preservation of the ileocecal valve, and preservation of the majority of colon were predictors of PN weaning in survivors with SBS (Table 3; Supplemental Fig. 3, Supplemental Digital Content, *http://links.lww.com/MPG/B646*). In our cohort, patients with the lowest percentage of expected small bowel length for age and/or the shortest absolute small bowel length who successfully weaned from PN was 4% (residual small bowel of 7 cm at 41 weeks gestational age) with an intact ileocecal valve, 12% (residual small bowel of 37 cm at 13 months of age) without an ileocecal valve, and 23 cm (at 31 weeks gestational age [20%]) without an ileocecal valve.

Vascular Access and Complications

A total of 227 tunneled CVADs were inserted and remained in situ for a median of 117 days (IQR 51–294, range 3–3410; mean 253) overall, 91 days (IQR 38–189; mean 164) for inpatient PN, and 328 days (IQR 105–581; mean 487) for home PN. One patient maintained their CVAD for >9.3 years up to the time of transition to adult care. The longevity of CVADs improved as patients grew older and had PN for a longer period ($P < 0.001$). Premature CVAD removal occurred due to infection (60.3%), displacement (23.5%), occlusion (6.2%), venous thrombosis (5.6%), and breakage (4.5%). Four patients had no readily accessible central veins for CVAD

TABLE 2. Characteristics of children with chronic intestinal failure according to survival status

	Survivors*	Nonsurvivors*	*P*		Log-rank test/Cox proportional hazard regression, *P*
Diagnosis					
SBS	79.6% (35/44)	100% (7/7)	0.187	SBS	0.198
NEC	15.9% (7/44)	42.9% (3/7)	0.095	NEC	0.081
Prematurity (GA <37 wk at PN onset)	43.2% (19/44)	71.4% (5/7)	0.164	Prematurity	0.152
Anatomy of remnant bowel in SBS					
SBL ≥30%	31.4% (11/35)	57.1% (4/7)	0.195	%SBL	0.154
ICV absent	48.6% (17/35)	71.4% (5/7)	0.269	ICV absent	0.287
Colon majority intact	68.6% (24/35)	71.4% (5/7)	0.881	Colon majority intact	0.740
CRBSI (episodes per 1000 CVAD days)					
Overall (n = 49), median (IQR)	9.4 (4.5–12.3)	13.5 (10.3–19.5)	0.021	Overall	0.022
First 2 y of PN (n = 48), median (IQR)	9.6 (5.1–13.7)	13.2 (10.3–19.5)	0.105	First 2 y of PN	0.120
IFALD	32.6% (14/43)	100% (7/7)	0.001	IFALD	0.001
Era (of PN onset)					
Pre-1992	43.2% (19/44)	57.1% (4/7)	0.491	Pre-1992	0.636

CRBSI = catheter-related bloodstream infection; CVAD = central venous access device; GA = gestational age; ICV = ileocecal valve; IFALD = intestinal failure–associated liver disease; IQR = interquartile range; NEC = necrotizing enterocolitis; PN = parenteral nutrition; SBL = small bowel length; SBS = short bowel syndrome.

*Survival to the date of study closure or to adulthood.

TABLE 3. Characteristics of short bowel syndrome survivors who weaned from parenteral nutrition versus those who remained parenteral nutrition dependent

	Weaned PN	Continued PN	*P*		Log-rank test/Cox proportional hazard regression, *P*
Diagnosis					
NEC	22.2% (6/27)	12.5% (1/8)	0.546	NEC	0.803
Full term (GA ≥37 wk at PN onset)	55.6% (15/27)	37.5% (3/8)	0.369	Full term	0.565
Anatomy of remnant bowel					
SBL ≥30%	40.7% (11/27)	0% (0/8)	0.029	%SBL	0.025
ICV present	55.6% (15/27)	37.5% (3/8)	0.369	ICV present	0.013
Colon majority intact	70.4% (19/27)	62.5% (5/8)	0.674	Colon majority intact	0.011
CRBSI (episodes per 1000 CVAD days)					
Overall (n = 33), median (IQR)	10.3 (8.3–12.3)	7.4 (5.4–16.1)	0.809	Overall	0.511
First 2 y of PN (n = 32), median (IQR)	11.6 (8.3–13.6)	8.2 (5.1–18.9)	0.750	First 2 y of PN	0.929
No IFALD	65.4% (17/26)	50.0% (4/ 8)		No IFALD	0.143
Era (of PN onset)					
Pre-1992	44.4% (12 /27)	25.0% (2/8)	0.324	1992–2011	0.265*

CRBSI = catheter-related bloodstream infection; CVAD = central venous access device; GA = gestational age; ICV = ileocecal valve; IFALD = intestinal failure–associated liver disease; IQR = interquartile range; NEC = necrotizing enterocolitis; PN = parenteral nutrition; SBL = small bowel length; SBS = short bowel syndrome.

*Shorter time to PN weaning for patients who commenced PN in the later era (i.e. 1992–2011).

placement after a median of 5.6 years of PN (range 3.9–12.4) and required thoracotomy for placement of a total of 11 further CVADs.

Data on CRBSI were analyzed in 49 children; 2 children, who were under joint care with other centers and did not present to the Royal Children's Hospital every time they experienced a septic event, were excluded from this analysis. A total of 423 episodes of culture-proven sepsis were documented in 57,848 CVAD days with an overall rate of 7.3 episodes per 1000 CVAD days. Five patients had no CRBSI. The overall CRBSI rate for inpatient and home PN were 9.4 and 6.0 episodes per 1000 CVAD days, respectively.

CRBSI occurred more frequently in patients' initial period of PN therapy and improved as they grew older ($P < 0.001$). Patients with SBS had more frequent CRBSI (SBS median 10.4 episodes per 1000 CVAD days [IQR 8.0–13.4]; non-SBS median 4.3 [IQR 2.2–5.0]; $P = 0.006$), but the association became statistically insignificant when analysis was limited to each child's first 2 years of PN therapy (SBS median 11.0 [IQR 8.2–15.1]; non-SBS median 5.5 [IQR 1.4–13.7]; $P = 0.161$). Premature infants (i.e., <37 weeks gestational age at time of PN onset) experienced similar CRBSI rates to term infants and older children. (Full PN duration: premature infants, median 10.1 [IQR 4.9–13.5] episodes per 1000 CVAD days; term infants and older children, median 9.8 [IQR 4.5–12.4]; $P = 0.771$. First 2 years of PN: premature infants, median 11.6 [IQR 9.5–15.1]; term infants and older children, median 9.5 [IQR 4.5–13.6]; $P = 0.196$.)

Of the microorganisms identified in blood cultures 53.2% (255/603) were Gram-positive, 42.3% (321/603) were Gram-negative, and 4.5% (27/603) were identified as fungal species. These include coagulase-negative *Staphylococcus* 26.1%, *Klebsiella* 18.8%, *Escherichia coli* 10.5%, *Enterococcus* 8.6%, *Staphylococcus aureus* 7.0%, *Enterobacteria* 5.0%, *Streptococcus* 4.3%, and *Candida* 4.3%.

Intestinal Failure-associated Liver Disease

Forty-two percent (21/50) of children fulfilled the definition of IFALD. One patient was excluded from this analysis as serum biochemistry and liver biopsy results were unavailable for assessment. Of the patients who fulfilled the definition of IFALD, 19 had persistent conjugated hyperbilirubinemia with moderate to severe fibrosis or cirrhosis confirmed in 10 of 14 patients where liver biopsy results were available (Fig. 2). An additional 2 patients transferred from an interstate centre had insufficient record at the Royal Children's Hospital to satisfy the biochemical definition of IFALD but had moderate to severe fibrosis on liver biopsy. Data of liver biochemical and biopsy results related to patient origin and outcome is outlined in Figure 2.

Risk factors for developing IFALD were prematurity, a diagnosis of SBS, and more frequent CRBSI (Table 4). In patients who had developed IFALD, the peak conjugated bilirubin level was significantly higher in those who died although no difference was found in the other clinical characteristics (Table 5).

DISCUSSION

We describe a survival rate of 84% over 20 years in patients with chronic intestinal failure managed with long-term PN. This is comparable to reports from other major pediatric centers (75%–94%) (15–17). IFALD was the key predictor of mortality. All patients who died as a child died in the first 2 to 3 years of life in the setting of end-stage liver failure, often following an episode of sepsis (15,18). Wales et al (19) described 2 periods of high mortality risk in neonatal SBS, the first immediately following resection and the second approximately 8 to 12 months later, coinciding with the development of IFALD. Innovative therapies, in particular, reduction in the volume of lipid administered, and fish-oil based emulsions have been shown to affect cholestasis and have contributed to a decrease in mortality of children with chronic intestinal failure (20–22). Nevertheless, persistent hyperbilirubinemia after treatment remains a strong predictor of poor outcome (21). Small bowel length and the absence of ileocecal valve were not predictors of mortality in our study, although a relationship has been reported in other studies (23,24). Ultrashort bowel no longer precludes survival (25,26). This may reflect improvements in the care of critical illness, nutritional management, and intestinal rehabilitation strategies (7).

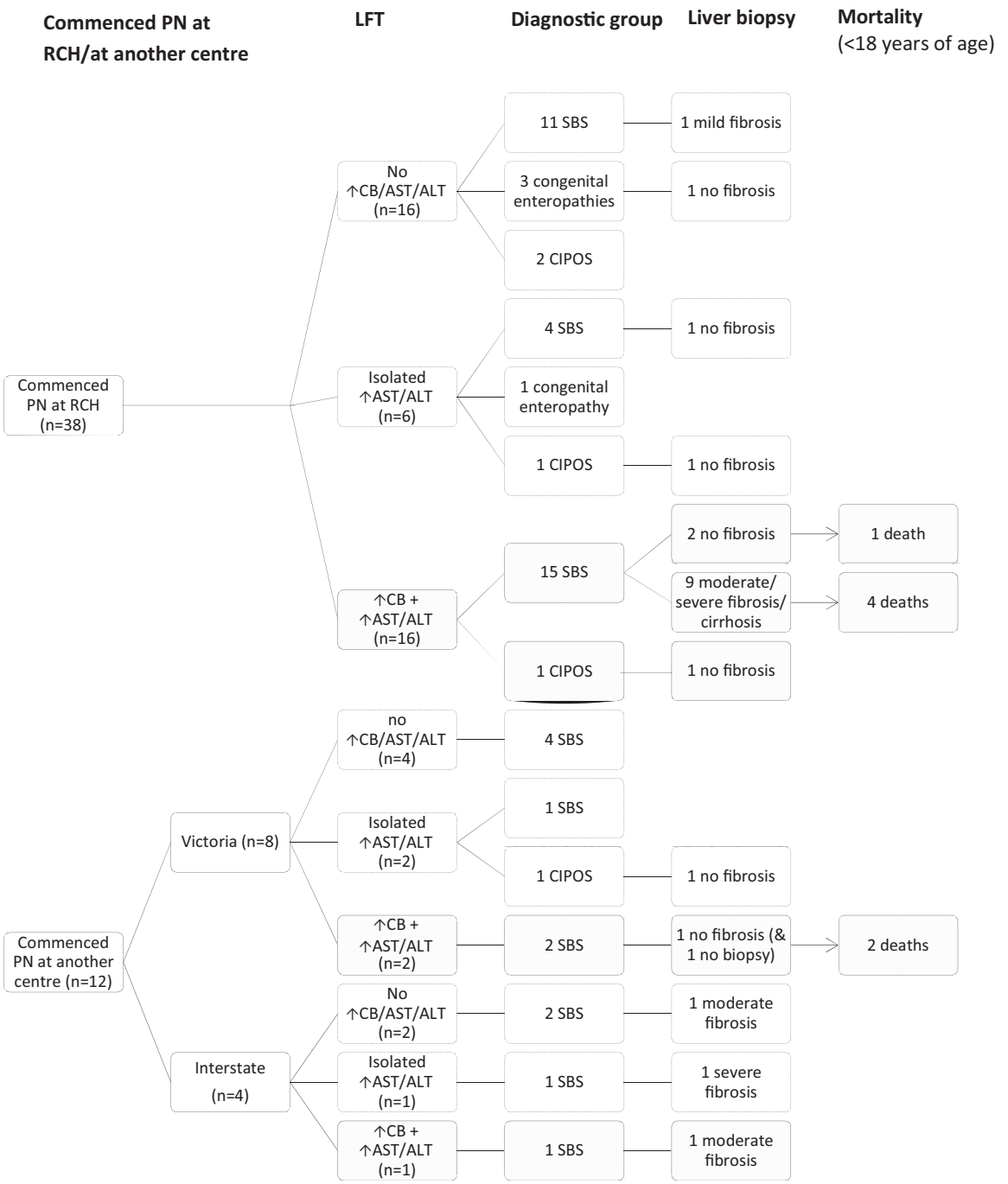

FIGURE 2. Evidence of liver disease. Patients who commenced PN at other Victorian hospitals were transferred after a median of 156 days (range 87–688); patients who commenced PN at interstate hospitals were transferred after a median of 578 days (range 174–1730). ↑CB means elevation in serum conjugated bilirubin to ≥34 μmol/L (≥2 mg/dL) persisting for ≥2 months; ↑AST/ALT means elevation in aspartate aminotransferase or alanine aminotransferase to ≥1.5 times above the upper limit of normal persisting for ≥2 months. CIPOS = chronic intestinal pseudo-obstruction syndrome; LFT = liver function test; PN = parenteral nutrition; RCH = Royal Children's Hospital; SBS = short bowel syndrome.

The majority (77%) of children with SBS in our cohort who survived the first 2 to 3 years were successfully weaned from PN. This compares well with other major centers (62%–77%) (17,23,27). We also found that the time from resection to full enteral autonomy can extend well beyond 3 years (15,25). Longer residual small bowel, the presence of ileocecal valve and the presence of the majority of colon were predictors of successful PN weaning in our patients with SBS. We also identified that ≥30% small bowel length was associated with PN weaning. Thirty percent small bowel length equates to approximately 43 cm at 35 weeks gestational age (12), which was the median gestational age of our SBS cohort. Therefore, our findings are similar to that of Khan et al

TABLE 4. Characteristics of patients with features of intestinal failure–associated liver disease versus patients with no features of intestinal failure–associated liver disease

	IFALD	No IFALD	*P*
Diagnosis			
SBS	95.2% (20/21)	72.4% (21/29)	0.038
NEC	19.0% (4/21)	17.2% (5/29)	0.870
Anatomy of remnant bowel in SBS			
SBL ≥30%	40.0% (8/20)	28.6% (6/21)	0.440
ICV absent	55.0% (11/20)	47.6% (10/21)	0.636
Colon half or less remaining	30.0% (6/20)	28.6% (6/21)	0.920
Prematurity (GA <37 wk at PN-onset)	66.7% (14/21)	31.0% (9/29)	0.013
PN duration ≥1 y	66.7% (14/21)	55.2% (16/29)	0.413
CRBSI (episodes per 1000 CVAD days)			
Overall (n = 48), median (IQR)	11.4 (9.6–15.8)	8.2(4.1–11.4)	0.012
First 2 years of PN (n = 47), median (IQR)	12.7 (9.6–17.8)	9.1 (4.2–13.0)	0.014

CRBSI = catheter-related bloodstream infection; CVAD = central venous access device; GA = gestational age; IFALD = intestinal failure–associated liver disease; IQR = interquartile range; NEC = necrotizing enterocolitis; PN = parenteral nutrition; SBS = short bowel syndrome.

(28) who proposed that a small bowel length of 41 cm could be used to predict eventual enteral autonomy. The benefit of preservation of the ileocecal valve or a colon in continuity has not been consistently reported (16,23,27,29). Resection of the ileocecal valve may increase the risk of small intestinal bacterial overgrowth and reduce transit time, both compromising the effectiveness of digestion and absorption in the remaining intestine (30). The role of the colon in assisting in the achievement of enteral autonomy by increasing absorptive capacity and the production of short-chain fatty acids as a significant energy source is now well recognized (30). The shortest small bowel length in our patients who had successfully weaned off PN was 7 cm with an ileocecal valve and 23 cm without an ileocecal valve. This is consistent with the study of Quiros-Tejeira et al (23) who reported success at weaning PN in children with <15 cm small bowel length with an intact ileocecal valve.

Morbidity and hospitalization in PN-dependent patients is inevitably linked to the need for a CVAD. Our experience of CVAD longevity reflects that reported at other major international centers (mean 487 days on home PN) (31,32), with an increase in lifespan of CVAD with time as patients grew older (23). Although thoracotomy was required for CVAD placement due to loss of central venous access in 4 patients in our cohort, we had no deaths due to inability to maintain intravenous access for PN delivery. Our cohort experienced an overall CRBSI rate of 7.3 episodes per 1000 CVAD days and 6.0 episodes per 1000 CVAD days for home PN, with less frequent infection in patients' later period of PN therapy compared to the initial period. This trend may be related to improved integrity of the intestinal wall and reduction in PN requirement over time, and improved maturity of the immune system and improved CVAD care with age. A wide variation in CRBSI rates have been reported by pediatric intestinal failure cohorts, ranging from 0.8 and 8.9 episodes per 1000 CVAD days (15,16,31–34). This variation may be partly explained by the use of different definitions. As a single positive blood culture may occur due to contamination (35), some studies have also required confirmation of systemic spread of the infection by positive culture from blood taken from a peripheral vein (16,32). This is not a consistent practice at our center. Gram-negative bacteria made up 42% of all microorganisms cultured in

TABLE 5. Characteristics of survivors with intestinal failure–associated liver disease versus nonsurvivors with intestinal failure–associated liver disease

	Alive	Died	*P*
Diagnosis			
SBS	92.9% (13/14)	100% (7/7)	1.000
NEC	7.1% (1/14)	42.9% (3/7)	0.088
Anatomy of remnant bowel in SBS			
SBL ≥30%	30.8% (4/13)	57.1% (4/7)	0.356
ICV absent	46.2% (6/13)	71.4% (5/7)	0.374
Colon majority intact	69.2% (9/13)	71.4% (5/7)	1.000
Prematurity (GA <37 wk at PN onset)	62.3% (9/14)	71.4% (5/7)	1.000
PN duration <1 y	28.6% (4/14)	42.9% (3/7)	0.638
CRBSI (episodes per 1000 CVAD days)			
Overall (n = 20), median (IQR)	10.3 (6.8–13.3)	13.5 (10.3–19.5)	0.143
First 2 years of PN (n = 19), median (IQR)	12.5 (8.9–17.2)	13.2 (10.3–19.5)	0.499
LFT			
Peak conjugated bilirubin, mmol/L, median (IQR; range)	155 (102–178; 70–415)	465 (279–673; 251–750)	0.001

CRBSI = catheter-related bloodstream infection; CVAD = central venous access device; GA = gestational age; IQR = interquartile range; LFT = liver function test; NEC = necrotizing enterocolitis; PN = parenteral nutrition; SBS = short bowel syndrome.

the blood of our patients. This is high compared to that reported in patients with a CVAD in a pediatric intensive care unit (29.7%) (36) and the available data from pediatric home PN cohorts (16%–38%) (32,37,38). High proportion of Gram-negative bacteria points the main source of infection to bowel flora, possibly via translocation from gut lumen into the circulation due to disturbed mucosal barrier function, although skin colonization as a route of infection is not excluded (34,39).

The incidence of IFALD was similar in our study compared with that reported elsewhere (42% vs 49.8%) (14). Risk factors associated with the development of IFALD were prematurity, frequent CRBSI, and a diagnosis of SBS. The association between prematurity and IFALD has been reported previously, and it may relate to functional immaturity of the liver in premature babies (40). Sepsis has also been recognized as a risk factor for IFALD in some studies but not all (40,41). Mutanen et al (42) reported that fibrosis on liver biopsy was negatively correlated with residual small bowel length and positively correlated with number of septic episodes in patients with SBS. The multifactorial etiology of IFALD suggests that prevention and management will require a multifaceted approach that includes optimization of mucosal barrier function of the residual bowel, good infection control and line management, and a balanced and targeted approach to nutrition support including novel strategies on the provision of intravenous lipid (22).

CONCLUSIONS

Children with chronic intestinal failure had a ∼85% chance of survival when managed with PN and intestinal rehabilitation (43). All deaths in children occurred in the setting of severe and refractory IFALD and this is the group in which intestinal transplantation may have offered benefit. The frequency of CVAD-related complications decreased with time as children grew older. Children with SBS who survived the first 2 to 3 years of life had a >75% chance of weaning off PN.

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REFERENCES

1. Diamanti A, Capriati T, Gandullia P, et al. Pediatric Chronic Intestinal Failure in Italy: report from the 2016 Survey on Behalf of Italian Society for Gastroenterology, Hepatology and Nutrition (SIGENP). *Nutrients* 2017;9:pii: E1217.
2. Barclay AR, Henderson P, Gowen H, et al. The continued rise of paediatric home parenteral nutrition use: implications for service and the improvement of longitudinal data collection. *Clin Nutr* 2015;34: 1128–32.
3. Neelis EG, Roskott AM, Dijkstra G, et al. Presentation of a nationwide multicenter registry of intestinal failure and intestinal transplantation. *Clin Nutr* 2016;35:225–9.
4. Groen H, Neelis EG, Poley MJ, et al. Intestinal rehabilitation for children with intestinal failure is cost-effective: a simulation study. *Am J Clin Nutr* 2017;105:417–25.
5. Bines JE. Intestinal failure: a new era in clinical management. *J Gastroenterol Hepatol* 2009;24(suppl 3):S86–92.
6. Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal transplant registry report: global activity and trends. *Am J Transplant* 2015;15: 210–9.
7. Pironi L, Joly F, Forbes A, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. *Gut* 2011;60:17–25.
8. The Royal Children's Hospital. Clinical practice guideline—parenteral nutrition RCH specific. *https://www.rch.org.au/gastro/clinical_nutrition/parenteral-nutrition-rch-specific/*. Accessed December 12, 2016.
9. The Royal Children's Hospital. Central venous access device management. *http://www.rch.org.au/policy/public/Central_Venous_Access_Device_Management/*. Accessed December 12, 2016.
10. Clinical Nutrition Program RCH. *Practical Paediatric Nutrition Support*. 2nd ed. Melbourne, Australia: Royal Children's Hospital; 2014.
11. Australian Demographic Statistics [Internet]. Australian Bureau of Statistics. 1991–2015 [December 2015]. *http://www.abs.gov.au/Population*. Accessed July 10, 2016.
12. Struijs MC, Diamond IR, De Silva N, et al. Establishing norms for intestinal length in children. *J Pediatr Surg* 2009;44:933–8.
13. Prevention CfDCa. Identifying Healthcare-associated Infections (HAI) for NHSN Surveillance 2015. *http://www.cdc.gov/nhsn/PDFs/pscManual/2PSC_IdentifyingHAIs_NHSNcurrent.pdf*. Accessed January 26, 2016.
14. Lauriti G, Zani A, Aufieri R, et al. Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review. *JPEN J Parenter Enteral Nutr* 2014;38:70–85.
15. Squires RH, Duggan C, Teitelbaum DH, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. *J Pediatr* 2012;161:723.e2–8.e2.
16. Diamanti A, Basso MS, Castro M, et al. Irreversible intestinal failure: prevalence and prognostic factors. *J Pediatr Gastroenterol Nutr* 2008;47:450–7.
17. Fullerton BS, Sparks EA, Hall AM, et al. Enteral autonomy, cirrhosis, and long term transplant-free survival in pediatric intestinal failure patients. *J Pediatr Surg* 2016;51:96–100.
18. Kaufman SS, Pehlivanova M, Fennelly EM, et al. Predicting liver failure in parenteral nutrition-dependent short bowel syndrome of infancy. *J Pediatr* 2010;156:580.e1-585.e1.
19. Wales PW, de Silva N, Kim JH, et al. Neonatal short bowel syndrome: a cohort study. *J Pediatr Surg* 2005;40:755–62.
20. Oliveira C, de Silva NT, Stanojevic S, et al. Change of outcomes in pediatric intestinal failure: use of time-series analysis to assess the evolution of an Intestinal Rehabilitation Program. *J Am Coll Surg* 2016;222:1180.e3–8e.
21. Burghardt KM, Wales PW, De Silva N, et al. Pediatric intestinal transplant listing criteria—a call for a change in the new era of intestinal failure outcomes. *Am J Transplant* 2015;15:1674–81.
22. Goulet O, Lambe C. Intravenous lipid emulsions in pediatric patients with intestinal failure. *Curr Opin Organ Transplant* 2017;22:142–8.
23. Quiros-Tejeira RE, Ament ME, Reyen L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. *J Pediatr* 2004;145:157–63.
24. Wilmore DW. Factors correlating with a successful outcome following extensive intestinal resection in newborn infants. *J Pediatr* 1972;80: 88–95.
25. Infantino BJ, Mercer DF, Hobson BD, et al. Successful rehabilitation in pediatric ultrashort small bowel syndrome. *J Pediatr* 2013;163:1361–6.
26. Pakarinen MP, Pakkasjarvi N, Merras-Salmio L, et al. Intestinal rehabilitation of infantile onset very short bowel syndrome. *J Pediatr Surg* 2015;50:289–92.
27. Fallon EM, Mitchell PD, Nehra D, et al. Neonates with short bowel syndrome: an optimistic future for parenteral nutrition independence. *JAMA Surg* 2014;149:663–70.
28. Khan FA, Squires RH, Litman HJ, et al. Predictors of enteral autonomy in children with intestinal failure: a multicenter cohort study. *J Pediatr* 2015;167:29.e1–34.e1.
29. Colomb V, Dabbas-Tyan M, Taupin P, et al. Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. *J Pediatr Gastroenterol Nutr* 2007;44: 347–53.
30. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 1. *Am J Gastroenterol* 2004;99:1386–95.
31. Gandullia P, Lugani F, Costabello L, et al. Long-term home parenteral nutrition in children with chronic intestinal failure: a 15-year experience at a single Italian centre. *Dig Liver Dis* 2011;43:28–33.
32. Colomb V, Fabeiro M, Dabbas M, et al. Central venous catheter-related infections in children on long-term home parenteral nutrition: incidence and risk factors. *Clin Nutr* 2000;19:355–9.
33. Wiskin AE, Cole C, Owens DR, et al. Ten-year experience of home parenteral nutrition in a single centre. *Acta Paediatr* 2012;101:524–7.

34. Robinson JL, Casey LM, Huynh HQ, et al. Prospective cohort study of the outcome of and risk factors for intravascular catheter-related bloodstream infections in children with intestinal failure. *JPEN J Parenter Enteral Nutr* 2014;38:625–30.
35. Falagas ME, Kazantzi MS, Bliziotis IA. Comparison of utility of blood cultures from intravascular catheters and peripheral veins: a systematic review and decision analysis. *J Med Microbiol* 2008;57:1–8.
36. Niedner MF, Huskins WC, Colantuoni E, et al. Epidemiology of central line-associated bloodstream infections in the pediatric intensive care unit. *Infect Control Hosp Epidemiol* 2011;32:1200–8.
37. Hojsak I, Strizic H, Misak Z, et al. Central venous catheter related sepsis in children on parenteral nutrition: a 21-year single-center experience. *Clin Nutr* 2012;31:672–5.
38. Mohammed A, Grant FK, Zhao VM, et al. Characterization of post-hospital bloodstream infections in children requiring home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2011;35:581–7.
39. Pierro A, Van Saene HK, Donnell SC, et al. Microbial translocation in neonates and infants receiving long-term parenteral nutrition. *Arch Surg* 1996;131:176–9.
40. Pichler J, Horn V, Macdonald S, et al. Intestinal failure-associated liver disease in hospitalised children. *Arch Dis Child* 2012;97:211–4.
41. Barclay AR, Paxton CE, Gillett P, et al. Regionally acquired intestinal failure data suggest an underestimate in national service requirements. *Arch Dis Child* 2009;94:938–43.
42. Mutanen A, Lohi J, Heikkila P, et al. Persistent abnormal liver fibrosis after weaning off parenteral nutrition in pediatric intestinal failure. *Hepatology* 2013;58:729–38.
43. Norsa L, Artru S, Lambe C, et al. Long term outcomes of intestinal rehabilitation in children with neonatal very short bowel syndrome: parenteral nutrition or intestinal transplantation. *Clin Nutr* 2019;38:926–33.