

ORIGINAL ARTICLE

Evidence vs experience in neonatal practices in necrotizing enterocolitis

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Introduction: Necrotizing enterocolitis (NEC) has been recognized for over 40 years as a cause of inflammation and necrosis of the small and large intestine of infants born at less than 36 weeks of gestation. NEC remains a significant health problem for infants born prematurely and may become the leading cause of morbidity and mortality among these infants worldwide. The sequence of events leading to NEC is complex and multifactorial, although damage to the intestinal epithelium and invasion by bacteria are known to play central roles in disease pathogenesis.

Study Design: Bacteria initiate a cascade of inflammation that may progress to intestinal necrosis and perforation with sepsis and death.

Result: Treatment of infants at risk for NEC with probiotic bacteria may be an area of great potential, as probiotic bacteria may promote maturation of the epithelial barrier and function to exclude bacterial pathogens from critical niches in the intestine, thereby disrupting a primary pathway in disease pathogenesis.

Conclusion: Understanding how probiotic bacteria, or other novel therapies, prevent or limit disease propagation in NEC will be paramount in limiting the impact of disease in a growing population of premature newborns.

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Introduction

Necrotizing enterocolitis (NEC) is the most common life-threatening surgical and medical emergency of the intestine encountered in premature infants. NEC is diagnosed in up to 5% of NICU admissions and accounts for nearly 10 000 infants yearly in the United States. More than 75% of cases occur in infants born at less than 36 weeks of gestation and weighing under 2000 g.¹ The

postnatal age of onset is a function of the gestational age, with the peak incidence occurring approximately 3 weeks after birth in infants born at <32 weeks, whereas disease develops approximately 2 weeks after birth in infants born between 32 and 36 weeks and under 1 week of postnatal age in infants born at >36 weeks of gestation. Although NEC occurs primarily in infants born prematurely, it has also been described in full-term infants in approximately 10% of cases.²

The events leading to the development of NEC are multifactorial and complex and include a history of a complicated early neonatal course, a poor intrauterine environment or perinatal transition. The only consistent epidemiological risk factors for NEC are, however, prematurity and a history of enteral feeding, which may include a rapid advancement in feeding or high osmotic strength formula feeding.^{1,3,4} By contrast, there are no consistent associations between gender, socioeconomic status or race and the development of NEC. In term infants, a history of cyanotic heart disease, polycythemia and a history of exchange transfusions are more commonly associated.

The overall mortality for patients with NEC ranges from 10 to 50%, but approaches 100% in infants with rapidly progressive disease, which typically includes the smallest and most premature infants.⁴ Moreover, infants who recover from NEC may still require prolonged hospitalization due to related complications, such as intestinal obstruction, short bowel syndrome and liver failure due to total parenteral nutrition requirements.^{5,6} Although prompt diagnosis and intervention are desirable tenants of disease management, there is no clear evidence proving that early diagnosis and interventions alter patient outcome.

The variability in the presentation and severity of NEC may mimic systemic sepsis with abdominal distension and gastric residuals from ileus or other etiologies of intra-abdominal catastrophe, including volvulus, intussusception, inspissated meconium syndrome and intestinal vascular accident. Radiologic imaging may, however, establish the diagnosis, although it does not definitively rule in NEC unless pneumatosis intestinalis, or air in the bowel wall, is present. Pneumatosis intestinalis is thought to be the hallmark of NEC disease but may also be present in

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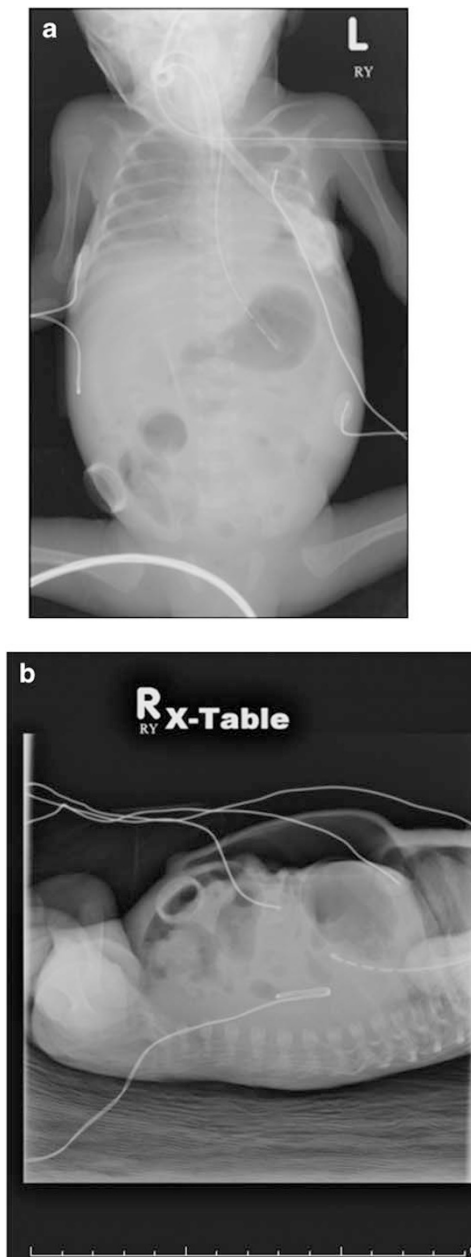


Figure 1 Radiographic findings in necrotizing enterocolitis and spontaneous intestinal perforation. (a) Supine abdominal X-ray in a neonate demonstrating thickened bowel walls, bowel distention, pneumatosis intestinalis and the outline of the falciform ligament indicative of free abdominal air. This patient was subsequently diagnosed with necrotizing enterocolitis. (b) A cross-table lateral view shows free air in the abdomen in a premature infant with spontaneous intestinal perforation (SIP).

advanced cases of Hirschsprung's enterocolitis or severe gastroenteritis (Figure 1). Pneumatosis intestinalis is thought to result from bacterial invasion, fermentation and hydrogen production in the intestinal wall, whereas portal venous air, which is noted in approximately 30% of advanced cases, occurs when intramural air is absorbed into the mesenteric venous circulation.

The finding of a fixed loop that remains unchanged for 24 to 48 h is often associated with transmural necrosis. Despite some reports indicating an association between fixed loops and pannecrosis, almost half of patients with this finding recover without surgical intervention. Free air in the abdomen can be seen as a central collection of air on the anteroposterior film of the abdomen, or can highlight the falciform ligament. Pneumoperitoneum in the absence of pneumatosis intestinalis may be more suggestive of spontaneous intestinal perforation (SIP), which has recently been recognized as a disease distinct from NEC⁷ (Figure 1). SIP usually occurs around the seventh day of life and is estimated to occur in up to 3% of infants born at <1000 g and 26 weeks of gestation. Moreover, unlike NEC, the majority of infants with SIP have not been fed nor have systemic, radiographic or histological signs of NEC.⁸ Although SIP may be associated with umbilical catheters and congenital defects of the intestinal musculature,^{9,10} the greatest predictors of disease are the use of postnatal dexamethasone and indomethacin which, in combination, have been shown to double the risk of SIP.¹¹ However, the overall morbidity and mortality of SIP is favorable when compared to NEC.¹² Ultimately, the diagnosis of NEC is based on clinical signs, symptoms and disease course.

The microbial flora in the intestine of hospitalized premature infants is markedly different than the intestinal microbial environment found in full-term, breast-fed infants.^{13,14} Premature infants are often colonized by pathogenic species, including *Klebsiella*, *Enterobacter* and *Clostridial* species, with a reduced degree of colonization by normal commensal microbial flora such as *Bifidobacterium* and *Lactobacillus* species, which are more characteristic of commensal microbial flora in normal term and breast-fed infants.¹⁵ Colonization by pathogenic bacteria or a paucity of commensal bacterial flora may contribute to the pathogenesis of NEC. Moreover, it is known that animal models devoid of bacteria fail to develop intestinal inflammation.^{16,17} Although bacterial overgrowth has also been associated with infants who develop SIP, *Candida* species and coagulase-negative *Staphylococcus* (CONS) are more commonly found in infants with SIP than with NEC.¹⁸ Thus far, although a single bacterial species or virus has not been consistently isolated in cases of NEC, a variety of bacterial species, including *Enterobacteriaceae* species, *Clostridia* species, *Staphylococcus* species and enteroviruses have been associated with NEC (Table 1). The data in Table 1 were derived from a PubMed-based search of the English literature for NEC-associated pathogens. Although *Candida* species and CONS have been associated with SIP, prematurity rather than pathogen-mediated intestinal inflammation appears to be most important in the pathogenesis of SIP.

Premature infants also exhibit a relative immune deficiency in their systemic as well as mucosal immune system that may permit bacterial overgrowth and invasion in the pathogenesis in NEC. The gastrointestinal tract is home to the greatest mass of lymphoid

Table 1 Microorganisms isolated from infants with confirmed cases of necrotizing enterocolitis

Type of microbe	Species included	Percentage of total cases (%)
Bacteria	<i>Escherichia</i> , <i>Salmonella</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Clostridium</i> , <i>Staphylococcus</i>	86
Virus	<i>Rotavirus</i> , <i>Echovirus</i> , <i>Coronavirus</i> , <i>Torovirus</i>	11
Fungal	<i>Candida</i>	1
No microbes isolated	NA	3

Abbreviation: NA, not applicable.

tissue in the body, and is responsible for coordinating immunologic defense mechanisms between the adaptive and innate immune systems.¹⁹ The gut-associated lymphoid tissue consists of cells of the adaptive immune system composed of B and T lymphocytes and cells of the innate immune system, including resident tissue macrophages, dendritic cells, specialized epithelial cells called M cells overlying the Peyer's patches and Paneth's cells. Paneth's cell secretion is stimulated by bacteria and by components of bacterial cell walls, such as lipopolysaccharide.²⁰ Antibacterial products secreted by Paneth's cells are found at significantly lower levels during fetal life when compared with the term newborn and adult.²¹ A decreased production of anti-bacterial products by Paneth's cells may predispose premature infants to bacterial overgrowth and NEC. Although polymorphonuclear (PMN) leukocytes are rarely seen in normal intestine, an increased number of PMN may be detected in the intestinal epithelium early in NEC. PMN production by the bone marrow and function is impaired in the newborn, potentially facilitating intestinal bacterial overgrowth and invasion.²² Despite considerable development of human T and B cells during fetal life, complete maturation occurs after birth.²³ The newborn lamina propria has few immunoglobulin A (IgA) secreting plasma cells. IgA is normally secreted into the mucus layer of the intestine and functions as a potent inhibitor of microbial proliferation and invasion. Human intestinal IgA production does not peak until 4 years of age, hence, the relative deficiency of IgA in the premature newborn likely contributes to the abnormal colonization of the intestine.²⁴ Therefore, it is plausible that the intestine of the premature infant has an altered host response to commensal microbes, thereby potentially contributing to the pathogenesis of NEC and SIP.

While the initial presentation of NEC is often variable, a common presentation of NEC would be that of a premature infant, who while advancing on feedings, develops signs of feeding intolerance. The initial signs may be subtle and include abdominal distention, elevated gastric residuals, signs and symptoms of sepsis, and guaiac-positive stool.²⁵ In cases of fulminate NEC, frankly blood stool, severe sepsis and cardiorespiratory failure are more

commonplace. Although prompt diagnosis and intervention are desirable, the management options are tailored based on an infant's clinical presentation and physiologic stability. The severity of NEC is classified based on the Bell's staging system.²⁵ When NEC is first suspected based on clinical signs and symptoms, including guaiac-positive stool and non-diagnostic radiography it is classified as stage I disease. In comparison, an infant with stage III disease would typically be critically ill, with systemic and radiographic signs of disease. Infants with SIP are characteristically younger and lack the radiographic and clinical signs associated with NEC.⁸

Despite the recognition of NEC as a surgical emergency in premature newborns, the majority of patients with NEC are managed medically. Prompt resuscitative measures, including evaluation of airway, breathing and circulation remain paramount in these patients. When a diagnosis of NEC is suspected, all enteric feeds should be stopped and the stomach decompressed with an orogastric tube. Serial measurements of abdominal girth, frequent abdominal exams and serial abdominal radiographs are obtained to monitor disease progression.²⁶ Many patients require ventilator support, and tracheal intubation is preferred to prevent further intestinal distension. Hypovolemia commonly occurs secondary to third spacing of fluid and requires adequate resuscitation with intravenous crystalloids. After blood cultures have been obtained, broad-spectrum antibiotics should be started. Currently, there is insufficient evidence regarding the choice of a specific antibiotic regimen or duration, although broad-spectrum antibiotics based on patterns of microbial resistance within individual neonatal intensive care units are recommended.²⁷ Appropriate antibiotic therapy has been shown to improve the outcome and survival in infants with NEC.^{28–30} The management of SIP is similar to that of NEC and consists of vigilance, broad-spectrum antibiotics, adequate resuscitation and supportive care.

There are several strategies aimed at preventing NEC, including breast milk feeding, antenatal steroids, enteral antibiotics and use of probiotic oral supplementation. Premature infants fed human breast milk have a reduced incidence of NEC, when compared with formula-fed infants.³¹ A prospective multicenter study of preterm infants found an almost tenfold increase in the incidence of NEC in formula-fed infants as compared with those who were fed breast milk.³² Defining the protective factors within breast milk is an area of active study, however, it may improve intestinal immunity and promote the growth of beneficial intestinal microflora. Although probiotics do not appear to offer an acute therapeutic benefit in infants with a pre-existing diagnosis of NEC, there have been several prospective randomized trials that have indicated that they may play an important role in the prevention of NEC. Hoyos³³ demonstrated a 40% decline in the rate of NEC after administration of *Lactobacillus* and *Bifidobacterium* to infants, and in 2005 Bin-Nun *et al.*³⁴ found an absolute risk reduction of 12% in the incidence of NEC and a decline in disease severity after daily feeding supplementation with *Bifidobacterium* and *Streptococcus*

species. Similarly, Lin *et al.*³⁵ found that probiotic administration decreased overall patient mortality and lowered the incidence of NEC (1.1 vs 5.3%). However, a study by Dani *et al.*³⁶ found no benefit of supplementation with *Lactobacillus*. A recent meta-analysis published in *Lancet* finds that probiotics may decrease the incidence of NEC in infants <33 weeks of gestation.³⁷ Although these data are generally promising, it is important to appreciate that these studies use differing probiotic species and that there have been, although rarely, reports of sepsis following probiotic supplementation.^{38,39} Despite these caveats, we believe that probiotics are a promising and generally safe option in the preventative medical armamentarium against NEC.

Despite appropriate and timely medical management, approximately 30% of patients with NEC require surgical intervention.⁵ The use of drainage or laparotomy in patients with NEC or SIP is an area of controversy and is beyond the scope of our discussion.

NEC and SIP are distinct clinical entities; however, neither disease process is uniform or well defined. In order to improve outcomes in patients with SIP and NEC, clinical vigilance with prompt diagnosis, aggressive fluid resuscitation and antibiotic therapy are essential. Preventative strategies, including probiotic therapy, are areas of great potential, providing several mechanisms to improve intestinal barrier function and immunity, but focused prospective randomized studies are required to support newer approaches to treatment.

Disclosure

Nothing to declare.

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