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Post-operative Enteral Nutrition Guidelines Reduce the Risk of Intestinal Failure-associated Liver Disease in Surgical Infants

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Abstract

Objective—To assess the effectiveness of post-operative feeding guidelines in reducing the incidence and severity of intestinal failure-associated liver disease (IFALD) among infants.

Study design—Two cohorts of infants <6 months old undergoing intestinal surgery were compared: pre-guideline (retrospective data from 2007-2013; n=83) and post-guideline (prospective data from 2013-2016; n=81). The guidelines included higher initial enteral nutrition volumes of 20 ml/kg/day and daily feeding advancement if tolerated. The primary outcomes were IFALD incidence (peak direct bilirubin [DB] >2mg/dl) and severity (DB>5 mg/dl for moderate-severe). Multiple logistic regression was used to determine the odds of developing IFALD. Other outcomes were time to reach 50% and 100% goal calories from EN, and the incidence of necrotizing enterocolitis (NEC) after feeding.

Results—The incidence of IFALD decreased from 71 to 51% ($P = .031$), and median peak DB decreased from 5.7 to 2.4 mg/dl ($P = .001$). After adjusting for diagnosis and prematurity, the odds of developing IFALD of any severity were reduced by 60% (OR: 0.40, 95% CI: 0.20-0.85) and the odds of developing moderate-to-severe IFALD were reduced by 72% (OR: 0.28, 95% CI: 0.13-0.58) with guideline use. Time to reach 50% EN decreased from a median of 10 to 6 days ($P = 0.020$) and time to reach 100% EN decreased from 35 to 21 days ($P = 0.035$) with guideline use. The incidence of NEC after initiating EN did not change (5 vs 9%, $P = 0.346$).

Conclusions—Implementation of feeding guidelines reduced time to reach feeding goals, significantly reducing IFALD incidence and severity.

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Keywords

short bowel syndrome; gastroschisis; atresia; necrotizing enterocolitis; cholestasis; feeding protocol

The optimal strategy for feeding infants after intestinal procedures for primary gastrointestinal disorders is not well understood, resulting in feeding variability as well as feeding-related risks, such as necrotizing enterocolitis (NEC).(1, 2) Feeding intolerance from intestinal dysmotility can be difficult to distinguish from the early signs of NEC, resulting in apprehension about feeding advancement in this fragile population. Minimal enteral nutrition (EN) volumes (<20 ml/kg/day), or “trophic feeding,” with subsequent cautious EN advancement are often employed as a means to stimulate the intestine but provide minimal calories, requiring parenteral nutrition (PN) for adequate caloric intake. Infants exposed to prolonged PN are at risk of complications, including central venous catheter-associated line infection and intestinal failure-associated liver disease (IFALD).(3–5)

IFALD typically manifests as cholestasis in infants.(6, 7) IFALD remains common following intestinal surgery, with an incidence ranging from 25–60% depending on the center, and up to 70% in infants with NEC.(8–10) For infants with intestinal failure, requiring PN for >30–60 days, IFALD becomes a significant risk factor for chronic liver disease and the need for liver transplantation.(11) The etiology of IFALD is multi-factorial, and is related to prematurity, prolonged PN exposure, lack of EN, and infection. As it is often unclear in the immediate post-operative period which infants will meet criteria for intestinal failure, carefully optimizing EN in all at-risk infants is advisable.

Historically, our institution had a high incidence of IFALD and variable feeding practices, prompting the creation of a post-operative feeding algorithm.(12) Our objective was to determine if adherence to feeding guidelines would shorten the time to reach enteral nutrition goals, which would in turn decrease PN exposure, and therefore, decrease IFALD incidence and severity, the primary outcomes of interest. Our feeding algorithm, implementation strategy, and interim success 15 months after implementation were previously reported.(13) In this study, we report our outcomes in an expanded cohort 6 years prior and 3 years after implementation of the feeding guidelines.

METHODS

We performed a pre- and post-guideline implementation comparison. Retrospective data were collected for the pre-guideline cohort from January 2007–June 2013, and prospective data were collected for the post-guideline cohort from October 2013–December 2016. Approval and waiver of consent were obtained from the Institutional Review Board, as the feeding guidelines were implemented as standard of care in the neonatal intensive care unit (NICU). Inclusion criteria were infants <6 months old at risk of intestinal failure due to intestinal surgery, who survived to be fed enterally, and required at least 7 days of PN (based on our observation of early cholestasis development in some infants). The primary diagnoses were NEC, spontaneous intestinal perforation (SIP), intestinal atresia, gastroschisis, and

volvulus. Infants were excluded if they had liver disease other than IFALD or if the primary surgical procedure was performed at an outside facility.

Consensus- and evidence-based guidelines were developed by our Intestinal Rehabilitation team, and have been previously published.(13) Major changes in the guidelines, compared with previous usual care, included a higher initial post-operative EN volume of 15-20 ml/kg/day and faster rate of feeding advancement by the same volume if there were no signs of intolerance (increased ostomy or stool output, increased emesis, increased abdominal girth of >10%, or change in vital signs). Exceptions included infants <1000 g who were not previously fed. Such infants followed another protocol prescribing 1-2 ml of feeding every 4 hours for 5 days, and then subsequently followed the post-operative guidelines. Breast milk, including donor milk, was the preferred type of EN, but formula could be used. The individualized goal caloric requirement generally ranged from 110-130 kcal/kg/day and was determined by a dietician based on gestational age and growth.

Only soy-based intravenous lipid was available at our center. PN lipid dosing remained the same in both study periods. The lipid dose was increased to 3g/kg/day in all non-cholestatic infants in both cohorts to meet caloric needs unless there were extenuating circumstances, such as hypertriglyceridemia. Lipids were restricted if the direct bilirubin rose to 2mg/dl.

Data Collection and Metrics

Demographic and clinical/surgical data were collected from the medical record. Initial feeding data included the first date, type, route, and volume (ml/kg/day) that enteral nutrition was attempted post-operatively. Weekly data included type, volume, and percent of calories of EN, PN lipid dose, weight and z-score, stool output, and laboratory values. The daily volume of first post-operative feeding and rate of advancement were used to monitor adherence to guidelines.

The primary outcomes were the incidence and severity of IFALD, defined as a direct bilirubin of 2mg/dl that persisted for at least 1 week in the absence of other known liver disease.(6) Mild IFALD was defined as direct bilirubin of 2-4.9mg/dl, moderate IFALD was defined as a peak direct bilirubin 5.0-9.9mg/dl, and severe IFALD was defined as a peak direct bilirubin 10 mg/dl.(14, 15) Feeding outcomes included time (days) to reach 50% EN (>60 ml/kg/day with weaning PN) and 100% EN (>120 ml/kg/day EN with discontinuation of PN) from both the time of surgery and from the time of the first post-operative feeding. Other secondary outcomes included achievement of 50% EN within 7 days (established a priori based on clinical expectation of tolerance), mortality, total number of PN days, culture-positive infection (blood, urine, or peritoneal fluid), NEC after post-operative feeding, length of stay, discharge weight z-score, and time to resolution of IFALD if it occurred.

Statistical Analyses

A sample size of 140 (70 per group) was estimated to detect a 20% improvement in IFALD incidence with 80% power and a type 1 error rate of 5%. We had 90% power (alpha=0.05) to detect a 20% improvement in incidence of moderate-severe IFALD.

Fisher exact tests were used to compare differences in categorical variables. Non-parametric Wilcoxon rank-sum tests were used to compare medians, and t-tests compared normally distributed means of continuous variables. Multivariable logistic regression was used to examine the associations between IFALD (any severity, moderate-severe, and severe) and exposure to feeding guidelines, with adjustment for clinically and statistically significant variables (from univariate analysis). A priori, diagnosis and gestational age were considered the most clinically relevant characteristics. Variables with a p-value of <0.1 were explored for use in the final model. Several variables were collinear and could not be used in the same model (type of surgery with diagnosis, age of surgery with diagnosis, baseline direct bilirubin with diagnosis, gestational age with birth weight). Diagnosis (NEC/SIP, gastroschisis, atresia, and other) and prematurity (gestational age <37 weeks) were the most clinically relevant and representative of the other variables, so were therefore used in the final model, along with race (white, black, and other) and sex. Model fit was evaluated with Akaike information criterion. All infants were included in the primary analysis. Missing data was assumed to be missing at random. Kaplan-Meier survival curves were used to compare times to reach events (50% EN, 100% EN, and resolution of IFALD) between those in the pre- and post-guideline cohorts. Non-overlapping confidence intervals were considered significant. Significance testing was also performed using the log-rank test for equality of survivor functions. Statistical testing was two-sided, and P-values <0.05 were considered statistically significant. Analyses were performed with STATA (StataCorp, 2011. Stata Statistical Software: Release 12. College Station, Texas: StataCorp LP).

RESULTS

In the pre-guideline cohort, 83 infants were included, and 81 infants were included in the post-guideline cohort. Fifty-seven pre-guideline and 33 post-guideline subjects were included in a previously published analysis.⁽¹³⁾ Baseline characteristics of both cohorts are described in Table 1. The difference in initial surgical procedures between cohorts was due to the more frequent use of peritoneal drains in infants with NEC or SIP prior to resection in the post-guideline cohort, compared with the more frequent ostomy use in these infants pre-guidelines, but the ultimate length of resection and percent residual bowel was similar between groups.

IFALD Incidence and Severity

The cumulative incidence of IFALD was lower in the post-guideline cohort compared with the pre-guideline cohort (51 vs. 71%, $P=0.031$), as were the odds of developing IFALD (odds ratio [OR] 0.40, $P=0.017$), even after adjusting for diagnosis, prematurity, sex, and race (Table 2). The adjusted odds of developing the more clinically relevant moderate-severe IFALD (DB ≥ 5 mg/dl) was also significantly reduced (OR 0.28, $P=0.001$) with guideline use. We performed a sensitivity analysis replacing diagnosis with the initial type of procedure in the multivariable analysis. The association between feeding guideline use and the outcome remains the same (OR 0.34, $P=0.004$) (Table 3; available at www.jpeds.com).

The median peak direct bilirubin decreased with guideline use from a baseline to 5.7mg/dl to 2.4mg/dl ($P=0.001$). Among those infants who developed IFALD, resolution of IFALD by

time of discharge was more likely to occur in the post-guideline cohort, 66% vs. 25% ($P<0.001$). Time to resolution was also reduced among those in the post-guideline cohort (Figure 1). The median discharge direct bilirubin was 0.8 mg/dl (0.3-1.9) in the post-guideline group, compared with 2.4 mg/dl (0.6-4.8) in the pre-guideline cohort ($P<0.001$). Ursodiol use was less among infants with IFALD in the post-guideline cohort, 21 (51%) vs. 42 (71%) ($P=0.032$).

Moderate-to-severe IFALD was most commonly found in infants with NEC or SIP. However, fewer infants in the post-guideline cohort with NEC/SIP developed moderate-to-severe IFALD, 13 (45%) vs. 33 (73%) ($P=0.016$). The median peak direct bilirubin for infants with NEC/SIP improved from 6.7 to 3.4 ($P=0.006$) with use of the guidelines. In the post-guideline cohort, infants with these diagnoses were prone to both feeding intolerance, as well as deviations from the guidelines prior to documented feeding intolerance. The median peak direct bilirubin was 5.3 mg/dl (2.8-10.7) among those with guideline deviations ($n=8$) versus 2.8 mg/dl (0.8-6.0, $P=0.008$) among those without deviations ($n=21$).

Feeding Outcomes and Adherence to Guidelines

Faster achievement of 50% and 100% of EN goals was seen in the post-guideline cohort compared with the pre-guideline cohort among those who were able to achieve these goals (Figure 2). The time to reach 50% enteral nutrition from the start of feeds decreased from a median of 10 to 6 days in post-guideline cohort ($P=0.020$). The time to reach 100% EN decreased from 35 days in the pre-guideline cohort to 21 days in the post-guideline cohort ($P=0.035$). As a measure of protocol adherence, the volume of the initial post-operative feeding increased from a median of 10 to 20 ml/kg/day ($P<0.001$). In the post-guideline cohort, only 2 infants did not tolerate the first 24 hours of EN and had feeds held (one started at 20 ml/kg/day and one started at 10 ml/kg/day). The odds of reaching 50% of EN within 7 days of starting EN were significantly higher in the post-guideline cohort (Table 2), even after adjusting for diagnosis and prematurity.

Breast milk was the initial type of EN used most frequently, 80% in the post-guideline cohort and 65% in the pre-guideline cohort ($P=0.011$). By discharge, breast milk was used in about 40% of both cohorts ($P=0.635$). The remainder of the post-guideline cohort was discharged with regular (32%), hydrolysate (14%), or elemental (16%) formula. Continuous feeding was initiated more frequently in the post-guideline cohort, 51% vs 32% ($P=0.022$). The mode of feeding (bolus vs. continuous) was not specified in the guidelines, and this difference is a likely reflection of provider preference and increased number of patients with gastroschisis, who are more prone to vomiting. Re-feeding via mucous fistula was not common in either cohort (6 vs 11%, $P=0.391$).

Guideline deviations were defined by either using a lower than recommended initial post-operative feeding volume or lack of advancement in the absence of signs of intolerance. A total of 20 infants had one or more deviations. There were 15 volume deviations and 12 advancement deviations. Nearly half of the deviations (45%) occurred in the initial few months prior to implementation of weekly multi-disciplinary rounds. The other deviations occurred at sporadic time points, but were most likely to occur in premature infants with an initial diagnosis of NEC or SIP (40% of deviations).

Other Outcomes

The adjusted odds of developing secondary outcomes for infants in the post-guideline cohort are also displayed in Table 2.

Seven infants in the post-guideline cohort and 4 infants in the pre-guideline cohort developed post-operative NEC ($P=0.364$). The original diagnoses were SIP (4), NEC (3), atresia (2), gastroschisis (1), and meconium ileus (1). Medical NEC (Stage II) occurred in 7 (63%) infants, and 4 (36%) developed surgical NEC (Stage III). Fewer infants in the post-guideline cohort had a positive blood, urine, or peritoneal culture. Three infants in each cohort had a positive culture around the time of surgery. All of the other positive cultures occurred at least 1 week after surgery.

The total days of PN use were decreased in the post-guideline cohort, 29 days (17–65) vs. 52 days (18–99, $P=0.037$). The number of infants who were discharged home on PN was 5 (6%) in the post-guideline cohort and 12 (14%) in the pre-guideline cohort ($P=0.122$). The median lipid dose was 3g/kg/day in the early post-operative period in both the pre- and post-guideline cohorts (IQR 2–3 and 2.5–3, respectively; $P=0.08$). Of the 100 infants who developed IFALD, 92% (92%) underwent lipid restriction within the week following diagnosis. The average lipid dose the week following the onset of cholestasis was 1.7g/kg/day (± 0.11) in the pre-guideline cohort and 1.2g/kg/day (± 0.12) in the post-guideline cohort ($P=0.005$).

Length of stay was similar between cohorts (57 days (27–106) vs. 80 days (33–124); $P=0.145$), even when stratified by prematurity. In a subanalysis by diagnosis, there was a significantly shorter length of stay only among those with gastroschisis, 50 (27–66) days vs 95 (66–139) days ($P=0.008$). Weight gain was similar in both cohorts, with a median discharge weight z-score of -1.0 (-1.7 – 1.2) in the post-guideline cohort and -1.4 (-2.0 – 1.3) in the pre-guideline cohort ($P=0.052$). Weight z-scores of <-2.0 represent the bottom 5th percentile. Nineteen infants (23%) had a discharge weight z-score <-2.0 (range -5.1 – 2.1) prior to the guidelines, compared with 9 (11%) in the post-guideline cohort.

Both mortality (3 vs 4; $P=0.718$) and need for intestinal transplant referral (1 vs 1; $P=1.000$) were relatively rare and similar between cohorts.

Missing Data

Baseline direct bilirubin, but not total bilirubin, was missing from 17 infants (10%). The baseline direct bilirubin was highly correlated with the diagnosis (the more clinically relevant variable). Direct bilirubin was therefore not included in the final analysis, and missing values did not affect the analysis. Missing feeding data from the pre-guideline cohort included 4 infants (5%) without the date of post-operative EN initiation, 30 infants (36%) without the first post-operative EN volume, 26 infants (31%) without the known date to reach 50% EN. Discharge growth measures were missing from 7 (8%) in the pre-guideline cohort.

DISCUSSION

IFALD remains a common complication in infants following intestinal surgery. The diagnosis of IFALD includes a wide range of direct bilirubin values, and the clinical significance of IFALD is associated with cholestasis severity. Infants with more severe cholestasis are at higher risk of chronic liver disease, and ultimately at a higher risk of needing liver transplantation, particularly if PN cannot be discontinued.(11, 16) Optimizing EN reduces the risk of IFALD, and feeding guidelines offer a systematic approach to feeding by reducing variability. After implementing post-operative feeding guidelines in our NICU, we have seen faster achievement of enteral feeding goals and reduced frequency and severity of IFALD.

The odds of developing at least moderately severe IFALD, a more clinically germane complication, were reduced by 72% in the post-guideline cohort compared with the pre-guideline cohort, and this difference remained significant with adjustment for diagnosis and prematurity. Severe cholestasis was rare in the post-guideline cohort. Infants in the post-guideline cohort who did develop IFALD were more likely to have resolution of cholestasis prior to discharge and resolution occurred more quickly compared with the pre-guideline cohort.

Feeding guidelines are becoming common in the NICUs to balance the benefits of EN with the risk of NEC in high-risk infant populations.(17, 18) Minimal EN regimens (trophic feeding) are often used in high risk patients, however broad ranges in trophic volumes (5-20 ml/kg/day) make studies of feeding practices difficult to compare to determine the ideal volume and duration of minimal EN.(19) A study of premature infants showed early feeding (within 48 hours of birth) improved feeding tolerance and decreased exposure to PN, without an increase in NEC.(20) In infants with very low birth weight or congenital heart disease, both at higher risk for NEC, feeding protocols resulted in faster achievement of EN goals without increased NEC.(21–23) The American Society for Parenteral & Enteral Nutrition (ASPEN) found sufficient evidence to support early initiation of EN and advancing by 30 ml/kg/day in non-surgical infants at-risk for NEC.(24) For surgical infants, a recent systematic review found improved outcomes in general when care was provided by multi-disciplinary intestinal rehabilitation team focused on nutrition support, but best practices for post-operative feeding have not yet been determined.(25)

The ideal “minimum” volume of EN needed to offer protection from IFALD in surgical infants is not known. In our pre-guideline cohort, infants were routinely kept on prolonged trophic volumes of EN (<20 ml/kg/day), and the incidence of IFALD was 70%. The incidence of moderate-to-severe cholestasis was 56%. In devising the guidelines, we hypothesized that 50% EN would be more protective against IFALD than trophic volumes. This goal volume was based on anticipated clinical tolerance, ability to wean PN calories at this volume, and our previous data suggesting protection from IFALD among infants fed more quickly. Although the study does encompass a heterogeneous group of infants, we believe the general principles for initiation and early advancement of EN are applicable to most infants with intestinal surgery. Nearly all infants tolerated an initial post-operative feeding volume of 20 ml/kg/day and were able to tolerate daily advancement of 20

ml/kg/day up to 60-80 ml/kg/day (50% of goal EN volume), even among infants <1000g. The ability to advance EN beyond 50% of goal calories was highly individualized and affected by motility, malabsorption and other co-morbidities that affect critically ill infants.

The incidence of NEC in the post-operative period was monitored as a potential adverse event of enteral feeding. NEC occurs in 2-7% of NICU admissions, most commonly in preterm infants.(26, 27) NEC recurs in 10% of infants.(26, 28) NEC has also been reported in 10-20% of infants with gastroschisis.(29) Careful monitoring with all feeding advancement is therefore necessary. Although not statistically different from the pre-guideline cohort or national norms, 7 cases of NEC occurred after post-operative feeding in the post-guideline cohort, three of which were fatal. The overall mortality was not different between cohorts (4% vs 5%). One such infant with NEC totalis was not being fed at the time, and two infants had already achieved 100% EN volume with fortification to 22 kcal/oz. Our guidelines do not specifically give recommendations for fortification, but a hydrolysate formula was frequently used. Strategies for fortification in infants at risk of NEC are currently debated in the literature without clear best practices.(30)

Other factors may have also affected severity of IFALD in our study, including the reduced infection rate in the post-guideline cohort. The difference in infection (positive culture in blood, urine, or peritoneal fluid) between cohorts is likely multi-factorial. Attention to central line care has improved in recent years. Additionally, improved EN promotes intestinal mucosal barrier function, thereby reducing intestinal bacterial translocation and reducing the risk of infection.(31, 32) Faster achievement of EN allows for sooner discontinuation of PN and the central catheter, also reducing risk. A potential modifying effect on IFALD severity cannot be entirely excluded, as infection can also cause elevation of bilirubin.

The limitations of the study include a relatively small sample size to adjust for potential confounders, and the data are from a single center. Due to chance, there was heterogeneity in diagnoses between cohorts, though not statistically significant. Gestational age and birth weight were very similar between cohorts. Our baseline IFALD risk was higher than the incidence reported at other centers. Nonetheless, we have seen continued improvement in outcomes once guideline adherence was achieved. Infants with intestinal failure typically require PN for at least 30 days; however, we included all infants with at least 7 days of PN as we have observed early development of cholestasis within 10 days in some infants. We were also suspicious that not all infants with prolonged PN use in the pre-guideline cohort truly had a prolonged PN requirement due to feeding intolerance, but rather feeding advancement was not attempted. The median total PN use was just under 30 days in the post-guideline cohort, and we believe that without the feeding guidelines those infants would have been on PN for a longer period of time, making them appear “sicker.” There were a similar number of subjects in each cohort who received PN for less than 14 days (15 subjects in the pre-guideline cohort and 13 in post-guideline cohort). Overall, the length of resection in both cohorts was relatively short. In a cohort of only infants with more substantial resection, the results of the feeding intervention may not be the same. Further studies are in progress with another site to test the generalizability of the guidelines, and will allow for

further risk stratification by diagnosis and other risk factors. As we collect more data, more refined strategies for EN advancement are also expected to emerge.

In conclusion, our post-operative feeding guidelines have been well tolerated. Guideline use has resulted in shorter times to initiate post-operative EN and reach 50% of the goal EN volume. With faster achievement of EN goals, we have seen a significant reduction in both overall IFALD incidence, as well as IFALD severity.

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Abbreviations

DB	direct bilirubin
EN	enteral nutrition
IF	intestinal failure
IFALD	intestinal failure-associated liver disease
NEC	necrotizing enterocolitis
PN	parenteral nutrition
SIP	spontaneous intestinal perforation

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Figure 1.

The time to resolution of intestinal failure-associated liver disease (IFALD) from the date of first occurrence was shorter in the post-guideline cohort ($P<0.001$).

Figure 2.

A. The time to reach 50% enteral nutrition (EN) was shorter in the post-guideline cohort ($P<0.001$). B. The time to reach 100% enteral nutrition (EN) was shorter in the post-guideline cohort ($P<0.001$).

Table 1

Demographic, Baseline, & Surgical Characteristics

	Pre-Guidelines N=83 ^a	Post-Guidelines N=81 ^a	P [*]
Demographics			
Male (%)	51 (61)	43 (53)	0.344
Ethnicity (% Hispanic)	4 (5)	5 (6)	0.746
Race (%)			0.406
Black	36 (43)	35 (43)	
White	38 (46)	41 (51)	
Other	9 (11)	5 (6)	
Gestational age, weeks, median (IQR)	33.0 (27.1–37.0)	34.4 (26.2–37.0)	0.842
Birth weight, g, median (IQR)	1610 (920–2575)	2035 (795–2700)	0.720
Birth weight z-score, median (IQR)	−0.1 (−0.8–0.9)	−0.2 (−0.8–0.4)	0.279
Baseline Characteristics			
Primary Diagnosis (%)			0.197
Atresia	15 (18)	21 (26)	
Gastroschisis	14 (17)	19 (23)	
NEC	30 (36)	15 (19)	
SIP	15 (18)	14 (17)	
Volvulus	2 (3)	3 (4)	
Other	7 (8)	9 (11)	
Age of first feed, days, median (IQR)	8 (3–18)	9 (3–14)	0.634
Pre-operative PN days, median (IQR)	5 (1–12)	4 (1–7)	0.136
Baseline DB mg/dl, median (IQR)	0.5 (0.3–1.5)	0.4 (0.2–0.7)	0.040
Surgical Characteristics			
Age at surgery, days, median (IQR)	7 (3–16)	5 (3–9)	0.124
Initial procedure (%)			0.001
Peritoneal Drain	3 (4)	13 (16)	
Resection/anastomosis	24 (29)	24 (30)	
Resection/ostomy	26 (31)	19 (23)	
Ostomy/no resection	17 (21)	4 (5)	
Abdominal wall closure	12 (15)	21 (26)	
Subsequent Procedures (%)			
Resection/anastomosis	26 (31)	6 (8)	<0.001

	Pre-Guidelines N=83^a	Post-Guidelines N=81^a	P[*]
Resection/Ostomy	6 (7)	8 (10)	0.587
Abdominal wall closure	3 (4)	2 (3)	1.000
Ostomy reversal (<i>>1 choice possible</i>)	34 (41)	16 (20)	0.004
Total resection length ^b , median cm (IQR)	12 (5–17)	10 (5–25)	0.677
Residual bowel ^a , percent (IQR)	92 (71–97)	89 (75–95)	0.966
Ileocecal valve present (%)	65 (78)	65 (80)	0.348
Colon preserved (%)	74 (89)	76 (93)	0.313

Abbreviations: IQR, interquartile range; PN, parenteral nutrition; DB, direct bilirubin

^a57 and 33 subjects, respectively, were part of a previous cohort

^bIf resection occurred (N=67 historical and N=33 guidelines)

^{*}P-values from Wilcoxon rank-sum and Fisher's exact tests

Table 2

Univariate and multivariable logistic regression of primary and secondary outcomes

	Pre-Guidelines N (%)	Post-Guidelines N (%)	OR (CI)	P	Adjusted OR* (CI)	P
Primary Outcomes						
IFALD (DB>2mg/dl)	59 (71)	41 (51)	0.42 (0.22–0.79)	0.008	0.40 (0.20–0.85)	0.017
Moderate-Severe IFALD (DB>5mg/dl)	46 (56)	22 (27)	0.29 (0.15–0.56)	<0.001	0.28 (0.13–0.58)	0.001
Severe IFALD (DB>10mg/dl)	16 (20)	6 (7)	0.33 (0.12–0.89)	0.029	0.31 (0.11–0.89)	0.029
Secondary Outcomes						
50% EN ^a <7 days	19 (23)	49 (60)	5.16 (2.62–10.17)	<0.001	6.03 (2.78–13.06)	<0.001
Resolved IFALD	15 (25)	27 (66)	5.65 (2.36–13.5)	<0.001	7.77 (2.85–21.1)	<0.001
Post-op NEC	4 (5)	7 (9)	1.8 (0.53–6.73)	0.324	1.9 (0.51–7.16)	0.339
Positive Culture	34 (41)	14 (17)	0.30 (0.15–0.62)	0.001	0.29 (0.13–0.66)	0.003
Mortality	3 (4)	4 (5)	1.38 (0.30–6.39)	0.676	2.96 (0.48–18.0)	0.240

Abbreviations: OR, odds ratio, CI confidence interval, IFALD, intestinal failure-associated liver disease, DB, direct bilirubin, EN, enteral nutrition, NEC, necrotizing enterocolitis, PN, parenteral nutrition

* Adjusted for diagnosis (necrotizing enterocolitis/spontaneous intestinal perforation, gastroschisis, atresia, and other), prematurity (gestational age <37 weeks), sex, and race (Black, White, Other)

^aTime to reach 50% EN from initial post-operative EN. Similar results seen to time to reach 50% EN from date of surgery

Comparison of multivariate logistic regression using diagnosis versus initial procedure in the development of intestinal failure associated liver disease

Table 3

Variable	Adjusted OR (CI)	P	Variable	Adjusted OR (CI)	P
Enrolled in guidelines	0.40 (0.19–0.85)	0.017	Enrolled in guidelines	0.33 (0.15–0.71)	0.004
Diagnosis		0.064	Initial Procedure		0.312
NEC/SIP	Ref		Peritoneal drain	Ref	
Atresia	0.28 (0.20–0.75)		Resection/anastomosis	0.24 (0.05–1.05)	
Gastroschisis	0.57 (0.06–1.57)		Resection/ostomy	0.52 (0.12–2.33)	
Other	0.33 (0.11–1.05)		Ostomy alone	0.41 (0.07–2.27)	
			Abdominal closure	0.42 (0.09–1.89)	
Prematurity	3.25 (1.40–7.54)	0.006	Prematurity	4.30 (1.92–9.58)	0.001
Sex (male)	1.0 (0.48–2.10)	0.991	Sex (male)	0.93 (0.45–1.55)	0.434
Race		0.672	Race		0.618
Black	Ref		Black	Ref	
White	0.87 (0.41–1.86)		White	0.73 (0.34–1.54)	
Other	0.53 (0.14–2.12)		Other	0.58 (0.15–2.23)	