Carol Rees Parrish, MS, RDN, Series Editor

Nutritional Management of Infants with Necrotizing Enterocolitis

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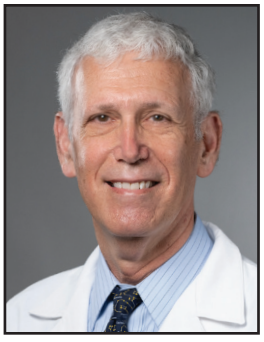

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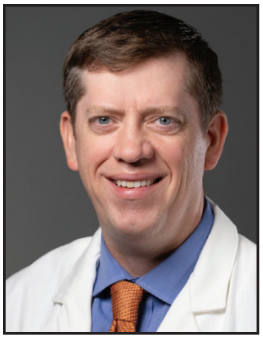

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Necrotizing enterocolitis (NEC) is an inflammatory disorder of the gastrointestinal (GI) tract that primarily occurs in premature infants, contributing to infant morbidity and mortality. Term infants are also at risk of NEC, particularly infants with congenital heart disease (CHD), although the pathophysiology differs from that in preterm infants. Optimal nutritional management, both during and following NEC, is imperative for the developing infant. Options for parenteral and enteral nutrition have expanded, necessitating this update to a previously published article on Nutritional Management of the Infant with Necrotizing Enterocolitis.

INTRODUCTION

Necrotizing enterocolitis (NEC) is an inflammatory disorder of the gastrointestinal (GI) tract that primarily occurs in premature infants. NEC represents the culmination of pathological processes involving dysfunction of the gut epithelium, immune and hemodynamic systems, and intestinal dysbiosis.[1] NEC is a leading cause of morbidity and mortality in the neonatal intensive care unit (NICU) and is associated with an increased risk of neurodevelopmental delay.[2,3]

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A meta-analysis published in 2020 reported the global incidence of NEC in very low birth weight (VLBW) infants (birth weight < 1500 g) at 7%.[4] Term infants are also at risk of NEC, particularly infants with congenital heart disease (CHD), yet the pathophysiology differs from that of preterm infants.[2,3,5] Optimal nutritional management during and following NEC is imperative for the developing infant.

The pathophysiology of NEC is multifactorial,[7] and shares overlapping clinical features with other acquired neonatal intestinal diseases.[8,9] Risk factors predisposing to NEC include maternal and in utero factors as well as infant perinatal and postnatal factors.[2,3,8,10-14] (Table 1)

The incidence of NEC in preterm infants peaks around 31 weeks post-menstrual age (PMA) with 95% of cases occurring by 34

Table 1. Risk Factors for Necrotizing Enterocolitis

Time Period	Risk Factor
Maternal/ In Utero	• Chorioamnionitis • Cocaine, heroin, amphetamine use • Placental insufficiency and fetal growth restriction • Intrahepatic cholestasis of pregnancy • Insufficient maternal IgG transfer
Perinatal	• Premature birth • Ischemia/hypoperfusion • Hypoxic event at birth • Polycythemia/hyperviscosity
Postnatal	• Congenital heart defects, particularly single ventricleor left-sided cardiac dysfunction • Bacterial or viral infections • Cow's milk protein exposure in very low birth weight (VLBW) infants, or cow's milk allergy • Transfusion of red blood cells and/or anemia • Dysbiosis; antibiotic exposure • Cold stress/hypothermia • Gastroschisis, congenital GI anomalies • Ingestion of a commercial product/formula associated with higher than normal incidence of NEC

weeks (PMA).[2,15] Preterm infants have decreased immunocompetence coupled with an immature GI tract and dysmotility. Mature peristaltic patterns do not develop until 34-36 weeks' PMA. Preterm intestinal defense systems against pathogens and toxins are underdeveloped. These systems include digestion, production of gastric acid, a mucin lining, and reduction of intestinal permeability.[16] Nutrient maldigestion and malabsorption coupled with reduced GI contractility may predispose to stasis, small intestinal bacterial overgrowth (SIBO), dysbiosis, and ischemic damage to the premature bowel.[16] Translocation of bacteria across the intestinal barrier precipitates an inflammatory cascade that can result in intestinal necrosis.[2,11] The pathophysiology of NEC in late preterm or term infants is primarily the result of diminished perfusion of the intestinal tract that occurs with hypoxic-ischemic encephalopathy, placental insufficiency, certain forms of congenital heart disease such as hypoplastic left heart syndrome and single ventricle defects, or polycythemia and associated hyperviscosity.

Prevention strategies proposed for both preterm and term infants include early human milk feeding,[2,14] antibiotic stewardship, probiotics,[11] avoidance of acid inhibitors, infection prevention, avoidance of anemia, and adherence to feeding protocols.[2]

Clinical Presentation and Medical and Surgical Management

The clinical presentation of NEC varies from one infant to another. Disease severity is based on clinical markers. Non-surgical NEC includes mild ileus to moderate illness with focal pneumatosis intestinalis and dilated loops with or without portal venous gas. Medical management is indicated in these conditions. Surgery is typically indicated if the clinical condition worsens, which can be marked by:

- hemodynamic instability
- severe thrombocytopenia
- disseminated intravascular coagulopathy (DIC)
- peritonitis or pneumoperitoneum.[7]

Although commonly used as a definition, Bell's criteria were not meant as a means of diagnosing NEC, but rather as a means of grading the severity of the NEC. There have been at least six more recent definitions of NEC, nearly all of which have better sensitivity and specificity than Bell's criteria alone.[17,18] The severity of the disease process determines which medical and/or surgical interventions are indicated.[12] (Table 2)

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Table 2. Medical and Surgical Management of Infants with NEC

Severity of NEC (including Bell's Stages)	Medical Interventions	Surgical Interventions
• Suspected NEC (Stage I) • Confirmed NEC with mild to moderate illness (Stage II A, B) • Confirmed NEC and improving clinical status during medical management (Stage III)	• Bowel rest, nil per os (NPO), gastric decompression • Parenteral nutrition (PN), fluid and electrolyte support • Antibiotic therapy (broad-spectrum +/- anaerobic coverage) • Cardiovascular and respiratory support • Management of DIC, acidosis, hyperkalemia, hyperglycemia, hypertriglyceridemia • Frequent clinical examinations, laboratory monitoring, and abdominal x-rays and/or ultrasound imaging	• N/A
• Clinical status refractory to medical management, worsening sepsis/shock (Stage III A) • Severe illness and pneumoperitoneum, perforated bowel (Stage III B)	• Same as above: medical management continues	• Percutaneous peritoneal drain placement, and/or, • Laparotomy with intestinal resection and removal of necrotic segment(s) • Creation of stoma and reanastomosis if primary anastomosis not feasible

NEC can present with abdominal distention, feeding intolerance, emesis, grossly bloody stools, diarrhea, and/or abdominal wall erythema. Differential diagnoses include sepsis-induced ileus, spontaneous intestinal perforation (SIP), meconium peritonitis, Hirschsprung-associated enterocolitis, food protein enterocolitis, malrotation with volvulus, or intestinal obstruction. Similar symptoms may result in misdiagnosis. Accurate diagnosis can impact reintroduction of feeds, particularly if cow's milk protein or other dietary proteins need to be excluded from the infant's or mother's diet. SIP typically occurs within the first 10 days after birth in very preterm VLBW infants and requires surgical intervention. The perforation is usually isolated in the terminal ileum and the remainder of the bowel is healthy. Feeding intolerance is typically demonstrated by increased gastric retention, abdominal distention or fullness, inadequate stooling, and/or increased apnea, all of which can be seen in NEC.[9]

Identification of pneumatosis intestinalis in conjunction with previously mentioned clinical symptoms is diagnostic for NEC, and the diagnosis is supported by thrombocytopenia, neutropenia, DIC, elevated lactic acid levels, and/or hyperkalemia and hyponatremia.

With severe NEC, infants may develop generalized edema due to capillary leak and poor vascular tone, necessitating aggressive fluid resuscitation and inotropic support. Hyponatremia may occur, requiring significant sodium in

Table 3. Potential Complications of NEC and Appropriate Nutritional Interventions

Potential Complications	Nutritional Interventions
IV fluids (IVF) competing with PN delivery	• Concentrate PN volume and/or increase fluid goal
Electrolyte abnormalities	• Correct hyponatremia, hyperkalemia, metabolic acidosis via PN and additional IVF or infusions
Hyperglycemia	• Maintain glucose infusion rate (GIR) > 4 mg/kg/min from PN and IVF; insulin may be indicated if GIR and calories cannot be maintained without hyperglycemia
Hypertriglyceridemia > 200-250 mg/dL	• Reduce PN lipid delivery to 1 gm/kg and recheck triglycerides; when < 200-250 mg/dL, advance by 0.5-1 gm/kg/d to achieve goal lipids
Cholestasis with conjugated bilirubin > 2 mg/dL; liver inflammation reflected in liver function tests	• IV lipid emulsions of soybean oil, MCTs, olive oil, fish oil (SMOFlipid®) at minimum of 2.2 gm/kg/day, or fish oil (Omegaven®) at 1-1.5 gm/kg/day, may reduce proinflammatory metabolites and provide anti-inflammatory omega-3 fatty acids. Monitor essential fatty acid (EFA) profile after 4 weeks of use, sooner if clinical signs of EFA deficiency; Triene:tetraene ratio > 0.2 may indicate EFA deficiency; Check vitamin E levels at 2 weeks, 4 weeks, then 3-6 months thereafter if receiving SMOF. • Trace element (TE) modification to reduce* or eliminate manganese and potentially copper; with reported deficiencies of copper with reduced dosing, consider monitoring instead. Monitor copper, manganese, zinc after 4 weeks of PN, if expected to continue on PN. • Cycling non-lipid PN (delivery in < 24 hours) – little evidence of efficacy in neonates; reserve for stable phase once calorie goals achieved.
GI losses via gastric suction and/or small bowel output via stoma or fistula	• Adjust sodium chloride or sodium acetate based on labs and fluid losses: gastric fluid is rich in sodium chloride and hydrochloric acid; small bowel fluid contains significant amounts of bicarbonate. Additional zinc and/or selenium may be indicated.
Intestinal strictures or adhesions with emesis and bowel obstruction requiring resection	• NPO and gastric decompression if surgery; continued PN with adjustments per laboratory results
Central venous line (CVL) sepsis	• Provide GI stimulation and early feeds to support tolerance and immune factors; prioritize EN tolerance to allow discontinuation of PN and CVL
SBS and intestinal failure with malabsorption	• Quantify ostomy output: goal output typically < 30-40 ml/kg/day; adjust feeds and/or increase fluid support; consider continuous for all or a portion of feeds; human milk for initial feeds with potential role for extensively hydrolyzed or elemental formula if persistent intolerance or growth failure.
Increased risk of micronutrient deficiencies: zinc; vitamins A, D, E, K and B12; copper; iron; selenium. Metabolic bone disease related to calcium, zinc, copper losses small bowel resection and/or fat malabsorption.	• Lab monitoring every 3 months, then longer if reassuring and improving growth, nutritional status. Monitor B12 and methylmalonic acid (may be elevated in B12 deficiency, and SIBO.) Infants with ileal resection: provide B12 supplements as injectable, nasal or sublingual forms. Water-soluble form of fat-soluble vitamins indicated if fat malabsorption present. Calcitriol may be needed if vitamin D deficiency does not respond to enteral sources. Calcium and iron supplements may be required.
Growth faltering and malnutrition; prolonged oral feeding difficulties	• Frequent nutritional assessment and monitoring of growth (weight, length, head circumference); liberal total fluids to allow both PN and EN with needed nutrition; evaluate for need for enteral zinc supplements; evaluate malabsorption and nutrient density; Speech Language therapist consult; consider early use of appropriate solids
Dysmotility and dysbiosis; small intestinal bacterial overgrowth (SIBO)	• Probiotics; consider empirical treatment for SIBO; consider prokinetic agent • Antibiotic therapy; probiotic therapy; consider prokinetic agent

*New FDA-approved fixed dose trace element products provide less manganese, zero chromium. https://americanregent.com/media/3174/pp-tr-us-0047productbulletin_03aug2021.pdf

parenteral nutrition (PN). Acidosis from tissue injury and necrosis often mandates more acetate in PN. An infant with rapidly worsening NEC is at risk for poor renal perfusion and hyperkalemia; PN potassium delivery should be limited and requires close monitoring. Poor hepatic perfusion or excessive glucose delivery may impair fatty acid oxidation; lipid delivery may need to be temporarily reduced during hypertriglyceridemia[24] which in infants may be defined as levels over 200-250 mg/dL. Clinical complications dictate nutritional adjustments. (Table 3)

In the post-acute catabolic phase, PN must then be optimized to provide 100% of estimated nutritional needs to support recovery and minimize lean tissue loss while continuing to promote growth.[25] Adequate PN delivery requires central venous access unless fluid volumes greater than 140 mL/kg are provided.[24] PN energy needs are generally estimated to be 10%–15% lower than enteral nutrition (EN) needs due to reduced stool losses and due to the absence of the thermic effect of food or the energy required for digestion and absorption. Energy needs of the sedated infant during the acute phase of NEC or post-surgery are lower and the timing of moving from catabolism to anabolism remains unclear.[26] PN provision of ~ 75-80 kcal/kg with mean protein delivery of 3.5 gm/kg in the first week after surgery in infants ≤ 32 weeks' gestational age with NEC has been associated with improved head circumference growth without negative impacts.[27] PN energy needs during the subsequent recovery phase need to be increased to support growth.

Enteral Nutrition Management Following NEC

Non-nutritive sucking during bowel rest, if feasible, can promote motility and mesenteric blood flow;[24] wiping or swabbing the baby's mouth (oral care) with colostrum or mom's milk can provide the benefits of human milk.[28] EN should be initiated as soon as clinically feasible following NEC to mitigate the negative impact of lack of GI stimulation and prolonged PN such as sepsis, cholestasis, SIBO, impaired growth, impaired neurocognitive development, and increased length of stay.[24,29] Feeds can be safely started when there is evidence of return of GI function, demonstrated by stable vital signs and resolving thrombocytopenia[7] reduction (not necessarily cessation) of nasogastric output, an improving abdominal exam, and normalization of abdominal x-rays or ultrasound.[29,30,31] In several retrospective cohort studies, earlier re-initiation of EN (< 5-7 days) as compared to later re-initiation of EN (≥ 7 days) was associated with a lower risk of recurrent NEC and/or post-NEC strictures.[32] Moreover, the risk of central line-associated bloodstream infection (CLABSI) was lower, likely the result of improved intestinal barrier function, and full feeds were reached sooner in the early EN group.[32]

Potential benefits of early feeding after GI surgery using human milk include digestibility, the delivery of immunoglobulins, and prebiotics (which may decrease the risk of infection), the delivery of mucin, and growth factors (which may promote intestinal adaptation), motility, and colonization with beneficial GI bacteria.[1,25,29,33] For VLBW infants, early feeding with human milk, both mother's own milk or pasteurized donor human milk (PDHM) as compared to intact cow's milk protein formulas may promote intestinal maturation and decrease the risk of intestinal inflammation.[1] Small cohorts of infants recovering from NEC experienced an increase in cytokine response with exposure to cow's milk beta-lactoglobulin and casein.[7]

Initial EN volume of 10 or 20 mL/kg/d for the infant recovering from medical or less severe surgical NEC is reasonable, and an advance of 20 mL/kg/d has been shown to be tolerated without negative outcomes.[30,31] Feeds should be advanced cautiously and fortified to meet protein and mineral needs. Feeding advances are tailored to the severity of illness and extent of surgical resection, if applicable, while monitoring clinical responses to advancing volumes. Quantification of ostomy output, if applicable, should be used to direct the rate of feeding advances and determine whether bolus versus continuous delivery of feeds is better tolerated. Bolus feeds may better stimulate intestinal adaptation than continuous feedings,[7] however, continuous feeds allow for slower nutrient delivery which may facilitate improved absorption and feeding tolerance, especially in infants with short bowel syndrome (SBS).[7] Overnight continuous

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feedings with small daytime boluses facilitate PO trials during the day. Continuous delivery via gastric or small bowel access may promote tolerance of goal EN volumes when dysmotility or malabsorption are present,[24] allowing the reduction or discontinuation of PN. Concentrating PN as feeds are advanced can optimize the delivery of energy, protein, and micronutrients until feeds can be fortified and advanced sufficiently to eliminate the need for PN.[25]

If mother's own milk or PDHM are unavailable or limited, formula choice post-NEC will depend on whether cow's milk protein intolerance is suspected. Some infants demonstrating cow's milk protein intolerance do not improve with extensively-hydrolyzed protein formulas and in such cases, an amino acid-based formula is appropriate. Infants with SBS may benefit from initial feeds with breast milk; if malabsorption with advancing volumes results in poor growth, dehydration, or electrolyte disarray, an extensively-hydrolyzed or amino acid containing formula containing medium chain triglycerides may aid absorption of nutrients, although evidence is limited and more research is needed.[1,7]

Human milk fortification or formula choice and concentration are tailored to the infant's gestational age and energy and protein needs to support recovery and growth. Achieving a conservative protein goal of 2.5 g/kg/d requires enteral intake of over 200 mL/kg/d of unfortified breast milk, rarely feasible for young infants. Fortification is therefore needed. Human milk-based fortifiers provide increased nutrition while preserving many of the beneficial effects of human milk for preterm infants.[34] Liquid cow's milk-based fortifiers contain hydrolyzed protein and can be effectively used

Table 4. Resources for Managing Intestinal Resection or Short Bowel Syndrome

For Clinicians
• Ou J, Courtney CM, Steinberger AE. Nutrition in Necrotizing Enterocolitis and Following Intestinal Resection. Nutrients. 2020 Feb 18;12(2):520.
• Wendel D, Kay R, Walsh, E, et al. Pediatric Short Bowel Syndrome: Nutritional Care. Practical Gastroenterology; 2021;206:10-23.
• NASPGHAN clinician focused website (NASPGHAN.org) https://naspghan.org/training-career-development/for-fellowship-directors/curricular-resources/congenital-disorders-gi-infections-intestinal-rehabilitation-sbs/
• NEC-Zero o https://neczero.nursing.arizona.edu/ with GutCheck^{NEC}
• NEC Society o https://necsociety.org
For Patients/Families
• Medico T, Parrish C. A Kid's Guide to Short Bowel Syndrome (sponsored by Takeda Pharmaceuticals); available at no cost at: https://www.shortbowelsyndrome.com
• Short Bowel Syndrome Support and Information o https://www.shortbowelsyndrome.com/sbs-in-children
• NEC-Zero o https://neczero.nursing.arizona.edu/parent-resources
• NEC Society o https://necsociety.org/resources-for-families-and-survivors/

to meet the nutritional needs of preterm infants when human milk-based fortifiers are not available. Fortification of human milk is often needed for term infants recovering from GI disease and the appropriate formula powder and/or modulars can be used to reach the needed calorie goal if human milk-based fortifiers designed for term infants are not available. Modulars are less frequently needed due to improved human milk fortifiers and formulas but may include a human milk-based calorie fortifier, protein modulars, medium chain triglycerides (MCT), or other oils, or a combination dextrose/MCT powder.

Preterm infants generally can absorb intact milk proteins; however, absorption may be impaired if pancreatic secretion is inadequate. Hydrolyzed protein, whether extensively or partially hydrolyzed, may promote protein absorption in the setting of pancreatic insufficiency. In the absence of cow's milk protein intolerance or allergy, formulas containing intact protein may be well-tolerated if human milk is unavailable. Human milk contains some peptides which may contribute to its digestibility.[1] Extensively hydrolyzed and elemental formulas do not contain lactose which is an important prebiotic. Undigested lactose in the large bowel undergoes fermentation which produces short-chain fatty acids (SCFAs), gas, and contributes to immune function and gut epithelial health.[1] Infants with SBS may produce less lactase initially due to loss of bowel surface area as well as immature bowel mucosa and may have increased abdominal distention related to increased gas production and rapid intestinal transit. This may result in increased stoma output or excoriated perineal areas.[1] This does not mean lactose needs to be eliminated; gradual introduction of lactose-containing feeds may promote mucosal adaptation and production of the lactase enzyme. However, when concentrating formula, lactose content may be an important factor to consider based on GI symptoms.

Amino acid-based formulas contain glucose polymers instead of lactose and some proportion of MCT instead of long chain triglycerides (LCT). While intended for infants with cow's milk sensitivity refractory to extensively hydrolyzed protein formulas, these are often used initially for infants recovering from NEC despite a lack of evidence to support this practice.[1] MCTs may be more efficiently absorbed than long chain triglycerides among infants with SBS, however, the optimal amount of MCT and the duration of use remains unclear.[1] LCT are important for production of docosahexaenoic and arachidonic acid, vital for eye and brain development[1] and potentially instrumental in intestinal adaptation after bowel resection.[7]

Complications of NEC

Complications secondary to NEC are varied and can range from strictures occurring weeks after diagnosis, to the most serious complication of short-bowel syndrome due to loss of small intestinal length with or without intact colon. Post-NEC strictures may result in partial or total bowel obstruction; more common symptoms are intermittent or persistent abdominal distension, feeding intolerance, and/or intermittent or recurrent vomiting, and chronic or recurrent diarrhea that is sometimes bloody. Persistent or intermittent SIBO caused by intestinal stasis above the stricture produce some of these same symptoms.[19]

Infants who have lost the distal ileum as a result of surgical NEC are at risk of developing vitamin B_{12} deficiency, fat malabsorption, and bile acid malabsorption which may result in steatorrhea as well as watery diarrhea. Loss of the ileocecal valve also increases the risk for rapid intestinal transit and SIBO.

SIBO may exacerbate malabsorption and diarrhea and can cause vomiting, bloating, and abdominal distension, feeding intolerance, recurrent abdominal pain, weight loss, and occasionally fever.[34] Diagnostic tests can be employed to diagnose SIBO, however, they are all poorly reproducible, and hence this largely remains a clinical diagnosis. Treatment is largely empiric, and a wide variety of antibiotics can be used. Recurring SIBO can be associated with chronic intestinal inflammation. Treatment with intermittent or rotating antibiotics may improve feeding tolerance, decrease the incidence of catheter associated infections, and decrease the risk of parenteral nutrition-associated liver disease.[36]

SBS describes a loss of functional bowel length which can occur following medical NEC and more commonly occurs following surgical NEC.

Key articles and resources can guide clinicians in managing short bowel syndrome. (Table 4)

Micronutrient Supplementation

Vitamin and mineral supplementation is an important component of EN support. If SBS, cholestasis, or fat malabsorption exist, a water-miscible form of the fat-soluble vitamins A, D, E, and K will be required. Additional vitamin D supplementation may be indicated when cholestasis and/or indications of metabolic bone disease are present.[37] A serum 25-hydroxy vitamin D level can help determine what level of vitamin D supplementation is needed and for how long. Prematurity and GI fluid losses such as enterostomy output contribute to frequent need for additional zinc above the recommended daily enteral intake of 1.4-2.5 mg/kg/d.[38] Zinc sulfate (10 mg/mL elemental zinc) suspension may be an option. Iron is absorbed in the duodenum and proximal jejunum. Adequate supplemental iron is needed if not provided by the formula or fortifier, or if absorption is impaired due to intestinal resection. Typically, a liquid iron such as Fer-in-sol^{R} at 2-4 mg/kg/d will meet iron requirements, taking into account enteral sources. Split dosing may promote better absorption.[37] Calcium and phosphorous intake through adequate fortification and/or formula intake is ideal, but if calcium and phosphorus supplements are required due to malabsorption and metabolic bone disease, doses must be carefully calculated and given at separate times with close monitoring for enteral intolerance as well as potential hypercalcemia or hyperphosphatemia.[39]

Infants with ileostomies are at high risk of excessive fluid and sodium losses in their ileostomy effluent, resulting in total body sodium depletion, metabolic acidosis, and growth failure. Assessment of total body sodium via urine sodium measurement and adequate sodium supplementation are essential to promote growth.[40]

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CONCLUSION

Successful nutritional management post-NEC requires teamwork and thoughtful attention to clinical signs and symptoms, growth, and GI tolerance with frequent problem-solving to reach nutritional goals. With current products and cautious advancements after early reintroduction of EN, it is possible to optimize nutritional and hydration status, as well as improve overall development. ■

References

1. Embleton ND, Zalewski SP. How to feed a baby recovering from necrotising enterocolitis when maternal milk is not available. Arch Dis Child Fetal Neonatal Ed. 2017;102(6):F543-F546.
2. Neu J, Pammi M: Pathogenesis of NEC: impact of an altered intestinal microbiome. Semin Perinatol. 2017; 41(1):29-35.
3. Lu Q, Cheng S, Zhou M, et al: Risk Factors for Necrotizing Enterocolitis in Neonates: A Retrospective Case-Control Study. Pediatr Neonatol. 2017;58:165-170.
4. Alsaied A, Islam N, Thalib L: Global incidence of necrotizing enterocolitis: a systematic review and meta-analysis. BMC Pediatr 2020;20;344.
5. Overman RE, Criss CN, Gadepalli SK. Necrotizing enterocolitis in term infants: A different disease process? J Pediatr Surg. 2019;54:1143-1146.
6. Perks P, Abad-Jorge, A. Nutritional management of the infant with necrotizing enterocolitis. Pract Gastroenterol. Feb 2008;59:46-60.
7. Ou J, Courtney CM, Steinberger AE, et al: Nutrition in Necrotizing Enterocolitis and Following Intestinal Resection. Nutrients. 2020 Feb 18;12(2):520.
8. Gordon PV, Swanson JR, MacQueen BC, et al: A critical question for NEC researchers: Can we create a consensus definition of NEC that facilitates research progress? Semin Perinatol. 2017;41:7-14.
9. Gordon PV, Swanson JR, Attridge JT, et al: Emerging trends in acquired neonatal intestinal disease: is it time to abandon Bell's criteria? J of Perinatol.. 2007;1-11.
10. Duci M, Frigo AC, et al. Maternal and placental risk factors associated with the development of necrotizing enterocolitis (NEC) and its severity. J Pediatr Surg. 2019; 54(10):2099-2102.
11. Ellis CL, Rutledge JC, Underwood MA. Intestinal microbiota and blue baby syndrome. Gut Microbes. 2010;1;6:359-366.
12. Kim JH, Abrams SA, Kim MS. Neonatal necrotizing enterocolitis: clinical features and diagnosis. UpToDate; accessed 7.8.2021.

13. Denning TW, Bhatia AM, Kane AF, et al: Pathogenesis of NEC: Role of the innate and adaptive immune response. Semin Perinatol. 2017; 41(1):15-28.
14. Lucas A, Boscardin J, Abrams SA. Preterm infants fed cow's milk-derived fortifier had adverse outcomes despite a base diet of only mother's own milk. Breastfeed Med. 2020;15(5):297-303.
15. Gordon PV, Clark R, Swanson JR, et al. Can a national dataset generate a nomogram for necrotizing enterocolitis onset? J Perinatol. 2014; 34(10):732-5. PMID 25078862
16. Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr. 2007;85(suppl):629S-634S.
17. Patel RM, Ferguson J, McElroy SJ, et al. Pediatr Res. 2020; 88(S1):10-15.
18. Lueschow SR, Boly TJ, Jasper E, et al. Pediatr Res. 2021; May 21.
19. Liu, W., Wang, Y., Zhu, J., et al. Clinical features and management of post-necrotizing enterocolitis strictures in infants: a multicenter retrospective study. Medicine. 2020;99(19):e20209.
20. Bazacliu C, Neu J. Necrotizing Enterocolitis: Long Term Complications. Curr Pediatr Rev, 2019; 15, 115-124.
21. Khan FA, Mitchell PD, Fisher JG, et al. Magnitude of surgical burden associated with pediatric intestinal failure: a multicenter cohort analysis. J Pediatr Surg 2014;49(12):1795-1798.
22. Ganapathy, V., Hay, J.W., Kim, J.H., et al. Long term healthcare costs of infants who survived neonatal necrotizing enterocolitis: a retrospective longitudinal study among infants enrolled in Texas Medicaid. BMC Pediatr 2013;13:127.
23. Halbrich M, Ben-Shoshan M, Rex G. Friend or foe? Figuring out the difference between FPIES, IgE-mediated allergy and food intolerance. BMJ Case Rep. April 2014
24. Christian VJ, Polzin E, Welak S. Nutrition Management of Necrotizing Enterocolitis. Nutr Clin Pract. 2018;33;476-482.
25. Hay, WW. Nutritional Support Strategies for the Preterm Infant in the Neonatal Intensive Care Unit. Pediatr Gastroenterol Hepatol Nutr. 2018;Oct 21(4):234-247.
26. Chwals WJ. Energy expenditure in critically ill infants. Pediatr Crit Care Med 2008;9:121–122.
27. Lin GC, Robinson DT, Olsen S, et al: Nutritional practices and growth in premature infants after surgical necrotizing enterocolitis. J Pediatr Gastroenterol Nutr; 2017;65:111-116.
28. Garofalo, N. A., & Caplan, M. S. Oropharyngeal Mother's Milk: State of the Science and Influence on Necrotizing Enterocolitis. Clin Perinatol. W.B. Saunders. 2019;March 1.
29. Hock, A. M., Chen, Y., Miyake, H., Koike, Y., Seo, S., & Pierro, A. Initiation of Enteral Feeding after Necrotizing Enterocolitis. Eur J Pediatr Surg, 2018;28(1), 44–50.
30. Bohnhorst B, Muller S. et al. Early Feeding after Necrotizing Enterocolitis in Preterm Infants. J Pediatr. 2003;Vol 143(4),pp 484-487.
31. Brotschi B, Baenziger O, Frey B, et al: Early enteral feeding in conservatively managed stage II necrotizing enterocolitis is associated with a reduced risk of catheter-related sepsis. J Perinat Med. 2009; 37:701-705.
32. Patel EU, Wilson DA, Brennan EA, et al: Earlier re-initiation of enteral feeding after necrotizing enterocolitis decreases recurrence or stricture: a systematic review and meta-analysis. J Perinatol. 2020;40:1679-1687.
33. Brindle ME, McDiarmid C, Short K, et al: Consensus guidelines for perioperative care in neonatal intestinal surgery: enhanced recovery after surgery (ERAS®) society recommendations. World J Surg. 2020;44:2482-2492.
34. Arslanoglu S, Boquien C, King C, et al. Fortification of Human Milk for Preterm Infants: Update and Recommendations of the European Milk Bank Association (EMBA) Working Group on Human Milk Fortification. Front. Pediatr., 2019;22 March.
35. McGrath, K.H., Pitt, J., Bines, J.E. Small intestinal overgrowth in children with intestinal failure on home parenteral nutrition. JGH Open 2019;3(5):394-399.
36. Kaufman, SS, Loseke CA, Lupo JV, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr 1997;131(3):356-361.
37. Groh-Wargo S, Sapsford A. Enteral Nutrition Support of the Preterm Infant in the Neonatal Intensive Care Unit. Nutr Clin Pract. 2009;l24(3):363-376.
38. Domellof, M. Nutritional Care of Premature Infants: Microminerals. In: Koletzko B, Poindexter B, Uauy R (eds): Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2014;110:121-139.
39. Bhatia J, Griffin I, Anderson D, Neelam K, Domellof M. Selected Macro/Micronutrient Needs of the Routine Preterm Infant. J Pediatr 2013;162:S48-55.
40. Zarraga CM, Borowitz SM. Growth failure and metabolic acidosis due to total body sodium depletion in an infant with an ileostomy. BMJ Case Rep. 2021 Mar 25;14(3):e241570.