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Necrotizing Enterocolitis: Pathophysiology and Prevention

Josef Neu, MD; and Michael D. Weiss, MD

From the University of Florida, Department of Pediatrics, Gainesville

ABSTRACT. Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in the neonatal intensive care unit. It is a disease of medical progress in that more very low-birth-weight neonates are surviving than ever before and are thus susceptible to this potentially devastating disease. NEC received very little attention in the literature before the 1970s but now is well known to all neonatologists and pediatric surgeons. The 1500 to 2000 infants that die every year from this disease in the United States and the large number of infants who develop short gut syndrome from this disease only represent the tip of the iceberg of the problems NEC causes. The widespread fear of NEC among neonatologists and pediatric surgeons has contributed in large part to the use of the IV route rather than the gastrointestinal tract for nourishing these infants for relatively long periods. The consequences of this include a high incidence of sepsis, high hospital costs, and potential long-term neurodevelopmental disability because of poor nutrition during a very vulnerable period of growth and development. The purpose of this review is to provide a brief overview of the clinical presentation and current treatment for NEC, then provide a discussion of the pathophysiology on which strategies for prevention can be formulated. (*Journal of Parenteral and Enteral Nutrition* **23**:S13–S17, 1999)

CLINICAL PRESENTATION

The age of onset of necrotizing enterocolitis (NEC) is highly variable but rarely occurs in the first 3 days of life. Our experience is that the lowest gestational age (24 to 28 weeks) infants develop NEC after the second week of life, whereas those at an intermediate gestational age (29 to 32 weeks) develop it within 1 to 3 weeks, and the most mature infants develop it in the first week of life. Severe respiratory distress, low Apgar scores, patent ductus arteriosus, and use of umbilical arterial catheters are not necessary antecedents to the onset of NEC because a large percentage of cases occur in premature infants with no previous signs of hypoxia or ischemia and who are convalescing as "feeders and growers" in an intermediate care setting.[1,2]

The clinical signs of NEC can vary markedly. The early signs of NEC are often so nonspecific that a definitive diagnosis cannot be made. A commonly used instrument that has been helpful in the diagnosis and management of NEC, originally developed by Bell et al,[3] stages the severity of disease on clinical, radiographic, and laboratory criteria as follows:

Stage 1: Represents a broad spectrum of signs that should lead the clinician to be suspicious of NEC but are not specific for the disease and may represent a myriad of problems including simple feeding intolerance, sepsis, gastroenteritis, ileus, or metabolic problems such as hypoglycemia.

Stage 2: Represents NEC that is proven, usually by abdominal radiographs showing intestinal dilatation and pneumatosis intestinalis (Fig. 1).

Stage 3: Represents advanced NEC in which the infant is exhibiting signs of septic shock, metabolic acidosis, disseminated intravascular coagulation, neutropenia, marked abdominal tenderness, and ascites. This most often progresses to bowel perforation, which can be manifested by pneumoperitoneum on abdominal radiographs (Fig. 2).

CURRENT TREATMENT STRATEGIES

Bell's staging criteria[3] can be highly useful as guidelines. In stage 1, there is only a strong suspicion that the disease might be developing. Precautions need to be taken. Clinical judgement based on the patient's condition should guide whether and how long the patient should be taken off enteral feedings; whether the bowel should be decompressed with suction; whether and how long IV antibiotics should be used; and how aggressively the patient should be monitored with radiographs and laboratory tests. We closely follow the platelet count and absolute granulocyte count along with left lateral decubitus x-rays looking for signs of progressive neutropenia and thrombocytopenia to track the severity of the disease.

If it is judged that the infant is deteriorating (progressing toward stage 2), the bowel should be decompressed using a large-bore orogastric tube with low intermittent suction. Systemic, broad-spectrum antibiotic therapy covering both Gram-positive and Gram-negative organisms are started after obtaining blood cultures. The surgical team should be notified early in order to aid in the diagnosis and to be prepared to

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Correspondence: Josef Neu, MD, Pediatric Neonatology, PO Box 100296, University of Florida, Gainesville, FL 32610-0296.

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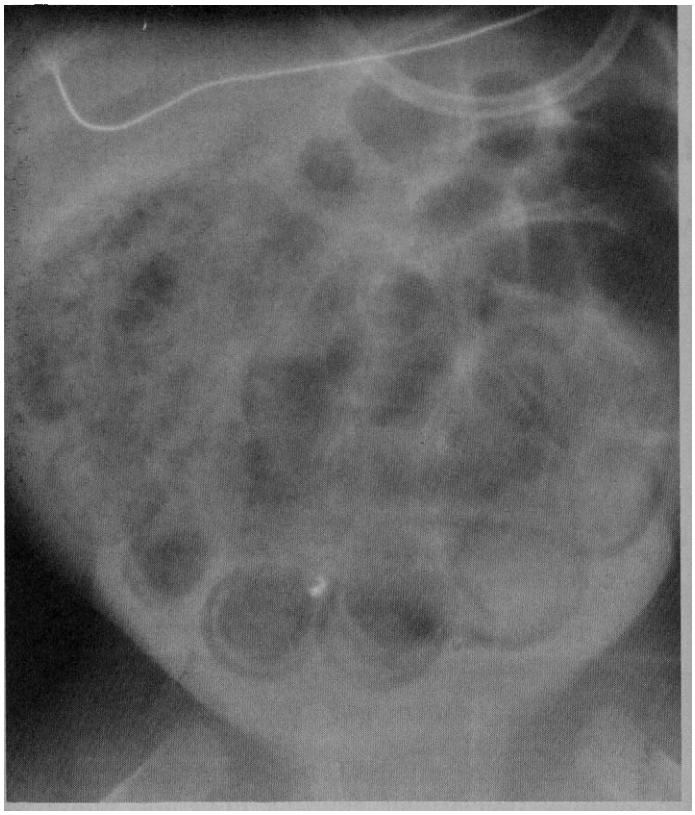

FIG. 1. Film of the chest and abdomen shows massive air-distended bowel with diffuse intramural air.

operate when necessary. Progression to stage 3, especially if associated with intestinal perforation, requires surgery. The various nuances of surgical techniques are beyond the scope of this review.

PATHOPHYSIOLOGY

The pathophysiology of NEC is not clearly understood. Much of what we know about the cause of NEC has been described in epidemiologic studies from which several important risk factors have been dissected. The putative risk factors that predominate are prematurity, aggressive enteral feedings, infectious agents, and hypoxic-ischemic insults. We will discuss each of these separately.

Prematurity

The primary risk factor for NEC is prematurity because approximately 90% of cases occur in premature infants.[4–6] This disease is rarely seen in older children and adults. An immature gastrointestinal tract appears to predispose premature infants to NEC. These include immaturity in immunologic function, lumenal digestion, barrier function, and motility.

A mature immune response to intestinal pathogens includes adequate secretory immunoglobulin A (sIgA), T lymphocytes, and antibody production in response to infectious agents or their toxins. Studies in immature animals have demonstrated decreased sIgA overlying the Peyer's patches of the ileum[7] with increased macromolecular uptake[8–10] and bacterial translocation[11] in this area. Infants of less than 35 weeks gestation have demonstrated a relatively poor response in the production of antibodies when compared with those of more than 35 weeks gestation.[12] The premature infant, accordingly, has a limited capability to respond immunologically.[12,13]

Immaturities in luminal digestion, which could act as important lines of defense against ingested pathogens, include a decreased gastric-hydrogen ion output[14] and proteolytic enzyme activity, especially enterokinase.[15] An immature gastric acidic environment and brush border proteolytic enzyme response in the upper small intestine could permit entry of pathogenic bacteria or their toxins into the distal small intestine.

There are also several apparent immaturities of the small intestinal epithelial barrier. The intestinal mucin blanket seems to be scant and have different composition in newborn infants[16,17] when compared with adults. Neonatal rabbits'[18] and rats'[19] microvillus membranes have higher lipid-protein ratios that those of adults. The fluidity (organization) of the microvillus membrane also changes as the animal matures and is shifted to a more mature pattern by glucocorticoids administered to the mother antenatally or the infant postnatally.[19,20] This contributes to a greater perme-

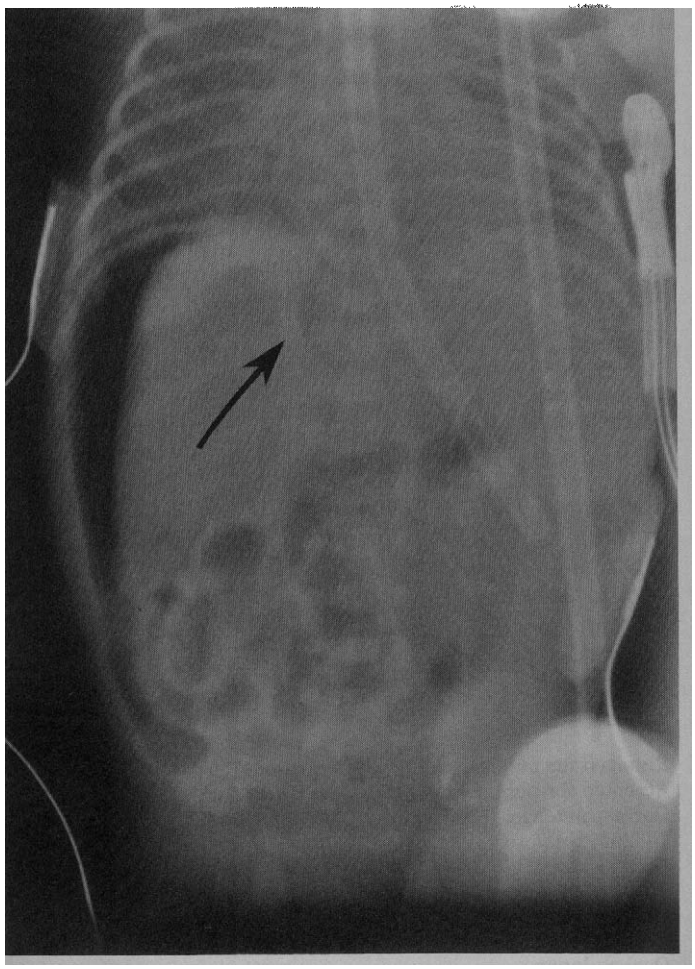

FIG. 2. Left lateral decubitus film of the abdomen shows free intraperitoneal air from a bowel perforation. Free air is shown on both sides of the falciform ligament (arrow).

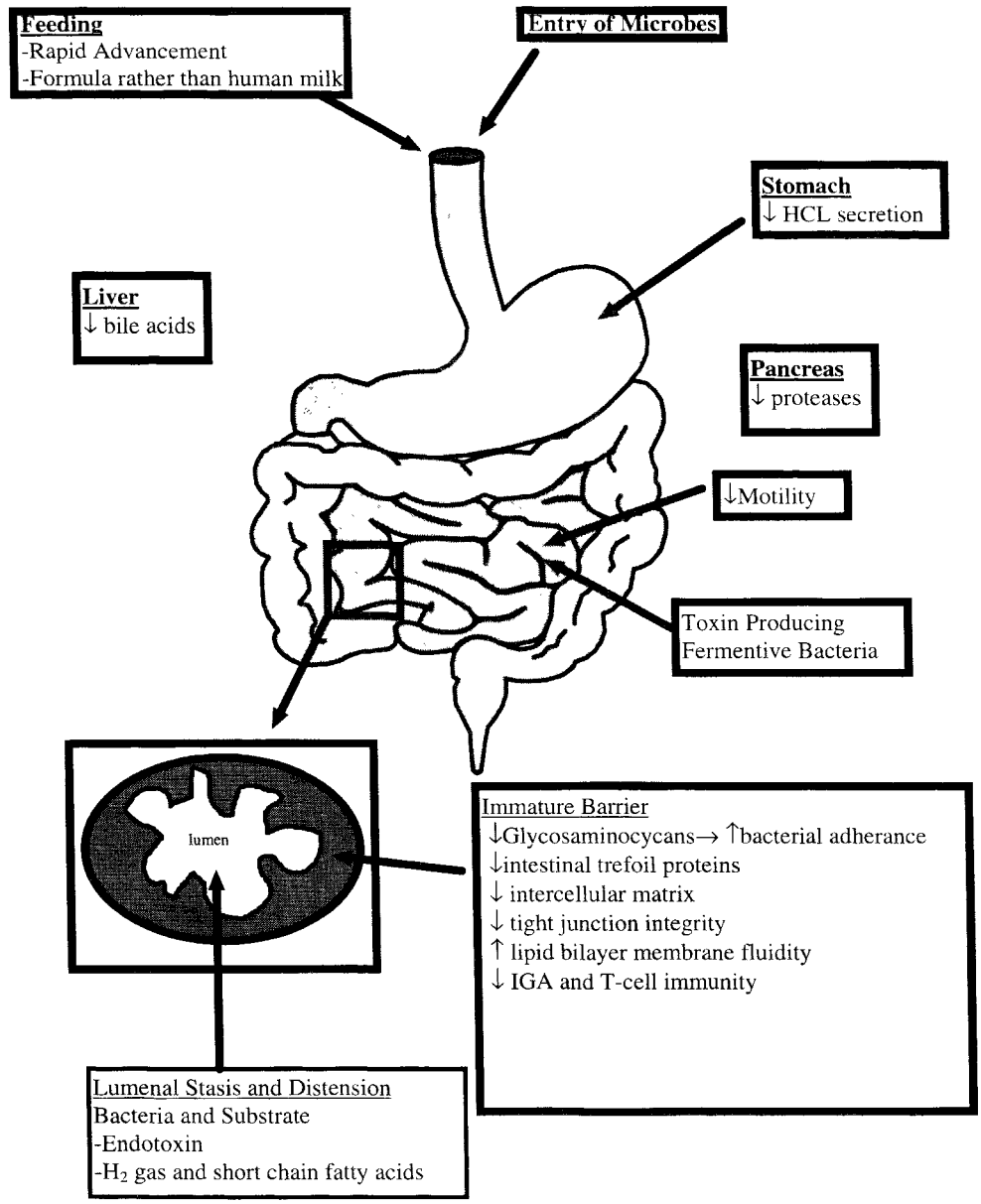

FIG. 3. Possible factors predisposing premature neonates to nectrotizing enterocolitis (NEC).

ability to high molecular weight molecules[21] and is likely to facilitate bacterial adherence to the epithelium.[4] In this scenario, luminal bacteria may translocate across the bowel wall into the blood or mesenteric lymph nodes.[11,22] Translocation is likely to be responsible for many of the positive bacterial cultures obtained from the blood of neonates with NEC.[23]

The motility of the small intestine in premature infants is considerably lower and less organized than in term infants.[24] Poor motility of the intestine is a major cause of feeding intolerance and can lead to bacterial overgrowth and distension and these contribute to the pathogenesis of NEC.

Aggressive Enteral Feedings

NEC occurs more frequently in premature infants whose enteral intakes are being aggressively increased. The advancement of formula feedings at rates greater than 20 kcal/kg per day has been found to be associated with an increase in the incidence of NEC.[25–28] Clinical studies of "minimal enteral feedings" or "priming" the GI tract by a very slow intake (usually <10 mL/kg/d increments) have not demonstrated an increased incidence of NEC.[29–33] Rather, these studies have shown improved tolerance to subsequent enteral feedings, a lower incidence of cholestasis, and increased serum concentrations of trophic gut hormones when compared with more rapid advancement of enteral feedings.

The possibility that human milk provides protection against NEC is supported by a multicenter trial that demonstrated a 1.2% incidence of NEC in infants fed expressed human milk and 7.2% incidence in premature infants fed formula.[34]

Infectious Agents

Several lines of evidence support the thesis that infection is necessary for the development of NEC.[35–38] Bacteria commonly isolated from infants with NEC are Gram-negative rods, including *Klebsiella* spp, *Escherichia coli* spp, *Enterobacter* spp, and *Pseudomonas* spp.[35] If one uses Bell's criteria for the diagnosis of proven NEC (stage 2), the radiologic finding of pneumatosis is a necessary component. The gas in pneumatosis is thought to be derived primarily from bacterial fermentation.[39,40]

Hypoxia-Ischemia

The clinical data, which support a hypoxic-ischemic role in the pathogenesis of NEC, is largely anecdotal. Subsequent epidemiologic case control studies showed that hypoxic-ischemic insults were not relevant risk factors in the development of NEC in preterm infants[1,5,40–42] The fact that so many cases of NEC occur in the intermediate or step-down intensive care unit in babies who had no known antecedent stresses, such as low Apgar scores, need for ventilator support, umbilical catheters, polycythemia, or significant apneic episodes, mitigates against hypoxia-ischemia as a major primary causative factor. However, if other triggers, such as bacterial toxins or chemical irritation, set off a cascade of events leading to endothelial disruption, triggering the inflammatory cascade with thromboxane production, cytokine activation, platelet activating factor release, and nitric oxide inhibition, this could in turn lead to a secondary vasoconstriction and hypoxic-ischemic injury. These inflammatory mediators can also lead to multisystem organ failure by affecting sites other than the intestine. Figure 3 illustrates a summary of many of the pathophysiologic features of NEC.

PREVENTATIVE STRATEGIES

Several measures are commonly used to prevent NEC outbreaks. Careful epidemic precautions are indicated when an outbreak of NEC is suspected. These include strict infection-control measures to prevent fecal and oral spread; cohorting of patients, contacts and personnel; and using a decreased threshold for early intervention, such as placing infants *nulla per os* (NPO). Although oral antimicrobial agents have been used for prophylaxis of NEC,[43,44] the possibility of emergence of resistant organisms limits their routine long-term use.[45]

The decreased incidence of NEC in babies of mothers who are treated with antenatal corticosteroid,[46] would provide an additional indication for the administration of corticosteroids to mothers in preterm labor. Whether the routine use of postnatal glucocorticoid prophylaxis for NEC would be effective without causing other significant risks to the infant such as increasing the incidence of sepsis or catabolism, is not known. Further studies are needed to determine the risks *vs* benefits of such prophylaxis.

Providing human milk to premature infants has been shown to decrease the incidence of NEC in one large multicenter study.[34] The possibility of banked or refrigerated donor milk providing benefits is less clear because the pasteurization or freezing process compromises the cellular components. However, many of the potentially protective components such as lactoferrin and immunoglobulins should be left intact. Thus it is the authors' opinion that premature infants should be provided with their own mother's milk (preferably fresh) whenever feasible.

Several other studies of prevention have been completed in humans and animal models of intestinal damage. These include acidification of formula,[47] providing an IgG-IgA preparation obtained from human serum,[48] platelet activating factor acetyl hydrolase,[49] and interleukin-11.[50] These need further study and validation before being considered as safe and effective prophylaxis of NEC in humans.

As the pathophysiologic cascade for NEC becomes more defined, the likelihood of effective prophylaxis for NEC increases. It is reasonable to assume that intervention aimed at the more proximal events of the cascade (Fig. 3) offer a greater likelihood of effective prophylaxis. Thus, prophylactic measures which alter the intestinal lumenal bacterial milieu or toughen the mucosal barrier (proximal factors) would interfere with the pathophysiologic cascade before some of the damage has already started via the cytokine and inflammatory cascade (distal factors). Examples of interference in the proximal portion of the cascade include the use of human milk or some of its components, eg, lactoferrin, nutritional supplements that affect the intestinal mucosa and immune system (glutamine, arginine), or provision of a microbial environment (eg, rich in bifidobacterium) that inhibits the growth of potentially pathogenic microorganisms.

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