Necrotizing Enterocolitis: Enhancing Awareness for the General Practitioner

Fiona Wertheimer, DO,*† Roxanne Arcinue, MD,†‡ Victoria Niklas, MD, MA†

*Division of Neonatology, Department of Pediatrics, LAC–USC Medical Center, Los Angeles, CA
†Keck School of Medicine, University of Southern California, Los Angeles, CA
‡Fetal and Neonatal Institute, Division of Neonatology, Department of Pediatrics, Children’s Hospital Los Angeles, Los Angeles, CA

Practice Gaps

Necrotizing enterocolitis (NEC) affects mostly premature infants but may develop in term infants with congenital malformations, including heart disease, abdominal wall defects, and sepsis. Following standardized feeding guidelines and prioritizing human milk feeding have decreased the rate of NEC in preterm infants, and, therefore, these approaches should be a priority in all infants at risk for NEC.

Objectives

After completing this article, readers should be able to:

1. Describe the epidemiological risk factors for necrotizing enterocolitis (NEC) in preterm and term infants.
2. Understand the pathophysiology of NEC relative to infant risk factors.
3. Describe the clinical signs and symptoms and briefly outline management strategies for infants with suspected and confirmed NEC.
4. Discuss preventive measures, such as human milk feeding, and the mechanisms underlying these benefits.
5. Recognize long-term complications of NEC, including neurodevelopmental disability and intestinal failure, and the appropriate follow-up care.

Abstract

Necrotizing enterocolitis (NEC) has been recognized for well over 5 decades yet remains the most common life-threatening surgical emergency in the newborn. The incidence of NEC has decreased steadily in preterm and very-low-birthweight infants over several decades and is typically uncommon in term newborns and infants with a birthweight greater than 2,500 g. Evidence accumulating during the past decade, however, suggests that practitioners should consider NEC in this broader context.
subset of term infants with chromosomal and congenital anomalies complicated by heart or gastrointestinal defects when signs and symptoms of feeding intolerance, abdominal illness, or sepsis are present. The short- and long-term consequences of NEC are devastating in all infants, and although early disease recognition and treatment are essential, promoting human milk feeding as a primary modality in prevention is critical. This article highlights our current understanding of the pathophysiology, the clinical presentation, the risk factors for NEC in term infants compared with premature infants, and the treatment of NEC and discusses strategies in the prevention of NEC. Finally, we review the long-term consequences of NEC and the importance of primary care practitioners in the long-term care of infants after hospitalization for NEC.

EPIDEMIOLOGICAL RISK FACTORS IN PRETERM AND TERM INFANTS

Necrotizing enterocolitis (NEC) has been recognized for more than 5 decades yet remains the most common life-threatening surgical emergency in the newborn, with dire short- and long-term consequences. (1)(2) Most NEC occurs in infants younger than 32 weeks of gestation and in very-low-birthweight (VLBW) infants (birthweight <1,500 g), although late preterm and term infants also develop NEC. (3)(4) The incidence of NEC is highest in infants born at less than 32 weeks of gestation, occurring in 1 to 3 per 1,000 live births. Although the national incidence of NEC varies, NEC affects 5% to 9% of VLBW infants. (5)(6)(7) In contrast, the incidence of NEC in term infants is significantly lower, with approximately 10% of all cases of NEC occurring in term infants. (8)

Unique risk factors for NEC have been described in preterm and term infants, although many risk factors are overlapping (Table 1). Prematurity is the most critical risk factor for the development of NEC, particularly in VLBW and small-for–gestational age infants (Table 1). (3) In more recent years, a history of packed red blood cell (PRBC) transfusion (9) has been associated with cases of NEC in VLBW infants; however, whether the degree of anemia or the response to transfusion is primary in the development of disease remains to be determined. (9)(10) Formula feeding, regardless of gestational age, is a common risk factor for all infants who develop NEC, whereas human milk feeding is protective. (6)(11)(12)(13) A history of birth asphyxia or hypoxia is present across gestational ages, although NEC may develop weeks after the event. (4) In late preterm and term infants, the development of NEC has also been linked to congenital malformations, including gastroschisis, chromosomal abnormalities, and congenital heart disease. In fact, congenital heart disease is 1 of the most common risk factors for NEC, with hypoplastic left heart syndrome and truncus arteriosus being the most common types associated with NEC. (4)(8)(14)(15) In addition, up to 20% of term infants with hypoplastic left heart syndrome develop NEC after Norwood palliation, suggesting that decreased perfusion to the gut, as well as hypoxemia, underlie the development of NEC. (16) However, as in preterm infants, late preterm and term infants may also develop NEC without predisposing risk factors. For this reason, practitioners must maintain a high index of suspicion for all infants with systemic signs of sepsis or feeding intolerance (Table 1). (8)(15) (17)(18)(19)

The onset of NEC is inversely related to gestational age such that the earlier the gestational age, the later the chronological age at which NEC develops. For example, the average age at onset is 20.2 days for infants born at less than 30 weeks of gestation, 13.8 days for infants born at 31 to 33 weeks of gestation, and 5.4 days for infants born after 36 weeks of gestation. In all infants, the timing of NEC onset often correlates with the timing of initiation or advancement of enteral feeds, which, in general, occurs earlier in term infants than in preterm infants. (8) The onset of NEC in term infants also highlights the impact of interventions such as surgery or exchange transfusion that increase an infant’s risk of NEC. For example, the timing and recovery from surgical repair in gastroschisis or congenital heart disease or the completion of exchange transfusion may more accurately predict the period of risk for NEC than an infant’s postnatal age. (14)(20)

The case fatality rate also varies with gestational age, with the smallest and least mature infants demonstrating the
The greatest risk of death and disability. In preterm infants, mortality ranges from 20% to 40% and increases sharply in infants with surgical NEC and in infants with lower birthweight and lesser gestational age and may approach 100% in the smallest and least mature infants. Moreover, at all gestational ages, a history of hypotension, metabolic acidosis, thrombocytopenia, and proven bacterial sepsis correlate with a poor prognosis. (15)(21) Hence, mortality after NEC depends on factors unique to each infant, such as the need for surgery and the complications that arise from life-sustaining care. (14)(16)

PATHOPHYSIOLOGY RELATIVE TO INFANT RISK FACTORS

The pathogenic sequence in NEC is multifactorial and complex. Some researchers have proposed that the definition of NEC be individualized to include risk factors associated with the onset of disease. (22) However, this level of distinction may not be necessary, and more general themes attributed to common pathophysiologic pathways underlying NEC are proposed. For example, 3 general features underlie NEC in all infants: 1) dysbiosis, 2) injury to the intestinal lining, and 3) activation of an immune response. Dysbiosis is the abnormal balance of gut microbiota favoring opportunistic and pathogenic bacteria, or pathobionts. The other features underlying the pathogenesis of NEC include injury to the intestinal lining and activation of proinflammatory immune responses in the gut and periphery. (23)(24)(25)(26)(27) As such, factors that contribute to critical components in the pathogenic sequence can be categorized as factors that incite, promote, and permit disease (Fig 1). (14)(20) Factors that incite NEC may do so through injury to the intestinal barrier resulting from decreased bowel perfusion or after direct damage to the intestinal lining from bacterial metabolites, toxins, or infant formula feeds. Poorly digested formula or the use of antibiotic agents may then result in dysbiosis or bacterial overgrowth conditions that promote disease. (25) Finally, circumstances unique to each infant, such as prematurity, congenital heart disease, or sepsis, are factors that permit NEC to occur. These factors, taken together, result in the conditions necessary for NEC, including bacterial overgrowth, loss of bowel wall integrity, and the generation of proinflammatory immune responses triggering bacterial invasion in the gut and disease progression. (24)(28)(29)(30) Although abundant evidence supports a role for pathogens in NEC, no specific bacterium, fungus, or virus has been shown to be causative in most cases. (25)

Next-generation sequencing of stool demonstrated dysbiosis before the development of NEC. (31)(32) Pathobionts present in the microbiota of the gut in infants who develop NEC may, therefore, be “bystanders” rather than the primary cause of disease. The inflammatory cascade generated in response to bacterial overgrowth may additionally damage the epithelium, leading to increased intestinal

<table>
<thead>
<tr>
<th>TABLE 1. Risk Factors for Necrotizing Enterocolitis by Infant Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREMATURE INFANTS (&lt;32 WEEKS)</strong></td>
</tr>
<tr>
<td>Very low birthweight (&lt;1,500 g)</td>
</tr>
<tr>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Anemia in need of packed red blood cell transfusion</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Umbilical lines</td>
</tr>
<tr>
<td>Maternal cocaine use</td>
</tr>
<tr>
<td>Severe anemia</td>
</tr>
</tbody>
</table>

Vol. 40 No. 10 OCTOBER 2019 519

Downloaded from http://pedsinreview.aappublications.org/ at Ukraine: AAP Sponsored on November 1, 2019
permeability and translocation of bacteria. Furthermore, immune activation and often a systemic inflammatory response syndrome results from decreased barrier function, leading to proinflammatory cytokine–mediated injury in the brain and subsequent neurodevelopmental injury. (24)(33)

The development of NEC after red blood cell transfusion, so-called transfusion-associated NEC (TNEC), has been recognized for 2 decades, although the mechanism remains poorly understood. (34) Retrospective cohort studies highlighted the association when more than 30% of VLBW infants developed NEC within 48 hours of receiving PRBC transfusion. (9) TNEC developed in infants born at earlier gestational ages with a history of PRBC transfusion. In addition, TNEC developed at later postnatal ages than did gestational age–matched controls, with an average onset at 3 to 5 weeks of postnatal age compared with 1 to 3 weeks of postnatal age in VLBW infants with NEC unrelated to transfusion. (9)(10) One controversial risk factor for TNEC may result from increased iron handling in the intestinal epithelium in response to the recycling of effete red blood cells after transfusion. (35)(36) Other authors suggest that PRBC transfusion may not cause NEC directly but that symptomatic anemia is an independent infant risk for the development of NEC. For example, infants with transfusion-related acute gut injury had a larger degree of anemia with lower hematocrit levels. (9) Furthermore, elevated levels of intestinal fatty acid binding protein, a marker of intestinal mucosal injury, were found before and after PRBC transfusion. (36) It is, therefore, possible that anemia results in decreased oxygen delivery to the gut, rendering the mucosa at increased risk for injury associated with feeding, a state that is suddenly reversed with PRBC transfusion, resulting in a reperfusion-type mucosal gut injury. (9) Further research is needed to determine the relationships among anemia, transfusions, and NEC.

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of NEC is suspected from infant demographics and clinical presentation but is confirmed by the presence of pneumatosis intestinalis on abdominal radiographs. The clinical symptoms in infants later confirmed to have NEC may vary from subtle to fulminant. Infants presenting with fulminant disease may have either focal abdominal signs and symptoms or nonspecific systemic signs and symptoms with cardiorespiratory collapse indistinguishable from sepsis, metabolic disease, or critical congenital heart disease. A subtle presentation may include signs and symptoms of feeding intolerance, with gastric feeding residuals, abdominal distention, and nonspecific findings on an abdominal radiograph. Abdominal signs and symptoms may progress to include gastric feeding residuals, distention, visible loops of bowel, discoloration of the abdominal wall, or presence of tenderness on abdominal examination, accompanied by bilious gastric drainage, bloody stools, and, less commonly, emesis. Systemic signs and symptoms may include lethargy, temperature instability, new or worsening apnea, bradycardia, decreased perfusion, mottling, and hypotension. Abnormal laboratory tests often encountered in patients with NEC, although not specific to NEC alone, are the presence of thrombocytopenia, neutropenia, elevated C-reactive protein level, metabolic acidosis, electrolyte abnormalities, and coagulopathy. (1)(36) Similar to the onset of NEC, disease progression may follow a slow and stepwise deterioration, or it may be rapid in onset, with fulminant progression and death. (37)
The Bell system was proposed nearly 40 years ago to enable uniform clinical staging stratifying infants into the categories of suspected (stage I), definite (stage II), and advanced (stage III) NEC based on clinical and radiographic findings. (38)(39) A subsequent version, modified Bell staging, included additional clinical signs and symptoms and predicted the likelihood of surgery (Table 2). (39) The signs and symptoms of suspected or stage I NEC overlap with feeding intolerance, whereas stage II NEC is defined by the presence of pneumatosis intestinalis on abdominal radiographs (Fig 2). Pneumatosis intestinalis is pathognomonic for NEC and results from intramural gas generated during anaerobic bacterial metabolism that becomes trapped in the submucosal layer of the bowel wall (Fig 3). Stage II NEC is a surgical emergency if injury progresses to full-thickness destruction of the bowel wall, leading to intestinal perforation. Intestinal perforation is visible as portal venous and free intraperitoneal air on abdominal radiography (Fig 2). Progression to stage III NEC often leads to hemodynamic instability and respiratory compromise requiring cardiorespiratory life support. Bell staging has also been shown to be useful in predicting disease outcomes as well as the likelihood of surgical intervention in NEC. For example, infants with stage II NEC are at higher risk for perforation and surgical intervention, correlating with increased morbidity and mortality. (2)(7)

Disease monitoring by clinical, laboratory, and radiographic parameters is crucial. Serial abdominal radiography is considered the gold standard to evaluate infants for disease progression. Radiography is used to determine the presence of pneumatosis intestinalis, pneumoperitoneum (free air in the abdominal cavity), or portal venous air. (1)(40) Intestinal perforation, as indicated by the presence of pneumoperitoneum, requires immediate surgical evaluation and intervention. (1)(41)(42) The radiographic appearance of abdominal free air may, however, be subtle and may become apparent in only 60% of infants with identified perforation intraoperatively. (41) Abdominal ultrasonography may be used as an adjunct to radiography in diagnosing NEC, with positive findings of pneumoperitoneum, focal fluid collection, portal venous gas, pneumatosis intestinalis, and Doppler-identified areas of bowel hypoperfusion. (1)(41)(43) However, expertise in abdominal sonography may not be widely available and is limited by observer variability. (44) Biomarkers in stool, urine, and serum to identify or confirm infants with early-stage or progressive NEC are under evaluation. Although many are appealing, such as fecal calprotectin and fatty acid binding protein in the urine, an ideal biomarker has yet to be identified, and further research is still needed. (26) Thus, having a high index of suspicion, performing serial physical examinations, and closely following the patient’s laboratory studies and abdominal radiographs, remain the standard for diagnosing NEC. (37)(39)(40)(43)

DISEASE MANAGEMENT AND OUTCOMES

Most infants with NEC are managed medically, with approximately 30% progressing to surgical disease. Nearly 85% of term infants survive when diagnosed as having suspected NEC (Bell stage I) compared with 25% survival for confirmed and advanced NEC (Bell stage II or III). (20) Hence, outcomes in NEC depend on factors unique to each infant.

| TABLE 2. Modified Bell Staging in Necrotizing Enterocolitis |
|----------------|----------------|----------------|
| **BELL STAGE** | **CLINICAL** | **RADIOGRAPHIC** | **GASTROINTESTINAL** |
| I               | Apnea and bradycardia, temperature instability | Normal gas pattern or mild ileus | Gastric residuals, occult blood in stool, mild abdominal distention |
| II A            | Apnea and bradycardia, temperature instability | Ileus gas pattern with ≥1 dilated loops and focal pneumatisis | Grossly bloody stools, prominent abdominal distention, absent bowel sounds |
| II B            | Thrombocytopenia and mild metabolic acidosis | Widespread pneumatosis, ascites, portal venous gas | Abdominal wall edema with palpable loops and tenderness |
| III A           | Mixed acidosis, oliguria, hypotension, coagulopathy | Prominent bowel loops, worsening ascites, no free air | Worsening wall edema, erythema and induration |
| III B           | Shock, deterioration in laboratory values and vital signs | Pneumatoneum | Perforated bowel |

the need for surgery, and complications arising from life-sustaining care. (14)(16) Again, it is imperative that index of suspicion for NEC in all infants remains high because early recognition of disease and treatment may lessen the severity of outcomes. (8)(40) Medical management for suspected and confirmed NEC overlap. Pediatric surgical consultation is advised in every case of suspected NEC, especially for cases with confirmed stage II NEC. Infants with suspected or confirmed NEC should be placed nil per os to allow for bowel rest. A gastric tube for bowel decompression and monitoring of aspirates should be placed. Parenteral nutrition is indicated to optimize delivery of calories during this period of bowel rest. A radiograph of the abdomen and a left lateral decubitus or crosstable view should be obtained to rule out evidence of free air. Serial and positional abdominal radiographs with a frequency consistent with the suspicion and cadence of advancing clinical disease should follow the initial series. A complete blood cell count with differential and platelet counts; measurement of electrolytes, arterial blood gas, lactate, and C-reactive protein; and studies to evaluate liver function and coagulation are warranted to monitor clinical disease and its progression. Correction of anemia, thrombocytopenia, electrolyte disturbances, and coagulopathy will be part of management.

Antimicrobial coverage should broadly target gram-negative and anaerobic bacteria (common gut-associated bacteria) with a duration of 7 to 14 days based on clinical suspicion, confirmation of disease, and the infant's clinical course. (1) The use of antifungal agents should be considered in severely ill patients or those who may not be responding to antibiotic drug therapy. Results of blood and, if available, peritoneal cultures will help narrow the antimicrobial coverage and guide the duration of therapy. Appropriate antibiotic drug therapy has been shown to improve the outcome and survival of infants with NEC. Infants with an advanced or rapidly progressive disease or cardiorespiratory compromise may necessitate resuscitative measures, including evaluation of airway, breathing, and...
circulation. Infants with NEC or signs and symptoms of NEC require hospitalization in a NICU or PICU.

The development of pneumoperitoneum is an absolute indication for surgical consultation and intervention. (45)(46) In the preterm infant with pneumoperitoneum, initial management may include placement of a peritoneal drain, exploratory laparotomy, and bowel resection. (47) In some cases, the bowel is severely affected, and a second-look surgical procedure is planned weeks to months after the primary diagnosis and surgery. (48) The area and extent of bowel involvement may also differ between premature and term infants. The most commonly affected sites are the jejunum and ileum for premature neonates, whereas the colon is typically affected for infants born at term. (8)

The complications of NEC can be devastating and include acute and chronic clinical complications such as sepsis, meningitis, abdominal abscess formation, coagulopathy and associated bleeding, respiratory and cardiovascular insufficiency, metabolic complications, and later-onset neurodevelopmental injury. The outcome is significantly affected in cases of surgical NEC compared with medical NEC and in premature newborns compared with term newborns. (49)(50)(51)

Intestinal stricture formation is present in 10% to 35% of cases of NEC. (52) Strictures may affect multiple areas of the bowel, but most frequently the colon. Strictures may be diagnosed using contrast studies of the bowel or become evident because of feeding intolerance on refeeding after NEC or because of fixed and dilated loops of bowel after disease resolution. Surgical resection with end-to-end anastomosis or ostomy creation and later anastomosis are potential management approaches. Surgical treatment of NEC may result in an anatomical short bowel syndrome and intestinal failure. Indeed, NEC can be a primary cause of intestinal failure that may lead to a long-term requirement for parenteral nutrition. In severe cases of intestinal failure, intestinal transplant is the only solution. Parenteral nutrition increases the risk of growth failure, central line–associated sepsis, and total parenteral nutrition–associated liver disease. Fortunately, infants with medically treated NEC are more likely to have return of normal intestinal function and feeding tolerance.

Neurodevelopmental injury resulting in an increased incidence of cerebral palsy, cognitive and visual impairment, and neurodevelopmental delay has been described in the premature infant with NEC and in term infants with severe disease. (51)(53) A recent prospective study showed that extremely-low-birthweight survivors of NEC had an increased risk of severe neurodevelopmental disability, postdischarge surgery, and tube feeding at 18 to 24 months.

Future studies are needed to assess the long-term risks of complications after NEC in late-preterm and term infants. (51)(54) Pediatricians who follow patients with a history of NEC should ensure appropriate ongoing and follow-up care for all medical, surgical, and neurodevelopmental needs. In many instances, a multidisciplinary team is necessary to provide the best outcomes from NEC.

DIFFERENTIAL DIAGNOSIS

The scope of the differential diagnosis in NEC depends on the gestational and postnatal ages of the infant, other clinical conditions and diagnoses, and the health status before the onset of symptoms. For example, in premature infants, feeding intolerance of prematurity and spontaneous intestinal perforation (SIP) should be considered. If previous patency and bowel function were noted before the development of signs of NEC, most congenital abnormalities can be ruled out, but if patency and bowel function were never established, then congenital malformations such as intestinal stenosis, meconium plug syndrome, or other functional disorders must be considered. Feeding intolerance and SIP develop in the same cohort of premature infants who develop NEC. Infants with feeding intolerance have increased pregavage residuals, mild abdominal distention, visible loops of bowel, constipation, and increased apnea, but blood studies will remain reassuring and abdominal radiographs will most likely not show abnormal findings. The feeding intolerance of prematurity, unlike the feeding intolerance of NEC, is self-limited and may be managed by a short period of withholding feeds and then a mindful, slow advancement of enteral feeds and rectal suppository use as clinically indicated. SIP affects infants with a birthweight of less than 1,000 g and usually during the first 2 weeks of life, often before the start of enteral feeds or during trophic feeding (introducing minute enteral feeds to stimulate gut maturation in preterm infants). Concurrent exposure to indomethacin and corticosteroids statistically increases the risk of SIP in infants. (55) The terminal ileum is the usual site of perforation in SIP, and on surgical exploration, there is little evidence of gross or microscopic inflammation, which distinguishes NEC from SIP. (56) The management of SIP overlaps with that of NEC and necessitates immediate gastric decompression, discontinuation of feeds, intravenous fluid hydration, antibiotic drug coverage, and prompt surgical consultation. In the first few hours to days after birth, neonates who are otherwise well-appearing but have bloody stools should be carefully evaluated for NEC. However, in the absence of predisposing risk factors (Table 1) or if there are no systemic signs or other intestinal signs of
injury, swallowed maternal blood during delivery, the presence of anal fissures, or allergic colitis should be considered. (57)(58)(59) The Apt test (hemoglobin alkaline denaturation test) may be used to determine the presence of maternal versus fetal blood. Maternal red blood cells are lysed under the assay’s conditions, whereas fetal cells are not. (58)(60) Once swallowed maternal blood is confirmed as the source of the neonate’s bloody specimen, no further intervention is needed. The presence of anal fissures is another common etiology for rectal bleeding in infants; therefore, a complete physical examination with close inspection of the perineum and anal mucosa should be performed. Application of skin barrier creams, such as petrolatum, will hasten healing of anal mucosal injury. (60) The development of cow milk protein allergy after exposure to cow milk–based formula or human milk fortified with bovine-based fortifiers may mimic the clinical presentation of NEC. Infants with this disease rarely present before 6 weeks of age. Common findings are abdominal distention, diarrhea with bloody stools, and, if severe, the presence of pneumatosis. Bowel rest and the use of elemental formula on refeeding may afford resolution of symptoms. (57)

Intestinal obstruction from atresia, intestinal duplications, malrotation with volvulus, meconium ileus, or intussusception may present similarly to NEC. Visible loops of bowel, abdominal distention, tenderness, failure to pass stool, or vomiting are often presenting signs. (36) Unlike NEC, congenital intestinal atresia or malrotation with mid-gut volvulus often show persistently dilated proximal and gasless bowel loops on abdominal radiographs with bilious emesis or gastric residuals. Infants with NEC are likely to show symmetrical distention with evidence of thickened loops of bowel (Fig 2). If abdominal radiographs or clinical presentation are equivocal, an upper gastrointestinal contrast study with small bowel follow-through or a lower gastrointestinal contrast enema may be recommended (water-soluble contrast if perforation is suspected). Additional consultation with radiology, pediatric surgery, and gastroenterology will enable the practitioner to refine the diagnostic approach and management strategy.

PREVENTION

Because NEC is a devastating disease, prevention and reducing the incidence are essential. Prevention of severe anemia with strategies such as delayed cord clamping if appropriate at birth and judicious blood sampling should be considered. The American Academy of Pediatrics endorsed the American College of Obstetricians and Gynecologists Committee on Obstetric Practice (61) in its recommendation of delayed cord clamping for 30 to 60 seconds after birth in vigorous term and preterm infants, which may help reduce the incidence of NEC. Other strategies to reduce NEC include limiting medications that reduce gastric acidity, especially in the preterm infant. For example, the use of histamine 2 antagonists alters the gut microbiota and may predispose the premature gut to the development of NEC. Similarly, antibiotic stewardship is an important effort to limit the risk of altering the microbiota of the intestine and other body sites, therefore likely decreasing the risk of NEC. (5)

The introduction of standardized feeding guidelines has been shown to be protective against the development of NEC. A recent systematic review including 15 observational studies demonstrated that having a standardized feeding guideline significantly reduced the incidence of NEC even when guidelines differed among NICUs. (62) A Cochrane review showed that there was no difference in NEC between NICUs that practice slower daily feed advancements (15–20 mL/kg per day) compared with NICUs that provide faster daily increments (30–40 mL/kg per day). (63) Generally, feeding guidelines initiate early minimal enteral feeds of less than or equal to 20 mL/kg per day of enteral nutrition and advance daily based on individual infant feeding tolerance. (5)(64) Regarding feeding anemic infants around a PRBC transfusion, at this time there are no clear guidelines, but current practice is to implement guidelines for enteral feeding as well as avoiding severe anemia, which may increase the likelihood of TNEC. (5)(65)

Of greater importance, however, is the role of human milk in the prevention of NEC. Human milk has been known for decades to reduce the incidence of NEC and bacteremia compared with infants fed formula, at least as far as premature and low-birthweight infants are concerned. If the mother’s milk is not available, pasteurized donor human milk has also been shown to decrease the risk of NEC, despite the known effects of pasteurization on the immune, antimicrobial, barrier-enhancing, and regenerative components in human milk. (30)(66) Indeed, the only known consistent intervention in the prevention of NEC is human milk. (12)(30)(67)(68)(69) However, the caloric requirements to maintain the fetal growth trajectory after birth in VLBW infants are not met with native human milk, thereby requiring milk fortification to meet the nutritional needs of these infants. (70)(71) More recently, randomized clinical trials have shown that an exclusive human milk diet consisting of human milk fortified with a human milk–derived fortifier (rather than a bovine-based fortifier) further decreased the rate of NEC and, more specifically, surgical NEC, (67)(69) as well as decreasing other outcomes,
including sepsis, days of parenteral nutrition, and death. (72) The American Academy of Pediatrics supports human milk as optimal nutrition for all neonates and supports its use as a protective strategy for preterm infants in the prevention of NEC. (73)(74)(75) Similarly, as in preterm infants, if the mother’s milk is not available, pasteurized donor human milk, which has been shown to decrease the risk of NEC, should be considered in term infants as well. (70)(66)

Relative abundances of certain human milk oligosaccharides have been shown to correlate with protection from NEC and to exert a protective effect. (76)(77) A prospective multicenter study of preterm infants found an almost 10-fold increase in the incidence of NEC in formula-fed infants compared with human milk–fed infants. Both observational and randomized studies demonstrate that formula-fed preterm infants have an increased risk of NEC compared with those fed human milk, although whether this association holds for term infants and those with congenital or chromosomal abnormalities remains an area in need of greater study. (6)(19)(68)(78) In any case, the positive effects of human milk are due to the wide array of antimicrobial and immune and regenerative factors present in human milk, including secretory immunoglobulin A, other immunoglobulins, oligosaccharides, lactoferrin, anti-inflammatory cytokines, and growth factors. (79) In addition, freshly expressed mother’s milk provides commensal flora, which results in colonization by beneficial bacteria such as Lactobacillus and Bifidobacterium species thought to have multiple effects on microbial homeostasis and immune and gut maturation. (27)

A meta-analysis was performed with 20 randomized controlled trials using Bifidobacterium and Lactobacillus species probiotics in the prevention of NEC. Probiotic supplementation with either probiotic or a combination of both significantly decreased the risk of NEC and death in preterm VLBW infants, without an increased risk of sepsis between the probiotic and placebo groups. (80) Term infants consuming formula supplemented with a single oligosaccharide, 2’-fucosyllactose, had increased Bifidobacterium species and decreased pathogenic bacteria in the microbiota of the stool. Also, the systemic cytokine profile of these infants was more like that of breastfed control infants. (81)(82) However, the vast array of human milk oligosaccharides naturally occurring in human milk coupled with other antimicrobial and immune and regenerative factors present in human milk argue that human milk feeding should remain the primary nutrition for these infants. (77) Despite promising results from multiple trials, the use of probiotics and prebiotics is not routine in the prevention of NEC in clinical practice. (83) In

the United States, this may be due to the lack of an approved drug (rather than the availability of products as over-the-counter nutritional supplements), product variability, unestablished dosing regimens, and variability in trial outcomes due to differences in clinical trial design. (82)(83)

Summary

- The incidence of necrotizing enterocolitis (NEC) in preterm infants has decreased during the past several decades.
- Strong evidence supports that human milk feeding and the avoidance of bovine-based infant formulas have had the greatest protective effect in preterm and low-birthweight infants. (12)(30)(67)(69)
- Multiple observational studies (8)(13)(16)(18)(20) and, more recently, a large retrospective study (19) demonstrate that NEC is proportionally increased in infants with congenital anomalies such as gastroschisis and congenital heart disease.
- Short- and long-term complications of NEC are devastating in all infants.
- Once NEC is diagnosed and/or strongly suspected, a pediatric surgical consultation and a management plan are warranted.
- Consistent practitioner guidelines for feeding, prioritizing the use of human milk, avoidance of severe anemia, and limiting medications that may alter gut microbiome should be considered standard approaches for the prevention of NEC.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/40/10/517.supplemental.

Necrotizing Enterocolitis: Enhancing Awareness for the General Practitioner

References for this article are at http://pedsinreview.aappublications.org/content/40/10/517.
1. You are caring for a term infant boy who has hypoplastic left heart syndrome. He had surgery with a Norwood procedure. Two days after surgery, low-volume feedings were initiated with human milk. Five days after surgery, he developed feeding intolerance, abdominal distention, and decreased blood pressure. His abdominal radiograph shows several dilated loops of bowel with small focal segments of pneumatosis. You diagnose necrotizing enterocolitis (NEC). Which of the following is the most likely underlying etiology for this infant’s presentation with NEC?
   A. Bowel malrotation.
   B. Bowel perforation.
   C. Decreased perfusion to the gut.
   D. Need for revision of the Norwood procedure.
   E. Reaction to human milk.

2. A 20-day-old infant girl is delivered at 32 weeks’ gestation because her mother had a stroke related to hypertension. Feedings are initiated with formula owing to the mother’s severe illness. The infant develops bilious emesis and abdominal distention. An abdominal radiograph is ordered. Which of the following radiographic findings is the most pathognomonic for a diagnosis of NEC in this patient?
   A. Focal fluid collection in the left lower quadrant.
   B. Gasless bowel loops.
   C. Markedly dilated loops of proximal bowel.
   D. Nonspecific bowel gas pattern.
   E. Pneumatosis intestinalis.

3. A 14-day-old boy born at 30 weeks’ gestation has increasing residuals noted with his feedings. Feedings with human milk were initiated 11 days ago. He has mild abdominal distention, temperature instability, and increasing frequency of apnea spells. His abdominal radiograph is nonspecific. Which of the following is the most appropriate next step in the management in this patient?
   A. Immediate intubation.
   B. Liver biopsy.
   C. Microbiome analysis.
   D. Serial abdominal radiographs.
   E. Surgical consultation.

4. You are caring for a term infant girl who has abdominal distention and vomiting. She is not passing stool. Your differential diagnosis includes malrotation with midgut volvulus, congenital intestinal atresia, and NEC. Which of the following findings on abdominal radiography is most likely to be concerning for NEC?
   A. Absence of air in the bowel.
   B. Evidence of stool throughout the bowel.
   C. Lack of rectal stool.
   D. Proximal dilated gasless bowel loops.
   E. Symmetrical distention with thickened loops of bowel.

REQUIREMENTS: Learners can take Pediatrics in Review quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2019 Pediatrics in Review articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2021, however, credit will be recorded in the year in which the learner completes the quiz.

2019 Pediatrics in Review now is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the AAP MOC Portfolio Program. Complete the first 10 issues or a total of 30 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as October 2019. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.
5. You are working on a committee for your hospital focused on preventing NEC in infants in the nursery. Which of the following is the most effective measure to advocate for to achieve this goal?
   A. Delayed cord clamping for 30 to 60 seconds after birth in vigorous infants.
   B. Early introduction of hypoallergenic formula feedings.
   C. Prescription of probiotics for all infants.
   D. Prophylactic antibiotic drug treatment of infants at risk for NEC.
   E. Prophylactic use of histamine 2 antagonists.
Necrotizing Enterocolitis: Enhancing Awareness for the General Practitioner
Fiona Wertheimer, Roxanne Arcinue and Victoria Niklas
Pediatrics in Review 2019;40;517
DOI: 10.1542/pir.2017-0338

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/40/10/517