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Prediction Of Feeding Difficulties In Post-Operative Neonates

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Abstract

PREDICTION OF FEEDING DIFFICULTIES IN NEONATES

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The purpose of this study was to determine whether feeding difficulties in post-operative neonates correlate with intraoperative findings.

A retrospective study of neonates undergoing gastrointestinal surgery between January 2002 and December 2005 was performed. Operative notes were used to classify infants into four groups based on post-operative anatomy and anticipated intestinal function: class 1: anatomically normal/normal function (n=22); class 2: anatomically normal/dysfunction (n=21); class 3: anatomically short/normal function (n=31); and class 4: anatomically short/dysfunction (n=21). Class 3 was further divided into two subgroups based on ostomy location: proximal ostomy (class 3a, n=11) vs. distal ileostomy (class 3b, n=21). Anatomically short was defined as loss of >50% of small bowel or high ostomy. Dysfunction was defined as decreased motility or absorptive capacity of the small bowel due to dilation, inflammation, or ischemia. Data were collected from the first day of enteral feeding until the infant reached full feeds or was discharged. Outcomes included: time to 50% and to full enteral feeds, days on TPN/lipids, and episodes of feeding intolerance (large aspirates, emesis) or malabsorption (increased volume or watery consistency of stools). Statistical analyses were performed using Kruskal–Wallis test for continuous variables and chi-square test for dichotomous variables.

We enrolled 95 patients. Time to full feeds was longer in anatomically short infants (class 3a and 4) than in anatomically normal infants (class 1 and 2, $p<0.05$). The same trend was seen in median days of exposure to TPN and lipids. Class 3b infants behaved more like anatomically normal infants despite having an ileostomy. Feeding intolerance occurred in 81% and 71% of infants in classes 2 and 4 respectively, which was significantly higher than in classes 1 (5%), 3a (55%), and 3b (30%), all $p<0.05$. The median days of feeding interruption due to intolerance were significantly higher in classes 2 and 4 ($p<0.05$). Malabsorption affected 62% and 64% of patients in classes 3a and 4, respectively, which was significantly higher than in classes 1 (5%), 2 (19%) or 3b (20%), all $p<0.05$. The median days of feeding interruption due to malabsorption were significantly higher in classes 3a and 4 ($p<0.05$).

These data demonstrate that surgeon-described post-operative anatomy and anticipated gastrointestinal function correlate with feeding difficulties in the post-operative period. We also found that infants with a distal ileostomy behave similarly to those who are anatomically normal, indicating feedings for these infants can likely be advanced more quickly. Feeding guidelines based on this classification system should be evaluated prospectively.

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Introduction

Disorders of the gastrointestinal (GI) tract are a major cause of morbidity and mortality in the newborn population. Generally speaking, these disorders can be placed in two categories – congenital defects of the GI tract or abdominal wall and necrotizing enterocolitis (NEC) [1]. Although the prevalence of these defects varies, many of them require surgical intervention and difficult decisions when it comes to post-operative nutritional management.

The appropriate manner of initiating and advancing feeds in newborns, especially premature infants, is a topic of ongoing controversy. This controversy is especially pronounced when working with post-operative newborns. Although the goals for feeding post-operative newborns are generally agreed upon, the manner of reaching these goals is far from clear. These goals include:

1. Initiating feeding as soon as clinically appropriate
2. Reaching goal enteral feeds as quickly as is safe to do so, where goal is equivalent to the caloric intake to support acceptable growth and weight gain
3. Minimizing episodes of feeding intolerance due to dysmotility and episodes of malabsorption
4. Minimizing days of total parenteral nutrition (TPN) support

This introduction begins with a brief review of congenital anomalies of the GI tract. Next, it will focus on infants in the neonatal intensive care unit (NICU) and will review the value of early enteral nutrition for this fragile population and the risks and benefits of TPN. It will then address the small body of literature on feeding post-operative infants, the nutritional management of infants with short bowel syndrome (SBS) and finally the value of standardized feeding protocols, which have been studied in premature infants, but not in infants who have undergone GI surgery.

Congenital defects of the GI tract

Congenital defects of the GI tract include esophageal atresia and tracheoesophageal fistula, omphalocele, gastroschisis, congenital diaphragmatic hernia, malrotation and obstruction and Hirschsprung's disease [1]. Esophageal atresia is a condition in which the esophagus ends in a blind pouch and may be present with or without a fistula, an abnormal connection between the esophagus and trachea. This condition occurs in approximately 1 in 3,000 births and is treated surgically with an end-to-end anastomosis of the esophageal segments, and, if necessary, ligation of fistula. Omphalocele and gastroschisis, in which a portion of the GI tract remains outside the abdominal cavity at birth, are defects of the abdominal wall that occur in approximately 1 in 6,000 live births and require surgical intervention [2]. In omphalocele, the bowel fails to return to the abdominal cavity through the umbilicus, an event that usually occurs around 10 to 12 weeks of gestation. The protruding abdominal contents are covered with a sac made of peritoneum and amniotic membrane. In gastroschisis, the bowel protrudes through a defect in the anterior abdominal wall and is not covered by a sac [1, 2]. Congenital diaphragmatic hernia

occurs in approximately 1 in 2,000 to 3,000 live births and involves herniation of the diaphragm and the potential for abdominal organs to move into the thorax. Although the diaphragmatic defect is not difficult to repair, if abdominal organs occupy space in the thorax, lung development is affected, leading to pulmonary hypoplasia and persistent pulmonary hypertension [3]. Congenital obstruction of the GI tract can be caused by atresia of the small intestine, and occurs in approximately 1 in 2000 births. It can also be due to malrotation, a failure of the intestine to rotate the normal 270 degrees, or volvulus, in which a loop of bowel twists upon itself, leading to ischemic necrosis. Finally, in Hirschsprung's disease, there is dysmotility of the colon due to a lack of ganglion cells. The aganglionic area is contracted but cannot propel feces [1].

Necrotizing enterocolitis (NEC) is one of the most serious GI disorders in neonates, especially in extremely preterm neonates. Although it may have a genetic component, NEC occurs after birth and is influenced by factors including intestinal immaturity, a change in microvascular tone of the gut and an altered population of gut flora, which leads to an exaggerated inflammatory response and tissue damage [4]. When NEC occurs, there is often a need for resection of the bowel, making NEC one of the major causes of SBS [5].

The fetal intestine

It is not uncommon to have infants born with gastrointestinal anomalies and admitted to the NICU receive nothing per os (NPO) and to initiate TPN. These infants often do not

receive enteral nutrition (either orally or via an orogastric or nasogastric tube) until after their procedure when bowel sounds have returned and post-operative ileus is believed to have resolved. However, it is important to remember that an infant is in fact not born "NPO" – fetuses are constantly swallowing amniotic fluid, which contains growth factors as well as numerous nutrients, including carbohydrates, fats and proteins. In a sense, they are providing their own enteral nutrition [6]. An early study by Pitkin et al. demonstrated that protein from amniotic fluid is broken down in the fetal gut and that the amino acids that result from this process are available for protein synthesis and can be found in a variety of fetal organs, including the lung, liver and brain [6].

Nutritional support in the NICU: TPN

Enteral nutrition for infants, although more physiologic than parenteral nutrition, is frequently not possible in the immediate post-operative period. Therefore, providing nutrition for newborns, especially those who have undergone surgery, is challenging. Unlike most adults, who have adequate nutritional stores to obviate the need for nutritional support for several days after an operation, the high metabolic demand and absent nutritional reserves of the neonate mandates, especially for preterm infants, the use of nutritional support until bowel function has resumed [7, 8]. Only once bowel function returns, can the volume of TPN can be decreased as the volume of enteral nutrition is increased.

The goal of using TPN is initially to provide enough calories and amino acids to prevent

weight loss and negative energy balance. Once this is achieved, the goal shifts to promoting growth and weight gain until the infant can fully tolerate enteral feedings [1]. Although it is necessary for many post-operative newborns, TPN comes with many risks. It is associated with an increased risk of sepsis, inadequate growth, intestinal mucosal atrophy, liver damage and cholestasis [9, 10]. TPN-related cholestasis, which most commonly takes the form of intrahepatic cholestasis, was first described in the 1970s [11], but its mechanism, which is likely multifactorial, remains unknown [12]. There are multiple theories regarding the etiology of cholestasis and parenteral nutrition-associated liver disease (PNALD). One suggests that a lack of enteral feedings disrupts the enterohepatic circulation, thereby altering the production of gut hormones and increasing endotoxins produced by bacterial translocation [13]. Total parenteral nutrition itself may also be toxic to the liver. Recent work has focused on the role of intravenous fat emulsion in the development of PNALD, especially phyto-sterols and vegetable oil-based lipid preparations [13]. Indeed, reduction of the dose of intravenous fat emulsion (from 3 mg/kg/day to 1 mg/kg/day) led to a significant decrease in total bilirubin levels in surgical patients dependent on TPN [14]. A further complicating factor to the story of PNALD is that, compared to term infants, premature infants may be at greater risk for PNALD [15].

Nutritional support in the NICU: the transition from TPN to enteral nutrition

Transitioning to enteral nutrition as soon as it is safe to do so clearly minimizes the risks associated with TPN including cholestasis, catheter-associated infections, and liver dysfunction or failure [16, 17]. Historically, there has been concern that enteral nutrition

may lead to the development of necrotizing enterocolitis (NEC) [18]. However, recent Cochrane Reviews have dispelled these concerns. It has been shown that enteral feeds and rapid rates of feed advancement do not necessarily increase the risk of NEC and may actually improve outcomes. Early initiation of enteral nutrition not only decreases the duration of TPN dependence, but also decreases the length of hospital stay and short-term morbidities and mortality and leads to improved growth and developmental outcomes [7, 19-23]. One study has also suggested that a rapid rate of advancement of enteral feeds leads to faster attainment of full feedings, although this is not a widely accepted view [24].

When considering the definition of the term "early" in the context of enteral nutrition, research suggests that providing infants with small volumes of milk or formula during their first week of life is beneficial. These very early feedings, also known as tropic feedings or minimal enteral feedings, have been shown to promote intestinal maturation, increase tolerance of feeding and decrease the time to reach full feeds. Early feedings are also important in motor development of infants as they stimulate suck and swallow reflexes [25, 26]. Minimal enteral feedings are not necessarily providing nutrition, but rather are serving as nonnutritive oral motor therapy. Importantly, this type of feeding has not been shown to increase rates of NEC [25, 26].

There are many distinct advantages to enteral nutrition over TPN, as has been shown in studies of premature infants. Enteral nutrition is superior at providing required calories – to provide an equivalent number of calories with TPN, high concentrations of dextrose

are required, which are often not well tolerated by premature infants [9]. It also promotes growth and adaptation of the gut by directly stimulating hyperplasia as well as stimulating production of trophic factors – both hormones and also upper gastric secretions, which have a trophic effect in the small intestine [27-29]. Not surprisingly, in the absence of enteral nutrition, gut atrophy can occur. In a study of piglets fed solely with TPN, one group reported reduced intestinal growth as well as atrophy of villae [30]. Burrin et al. demonstrated that the minimal enteral nutrient intake needed to sustain normal growth of the jejunal mucosa is greater than 60% of the total nutritional intake and that enteral nutrition that is <40% of the total nutrient intake does not have a significant trophic effect on the intestine [30]. Enteral feedings may also reinforce the ability to tolerate feedings, as they are known to increase intestinal lactase activity. Finally, early enteral nutrition is associated with decreased intestinal permeability and decreased bacterial translocation, which may play a protective role against the development of NEC [9]. It has been shown that delaying enteral feedings leads to inadequate growth, which is concerning as growth velocity in the NICU has been found to be associated with growth and neurodevelopment later in life [31].

Early nutrition in the post-operative neonate

Unlike feeding regimens in non-operative neonates, there is limited information on feeding regimens in neonates who have undergone surgery, and feeding regimens guided by the post-operative anatomy and anticipated gut dysfunction have not been specifically studied [32, 33]. Therefore, management of the post-operative feedings has been widely variable, based primarily on the surgeon's preference and anecdotal experience.

The goal of any feeding regimen is to achieve full enteral feedings as quickly and safely as possible. In infants who have undergone surgery, post-operative feeding management has the additional goals of minimizing episodes of intolerance or malabsorption and facilitating intestinal adaptation in those patients with limited length or function of the remaining bowel [15, 34, 35]. In infants with surgically-corrected small bowel obstruction, feeding is often delayed until post-operative ileus has resolved, but as has already been discussed, even short periods of inadequate nutrition may result in delayed gut maturation, thinning of the enteric mucosa, atrophy of villae, bacterial translocation and immune deficiency [28]. A few small studies have shown benefits for early initiation of enteral feeding in infant who have undergone surgery for congenital anomalies (including gastroschisis, omphalocele, diaphragmatic hernia, and small bowel atresias). These benefits include a reduction in time to full feeds, length of hospital stay, costs of hospital stay, and duration of TPN [33, 36, 37]. Garza et al. demonstrated that for infants undergoing pyloromyotomy for hypertrophic pyloric stenosis, allowing small feeds of formula or breast milk immediately post-op (as soon as anesthesia had been reversed) decreased time to full feeds and time to discharge without increasing rates of readmission. Another study found that early trophic feeds reduced time to first stool in infants with a variety of GI congenital anomalies who had undergone either laparotomy or intestinal anastamosis, demonstrating that early feeding may actually promote resolution of postoperative ileus and that the concept of using TPN for "bowel rest" may not be beneficial [36].

Early nutrition in the post-operative neonate: what we have learned from short bowel syndrome

Short bowel syndrome (SBS) is a state of malabsorption that can occur after resection of the small intestine. It is the most common cause of intestinal failure in infants and is often due to congenital intestinal anomalies (bowel atresias, malrotation with midgut volvulus) or extensive bowel resection for NEC [38]. Malabsorption in SBS occurs for two reasons: (1) the loss of absorptive and digestive surfaces, and (2) because remaining bowel may have compromised function and reduced ability to adapt (such as is seen in gastroschisis with bowel wall edema). Because of these issues, SBS has been extensively studied and there is a great deal to learn from nutritional management of neonates with SBS.

Clinically, SBS is initially managed with TPN. The duration of TPN depends on the kind and length of residual bowel, the percent of daily calories given enterally, and the type of formula used -- breast milk and amino acid-based formulas are associated with a shorter duration of TPN [35, 39]. Olieman et al. [40] advocate for starting enteral nutrition as soon as possible after bowel resection to promote adaptation of the intestine. Compared to controls, infants with SBS who received enteral feeds prior to resolution of postoperative ileus had a shorter time to first stool, time to reach full feeds and hospital stay [34, 36, 40]. One study used the absence of portal vein gas on ultrasound (for three days) to determine when to start enteral feeding in infants treated medically for NEC and found that this led to shorter time to full feeds, less catheter-related sepsis and shorter hospital stays [32].

Although there is evidence to support early initiation of enteral nutrition in SBS, there is no consensus on how quickly to advance feeds. Traditionally, feed advancement has been based on stool output. Some studies have suggested an upper limit of 30-40 mL/kg for enterostomy output because above this cutoff, infants may develop electrolyte imbalances [15]. However, some groups tolerate higher outputs by replacing lost fluids and electrolytes [15, 41]. This problem can also be viewed from the perspective of promoting tolerance of feedings, for example Vanderhoof et al. suggested that advancing feeds by 1mL/hr/day increments may be sufficient to establish tolerance of enteral feeds [25]. When considering the schedule of feedings, numerous studies have supported the use of continuous feeds for infants with surgically-created short bowel. Slow continuous feeds are associated with greater energy, protein, and mineral absorption as well as daily weight gain [42], whereas bolus feedings are associated with mineral deficiencies and weight loss. Slow continuous feeds also lower the risk for developing osmotic diarrhea [34, 40]. Numerous reports have advocated for breast milk and/or elemental formulas in infants with SBS [15, 35].

The value of standardized feeding protocols

Although there is no body of work on the use of feeding protocols in neonates who have undergone GI surgery, there have been studies on other post-operative neonates as well as very low birthweight (VLBW) infants, all of which have shown that the use of standardized guidelines for feeding are associated with better outcomes.

Several studies have addressed the value of standardized feeding protocols for infants with congenital heart disease who are undergoing cardiac surgery. In a retrospective study of term infants who underwent surgery for complex congenital heart disease, Anderson et al. reported that early initiation of enteral nutrition was associated with improved weight gain [43]. A recent retrospective review comparing post-operative infants with hypoplastic left heart syndrome found that prior to the institution of a feeding protocol, 27% of the infants developed medical NEC whereas after the initiation of the protocol, only 6.5% of the infants were diagnosed with this condition [44]. Interestingly, enteral feeds were initiated later in the "post-protocol" infants and these infants also took more days to reach full feeds. However, the length of hospital stay was still shorter in the post-protocol group. Most interestingly, del Castillo et. al reported that the greatest advantage of their feeding protocol was to eliminate practice variation amongst physicians and nurse practitioners caring for these infants [44]. Although this is a difficult claim to prove, if true, this statement could have profound implications for all post-operative infants.

Studies of VLBW infants have demonstrated that standardized feeding guidelines lead to earlier attainment of full enteral feeds, better growth, a lower incidence of NEC and a decrease in length of hospital stay and associated costs [45-48]. Street et al. demonstrated that implementing feeding guidelines for infants under 2000 g resulted in decreased variability in feeding-related outcomes, including the number of days of TPN and the number of days required to reach a caloric intake of 100 kcal/kg/day [47]. McCallie et al. demonstrated similar outcomes in two groups of infants – VLBW infants

and extremely low birth weight (ELBW infants), who are less than or equal to 1000 g [46]. They also reported a reduction in episodes of culture-proven late-onset sepsis, which could not be fully explained by a reduction in the average days that an infant had a central line [46]. One systematic review reported that standardized feeding regimens may "provide the single most important global tool to prevent/minimize NEC is preterm neonates" [49]. There is growing interest in the value of standardization of medical care and a recent Cochrane review highlighted this, demonstrating that "clinical pathways" (document-based tools that provide recommendations, processes and time-frames for the management of specific medical issues or procedures) reduce in-hospital complications [50]. Guidelines are not only valuable because they may improve outcomes, but also because they may help control the effects of other often unrecognized factors on feeding. For example, in ELBW infants, decisions regarding early nutritional support have been shown to be related to perceived severity of illness [19]. Thus the use of feeding protocols may not only reduce variation, but also make decision-making more straightforward when it comes to work with a very fragile population of infants.

Hypothesis and Aims

In an effort to standardize feeding in post-operative neonates with the goal of reaching full enteral feeds faster, a classification system for these infants based on the primary surgical problem and the surgeon's assessment of anatomy, bowel length, and anticipated function was developed (Appendix 1). Based on this classification system, problems

with advancing feeds in a non-standardized manner could be predicted. The purpose of this study is to verify that the classification of patients based on their post-operative anatomy and expected function accurately predicts the feeding difficulties within that class and that each class is distinct from the others. Confirmation of the predictive value of this classification system will provide the foundation for prospective feeding guidelines focused on preventing the specific feeding problems of each class.

Methods

Study design

We conducted a retrospective analysis of 95 infants managed in the Yale New Haven Children's Hospital Neonatal Intensive Care Unit (NICU) who underwent gastrointestinal (GI) surgery between January 1, 2002 and December 31, 2005. Performance of this project was approved by the IRB (1102008085).

Study population

Eligible infants underwent GI surgery while being patients in the NICU and subsequently received enteral nutrition. Possible subjects were identified from the clinical log maintained by the Section of Pediatric Surgery from 2002-2005. Infants were excluded if they: (1) died or were transferred to an outside hospital prior to initiating enteral nutrition, (2) had incomplete or missing medical records, (3) underwent their initial GI operation prior to 2002 or at an outside institution, or were not in the NICU at time of initial GI surgery, or (4) did not undergo GI surgery.

Post-operative classification

Operative notes were used to initially classify eligible infants into four groups based on post-operative anatomy (distal to the ligament of Treitz) and anticipated intestinal function as described by the surgeon. Post-operative anatomy was defined as either

normal or short (loss of >50% of small bowel or ostomy located in the proximal half of the small bowel). Expected function was defined as either normal or dysfunctional (decreased motility or absorptive capacity of the small bowel due to dilation or ischemia). Table 1 describes the characteristics of the classification system class 1: anatomically normal/expected normal function (n=22); class 2: anatomically normal/expected dysfunction (n=21); class 3: anatomically short/expected normal function (n=31); and class 4: anatomically short/expected dysfunction (n=21). Class 3 was further divided into two subgroups based on ostomy location: proximal ostomy (Class 3a, n=11) vs. distal ileostomy (Class 3b, n=21). We hypothesized that Class 1 infants would have the fewest episodes of feeding intolerance and malabsorption episodes, infants with expected dysfunction (Class 2 and Class 4) would have higher number of episodes of feeding intolerance, and infants with anatomically short bowel (Class 3a and Class 4) would have the highest number of episodes of malabsorption. Furthermore, we hypothesized that Class 3b infants would behave similarly to Class 1 infants.

Data collection

Baseline demographic and perinatal data including date of birth, gestational age, birth weight, gender, and race were collected through review of medical records. Operative data collected included date of surgery, surgeons present, date of admission to the NICU, and the surgeon's description of the operation and operative findings.

Data were also collected on daily aspects of the post-operative course, from the first post-operative enteral feed until the infant reached full enteral feeds [defined as a minimum of

Class	Post-operative class descriptions	Examples of intra-operative findings
1	Anatomically normal with expected normal function in motility and /or absorption	• Tracheo-esophageal fistula +/- esophageal atresia • Hirschsprung's Disease, anorectal anomalies • NEC isolated to colon with no disease in small bowel • Malrotation/volvulus with no resection required and no significant ischemia
2	Anatomically normal with expected dysfunction in motility and /or absorption	• Gastroschisis with thickened, edematous, inflamed, or ischemic bowel • Malrotation/volvulus with minimal or no resection required but bowel thickened, edematous, or ischemic • Duodenal atresia/stenosis • Intestinal atresia with no significant loss of bowel
3a	Anatomically abnormal with expected normal function in motility and absorption	• NEC requiring small bowel resection <50%, proximal ostomy, remaining bowel appears healthy • Intestinal atresia with significant shortening of bowel, remaining tissue appears healthy
3b	Anatomically abnormal with expected normal function in motility and absorption	• NEC requiring small bowel resection <50%, distal ostomy, remaining small bowel appears healthy • Isolated small bowel perforations with distal ostomy, remaining small bowel appears healthy
4	Anatomically abnormal with expected dysfunction in motility and absorption	• NEC requiring small bowel resection >50% and proximal ostomy • NEC requiring small bowel resection <50% but remaining bowel edematous, ischemic, or inflamed • Gastroschisis or malrotation/volvulus with extensive damage loss/shortening of bowel and extensive damage to remaining bowel

Table 1 Assignment of class by operative findings Infants were classified based on their post-operative anatomy (distal to the ligament of Treitz) and expected intestinal function as described by the surgeon. Examples of the specific types of intra-operative findings relating to each class are shown. Abbreviations: necrotizing enterocolitis (NEC).

100 kcal/kg/day, discontinuation of any intravenous nutritional support including total parenteral nutrition (TPN) and intravenous fat emulsion (IFE), and then a minimum weight gain of 10 grams/day for three consecutive days]. Nutritional data included: type of formula, route (oral vs. feeding tube, schedule of feedings (continuous vs. intermittent), caloric density of nutritional support, and daily volume of all nutritional support.

Changes in formula (to more elemental formulas or clear liquids)[1] and alterations in the rate of feeds were tracked. Data were also recorded on episodes of feeding intolerance and/or malabsorption and the number of days that the infant was nil per os (NPO) due to feeding intolerance, malabsorption, sepsis evaluations, or additional surgery. Feeding intolerance and malabsorption were defined as (Table 2):

Feeding intolerance	▪ Emesis ▪ Abdominal distention ▪ Gastro-esophageal reflux ▪ Aspirates (bilious, >50% volume of intermittent feedings, or >1 hour volume of continuous feedings).
Malabsorption	▪ Increased stool frequency or volume ▪ Watery consistency of stools ▪ Bloody stools ▪ Electrolyte abnormality (requires any combination of two labs: low sodium, low potassium, low bicarbonate) ▪ Positive reducing substance test

Table 2 Definition of feeding intolerance and malabsorption

[1] Formulas ranked from least to most elemental: (1) Human milk with fortifiers, (2) human milk alone, standard formulas (Similac, Enfamil, Neosure, Goodstart) or soy-based formulas (Isomilk, prosobee), (3) semi-elemental formulas (Pregestimil, Nutramigen, Alimentum), (4) elemental formulas (Neocate), and (5) clear liquids (Pedialyte).

Data were recorded until an endpoint was reached: full enteral feeding, death, or discharge prior to full enteral feeding. The types of feeding at the endpoint and at discharge were also recorded.

Results of liver function tests [LFT's: aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct and total bilirubin] were recorded when available. LFT's were used to categorize infants by degree of cholestasis using the highest ever laboratory results when multiple results were available (Table 3):

Category 1	No TPN cholestasis (all laboratory results in normal ranges)
Category 2	Cholestasis (elevated direct bilirubin $\geq$ 0.5 or < 2.0mg/dL)
Category 3	Significant cholestasis secondary to TPN (elevated direct and total bilirubin; direct bilirubin $\geq$2.0mg/dL)
Category 4	Parenteral nutrition-associated liver disease (PNALD; elevated AST, ALT, total bilirubin, and direct bilirubin). AST or ALT > 50U/L is considered elevated, even in the setting of a direct bilirubin < 2.0mg/dL.

Table 3 Categories of cholestasis Liver function tests were used to quantify the level of cholestasis.

Outcomes

The primary outcome was the number of days to reach full enteral feeds. Other nutritional outcomes included the number of days to reach 50% feeds, alterations in feeding (changing to more elemental formula, switching from intermittent bolus to continuous feeds or decreasing volume of feeds), number of days the infant was made NPO due to intolerance or malabsorption, and whether the infant was receiving bolus feeds at the time full enteral feeds were reached.

Secondary outcomes included the number of days the infant had a central line, the number of days the infant received TPN and/or IFE, the number of evaluations for sepsis, culture-proven infection or sepsis, discharge status (home, to another institution, or deceased) and length of hospital stay.

Statistical analysis

Data analysis was performed using SPSS (SPSS Statistics, version 21.0; IBM, SPSS Inc., Chicago, IL) Normally-distributed data were analyzed using a one-way ANOVA with post-hoc analysis with a Tukey test. Nonparametric tests were used when the parametric test assumption of a normal distribution was violated. For categorical variables, the Chi-squared test followed by Fisher's exact test was used. For continuous variables, the Kruskall-Wallis test was used followed by the Mann-Whitney post-hoc test.

Results

Study flow

Study flow is shown in Figure 1. Our goal was to enlist 25 patients/year, averaging five infants/class for a target total of 100 subjects, and to review infants sequentially by date of surgery. The average of five infants/class was chosen due to the small number of infants in certain classes (2, 3a, and 4). These numbers were based on pre-study power calculations, which indicated that 100 infants for the period 2002-2005 would be required to achieve 80% power to detect a difference in the range of 4 to 7 days in the mean number of days to reaching full enteral feeds between two groups, with a significance level (alpha) of 0.05 (Appendix 2). Charts from 316 infants who underwent gastrointestinal (GI) surgery were initially reviewed. Exclusion of 136 infants was necessary. The two most common causes of exclusion were that the infant was deceased after surgical intervention prior to beginning enteral feeds or that the infant undergoing surgery was not admitted to the NICU. A total of 95 subjects comprised the final study population: 22 in Class 1, 21 in Class 2, 31 in Class 3 (3a = 11 and 3b = 20), and 21 in Class 4.

Baseline characteristics and intraoperative findings

As shown in Table 4, there were no significant differences between the classes in baseline demographics or perinatal characteristics (birth weight and gestational age) across the four years. Data for birth weight was stratified into four groups: <1000g, 1000

- <1500g, 1500 - <2500g, and >=2500g. Data for gestational age was also stratified: <29 weeks, 29 - <32 weeks, 32 - <37 weeks, and ≥37 weeks. Causes of death in each class were as follows: class 3a (multi-organ failure), class 3b (sepsis, respiratory distress syndrome, acute renal failure), and class 4 (TPN cholestasis, sepsis, CNS infection, pulmonary hypertension).

Date of surgery	2002	2003	2004	2005	p-value
Number of patients	n = 22	n = 26	n = 23	n = 24	0.95
Gender	n (%)	n (%)	n (%)	n (%)	0.15
Male	9 (41)	14 (54)	16 (70)	14 (58)	-
Female	13 (59)	12 (46)	7 (30)	10 (42)	-
Ethnicity					0.23
White	11 (50)	12 (46)	12 (52)	9 (38)	-
Black	1 (5)	5 19)	6 (26)	2 (8)	-
Hispanic	2 (9)	4 (15)	4 (17)	3 (13)	-
Asian	0 (0)	2 (8)	0 (0)	2 (8)	-
Unknown	7 (32)	3 (12)	1 (4)	3 (13)	-
Other	1 (5)	0 (0)	0 (0)	0 (0)	-
Birth weight					0.45
<1000g	4 (18)	8 (31)	6 (26)	7 (29)	-
1000 - <1500g	2 (9)	6 (23)	3 (13)	3 (13)	-
1500 - < 2500g	6 (27)	9 (35)	6 (26)	6 (25)	-
≥2500g	10 (45)	3 (12)	8 (35)	8 (33)	-
Gestational age					0.08
<29 wks	4 (18)	11 (42)	8 (35)	6 (25)	-
29 - <32 wks	2 (9)	3 (12)	1 (4)	5 (21)	-
32 - <37 wks	7 (32)	9 (35)	12 (52)	6 (25)	-
≥37 wks	9 (41)	3 (12)	2 (8)	7 (29)	-

Table 4 Baseline demographic and perinatal characteristics of infants by year
Data was collected on gender and ethnicity as well as birth weight and gestational age. No significant differences were found between the years for any of these variables ($p>0.05$, Chi-squared test).

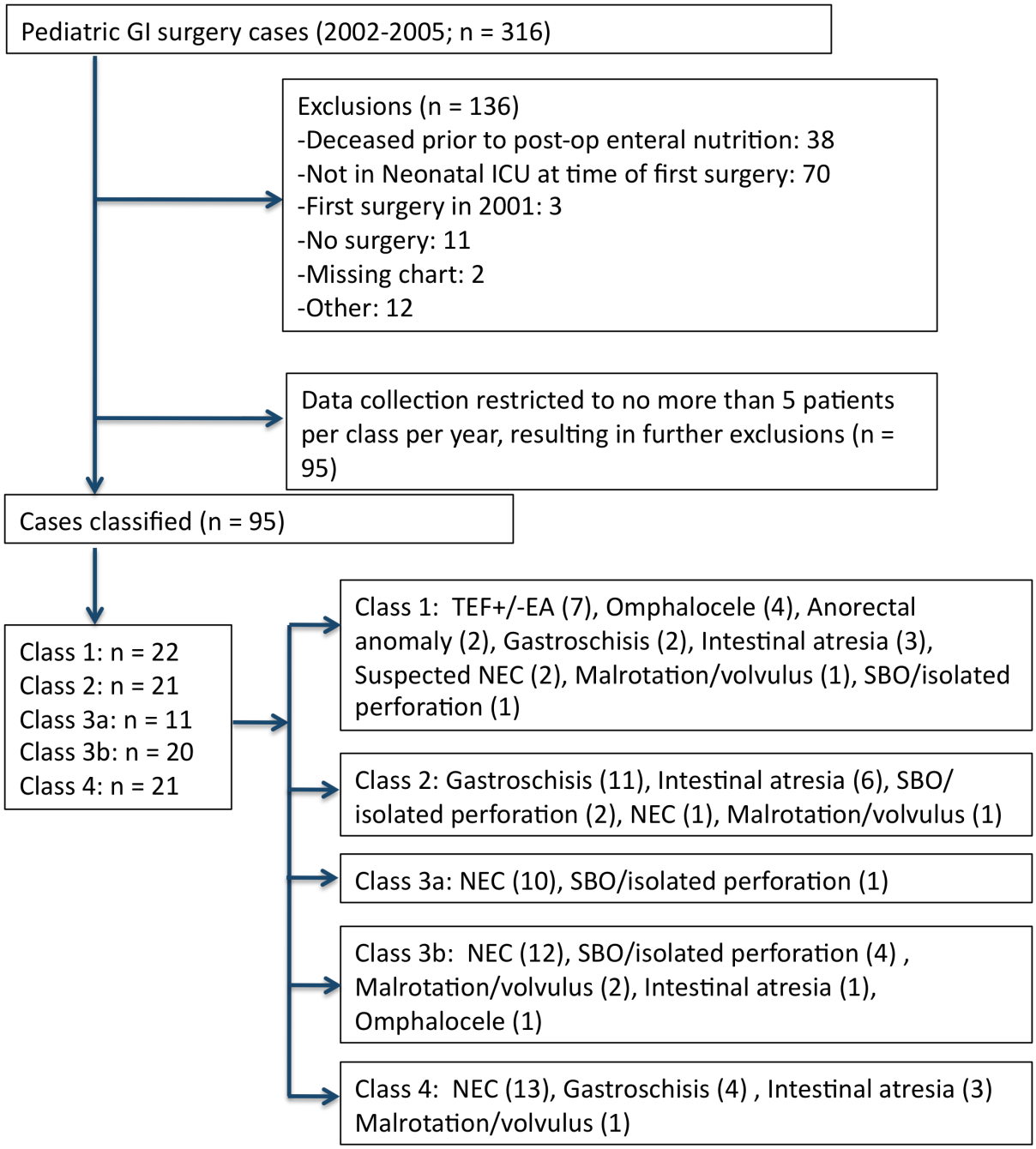


Figure 1 Study flow From 316 medical charts, 95 cases were selected based on eligibility criteria. Each infant was classified using the operative note into class 1, 2, 3a, 3b, or 4. The distribution of diagnoses (number of infants) in each class is listed. Abbreviations: esophagael atresia (EA), necrotizing enterocolitis (NEC), small bowel obstruction (SBO), tracheoesophagael fistula (TEF).

There was no difference in the distribution of principal diagnoses across the four years ($p>0.05$; Table 5). For each of the principal diagnoses, the distribution between classes is shown in Figure 2. NEC was by far the most common diagnosis in this study: 39 of 95 (40%) cases. Abnormalities proximal or distal to the small bowel (TEF with or without EA, anorectal anomalies) were assigned to Class 1. Omphalocele usually was in Class 1, whereas gastroschisis was often found in Class 2 and 4 infants. NEC was rarely seen in Class 1 infants, but was approximately equally distributed between Classes 3a, 3b and 4.

Days to full feeds

At the time of full feeds, the average calorie count was 107 kcal/kg/day. A total of 87 infants reached 50% feeds (defined as the day on which the infant reached 50kcal/kg/day, which is approximately 50% of the calories at full feeds) and 69 reached full feeds. Infants who did not reach these endpoints died (6 infants; Class 3a n=1, 3b n=1, 4 n=4), were transferred to another institution (3 infants, Class 4 n=3), or were discharged (17 infants, Class 1 n=7, 2 n=44, 3a n=1, 3b n=2, 4 n=3) prior to reaching full feeding. Compared to Class 1, infants in Classes 2 and 4 took significantly longer to reach 50% feeds ($p<0.05$; Figure 3a, gray bars), while infants in Classes 2, 3a and 4 all took significantly longer to reach full feeds ($p<0.05$, Figure 3a, black bars). Class 3b was not different from class 1 in terms of mean days to reach 50% or full feeds ($p>0.05$; Figure 3a). Similar results were seen the mean number of days that infants took to reach full feeds from 50% of feeds was analyzed. Infants in Classes 3a and 4 all took significantly longer to reach full feeds than Class 1 ($p<0.05$, Figure 3b). The mean days were not different between Class 1 and Classes 2 and 3b ($p>0.05$, Figure 3b).

	2002	2003	2004	2005	**Totals by condition**
NEC	5	15	9	10	39
Gastroschisis	7	2	4	4	17
Intestinal atresia	2	1	5	3	11
TEF +/- EA	1	3	2	1	7
SBO or isolated perforation	0	2	2	3	7
Omphalocele	1	1	1	2	5
Malrotation +/- volvulus	3	1	0	1	5
Anorectal anomaly	3	1	0	0	4
Totals by year	22	26	23	24	95

Table 5 Principal diagnosis by year Distribution of principle diagnoses was not significantly different across the four years (p>0.05, chi-square test). Abbreviations: Tracheoesophageal fistula (TEF) with or without esophageal atresia (+/-EA), necrotizing enterocolitis (NEC).

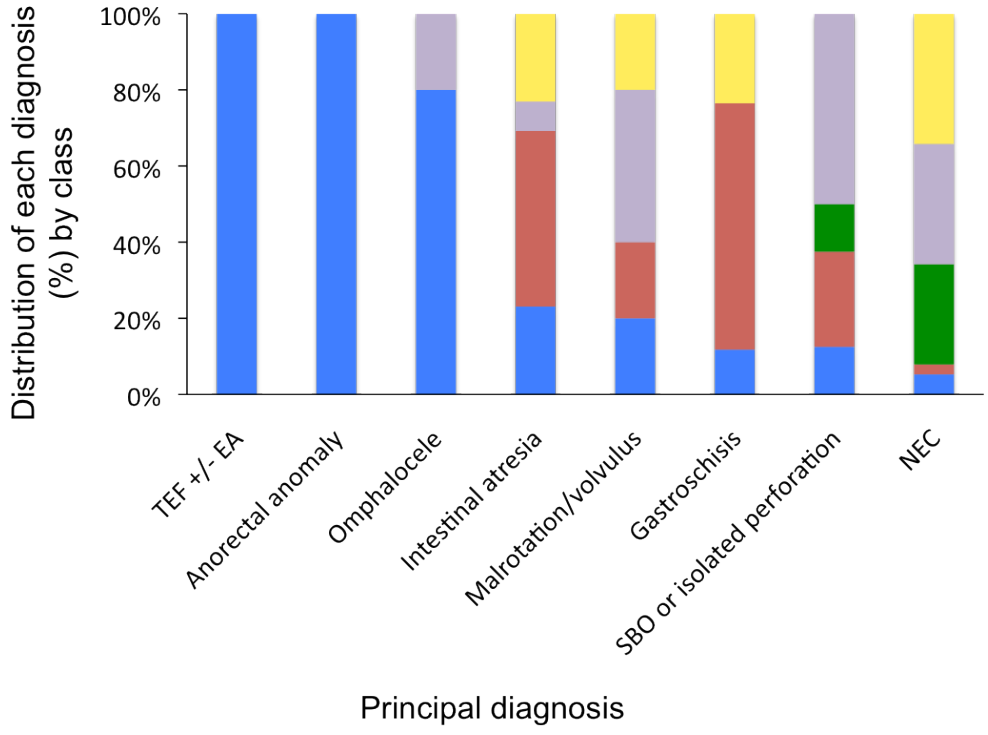


Figure 2 Distribution of classes in each principal diagnosis Principal diagnoses varied between classes 1 (blue, n=22), 2 (pink, n=21), 3a (green, n=11), 3b (purple, n=20), and 4 (yellow, n=21).

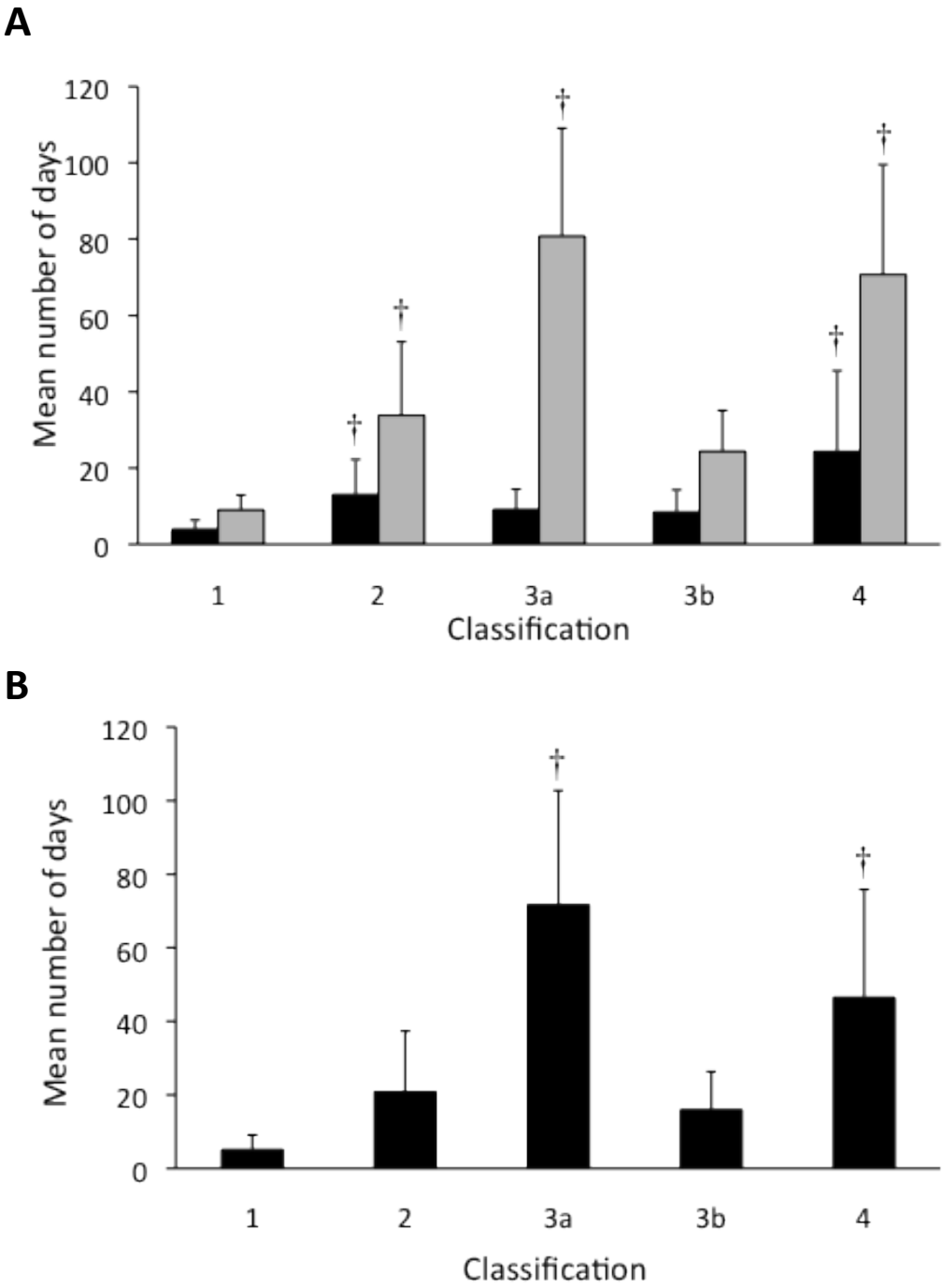


Figure 3 Mean days to reach 50% feeds, full enteral feeds, and full enteral feeds from 50% feeds. ***(A)*** A total of 87 infants reached 50% feeds (50kcal/kg/day, gray bars) and 69 reached full feeds (100kcal/kg/day, black bars; others died or were discharged prior to reaching full feeds). Mean days to reach 50% feeds (n) are shown for classes 1 (n=22), 2 (n=21), 3a (n=11), 3b (n=20), and 4 (n=13). Mean days to reach full feeds (n) are shown for classes 1 (n=15), 2 (n=17), 3a (n=9), 3b (n=17), and 4 (n=11). ***(B)*** The mean days to reach full feeds from 50% feeds (n) were calculated for the 69 infants that reached full feeds (black bars): classes 1 (n=15), 2 (n=17), 3a (n=9), 3b (n=17), and 4 (n=11). Data are displayed with standard deviations. †, $p<0.05$ *versus* class 1 (One-Way ANOVA + Tukey Test).

Of the 41 infants who had small bowel ostomies after their initial surgery, only 17 still had ostomies when they reached full feeds. Most of these were Class 3b infants (78%), while fewer were in Classes 3a (20%) and 4 (23%). Three Class 1 infants had colostomies during this study, and at the time of full feeds, two of them still had colostomies. No Class 2 infants had ostomies at any point during the study period.

Episodes of intolerance, malabsorption and feeding interruptions

Overall, Classes 2 and 4 had significantly more feeding interruptions due to either intolerance or malabsorption ($p<0.05$; Table 2, methods section). Amongst specific types of intolerance, Classes 2 and 4 had the most episodes of abdominal distention, although this did not reach significance (Table 6). There was a trend towards having more episodes of mild-to-moderate and severe malabsorption in Classes 3a and 4 than the other classes (Table 6).

Feeding interruptions due to feeding intolerance (in which each interruption is defined as being NPO for one day) occurred for significantly more days in Classes 2 and 4 compared to Classes 1, 3a, and 3b ($p<0.05$; Figure 4a). The percent of infants with greater than or equal to five days of feeding interruptions (not necessarily consecutive) was also greatest in class 2 and 4, although this did not reach significance versus class 3a ($p>0.05$, Figure 4b). Feeding interruptions due to malabsorption occurred significantly more often in Classes 3a and 4 compared to Classes 1, 2 and 3b ($p<0.05$; Figure 4c). This was also seen when the percent of infants with any or greater than or equal to five days of feeding interruptions due to malabsorption were examined ($p<0.05$; Figure 4d).

Nutritional outcomes

Additional nutritional outcomes are shown in Table 6. A greater percentage of infants in Classes 2, 3a and 4 were changed to more elemental formulas (71%, 100%, and 80%, respectively) than those infants in Classes 1 and 3b (14% and 55%; $p<0.05$). The mean number of times that the total daily volume of feedings was decreased was significantly greater in Classes 3a and 4 (14.3±6.8 and 10.6±7.5) versus Classes 1, 2 and 3b (1.5±1.5, 3.8± 3.1, and 3.3±2.8, respectively; $p<0.05$). This trend was also seen for the total number of days that infants received intravenous nutrition (TPN and/or IFE) through a central line and the length of hospital stay. However, despite this trend, the number of sepsis evaluations done, the number of positive blood cultures reported and the discharge location were not different between groups ($p>0.05$). When the type of feeding at the endpoint was examined for infants who were still being fed at this point (79 infants), there was no difference between the percent of infants in any group receiving bolus feeding (either orally, using a tube or a combination of these two).

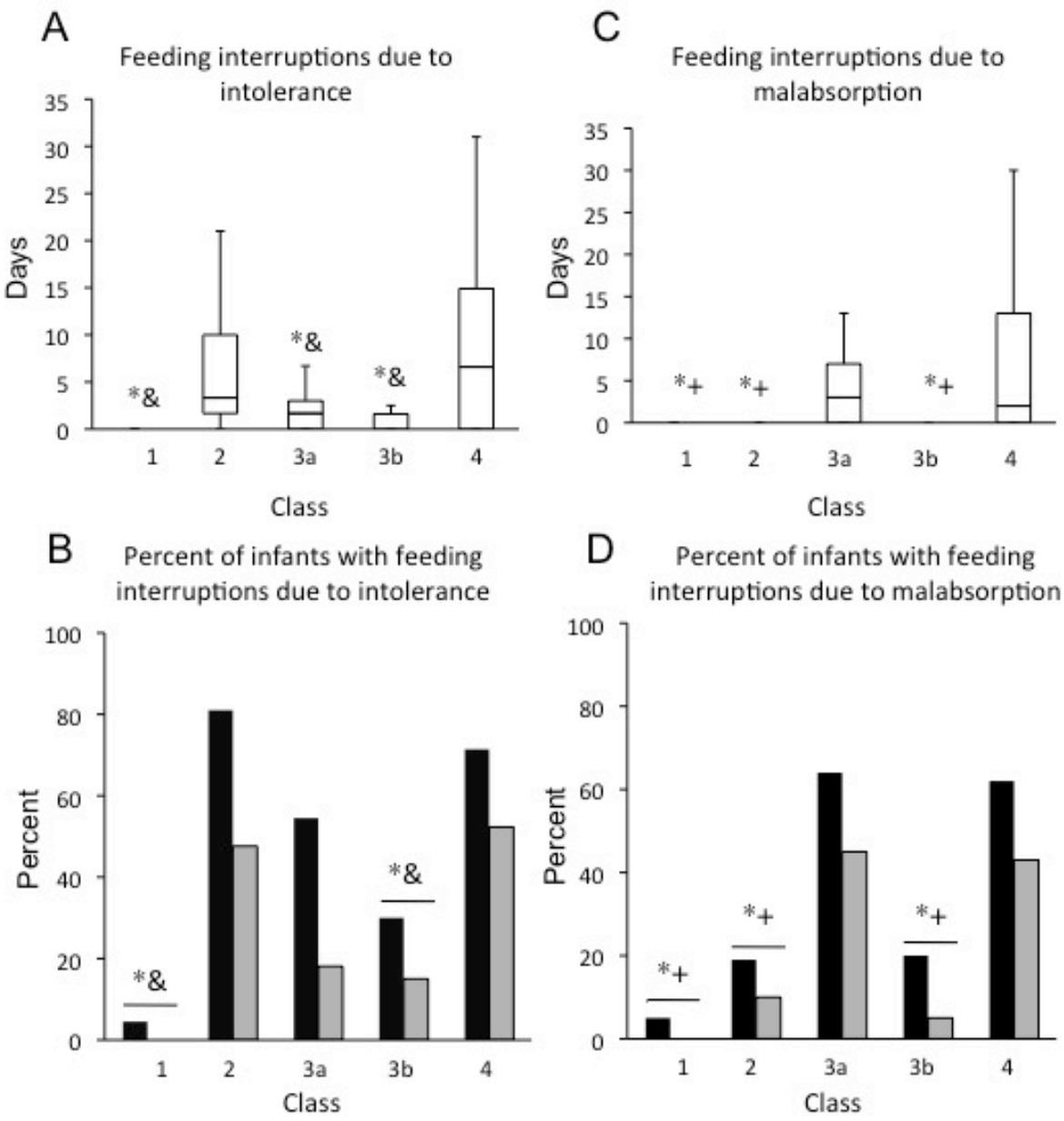


Figure 4 Feeding interruptions due to feeding intolerance and malabsorption The median days of feeding interruption due to intolerance **(*A*)** or malabsorption **(*C*)** were assessed from the first day of enteral feeds until full feeds or another endpoint in class 1 (n=22), 2 (n=21), 3a (n=11), 3b (n=20) and 4 (n=21). The percent of infants in each class with any feeding interruption (black bars) or ≥5 days of interruptions (gray bars) due to intolerance **(*B*)** and malabsorption **(*D*)** were calculated. *, p<0.05 *versus* class 4; +, p<0.05 *versus* class 3a; &, p<0.05 *versus* class 2; #, p<0.05 *versus* class 3b (A+C: Kruskall Wallis + Mann-Whitney Test; B+D: Chi-square + Fisher's exact test).

	Class 1 (n=22)	Class 2 (n=21)	Class 3a (n=11)	Class 3b (n=20)	Class 4 (n=21)
Enteral feeding					
Switched to more elemental feeds	3 (14)[abcd]	15 (71)	11 (100)	11 (55)[ab]	18 (86)
Switched from bolus to continuous feeds	3 (14)	3 (14)	4 (36)	4 (20)	2 (10)
Total daily volume decreased (mean events/infant ± SD)	1.5 ± 1.5[e]	3.8 ± 3.1[e]	14.3 ± 6.8	3.3 ± 2.8[e]	10.6 ± 7.5
Any feeding interruptions	0 (0-1)[ad]	3 (0-21)	0 (0-7)[ad]	0 (0-8)[ad]	4 (0-40)
Due to intolerance					
Emesis	0 (0-5)[d]	4 (0-26)	0 (0-12)	1 (0-8)	1 (0-46)
Abdominal distention	0 (0-5)[abd]	8 (0-51)	2 (0-65)	0 (0-15)[ad]	14 (0-50)
Due to malabsorption					
Mild to moderate	0 (0-3)[bcd]	0 (0-14)[ab]	19 (0-38)	0 (0-14)[ab]	16 (0-124)
Severe	0 (0-4)[bcd]	4 (0-28)[ac]	7 (0-26)	0 (0-14)[ab]	11 (0-119)
Parenteral nutrition					
Days with central line	10 (0-54)[abc]	32 (7-156)[ab]	86 (36-160)	62 (8-114)[ab]	105 (52-215)
Days on TPN	10 (0-51)[abcd]	36 (3-51)[ab]	103 (41-153)	53 (8-86)[ab]	99 (48-208)
Days on IFE	9 (0-51)[abcd]	34 (3-151)[ab]	94 (41-140)	48 (8-86)[ab]	93 (35-208)
Septic work-ups	0 (0-0)	0 (0-6)	2 (1-17)	0.5 (0-4)	4 (0-19)
Positive blood cultures	0 (0-0)	0 (0-5)	2 (0-9)	0 (0-6)	0 (0-11)
Discharge location					
Home (n,%)	20 (91)	20 (95)	10 (91)	18 (90)	14 (67)
Other institution (n,%)	0 (0)	0 (0)	1 (9)	2 (10)	4 (19)
Deceased (n,%)	2 (9)	1 (5)	0 (0)	0 (0)	3 (14)
Length of stay	18 (4-109)[abcd]	43(19-227)[abc]	116 (54-165)	76 (26-290)[ab]	112 (56-274)
Endpoint feeding	Class 1 (n=22)	Class 2 (n=21)	Class 3a (n=10)	Class 3b (n=19)	Class 4 (n=17)
Bolus feeding (n,%)	20 (91)	20 (95)	9 (90)	17 (89)	12 (67)

Table 6 Nutritional and Clinical Outcomes. Data is expressed as median (range) days or number of infants (% of total infants). Mild-to-moderate malabsorption includes increased stool frequency/volume or watery stool. Severe includes bloody stool, electrolyte abnormalities, or positive reducing substance test. Bolus feeding includes feeds that were given orally, by tube, or both. a, $p<0.05$ *vs* 4; b, $p<0.05$ *vs* 3a; c, $p<0.05$ *vs* 3b; d, $p<0.05$ *vs* 2 (Chi-square + Fisher's exact test for categorical variables, Kruskall-Wallis + Mann-Whitney test for continuous variables). e, $p<0.05$ *vs* 3a and 4 (One-way ANOVA + Tukey test). Abbreviations: total parenteral nutrition (TPN), intravenous fat emulsion (IFE).

Liver function

Liver function tests (LFT's) were not drawn for all infants in all classes. LFT's were collected but missing for two infants (one in class 1 and one in class 3b). In Classes 3a and 4, 100% and 95% of the infants, respectively, had at least one set of LFT's. In Class 1, however, only 10 of the 22 infants had at least one set of LFT's (45%). Most infants in Classes 2 and 3b had LFT's measured (Class 2: 18/21, 86%; Class 3b: 15/20, 75%). Of these infants, the number and percent who ever had a direct bilirubin ≥0.5 are shown in Table 7. Infants were separated into one of four categories of cholestasis based on their

	Direct bilirubin ≥ 0.5	Category 1	Category 2	Category 3	Category 4
Class 1	8/10 (80%)	1/10 (10%)	5/10 (50%)	2/10 (20%)	1/10 (10%)
Class 2	15/18 (83%)	3/18 (17%)	6/18 (33%)	1/18 (6%)	8/18 (44%)
Class 3a	11/11 (100%)	0 (0%)	2/11 (18%)	1/11 (9%)	8/11 (73%)
Class 3b	14/15 (93%)	0 (0%)	3/15 (20%)	5/15 (33%)	6/15 (40%)
Class 4	20/20 (100%)	0 (0%)	2/20 (10%)	2/20 (10%)	16/20 (80%)

Table 7 Quantification of cholestasis secondary to TPN in infants. Data is reported as number of infants/total infants (percent). Of infants who had any LFT's, the number with any direct bilirubin ≥0.5mg/dL were counted. The categories for quantifying cholestasis were as follows: category 1 (no cholestasis), category 2 (cholestasis with d. bili ≥0.5mg/dL or <2.0), category 3 (significant cholestasis with d. bili ≥2.0 mg/dL) and category 4 (parenteral nutrition-associated liver disease, PNALD). Abbreviations: total parenteral nutrition (TPN).

highest ever LFT's (Table 7). When category 4 (parenteral nutrition-associated liver disease, PNALD) was examined, it was found that Classes 3a and 4 had significantly more infants who met this criteria as compared to Class 1 ($p<0.05$, Figure 4a). We also looked at the percent of infants who had greater than three sets of LFT's drawn during the

study period. There were no infants in Class 1 who had greater than three sets of LFT's drawn. However, the pattern seen when Classes 2, 3a, 3b, and 4 are examined is similar to the pattern seen in rates of PNALD. The average volume of TPN, volume of IFE, and grams of lipids/kg bodyweight were not different between the groups ($p>0.05$).

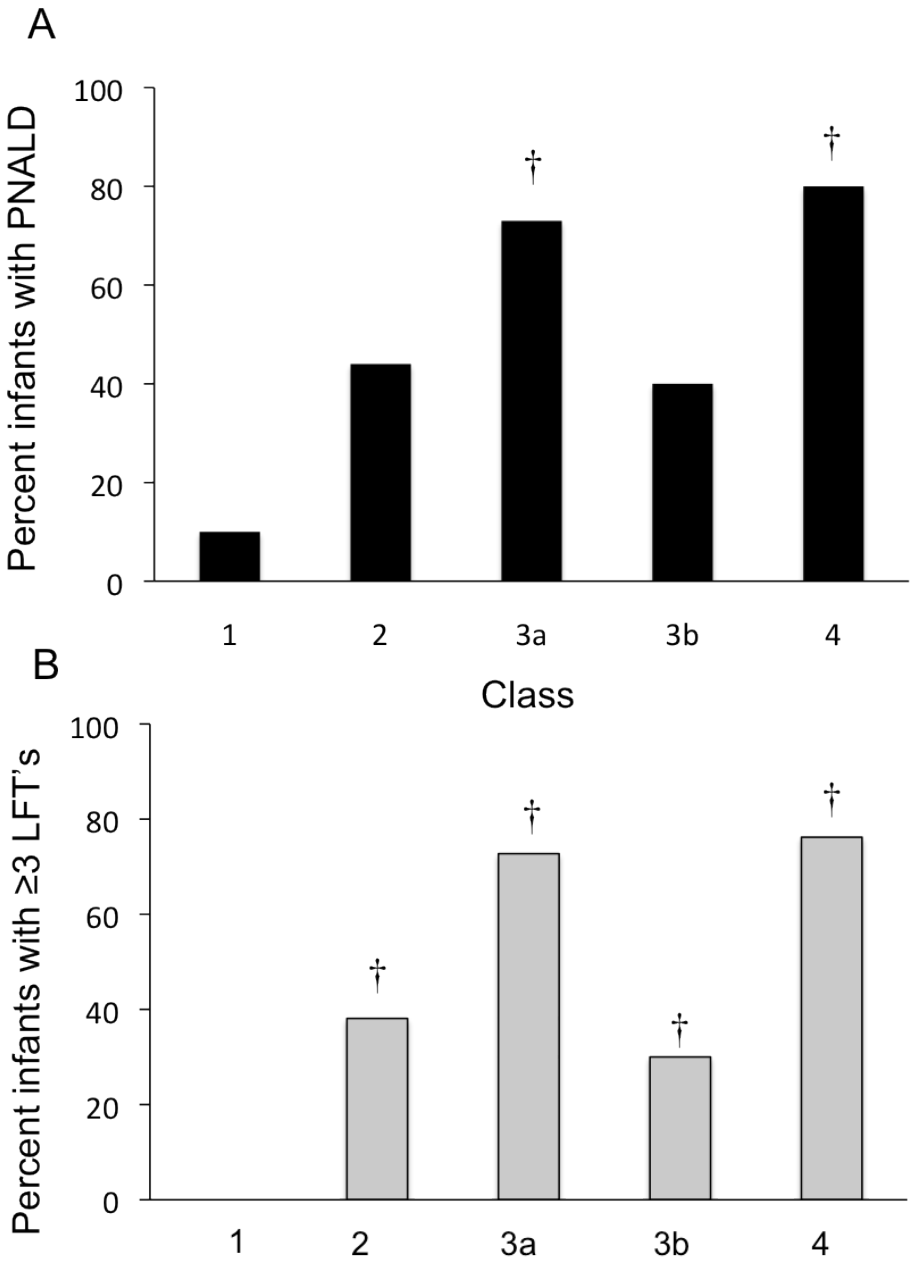


Figure 5 Liver function testing. ***(A)*** The percent of infants in each class who met criteria for PNALD based on LFT's is shown. ***(B)*** The percent of infants in each class who had greater than or equal to three sets of LFT's drawn during the study period is shown. †, $p<0.05$ *versus* class 1 (Chi-Square + Fisher's Exact Test). Abbreviations: liver function tests (LFT's), parenteral nutrition-associated liver disease (PNALD).

Discussion

Although feeding regimens for premature infants have been reported, they are focused on advancement of feeds with reference to gut maturity and do not take into account the effect of surgery on the intestine or of the specific disease/disorder that required surgical intervention [45, 48, 51-53]. Understanding the specific feeding difficulties that each class of GI surgical patients may face allows for goal-directed criteria for advancement of feedings. Infants in this retrospective study were managed according to usual practices in the NICU without standardization of management based on surgical disease, post-operative anatomy, or expected function or dysfunction. This allowed an assessment of the time to full enteral feeds and the number of episodes of intolerance and malabsorption as well as the number of times there was a setback in feeding (including cessation of feeds, decreased volume of feeds, or changing of formulas).

The main objective of this study was to determine if a classification system based on surgeon-described intraoperative findings (specifically intestinal anatomy and expected function) successfully predicts feeding difficulties in post-operative infants, specifically those who have undergone GI surgery.

The principle findings of this study were:

1. Compared to Class 1 infants, those in Classes 2 and 4 took significantly longer to reach 50% feeds, while those in Classes 2, 3a and 4 all took significantly longer to reach full feeds. Class 3b was not different from Class 1 in either case.

2. Infants in Class 1 had the lowest number of episodes of feeding interruption due to either feeding intolerance or malabsorption.
3. Overall, infants in Classes 2 and 4 had significantly more feeding interruptions due to intolerance and for significantly more days compared to Classes 1, 3a, and 3b.
4. Overall, infants in Classes 3a and 4 had significantly more feeding interruptions due to malabsorption and for significantly more days compared to Classes 1, 2, and 3b.
5. Infants in Classes 3a and 4 spent significantly more days on TPN and IFE compared to Classes 1, 2 and 3b. Significantly more infants in Classes 3a and 4 also met criteria for PNALD compared to the other classes.

Days required to reach 50% and full feeds

Infants in Classes 3a and 4 took significantly longer to reach full feeds compared with other classes and the majority of this time occurred between 50% and full feeds. Focusing on Class 3a, the time to reach 50% feeds was not different from that required by Class 1 infants. In addition, all of the Class 1 and 3a infants reached 50% feeds. Between 50% and full feeds, however, Class 3a infants took significantly more time to reach full feeds than those in Class 1. Although only 68% of Class 1 infants reached full feeds (as compared to 82% of Class 3a infants), this was most likely because many Class 1 infants were discharged just prior to reaching full feeds (presumably because they were believed to be healthy enough to do so). Class 4 infants, arguably the sickest and most fragile infants in this study, required significantly more time than Class 1 infants to reach 50%

feeds, a difference that was amplified between 50% and full feeds. Only 52% of these infants reached full feeds. The remaining infants either died, or were discharged on supportive nutrition (either TPN or a feeding tube).

Class 2 infants took significantly longer than Class 1 infants to reach 50% feeds and full feeds, but not to reach full feeds from 50% feeds. In other words, most of their time towards reach full feeds occurred after they had reached 50% feeds, which is the opposite of what was seen in Class 3a infants. Class 2 infants have normal length intestine, but are expected to have intestinal dysfunction (and thus experience feeding intolerance) whereas Class 3a infants have short intestine, but are expected to have normal function (and thus experience malabsorption). Feeding intolerance would be expected to resolve as the intestine recovers post-operatively, whereas malabsorption (i.e. dumping) would not be expected to begin until a certain volume/caloric density of feeds was reached. Indeed, studies of infants with short bowel syndrome have demonstrated that slow continuous feeds promote weight gain and better nutrient absorption, whereas bolus feeds are associated with weight loss and a risk for osmotic diarrhea [34, 40, 42]. Thus grouping these infants using a classification system would help address these distinct feeding needs and might reduce the episodes of feeding interruptions in these infants.

Interestingly, Class 3b infants did not require significantly more time to reach 50% or full feeds compared to Class 1. They also had similar numbers of feeding interruptions. However, compared to Class 1 infants, Class 3b infants did have significantly longer exposure to central lines, TPN and IFE. These differences are of interest because these

infants have an ostomy and, anecdotally, are often fed more cautiously than an infant who has no stoma. However, our data suggests that more cautious feeding may not be necessary for this class of infants. It has been shown in ELBW infants, perceived severity of illness influences decisions regarding early nutritional support [19]. It is also known that delaying enteral feedings leads to inadequate growth, and that growth velocity in the NICU is related to growth and development later in life [31]. In addition to this, it has been well documented that prolonged exposure to TPN and IFE is detrimental to health and although the Class 3b infants did not have significantly more PNALD than Class 1 infants in this study, there were more Class 3b infants with PNALD than Class 1 infants (6/15, 40% vs. 1/10, 10%).

Notably, at the time of full feeds, 17 infants had ostomies in place, and 78% of those were Class 3b infants. Thus, Class 3b infants are able to reach full feeds despite having an ostomy in place, whereas most Class 3a and 4 infants reached full feeds only after reanastomosis.

Feeding interruptions due to intolerance and malabsorption

This study demonstrated that infants classified as Class 2 and 4 had significantly more feeding interruptions due to feeding intolerance, whereas those classified as Class 3a and 4 had significantly more feeding interruptions due to malabsorption. This was seen both when examining the median number of days of feeding interruptions and also the percent of infants who had ≥5 days of interruptions.

One way of assessing feeding difficulties is to examine the number of times an infant had to be switched to more elemental feeds, switched from bolus to continuous feeds or have the total daily volume of feeds be decreased. In this study, there were significantly more times that the total daily volume of feeds had to be decreased in Classes 3a and 4 infants as compared to Class 1 infants. A similar trend was seen with the number of times that an infant had to be switched to more elemental feeds. This data is difficult to interpret in a retrospective study, as there was no standardization of the initial type of enteral feeding an infant received.

In this study, the initial "Class 3" group was subdivided into Class 3a and 3b to differentiate between those infants with a proximal and distal ostomy, respectively. We anticipated that infants with a proximal ostomy would behave like infants with SBS, whereas those with a distal ostomy and otherwise healthy bowel would behave more similarly to infants who had no change in their small bowel anatomy or expected function (Class 1). Our data are consistent with that expectation.

Class 2 infants are those with normal intestinal anatomy but with expected dysfunction and, in this study, often had conditions such as gastroschisis or intestinal atresia with bowel that was thickened, ischemic, or edematous. Feeding problems in infants with gastroschisis are thought to be due to foregut dysmotility and clinical studies have demonstrated that these infants experience more gastroesophageal reflux disease as well as deficits in esophageal motor function [54].

Liver function tests and cholestasis

In this study, the percent of infants who had greater than or equal to three sets of LFT's drawn was significantly greater in all classes when compared to Class 1 infants. In Classes 3a and 4, approximately 80% of infants had greater than or equal to three sets of LFT's drawn, where as the numbers in Classes 2 and 3b were lower (40% and 36%, respectively). The difference between Class 3b and Classes 3a and 4 is interesting. The trends seen mirror those seen for days of parenteral nutrition, suggesting that the percent of infants with multiple sets of LFT's reflects the fact that LFT's are drawn weekly or even more often for infants on prolonged TPN and/or IFE. However, it may also reflect the perceived sickness of the infant. If this is the case, then, as suggested above, Class 3b infants may be perceived to be "sicker" than Class 1 infants. The percent of infants who developed PNALD (diagnosed by LFT's only) in this study is alarming, especially in Class 3a and 4 infants, but also in Class 2 and 3b infants. In these classes, greater than 40% of the infants met criteria for PNALD at some point during the study. Given that premature infants are at greater risk for PNALD (Wessel 2007), these data are a reminder that although TPN may be necessary at times, it is important to limit its use as much as possible. New studies on reduction of the dose of IFE have demonstrated significant decreases in total bilirubin levels in TPN-dependent surgical patients [14]. It will be important to see in the future if the use of a standardized feeding protocol could also reduce PNALD in addition to reducing the dose of IFE.

Limitations

The biggest limitation in this study is the small number of subjects. Such a small number of subjects was used to ensure equal numbers in each classification group. Although there were often plentiful class 1 cases, class 3a and 4 cases were rarer and there were often only three to five cases in each class in which the infants began enteral feeds. The retrospective nature of this study also makes it difficult to draw conclusions. However, given the positive results of this study, we are planning to undertake a prospective study using the proposed feeding guidelines.

Clinical significance

There have been many studies establishing the benefit of feeding guidelines for premature infants [45-48]. In contrast, there are only a handful of studies on feeding regimens in infants who have undergone any type of surgery, and no studies on infants who have undergone GI surgery. The studies that do exist have specifically focus on early induction of feeds, on a specific diagnosis such as gastroschisis, or have excluded patients with the potential for feeding difficulties [15, 33]. The literature has many reports of nutritional regimens for the management of short gut syndrome. The goals of both enteral and parenteral nutritional support in these infants include providing adequate nutrition to support growth, preventing fluid and electrolyte disturbances, and maximizing bowel adaptation [15, 34, 35, 40]. While enteral nutrition is crucial for the latter goal, in this fragile post-operative population, it is incapable of accomplishing the first goal and may be counter-productive to the second.

Specific feeding regimens for post-operative neonates are not well described and likely vary between institutions. The use of a classification system such as the one proposed would allow for standardized post-operative management based on expected function and anatomy with the goal of more rapid progress in those patients with minimal or no limitations in ability to tolerate enteral feedings while applying specific criteria for advancement in those patients with expected dysfunction and/or short anatomy.

Conclusion and future directions

This is the first classification system of post-operative neonates for the purposes of guiding post-operative feeding. Based on the information in the operative and pathology reports, any member of the healthcare team can apply this classification system. Formal feeding guidelines based on the anticipated feeding difficulties of each class of post-operative infants have been developed with interventions specifically geared to prevent episodes of feeding intolerance and malabsorption. These guidelines need to be prospectively evaluated.

Appendix 1: Enteral Feeding Guidelines for Pediatric Surgery Post-op Neonates

Post –op Classifications	Diet	Route	Feeding Schedule	Advancement	Additional Therapy
I. Anatomically Normal /Expected Normal Function in gut distal to Ligament of Treitz • TEF, CDH, Hirschsprungs, Anorectal anomalies, malrotation/volvulus • NEC in colon only, with colostomy, and minimal or no disease in remaining colonic tissue • Gastroschisis with tissue that looks good, is non-edematous, or quickly "pink's up"(if not described , default to Class 2) • Simple anastomosis (case by case)	HM / Std Formula	PO / PG	Intermittent (TEF continuous due to GERD)	<u>For Preemie</u>: Start 10-20cc/kg/d (ave.12) Advance @ 10-20/kg/d until about 75 cc/kg/d, but then faster if well tolerated <u>For Full-term</u>: Initiate feeds and advance at accelerated rate depending on anomaly	
II. Anatomically Normal / Expected Dysfunction • Gastroschisis with tissue that looks thickened, gray, ischemic, inflamed, edematous,or with peel • Duodenal stenosis and atresias • Malrotation/Volvulus with tissue that looks gray, with evidence of sloughing, but no resection	HM / Std Formula? ↓ Pregestimil ↓ Neocate (if malabsorption)	PO / PG	Intermittent Continuous if not tolerated	Start minimum 10-20cc/kg/d Advance minimum of 10-20cc/kg/d	

• NEC in colon only, with colostomy, and extensive disease in remaining colon. • Post op expectation for poor motility and/or absorption.					
IIIA. Anatomically Abnormal / Expected Normal Function • NEC, resection(s), perforation(s) with < 50 % small bowel loss in the duodenum or jejunum • Proximal small bowel ostomy (i.e., jejunostomy) • Remaining gut tissue looks good and expected to have normal motility and absorption	HM / Pregestimil? ↓ Neocate (if malabsorption)	PG	Start Continuous Condense feedings after tolerating full continuous feeding	Start 10cc/kg/d Advance 10cc/kg/d *Slower start and advance as long as tolerated, specifically no evidence of malabsorption	- Adjust TPN to 1 g/kg/d of fat maximum - Zantac 5 mg/kg/day - Caloric goal starting at 90/kg/day and then titrate to weight gain of 10 g/d - Consider small po feeds for oral aversion therapy after tolerating > 75% goal feeds
IIIB. Anatomically Abnormal / Expected Normal Function • NEC, resection(s), perforation(s) with < 50 % small bowel loss in the ileum • Distal small bowel ostomy (i.e., ileostomy) • Remaining gut tissue looks good and expected to have normal motility and absorption	HM / Pregestimil? ↓ Neocate (if malabsorption)	PG	Start Continuous Condense feedings after tolerating full continuous feeding	Start 10cc/kg/d Advance 10cc/kg/d *Slower start and advance as long as tolerated, specifically no evidence of malabsorption	- Adjust TPN to 1 g/kg/d of fat maximum - Zantac 5 mg/kg/day - Caloric goal starting at 90/kg/day and then titrate to weight gain of 10 g/d - Consider small PO feeds for oral aversion therapy after tolerating > 75% goal feeds
IV. Anatomically Abnormal (Short) /	Consider HM	PG	Start Continuous	Start 10 cc/kg/d	- Adjust TPN to 1

Expected Dysfunction • Gastroschisis: severe gut damage/vanishing with same • Atresias, malrotation, volvulus with extensive damage • NEC, resection(s), perforations with >60% small bowel loss • Very high small bowel ostomy • All of above with gut that is ischemic, necrotic, dusky, gray, edematous, thickened, thick peel, etc and expected to have poor motility and/or absorption	Otherwise Neocate		Condense feedings after tolerating full continuous feeding	Advance ?5-10 cc/kg/d vs. 10 cc/kg/qod *Slower start and advance as long as tolerated, specifically no evidence of malabsorption	g/kg/d of fat maximum - Zantac 5 mg/kg/day - Caloric goal starting at 90/kg/day and then titrate to weight gain of 10 g/d - Consider small po feeds for oral aversion therapy after tolerating > 75% goal feeds

Neocate is most elemental formula available. Pregestamil is not as elemental as Neocate, but because it contains 55% MCT, should be considered first if appropriate.

*Malabsorption in patients with ostomy defined as ostomy output > 20 cc/kg/d, more than a 2 fold increase in volume, or change in consistency to watery

*Malabsorption in patients with no ostomy defined as a marked change in stool frequency (eg, > 1.5-2 fold increase) or in consistency (eg, increased watery or liquidy).

Aspirates only if clinical concern. Protocol does not preclude refeeding stoma output; final stool output from most distal location used for feeding protocol.

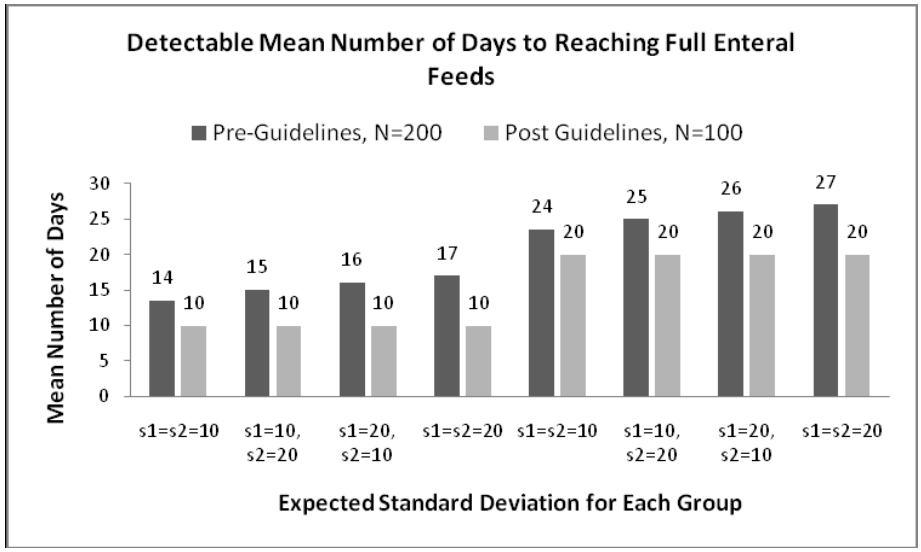
Appendix 2: Power calculations

The primary outcome of interest, the number of days to reaching full enteral feeds (defined as a minimum of 90kcal/kg/day), will be summarized descriptively for the period prior to initiating the feeding guidelines (2002-2010) and for the period when the guidelines were implemented (2011-2014) using means and standard deviations. We do not expect the distribution of the outcome to be normal, but rather follow the Poisson distribution, with the mean being equal to the standard deviation. Furthermore, individual patients will be clustered within a year of data collection; therefore, the outcome will be modeled in SAS 9.2 (Cary, NC) using the Proc Glimmix procedure with 'dist=poisson', which also allows to introduce a random effect for the year of data collection. In addition to evaluating the primary independent effect of the guideline period (pre- vs. during-implementation) on the number of days to reaching full enteral feeds, the model will also include the post-op classification variable (Class I, II, IIIA, IIIB, IV), and an interaction between period and classification variables (an exploratory analysis). Patient demographic and clinical characteristics will also be included in the model as adjustment variables (e.g., birth weight, gender, ethnicity).

Statistical analyses for the other outcome of interest, the number of days to having weight gain of a minimum of 10 g/day for 3 consecutive days, will follow the same analytical plan.

The figure below summarizes our sample size and power analysis, which was conducted using the Power Analysis and Sample Size software (PASS 2008). Group sample sizes of 200 for the pre-guideline period and 100 for the during-guideline period achieve 80%

power to detect a difference in the range of 4 to 7 days in the mean number of days to reaching full enteral feeds between the two groups, with a significance level (alpha) of 0.05. Based on some pilot data from our hospital, we assumed the observed mean number of days in the group that was treated when the guidelines were implemented as either 10 or 20 days, and varied the corresponding within-group standard deviations (either 10 days or 20 days).



Since we are also interested in describing the outcomes for each class of the post-operative feeding guidelines, we are planning to collect data on 5 patients for each of the five classifications per year (yielding 25 patients per year). We will be examining 8 years for the pre-period (01/01/2002-12/31/2010) and 4 years for the during-period (01/01/2011-12/31/2012), therefore, the groups sample sizes are 8*25=200 and 4*25=100 for each period respectively.

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