Necrotizing Enterocolitis

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Epidemiology

The incidence of NEC varies greatly between NICUs, with an overall incidence of approximately 5% for all infants <32 weeks gestation [1]. The incidence increases as gestational age and birth weight decrease, with an incidence of approximately 12% in infants born between 501 and 750 g, and approximately 9% in infants with a birth weight of less than 1500 g [2]. However, full-term infants comprise 10% of NEC cases [3]. There does not appear to be a differential incidence by sex, and the role of race in NEC is unclear. Outbreaks of NEC have been described, lending support to bacterial or viral agents contributing to disease.

Pathogenesis

NEC is typically described as a multifactorial disease with many predisposing elements interacting with each other in a complex manner, making the contribution of individual risk factors difficult to assess. As well, most studies evaluating risk factors are retrospective, showing associations but not causation. Most unifying theories about the etiology of NEC involve a combination of abnormal inflammatory response (both systemically and in the gut environment), colonization of intestinal mucosa by pathogenic bacteria (dysbiosis), and abnormal vascular regulation in a vulnerable host with intestinal immaturity [3].

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Prematurity is the single most consistent risk factor for NEC, with the incidence of the disease inversely proportional to gestational age [2, 4, 5]. Low birth weight, independent of gestational age, has been cited as a risk factor, implying that prenatal factors that cause growth restriction can predispose the developing gut to be vulnerable to NEC [6, 7]. Other risk factors include infants born to mothers with chorioamnionitis, preterm premature rupture of membranes, and neonatal sepsis, all of which presumably increase risk by increasing inflammation [8]. Infants who have experienced hypotension have been shown to be at higher risk of NEC, and the association between NEC and a hemodynamically significant patent ductus arteriosus has been described, with the "steal" of blood flow from the ductus implicated in vascular compromise of the preterm intestine [9, 10].

Enteral feeding practices and use of medications, specifically antibiotics and histamine-2 (H2) antagonists, are well-established targets for interventions to prevent NEC.

Enteral feeding. Most infants who get NEC have been fed; however, most infants who are fed do not develop NEC. The optimal feeding strategy for preterm infants is unknown; the optimal rate of advancement, target volume, and composition of enteral feeds in infants at risk for NEC are unclear. Many studies clearly show the protective effect of human milk**,** and this has led to the extrapolation of formula use as a risk factor for NEC [11, 12]. Most authors would cite prolonged delay in initiation of feeds and exclusive use of formula in place of breast milk as risk factors for NEC. High osmolarity of feeds via the use of bovine fortification products and rapid advancement of feeds (>30 cc/kg/day) are felt to be associated with NEC; however, the optimal osmolar threshold and timing of feeding fortification and advancement to promote growth but mitigate NEC risk are unclear.

Antibiotic use. Several observational studies have shown and increased risk of NEC or death with prolonged (typically ≥5 days) duration of antibiotics in the early neonatal period. This association is now felt to be mediated by changes in the intestinal microbiome [13, 14]. These epidemiologic studies are being confirmed with the advent of techniques that allow rapid and detailed identification of the intestinal microbial community. Through amplification and sequencing of the 16S ribosomal RNA subunit DNA or whole-genome sequencing, the contribution of the neonatal microbiome to the development of NEC has become clear. Infants with NEC have been shown to have a higher predominance of gram-negative organisms and a decreased diversity of bacteria prior to disease onset [15].

H2 Antagonists. Infants receiving H2 blockers (e.g., ranitidine, cimetidine, famotidine) have shown an increased risk of NEC. The mechanism of this association is also likely mediated in part by the alterations in the gut microbiome as well through loss of the protective effect of lowered gastric pH [16, 17].

Packed Red Blood Cell (PRBC) Transfusion. NEC temporally related to PRBC transfusion is well described and often termed transfusion-associated acute gut injury. Although the mechanism of this association is not clear, both age of blood, changes in mesenteric vascular regulation during transfusion, and degree of anemia at transfusion have been implicated [18, 19].

Full-term infants who develop NEC have a unique risk factor profile, likely because NEC in these infants is due to different underlying processes. Intestinal anomalies such as gastroschisis or Hirschsprung's disease, cyanotic congenital heart disease, maternal cocaine use, perinatal asphyxia, and growth restriction have been linked to NEC in term and near-term infants. This risk factor profile suggests perinatal or congenital conditions which result in reduced blood flow to the neonatal intestine as an important consideration in older infants who develop NEC [20, 21].

Clinical Findings

The age at presentation of NEC is inversely proportional to gestational age. In the smallest infants, the median time to onset is approximately 20 days of life, corresponding to a post-menstrual age of 28–32 weeks, when patients are typically beginning the convalescent phase of extreme prematurity [22]. Full-term or late preterm infants typically present within the first week of life, again indicating the strong contribution of perinatal insults or congenital conditions.

Clinical signs. The initial stages of NEC are comprised of non-specific signs and symptoms which overlap with other conditions such as sepsis, apnea, or feeding intolerance. Increased episodes of apnea, temperature instability, decreased activity level, oliguria, as well as intestinal signs such as feeding intolerance and abdominal distention may be present. More specific local signs include abdominal tenderness and bloody stool; abdominal wall erythema and abdominal mass are specific signs of NEC but often difficult to discern [23, 24]. Infants may rapidly progress to severe systemic signs, such as hypotension, circulatory arrest, renal failure, or respiratory failure.

Laboratory signs. Abnormal lab indices include abnormal serum glucose, hyponatremia, leukopenia, neutropenia, thrombocytopenia, and accompanying anemia. Elevated inflammatory makers are typically present. Severely affected patients will show metabolic acidosis and associated hyperkalemia as well as disseminated intravascular coagulopathy (DIC) [25]. Elevated eosinophil count, when present, may be specific for NEC.

Radiographic signs. Pneumatosis intestinalis, or the projection of gas in the bowel wall as seen on X-ray, is the pathognomonic finding of NEC. Portal venous gas, which is an extension of this intraluminal air into the portal venous system, is also classic radiographic criterion of NEC. Infants who progress to intestinal perforation may display free intraperitoneal air on radiographs; this can be illustrated by the "football sign," an illumination of the falciform ligament by free intra-abdominal air. Other, less specific findings of NEC that may overlap with other conditions are fixed and/or dilated intestinal loops of bowel, bowel wall edema, and/or stacked loops of bowel with or without air fluid levels [23, 26]. Figure 1 shows radiographic examples of pneumatosis, portal venous gas, and perforation.

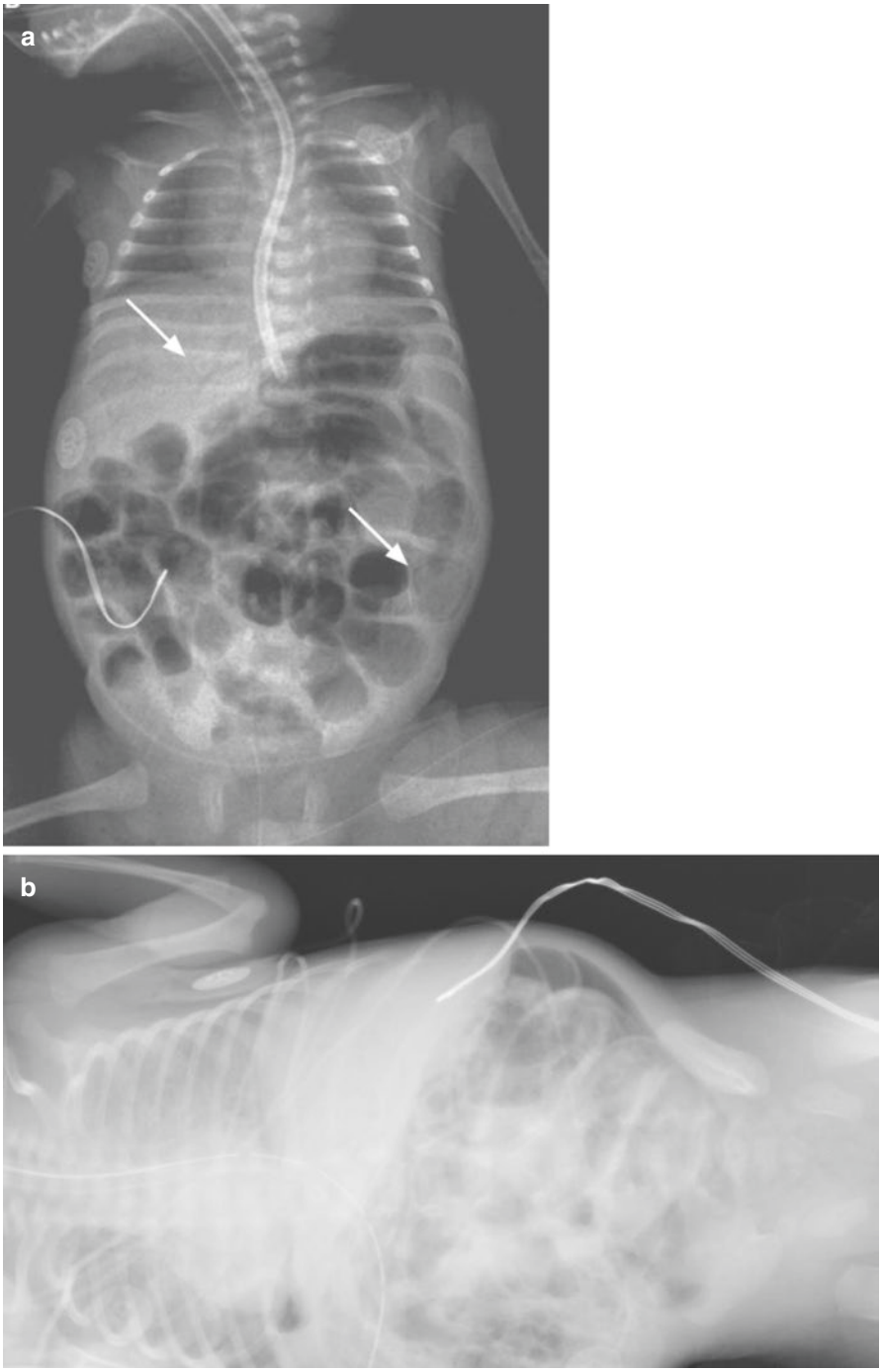

Fig. 1 Radiographic findings of necrotizing enterocolitis. (**a**) Pneumatosis intestinalis (lower arrow) and portal venous gas (upper arrow); (**b**) free intraperitoneal air as seen on a decubitus radiograph. Used with permission from [23]

Diagnosis

The diagnosis of NEC is based on a combination of clinical, radiological, and lab findings as mentioned above. Historically, the most common clinical staging system is the modified Bell's staging (Table 1), which categorizes NEC into Stages I, II, and III (i.e., suspected, definite, and advanced/surgical) [27–29]. The Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN) has also developed diagnostic criteria for NEC, which is categorized as a healthcare-acquired infection [30]. These overlap with the Vermont Oxford Network definition of NEC, which is widely used for quality assurance and research purposes among nurseries [31].

Table 1 Modified Bell's staging for necrotizing enterocolitis (NEC)

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric residuals, abdominal distention, emesis, occult blood in stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics for 3 days, pending cultures and stomach decompression
IB	Suspected	Same as IA	Grossly bloody stool	Same as above	Same as IA
IIA	Definite, mildly ill	Same as IA	Same as above; plus absent bowel sounds, +/− abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	Same as IA; NPO and antibiotics for 7–10 days
IIB	Definite, moderately ill	Same as IA, plus mild metabolic acidosis and thrombocytopenia	Same as above; absent bowel sounds, definite tenderness, +/− abdominal cellulitis or mass	Same as IIA, +/− ascites, +/− portal venous gas	Same as IIA, NPO and antibiotics for 14 days
IIIA	Advanced, severely ill, intact bowel	Same as above, plus hypotension, bradycardia, apnea, severe acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus definite ascites	Same as IIB plus volume replacement, inotropic and ventilator support. If no improvement, consider surgical intervention
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as IIIA, plus pneumoperitoneum	Same as IIIA plus surgical intervention

DIC disseminated intravascular coagulation. Adapted from 26–28

These classification systems are often used as a diagnostic tool, although Bell criteria are meant to be applied to infants already diagnosed with NEC. Abdominal radiographs in preterm neonates may be difficult to evaluate, and diagnosis of radiographic findings such as pneumatosis intestinalis may vary from reader to reader [26, 32, 33]. Some infants with severe disease requiring surgical management never develop pneumatosis or portal venous gas. Additionally, NEC in very preterm infants may not present with bloody stools. In this population, intestinal necrosis develops proximal to the ileocecal valve; when ileus is present, blood will fail to pass into the distal part of the colon. Pneumoperitoneum on radiographs may or may not be associated with intestinal necrosis; spontaneous intestinal perforation – an entity which is clinically and pathologically distinct from NEC – often presents as free air in the abdominal cavity. Table 2 highlights the differences between SIP and NEC. Rarely, dissected air from the pleural cavity in infants with severe lung disease or pneumothorax may present with pneumoperitoneum [34, 35]. Ultrasonography may detect bowel wall edema, pneumatosis, alterations in the intestinal vascular state, ascites, or intra-abdominal collections in infants with NEC. This technique provides specificity of diagnosis but requires both operator skill and an experience in interpretation [36, 37].

As discussed, many laboratory abnormalities occur with NEC, and inflammatory markers are usually quite elevated. However, specific serum, urine, or stool biomarkers have not yet been validated. Intestinal fatty acid-binding protein, a protein present in enterocytes and released with cell injury; fecal calprotectin, released from neutrophils during an inflammatory response; and serum amyloid A and IL-8,

Table 2 Clinical features of spontaneous intestinal perforation versus necrotizing enterocolitis

	Spontaneous intestinal perforation	Necrotizing enterocolitis
Onset	Age < 10 days	Age > 14 days
Abdominal signs		
Distention	+++	+++
Erythema	–	+
Tenderness	+/–	+++
Bilious aspirates	++/–	++
Laboratory markers		
Leukopenia/neutropenia	–	+++
Thrombocytopenia	–	+++
DIC	–	++
Physiologic signs		
Apnea	+/–	++
Temperature Instability	–	++
Hypoperfusion/shock	–	+++
Radiographic signs		
Pneumatosis intestinalis	–	+++/–
Hepatobiliary gas	–	++/–
Pneumoperitoneum	+++	++/–

DIC disseminated intravascular coagulation

general markers of inflammation, have been studied alone or in combination. However, none are in widespread use, and normal values in infants have not been established [38, 39].

Treatment

Treatment for NEC includes bowel decompression and rest, fluid resuscitation, antibiotic therapy, and supportive care.

Medical Therapy. Antibiotic treatment is indicated as bacteremia occurs in 20–30% in infants with NEC primarily from translocation of organisms through a compromised intestinal barrier [40]. The superiority of one regimen over another has not been well established by clinical trials. Most regimens consist of broad gram-negative and anaerobic coverage (e.g., ampicillin *AND* an aminoglycoside ± clindamycin or metronidazole, or piperacillin/tazobactam ± an aminoglycoside). Use of vancomycin is not routinely indicated but could be considered if the infant is colonized with methicillin-resistant *Staphylococcus aureus.* Although studies exist linking the addition of anaerobic therapy with later stricture formation, authors of a large multicenter cohort study note that this association is most likely caused by a "survival bias" in infants treated with these agents who then live to develop strictures [41, 42]. Duration of therapy is generally 10–14 days for medical NEC and may be longer for disease requiring surgical intervention. Most providers also continue bowel rest for this duration. However, as with antibiotic choice, no evidenced-based recommendations for resumption of feeding or cessation of antibiotics exist, and shorter courses of both may be indicated when evidence of intestinal inflammation has remitted.

Surgical Therapy. Pneumoperitoneum is an indication for urgent surgical intervention in infants with NEC. Treatment options include either primary peritoneal drain and/or exploratory laparotomy. Studies have failed to show consistent benefits of one approach [43, 44]. Relative indications for surgical exploration include refractory thrombocytopenia, acidosis, or shock, all of which may be indicative of necrotic bowel. The decision to operate and the specific intervention should be determined in collaboration with the pediatric surgeon. Weighing the risks and benefits of performing an operation on a severely ill neonate is always challenging; additionally, demarcating unsalvageable bowel from that which could potentially recover is not always a clear-cut surgical decision.

Prevention

Prevention of NEC is based on targeting modifiable risk factors.

Feeding Strategies

1. Swabbing of the mouth with colostrum may be protective against NEC by stimulating the production of secretory IgA and lactoferrin, substances known to have

a protective effect on the intestinal mucosa, and specifically targeting gram-negative bacteria [45].
2. As previously stated, feeding with mother's own milk has been shown to be protective against NEC, and maternal support and resources for breastfeeding and providing fresh expressed milk should be provided from birth. The amount and duration of milk provided needed to provide optimal protection is unclear, but exclusive use of breast milk should be a goal for as long as feasible for mother and infant [11, 12, 46–48]. The benefits of pasteurized donor or processed human milk products over formula are still unclear [49, 50].
3. The decision of when to initiate feeds, especially in in the smallest infants, is much debated and displays both inter- and intra-institution variability. A period of trophic feeding (approximately 10–20 cc/kg/day) initiated within 24–72 h of birth, followed by advancement of 20–30 cc/kg/day of milk, is generally considered as acceptable method of feeding very-low-birth-weight (<1500 g) infants. More aggressive pathways may be safe and preferable in larger infants to reduce central line and parenteral nutrition [51].
4. Despite a lack of precise evidence on the "correct" feeding strategy, there is clear evidence that the mere presence of a unit-wide standardized feeding protocol is preventative for NEC [52–54].

Medication Stewardship. Several studies have linked the prolonged use of antibiotics in the early neonatal period with an increase in NEC through the manipulation of the microbiome with a shift toward aberrant colonization, or dysbiosis. H2 antagonists (i.e., ranitidine, famotidine, cimetidine) are also associated with increased odds of NEC (and *Candida*—see chapter "*Candida*") [13, 14, 16, 17]. Recognition of this association has led to successful reduction in utilization of both medications, as well as development of antimicrobial stewardship programs targeted to the NICU population [55, 56]. Antimicrobial stewardship strategies are further discussed in chapter "Antibiotic Stewardship."

Probiotics. Probiotics have been shown in randomized trials and subsequent meta-analyses to be protective against NEC, primarily through the establishment of favorable intestinal microbiota in preterm infants. The most common strains used in the United States are *Lactobacillus acidophilus*, *Bifidobacterium infantis*, and *Lactobacillus rhamnosus*. Though the trials are compelling, there is a great deal of heterogeneity in the exposure [57–60]. As such, administration of probiotics for the prevention of NEC is not recommended by the American Academy of Pediatrics due to the lack of a commercial formulation that has been studied for dose, consistency, and safety. Case reports of bacteremia with study products, as well as infection from impure products, have been reported [61, 62].

Other Biologic Agents. The role of epidermal growth factors, prebiotics, glutamine, and oral lactoferrin on mitigating the risk of NEC has not yet been confirmed, with investigations into these products, particularly prebiotics, presently underway [63–66].

Quality Improvement Initiatives. Implementing the above preventative measures as bundled strategies rather than individual interventions alone is the most effective

approach to reducing NEC [67, 68]. Clinical risk assessment tools such as GutCheck [69], developed and validated by a large national dataset, highlight the need for timely provider awareness with a focus on multifactorial nature of risk factor profiles in preterm infants. Predictive models for NEC integrating real-time patient data and machine learning to predict impending disease are exciting uses of technology [70, 71].

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