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Predictors of Enteral Autonomy in Children with Intestinal Failure: A Multicenter Cohort Study

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Abstract

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*List of members of the Pediatric Intestinal Failure Consortium is available at www.jpeds.com (Appendix).

The authors declare no conflicts of interest.

Objectives—In a large cohort of children with intestinal failure (IF), we sought to determine the cumulative incidence of achieving enteral autonomy and identify patient and institutional characteristics associated with enteral autonomy.

Study design—A multicenter retrospective cohort analysis from the Pediatric Intestinal Failure Consortium (PIFCon) was performed. IF was defined as severe congenital or acquired gastrointestinal diseases during infancy with PN dependence >60 days. Enteral autonomy was defined as PN discontinuation >3 months.

Results—272 infants were followed for a median (IQR) of 33.5(16.2, 51.5) months. Enteral autonomy was achieved in 118(43%); 36(13%) remained PN dependent and 118 (43%) patients died or underwent transplantation. Multivariable analysis identified NEC [OR 95% CI: 2.42 (1.33, 4.47)], care at an IF site without an associated intestinal transplant (ITx) program [OR 2.73 (1.56, 4.78)] and an intact ileocecal valve (ICV) [OR 2.80 (1.63, 4.83)] as independent risk factors for enteral autonomy. A second model (n=144) including only patients with intra-operatively measured residual small bowel length (RSB) found NEC [OR 3.44 (1.36, 8.71)], care at a non-ITx center [OR 6.56 (2.53, 16.98)] and RSB (cm) [OR 1.04 (1.02, 1.06)] to be independently associated with enteral autonomy.

Conclusions—A substantial proportion of infants with IF can achieve enteral autonomy. Underlying NEC, preserved ICV and longer bowel length are associated with achieving enteral autonomy. It is likely that variations in institutional practices and referral patterns also affect outcomes in children with IF.

Keywords

Intestinal failure; short bowel syndrome; enteral autonomy

Intestinal failure (IF) is characterized by the reduction of functional intestinal mass necessary to meet nutrient, electrolyte and fluid requirements.[1, 2] The most common cause of IF in children is a loss of intestine due to congenital or acquired conditions that results in short bowel syndrome (SBS).[3] The institution of multidisciplinary care of patients with IF has substantially reduced mortality,[4] but significant morbidity remains for affected infants. Long term PN use is associated with multiple serious complications, including mechanical, infectious, hepatic and metabolic disease as as well as financial and psychosocial morbities.[5, 6, 7, 8, 9] Achievement of enteral autonomy avoids the significant morbidity associated with long-term PN dependence and is therefore the primary aim of modern management of IF.[10]

Data describing the cumulative incidence of enteral autonomy in pediatric IF are relatively sparse, with estimates ranging between 42–86%. [3, 11, 12] In addition, the process of intestinal adaptation from intestinal resection to a theoretical plateau phase in bowel adaptation is controversial, and has been variably reported in the literature to occur within 1–3 years in children.[13, 14] The extent of adaptive response is influenced by several factors such as age of the patient at the inciting event leading to IF, magnitude and location of bowel loss, [14, 15] presence of an intact ileocecal valve (ICV), [9, 16] residual colon in continuity,[9, 16] composition, timing and advancement of enteral feeds and the luminal environment (absence of bacterial overgrowth).[17, 18, 19] However the interpretation of these published

data is limited due to variability in patient populations studied, criteria used to define IF, duration of patient follow-up, and characteristics of patient management, among other factors.

Due to these gaps in the literature, a multi-institutional collaborative (the Pediatric Intestinal Failure Consortium (PIFCon) was established.[20] The current study was performed as an ancillary analysis of data collected by PIFCon, to more accurately track intestinal adaptation and achievement of enteral autonomy. Our specific aims were to measure the cumulative incidence of enteral autonomy and identify patient and institutional characteristics associated with achieving enteral autonomy.

Methods

We performed a multicenter retrospective cohort study among the Pediatric Intestinal Failure Consortium. The group was initiated in June 2006 as a collaboration among 14 sites with established multidisciplinary programs for treatment of pediatric intestinal failure; 9 of the 14 sites also had affiliated intestinal transplantation programs. After Institutional Review Board approval from each participating center, records of patients who met inclusion criteria were retrospectively reviewed. Infants with IF were included if they had severe congenital or acquired gastrointestinal diseases, were less than 1 year of age, and required prolonged support with PN (defined as ≥ 60 out of 74 consecutive days). This specific PN duration was chosen to allow for brief interruptions such as loss of intravenous access or perioperative cessation. Participants at 13 sites met the age and PN criteria between January 2000 and December 2004, whereas at 1 site the end date for study entry was extended to December 2005. Data were collected through December 2006 for 13 sites and December 2007 at the remaining site to allow at least a 2-year follow up for all children. Baseline clinical data were collected at study inclusion; subsequent clinical data were collected at 1, 3, 6, 9, and 12 months following study enrollment and annually thereafter. The results of the original study have been previously published.[20]

The outcome variables for the current study were the achievement of enteral autonomy (defined as discontinuation of PN for >3 consecutive months with maintenance of acceptable growth variables), persistent dependence on PN, and the combined outcome of death or undergoing intestinal or multi-visceral transplantation. Statistical analysis was conducted using SAS® version 9.3 (Cary, NC). Categorical data are summarized as frequency counts and percentages. Continuous data are shown as mean ± standard deviation (SD) when normally distributed, and nonparametric data are presented as median and interquartile range (IQR). Cumulative incidence curves with adjustment for competing risks for the three main outcomes were plotted.[21] Potential factors associated with achievement of enteral autonomy were evaluated using bivariate analysis. Variables that reached statistical significance in the bivariate analysis ($p<0.2$) or were deemed clinically relevant were selected for inclusion in multivariable logistic regression models to identify independent patient and institutional characteristics associated with achievement of enteral autonomy. Intra-operative measurements of residual small bowel (RSB) length were available for a limited number of subjects, so two multivariable models were created: one considering the entire dataset and one for only those with RSB measurements. Post-hoc analysis was

performed to identify the threshold RSB predicting probability of enteral autonomy with the highest combined sensitivity and specificity using a Receiver Operating Characteristic (ROC) curve. Cumulative incidences of enteral autonomy for patients with different diagnoses were compared using Gray's test.[22]

Results

Select patient demographic and baseline characteristics are summarized in Table I. The 272 infants who met study inclusion criteria were followed for a median of nearly 3 years. Complete enteral autonomy was achieved in 118 (43%) by the end of the study follow up period; 36 patients (13%) remained partially or exclusively PN dependent and 118 (43%) patients died (n = 58), underwent intestinal/multivisceral transplantation (n = 50) or underwent transplant and then died (n=10). The cumulative incidences of enteral autonomy, PN dependence and death/transplantation with adjustment for competing risk by study follow up period are depicted in Figure 1.

Patient, clinical, and institutional factors associated with enteral autonomy on bivariate analysis are shown in Table II. Children who achieved enteral autonomy by the end of the follow up period were slightly older at the time of study inclusion, were more likely to have NEC as the underlying diagnosis, had preserved ICV and significantly longer intra-operatively measured RSB compared with those not achieving autonomy. Conversely, patients cared for at a PIFCon site with an affiliated intestinal/multi-visceral transplant program and those with more advanced liver disease (as evidenced by higher baseline direct and total bilirubin levels and a higher aspartate aminotransferase to platelet ratio (APRI) [23] were less likely to achieve enteral autonomy.

Multivariable logistic regression analysis using forward selection in the full cohort (n=272) found that children with an underlying diagnosis of NEC [OR 2.42 (95% CI: 1.33, 4.47)] and those with an intact ICV [OR 2.80 (95% CI: 1.63, 4.83)] were more than two times more likely to achieve enteral autonomy than infants with other underlying diagnoses or an absent ICV. Children cared for at an IF site without an associated intestinal transplant program were also significantly more likely to achieve enteral autonomy [OR: 2.73 (1.56, 4.78)]. The multivariable odds of achieving enteral autonomy in infants receiving human milk was 1.92 (0.87, 4.25), p= 0.11. Similarly for those receiving amino acid based formulae the multivariable odds of achieving enteral autonomy were 0.64 (0.34, 1.22), p= 0.18.

A second multivariable model employing the same selection technique involving only patients with baseline RSB measured intra-operatively (n=144) noted similar associations whereby children cared for at an IF site without an associated intestinal transplant program were significantly more likely to achieve enteral autonomy [OR: 6.56 (2.53, 16.98)], those with NEC were more than three times more likely to achieve enteral autonomy [OR 3.44 (95% CI: 1.36, 8.71)]. Longer RSB was additionally identified as an independent factor influencing achievement of enteral autonomy [OR 1.04 (95% CI: 1.02, 1.06)]. For every 1 cm increase in RSB the odds of achieving enteral autonomy increased by 4%, taking into consideration both underlying diagnosis and care at an ITx site (Table III).

Given these findings concerning ITx sites, we compared select patient baseline characteristics between the 9 centers with and 5 centers without ITx programs. We found that compared with non-ITx center infants, patients seen at centers with ITx programs were significantly more likely to be premature (GA<37 weeks) (p=0.01), had a higher proportion of very low birth weight (<1500 grams) neonates (p=0.05), were younger at study entry (p<0.001), were less likely to have NEC (p<0.001), more likely to have received human milk at baseline (p=0.005) and had shorter RSB (p=0.006). However no significant differences were noted in the extent of liver disease between the two groups as measured by direct bilirubin (p=0.37), total bilirubin (p=0.89) and APRI (p=0.40).

Post hoc analysis using receiver operating characteristic (ROC) curve analysis identified RSB ≥ 41cm to have the highest combined sensitivity and specificity to predict achievement of enteral autonomy. The cumulative incidence of enteral autonomy by study follow up duration among children with NEC as their sole underlying IF diagnosis compared with children with other diagnoses was also noted to be significantly different (p<0.001) using Gray's test (Figure 2; available at www.jpeds.com).

Discussion

In this multicenter retrospective cohort of a large number of infants with intestinal failure, we found that almost half of all patients achieved enteral autonomy within the nearly three years of follow up. Medical care at a non-transplant IF program, underlying NEC, and a preserved ICV were all independently associated with enteral autonomy. A second multivariable model confirmed that longer measured residual small bowel length was also an independent predictor of successful weaning from PN.

Our finding of a rate of enteral autonomy of 43% is similar to rates reported in studies involving patients with similar disease severity.[3, 16] Authors who have reported higher rates of weaning from PN support have generally included infants with less severe manifestations of intestinal failure. In some instances, a combination of RSB and duration of PN dependence were used to define IF, inherently meaning a heterogeneous population of patients with varying disease severity.[9, 24, 25, 26] Moreover review of pediatric IF literature tracking outcomes reveals that several previous investigators, reporting excellent outcomes, either did not comment on the severity of liver dysfunction in the studied population, or conversely had a relatively smaller proportion of patients with evidence of cholestasis, as opposed to the 74% prevalence of cholestasis seen in this cohort.[1, 9, 17, 27, 28, 29]

The natural history of the adaptive response following bowel resection is unclear, as some observational studies suggest maximal adaption occurs within 24–36 months of the initial insult. Therefore the probability of weaning off PN was thought to drastically decrease beyond this time frame.[3, 14] Children in this present cohort, however, continued to demonstrate achievement of enteral autonomy well beyond three years after the initial insult leading to IF. These data support continued efforts at intestinal rehabilitation even in children with very short RSB. This observation may be explained by the significant potential for the gastrointestinal tract to progressively lengthen in infants and young children.[30]

Certain IF diagnoses have been previously suspected to be associated with overall worse outcomes. Although Georgeson et al reported no differences in the probability of weaning from PN in those with NEC compared with other diagnoses, our data suggest that infants with NEC are not only more likely to achieve enteral autonomy compared with patients without NEC, but do so more rapidly, adjusted for RSB, status of ICV and institution where care is provided. It is possible that previous investigators did not identify this association due to smaller number of patients studied and/or high rate of associated morbidities of prematurity.[29]

Previous studies have demonstrated improved outcomes for IF patients transferred to specialized centers at a relatively early phase of their illness.[31] In contrast, we found that being referred to or cared for at a center with transplantation capability was associated with lower rates of enteral autonomy, even adjusting for RSB, status of the ICV and underlying diagnosis. One possible explanation for this finding is the selection biases inherent in a retrospective study (i.e., a tendency to refer only the most severely ill children to sites with transplant capacity). This is supported by our findings that patients at transplantation sites had shorter RSB, were more likely to be premature and of very low birth weight, compared with patients at non-transplant sites. Alternatively, our findings might be due to a philosophical predisposition away from intestinal rehabilitation towards transplantation at these sites. This is perhaps suggested by the comparable measures of cholestasis and some but not all measures of liver dysfunction. The nature of available data limit further characterization of this association; large, prospective studies are warranted to better identify the influence of institutional and referral patterns on patient outcomes.

Previous studies have identified RSB as a major factor in determining whether a patient with SBS will wean off PN support.[3,19] Prior to the widespread implementation of PN support among infants requiring significant bowel resections Wilmore reported 100% mortality for infants with less than 40 cm RSB without ICV.[32] Based on data from this more recent cohort, a threshold value of 41cm or greater appears to be best predictive of the ability to wean off from PN support, although as mentioned above, RSB less than this are no reason to abandon efforts at rehabilitation. Previous investigators have reported improved rates of survival and successful intestinal rehabilitation in IF patients with an intact ICV.[9, 11] The improved outcomes seen in IF patients with an intact ICV and therefore at least some terminal ileum may in part be due to the significantly higher adaptive potential of distal small bowel. Other factors such as a preserved ileo-gastric reflex[35] and over all slower transit of luminal contents through the distal small bowel are likely contributory. RSB and the status of ICV can therefore be utilized to risk stratify children with IF, identify those likely to require prolonged PN support and are thereby likely to experience higher level of IF-related morbidity.

Although the correlation between human milk feeding and enteral autonomy did not achieve statistical significance, available evidence suggests not only mode (enteral vs. parenteral nutrition) but also the content of enteral nutrition (EN) has an influence on outcomes in IF.[10, 18] The lack of a statistically significant association of the use of human milk with enteral autonomy in this cohort may be due to the small proportion of children who received human milk, and the possibility of confounders (differences in institutional practices and

severity of illness, among other factors). Due to the several advantages afforded by human milk over commercially-prepared formulas, including the presence of secretory IgA, amino acids, numerous growth factors and other components which bolster systemic and mucosal immune response and likely assist intestinal adaptation, the use of human milk as the primary type of EN for infants with IF should still be strongly considered in the absence of specific intolerance.[34]

The large, geographically diverse cohort of infants who were followed for a median duration of approximately 3 years enhances the validity and generalizability of our findings. This study is, however, limited by its retrospective design and incomplete data collection of some variables. Since the collection of these data, improvements in IF management (eg, alterations of the dose and type of intravenous fatty acid emulsions, ethanol locks for CLABSI prophylaxis, and more) have been reported, which in part may explain the relatively small number of patients dependent on PN at the end of the study follow up period. Even though all the participating sites had independent multidisciplinary programs for management of IF, there were likely variations in patterns of clinical practice within and between the participating centers, which may partly be responsible for the association noted between enteral autonomy and care at specific IF programs. Nonetheless these data can serve as effective bench marks for future prospective multi-center studies needed to further improve outcomes in children with IF.

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Abbreviations and Acronyms

CLABSI	Central line-associated bloodstream infection
EN	Enteral nutrition
IQR	Interquartile range
IF	Intestinal failure
IFALD	Intestinal failure-associated liver disease
ITx	Intestinal transplantation
NEC	Necrotizing Enterocolitis
OR	Odds Ratio
PIFCon	Pediatric Intestinal Failure Consortium
PN	Parenteral nutrition
ROC	Receiver Operating Characteristic
RSB	Residual small bowel length
ICV	Ileocecal Valve

SBS Short bowel syndrome

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Appendix

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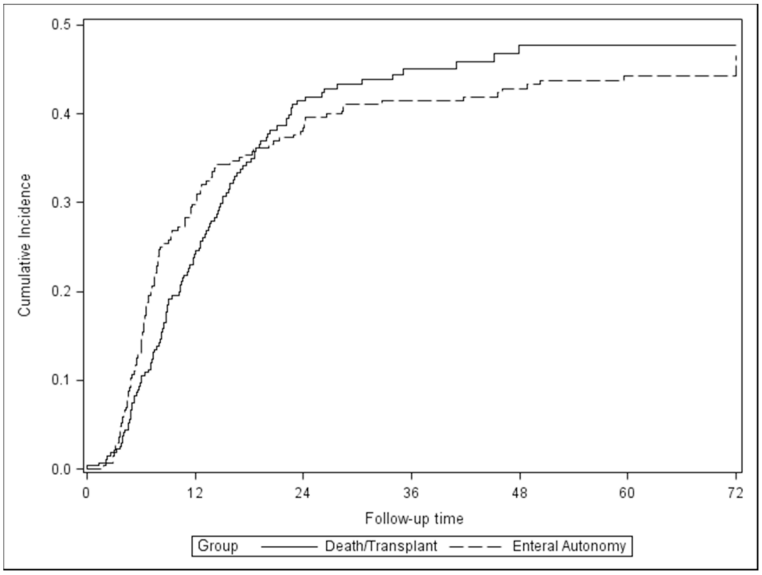
A)



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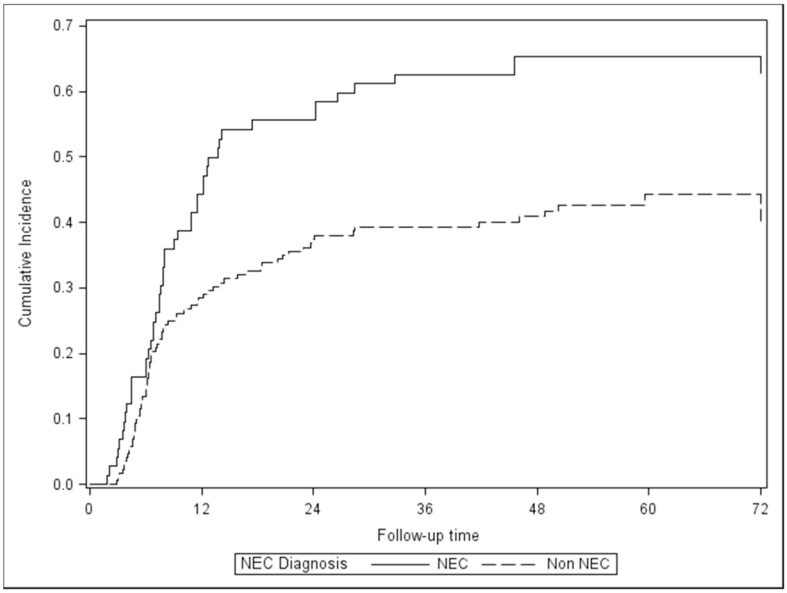

Figure 1.

A) Cumulative incidence of death/transplant and enteral autonomy in months after study entry in 272 infants with intestinal failure.

B) Cumulative incidence of enteral autonomy by NEC diagnosis in months from time entry criteria was met.

*P<0.001 from Gray's test comparing cumulative incidence rates.

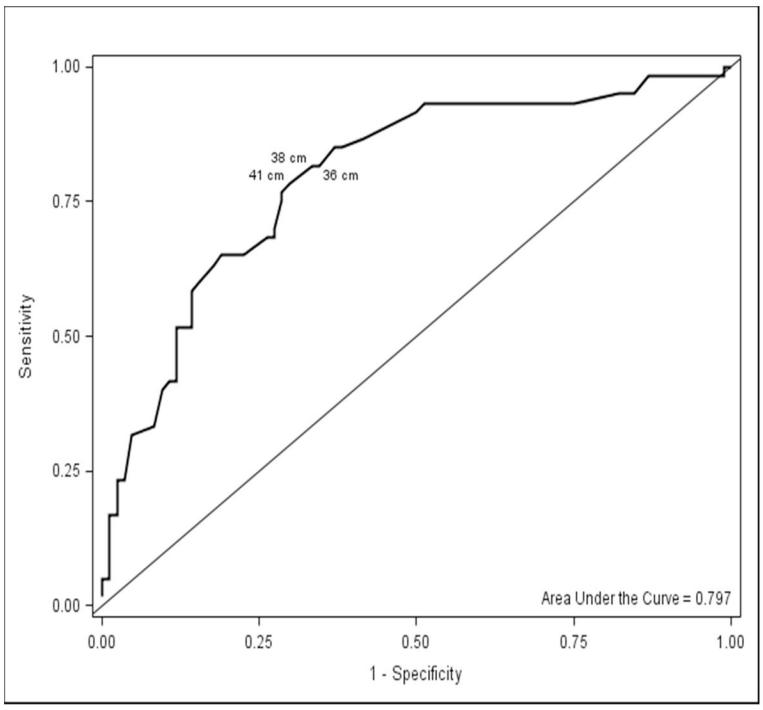

Figure 2.

Receiver operating characteristic curve analysis of threshold residual bowel length associated with achievement of enteral autonomy

The threshold of 41cm for residual bowel length yields the highest combined value of sensitivity (78.3%) and 1-specificity (29.8%). The thresholds of 36 cm and 38 cm have sensitivity of 81.7% and 34.5% and 33.3%, respectively.

Table 1

Baseline characteristics in 272 infants with intestinal failure.

Characteristic	N (%) or median (IQR)
Age at study entry (days)	63 (61, 73)
GA (weeks) (n=264)	34 (30, 36)
Months in study (n=271)	33.5 (16.2, 51.5)
Male sex	156 (57%)
Race (n=257)	
White	210 (82%)
Black	30 (12%)
Asian	13 (5%)
Other	1 (<1%)
Birth weight (kg) (n=221)	2.1 (1.2, 2.7)
Cholestasis at baseline (n=168)*	125 (74%)
Very low birth weight (≤1.5kg)	66 (30%)
Diagnosis	
NEC	76 (28%)
Gastroschisis	44 (16%)
Small bowel atresia	27 (10%)
Volvulus	30 (11%)
Long segment Hirschprung disease	11 (4%)
Tufting or microvillus inclusion disease	3 (1%)
Other single diagnoses	11 (4%)
Unknown	5 (2%)
Multiple Single Diagnoses	65 (24%)
Residual small bowel length (n= 144)	40.5 (25.0, 65.5)
Preserved ileocecal valve	133 (52%)

* Cholestasis defined as total bilirubin ≥ 5mg/dL or direct bilirubin ≥ 2mg/dL

Table 2

Bivariate relationships between select baseline demographic and clinical factors and the achievement of enteral autonomy in 272 children with intestinal failure.

Characteristic	Achieved enteral autonomy (n=118)	Did not achieve enteral autonomy (n=154)	p*
	[N (%) or median (IQR)]		
Gestational age (wks) (n=264)	34 (29, 36)	34 (31,36)	0.56
Gestational age <37 weeks (n=264)	88/117 (75.2%)	114/147 (77.6%)	0.66
Birth weight (kg) (n=221)	2.0 (1.2, 2.6)	2.2 (1.3, 2.8)	0.42
Birth weight <1.5 kg (n=221)	31/104 (29.8%)	32/117 (27.4%)	0.69
Male sex	54/118 (45.8%)	62/154 (40.3%)	0.36
Age at study entry (d)	63.5 (62, 74)	62.5 (61, 72)	0.04
Diagnosis of NEC	46/118 (39.0%)	30/154 (19.5%)	<0.001
Preserved ileocecal valve	72/112 (64.3%)	61/145 (51.8%)	<0.001
Colon in continuity with small bowel	55/112 (49.5%)	70/145 (48.3%)	0.89
Diagnosis of gastroschisis	31/118 (26.3%)	50/154 (32.5%)	0.27
Care at a transplant center	62/118 (52.5%)	117/154 (76.0%)	<0.001
Direct bilirubin at inclusion (n= 93)	2.3 (0.9, 4.0)	4.0 (2.5, 6.2)	0.001
Total bilirubin at inclusion (n= 131)	4.4 (2.6, 5.9)	6.3 (4.3, 8.5)	<0.001
Cholestasis** (n= 168)	62/89 (69.7%)	63/79 (79.8%)	0.13
Aspartate aminotransferase to platelet ratio (APRI) at inclusion (n= 127)	0.89 (0.48, 1.42)	1.43 (0.82, 2.59)	0.001
APRI > 1.5 (n= 127)	15/63 (23.8%)	30/64 (46.9%)	0.007
Human milk at baseline	20/118 (17.0%)	16/154 (10.4%)	0.11
Amino acid based formula at baseline	31/118 (26.3%)	50/154 (32.5%)	0.27
Bacterial overgrowth*** (n=265)	23/112 (20.5%)	29/153 (19.0%)	0.75
Residual small bowel length (cm) (n=144)	60 (40, 84.5)	28 (19, 50)	<0.001
No. of small bowel resections (n= 268)	1 (1, 2)	1 (1, 2)	0.35
Underwent intestinal lengthening procedure (n= 268)	7/117 (6.0%)	19/151 (12.6%)	0.07

* Calculated from Wilcoxon rank sum tests or chi-square tests as appropriate.

** Serum total bilirubin ≥ 5.0 mg/dL or direct bilirubin ≥ 2 mg/dL at baseline.

*** Use of antibiotics specifically for small bowel bacterial overgrowth was used as the metric to define bacterial overgrowth

Table 3

Results from bivariate and multivariable logistic regression modeling of demographic and clinical factors associated with achievement of enteral autonomy in children with intestinal failure (n=272). Model 1 includes data from all 272 children; model 2 includes only those children with intra-operatively measured residual small bowel length (n=144).

Model	Characteristics	Bivariate OR (95% CI)	P Value[1]	Multivariable OR (95% CI)	P Value[2]
Model 1: all children, n=272	NEC		0.005		0.004
	No	Reference		Reference	
	Yes	2.64 (1.53, 4.55)		2.42 (1.33, 4.47)	
	ITx Site		<0.001		<0.001
	Yes	Reference		Reference	
	No	2.86 (1.70, 4.79)		2.73 (1.56,4.78)	
	Preserved ICV		<0.001		<0.001
	No	Reference		Reference	
	Yes	2.48 (1.49, 4.12)		2.80 (1.63, 4.83)	
Model 2: measured bowel length, n=144	NEC		0.002		0.009
	No	Reference		Reference	
	Yes	3.22 (1.54,6.73)		3.44 (1.36, 8.71)	
	ITx Site		<0.001		<0.001
	Yes	Reference		Reference	
	No	7.91(3.44,18.18)		6.56 (2.53,16.98)	
	Residual small bowel length	1.04 (1.03,1.06)	<0.001	1.04 (1.02,1.06)	<0.001
	Preserved ICV		0.02		0.36
	No	Reference		Reference	
	Yes	2.21(1.12, 4.34)		1.52 (0.62, 3.74)	

[1] OR (95% CI) and p-value obtained from separate logistic regression models with each characteristic considered as a single predictor of achievement of enteral autonomy.

[2] OR (95% CI) and p-value obtained from multivariable logistic regression model with all characteristics considered as predictors of achievement of enteral autonomy. Variables selected for inclusion in the model using a forward-selection type model building procedure, beginning by ranking the variables by significance level. Model includes only those children with intraoperatively measured residual small bowel length.