OPTIMIZING NUTRITION IN INFANTS AT RISK OF INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE

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Abstract

Statement of Problem: Infants undergoing intestinal surgery are at risk for feeding intolerance and resultant complications, including intestinal failure and intestinal failure-associated liver disease (IFALD). In infants, IFALD is defined as a persistent direct bilirubin (DB) >2mg/dl for >1 week in the setting of parenteral nutrition (PN) and can lead to liver failure. The optimal strategy for feeding post-operative infants to reduce PN exposure is poorly understood. We hypothesized that a more systematic approach to providing enteral nutrition (EN) would reduce the risk of IFALD.

Methods: We conducted three studies: 1) A retrospective descriptive analysis of the baseline feeding practices and incidence of IFALD among surgical infants in the Neonatal Intensive Care Unit, 2) An interval analysis (pre- and post-intervention) 15 months after implementation of newly devised feeding guidelines using run-charts to measure adherence to feeding recommendations and peak direct bilirubin in real-time, and 3) A final analysis 2.5 years after guideline implementation to measure the overall impact of the feeding guidelines on IFALD incidence and severity using logistic regression.

Results: We identified variable feeding practices and a high baseline incidence of IFALD, 66% (confidence interval [CI] 0.55 - 0.76) among all surgical infants and 90% (CI 0.78 – 1.01) among those needing >60 days of PN from 2007-2012. In the 15-month post-guideline analysis, a shift to reduced time to reach feeding goals (initiation and 50% EN) and decreased peak DB were seen on run-charts. In the final analysis, the initial post-operative EN median volume increased from 10 to 20 ml/kg/day (P=0.001). Time to reach 50% EN decreased from a median of 10 to 5 days (P=0.013). The overall incidence of IFALD improved from 71 to 53% in infants needing >7 days of PN (P=0.03), and the median peak DB decreased from 5.7 to 2.3 mg/dl (P=0.003). The adjusted odds for developing moderate-severe IFALD were reduced by 67% in the post-guideline cohort, compared to the pre-guideline baseline (P=0.002).

Conclusions: The feeding intervention was well tolerated and resulted in shorter time to initiate EN and reach 50% of goal EN post-operatively. The incidence and severity of IFALD also improved.

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Preface

It is with great honor that I submit this thesis to the Johns Hopkins University Bloomberg School of Health. This thesis is dedicated to my husband, Jaimie Shores, and my parents, Camille and the late Louis Roye, who have been and continue to be a great source of strength and support.

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CHAPTER 1: INTRODUCTION

The Impact of Intestinal Surgery in Infants

Infants requiring intestinal surgery are at risk of multiple complications, including severe malabsorption and dysmotility that results in intestinal failure (IF). IF is the inability of the intestine to absorb sufficient fluid, nutrients, and calories, and requires parenteral nutrition (PN) to meet metabolic demands and sustain growth. Dependence on parenteral nutrition (PN) for at least 30-60 days is needed to meet the definition of IF. IF occurs in up to 24 per 100,000 live births and is associated with high rates of morbidity and mortality.[1,2] IF patients have prolonged hospitalizations, with estimated costs over $500,000 in the first year of life and approaching $1.6 million by five years of age.[3] Children requiring home PN have more frequent ambulatory visits, hospital admissions, and total care costs compared to those not requiring PN.[4] Children with IF are also at risk for neurodevelopmental delay.[5]

The most common etiology of IF in infants is surgical intestinal resection (short bowel syndrome), and the most common reason for intestinal resection is necrotizing enterocolitis (NEC), which can result in massive intestinal necrosis. Despite numerous advances in neonatal intensive care, NEC continues to affect 7% of preterm infants and remains a highly morbid condition.[6,7] Other etiologies of IF in the infant population are spontaneous intestinal perforation (SIP), gastroschisis, intestinal atresia, volvulus, omphalocele, and Hirschsprung's disease.

One of the most common complications of IF is intestinal failure-associated liver disease (IFALD). As IFALD manifests as cholestasis in infants, a general definition is persistent direct bilirubin >2mg/dl for > 1 week in the setting of PN use and absence of other liver disease.[8,9] The terminology has changed over the years to better reflect the multi-factorial process associated with IFALD, and it has previously been known as PN-associated cholestasis (PNAC) and PN-associated liver disease (PNALD). Cholestasis can occur in less than 14 days of PN exposure.[10]

IFALD is common, occurring in 25-60% of surgical infants, but occurs in up to 80% of infants with necrotizing enterocolitis (NEC).[10-13]

IFALD is a significant burden for surgical infants. Chronic liver disease may develop in up to two-thirds of neonates with IF.[11] Liver failure develops in 25-40% of patients with IF after bowel resection, who ultimately require liver or liver/bowel transplantation.[14] Over 900 pediatric patients were listed for combined liver and bowel transplantation from 1987-2004.[15] The mortality of IFALD alone can be 10-15% in the non-transplanted population.[2,16] In the immediate post-operative period, anticipating which infants will develop IFALD is difficult. Furthermore, even if serum bilirubin and transaminases normalize after IFALD, liver fibrosis may continue to progress to cirrhosis, especially in infants still requiring PN.[17,18] It is therefore prudent to reduce IFALD risk in all surgical infants.

The Etiology of IFALD

IFALD is a multifactorial process most impacted by 1) chronic exposure to the hepatotoxic effects of PN, 2) insufficient EN, which alters gut barrier function and disrupts immune function, and 3) systemic inflammation, including infection (Figure 1).[11,19-22] Currently, the only intravenous lipid preparation approved by the Federal Drug Administration is a soy-derived preparation rich in linoleic acid, a fatty acid that is readily metabolized along the arachidonic pathway into pro-inflammatory eicosanoids. Soy based lipids also contain phytosterols which have been shown to have direct toxic effects on the liver. These plant sterols accumulate in the liver of patients with intestinal failure and are correlated with liver injury.[23] Limiting the dose and frequency of exposure soy lipids has reversed IFALD in some cases.[24,25] Complete removal of lipids from PN is imprudent, as essential fatty acids are crucial for growth and development. Other surgical factors that contribute to risk of IFALD include absence of an ileocecal valve and the length of remaining bowel.[26]

Prematurity and low birth weight are both risk factors for IFALD.[27,28] These infants typically receive PN within the first 1-2 days of life to prevent growth failure. They are also susceptible to multiple feeding interruptions requiring ongoing PN supplementation, so the cumulative exposure to PN is greater than term infants.[29] The immature livers of preterm infants are less able to process the toxic components of PN, and the enterohepatic bile circulation may not be fully developed.[28,30] Given their lengthier hospitalizations compared to term infants, preterm infants are at greater risk for infection, especially catheter related blood stream infections.[31] Preterm infants are also at higher risk of developing NEC.

The Benefits of Enteral Nutrition

Enteral nutrition (EN) is necessary for both preventing and reversing IFALD by maintaining a normal intestinal barrier function.[32,33] When functioning normally, tight junctions between intestinal cells form a physical barrier that keep commensal bacteria, pathogens, ingested food, and other antigens within the intestinal lumen.[34] The intestine has a direct role in immune modulation, and tolerance is regulated by "sensing" the microbial milieu and presenting antigens to innate and adaptive immune cells.[35] Injury to the intestine disrupts the mucosal barrier, leading to inflammation, antigen permeability, microbiome alteration, and bacterial translocation, all of which increase immune activity.[36] In animal models of bowel resection, radiolabeled bacteria and lipopolysaccharide (LPS), a pro-inflammatory gram-negative bacterial membrane product, are readily detected in the serum.[37,38] LPS has also been detected in the serum after other forms of intestinal injury, including cholecystectomy and inflammatory bowel disease.[39,40] Aberrant immune interactions with bacteria colonizing the intestine are implicated in the pathogenesis of NEC.[7,41,42] Similarly, alterations in permeability likely exacerbate IFALD, as seen in other etiologies of chronic liver inflammation.[43] The liver is perfused by blood leaving the GI tract through the portal vein- rich in nutrients but potentially laden with bacteria, antigens, and inflammatory cytokines. Intestinal injury and IFALD are therefore inter-related.

The intestine requires direct stimulation from enteral nutrients to prevent mucosal atrophy, preserve tight junctions, and maintain appropriate immune interactions.[44-47] In animal studies, intestinal atrophy occurs in a few days of withholding feeding; the timing is less clear in infants. EN is a substrate for the commensal microbiota and can influence which organism populations thrive.[48] EN induces the brush border disaccharidases (i.e. lactase, isomaltase) necessary for carbohydrate digestion and absorption.[49] EN also stimulates trophic hormones that regulate bowel and biliary function - cholecystokinin, glucagon, motillin, and secretin.[50] These hormones are critical for adaptation, the process where the residual gut hypertrophies and takes on the role of absorbing specific nutrients previously performed by the resected bowel.[44,51,52] Breast milk is particularly beneficial in helping the bowel adapt, providing immunoglobulins, glutamine, and hormonal and other growth factors.[53,54] If breast milk is not available or not tolerated, a common substitution is an elemental (amino acid based) formula.[55-57] These formulas also have a higher concentration of medium-chain fatty acids, which can be directly absorbed by the enterocytes, and do not require a functioning enterohepatic pathway for lipid metabolism. The sooner EN begins, the sooner adaptation begins.

Despite the known importance of starting EN "as soon as possible" to induce adaption and prevent IFALD, best-practice guidelines are lacking.[32,57,58] Significant variability therefore exists in post-surgical nutrition practices for infants. The optimal timing of EN after injury, delivery (bolus vs. continuous), and rate of advancement are poorly understood and are provider-dependent.[55] The Pediatric Intestinal Failure Consortium, consisting of 14 sites with specialized care for infants with IF performed a retrospective review of children less than 12 months of age who had received at least two months of PN due to IF.[59] Twenty-two different formulas were used and only 19% of infants received breast milk. The investigators reported a wide range of feeding practices within and between sites, and highlighted the need for multi-centered trials to investigate feeding practices for children with IF.

Barriers to Enteral Feeding

While it is recognized that enteral feedings are important, barriers do exist to using enteral feeds in neonates after surgery. Historically, patients are not fed after bowel surgery for several days until bowel function returns (passage of flatus or stool), though this notion has recently been challenged in both the adult and pediatric literature, and earlier feedings (sometimes within 24 hours) have been proven safe.[60,61] The same studies have not been done in the more fragile neonatal population, but they do suggest that a prolonged waiting period to begin feeding may not be necessary. Following necrotizing enterocolitis (NEC), the most common cause for bowel resection, feeding is withheld as part of treatment. Traditionally, neonates are not fed for 7-14 days, sometimes longer if the infant remains critically ill. Two small studies have recently shown that earlier feedings, beginning 5 days post-NEC in one group and a mean of 8 days post-NEC in the other, resulted in fewer complications, including recurrence of NEC and catheter-related sepsis episodes.[62,63] However, given the high mortality rate and risk of recurrence, many providers are apprehensive about feeding after NEC.

Utility of Feeding Protocols in Neonatal Settings

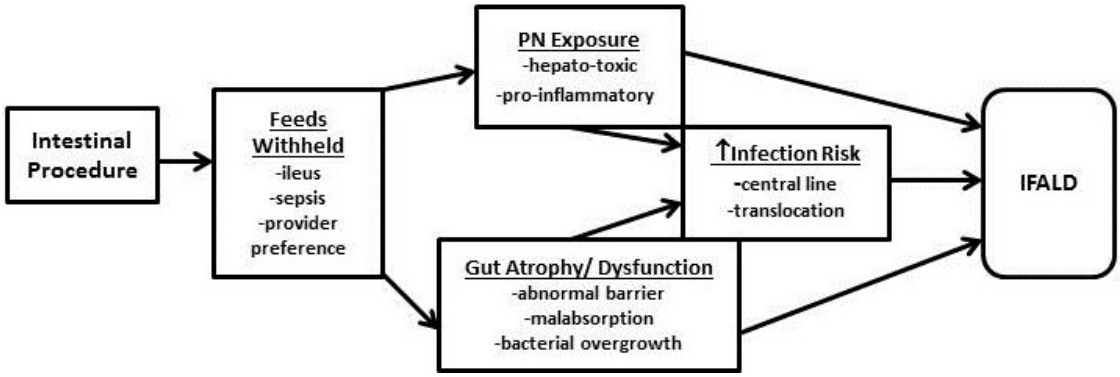
Feeding guidelines are emerging in an effort to balance the benefits of EN with the risk of NEC in high-risk infant populations.[29,64] Early feeding likely has advantages. A study of premature infants showed early feeding (within 48 hours of birth) improved feeding tolerance and decreased exposure to PN, without an increase in NEC.[65] Recent studies evaluating feeding protocols in surgical infants show that early feeding actually improves motility and decreases exposure to PN, without an increase in complications.[55] To begin EN, many centers have implemented minimal EN (trophic feeding) regimens as a strategy to stimulate intestinal mucosa without providing significant calories, thought to reduce the occurrence of feeding intolerance and NEC; however, broad ranges in volume from 5-25 ml/kg/day make these studies difficult to

compare and determine the ideal volume and duration of minimal EN.[66] A Cochrane review found no difference in advancing EN by 15-20 ml/kg/day vs. 30-35 ml/kg/day in preterm infants, but had limited data on extremely preterm infants.[67] Feeding protocols have also been implemented in other populations at higher risk for NEC, including infants with very-low-birth-weight and congenital heart disease, which have resulted in both faster and safer achievement of feeding goals, without increased risk of intestinal perforation due to NEC.[62,63,68] 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, but initial volume is not specifically mentioned.[69] They did not find sufficient evidence to recommend timing of EN following NEC. While questions about EN for surgical infants remain, a recent systematic review reported improved outcomes in general among surgical infants cared for by multi-disciplinary Intestinal Rehabilitation teams focused on nutrition support.[70]

How best to feed infants after bowel injury or resection is an unanswered question, and is of significant importance for preventing IFALD. Given the potential for progressive liver disease and its associated mortality, primary prevention is preferable to treatment. Earlier, systematic introduction of enteral feeding has potential to improve gut function and adaptation, including systemic immune regulation, thereby reducing IFALD risk. The following chapters describe the baseline incidence if IFALD and post-operative feeding practices at our institution, the development and implementation of a post-operative feeding protocol, including our implementation strategies, and our outcomes after 15 months and 30 months.

FIGURES

Figure 1. Conceptual Framework of Factors in IFALD Development



CHAPTER 2. ANALYSIS OF NUTRITION PRACTICES AND INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE IN INFANTS WITH INTESTINAL SURGERY[71]

ABSTRACT

Introduction: The incidence of intestinal failure-associated liver disease (IFALD) varies following intestinal surgical intervention in infants, ranging from 25-60%. While IFALD resolves in some infants, 40% of infants who require long-term parenteral nutrition (PN) progress to liver failure. The purpose of this study was to investigate the incidence of IFALD at our center among infants requiring intestinal procedures and to assess post-operative feeding practices.

Methods: We performed a retrospective review of infants with intestinal surgical procedures before six months of age from 2007-2012. Infants with pre-existing liver disease, other than IFALD, were excluded. The primary outcome was incidence of IFALD during the initial hospitalization. Timing of IFALD development and median time to reach enteral nutrition goals were investigated.

Results: Of the 82 surgical infants, the overall incidence of IFALD was 66% (confidence interval [CI] 0.55 - 0.76), and among the 30 infants requiring >60 days of PN, the incidence was 90% (CI 0.78 – 1.01). Median direct bilirubin of those with IFALD was 7.5 mg/dl. Infants with IFALD were more likely to be premature (29 vs. 38 weeks, P<0.001), have necrotizing enterocolitis (54% vs. 17%, P=0.002), and have culture-positive infection (42% vs. 7%, P=0.001). Among the most recent 24 infants, median time to introduce enteral nutrition post-operatively was 17 days (interquartile range [IQR] 9-26), and median time to reach 50% of calories from enteral nutrition was 34 days (IQR 23-50).

Conclusions: The risk of IFALD is common at our center. Multi-disciplinary preventive and therapeutic strategies need to be investigated. Future investigation will focus on the time to reach enteral nutrition goals as a modifiable risk factor.

INTRODUCTION

Infants who require intestinal procedures, such as bowel resection, are at risk for developing intestinal failure-associated liver disease (IFALD). IFALD is poorly defined, but a commonly used definition for infants is persistent cholestasis (serum direct bilirubin >2mg/dl for at least 7 days) in the setting of parenteral nutrition (PN) use and in the absence of other primary liver disease.[8,9] While IFALD may be perceived as a temporary, even anticipated, side effect, it can be detrimental in infants who require prolonged (>60 days) PN. In this population, IFALD frequently persists and becomes a significant predictor for chronic liver disease and death.[2,11,14,59,72] End-stage liver disease develops in up to 40% of such patients, necessitating liver and/or small bowel transplant.[14]

IFALD reportedly occurs in 25-60% of infants undergoing bowel resection.[10-12] Following resection, it may not be known for several weeks which infants will eventually tolerate enteral nutrition (EN). By that time, significant liver damage may have occurred. Though serum markers of liver injury may return to normal and liver biopsies improve as IFALD resolves, fibrosis of the liver can persist.[17,18,73,74] If progressive, hepatic fibrosis ultimately leads to cirrhosis and liver failure. Furthermore, it remains unknown if infants who've had normalization of liver tests after IFALD will be more susceptible to other hepatic insults as they age, such as viruses and alcohol. Preventing, or at least decreasing, the severity of IFALD in all infants is therefore prudent.

Preterm infants are at greater risk for developing IFALD after intestinal procedures.[27,28] Preterm infants have multiple interruptions in feeding, resulting in a higher cumulative exposure to PN. Their premature livers may also be more susceptible to the accumulation of phytosterols found in the lipid component of standard soy-based PN.[30,75,76] Additional factors such as poor *in utero* growth can further impair liver function.[77] Prolonged lack of feeding can disrupt the gut barrier, altering immune function and increasing risk of infection.[44,50] Though EN is important for

preventing IFALD, post-surgical feeding practices are not well described in the literature. In fact, very little evidence exists to guide providers as to the appropriate time to initiate and advance EN post-operatively.[58]

As part of a quality improvement initiative to coordinate multispecialty care for infants undergoing intestinal procedures, we performed a retrospective cohort study to determine the risk of IFALD at our institution. The purpose of this study was to perform a critical analysis of the risk factors for IFALD in our population, including enteral feeding practices, to provide a rational basis for future strategies to decrease IFALD risk in infants who require intestinal surgical intervention.

METHODS

Study Design and Population

We performed a retrospective cohort study using billing codes for abdominal surgical procedures in the neonatal intensive care unit (NICU) from January 2007 to December 2012 after approval from the Institutional Review Board. Intestinal resection was the primary surgical procedure included; however, stoma creation and peritoneal drain placement for intestinal perforation were also included in the absence of bowel resection for appropriate diagnoses. Patients were included if the surgical intervention occurred before six months of age and PN was received post-operatively. Patients were excluded for pre-existing liver disease, other than IFALD. In the case of multiple procedures or admissions, data pertained to the hospitalization in which the first intestinal procedure occurred. Data were collected over the course of the entire hospitalization, which could include transfer to an acute care unit. Due to a change in electronic medical record format, specific feeding data were only available for the most recent 24 patients who had procedures from July 2010 to December 2012.

Assessment of Risk Factors and Outcomes

For all patients, we recorded race/ethnicity, sex, gestational age, gastrointestinal diagnosis, age at time of surgery, length and location of resection, positive blood/urine/peritoneal cultures, peak and final direct bilirubin by time of hospital discharge, cumulative days of PN before and after surgery, dependence on PN at hospital discharge, development of necrotizing enterocolitis (NEC) after resuming EN, mortality and cause of death. Length of bowel resection was obtained from the operative and/or surgical pathology report. Residual small bowel length was taken from the operative report when available. Liver function tests were measured 1-2 times per week, with more frequent measurements as indicated for changing clinical status.

The PN formulation was written daily by the primary neonatology service with recommendations from registered dieticians. The total volume varied by gestational age, and ranged from 80-120 ml/kg/day. Soy-based lipid emulsions were typically advanced to 3 g/kg/day. Lipid-sparing strategies were implemented on an individual basis once direct bilirubin reached 2mg/dl. If growth was acceptable, the goal was a reduction of lipid to 1-1.5 g/kg/day, along with cycling of trace elements (copper and manganese) three times weekly. Zinc and selenium were still given daily, as was chromium when available. Intravenous fish oil lipid emulsion was not available for use.

The decision of when to initiate EN post-operatively, the starting volume, route, and criteria for advancing feeding was NICU provider dependent with input from the surgical service. Initial feeding volumes and rate of advancement were dependent on the underlying condition in addition to the gestational and chronologic age of the infant. Caloric requirements were determined by registered dieticians based on post-natal age and growth parameters. However, there was not an integrated intestinal rehabilitation service.

The primary outcome was cumulative incidence, or risk, of IFALD. IFALD was defined as cholestasis attributed to PN, with serum direct bilirubin of ≥2.0 mg/dl on two occasions at least one week apart, in the absence of other known liver disease. Onset of IFALD was defined as the

first date where direct bilirubin was ≥2.0 mg/dl. We defined severe IFALD as a direct bilirubin >10mg/dl, based upon previously reported severity levels that predict worse outcomes.[2,78] Feeding outcomes included the number of post-procedure days to initiate EN, days to reach 50% of goal calories from EN (50-60kcal/kg/day), and days to reach 100% of goal calories from EN (>100kcal/kg/day with cessation of PN).

Statistical Analysis

Fischer's exact test was used to determine differences in categorical characteristics between the infants who developed IFALD and those who did not. Non-parametric Wilcoxon rank-sum tests were used to compare the medians of continuous variables between the groups. Student t-tests were used to compare the means of continuous variables. A two-sided p-value of <0.05 was considered statistically significant. The Nelson-Aelen cumulative hazard estimates of the rate of IFALD after the start of PN were generated and plotted. Most infants received continuous PN through the peri-operative period. We explored calendar days from the time of PN start and actual days of PN. There was no difference between the two. We investigated this outcome and all the potential risk factors through a multivariate Cox proportional hazard regression model. The risk factors considered were sex, race (White versus other), prematurity (gestational age <28 weeks, 28-35 weeks, and >35 weeks), age at surgery, etiology (NEC versus other), culture positivity for any infection, and presence of ileocecal valve. The final model included sex, race, etiology, and prematurity as those were the most clinically and statistically relevant variables. STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) was used to perform all statistical analyses.

RESULTS

From the 2007-2012 billing data, 83 infants met inclusion criteria. One infant was excluded for a diagnosis of biliary atresia, leaving a total of 82 infants. Given the lag in billing data, 8 patients had their initial procedure in 2006 but were billed in 2007. Seventy-one infants

had bowel resection (26 had a primary anastomosis and 45 had stomas). Eleven infants had stomas without resection.

The clinical characteristics of those infants with and without IFALD are displayed in Table 1. Infants who developed IFALD were more likely to be premature (P<0.001), have NEC (P=0.002), have culture-positive infections (P=0.001), and have longer PN requirements (P<0.001). Infants who did not develop IFALD were more likely to have Hirschsprung's disease or simple intestinal atresia. Of the 71 infants with resection, resection length was available for 51 infants. There was no difference in length of documented intestinal resection between the groups; however more infants with IFALD had a residual small bowel length less than 50 cm. Eight infants with short bowel syndrome had residual bowel measured, ranging from 12 – 39 cm. Only one such infant did not develop IFALD (residual small bowel 20 cm). The location of bowel injury was 50% ileum, 19% jejunum, 18% multiple small bowel locations, 7% colon, and 6% duodenum.

The overall incidence of IFALD was 66% (95% Confidence Interval [CI] 0.55 - 0.76). The cumulative hazard for developing IFALD after initiation of PN is displayed in Figure 2. The rate of IFALD began to rise steeply after 10 days of PN. Of the 49 infants requiring at least 30 days of PN, 47% (95% CI 0.31- 0.61) had developed IFALD by 30 days. By 60 days of PN, 27 of 30, 90% (CI 0.78 – 1.01), had developed IFALD. Thirteen infants (25%) had IFALD prior to surgery. Sixteen infants (20% of the total cohort) required PN at hospital discharge, 88% of who had IFALD (CI 0.69 – 1.06).

The final Cox regression model included sex, race, etiology, and prematurity. Prematurity remained the only significant risk factor, with extremely premature infants (gestational age <28 weeks) having an increased hazard of developing IFALD compared to term infants (gestational age >35 weeks), hazard ratio=3.2 (CI 1.05-9.9, P=0.04).

The degree of cholestasis varied by diagnosis, which was related to the overall length of PN exposure. Infants with gastroschisis had the highest median peak direct bilirubin, followed by infants with NEC (Figure 3). Among infants with IFALD, 26% (14/54, CI 0.14-0.38) developed severe cholestasis with a direct bilirubin >10mg/dl. Eight infants (15%, CI 0.05-0.25) had resolution of IFALD by discharge, with a direct bilirubin <2 mg/dl. Five patients (9%, CI 0.01-0.17) eventually developed chronic liver disease (defined as coagulopathy with abnormal liver enzymes or evidence of liver fibrosis/cirrhosis).

Mortality during the first hospitalization was similar among those infants with and without IFALD (6% vs. 7%, P=0.56). Of the five infants who died, four had NEC and one had volvulus with necrosis of the entire bowel. Among those with NEC, one died in the first 24 hours of life due to ischemic bowel/peritonitis, one died of a massive pulmonary hemorrhage shortly after bowel resection, and two died of respiratory failure several weeks after bowel resection. Four patients developed NEC post-operatively after EN was started (7%, CI 0.02-0.17).

The clinical characteristics of the most recent 24 infants with EN data were similar to those of the entire group. The most common diagnosis was NEC (54%), and the mean gestational age was 29.8 weeks (IQR 25.3 – 34.1). All infants required at least 14 days of PN, with a mean of 71 days (IQR 48-112). One third of the infants were discharged with home PN.

The time to reach specific EN goals in the 24 infants is displayed in Table 2. Twenty-two infants started on trophic feeding, generally between 5-10 ml/kg/day, though the range was 2-14 ml/kg/day. Fifteen infants received breast milk, one infant received cow's milk formula, two infants received partial hydrolysate formula, and six infants received elemental formula. Bolus feeding was started in 67% of the infants, and the others received continuous feeding. Not all patients reached 50% or 100% of goal calories from EN by the time of hospital discharge. When comparing all etiologies of bowel resection, only 38% of the infants achieved 50% of goal calories from EN within 30 days of surgery. All but three infants (88%) developed IFALD. Six

infants (25%) had IFALD by the time of surgery, 13 infants (54%) developed IFALD within 30 days of surgery, and two infants (8%) developed IFALD after 30 days. The median peak direct bilirubin was 6.9 mg/dl (IQR 5.3-12).

Among the 24 patients, lipid reduction was employed once direct bilirubin was above 2mg/dl. At the time of meeting criteria for IFALD, 4 infants were already on 1g/kg/day of lipid, and 2 infants were off of lipid completely. The lipid dose was lowered from 2-3 g/kg/day to 1-1.5g/kg/day within 24 hours for 6 infants and within 3-4 days for another 4 infants. Five infants had their lipid dose lowered from 3g/kg/day to 2g/kg/day within 24 hours, but the dose was not lowered further until 10-27 days after meeting criteria. Three infants never developed IFALD despite receiving 3 g/kg/day of lipid for a minimum of 14-30 days after their procedure.

Serum direct bilirubin, which is required for the diagnosis of IFALD, was not always routinely monitored in the post-operative period, though other liver tests including total bilirubin were measured at least 1-2 times per week. Direct bilirubin is not always measured if the total bilirubin remains below 2 mg/dl. Fourteen of the infants without IFALD did not have a post-operative direct bilirubin level. Nine of these infants had relatively short hospitalizations and were not clinically jaundiced so IFALD was not suspected. Five infants did have elevated total bilirubin levels, so may have been misclassified as not having IFALD. Many of the IFALD infants did not have a direct bilirubin measured for 2-4 weeks post-operatively, and the first available date was used.

DISCUSSION

Historically, the incidence of IFALD among surgical infants ranged from 40-60%, but the incidence varied by center and patient population.[10-12] A recent systematic review reported an overall incidence of 30% among all infants (including preterm) and children with at least 14 days PN exposure, and 50% incidence among infants with intestinal failure.[12] While not included in the systematic review, one center with an active intestinal rehabilitation program reported an even

lower incidence of 25% among surgical infants.[10] Compared to other centers, our incidence of 66% was at the higher end of the spectrum. Among infants with prolonged PN exposure for >60 days, our incidence was 90%. This incidence was again higher, but along the same trend of the 75% risk recently published by the National Intestinal Failure Consortium which evaluated a cohort of 272 infants from 14 sites with at least 60 days of PN exposure.[59] Early prognostic factors for IFALD include low birth weight (<750 g), and etiology of intestinal disease, with gastroschisis, jejunal atresia, and NEC portending higher risk.[13,79] The risk of IFALD among surgical NEC patients ranges from 56-85%.[13] The most common diagnoses among our infants with IFALD were NEC, atresia, and gastroschisis. Our higher risk may be related to a case mix of higher acuity infants, other etiologies being attributed to IFALD (sepsis or multi-organ system failure), or chance, given the relatively small cohort. Another important consideration is that feeding practices contributed to IFALD, given the time to initiate and advance EN.

Early advancement of EN has been associated with preventing and resolving IFALD;[32,33] however, reaching feeding goals can be difficult for multiple reasons. Infants may have significant feeding intolerance related to the location and size of resection, dysfunction of the residual bowel, and may have other severe organ dysfunction necessitating interruption of EN. Furthermore, providers may be hesitant about aggressive feeding for fear of causing another episode of NEC. The ideal composition of EN that is best tolerated and able to stimulate bowel adaptation is also unclear. Breast milk is an appealing option given the nutritional and immune benefits, as well as reduced risk of NEC.[80] The use of breast milk and amino acid formulas has been associated with less PN use, which may impact the development of IFALD, but this has not been conclusively demonstrated.[81] Providers have limited evidence to guide them in initiating and advancing EN after intestinal injury, leading to practice variability.[58]

The majority (54%) of our patients with IFALD had bowel resection due to NEC. The median time to initiate EN after resection in infants with NEC was 21 days, and the median time

to reach 50% of goal EN was 47 days, though some cases were significantly longer. Infants with NEC requiring surgical resection often have concomitant multi-organ dysfunction which may contribute to delayed initiation of EN. When comparing all etiologies of bowel resection, nine of the 24 infants (38%) achieved 50% of goal EN within 30 days of surgery. Again the delay in advancing EN may be a reflection of overall severity of illness and feeding intolerance; however, another contributing factor may be low starting volumes of trophic feeding and slow advancement regardless of tolerance. Over half of our infants (60%) received breast milk post-operatively, but the volume and timing may not have been sufficient to offer protection against IFALD.

Once IFALD occurs, it can be difficult to resolve if EN is not advanced so that PN can be weaned. Many of our infants (65%) had an improved direct bilirubin (decrease of at least 1 mg/dl), but only 19% had resolved IFALD by discharge from the hospital. Among the 14 infants with IFALD who were discharged home with PN, 78% still had a direct bilirubin >2 mg/dl. In this setting of intestinal failure and prolonged PN exposure, IFALD becomes a significant predictor of mortality and need for transplantation.[2,14]

Other treatment options for IFALD are few. Ursodeoxycholic acid, which improves bile flow, has been used with limited success.[82] Glutamine, a preferred fuel for enterocytes, has shown promise in animal studies by stimulating mucosal growth and barrier function, but has yet to be proven beneficial in human infant studies.[83] Another common practice is to reduce the dose of soy-based lipid once cholestasis occurs.[24,27]

In our population, those infants not already receiving ≤1 g/kg/day had at least some reduction in lipid dose, but lipids were given daily. It is unclear if the timing or degree of lipid reduction, such as limiting lipids to 2-3 days per week, may have impacted the degree of cholestasis. Although retrospective, a recent publication by Nehra et al, showed no difference in the development of IFALD when infants only received 1 g/kg/day of soy-based lipid versus the

standard 2-3 g/kg/day.[84] A study by Levit also found no difference in incidence of cholestasis among preterm infants given 1g/kg/day vs. standard doses of soy lipid in first two weeks of life; however, their definition of cholestasis included many infants with a direct bilirubin <1mg/dl and few infants required intestinal surgery.[85] These findings call into question the utility of this practice, though further lipid restriction may offer more benefit. Cober et al did show an improvement in total bilirubin level over time when infants with IFALD were treated with severe lipid restriction to 1g/kg/day given twice weekly compared to historical controls given standard doses. This practice was also associated with mild essential fatty deficiency, so careful monitoring is warranted.[86]

Alternative lipid preparations containing omega-3 fatty acids are widely used across Europe to treat IFALD in infants and show promising results for reversing IFALD.[78,87] Unfortunately, these preparations are not yet approved by the Federal Drug Administration in the Unites States. While these emulsions can be obtained for compassionate use after the onset of IFALD as an investigational new drug, the cost is prohibitive to many institutions and individual families. Furthermore, even if cholestasis improves with fish oil lipid emulsion, liver fibrosis may not always be reversible, and may still ultimately progress to liver failure.[17,73,74]

Multi-disciplinary strategies for advancing EN, PN manipulation, and infection control aimed at primary prevention of IFALD may be of benefit. Earlier introduction of EN with careful but consistent advancement may reduce the burden of IFALD by 1) enhancing gut barrier function and motility, thereby reducing bacterial translocation and subsequent infection,[21,44,50] 2) attenuating gut-immune system interactions that influence pro-inflammatory responses,[88] and 3) reducing exposure to hepato-toxic PN components. Feeding protocols have been successfully implemented in other high-risk infant populations, including very-low birth weight infants and those with hypoplastic left heart syndrome.[68,89-91] While both groups have an increased risk of NEC at baseline, infants who followed a feeding protocol had better growth with either the same

or decreased incidence of NEC, compared to controls. In adults, it is now standard practice to introduce EN within 24-48 hours after uncomplicated bowel resection, rather than the traditional practice of waiting several days for bowel function to return.[61] Small studies have begun to look at earlier introduction of feedings in pediatric post-operative populations, with promising results regarding tolerance and length of hospitalization.[60] Of course, infants with complicated bowel resection, such perforation from NEC, will likely need different guidelines than those with simple resection, due to potential injury in the residual intestine.

Our study has several limitations. This is a single-center retrospective study with a relatively small population. Direct bilirubin levels were not monitored in a systematic fashion post-operatively and length of bowel resection or residual bowel was not readily identifiable for all patients. Details regarding enteral feeding were only available for the most recent 24 patients. Due to the sample size and heterogeneous population, we could not create a risk score for developing IFALD, which would ultimately require a multi-center database to capture sufficient patients. The analysis only reflects short-term outcomes that occur within the initial hospitalization.

In conclusion, IFALD is common at our institution, occurring in about two-thirds of infants requiring intestinal procedures, and in 90% of infants with prolonged PN requirements. While many factors contribute to IFALD, the timing and volume of EN post-operatively may be important and modifiable in many infants. Being aware of high-risk infants should prompt careful monitoring of liver function, attention to enteral and parenteral nutrition prior to the development of IFALD, and meticulous line care to prevent infection. Our findings have motivated us to form a multi-specialty intestinal rehabilitation team to address these issues. Our future plans include evaluating the effect of feeding modification on IFALD risk and monitoring longer-term outcomes.

TABLES

Table 1 – Baseline Characteristics, Risk Factors & Outcomes by IFALD, unadjusted

	IFALD N=54	***No IFALD N=28***	***P****
Sex Male (%)	39 (72)	18 (64)	0.310
Race/Ethnicity (%)			0.015
Black (non-Hispanic)	23 (43)	8 (28)	
White (non-Hispanic)	26 (48)	11 (39)	
Hispanic	0 (0)	5 (18)	
Asian	1 (2)	1 (4)	
Other	4 (7)	3 (11)	
Gestational age, weeks median (IQR)	29 (26-35)	38 (34-39)	<0.001
Diagnosis (%)			0.002
NEC	29 (54)	5 (17)	
SIP	4 (7)	2 (7)	
Atresia	7 (13)	10 (36)	
Volvulus	4 (7)	1 (4)	
Gastroschisis	6 (11)	1 (4)	
Hirschsprung's	3 (6)	6 (21)	
Meconium ileus	0 (0)	2 (7)	
Other	1 (2)	1 (4)	
Age at surgery, days median (IQR)	10 (3-28)	4 (2-11)	0.019
Type of Procedure (%)			0.237
Resection/anastomosis	12 (43)	14 (26)	
Resection/stoma	12 (43)	33 (61)	
Stoma without resection	4 (14)	7 (13)	
Resection length**, cm			
median (IQR)	8 (3-20)	11 (4-20)	0.459
mean (SD)	15 ±18	15 ± 15	0.880
Ileocecal valve preserved, (%)	44 (86)	23 (88)	0.547
PN pre-surgery, days median (IQR)	8 (1-20)	1 (0-3)	<0.001
PN post-surgery, days median (IQR)	46 (25-72)	7 (4-12)	<0.001
PN total, days median (IQR)	60 (35-100)	9 (7-13)	<0.001
Positive blood culture, (%)	11 (20)	1 (4)	0.051
Any positive culture, (%)	23 (42)	2 (7)	0.001
Peak direct bilirubin, mg/dl median (IQR)	7.5 (5-10)	0.5 (0.3-0.8)	<0.001
Discharge direct bilirubin, mg/dl median (IQR)	3.9 (2.1-6.4)	-	-
NEC after re-feeding (%)	4 (7)	0 (-)	0.181
Deceased (%)	3 (6)	2 (7)	0.560

IFALD= intestinal failure-associated liver disease; IQR=interquartile range; NEC=necrotizing enterocolitis; SIP=spontaneous intestinal perforation; mg/dl= milligrams per deciliter; PN= parenteral nutrition.

*P value from Wilcoxon rank-sum test, student t-test, or Fischer exact test

**Resection length available for 32 infants with IFALD and 19 infants without IFALD

Table 2. Clinical and Nutritional Data for the 24 Most Recent Patients by Diagnosis, median (IQR)

Diagnosis (N)	Gest Age	Post-op Days to Initiate EN	Post-op Days to 50% EN	Post-op Days to 100% EN	Days to IFALD from PN	Post-op Days to IFALD	Peak DB mg/dl
All (24)	28.7 (25.2-34.1)	17 (9-26) N=24	34 (23-50) N=21	55 (35-90) N=18	29 (20-31)	9 (-3 -25)	6.9 (5.3-12)
NEC (13)	26.9 (25-28.6)	21 (11-41) N=13	47 (35-78) N=12	89 (53-107) N=11	31 (25-34)	10 (-4-27)	9.6 (5.6-15.3)
SIP (2)	25 (25-25.1)	12 (8-15) N=2	37 (24-50) N=2	64 (35-93) N=2	12 (9-15)	5 (5-9)	5.3 (5-5.6)
Atresia (3)	36.9 (31.3–38.1)	6 (5-9) N=3	8 (7-8) N=2	14 (9-19) N=2	29 (29-29)	25 (20-29)	6.2 (0.6-12)
Volv (1)	34	13 (-) N=1	23 (-) N=1	(-)	9	9	7.6
Gastro (2)	33.4 (32.6-34.3)	36 (17-54) N=2	29 (-) N=1	34 (-) N=1	26 (20-31)	-4.5 (-11-2)	8.4 (4.8-12)
Hirsch (2)	37.4 (35.7-39)	13 (3-23) N=2	20 (12-28) N=2	29 (14-44) N=2	25	25	3.1 (0.3-5.9)
CDH (1)	28.9	17 (-) N=1	28 (-) N=1	(-)	30	-8	11.3

IQR= interquartile range; Gest=gestational; EN=enteral nutrition; IFALD=intestinal failure-associated liver disease; PN=parenteral nutrition; NEC=necrotizing enterocolitis; SIP=spontaneous intestinal perforation; Volv=volvulus; Gastro=gastroschisis; Hirsch=Hirschsprung's disease; CDH=congenital diaphragmatic hernia.

Twenty-four patients initiated feeds. Twenty-one patients achieved 50% enteral calories. Eighteen patients achieved 100% enteral calories. 21 of 24 infants developed IFALD (excludes 1 infant each with NEC, atresia, & Hirschsprung's).

FIGURES

Figure 2. The cumulative hazard estimate of developing intestinal failure-associated liver disease (IFALD) rises as the number of days of parenteral nutrition (PN) exposure increases.

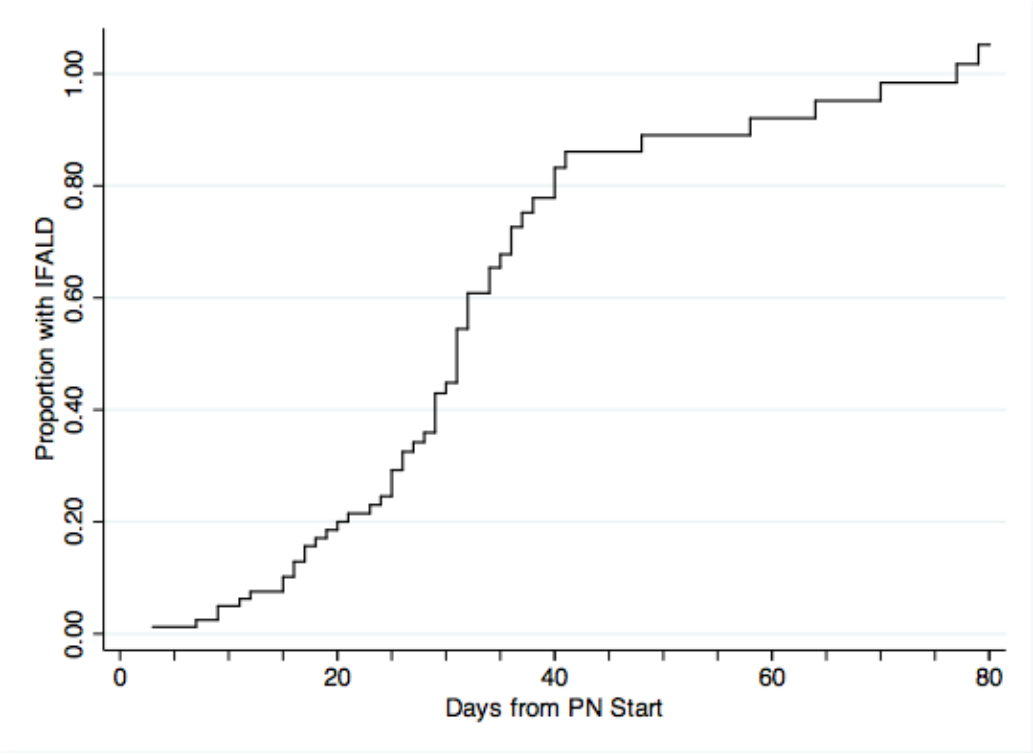
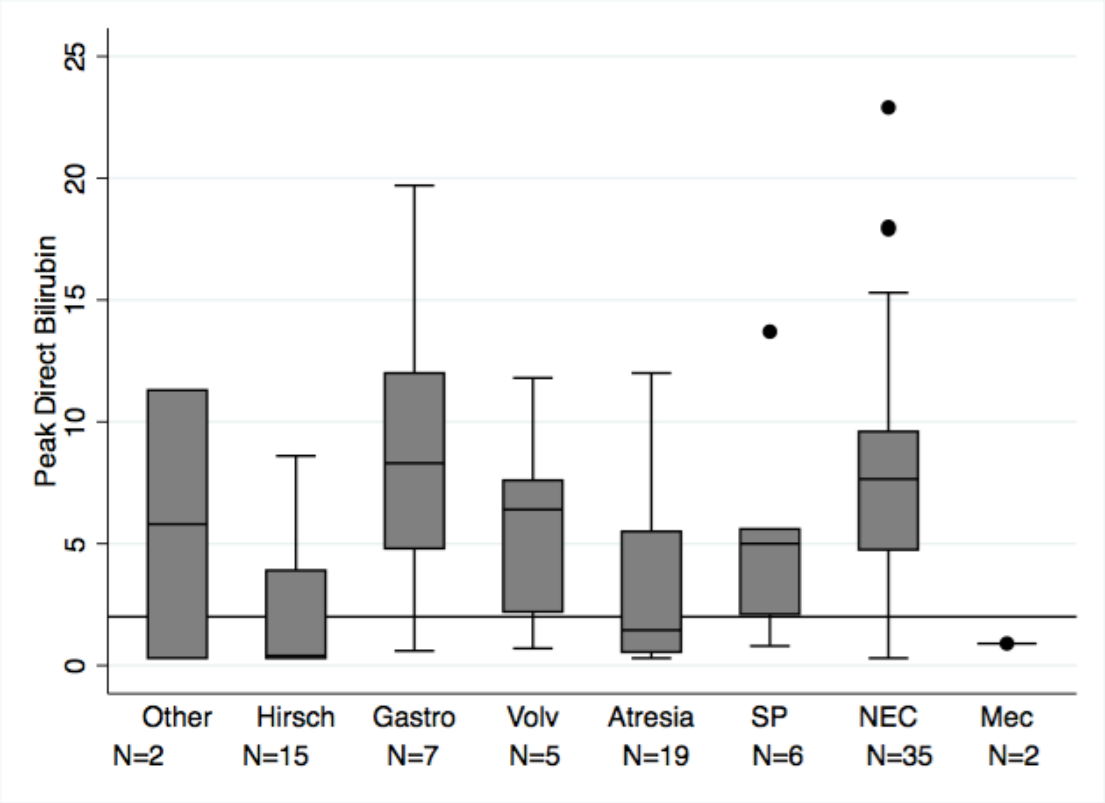


Figure 3. Median Peak Direct Bilirubin by Diagnosis. Boxes represent the 25-75th interquartile range and bars represent the 10-90th percentile range. The line within the box is the median. Dots represent outliers above the 90th percentile. The reference bar is at 2mg/dl, the cut-off for cholestasis. Hirsch=Hirschsprung's disease; Gastro=gastroschisis; Volv=volvulus; SP=spontaneous perforation; NEC=necrotizing enterocolitis; Mec=Meconium ileus



CHAPTER 3. IMPLEMENTATION OF FEEDING GUIDELINES IN INFANTS AT RISK OF INTESTINAL FAILURE[92]

ABSTRACT

Introduction: The objective was to implement feeding guidelines to reduce advancement time and the incidence of intestinal failure-associated liver disease (IFALD) among intestinal surgical infants requiring parenteral nutrition (PN).

Methods: Feeding guidelines with higher initial enteral nutrition (EN) volume and specific advancement criteria were implemented for surgical infants <6 months old. Outcomes were compared between the pre- and post-guideline cohorts.

Results: There were 57 pre-guideline and 33 post- guideline infants. The initial median EN volume improved from 10 to 20 ml/kg/day (P<0.001). Time to reach 50% of goal calories from EN decreased by a median of 6 days (P=0.012) without a change in NEC incidence after resuming feeding. IFALD incidence decreased from 70 to 48% (P=0.041), and median peak direct bilirubin (DB) decreased from 5.6 to 2.3 mg/dl (P=0.011).

Conclusions: Feeding guideline implementation with higher initial feeding volume was well tolerated and resulted in faster achievement of 50% goal EN calories. IFALD incidence and peak DB were reduced.

INTRODUCTION

Infants who have undergone intestinal surgery often have feeding difficulty requiring parenteral nutrition (PN) and are at risk for intestinal failure (IF).[57] IF is loosely defined as insufficient absorption necessitating prolonged PN, with PN use ranging from >30 to >60 days.[58,59] A common complication is intestinal failure-associated liver disease (IFALD), defined as cholestasis (direct bilirubin [DB] >2mg/dl) for a least one week in the setting of PN exposure and absence of primary liver disease.[8] IFALD is a multi-factorial process related to lack of enteral nutrition (EN), high dose soy-based PN, and inflammation that can progress to liver failure.[11,14,93] Prematurity, low birth weight, necrotizing enterocolitis (NEC), and sepsis are risk factors for IFALD, often occurring simultaneously in this high-risk population.[13,27] EN is critical for intestinal barrier function, helping prevent and reverse IFLAD.[33] Lack of EN results in intestinal atrophy, translocation of bacteria, and intestinal permeability to dietary antigens, all of which promote systemic inflammation and exacerbate IFALD.[57,88]

We previously reported a IFALD incidence of 66% among all intestinal surgical infants at our institution with 90% incidence among infants needing >30 days of PN.[71] Other centers report 25-60% incidence among similar infants.[10,11,58] We discovered significant variability in trophic feeding practices following surgery, which may have contributed to our IFALD risk. The initial EN volume ranged from 2-14 ml/kg/day, independent of gestational age or size, and consensus for advancing EN was lacking.

We hypothesized that adherence to a systematic approach to EN would reduce the time to reach goal EN compared to historical controls, and therefore would reduce overall PN exposure and the risk of IFALD. The specific aim of the project was to decrease the time to reach 50% of goal EN from a median of 11 days to <5 days, with the ultimate goal of reducing our overall incidence of IFALD from approximately 70% to <50% within two years. We anticipated that most infants would tolerate the lower volumes of EN with a noticeable reduction in time to reach

50% EN and greater variability in time to reach 100% EN, depending upon clinical factors and weight gain.

METHODS

The study protocol was granted approval and waiver of consent by the Institutional Review Board as the study was determined to be "quality improvement."

*Setting***.** Our academic children's center has a 45-bed neonatal intensive care unit (NICU). Annually, there are 750 NICU admissions with 15-30 intestinal surgical procedures. Neonatal dieticians round daily with the NICU teams, with daily consults from general surgery and as-needed consults from gastroenterology. Prior to the intervention, we did not have formal intestinal rehabilitation (IR) team that convened in the immediate post-operative period.

Planning and Study of the Intervention

Development of the Intestinal Rehabilitation Team and Feeding Guidelines. We formed a multi-disciplinary IR team, comprised of representatives from neonatology, pediatric surgery, pediatric gastroenterology, nutrition, pharmacy, and nursing, and we developed feeding guidelines for NICU infants requiring intestinal surgery. Feeding guidelines were based on evidence and consensus when evidence was lacking, and were in parallel with the existing NICU protocol for initial feeding of extremely low birth weight preterm infants (Figure 4).

Though questions about best practices remain, there is agreement that EN should be started as soon as possible in surgical infants.[57] Earlier and higher initial volumes of minimal EN (trophic feeding), up to 20 ml/kg/day, have been demonstrated to be safe in other high-risk neonatal populations, including those with low birth weight, prematurity, and cyanotic heart disease.[9,65,69] Breast milk is preferred in most situations, and may be beneficial for intestinal adaptation and further protection against NEC.[69] Based on published data and clinical experience, we anticipated most infants would tolerate moderate volumes of EN.[94] Our guidelines therefore recommended using the upper spectrum of minimal EN and advancing daily unless signs of

intolerance were encountered (Figure 4). Since implementing our guidelines, another review reported similar recommendations to ours for monitoring tolerance by stool and ostomy output.[95]

The decision to use bolus or continuous EN was provider-dependent as evidence favoring a single feeding route is inconclusive;[57] continuous EN was used if bolus EN was not tolerated. If breast milk was not available or declined, the type of formula was also provider-dependent; however, elemental formula was recommended in specific situations. Infants began oral feeding when developmentally appropriate.

Soy-based lipid was the only intravenous lipid available at our institution, and lipid restriction strategies did not change with the guidelines. PN goal calories were generally 100 kcal/kg/day, based on age, growth and other needs. Lipid doses were typically advanced to 3g/kg/day, unless cholestasis occurred. PN was weaned as absorption and weight gain allowed.

Implementation of Guidelines. Key drivers for implementation are displayed in Table 3. Initially, the IR team met monthly to discuss issues and modify the guidelines. Run charts were analyzed quarterly. After the first quarter analysis, we realized more immediate communication with the rounding teams was needed and weekly team rounds were implemented at five months with representatives from neonatology, nutrition, surgery, and gastroenterology.

Methods of Evaluation

Study Design and Duration. This is a pre- and post-intervention study. Electronic medical records were available after 2010. Given the rarity of intestinal surgery, historical data was collected between January 2010 and June 2013, using billing codes to identify infants. Post-guideline data were prospectively collected from infants admitted after October 14, 2013 who were discharged by February 28, 2015. As this was a quality improvement initiative, data was analyzed at 15 months (1 year following the first quarter ramp up period) to verify the utility and safety of guidelines.

Study Population. Enrollment criteria included infants <6 months old with intestinal surgery at our institution at risk for IF based on diagnosis, procedure, and requirement of PN in the post-operative period. Target diagnoses were intestinal atresia, gastroschisis, omphalocele, volvulus, NEC, spontaneous intestinal perforation (SIP), or other primary intestinal conditions where >14 days of PN was expected. As the length of PN requirement is difficult to anticipate and we desired to capture all at-risk infants, infants with >7 days of post-operative PN were included. The target procedures were intraperitoneal drain, enterostomy or enterotomy with and without intestinal resection, and abdominal wall closure. Infants were excluded for primary surgical procedures performed at outside facilities or for liver disease other than IFALD.

Data Source and Metrics. Electronic medical records were reviewed by two trained analysts with periodic duplicate data review to ensure quality data extraction. Data were collected and managed using REDCap.[96] Demographics, diagnoses, and surgical characteristics were recorded. Metrics were designed to be relevant, patient-centered outcomes, including process measures for adherence and balancing measures for safety. The primary outcome was IFALD incidence (DB >2mg/dl). Other outcome metrics included IFALD severity (peak DB), discharge DB, days of PN, culture-positive infection (blood, urine, or peritoneal fluid), liver and/or intestinal transplantation evaluation, and length of stay. Process measures included days to initiate EN post-operatively, starting EN volume, days to reach 50% (>60 ml/kg/day with weaning PN) and 100% (>120 ml/kg/day and PN discontinued) of goal EN, and guideline adherence. Balancing measures included incidence of NEC (stage II or III) and mortality after post-operative feeding.

Data Analysis. Characteristics and outcomes between pre- and post-guideline cohorts were compared. Sub-analyses included evaluation of infants with NEC/ SIP diagnoses, preterm infants <34 and <28 weeks gestation, and exclusion of infants with <14 days of PN exposure. Given the small sample size and non-normal distribution of the data (determined by Shapiro-Wilk

test), non-parametric Wilcoxon rank-sum tests were used to compare the medians of continuous variables. Fisher exact tests were used to compare categorical variables. Statistical significance was set at a two-sided p-value of <0.05. Analyses were performed using STATA (StataCorp. 2011. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Individual data for specific outcomes were plotted in run-chart format to monitor performance over time. A "shift" was considered significant if 6 or more consecutive points were above or below the median as per Perla, et al.[97]

RESULTS

Fifty-eight infants were identified in the pre-guideline cohort. One infant was excluded for pre-existing liver disease (biliary atresia); 57 infants were included. In the post-guideline cohort, 37 infants were identified. Two infants were excluded for other etiologies of liver disease (multi-organ failure and ischemic injury) and two infants with NEC died within 24 hours of surgery; therefore 33 infants were fed in the post-guideline period.

Baseline Characteristics. Baseline and surgical characteristics in the pre- and post-guideline cohorts are presented in Table 4. There was not a statistical difference in gestational age or diagnosis between cohorts. The proportions of initial procedures were similar. Forty-four (77%) infants in the pre- and 20 (61%) infants in the post- guideline cohort had at least one resection, with more infants in the pre-guideline cohort requiring resection as a subsequent procedure (P=0.006). Most resections were relatively small and there was no difference in median total length of resection between cohorts. Residual bowel length was measured at the surgeon's discretion and was only available for a few cases with large resections. Among 9 pre-guideline infants, the median residual bowel was 30cm (28% of expected length based on gestational age), vs. 53 cm (34% of expected length), among 3 post-guideline infants (P=0.578).

Guideline Adherence. Nine infants had a total of 11 deviations from the guidelines, with all but two deviations occurring in the first four months of implementation, prior to weekly

rounds. Initial EN volume was lower than recommended for seven infants. Four infants had EN advancement that was slower than recommended. The deviations that occurred after implementation of weekly rounds were due to miscommunication. Previously unfed infants weighing <1000g who started at guideline-specific lower volumes were not considered deviations.

Changes in Feeding Practices. Nutrition metrics are displayed in Table 5. Most infants in both cohorts were fed breast milk initially. The initial volume increased from a median of 10 to 20 ml/kg/day post-guideline implementation (P<0.001). The run chart shows a shift to higher feeding volumes (Figure 5) after introduction of weekly team rounds. The median time to initiate EN and to reach 50% of goal calories both decreased post-guidelines from 13 to 8 days (P=0.048) and 11 to 5 days (P=0.012), respectively. Run charts show a shift toward shorter time to reach 50% EN (Figure 6) and 100% EN (Figure 7). In the subanalyses of preterm infants, improvement in time to reach 50% EN remained statistically significant (data not shown).

IFALD Incidence and Severity. IFALD incidence decreased from 70 to 48% (P=0.046) (Table 5), and the severity of cholestasis improved. The median peak DB decreased from 5.6 to 2.3 mg/dl (P=0.011). The run chart shows a shift to lower peak DB among consecutive infants (Figure 8). As most infants received >14 days of PN, a sub-analysis of this group showed similar results. Infants with NEC or SIP had the highest peak DB, and a sub-analysis (N=30 pre-guideline and N=9 post-guideline) showed a median decrease in DB from 7.3 to 4.7 mg/dl (P=0.020). The significant reduction in peak DB was also seen in the subanalyses of preterm infants, but the proportion of IFALD was no longer statistically significant (data not shown).

Other Outcomes. Weight percentile by discharge was slightly better in the post-guideline cohort, with only 2 infants (6%) discharged below the corrected 10th percentile for age (z-score <2). The development of NEC after starting EN post-operatively was rare and similar between cohorts (Table 5). In the pre-guideline cohort, there were two cases of medical (stage II) and one

case of surgical (stage III) NEC after post-operative feeding. Post-guidelines, one infant developed medical NEC. Death was also a rare event. Two infants with a primary diagnosis of NEC died from respiratory failure in the pre-guideline period after resuming EN. Post-guidelines, two infants died within 24 hours of developing NEC; none have died since starting EN. One infant from each cohort was referred for intestinal transplantation.

Missing Data. In one pre-guideline infant, DB was never assessed. Total bilirubin was 6.5 the first week of life; the infant was classified as "no IFALD." For 10 infants, a total but not a direct bilirubin was assessed at the time of procedure (8 pre- and 2 post-guideline), but there were multiple subsequent DB measurements.

DISCUSSION

We implemented a feeding intervention for surgical infants in the NICU at risk for IF. Compared to traditional trophic feeding volumes and advancement, the intervention resulted in higher volumes of initial post-operative feeding and shorter times to initiate and reach 50% of goal EN without unintended deleterious consequences, such as NEC, infection, or poor weight gain. We also report decreased IFALD incidence and decreased peak DB. Though the incidence of IFALD remains common in this high-risk population, the decrease in peak DB is clinically relevant - IF infants with higher DB are at greater risk for liver failure, liver transplantation, and mortality.[2,14] The lack of statistical significance in reaching 100% EN may be a reflection of feeding difficulty seen as higher volumes are given, need for additional calories from PN, small sample size, and/or less stringent adherence to guidelines initially.

Despite education and evidence that higher initial volumes are tolerated in other high-risk infants, initial adherence to the guidelines was suboptimal.[9,29,65,98] Adherence improved after implementing weekly nutrition rounds in the NICU, which facilitated communication, guideline adherence, and coordinating care. Other centers have also found that IR teams in general improve outcomes, as supported by a recent systematic review.[33,70]

Confounding factors such as diagnosis, gestational age, method of feeding, infection, and lipid reduction strategies should be taken into consideration when interpreting these results. Though not statistically significant, the gestational age was higher in the post-guideline group. Thus far, there have been fewer cases of NEC as a primary diagnosis in the post-guideline cohort. We've seen an increase in infants with duodenal atresia and gastroschisis, similar to national trends, who required fewer and shorter resections.[99] Since gestational age, percentage of residual bowel and NEC are risk factors for IFALD, the post-guideline infants may have been less prone to IFALD and IF. However, the decrease in IFALD severity is sustained in a sub-analysis of infants with NEC and SIP, and among the lower gestational ages. We also saw fewer culture-proven infections in the post-guideline cohort, which may contribute to the severity of cholestasis. By chance, more infants were fed continuously initially in the post-guideline group, which may have impacted feeding tolerance and advancement. There was not a difference in the proportion of infants fed breast milk. The soy lipid restriction strategy for cholestasis did not change between periods; however, since starting weekly rounds, lipid restriction may be more consistently implemented, which may ultimately impact the severity of IFALD. There is conflicting evidence whether earlier and more aggressive lipid restriction strategies will further reduce IFALD risk.[84,86]

Since implementation of feeding guidelines, we have seen fewer days of PN use and a trend toward shorter lengths of stay. This may also be reflective of the difference in primary diagnoses, rather than a direct result of guideline use alone. None-the-less, the guidelines were relatively inexpensive to implement with only a modest increase in time commitment, and the potential cost-savings of reduced PN use and NICU hospitalization may ultimately have a significant impact on health care resource utilization.

Limitations of the study are the small sample size, heterogeneity of diagnoses and procedures, and single-center location. While these limitations are important, this pragmatic study

reflects “real world” experience with relatively rare surgical disorders. We plan to continue enrolling infants to increase the sample size, allowing for more complex statistical modeling, a better understanding of feeding tolerance among specific surgical subsets, and determination of sustainability over time. We also intend to evaluate the guidelines at another community-based children’s hospital to gain further insight about generalizability.

In conclusion, implementation of feeding guidelines for surgical infants was feasible, well tolerated, and resulted in shorter times to reach feeding goals. We also report reduced IFALD incidence and peak direct bilirubin after implementation of the guidelines. Adherence to guidelines greatly improved once weekly multi-disciplinary rounds were implemented.

TABLES

Table 3. Key Drivers and Interventions Used to Facilitate Implementation	
Key Drivers	**Interventions**
Multi-disciplinary Collaboration	Formed IR team with key stakeholders Developed guidelines based on evidence and consensus Agreement by individual departments for implementation
Education	Nursing education through QI committee in-service and newsletter Provider education during faculty meetings and email distribution
Accessibility of Guidelines	Posted on nursing website Hard copies available bedside for rounds, posted in work rooms Daily reminders on rounds by dieticians
Objective Measures	Clear criteria for initiating and advancing EN Clear criteria for monitoring tolerance
Data Sharing	Pre-/post-guideline metrics shared quarterly with all providers
Team meetings	Monthly IR meetings to trouble shoot implementation and improve guidelines Weekly team rounds with NICU, Surgery, Nutrition & GI providers to facilitate real-time clinical decision making

Abbreviations: IR, intestinal rehabilitation; QI, quality improvement; EN, enteral nutrition; NICU, neonatal intensive care unit; GI, gastrointestinal

Table 4. Demographics, Clinical, & Surgical Characteristics			
	Pre-guidelines N=57	**Post-guidelines N=33**	***P****
Demographics			
Male (%)	33 (57)	17 (51)	0.661
Ethnicity (% Hispanic)	1 (2)	2 (6)	0.552
Race (%)			0.833
Black	26 (46)	13 (39)	
White	25 (44)	18 (55)	
Asian	2 (3)	1 (3)	
Other	4 (7)	1 (3)	
Gestational age, weeks, median (IQR)	31.3 (27.2-36.9)	35.2 (31.4-37.1)	0.203
Birth weight, g, median (IQR)	1523 (890-2680)	2170 (1325-2770)	0.293
Birth weight z-score, median (IQR)	-0.04 (-0.8 – 0.9)	-0.25 (-0.95 – 0.29)	0.169
Baseline Characteristics			
Diagnosis (%)			0.200
Atresia	11 (19)	11 (33)	
Gastroschisis	9 (16)	9 (27)	
Hirschsprungs	2 (4)	0 (0)	
NEC	21 (37)	5 (15)	
Other	3 (5)	2 (6)	
SIP	9 (15)	4 (12)	
Volvulus	2 (3)	2 (6)	
Pre-operative PN days, median (IQR)	5 (1-12)	2 (0-6)	0.042
Baseline DB mg/dl, median (IQR)	0.5 (0.3 – 1.5)	0.4 (0.2-0.8)	0.105
Surgical Characteristics			
Location of disease, *>1 possible* (%)			
Duodenum	4 (7)	11 (33)	0.002
Jejunum	30 (53)	11 (33)	0.085
Ileum	32 (56)	14 (42)	0.275
Colon	11 (19)	5 (15)	0.777
Initial procedures (%)			0.127
Peritoneal Drain	2 (3)	3 (9)	
Resection/anastomosis	17 (30)	10 (30)	
Resection/ostomy	18 (32)	10 (30)	
Ostomy/no resection	11 (19)	1 (3)	
Abdominal wall closure	9 (16)	9 (27)	
Subsequent Procedures, *>1 possible* (%)			
Resection/anastomosis	20 (35)	3 (9)	0.006
Resection/Ostomy	3 (5)	1 (3)	1.000
Abdominal wall closure	1 (2)	0 (0)	1.000
Ostomy reversal	24 (42)	5 (15)	0.010
Total resection length[a], median cm (IQR)	12 (6-22)	8 (0-22)	0.170
Ileocecal valve present (%)	47 (82)	28 (85)	1.000
Colon preserved (%)	50 (88)	32 (97)	0.311

Abbreviations: IQR, interquartile range; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; PN, parenteral nutrition; DB, direct bilirubin

[a]N=44 pre-guideline and N=20 post-guideline

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

Table 5. Nutrition Metrics, IFALD & Other Outcomes			
	Pre-guidelines *N*=57	**Post-guidelines *N*=33**	***P* ***
Nutrition Metrics			
1st post-operative feed, days median (IQR)	13 (7-23)	8 (6-15)	0.048
Type of post-operative feed (%)			0.156
Breast milk	37 (65)	23 (70)	
Donor milk	3 (5)	2 (6)	
Regular	1 (2)	4 (12)	
Hydrolysate	3 (5)	1 (3)	
Amino acid	13 (22)	3 (9)	
Initial feed volume, ml median (IQR)	10 (6-14)	20 (10-20)	<0.001
Bolus feeds initially (%)	43 (77)	14 (42)	0.001
50% EN,[a] days, median (IQR)	11 (5-21)	5 (3-12)	0.012
100% EN,[a] days, median (IQR)	21 (8-36)	11 (6-20)	0.089
Type of EN at discharge (%)			
Breast milk	24 (42)	15 (44)	0.827
Regular	14 (25)	12 (36)	0.334
Hydrolysate	9 (16)	4 (12)	0.761
Elemental	16 (28)	3 (9)	0.036
(>1 possible)			
Mucous fistula feeds (%)	8 (14)	2 (6)	0.315
IFALD & Other Outcomes			
IFALD (%)	40 (70)	16 (48)	0.046
Peak DB, mg/dl, median (IQR)	5.6 (0.8 – 9.5)	2.3 (1.5-5.0)	0.011
DB >10mg/dl (%)	12 (21)	1 (3)	0.027
Total PN, days, median (IQR)	52 (31-99)	22 (14-49)	0.012
Home PN required (%)	9 (16)	1 (3)	0.084
NEC after feeding (%)	3 (5)	1 (3)	1.000
Culture-positive infection (%)	23 (40)	6 (18)	0.036
Length of stay, days, median (IQR)	82 (33-113)	52 (25-81)	0.077
Discharge weight z-score, median (IQR)	-1.5 (-2 - -0.8)	-1.0 (-1.5 – 0.9)	0.0451

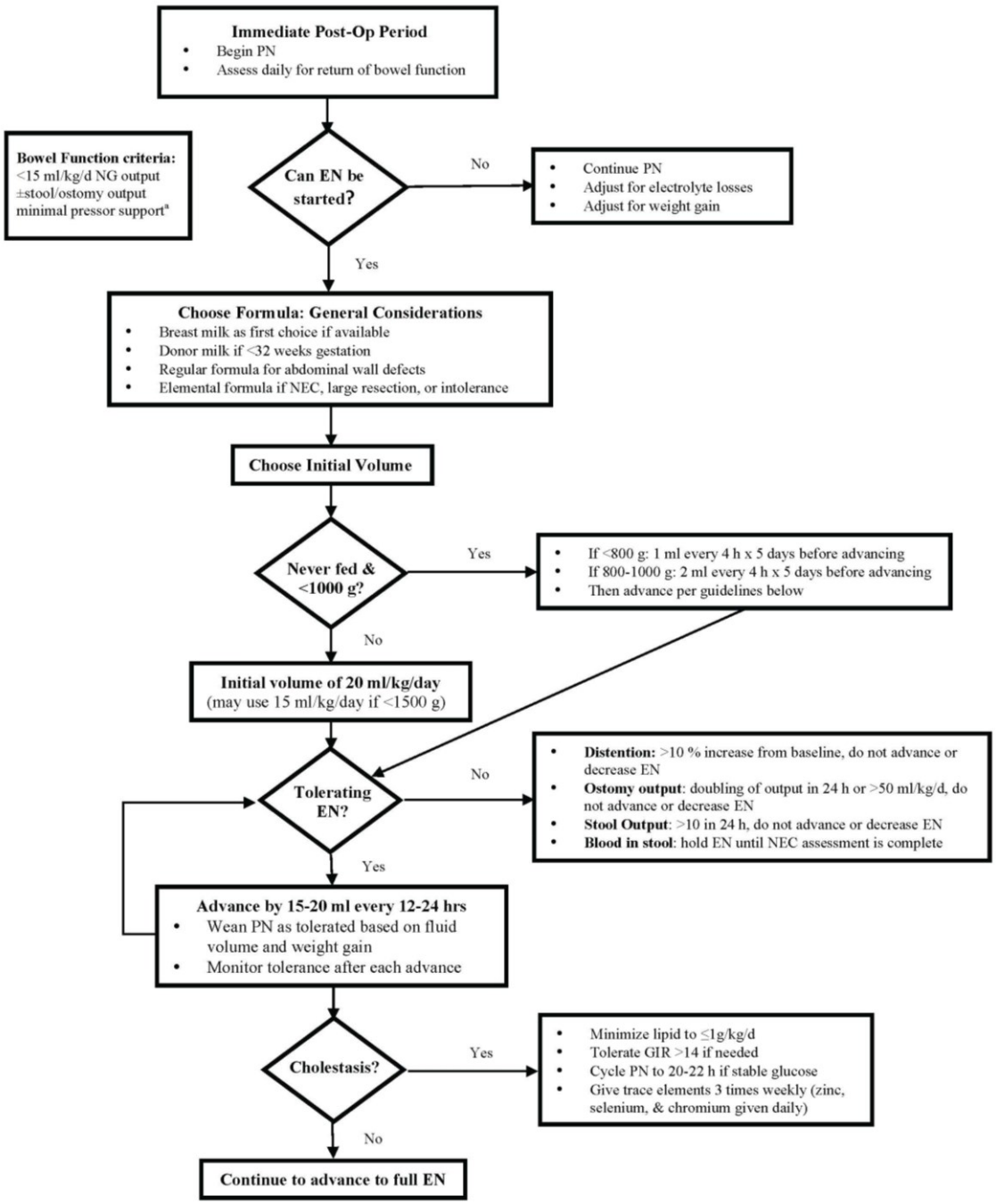
Abbreviations: IQR, interquartile range; EN, enteral nutrition; DB, direct bilirubin; IFALD, parenteral nutrition-associated liver disease; PN, parenteral nutrition; NEC, necrotizing enterocolitis

[a]days from start of post-operative feeds; pre-guidelines: 50 infants reached 50%, 47 reached 100%; post-guidelines: 32 infants reached 50% and 100%

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

FIGURES

Figure 4. Feeding Guideline Decision Diagram.



Abbreviations: PN, parenteral nutrition; EN, enteral nutrition; NG, nasogastric; NEC, necrotizing enterocolitis; DB, direct bilirubin; GIR, glucose infusion rate
[a]<5mcg/kg/min dopamine

Figure 5. Run chart of initial post-operative feeding volume among consecutive infants. The dashed gray line represents the baseline median. Once team meetings were implemented, a shift to higher initial volumes was seen (black line), with most infants starting enteral nutrition above the median of 10 ml/kg/day.

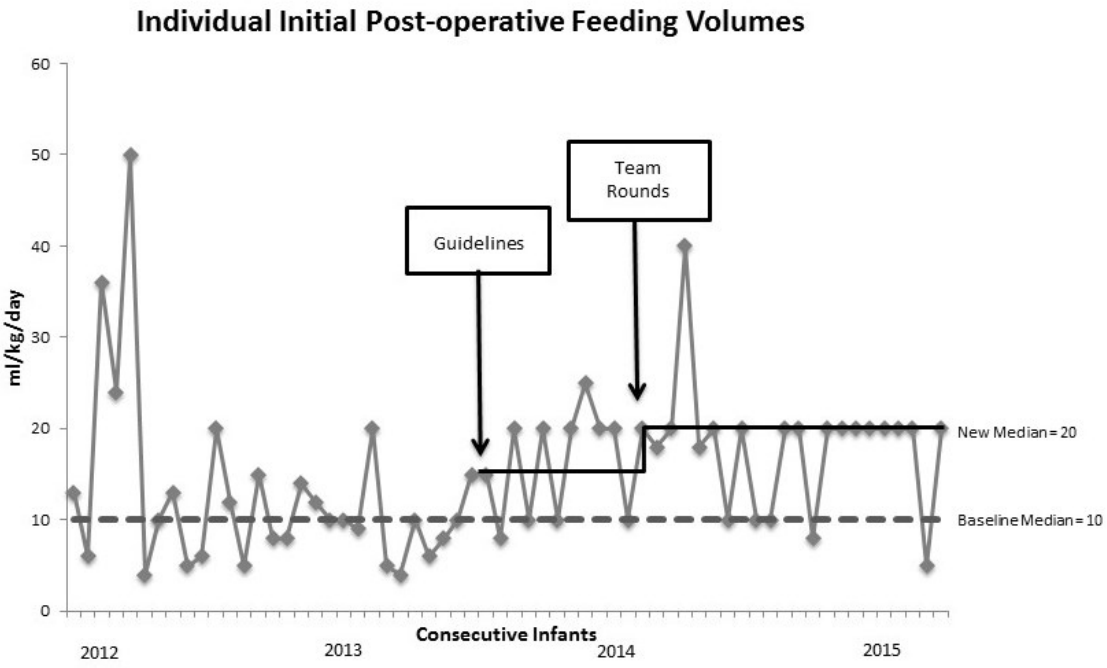


Figure 6. Run chart of days to reach 50% enteral nutrition (EN) after resuming feeding. The dashed gray line represents the baseline median. Once team meetings were implemented, a shift was seen (black line), with most infants reaching 50% EN in <11 days. Gaps indicate infants who did not achieve 50% EN by discharge.

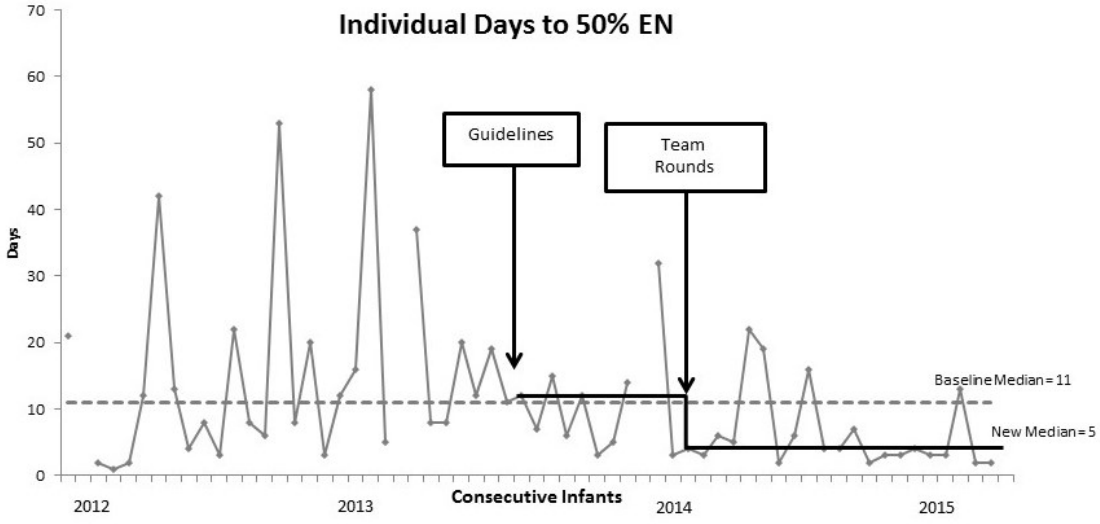


Figure 7. Run chart of days to reach 100% enteral nutrition (EN) after resuming feeding. The solid gray line represents the baseline median. Once team meetings were implemented, a shift was seen, with most infants reaching 100% EN in <21 days. Gaps indicated infants who did not achieve 100% EN by discharge.

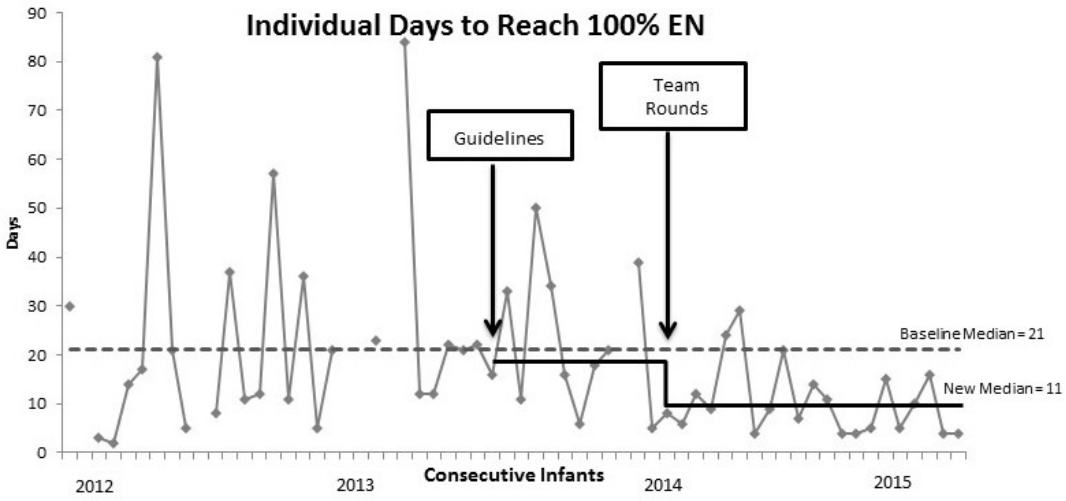
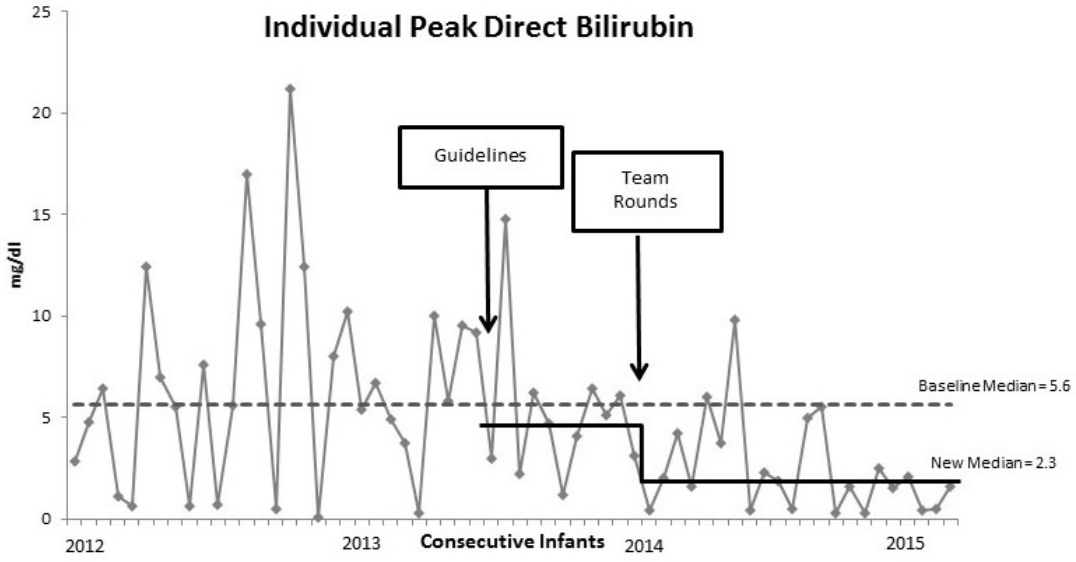


Figure 8. Run chart of peak direct bilirubin (DB) among sequential infants. The solid gray line represents the baseline median. After guideline implementation, a shift was seen; most infants had a peak DB below the median.



CHAPTER 4. IMPROVED POST-OPERATIVE ENTERAL NUTRITION REDUCES THE RISK OF INTESTINAL FAILURE ASSOCIATED-LIVER DISEASE IN SURGICAL INFANTS

ABSTRACT

Background: Feeding practices vary for surgical infants at-risk for intestinal failure, and insufficient enteral nutrition (EN) is thought to contribute to intestinal failure-associated liver disease (IFALD). Our objective was to implement feeding guidelines to reduce the time to reach 50% of EN and the incidence and severity of IFALD.

Methods: Guidelines were implemented October 2013, and pre- (2007-2013) and post-guideline (2013-2016) cohorts were compared. Infants <6 months old undergoing intestinal surgery were included; those with pre-existing liver disease or surgery at outside facilities were excluded. Key modifications in the guidelines included higher initial EN volumes of 20 ml/kg/day and daily advancement if tolerated compared to pre-guideline practices. The primary outcomes were IFALD incidence (peak direct bilirubin [DB] >2mg/dl) and severity (DB>5 mg/dl). Other measures included initial EN volume, time to reach 50% and 100% goal calories from EN, and the incidence of necrotizing enterocolitis (NEC) after feeding.

Results: There were 83 pre-guideline and 73 post-guideline infants. IFALD incidence decreased from 71 to 53% (*P*=0.03), and median peak DB decreased from 5.7 to 2.3 mg/dl (*P*=0.003). After adjusting for diagnosis and prematurity, the odds of developing moderate-to-severe IFALD was 68% lower among infants in the post-guideline cohort (*P*=0.002). Comparing pre- and post-guideline practices, the initial post-operative EN volume increased from 10 to 20 ml/kg/day (*P*=0.001), and time to reach 50% EN decreased from a median of 10 to 5 days (*P*=0.013). The incidence of NEC after initiating EN did not change (7 v 4, *P*=0.346).

Conclusions: Implementation of feeding guidelines resulted in reduced time to reach 50% goal EN calories and reduced IFALD incidence and severity.

INTRODUCTION

The optimal strategy for feeding infants after intestinal procedures for disorders such as necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), gastroschisis, and atresia, is not well understood, resulting in variability amongst providers as well as feeding-related risks.[57,59] Such infants are at risk of complications of over-feeding, such as post-operative NEC, a highly morbid inflammatory process that can result in massive intestinal necrosis. Feeding intolerance from intestinal dysmotility can be difficult to distinguish from the early signs of NEC, resulting in understandable apprehension about feeding advancement. Infants may be kept on trophic feeding volumes for extended periods of time. Trophic EN volumes are meant to stimulate the intestine but provide minimal calories, and parenteral nutrition (PN) is therefore needed. Infants are also at risk of complications from under-feeding. Inadequate enteral nutrition and prolonged reliance upon PN increases the risk of central venous catheter-associated line infections and intestinal failure-associated liver disease (IFALD).[11,19,22]

IFALD typically manifests as cholestasis in the infant population, and is therefore defined as a direct bilirubin (DB) >2mg/dl that persists for >1 week in the setting of PN use and the absence of other etiologies of liver disease.[8,9] 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.[10,13,58] For infants with intestinal failure, those requiring PN for >30-60 days, IFALD becomes a significant risk factor for chronic liver disease and the need for liver transplantation.[14] 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.

In response to our previously reported high rate of IFALD and variable feeding practices, we created an intestinal rehabilitation team to guide post-operative feeding with the goal of

reducing the incidence of IFALD.[71] Our feeding algorithm, implementation strategy, and interim success in reducing the time to reach feeding goals, overall PN exposure, and incidence and severity of IFALD were previously reported, comparing a baseline period 3 years prior to guideline implementation (57 infants) and 15 months after the implementation (33 infants).[92] In this study we report our outcomes in an expanded cohort 6 years prior to and 2 ½ years after implementation of the feeding guidelines.

Our hypothesis was that 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.

METHODS

Study Design and Population

We performed a pre- and post-guideline implementation comparison. Retrospective data were collected on the pre-guideline cohort from January 2007-June 2013, and prospective data were collect on the post-guideline cohort from October 2013-June 2016. Approval and waiver of consent were obtained from the Institutional Review Board, as the feeding guidelines were implemented standard of care in the Neonatal Intensive Care Unit (NICU). Infants in the NICU with intestinal surgery prior to 6 months of age who survived to be fed enterally and required at least 7 days of PN were enrolled. Surgical procedures included enterotomy and enterostomy with and without resection, abdominal wall closure, and peritoneal drain. The principal diagnoses were NEC, 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 outside facility.

Feeding Guidelines. Consensus- and evidence-based guidelines were developed by our Intestinal Rehabilitation team, which included representatives from neonatology, surgery, gastroenterology, nutrition, and nursing. These guidelines have been previously published.[92] Major changes in the guidelines, compared to previous usual care, included a higher initial post-

operative EN volume and rate of feeding advancement. The initial recommended starting volume was 15-20 ml/kg/day. Exceptions included infants <1000 g who were not previously fed – such infants were fed according to another protocol of 1-2 ml every 6 hours for 5 days, and then the post-operative guidelines were followed. The recommended advancement rate was 20 ml/kg/day every day if there were no signs or symptoms of intolerance. Signs of intolerance included increased ostomy or stool output, increased emesis, increased abdominal girth of >10%, or change in vital signs, such was increased apnea or bradycardia events. If signs of intolerance were present, EN was held at the current rate or decreased by 10-20%. If more worrisome signs such as blood in stools or clinical decompensation occurred, EN was discontinued. The individualized goal caloric requirement generally ranged from 110-130 kcal/kg/day and was determined by the dietician based on gestational age and growth.

Parenteral Nutrition. Only soy-based intravenous lipid was available at our center. PN lipid dosing remained the same in both study periods, and was generally increased to 3g/kg/day to meet caloric needs. Lipid restriction of 1mg/kg/day was employed once direct bilirubin was >2mg/dl.

Data Collection and Metrics

Data were collected from the medical record and managed in an electronic database. Pre-guideline infants were identified through surgical billing records. Post-guideline infants were identified at the time of surgery. *Baseline Metrics*. Sex, race, ethnicity, gestational age, birth weight, diagnosis, age at surgery, type of procedure, length and location of resection, residual small bowel, PN exposure prior to surgery, and baseline direct bilirubin at the time of surgery were recorded.

Post-operative Metrics. The first date, type, route, and volume of enteral nutrition were recorded. Weekly data included type, volume, and percent of calories of EN, PN lipid dose, weight and z-score, ostomy/stool output, and serum transaminases, total and direct bilirubin. The

volume of first post-operative feeding and rate of advancement were used to monitor adherence to guidelines, and potential deviations were clarified with the primary teams to determine lack of feeding advancement was due to EN intolerance vs. guideline deviation.

Outcomes. The primary outcomes were the incidence and severity of IFALD. The commonly utilized definition of IFALD in infants was used, defined as a direct bilirubin of ≥2mg/dl that persisted for at least 1 week in the absence of other known liver disease.[8] 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.[2,78] 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 mortality, total number of PN days, culture-positive infection (blood, urine, or peritoneal fluid), development of NEC after post-operative feeding, length of stay, discharge weight z-score, and time to resolution of IFALD if it occurred.

Statistical Analysis

The sample size estimate was based on our original IFLAD incidence of 70% among surgical infants. A sample size of 140 (70 per group) was estimated to be able to detect a 20% improvement in IFALD incidence with 80% power and a type 1 error rate of 5%. With the current sample size, we had 90% power (alpha=0.05) to detect a 20% improvement in incidence of moderate-severe IFALD as well.

Given the relatively small sample sizes within the strata of the categorical variables and non-normal distribution of most continuous variables, we used Fischer exact tests to compare differences in categorical variables and non-parametric Wilcoxon rank-sum tests to compare the medians of continuous variables between the study periods. Non-normal continuous variables were log transformed and evaluated for normal distribution (using Shapiro-Wilk test)

We used multiple logistic regression to examine the associations between IFALD (any severity, moderate-severe, and severe) and exposure to feeding guidelines, with adjustment for clinically and statistically significant patient characteristics (from bivariate analysis). We examined the potential confounding and modifying effects of gestational age, birth weight, sex, race, diagnosis, primary surgical procedure, and baseline direct bilirubin. A priori, diagnosis and gestational age were considered the most clinically relevant characteristics. Characteristics 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 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 also 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, TX: StataCorp LP).

RESULTS

In the pre-guideline cohort, 83 infants were included, and 73 infants were included in the post-guideline cohort (Figure 9).

Baseline characteristics of both cohorts are described in Table 6. Age, sex, ethnicity/race, and gestational age were similar in both groups. The diagnoses of NEC, SIP, gastroschisis,

atresia, and other were also similar between cohorts. The difference in surgical procedures between cohorts was due to the more frequent use of peritoneal drains in infants with NEC or SIP in the post-guideline cohort, compared to the more frequent ostomy use in these infants pre-guidelines.

Feeding Outcomes and Adherence to Guidelines

Similar to our previous interim results at 15 months post-implementation of guidelines, achievement of feeding goals was improved in the post-guideline cohort compared to the pre-guideline cohort (Table 7). The time to initiation of EN post-operatively was decreased by a median of 5 days (P=0.017). 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 two 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). To account for differences in post-operative readiness to feed, longer *nil per os* (NPO) requirements for NEC, feeding tolerance once EN began and adherence to guidelines, time to reach 50% of goal EN was measured from both the time of surgery and time of initiation of post-operative EN. Time to reach 50% EN decreased by a median of 9 days from the time of surgery (P=0.005) and by a median of 5 days from the first post-operative feed (P=0.019). Time to reach 100% EN was still variable given the nature of critically ill premature infants with intestinal failure, and the difference in time was not statistically significant.

The odds of reaching 50% of EN within 7 days of starting EN were significantly higher in the post-guideline cohort (OR 6.5, P<0.001), even after adjusting for diagnosis and prematurity (Table 8). Time (in weeks) to reach 50% and 100% EN goals are also displayed using Kaplan-Meier curves (Figure 10 & 11). Improved time to reach feeding goals in the post-guideline cohort was again demonstrated. Time to reach feeding goals among infants with guideline deviations was intermediate between the other two groups, suggesting some improvement in reaching feeding goals even if guidelines were not strictly adhered to.

Guideline adherence was overall good. 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 19 infants had at least one deviation. There were 14 volume deviations (19%) and 12 advancement deviations (16%). Nearly half of the deviations (45%) occurred in the initial few months of the study prior to implementation of weekly multi-disciplinary rounds. There were also intermittent deviations when new faculty less familiar with the guidelines were managing patient care. Deviations were most likely to occur in infants with a diagnosis of NEC or SIP (42%).

Breast milk was the type of EN used most frequently in both groups (Table 7). Continuous feeding was started more frequently in the post-guideline cohort. 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.

IFALD Incidence and Severity

When exploring all cases of IFALD, the cumulative incidence in the post-guideline cohort was lower compared to the pre-guideline cohort (53 vs. 71%, *P*=0.031); however, after adjusting for diagnosis and prematurity, this association was attenuated (odds ratio [OR] 0.50, *P*=0.076) (Table 8). The univariate analysis used to determine model selection for moderate-severe IFALD is shown in Table 9. When exploring the more clinically relevant moderate-severe IFALD (DB ≥5mg/dl), the incidence was also less in the post-guideline group (29 v 56%, *P*=0.001), and the odds of developing IFALD remained statistically significant once adjusting for diagnosis and prematurity (OR 0.32, P=0.002).

Peak direct bilirubin and resolution of IFALD. The median peak direct bilirubin was lower in the post-guideline cohort (2.3 vs. 5.7 mg/dl, *P*=0.003). Among those infants who developed IFALD, resolution of IFALD by time of discharge was more likely to occur in the

post-guideline cohort, 64% vs. 25% (P<0.001). Time to resolution was also faster among those in the post-guideline cohort (*P*<0.001), displayed in Figure 12. The median discharge direct bilirubin was 1.0mg/dl (0.3-1.9) in the post-guideline group, compared to 2.4 mg/dl (0.6-4.8) in the pre-guideline cohort (*P*=0.001).

Moderate-to-severe IFALD was most commonly found in infants with NEC or SIP. Within the post-guideline cohort, 12 (48%) of infants with NEC/SIP developed moderate-to-severe IFALD vs. 33 (73%) in pre-guideline cohort (*P*=0.041). Infants with these diagnoses were also prone to both feeding intolerance, as well as deviations from the guidelines (33%). The median peak direct bilirubin was 5.3 mg/dl (2.8-10.7) among those with guideline deviations (n=8) versus 4.7 mg/dl (1.7-6.0, *P*=0.008) among those without deviations (n=16).

Other Outcomes

The adjusted odds of developing secondary outcomes for infants in the post-guideline cohort are also displayed in Table 8.

PN length use, length of stay, and discharge weight. The total days of PN use were decreased in the post-guideline cohort, 25 days (17-59) vs. 52 days (18-99, *P*=0.026). The number of infants who were discharged home on PN was 4 (6%) in the post-guideline cohort and 12 (14%) in the pre-guideline cohort (*P*=0.070). Length of stay was shorter in post-guideline cohort, 52 days (26-84) vs. 80 days (33-124; *P*=0.027). Weight gain was similar in both cohorts, with median discharge weight z-score of -1.0 (-0.5-1.7) in the post-guideline cohort and -1.4 (-0.7-2.0) in the pre-guideline cohort (*P*=0.070). Weight z-scores of <-2.0 represent the bottom 5th percentile. Among the infants in the pre-guideline cohort, 19 (23%) had a discharge weight z-score <-2.0 (range -2.1-5.1). In the post-guideline cohort, 8 (11%) infants had a discharge weight z-score <-2.0 (range -2.1- -4.7).

*Post-operative necrotizing enterocolitis***.** Seven infants in the post-guideline cohort and 4 infants in the pre-guideline cohort developed post-operative NEC (*P*=0.346). The original

diagnoses were SIP (4), NEC (3), atresia (2), gastroschisis (1), and meconium ileus (1). Medical NEC developed in 7 (63%), and 4 developed surgical NEC (36%). Three infants in the post-guideline cohort developed NEC totalis and died. One infant had SIP, had only received a day of trophic elemental formula feeding and had remained in critical condition 3 weeks prior to the NEC event. The second infant had gastroschisis, had been tolerating full enteral feeds of 22 kcal/oz. cow's milk formula, and had been transferred out the NICU to the general floor for several days prior to sudden NEC event. The third infant had an original diagnosis of NEC and had achieved full EN with donor breast milk fortified to 22 kcal/oz. for 3 days prior to NEC event. This infant had guideline departures for both lower than recommended initial volume (10 ml/kg/day) and slower initial advancement.

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

Enteral Nutrition as a Predictor of IFALD Sub-analysis

A sub-analysis was performed to evaluate the impact of timing of EN and IFALD irrespective of cohort assignment, to account for those infants fed more assertively prior to guideline development and those in the post-guideline cohort that had significant deviations from the guidelines. The odds of developing moderate-severe IFALD was explored based on time to reach 50% EN rather than participation in the guidelines (Table 10). Only infants with complete feeding data were included (N=128). The following were excluded: NEC (1), SIP (5), gastroschisis (5), atresia (5), Hirschsprungs (1), and volvulus (1). Exploration of the data showed an association between the rise in peak direct bilirubin and length of time to reach 50% EN, particularly within the first 21 days of surgery. None of the infants developed moderate-severe cholestasis if 50% EN was reached with 7 days of surgery, but only 14 (18%) infants were able to achieve feeds this quickly. Among the 44 infants (34%) who were able to achieve 50% EN within 14 days, only 3 developed moderate cholestasis (all 3 had atresia). Reaching 50% EN within 21

days was feasible for 79 (56%) of the infants. The adjusted odds of developing moderate severe IFALD was reduced by 89% if 50% EN was reached within 21 days of surgery ($P<0.001$). With each additional week required to reach 50% EN, the odds of developing moderate-severe IFALD increased. Figure 13 shows the distribution of peak DB by diagnosis, comparing those reaching 50% EN within 21 days to those infants that took longer.

In a separate analysis, how quickly EN was achieved once feeding began (regardless of time to start EN post-operatively) was also evaluated. The adjusted odds of developing moderate-severe IFALD was decreased by 87% if 50% EN was reached within 7 days of initiating EN ($P<0.001$); however 12 of 64 (19%) of infants reaching 50% EN within 7 days still developed moderate-severe cholestasis. Those diagnoses included NEC (4), atresia (4), SIP (3), and volvulus (1). These results suggest there was benefit in quickly advancing EN to 50% once post-operative feeding began, but a delay in starting feeds post-operatively can still result in moderate-severe IFALD.

Missing Data

Baseline direct bilirubin was missing from 17 infants (11%); 11 were in the pre-guideline cohort and 6 were in the post-guideline cohort. As the baseline direct bilirubin was collinear the diagnosis, this variable was not included in the final analysis and therefore 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. In the post-guideline cohort, 3 infants were not yet discharged, so length of stay and discharge growth parameters were missing. Discharge growth parameters 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 varies by 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.[14,81] Optimizing EN reduces the risk of IFALD, and feeding guidelines offer a systematic approach to feeding by reducing inter-provider variability. After implementing post-operative feeding guidelines in our NICU, we have seen faster achievement of enteral feeding goals and reduced IFALD severity.

While the overall risk of IFALD decreased with the use of the guidelines, 50% of infants still developed at least mild IFALD. The odds of developing at least moderately severe IFALD, a more clinically germane complication, were significantly reduced in by 68% the post-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 to the pre-guideline cohort.

Feeding guidelines are emerging in NICUs in effort to balance the benefits of EN with the risk of NEC in high-risk infant populations.[29,64] 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.[66] Early feeding likely has advantages. 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.[65] 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.[63,68,100] 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.[69] 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.[70]

The ideal 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 feeds. 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. While 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. However, infants who were <1000 g and not previously fed were kept on trophic feeding volumes for the first 5 days in accordance with our very low birth weight feeding protocol. How quickly EN could be advanced past 50% EN was highly individualized and affected by motility, malabsorption and other co-morbidities that affect critically ill infants (interruptions in EN for other procedures, possible infection, changes in respiratory status, etc.).

Achieving 50% of goal calories from EN within 14-21 days of surgery appeared to be protective against moderate-severe IFALD, regardless of diagnosis of NEC, SIP, gastroschisis, or atresia. The infants who were able to quickly achieve 50% of EN had lower odds of developing moderate-severe IFALD even if the time to reach 100% EN was still prolonged. Part of the challenge of achieving 50% of EN more quickly is being able to start post-operative EN in a timely manner.

The ideal time to begin feeding post-operatively is also unclear. In the post-guideline cohort, the time to initiate post-operative EN was shorter. This change is likely a combination of purposeful earlier introduction of feeding based on weekly discussions and increased comfort with earlier feeding among providers, as well as fewer infants in the cohort with a diagnosis of NEC. Infants with NEC rarely started EN prior to 14 post-operative days, and often had slower advancement, both due to feeding intolerance and due to provider reluctance to advance PN. Readiness to feed is often based on clinical signs such as abdominal distention and stool or ostomy output. More informative criteria for determining readiness to feed are needed to guide clinical care.

The feeding guidelines were generally well tolerated. 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.[7,101] NEC most commonly occurs in preterm infants and recurs in 10% of infants.[7,102] NEC has also been reported in 10-20% of infants with gastroschisis.[103] Careful monitoring with all feeding advancement is therefore necessary. While not statistically different from the pre-guideline cohort or outside the incidence reported at other centers, 7 cases of NEC occurred after post-operative feeding in the post-guideline cohort. In one of the deaths following NEC, the infant was not being fed. In the other two cases, the infants had already achieved 100% EN volume and EN had been fortified to 22 kcal/oz. While our guidelines do not specifically give recommendations for fortification, it is generally our practice not to fortify above 24 kcal/oz. unless significant growth restriction persists. Strategies for fortification in infants at risk of NEC are currently debated in the literature without clear best practices.[104]

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, reducing the risk of infection. Improved EN promotes intestinal mucosal

barrier function, thereby reducing intestinal bacterial translocation and reducing the risk of infection.[31,105] Faster achievement of EN also allows for sooner discontinuation of PN and the central catheter, 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 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. None-the-less, we have seen continued improvement in outcomes once guideline adherence was achieved. 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 goal EN. With improved EN, we have seen a modest reduction overall IFALD incidence and a significant reduction in moderate-severe IFALD.

TABLES

Table 6. Demographic, Baseline, & Surgical Characteristics			
	Pre-Guidelines N=83	**Post-Guidelines N=73**	***P* ***
Demographics			
Male (%)	51 (61)	38 (52)	0.260
Ethnicity (% Hispanic)	4 (5)	4 (5)	1.000
Race (%)			0.498
Black	36 (43)	32 (44)	
White	38 (46)	37 (50)	
Other	9 (11)	4 (6)	
Gestational age, weeks, median (IQR)	33.0 (27.1-37.0)	34.4 (27.7-37.0)	0.582
Birth weight, g, median (IQR)	1610 (920-2575)	2065 (910-2700)	0.558
Birth weight z-score, median (IQR)	-0.1 (-0.8-0.9)	-0.2 (-0.9-0.3)	0.185
Baseline Characteristics			
Primary Diagnosis (%)			0.135
Atresia	15 (18)	19 (26)	
Gastroschisis	14 (17)	18 (25)	
NEC	30 (36)	14 (19)	
SIP	15 (18)	11 (15)	
Volvulus	2 (2)	3 (4)	
Other	3 (4)	8 (11)	
Age of first feed, days, median (IQR)	8 (3-18)	9 (3-14)	0.701
Pre-operative PN days, median (IQR)	5 (1-12)	4 (1-7)	0.158
Baseline DB mg/dl, median (IQR)	0.5 (0.3-1.5)	0.4 (0.2-0.7)	0.058
Surgical Characteristics	5 (1-12)	4 (1-7)	0.158
Age at surgery, days, median (IQR)	7 (3-16)	6 (3-9)	0.170
Initial procedure (%)			0.001
Peritoneal Drain	3 (4)	11 (15)	
Resection/anastomosis	24 (29)	22 (30)	
Resection/ostomy	26 (31)	17 (23)	
Ostomy/no resection	17 (21)	3 (4)	
Abdominal wall closure	12 (15)	20 (27)	
Subsequent Procedures (%)			
Resection/anastomosis	26 (31)	6 (8)	<0.001
Resection/Ostomy	6 (7)	6 (8)	1.000
Abdominal wall closure	3 (4)	1 (1)	0.623
Ostomy reversal	34 (41)	13 (18)	0.002
(>1 choice possible)			
Total resection length[a], median cm (IQR)	12 (5-17)	10 (6-25)	0.941
Residual bowel[a], percent (IQR)	92 (68-97)	89 (79-94)	0.896
Ileocecal valve present (%)	65 (78)	61 (83)	0.350
Colon preserved (%)	74 (89)	68 (93)	0.335

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

[a]If resection occurred (N=67 historical and N=33 guidelines)

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

Table 7. Feeding Metrics & Outcomes			
	Pre-Guidelines N=83	**Post-Guidelines N=73**	***P* ***
1st post-operative feed, days median (IQR)	13 (7-25)	9 (6-15)	0.017
Type of post-operative feed (%)			0.024
Breast milk	51 (65)	57 (78)	
Donor milk	3 (4)	5 (7)	
Regular	4 (5)	6 (8)	
Hydrolysate	5 (6)	1 (1)	
Amino acid	16 (20)	4 (6)	
Initial feed volume, ml/kg/day median (IQR)	10 (8-14)	20 (10-20)	<0.001
Bolus feeds initially (%)	50 (68)	36 (49)	0.028
50% EN,[a] days, median (IQR)	10 (4-20)	5 (3-12)	0.019
100% EN,[a] days, median (IQR)	19 (6-32)	11 (6-21)	0.115
Type of EN at discharge (%)			
Breast milk	33 (40)	29 (40)	1.000
Regular	20 (24)	24 (33)	0.285
Hydrolysate	11 (13)	9 (12)	1.000
Elemental	30 (36)	10 (14)	0.002
(>1 choice possible)			
Mucous fistula feeds (%)	8 (11)	4 (6)	0.370

Abbreviations: IFALD, intestinal failure-associated liver disease, IQR, interquartile range; DB, direct bilirubin PN, parenteral nutrition; NEC, necrotizing enterocolitis, SB, small bowel

[a]Days to reach feeding goals from time of first post-operative feed

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

Table 8. Univariate and multivariate 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)	39 (53)	0.47 (0.24-0.90)	0.024	0.50 (0.24-1.07)	0.076
Moderate-Severe IFALD (DB>5mg/dl)	46 (56)	21 (29)	0.30 (0.15-0.58)	<0.001	0.32 (0.15-0.67)	0.002
Severe IFALD (DB>10mg/dl)	16 (20)	6 (8)	0.37 (0.14-0.42)	0.050	0.36 (0.12-1.05)	0.062
Secondary Outcomes						
50% EN[a] <7 days	19 (23)	45 (64)	5.4 (2.70-10.86)	<0.001	6.54 (2.92-14.61)	<0.001
Resolved IFALD	15 (25)	25 (64)	5.24 (2.17-12.6)	<0.001	6.96 (2.55-19.0)	<0.001
Post-op NEC	4 (5)	7 (10)	2.0 (0.58-7.46)	0.254	2.10 (0.56-7.91)	0.270
Positive Culture	34 (41)	12 (16)	0.28 (0.13-0.60)	0.001	0.29 (0.13-0.67)	0.004
Mortality	3 (4)	3 (4)	1.1 (0.22-5.84)	0.873	2.10 (0.32-14.0)	0.441

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)

[a]Time to reach 50% EN from initial post-operative EN. Similar results seen to time to reach 50% EN from date of surgery.

Table 9. Univariate and multivariate analysis of odds of developing moderate IFALD by risk factors				
Variable	**Unadjusted OR (CI)**	***P***	**Adjusted OR* (CI)**	***P***
Enrolled in guidelines	0.32 (0.16-0.62)	0.001	0.32 (0.15-0.67)	0.003
Diagnosis		<0.001		0.012
NEC/SIP	Ref		Ref	
Atresia	0.18 (0.07-0.45)		0.29 (0.10-0.85)	
Gastroschisis	0.15 (0.06-0.41)		0.20 (0.07-0.58)	
Other	0.30 (0.11-0.85)		0.50 (0.15-1.63)	
Prematurity	3.52 (1.62-7.64)	0.001	2.18 (0.85-5.53)	0.090
Sex (male)	0.80 (0.42-1.53)	0.505	0.71 (0.33-1.51)	0.374
Race		0.348		0.465
Black	Ref		Ref	
White	0.51 (0.18-1.46)		0.88 (0.41-1.89)	
Other	0.39 (0.07-2.23)		0.40 (0.09-1.71)	
Gestational age (log)	0.004 (0.0005-0.037)	<0.001		
Birth weight (log)	0.20 (0.10-0.37)	<0.001		
Age at surgery (log)	0.21 (1.10-1.93)	0.009		
Baseline DB (log)	4.44 (1.99-9.90)	<0.001		
PN prior to surgery (log)	1.65 (1.13-2.41)	0.009		
Positive culture	7.66 (3.46-16.92)	<0.001		

Abbreviations: IFALD, intestinal failure-associated liver disease, OR, odds ratio, CI confidence interval, NEC, necrotizing enterocolitis, SIP, spontaneous intestinal perforation, DB, direct bilirubin, 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)

Table 10. Univariate and multivariate analysis of odds of developing moderate IFALD based on time to reach 50% EN after the date of surgery irrespective of guidelines						
	Moderate-Severe IFALD (N=51)	**None (N=77)**	**OR (CI)**	***P***	**Adjusted OR (CI)**	***P***
50% EN ≤14 days	3[a] (6)	41 (53)	0.05 (0.02-0.19)	<0.001	0.03 (0.01-0.15)	<0.001
50% EN ≤21 days	13 (25)	59 (76)	0.10 (0.05-0.24)	<0.001	0.11 (0.04-0.29)	<0.001

Abbreviations: IFALD, intestinal failure-associated liver disease; EN, enteral nutrition

*Adjusted for diagnosis (NEC/SIP, Gastroschisis, Atresia, and Other), prematurity (gestational age <37 weeks), sex, and race (Black, White, Other)

[a]all 3 had atresia

FIGURES

Figure 9. Diagram of study design, enrollment, and participation

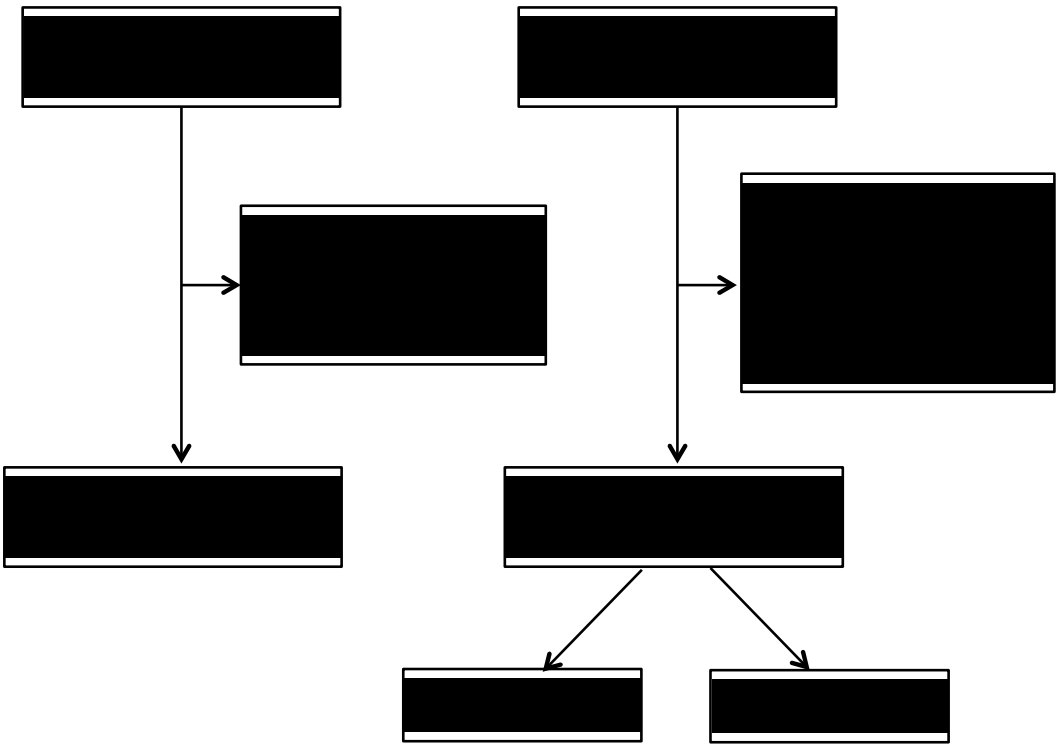


Figure 10. The time to reach 50% enteral nutrition (EN) was shorter in the post-guideline cohort (*P*<0.001).

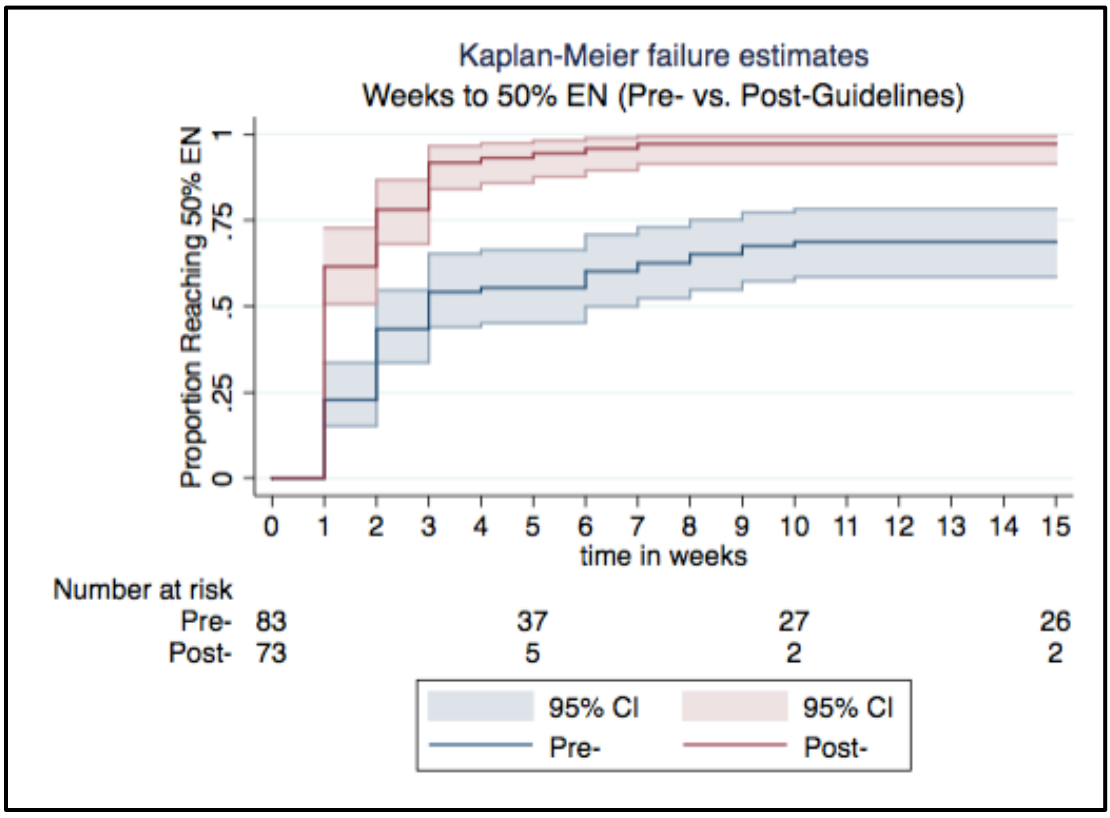


Figure 11. The time to reach 100% enteral nutrition (EN) was shorter in the post-guideline cohort (*P*<0.001).

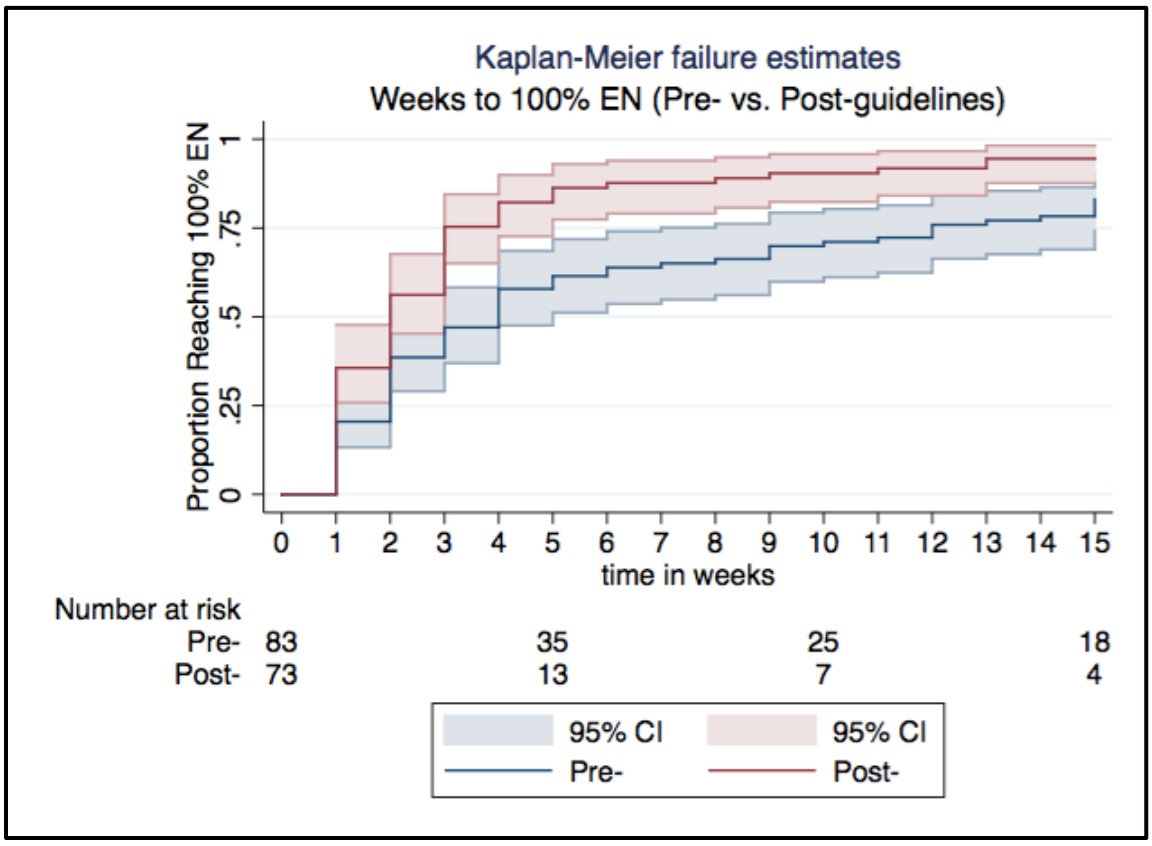


Figure 12. The time to resolution of intestinal failure-associated liver disease (IFALD) from the date of first occurrence was shorter in the post-guideline cohort (P<0.001).

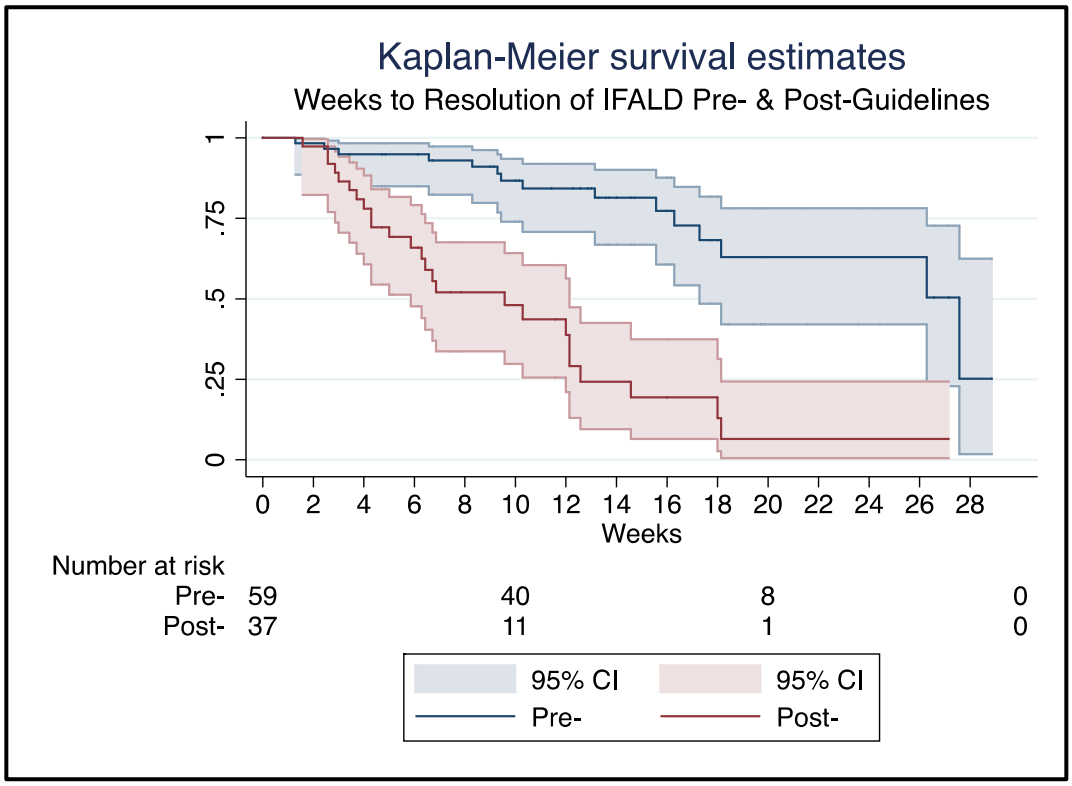
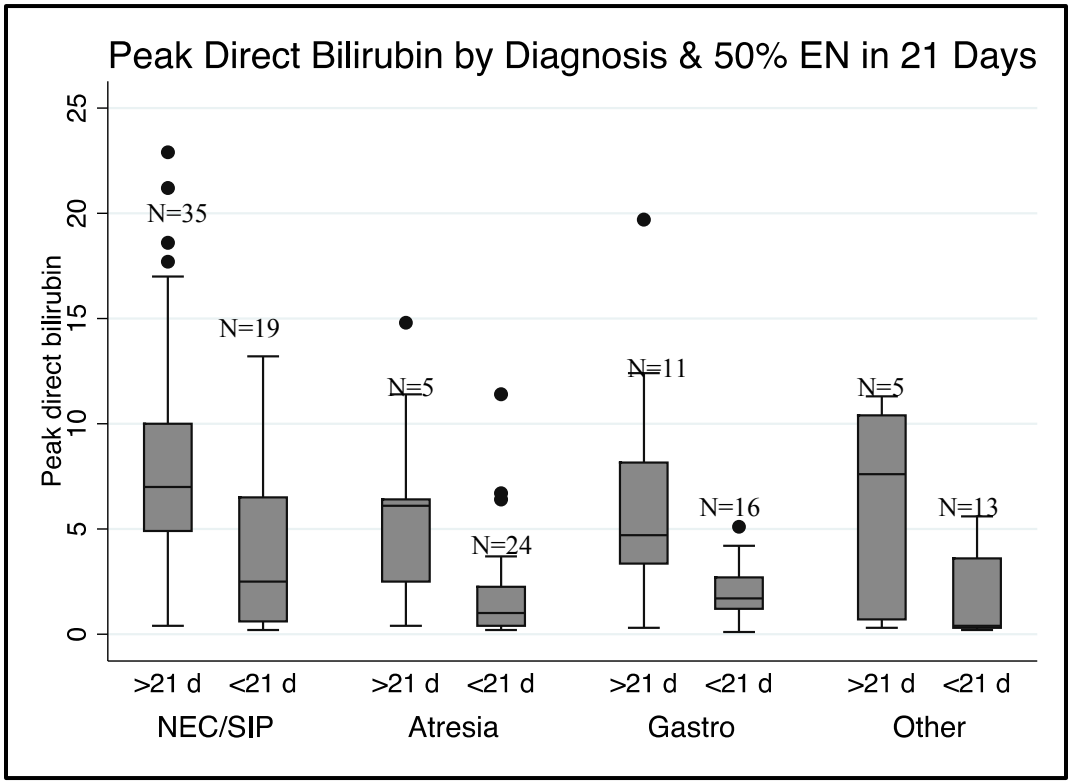


Figure 13. The peak direct bilirubin is shown by diagnosis, comparing infants able to reach 50% enteral nutrition (EN) within within 21 days to those who were not.



Chapter 5: Conclusions

Feeding infants after intestinal surgery is challenging, and such infants are at risk of developing intestinal failure and intestinal failure-associated liver disease (IFALD) as complications. To better understand the impact of enteral nutrition (EN) on the risk of IFALD among infants who have had intestinal surgery, we have conducted three separate studies.

In our baseline assessment of post-operative feeding practices and incidence of IFALD in the preceding five years, we found an unexpectedly high incidence of IFALD (60-90%), including a high incidence of moderate-severe IFALD with a median peak direct bilirubin of 7.5mg/dl. We also found considerable variability in feeding practices and prolonged use of trophic feeding with EN volumes <20 ml/kg/day. With that data, we then formed a multi-disciplinary neonatal intestinal rehabilitation team and created post-operative feeding guidelines for initiating and advancing EN and managing parenteral nutrition.

In our second study, we evaluated the implementation process of the feeding guidelines, adherence to guidelines, and the interim impact of the guidelines upon reducing the time to reach EN goals, and the incidence and severity of IFALD, compared to a pre-guideline cohort. In the first few months, there was suboptimal adherence to the guidelines, but after implementing weekly multi-disciplinary rounds, adherence improved. In real time, we saw shifts to higher initial EN volumes, reduced time to reach 50% of goal enteral nutrition, and a reduction in both IFALD incidence and peak direct bilirubin. During this time period, we also saw fewer cases of NEC, which have the highest risk of IFALD. However, even among infants with NEC, the severity of peak direct bilirubin decreased. We did not identify any unintended deleterious consequences from implementation of the guidelines, and the incidence of post-operative NEC was similar between cohorts.

Two and a half years after implementation of the guidelines, we reached our target sample size to evaluate whether being enrolled in the feeding guidelines reduced the odds of

developing IFALD. We found that IFALD remained fairly common, but the severity of IFALD was significantly improved in infants in the post-guideline cohort. The overall incidence of IFALD decreased from 70% to 53% (P=0.03). We found a significant reduction in the adjusted odds of developing moderate-to-severe IFALD (OR 0.32, P=0.002) among infants fed via the guidelines. Since infants with higher peak direct bilirubin are at higher risk of having chronic liver disease, a reduction in moderate-severe IFALD is of clinical importance. We also found that infants in the post-guideline cohort had a shorter length of PN use, shorter hospital length of stay, fewer infections with positive culture, and were more likely to have resolution of IFALD prior to discharge if IFALD did occur.

The higher initial feeding volume of 20 ml/kg/day recommend in the guidelines was well tolerated. Infants who were adherent to the guidelines reached 50% EN in the shortest amount of time. We found that even if full EN could not be reached for a prolonged period of time, reaching 50% of goal EN within 2-3 weeks of surgery still offered protection against moderate-severe IFALD.

While we have made significant progress in improving enteral feeding in surgical infants, barriers still remain for feeding the sickest of the infants, who are also most at risk of IFALD. We plan to continue monitoring the impact of our feeding guidelines on surgical infants to further define optimal feeding based on prematurity and diagnosis. Collaboration with a second site is already underway, which will evaluate the generalizability of the guidelines, and will provide a larger sample size to allow for further risk stratification. One major barrier to feeding has been predicting readiness to feed. Identifying which infants are ready to initiate EN and which require longer withholding of EN is based on non-specific assessment of vital signs, physical examination, and gastrointestinal output. Clinically available testing to assess readiness to feed is not yet available. Our future work will also evaluate potential serum biomarkers of several

mechanisms of intestinal injury, including enterocyte damage, barrier dysfunction, and inflammation, which may provide clinically useful adjunct testing to predict readiness to feed.

Taken together, these studies suggest that EN plays an important role in mitigating the risk of IFALD. Feeding guideline implementation was feasible and well tolerated. We have seen improved outcomes since implementing the guidelines, and we will continue with our efforts to refine the guidelines.

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34. Guzman JR, Conlin VS, Jobin C. Diet, microbiome, and the intestinal epithelium: an essential triumvirate? BioMed research international 2013;2013:425146.
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36. Turner JR. Intestinal mucosal barrier function in health and disease. Nature reviews Immunology 2009;9:799-809.
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38. Yue C, Wang W, Tian WL, et al. Lipopolysaccharide-induced failure of the gut barrier is site-specific and inhibitable by growth hormone. Inflammation research : official journal of the European Histamine Research Society [et al] 2013;62:407-15.
39. Schietroma M, Carlei F, Cappelli S, Amicucci G. Intestinal permeability and systemic endotoxemia after laparotomic or laparoscopic cholecystectomy. Annals of surgery 2006;243:359-63.

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42. Morrow AL, Lagomarcino AJ, Schibler KR, et al. Early microbial and metabolomic signatures predict later onset of necrotizing enterocolitis in preterm infants. Microbiome 2013;1:13.
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57. Goulet O, Olieman J, Ksiazyk J, et al. Neonatal short bowel syndrome as a model of intestinal failure: Physiological background for enteral feeding. Clin Nutr 2012.
58. Barclay AR, Beattie LM, Weaver LT, Wilson DC. Systematic review: medical and nutritional interventions for the management of intestinal failure and its resultant complications in children. Aliment Pharmacol Ther 2011;33:175-84.

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86. Cober MP, Killu G, Brattain A, Welch KB, Kunisaki SM, Teitelbaum DH. Intravenous fat emulsions reduction for patients with parenteral nutrition-associated liver disease. J Pediatr 2012;160:421-7.
87. Fallon EM, Le HD, Puder M. Prevention of parenteral nutrition-associated liver disease: role of omega-3 fish oil. Curr Opin Organ Transplant 2010;15:334-40.
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95. Gosselin KB, Duggan C. Enteral Nutrition in the Management of Pediatric Intestinal Failure. J Pediatr 2014.
96. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics 2009;42:377-81.
97. Perla RJ, Provost LP, Murray SK. The run chart: a simple analytical tool for learning from variation in healthcare processes. BMJ quality & safety 2011;20:46-51.
98. van Elburg RM, Neu J. Nutrition support of neonatal patients at risk for necrotizing enterocolitis: response to Fallon et al (2012). JPEN J Parenter Enteral Nutr 2013;37:11.
99. Kirby RS, Marshall J, Tanner JP, et al. Prevalence and correlates of gastroschisis in 15 states, 1995 to 2005. Obstetrics and gynecology 2013;122:275-81.
100. Slicker J, Hehir DA, Horsley M, et al. Nutrition algorithms for infants with hypoplastic left heart syndrome; birth through the first interstage period. Congenital heart disease 2013;8:89-102.
101. Sharma R, Hudak ML. A clinical perspective of necrotizing enterocolitis: past, present, and future. Clinics in perinatology 2013;40:27-51.
102. Patel RM, Kandefer S, Walsh MC, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. The New England journal of medicine 2015;372:331-40.
103. Snyder CW, Biggio JR, Brinson P, et al. Effects of multidisciplinary prenatal care and delivery mode on gastroschisis outcomes. J Pediatr Surg 2011;46:86-9.
104. Abrams SA, Schanler RJ, Lee ML, Rechtman DJ. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine 2014;9:281-5.
105. Robinson JL, Casey LM, Huynh HQ, Spady DW. Prospective cohort study of the outcome of and risk factors for intravascular catheter-related bloodstream infections in children with intestinal failure. JPEN Journal of parenteral and enteral nutrition 2014;38:625-30.

Curriculum Vitae
Darla Roye Shores, M.D.

Current appointment: Assistant Professor of Pediatrics
Division of Pediatric Gastroenterology and Nutrition
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EDUCATION AND TRAINING

Undergraduate
1992-1997 B. A., Magna cum Laude, University of New Mexico, Albuquerque, NM

Doctoral
1997-2002 M.D., University of New Mexico School of Medicine, Albuquerque, NM
1999 Post-Sophomore Fellowship, Pathology, UNM, Albuquerque, NM
2016 (Pending) Ph.D./Clinical Investigation. Johns Hopkins School of Public Health, Baltimore, MD

Postdoctoral
2002-2005 Resident, Pediatrics, Loma Linda University, Loma Linda, CA
2008-2011 Fellow, Pediatric Gastroenterology, Children's Hospital of Pittsburgh, Pittsburgh, PA

PROFESSIONAL EXPERIENCE

2005-2006 Chief Resident/Assistant Program Director, Department of Pediatrics, Loma Linda University School of Medicine
2006-2008 Assistant Professor, Department of Pediatrics, Loma Linda University School of Medicine
2011-present Assistant Professor, Division of Pediatric Gastroenterology & Nutrition, Department of Pediatrics, Johns Hopkins University School of Medicine
2015-present Co-director, Center for Intestinal Rehabilitation & Care Using Science (CIRCUS)

RESEARCH ACTIVITIES

Publications

1. **Shores D**, Bocklage T. Malignant ascites in young adult men. *American Society of Clinical Pathologists: Cytopathology.* 2000; 28 (7): 103-118.
2. **Shores DR**, Binion DG, Freeman BA, Baker PR. New insights into the role of fatty acids in the pathogensis and resolution of inflammatory bowel disease. *Inflamm Bowel Dis*. 2011, 17(10): 2192-204.

3. **Shores D**, Kobak G, Pegram L, Whitington P, Shneider B. Giant cell hepatitis and immune thrombocytopenic purpura – Reversal of liver failure with Rituximab therapy. *J Pediat Gastroenterol Nutr* 2012, 55(4):e128-30.
4. Bonacci G, Baker PR, Salvatore SR, **Shores D**, Khoo NK, Koenitzer JR, Vitturi DA, Woodcock SR, Golin-Bisello F, Cole MP, Watkins S, St Croix C, Batthyany CI, Freeman BA, Schopfer FJ. Conjugated linoleic acid is a preferential substrate for fatty acid nitration. *J Biol Chem*. 2012, 287(53):44071-82.
5. **Shores D**, Bullard J, Aucott S, Stewart F, Haney C, Nonyane B, Schwarz K. Analysis of Nutrition Practices and Intestinal Failure-Associated Liver Disease in Infants with Intestinal Surgery. *Infant Child Adolesc Nutr*. 2015; 7(1):29-37
6. **Shores D**, Bullard J, Aucott S, Stewart F, Haney C, Tymann H, Miller M, Nonyane B, Schwarz K. Implementation of feeding guidelines in infants at risk of intestinal failure. J Perinatol. 2015 Nov; 35(11):941-8. PubMed PMID: 26313054.

Abstract/Poster Presentations

1. **Shores D**, Ngo K, Chi E, Baerg J, Moores D, Gollin G, Yanni G, Klooster M, Shah M. Small Bowel Disease and Capsule Endoscopy in Pediatric Patients with Total Colectomy for Presumed Ulcerative Colitis. JPGN 43(4), October 2006, pp E40-E41.
2. Yanni G, **Shores D**, Yorgin P, Sahney S, Cutler D, Shah M. Successful Use of Plasmapheresis Combined with Continuous Renal Replacement Therapy in Treating Children with Acute Hepatic Failure and Acute-On-Chronic Hepatic Failure. Transplantation 86(S):2008.
3. Nelson K, **Shores D**, Simpson L, Thompson R. Impact of Enteral Feeding Protocol for Pediatric Post-op Cardiac Patients. Society for Critical Care Medicine Meeting, Jan 2014.
4. **Shores D**, Bullard J, Aucott S, Stewart F, Haney C, Nonyane B, Schwarz K. Implementation of Feeding Guidelines for Infants with Intestinal Surgical Intervention. Clinical and Translational Science Meeting, May 2014.
5. **Shores D**, Bullard J, Aucott S, Stewart F, Haney C, Nonyane B, Schwarz K. Preliminary Results Following Implementation of Feeding Guidelines in Intestinal Surgical Infants at Risk for Intestinal Failure. International Pediatric Intestinal Failure & Rehabilitation Symposium, Sept 2014.
6. Miller S, **Shores D**. Inflammatory Bowel Disease & Hashimoto's Thyroiditis in a Young Woman with Congenital Chloride Diarrhea. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, Oct 2014.
7. **Shores D**, Bullard J, Aucott S, Stewart F, Miller M, Haney C, Tymann H, Schwarz K. Feeding Guideline Implementation in Infants at Risk of Intestinal Failure. Digestive Diseases Week, May 2015.
8. **Shores D**, Bullard J, Aucott S, Stewart F, Miller M, Haney C, Tymann H, Schwarz K. Feeding Guideline Implementation in Infants at Risk of Intestinal Failure. NASPGHAN, October 2015.

Extramural Support

<u>Current</u>

7/13-6/16 Development and implementation of a feeding protocol for neonates following bowel resection to improve feeding tolerance and reduce liver injury
Thomas Wilson Sanitarium for the Children of Baltimore City

$18,000
PI: Darla Shores

11/15-10/17 Optimizing Feeding in Infants with Intestinal Surgery
All Children's Hospital Foundation
$120,284
Role: Co-PI

01/16-12/16 Biomarkers of Intestinal Injury in Infants
ASPEN Rhoads Research Foundation
$25,000
Role: PI

07/16-06/17 Optimizing Enteral Nutrition in Infants at Risk of Intestinal Failure
Johns Hopkins Clinician Scientist Award
Role: PI
$80,000

Completed

2013-2015 Clinical Scholar Award
1KL2TR001077-01
Institute for Clinical and Translational Research
PI: Daniel Ford

EDUCATIONAL ACTIVITIES

Educational Publications

1. Shores D, Lowe, M. (2011). Appendicitis. In Sondheimer, J. & Hurtado, C. (Eds.), *The NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition* (pp. 99-100). New York, NY: CCGMP.
2. Shores D, Lowe, M. (2011). Drugs -Pancreatic Enzymes. In Sondheimer, J. & Hurtado, C. (Eds.) *The NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition* (pp. 517-518). New York, NY: CCGMP
3. Chapter Advisor for Gastroenterology Chapter (2014). In Engorn, B. & Flerlage, J. (Eds.) *The Harriet Lane Handbook*, 20th edition,(pp). Philadelphia, PA: Mosby Elsevier.
4. Tibesar, E and Shores, D. The comparative merits of IV soybean oil-based lipid emulsions and parental omega-3 lipid emulsions in the PNALD setting. eNeonatal Review & Podcast, December 2014.

TEACHING

Classroom Instruction

2005-2008 Pediatric GI lecture series, Pediatric Resident Noon Conference, Loma Linda University, Instructor

2008-2011 Pediatric Gl Lectures, Pediatric Gl Academic Conference, Children's Hospital of Pittsburgh

2011-present Pediatric Gastroesophageal Reflux, Medical Students CORE Lectures, Johns Hopkins University

2011-present Intestinal Failure, Pediatric GI Academic Conference series, Johns Hopkins Children's Center

2012-present Neonatal Cholestasis, Neonatology Fellow Lecture series, Johns Hopkins Children's Center
2015-present Neonatal Intestinal Failure, Neonatology Fellow Lecture series, Johns Hopkins Children's Center

Clinical Instruction

2006-2008 Pediatric GI Inpatient Teaching Rounds, Loma Linda University
2011-present Pediatric GI Inpatient Teaching Rounds, Johns Hopkins Children's Center
2011-present Pediatric GI Fellow's Clinic, Johns Hopkins Children's Center, Preceptor

CME Instruction

2008 Probiotics and Gastrointestinal Disorders, Pediatric Grand Rounds, Loma Linda University
2012 Failure to Thrive, Pediatric Trends, Johns Hopkins Children's Center

Grand Rounds

2015 Intestinal Failure/Center for Intestinal Rehabilitation & Care Using Science. Mount Washington Pediatric Hospital.

CLINICAL ACTIVITIES

Certification

2005 American Board of Pediatrics
2011 American Board of Pediatrics, Pediatric Gastroenterology

Licensure

2003 California Medical Board
2008 Pennsylvania Medical Training
2011 Maryland Board of Physicians

ORGANIZATIONAL ACTIVITIES

Professional Societies

2002 American Academy of Pediatrics
2008 Alpha Omega Alpha
2008 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
2009 American Gastroenterological Association
2015 American Society of Parenteral and Enteral Nutrition

Committees/Service

2003-2004 Resident Handbook Editor, LLUCH
2003-2004 Resident Counsel, LLUCH
2005-2006 Pediatric Resident Academic Committee, LLUCH

2005-2006	Pediatric Morbidity & Mortality Committee, LLUCH
2006-2008	Acute Pediatrics Quality Improvement Committee, LLUCH
2006-2007	Medical Student Advisory Committee, small group leader, LLUCH
2006-2008	Pediatric Resident Mentor, LLUCH
2011-present	Johns Hopkins National Pediatric Cardiology Quality Improvement, JHH
2013-present	Intestinal Failure Multi-specialty Team, JHH
2014-present	Fellowship Scholarly Oversight Committee, JHH
2014-present	Pediatric Gastroenterology Core Curriculum Committee, JHH
2015-present	Pediatric Intern Selection Committee , JHH
2016-present	American Academy of Pediatrics *PREP GI* Advisory Board

RECOGNITION

2003	NASPGHAN Teaching and Tomorrow Program
2003	The Outstanding Resident Award, LLUCH
2008	Pediatric Attending of the Year, LLUCH
2010	AGA Academic Skills Workshop Scholarship

OTHER PROFESSIONAL ACCOMPLISHMENTS

2010	Quality Improvement and Innovation Education Series, UPMC
2015	Certificate in Quality, Patient Safety, and Outcomes Research, JHSPH
2015-16	Leadership Program for Women Faculty, JHH