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Necrotizing enterocolitis is associated with earlier achievement of enteral autonomy in children with short bowel syndrome☆,☆☆,★

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ABSTRACT

Purpose: Necrotizing enterocolitis (NEC) remains one of the most common underlying diagnoses of short bowel syndrome (SBS) in children. The relationship between the etiology of SBS and ultimate enteral autonomy has not been well studied. This investigation sought to evaluate the rate of achievement of enteral autonomy in SBS patients with and without NEC.

Methods: Following IRB approval, 109 patients (2002–2014) at a multidisciplinary intestinal rehabilitation program were reviewed. The primary outcome evaluated was achievement of enteral autonomy (i.e. fully weaning from parenteral nutrition). Patient demographics, primary diagnosis, residual small bowel length, percent expected small bowel length, median serum citrulline level, number of abdominal operations, status of the ileocecal valve (ICV), presence of ileostomy, liver function tests, and treatment for bacterial overgrowth were recorded for each patient.

Results: Median age at PN onset was 0 weeks [IQR 0–0]. Median residual small bowel length was 33.5 cm [IQR 20–70]. NEC was present in 37 of 109 (33.9%) of patients. 45 patients (41%) achieved enteral autonomy after a median PN duration of 15.3 [IQR 7.2–38.4] months. Overall, 64.9% of patients with NEC achieved enteral autonomy compared to 29.2% of patients with a different primary diagnosis ($p = 0.001$, Fig. 1). Patients with NEC remained more likely than those without NEC to achieve enteral autonomy after two (45.5% vs. 12.0%) and four (35.7% vs. 6.3%) years on PN (Fig. 1). Logistic regression analysis demonstrated the following parameters as independent predictors of enteral autonomy: diagnosis of NEC ($p < 0.002$), median serum citrulline level ($p < 0.02$), absence of a jejunostomy or ileostomy ($p = 0.013$), and percent expected small bowel length ($p = 0.005$).

Conclusions: Children with SBS because of NEC have a significantly higher likelihood of fully weaning from parenteral nutrition compared to children with other causes of SBS. Additionally, patients with NEC may attain enteral autonomy even after long durations of parenteral support.

Intestinal failure (IF) describes a state of inadequate bowel function resulting in the inability to absorb sufficient nutrients, fluids, or electrolytes in order to maintain proper growth and development [1]. IF most frequently results from congenital or acquired short bowel syndrome (SBS) [2]. Modern advances in multidisciplinary management and parenteral nutrition have improved outcomes for patients with IF, but significant morbidity and mortality remains [3].

Enteral autonomy is a desired endpoint for all children with IF, as those who remain on indefinite parenteral nutrition or proceed to intestinal transplant have higher mortality rates [4–6]. While many clinical factors associated with weaning from PN are described, accurate early prediction of which children will reach this outcome remains difficult [3,29]. This investigation sought to quantitate the rate of achievement of enteral autonomy in patients with NEC compared to other SBS patients.

Abbreviations: APRI, AST to platelet ratio index; CIPO, Chronic intestinal pseudoobstruction; CLABSI, Central line associated blood stream infection; ICV, Ileocecal valve; IQR, Interquartile range; IF, Intestinal failure; IFALD, Intestinal failure associated liver disease; PN, Parenteral nutrition; NEC, Necrotizing enterocolitis; SBBO, Small bowel bacterial overgrowth; SBS, Short bowel syndrome; VLBW, Very low birth weight.

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★ Level of Evidence: IIb, retrospective cohort study.

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1. Methods

1.1. Study design

Following IRB approval (protocol #M06-01-0049), the records of 118 patients treated at a single institution between February 2002 and June 2014 were reviewed (Center for Advanced Intestinal Rehabilitation, Boston Children's Hospital). Nine patients were excluded from analysis because of primary diagnosis of intestinal dysmotility or pseudoobstruction. Intestinal failure was defined as duration of PN dependence greater than 90 days. Clinical characteristics recorded for each patient included demographic information, etiology of short bowel syndrome, age at PN initiation, measured residual small bowel length, number of abdominal operations, presence of a stoma, presence of the ileocecal valve, treatment for small bowel bacterial overgrowth, serum citrulline concentration, and liver function tests. Percent expected bowel length was calculated by comparing measured bowel length for each patient with normal bowel length for postconception age [7]. Each patient was categorized as successfully weaning off of PN, remaining PN duration at the end of the study period, undergoing intestinal transplant, dead, or lost to follow-up.

1.2. Statistical methods

The primary outcome measure for this analysis was weaning from PN support. Continuous data were reported as medians and interquartile ranges, and categorical data were reported as counts and percentages. Data normality was assessed using a Kolmogorov–Smirnov test. Demographic and clinical characteristics related to PN outcomes were identified using Mann–Whitney U tests for continuous variables and Fisher's rank test for categorical variables. Multivariable analysis was performed by a logistic regression model for each possible predictor of enteral autonomy. Variables with a p value ≤0.20 were considered for inclusion in the final model. Collinear variables (e.g., first recorded CIT and median recorded CIT) were assessed in separate models. Kaplan–Meier [8] survival tables and curves were generated and factors compared using the log rank (Mantel–Cox) test. Statistical analysis was conducted using Base SAS 9.3 (Statistical Analysis Software, SAS Institute Inc., Cary, NC).

2. Results

The study population is described in Table 1. 109 patients with short bowel syndrome were included, with necrotizing enterocolitis (NEC) being the most common etiology (34%), followed by gastroschisis (20%), midgut volvulus (14%), intestinal atresia (10%), Hirschsprung's disease (9%), intraabdominal tumors (3%) and other miscellaneous diagnoses (10%). 84% of patients were less than 1 month of age at initiation of PN. The median residual bowel length was 33.5 cm (20–70), representing a median percent expected bowel length of 16% (8–37). 21 patients (19%) received empiric treatment for small bowel bacterial overgrowth.

In this cohort 45 patients (41.3%) achieved enteral autonomy after a median PN duration of 15.3 [IQR 7.2–38.4] months. Predictors of attaining enteral autonomy as identified on univariate analysis are shown in Table 2. From this analysis, four parameters associated with a higher likelihood of enteral autonomy remained significant during a multivariable regression. These were diagnosis of NEC ($p = 0.002$), higher percent expected bowel length ($p = 0.005$), absence of an ileostomy or jejunostomy ($p = 0.013$), and higher median serum citrulline concentration ($p = 0.020$). Measurements of serum bilirubin and the empiric treatment of small bowel bacterial overgrowth showed no association with enteral autonomy. AST to platelet ratio index (APRI) and the presence of an ileocecal valve were associated with weaning from PN on univariate analysis, but failed to reach significance on multivariable analysis.

Table 1
Descriptive characteristics and clinical variables of 109 children with intestinal failure.

Diagnosis, *n* (%)	
NEC	37 (34)
Gastroschisis	22 (20)
Volvulus	15 (14)
Intestinal atresia	11 (10)
Hirschsprung's disease	10 (9)
Intraabdominal tumor	3 (3)
Other	11 (10)
Median age at PN onset, median (IQR), days	0 (0–0)
Male sex, *n* (%)	59 (54)
Use of antibiotics for SBBO, *n* (%)	21 (19)
Anatomy:	
Bowel length, cm, median (IQR)	33.5 (20–70)
Percent expected bowel length (IQR)	16 (8–37)
Presence of ICV, *n* (%)	39 (36)
Ileostomy or jejunostomy, *n* (%)	23 (21)
Number of operations, median (IQR)	3 (2–5)
Follow-up duration (months)	52 (37–71)
Outcome:	
Weaned from PN, *n* (%)	45 (41)
Transplant, *n* (%)	2 (2)
Death, *n* (%)	1 (1)

Continuous variables are reported as median (IQR = interquartile range); frequencies are reported as *n* (%). NEC = necrotizing enterocolitis, PN = parenteral nutrition, SBBO = small bowel bacterial overgrowth.

Fig. 1 shows Kaplan–Meier curves comparing enteral autonomy in patients with NEC to those with other diagnoses. 64.9% of patients with NEC achieved enteral autonomy during the study period, compared to 26.7% of patients with a different primary diagnosis ($p = 0.001$). Likelihood of enteral autonomy after two years on PN was 45.5% in patients with NEC compared with 12.0% for other patients. Children with a history of NEC remained more likely than those without NEC to achieve enteral autonomy after four years on PN (35.7% vs. 6.3%).

3. Discussion

Recent advances in multidisciplinary management, parenteral nutrition, and surgical therapy have improved outcomes for patients with intestinal failure [9–14]. However, children who are unable to wean from PN have increased mortality and additional burdens, including risk of

Table 2
Descriptive and clinical variables for patients who achieved and did not achieve enteral autonomy.

	Weaned from PN ($n = 45$)	Did Not Wean from PN ($n = 64$)	p Value
Age at PN onset (months)	0 (0–0)	0 (0–6)	0.15
Male sex	22 (49)	37 (64)	0.71
Direct bilirubin at PN onset (mg/dL)	0.4 (0.2–3.3)	0.4 (0.2–0.7)	0.71
Peak direct bilirubin (mg/dL)	4.4 (0.9–8.1)	3.0 (0.6–7.1)	0.35
APRI at PN onset	0.4 (0.2–0.7)	0.5 (0.3–1.0)	0.09
Peak APRI	1.5 (0.6–5.8)	2.6 (1.2–5. 9)	0.07
First recorded citrulline (μmol/L)	13 (9–22)	11 (6–15)	0.034
Median recorded citrulline (μmol/L)	18 (13–24)	13 (8–17)	<0.001
History of NEC	24 (53)	13 (20)	<0.001
History of gastroschisis	6 (13)	16 (28)	0.15
Antibiotic treatment for SBBO	8 (18)	13 (23)	0.63
Presence of ICV	21 (47)	18 (31)	0.15
Ileostomy or jejunostomy	5 (11)	18 (32)	0.017
Number of operations	3 (2–4)	3 (2–5)	0.36
Follow-up duration (months)	49 (36–68)	54 (38–74)	0.33
Bowel length, cm, median (IQR)	52 (26–87)	27 (15–59)	0.02
% expected bowel length	29 (12–44)	12 (7–25)	0.009

PN = parenteral nutrition, NEC = necrotizing enterocolitis, APRI = AST to platelet ratio, SBBO = small bowel bacterial overgrowth; data are reported as either median (IQR = interquartile range) or frequency (%); p values calculated using Fisher's Exact test or Mann–Whitney U test as appropriate. p Values from univariate analysis are listed.