



Published in final edited form as:

J Neonatal Biol. 2015 ; 4(4): .

Necrotizing Enterocolitis (NEC): A Devastating Disease of Prematurity

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Abstract

Necrotizing Enterocolitis (NEC) is a common and devastating gastrointestinal emergency that primarily affects premature infants. The incidence of necrotizing enterocolitis is 6–10% among infants with birth weight less than 1500 grams. The mortality due to NEC has not improved significantly despite advances in neonatal care and better understanding of clinical and basic sciences. The pathogenesis of NEC is not well understood and several factors such as prematurity, abnormal colonization with pathogenic bacteria, feeding practices, blood transfusion and altered intestinal barrier function may be involved. The clinical presentation of NEC could be sudden and the treatment plan could vary with the stage and type of presentation. Further research is needed to better understand the pathophysiology of NEC and, biomarkers for prediction, prevention and treatment need to be developed. Further clinical trials are needed to determine prevention and treatment modalities for this devastating disease.

Introduction:

Necrotizing enterocolitis (NEC) is a common and devastating gastrointestinal emergency that primarily affects premature infants in neonatal intensive care units worldwide. Despite major advances in the medical care of premature infants, the etiology of NEC is still incompletely understood, and has become a research priority [1].

Epidemiology:

The incidence of NEC is 6 to 10% among infants with birth weight less than 1500 gms and varies among different US centers and across the world [2, 3] The disease is primarily seen in premature infants, however some term infants may also develop NEC. NEC in term infants is usually associated with predisposing factors such as asphyxia, polycythemia, congenital heart disease and congenital gastro-intestinal anomalies, and the disease pathophysiology in term infants is different from that in preterm infants. In the long term, survivors of NEC are at an increased risk of neurodevelopmental delays [4, 5].

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Due to technological advances in the recent years, the mortality in preterm infants due to pulmonary causes, infection and central nervous system injury have been on the decline but NEC related deaths have steadily increased [6]. Over the past three decades, the NEC related mortality (up to 40%) has not improved significantly despite advances in neonatal care and better understanding of clinical and basic sciences [4]. The annual cost of managing NEC infants in United States is between \$500 million and \$ 1 billion. The mean cost of care over 5 year's period for a child with short bowel syndrome has been estimated to be around \$1.5 million [7]

Pathogenesis:

Prematurity:

Prematurity is the single most important risk factor for NEC. 90% of the cases occur in very low birth weight infants although the exact underlying mechanisms responsible for NEC, still remain unknown. Animal and human studies have identified alterations in the intestinal host immune [8] defense[9], bacterial colonization[10], blood flow regulation[11], motility[12] and inflammatory response[13, 14] to be responsible for gut inflammation and injury. Low gastric acid secretion in preterm infants and its inhibition by use of H2 blockers has also been linked to development of NEC [8].

Role of Feeding:

Delayed introduction of enteral feeding has been associated with the development of NEC. Total parental nutrition leads to intestinal mucosal atrophy and increases the risk of NEC [15] and recent data suggests that early enteral feeding may reduce the risk of NEC [16, 17]. Preterm infants given exclusive diets of preterm formula had a significantly greater duration of parenteral nutrition, and higher incidence of surgical NEC compared to infants who were administered human milk [18, 19]. In preterm and low birth weight infants, feeding with formula milk compared with donor breast milk resulted in a higher rate of short-term growth but also a higher risk of developing NEC [20]. Larger randomized control trials are currently underway to provide insights into the long term outcomes of donor human milk on preterm infants.

Role of Inflammation and Immunological Factors:

Inflammatory and immunological factors play a vital role in the pathogenesis of NEC. A large body of data suggests that imbalance between Toll like receptors 4 (TLR) and TLR 9 is responsible for development of the disease. TLR4 activation leads to apoptosis and effects enterocyte proliferation and migration[21]. Some studies have implicated the role of Paneth cells (PCs) in NEC. Cooperation between intestinal stem cells and Paneth cells in a niche localized to the crypts is essential for normal renewal of intestinal surface. Moreover, after the intestine is seriously damaged by infection or other insults, Paneth cell dysfunction leads to NEC [22].

Intestinal macrophages progressively acquire a non-inflammatory profile during gestational development. Transforming Growth Factor β (TGF- β), particularly the TGF- β 2 isoform, suppresses macrophage inflammatory responses in the developing intestine and protects

against inflammatory mucosal injury. Enterally administered TGF- β 2 protects mice from experimental NEC like injury [23]. The infants who developed NEC have low levels of circulating TGF- β on postnatal day one as compared to non-NEC controls [24]. Data suggests there are low levels of TGF- β , and increased level of in the tumor necrosis factor and IL-1beta in surgically resected human NEC tissue. Some studies suggest that an increased IL-8 secretion by fetal enterocytes may trigger an excessive inflammatory response responsible for intestinal injury [25, 26].

Role of Blood Transfusion:

In the recent years, packed red blood cell (PRBC) transfusions have been associated with onset of NEC. Transfusion associated NEC (TANEC) has been reported in multiple studies, although the causality between PRBC transfusion and NEC has not yet been established [27, 28, 29]. Majority of very low birth weight (VLBW) infants require one or more PRBC transfusions during their stay in the neonatal intensive care unit (NICU [30], thus making TANEC, an important entity to consider. Some studies although show contradictory results and indicate that blood transfusions are not a risk factor for NEC [31]

Preterm splanchnic tissue undergoes a large degree of tissue oxygenation variability during RBC transfusions and does not change with increasing maturity. This combined with lower average tissue oxygenation, may explain susceptibility of the preterm gut to transfusion-related acute gut injury (TRAGI) [32]. PRBC transfusion in enterally fed preterm lambs promotes mesenteric vasoconstriction and impairs vasorelaxation by reducing mesenteric arterial endothelial NO synthase (eNOS) [33]. In addition stored PRBC may be less deformable and may not pass well through the gut microcirculation.

Feeding during blood transfusion is controversial and different neonatal units have different practices [34]. Some investigators have suggested that withholding feeds during transfusion could prevent NEC [35], and few believe that the infant remain on small volume feeds during transfusion. Overall, the current body of literature suggests that transfusion may be 'associated' with severe form of NEC (stage 3, Surgical NEC) in the extremely premature (less than 28 weeks), and low birth weight infants. In our view, TANEC may represent a different subset of NEC, and more evidence is needed before making any major practice changes.

Role of Intestinal Barrier:

Experimental NEC been has associated with disruption of the intestinal barrier. Epithelial growth factor helps in intestinal integrity at the site of injury by accelerating goblet cell maturation and mucin production and normalizing expression of tight junction proteins [36]. The administration of probiotics (*B. bifidum*) protects against NEC in the neonatal rat model. This protective effect was associated with reduction of inflammatory reaction in the ileum, regulation of main components of mucus layer, and improvement of intestinal integrity [37, 38]

Intestinal barrier function can be assessed by urinary measurement of Biomarkers such as intestinal fatty acid-binding protein (I-FABP) and fecal measurement of calprotectin [39, 40] and optimising intestinal barrier function may be important in preventing NEC [41].

Altered Microbial Colonization:

‘Microbiota’ can be defined as the microbes associated with a particular context. Unlike traditional microbiological approaches that aim to identify individual pathogens, microbiome analysis characterizes all of the bacterial species present both in terms of their identities and relative abundance[42]. Technological advances have revolutionized the efforts to understand the role played by microbes in disease physiology in recent years. High-throughput sequencing of 16S rRNA gene generated from bacteria-containing samples yields a large number of short sequences that can be subsequently aligned and sorted according to a predefined level of homology. Then, these are classified according to publicly available taxonomic databases [43, 44]. Recent evidence suggests, that alteration in gut microbiome may contribute to intestinal injury and NEC in preterm infants. Hospitalized premature infants intestines are colonized with less diverse bacterial species as compared to healthy breast fed infants which are colonized predominantly with anaerobic species of *Bifidobacteria* and *Lactobacilli* [45, 46]. Data suggests that preterm infants are colonized with less diverse bacterial population, more predominantly with *Proteobacterial* species and less *Clostridia* species [10, 47, 48]. Nevertheless, a recent study indicates that no consistent pattern in the microbiome composition was seen in infants who developed NEC and strains colonizing each baby were typically distinct [49]. In animal models, investigators have examined the correlation of mucosa-associated microbiome abundance with the severity of intestinal injury, and found that animals developing NEC have higher quantities of bacterial micro colonies along the villi and in the intestinal crypts compared to healthy animals [50]. Another recent study, supports this hypothesis and indicates that depth of bacterial invasion in resected intestinal tissue predicts mortality in surgical NEC [51].

The different etiological factors have been summarized in figure 1.

The study of systems biology of NEC is a fascinating new field of research and includes employing microbiomics, metabolomics, transcriptomics and other ‘OMIC’ strategies. As our understanding about host-microbiome interactions and the development of NEC moves forward, we must be mindful of an extremely complex ecology that houses 10 times more cells and 100 times more genes than the human host. Continued awareness of underlying processes and recognition that associations are not the same as mechanistic explanations, remain essential [52]

Clinical Presentation:

The clinical presentation of NEC may be extremely variable. NEC may present with symptoms of increased gastric residuals, feeding intolerance, bradycardia, tachycardia, apnea, vomiting, abdominal distension, blood in stools, abdominal discoloration, metabolic acidosis and if severe, with the clinical picture of shock and sepsis. The hematological abnormalities seen in NEC are anemia, thrombocytopenia, disseminated intravascular coagulopathy, significant decrease in the number of absolute monocyte count, increased or decreased level of neutrophils, eosinophilia [53]. A recent study has shown that NEC leads to renal dysfunction, metabolic acidosis through disruption of tight junction proteins [54, 55].

Diagnosis:

Clinical and radiological features are primarily employed for the diagnosis of NEC. Bell and colleagues suggested a classification scheme that differentiates suspected NEC (stage 1) from proven (stage 2) and advanced NEC (stage 3). Stage 1 presents with nonspecific symptoms and stage 2 is definitive NEC with radiological evidence of pneumatosis intestinalis and/or portal venous gas. Stage 3 NEC is presents with systemic signs with radiographic evidence of intestinal perforation (pneumoperitoneum) [56]. The Bell's staging is shown in table 1.

A very close differential of NEC is spontaneous intestinal perforation (SIP) as shown in table 2 which is usually seen first few days of life in extremely preterm infants. In SIP, the inflammatory response is less marked as compared to NEC, and both diseases have completely different pathophysiological mechanisms [57]. Indomethacin and early use of steroids have been shown to increase the incidence of SIP [58, 59].

Patients with NEC stage 1 and 2 are usually managed conservatively, while infants with stage 3 NEC may require surgical intervention, which may include laparotomy or a peritoneal drain placement. A multicenter randomized trial comparing outcomes of primary peritoneal drainage with laparotomy in preterm infants with perforated NEC found no significant differences and hence, further larger studies are underway [60]

Recent evidence suggests that, fecal volatile organic compounds (VOCs) analysis by an electronic nose (eNose) may allow for an early detection of NEC [61]. Due to low specificity, immunologic and hematological abnormalities are likely to be less useful as diagnostic tests and may be a “early-warning” systems that indicate a need for clinical monitoring and/or imaging [53, 62]

Prevention:

Breast milk contains multiple factors, which may improve the preterm intestinal host defenses, and early human milk feedings have been shown to be protective against NEC [17, 63]. Donor breast milk has also shown promise in the prevention of NEC compared to formula feeds [64], although larger long term studies are still underway. In addition, standardized feeding protocols may help in decreasing the incidence of NEC [65]. Although probiotics may decrease the incidence of NEC, they have not been shown to change NEC related mortality [66–68]. Most reports support routine administration of probiotics as safe and efficacious in the preterm population, however the long-term effects such as neurodevelopmental outcomes and growth patterns, are yet to be investigated. The FDA has not yet approved the routine use of probiotics in preterm infant and further trials are needed before their routine usage. Some data suggests that supplementing feeds with prebiotics such as oligosaccharides, which increases the growth of beneficial intestinal flora may be beneficial [69, 70]. Very few studies have examined the effects of synbiotics (combination of prebiotic and probiotic preparations) in the preterm population. Although the use a symbiotic combination (*Lactobacilli* + *Fructooligosaccharides* + *Bifidobacteria*) resulted in an increased stool content of *Bifidobacteria* in preterm infants, no differences in stool short

chain fatty acids content, weight gain, or incidence of NEC were observed when compared to placebo [71].

Liberal use of antibiotics in premature infants is associated with an increased incidence of NEC [72]. With the mounting evidence regarding the role of the gut microbiome dysbiosis in NEC pathogenesis, excessive use of antibiotics and H2 blocker in preterm infants, should be discouraged. Antibiotic stewardship in preterm infants is the need of the hour.

Future Directions:

The understanding of cellular processes in the pathogenesis of NEC is still in its nascent phases. Hence, more translational and basic science studies are required to further enhance our understanding about innate immune, barrier function and inflammatory response in the premature gut. Sensitive and specific biomarkers using newer systems biology approaches need to be developed, for the prediction, early diagnosis and progression of NEC. Moreover, well-designed prospective clinical trials with long term outcome data are needed for the prevention and treatment of this devastating disease.

Funding:

The article is supported by NIH funding K08HL141652 awarded to CVL.

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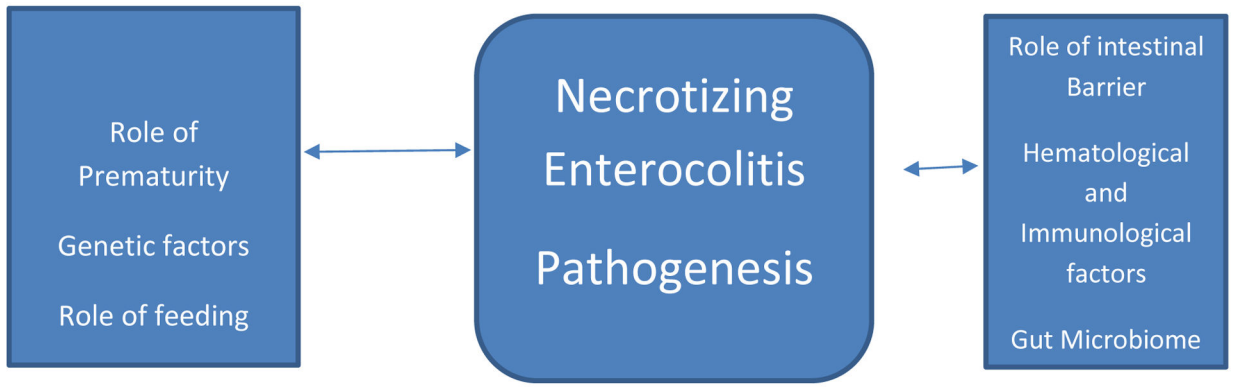


Figure 1-
NEC pathogenesis

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Table 1:

NEC Staging

Staging	Common Clinical findings	Common Radiological findings	Common Gastrointestinal findings
Stage I	Apnea and bradycardia, temperature instability	Normal gas pattern or mild ileus	Gastric residuals, occult blood in stool, mild abdominal distention
Stage II	Apnea and bradycardia, temperature instability, Thrombocytopenia and mild metabolic acidosis	Ileus gas pattern with one or more dilated loops and pneumatosis, ascites, portal-venous gas	Grossly bloody stools, prominent abdominal distention, absent bowel sounds, abdominal wall edema with palpable loops and tenderness
Stage III	Worsening metabolic acidosis, oliguria, hypotension, coagulopathy, shock, deterioration in laboratory values and vital signs	Prominent bowel loops, worsening ascites, Pneumoperitoneum	Worsening wall edema, erythema and induration, Perforated bowel

Table 2:

Difference between NEC and SIP in preterm infants

	NEC	SIP
Age	>2 weeks	First 2 weeks
Bloody stools	Uncommon	No
Ileus	Yes	Variable
Pneumoperitoneum	In advanced NEC	Always
Pneumatosis Intestinalis	Yes	No
Inflammatory response	Yes	Variable/No
Prognosis	Variable-Worse if surgical NEC	Relatively better than NEC

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Table 4:

NEC: Summary of risk factors and prevention strategies

Risk Factors for Necrotizing Enterocolitis :
Prematurity[8–14]
Role of inflammation/immunological factors [21–26]
Role of feeding[15–20]
Role of intestinal barrier[36–41]
Role of hematological factors[27–35]
Gut microbiome [42–51]
Possible prevention strategies :
Breast milk [17,63]
Donor breast milk [64]
Standardized feeding protocol[65]
Probiotics[66–68]
Prebiotics[69,70]
Synbiotics[71]
Minimal use of antibiotics[72]

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