

Carol Rees Parrish, R.D., M.S., Series Editor

Nutritional Management of the Infant with Necrotizing Enterocolitis



Patti Perks



Ana Abad-Jorge

Necrotizing enterocolitis (NEC), an inflammatory gastrointestinal disease, occurs in 1%–5% of infants in neonatal intensive care units with a reported mortality rate of 25%–66%. Research efforts are directed at elucidating the cause and pathogenesis of NEC in attempts to improve preventive as well as treatment measures. Current preventive strategies include: trophic feedings, standardized feeding regimens, provision of breast milk, arginine supplementation, probiotic therapy, and infection control measures. Nutritional management with adequate parenteral nutrition and reintroduction of enteral feeding, avoiding reoccurrence of NEC and minimizing complications, is essential. The following article will present an overview of nutritional management of NEC and related complications.

INTRODUCTION

Necrotizing enterocolitis (NEC) is an inflammatory gastrointestinal (GI) disease process characterized by tissue necrosis and, while commonly seen in the neonatal intensive care unit (NICU), can also occur in critically ill term infants (1–3). The precise etiology of NEC remains unclear; however, there

are a variety of factors which contribute to its development and pathophysiology (2,4,5). While 90%–93% of all infants who develop NEC are preterm, there have been no documented cases of intrauterine NEC, which may be related to the sterility of the intrauterine GI tract. The most recent data suggests that NEC affects between 5%–10% of very low birth weight (VLBW) infants (<1500 grams), with the most susceptible infants being the extremely low birth weight (ELBW) infants, (<1000 grams) (1,6). Overall, NEC occurs in 1%–5% of neonates admitted to the NICU, although the incidence of NEC has been found to be unit dependent. The overall mortality of NEC is 25%, but has been reported as high as 66% in VLBW infants (7). In
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Patti Perks, MS, RD, CNSD, NICU Nutrition Support Specialist, UVA Health System, Department of Nutrition Services, Charlottesville, VA. Ana Abad-Jorge, MS, RD, CNSD, Director, Dietetic Internship Program, Pediatric Nutrition Support Specialist, UVA Health System, Department of Nutrition Services, Charlottesville, VA.

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a recent study by Ostlie, et al (3), full term infants with NEC were found to differ from preterm infants in several distinct ways. Full term infants developed NEC at a significantly earlier age (five days versus 13 days), which may be attributed to having enteral feedings initiated earlier. Furthermore, there was a clear association between congenital heart disease and the development of NEC in the term infants. Interestingly, this study also found no outcome differences between the term and preterm infants.

RISK FACTORS AND PATHOGENESIS

Risk Factors

Risk factors for NEC include maternal risk factors as well as perinatal and postnatal risk factors related to the infant’s clinical and infectious status in addition to their medical and nutritional management. The predominant risk factors for NEC are presented in Table 1. Prematurity is one of the most significant risk factors underlying NEC for a variety of reasons. Preterm infants have decreased immunocompetence, an immature GI tract, and abnormal peristalsis. These factors lead to nutrient maldigestion and malabsorption, setting the stage for small intestinal bacterial overgrowth, fermentation and ischemic damage to the premature bowel. Decreased immunocompetence in preterm infants increases the incidence of infections, including pathogenic bacterial colonization of the GI tract. Moreover, due to their increased incidence of cardiorespiratory, homeostatic instability and poor autoregulation of blood flow, preterm infants are more susceptible to ischemic or hypoxic events, putting them at risk for NEC.

Feeding regimens, both formula composition as well as feeding approach, have been demonstrated to impact the development of neonatal NEC. Various studies conducted in the mid-to-late-seventies demonstrated a high incidence of NEC in infants fed hyperosmolar formulas and in those receiving medications and supplements added to the formula (10,11). More than 90% of infants diagnosed with NEC have received enteral nutrition (EN) (12). Enteral feeding factors considered to increase the risk of NEC include increased formula osmolality and rapid daily advance-

**Table 1
Risk Factors for Necrotizing Enterocolitis (1,4,7-9)**

<i>Risk Factor Category</i>	<i>Risk Factor Examples</i>
Maternal	Prenatal indomethacin therapy Placental insufficiency Cocaine use
Perinatal	Prematurity Perinatal ischemia Hypoxic events
Postnatal Factors	Use of umbilical arterial catheters Ischemia of intestinal mucosa Congenital heart defects Rapid feeding advancements Use of hyperosmolar formulas or medications Presence of infectious agents

ments of formula volume. The impact of other factors, such as route, method of delivery, and the differences between breast milk, preterm formulas and term formulas on the incidence of NEC, however, are not as clear (13). Studies looking at continuous versus bolus feedings in preterm infants have not demonstrated a difference in the incidence of NEC (1). Whether the use of human milk reduces the incidence of NEC remains somewhat controversial due to limited data. Most studies indicate that while breast milk reduces the incidence of NEC, in some cases by one-half, it does not offer complete protection (12,13).

Pathogenesis

The pathogenesis of NEC is thought to be related to the interaction of a number of physiological mechanisms including compromised mesenteric circulation, increased mucosal inflammation, and increased apoptosis of the intestinal epithelial cells. Physiological triggers leading to the inflammatory process are mediated by factors including platelet-activating factor (PAF), thromboxanes, and cytokines, to name a few (13,14). Another reason for the increased risk of NEC

in preterm infants is their immature mucosal barrier, which may potentiate the translocation of bacteria into the splanchnic bed and activate the inflammatory mediator cascade. Moreover, increased damage to the immature mucosal barrier may occur in preterms through the phenomenon of increased apoptosis, or programmed cell death, thus further compromising the integrity of the mucosal barrier (14).

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of NEC can vary significantly from one infant to another, ranging from mild to severe feeding intolerance or from mild abdominal distention to fulminant shock or death. Common clinical manifestations of NEC include increased gastric residual volumes, increased emesis, increased abdominal distention, and mildly to grossly bloody stools (15). Gastric residual volumes indicative of feeding intolerance as a possible sign of early NEC is dependent on the infant's weight and the individual neonatal clinician. Laboratory abnormalities include an elevated white blood cell count, neutropenia, thrombocytopenia and disseminated intravascular coagulation. In addition, the infant may experience metabolic acidosis and electrolyte abnormalities. Pneumatosis intestinalis, or intraluminal gas produced by bacteria, is considered to be the defining radiologic finding in the diagnosis of NEC; documented in 70%–80% of confirmed cases. Bell, et al established a staging system for NEC, which has become a commonly used tool in its diagnosis and management. This staging system, presented in Table 2, is based on clinical, radiographic and laboratory criteria (16).

PREVENTION STRATEGIES

Various prevention strategies have been identified which may decrease the incidence of NEC. These include the use of trophic or minimal EN feedings, slow advancement of feedings, the use of standardized feeding regimens, and the use of breast milk for EN (15,17,18). Additionally, the use of arginine supplementation as well as antenatal steroid, oral antibiotic and immunoglobulin administration have been investigated with regards to their potential role in the prevention of NEC (19,20). Standardized infection control

Table 2
Bell's Stages of Necrotizing Enterocolitis (16)

<i>Stage</i>	<i>Clinical Signs and Symptoms</i>
Stage 1	Broad spectrum but non-specific signs: simple feeding intolerance, sepsis, gastroenteritis, ileus, metabolic abnormalities, i.e. hypoglycemia
Stage 2	Proven NEC via abdominal radiographs showing intestinal dilatation and pneumatosis intestinalis
Stage 3	Advanced stage in which infant demonstrates signs of septic shock, metabolic acidosis, disseminated intravascular coagulopathy, neutropenia, abdominal tenderness, ascites

practices such as strict handwashing, and the use of probiotic administration have also been found to have a positive impact on the incidence of NEC (21,22).

Minimal enteral nutrition or trophic feedings in the first few weeks of life have been shown to decrease the incidence of NEC in VLBW infants. Berseth, et al conducted a randomized controlled trial of 141 preterm infants, fed either a trophic schedule of 20 mL/kg/day for 10 days or an advancing schedule beginning at 20 mL/kg on Day 1 and then advancing by 20 mL/kg/day to a goal of 140 mL/kg (17). The incidence of NEC was only 1.4% in the trophic group versus an incidence of 10% in the advancing volumes group. A recent meta-analysis conducted by Patole and de Klerk (18) found that the use of standardized feeding regimens significantly reduced the incidence of NEC in preterm infants. Overall, the numerous studies conducted in this area have demonstrated that the variability in GI response among preterm infants warrants larger clinical trials to better characterize the mechanisms regulating feeding tolerance.

Various recent studies have demonstrated that probiotic administration has a positive impact on reducing the incidence of NEC (21,22). The widespread use of antibiotics in preterm infants in the NICU setting leads to a decrease in the colonization of the gut by commensal organisms such as *Bifidobacterium* and *Lactobacillus* species, and promotes the growth of pathogenic

Table 3
Estimated Calorie and Protein Needs for Infants (23,25,26)

Nutrient	Parenteral		Enteral	
	Preterm	Term	Preterm	Term
Calories/kg	85–115	85–100	110–130*	100–115*
Protein gm/kg	3–4	2.4–2.8	3.5–4	2.8–3.5

*Catch up growth may require 10%–20% or more calories and higher levels of protein.

organisms. The combination of pathogenic bacteria and an immature GI tract may be a clinical set-up for colonization of the bowel, the pathogenesis of NEC and, ultimately, bacterial translocation (21). Bin-Nun, et al (22) found that the incidence of NEC in the infants randomized to receive daily supplementation with a probiotic mixture was only 4% compared to the infants who did not receive the probiotic supplementation (16.4%), resulting in a relative risk reduction of 75%.

NUTRITION FOLLOWING THE ONSET OF NEC

Despite preventive measures, the multiple risk factors present in premature and critically ill term infants may culminate in the diagnosis of NEC; the severity of intestinal involvement influences the decision for medical or surgical management. Each course of treatment introduces particular nutritional concerns; however, some aspects of nutritional management are common to both medical NEC and surgical NEC.

PARENTERAL NUTRITION SUPPORT

Once NEC is strongly suspected and/or confirmed, the infant should be made NPO until deemed clinically ready for EN. Management of fluids and electrolytes is critical in the initial phase of severe NEC, and intravenous fluids in addition to parenteral nutrition (PN) may be required to treat acidemia, support euolemia, and adjust electrolytes. PN should be initiated as soon as possible, utilizing central access if adequate enteral support will not be reached within two weeks (23). Adequate protein and calories (kcal) are essential to prevent breakdown of somatic protein for energy and for the production of inflammatory factors. Peripheral PN is frequently restricted in nutrient concentration due to

osmolality limitations and rarely provides sufficient calories to prevent utilization of exogenous protein for fuel unless fluids are liberalized (23).

In medically-managed NEC, duration of NPO status and full PN support traditionally varies from seven days to two weeks, (24) depending on severity of NEC, clinical indicators, and the results of abdominal evaluations. Surgery further delays feedings. Given the

potential duration of PN, a key goal of nutritional management is provision of adequate, but not excessive, nutrients in order to prevent or delay the onset of PN-related complications.

Estimated PN protein and calorie requirements for preterm and term infants (23,25,26) are represented in Table 3. Parenteral energy needs are estimated to be 10%–15% lower than EN needs due to reduced stool losses and the absence of digestion and absorption which are energy-requiring processes (23). The ELBW infant may require closer to 105–115 kcal/kg (25–27). Whether NEC or sepsis increases energy needs significantly is unclear. Energy needs during the acute phase of critical illness, with potential sedation and pain medications given, may be close to basal needs, sufficient to prevent catabolism and weight loss. Within one to three days postoperatively or post-acute response, energy needs likely return to normal or greater, allowing for growth and movement (23,25). Infants generally require at least 115 mL of fluid for every 100 kcal given (23,25). Nutrient and fluid delivery during and post-NEC require frequent monitoring.

Achieving growth during the acute phase of NEC is difficult; this may be due to suboptimal delivery or reduced utilization of PN versus EN, or to the activation of cytokines and growth-impeding hormones in response to the inflammatory process. Adequate nutrition during the catabolic phase of NEC minimizes the loss of somatic proteins and provides for anabolism when the acute phase has passed.

Micronutrient requirements may be affected by the inflammatory process. Zinc stores are diminished in the premature infant and most PN formulations pro-

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vide minimal if any zinc. Adequate zinc is essential for the immune response, antioxidant functions, growth, and neurological development. PN should provide 400 $\mu\text{g}/\text{kg}$ zinc to preterm infants weighing <2500 grams, larger infants on prolonged PN, or when there is ostomy output (28).

Carnitine is used in the mitochondrial oxidation of long-chain fatty acids and frees CoA from long-chain acyl CoA, thereby supplying CoA for many metabolic pathways such as the citric acid cycle, ketogenesis, and gluconeogenesis, as well as adenosine triphosphate (ATP) production. Carnitine deficiency induced in piglets receiving PN resulted in metabolic and functional deterioration (29). Breast milk and infant formulas contain carnitine; PN does not however, unless added. Premature infants appear to have a reduced ability to convert lysine and methionine to carnitine and, therefore, may require exogenous carnitine to keep up with demand. Deficiency can also occur in preterm or term infants due to prolonged PN and with decreased enteral absorption, such as in short bowel syndrome (SBS). Recommendations for parenteral carnitine range from 2–5 mg/kg/day to 10–20 mg/kg/day. During enteral feeding, the same daily dose may be given enterally as divided doses throughout 24 hours, if needed (25,30).

During prolonged PN, serum conjugated bilirubin levels should be monitored weekly for cholestasis (conjugated bilirubin >2 mg/dL); PN copper and manganese should be reduced or removed to prevent toxicity due to impaired excretion through the biliary tract (31). Other recommendations for nutritional management of biliary cholestasis are discussed later.

ENTERAL NUTRITION

Estimated EN calorie and protein requirements for preterm and term infants (26,27) are listed in Table 3. Infants who experience repeated episodes of NEC or who require surgery often exhibit delayed growth and neurological development (24). Post-NEC growth and nutrient needs may be 10%–50% higher than in other infants (27,28). While appropriate concerns about overfeeding have resulted in more conservative calorie and protein goals for infants, nutritional intake should be tailored to the infant's gestational age, birth weight, growth history, and needs to provide adequate nutrition as the

infant moves from the acute inflammatory response into the anabolic phase when growth can resume. When fluid restrictions are physiologically necessary, feedings can be gradually concentrated to provide the calories and protein required to achieve desired growth.

There is a lack of consensus on when enteral feedings should be reintroduced and the method and rate of reaching goal feeding volumes. Atrophy of the epithelial villi may occur within one week of NPO status, creating an environment for feeding intolerance and bacterial translocation (32). Research suggests that hormonal responses to enteral stimulation remain functional despite surgery, as evidenced by the release of cholecystikinin and peptide YY in the post surgical gut (33). The standard practice of prolonged bowel rest may not be evidence-based and, given the associated morbidity of prolonged PN should be questioned and reevaluated based on newer evidence (32,34).

Bohnhorst and associates compared early versus late EN in post-NEC infants. The prerequisite for starting EN was three consecutive days of abdominal ultrasounds showing no portal venous gas. The median start of EN for the early group was day four after onset of NEC in those medically treated and day seven post-NEC in those surgically treated. In the late EN group, the median initiation of EN was 10 days post-onset of NEC in medically-managed infants, and 13 days post-NEC in the surgical group. Early EN post-NEC did not result in any negative events and was associated with significantly fewer catheter-related infections and a significantly shorter hospitalization. As expected, time to reach goal EN was significantly less, nearly half the number of days. Duration of antibiotic therapy was also significantly reduced. The authors proposed that early enteral substrate may assist in the rejuvenation of the intestinal mucosa and protect the mucosa from penetration by pathogenic bacteria (32).

EN promotes cellular hyperplasia, regeneration of the brush border, intestinal lengthening, motility regulation, and bile flow; trophic volumes prepare the GI tract for advancement of EN (28,35). A simple intervention of encouraging pacifier sucking (nonnutritive sucking) prior to EN may also stimulate mesenteric vascular circulation and help prepare the gut for feedings (36).

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The optimal rate of EN advancement post-NEC remains elusive. While evidence supports that standardized feeding progression reduces the incidence of NEC (37), there is less data on advancement in post-NEC infants. The dilution of formula to half-strength is controversial; current recommendations are to advance EN by 10–35 mL/kg/day, depending on the severity of NEC, reaching goal volumes first, then fortifying or concentrating to provide goal nutrition (26,32).

The choice of feedings post-NEC remains controversial. In most instances, breast milk is the optimal feeding when available. Breast milk contains growth hormones that may promote GI adaptation and contains lactase that helps digest lactose. Depending on the mother's diet, breast milk is usually a good source of docosahexaenoic acid (DHA) and arachidonic acid (ARA). DHA and ARA are long-chain polyunsaturated acids, vital to the structure and function of cell membranes, with current research elucidating their contribution to retinal and central nervous system development and immune function (28, 38).

In the absence of breast milk, premature infants with limited GI injury can be started on premature formulas such as Enfamil® Premature Lipil® 24 (Mead Johnson) or Similac® Special Care Advance® 24 (Ross Products). Corn syrup or maltodextrin has replaced some of the lactose in these formulas and the fat is a blend of 40%-50% medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) (28).

Research is investigating the role of pre- and probiotics post-NEC in alleviation of GI inflammation through the increased production of anti-inflammatory cytokines and in protection against allergies related to increased intestinal permeability. Delayed feedings, the relatively sterile environment of incubators, and frequent use of broad-spectrum antibiotics, all common during treatment of NEC, exacerbate the preterm infant's delayed colonization with desirable bacteria (21). Preterm neonates are more likely to have pathogenic bacteria such as *Klebsiella*, *Enterobacter*, and *Clostridium* organisms. While breast milk appears to provide *Bifidobacteria* and *lactobacilli*, VLBW infants receiving breast milk still show a relative lack of these organisms until after the third week of life. The provision of probiotics, *Lactobacillus acidophilus* and *B. infantis*, appears to reduce the incidence and severity of NEC

with no adverse effects (21). Once ischemic areas are healed, *Bifidobacteria* and some *Lactobacillus* species appear to improve gut integrity and reduce permeability, with protection against enteral pathogens, softer stools and possibly improved GI tolerance to EN (39,40).

NUTRITIONAL MANAGEMENT OF NEC COMPLICATIONS

Major complications following NEC are cholestasis, secondary to long-term PN, short bowel syndrome (SBS), and small intestine bacterial overgrowth (SIBO). Twenty-five percent of infants with surgical resection for NEC develop SBS (24). Extensive or multiple surgeries increase the risk of each complication, all of which can coexist. Persistent gastric residuals with abdominal distention and bilious emesis suggest the development of a stricture or narrowing in the intestine which can form from thickened and contracted scar tissue that forms in a previously ischemic area of bowel. The symptoms of SIBO can mimic those of a stricture, and radiographic exam may be necessary to rule out a stricture. If a stricture is confirmed, extensive bowel rest to allow complete healing of the affected area is necessary.

Multiple surgeries may be required in cases of severe NEC to remove all of the affected necrotic areas and to reanastomose resected lengths of bowel. Current practice is to provide six weeks of bowel rest between resection and reanastomosis (24).

SBS is an anatomical or functional loss of more than 50% of the small intestine, resulting in symptoms of diarrhea, and fluid and electrolyte losses due to impaired digestion and malabsorption. Nutritional and medical management in infants with severe GI impairment has been discussed in depth elsewhere (41-43). Fluid and electrolyte replacement remains critical as EN advances. For infants with an ostomy, management of electrolytes is essential. Ostomy output and stool may contain 80–140 mEq/L of sodium, 15 mEq/L of potassium, 115 mEq/L of chloride, 40 mEq/L of bicarbonate, and 12–16 mg/L of zinc, plus magnesium, zinc and selenium. Hypomagnesemia impairs parathyroid hormone release, thereby potentially precipitating calcium deficiency. Therefore, correction of magnesium deficits as well as provision of optimal calcium is important (28). If metabolic acidosis is present, a com-

bination of sodium citrate and sodium chloride is appropriate as a source of bicarbonate (28).

Decisions regarding choice and delivery of EN are affected by the extent of GI injury, potential for protein sensitivity, and symptoms of fat and/or carbohydrate malabsorption. While bolus feeding appears to be beneficial in gut maturation and function, the use of continuous feeding following severe NEC or with SBS allows gradual introduction of nutrients to the intestinal lumen, with less abdominal distention and diarrhea, promoting improved absorption and tolerance (26,28,41,42). PN can be cycled off for four-to-six hours with continuous EN gradually changed to a 12-hour cycle with small bolus feeding introduced during the remaining 12 hours. An effective strategy is to start initial boluses equal to the amount of feeding per hour (i.e. continuous EN at 10 mL/hour would suggest an initial bolus of 10 mL per feed). Given that PN has no malabsorption factor as compared to 30% or greater of EN likely malabsorbed in severe GI disease (23,28), for every increase in EN, the PN rate can be decreased by one-third of the enteral increase. For example, if EN is advanced by 2–3 mL/hour, the PN rate can be reduced by 1 mL/hour.

Once the combination of 12-hour continuous EN and daytime boluses provides 100–120 mL/kg/day and is tolerated with acceptable stooling or ostomy output, PN can be discontinued and replaced with an appropriate IV fluid for the additional fluid and electrolytes required until full EN goals can be reached. Inadequate EN tolerance necessitates decreasing EN and possibly returning to all continuous delivery; this should be considered if ostomy output exceeds 20 mL/kg/d or stool losses exceed 40–50 mL/kg/d (26). Once PN is discontinued, fat-soluble vitamins, iron, folate, magnesium, calcium and additional vitamin B₁₂ may need to be supplemented in cases of severe SBS and SIBO (26,28,41).

As the volume of bolus EN is increased and tolerated, the duration and rate of the overnight EN can be reduced, working towards full bolus EN. This process may require weeks, months, or up to a year, depending on the length of intact bowel and GI adaptation. If infants are unable to transition to adequate oral feedings and will require continuous delivery of EN for more than three months, a gastrostomy tube is recommended. *Oral motor stimulation is vital*, and when able, small amounts of oral (bolus) feedings can be given to help stimulate feeding skills.

SIBO can occur after intestinal resection, and therefore should be included in the differential diagnosis of infants with abdominal tenderness, watery or increased volume stools, abdominal distention or air in the bowel wall, and/or emesis (28). Infants at risk of SIBO are those with impaired motility, partial small bowel obstruction, bowel dilatation as occurs following resection, cholestasis, resection of the ileocecal valve, antibiotic therapy, and prolonged lack of enteral nutrients (28). Prolonged use of acid suppression therapy increases the risk of SIBO (28). Some medical centers cycle infants on an antibiotic such as metronidazole (Flagyl) for five to 10 days (28).

Breast milk is the feeding of choice in nearly every case, the growth factors and prebiotic and probiotic factors contributing to recovery of the GI tract. Feeding selection in the absence of breast milk after extensive resection and/or inflammation offers many options. Protein hydrolysate formulas with no lactose and variable amounts of medium chain triglycerides (MCT) may provide improved absorption while GI adaptation begins. MCT diffuse from the GI tract to the portal system without requiring energy or emulsification with bile acids, and do not require lipase for digestion. Of these formulas, Alimentum[®] Advance[®] (Ross Products) has 33% MCT oil and a blend of sucrose and modified tapioca starch; Pregestimil[®] Lipil[®] (Mead Johnson) has 55% MCT oil and a blend of corn syrup solids and modified starch (28). Refer to Table 4 for the nutrient content of various specialized infant and pediatric formulas.

Premature infants recovering from mucosal inflammation and prolonged periods of bowel rest are potentially at increased risk for antigen response to intact protein, whether from cow's milk or soy (26). In view of this, there may be a theoretical advantage to selecting a hypoallergenic, lactose-free, semi-elemental or amino acid-based formula initially. Examples of these include Neocate[®] (Nutricia) with corn syrup solids and 5% MCT oil, 95% LCT, available with DHA and ARA. Elecare[®] (Ross Products) and Neocate Junior[®] (Nutricia) are also amino acid-based with one-third of fat as MCT for severe cholestasis, formulated for malabsorption, and appropriate for infants when mixed at 20 kcal/oz. To transition to the appropriate preterm formula, once goal volumes are well-tolerated, the practitioner may decide to gradually phase in the appropriate

Table 4
Elemental and Partially Hydrolyzed Formulas for Use in Pediatric Short Bowel and Severe GI Malabsorption
(per 100 mL) (43)

<i>Nutrient</i>	<i>Pregestimil® Lipi® (MeadJohnson)</i>	<i>Alimentum® (Ross Products)</i>	<i>Neocate Infant® (Nutricia)</i>	<i>EleCare® (Ross Products)</i>	<i>Pepdite Junior® (Nutricia)</i>	<i>Neocate Junior® (Nutricia)</i>
kcal/mL	0.67	0.67	0.67	1.0*	1.0*	1.0*
Protein (g)	1.9	1.9	2.08	3.01	3.1	3
Protein Source	Hydrolyzed casein	Hydrolyzed casein, L-cysteine, L-tyrosine, L-tryptophan	Free amino acids	Free amino acids	Soy and meat hydrolysates + free amino acids	Free amino acids
Carbohydrate (g)	6.8	6.9	7.8	10.7	10.6	10.4
Carbohydrate Source	Corn syrup and tapioca	Tapioca starch and sucrose	Corn syrup solids	Corn syrup solids	Maltodextrin and corn syrup	Corn syrup solids
Fat (g)	3.8	3.8	3.0	4.76	5	5
Fat Source	MCT oil, corn oil	MCT, soy, safflower oil	Safflower, soy, coconut oil	Safflower, coconut, soy oil	Coconut safflower, soy oil	Coconut canola, safflower oil
Energy Distribution						
Protein	11%	11%	12%	15%	12%	12%
Carbohydrate	41%	41%	47%	43%	42%	42%
Fat	48%	48%	41%	42%	46%	46%
LCT	45%	67%	95%	67%	65%	65%
MCT	55%	33%	5%	33%	35%	35%
Osmolality (mOsm/kg)	340	370	375	560	430 (unflavored) 440 (banana)	607
Indications	Mal-absorption, SBS	Mal-absorption Short bowel syndrome	Cow's milk or multiple food allergies, gastroesophageal reflux, SBS	Mal-absorption, severe food allergies, SBS	Mal-absorption, severe food allergies, SBS	Multiple food allergy, malabsorption, SBS

Short Bowel Syndrome (SBS): formulas with less carbohydrate and higher % of calories from fat may be better tolerated.

*These formulas are generally used with patients > 1 year old. However when mixed at 20 kcal/oz, and a daily vitamin/mineral supplement provided, nutrient levels are appropriate for term infants who cannot tolerate other infant formulas. Preterm infants who continue on a non-premature formula may require concentrated formula.

preterm feeding. If the preterm infant needs to remain on either a hypoallergenic or hydrolysate formula, the formula can be gradually concentrated to provide improved calorie, protein, vitamin and mineral delivery.

Simple carbohydrates may contribute to EN intolerance due to bacterial fermentation producing gas and

bloating (44), or due to the increased osmotic effects contributing to dumping symptoms (41). Ideally, 40% or less of calories should come from carbohydrates (41). Table 4 notes the percent of carbohydrates and fats in formulas commonly used for GI impairment. While
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Table 5
Nutritional Management Strategies Post-NEC

Medical NEC

- Feeding Choice: Breast milk or Preterm formula (term formula if term infant)
- Delivery: Bolus
- Rate of advance: 10–35 mL/kg/day

Severe or Surgical NEC

- Feeding Choice: Breast milk, semi-elemental or amino acid-based EN initially
- Delivery: Continuous, with gradual introduction of bolus as tolerated
- Rate of advance: 10–35 mL/kg/day
- Consider added zinc and levo-carnitine if prolonged TPN and/or significant ostomy/stool losses
- Evaluate for SIBO if prolonged TPN/NPO and appropriate med therapy

Short Bowel Syndrome

- Feeding Choice: Breast milk or semi-elemental, higher fat feedings
- Delivery: Continuous, gradual introduction of bolus as tolerated
- Rate of advance: 10–35 mL/kg/day
- Consider added zinc, levo-carnitine, fat-soluble vitamins, calcium, iron
- Evaluate for SIBO and appropriate med therapy
- Fluid and electrolyte replacement based on volume and source of losses

Cholestasis

- Feeding choice: trophic EN as soon as possible, appropriate EN related to other conditions (prematurity, post-surgical NEC, SBS, etc)
- Delivery: If SBS or Severe/Surgical NEC, continuous. Otherwise, bolus.
- Rate of advance: 10–35 mL/kg/day
- Consider reduced delivery of copper and manganese in trace elements and potentially increased need for fat-soluble vitamins
- Evaluate for SIBO and appropriate medical treatment
- Fluid and electrolyte replacement if increased stool losses
- Cycle PN, providing 4 to 6 hours off, as tolerated

higher-MCT formulas may be beneficial in the presence of severe cholestasis due to less availability of bile for fat digestion, long chain fatty acids exert a trophic effect

on the GI tract and have a lower osmotic impact than MCT (41,44). In cases of ileal resection with an intact colon, reduced bile salt reabsorption may cause secretory diarrhea and irritation. Cautious use of cholestyramine may aid in binding malabsorbed bile acids, but also may increase fat malabsorption, exacerbate metabolic bone disease, and induce constipation (26,42).

Cholestasis occurs in 30% to 60% of infants with SBS; 3% to 19% of neonates with SBS develop liver failure (26). In addition to the potential role of PN, the length of time without GI stimulation, and the development of bacterial or fungal infections are potential contributing factors. Aggressive prevention of SIBO has been effective in reducing the incidence of cholestasis (26). Cycling PN interrupts the otherwise constant presentation to the liver of nutrients and insulin and, in theory, may help delay the onset of PN-liver disease. A typical four hour cycle off might include one-half hour at half-rate before and after the three hour off period. Therefore the PN rate is calculated on 20 hours, not 24 in order to deliver the equivalent amount of volume and nutrients over the shorter time.

In prolonged severe cholestasis with fat malabsorption, water-soluble forms of vitamins A, D, E, and K may be needed once PN is stopped. Serum levels of vitamin A and 25-hydroxy-vitamin D should be checked periodically. Preterm formulas contain approximately 50% of fat as MCT, therefore as long as stools appear relatively normal and *adequate growth continues*, no change is necessary.

Prevention of overfeeding and promotion of early EN remain key deterrents to PN-related liver disease. Current research is evaluating the impact of a PN fat emulsion (Omegaven) containing primarily omega-3 fatty acids, with reversal of cholestasis (45). The current lipid suspension (Intralipid®) is made of soybean oil, high in omega-6 fatty acids which have an inflammatory effect. Omegaven is currently available for compassionate-use and approved research, until efficacy and safety are determined (45). As soon as feasible, trophic or minimal EN serves to stimulate biliary tract function. An excellent review of treatment options for PN-associated liver disease is presented elsewhere (46). Table 5 provides a brief summary of interventions discussed in this article.

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CONCLUSION

The nutritional management of post-NEC infants can be complex, depending on the severity of the medical and surgical procedures required. Subsequent studies are needed to clarify the optimal parenteral and enteral nutrient regimens to reduce the severity of NEC and the incidence of post-NEC complications such as SBS, cholestasis and SIBO. ■

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