Immunologic and Hematological Abnormalities in Necrotizing Enterocolitis

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KEYWORDS

• NEC • Blood counts • Inflammation • Macrophages • Signaling • Neutrophils • Platelets • Monocytes

KEY POINTS

- Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in preterm infants born before 32 weeks' gestation or with a birth weight less than 1500 g.
- Bacterial flora plays a central pathophysiological role in NEC.
- Premature intestine is at risk of NEC because of mucosal sensitivity to bacterial products and paucity of mechanisms that normally limit the interaction of luminal bacteria with mucosal cells.
- The onset of NEC is associated with elevated plasma concentrations of several inflammatory cytokines. Increased circulating interleukin-8 concentrations may provide prognostic information.
- Low circulating TGF-β concentrations on the first postnatal day may predict later occurrence of NEC.
- Hematological abnormalities such as thrombocytopenia, disseminated intravascular coagulation, increased or decreased neutrophil counts, eosinophilia, and anemia occur frequently in infants with NEC.
- In a premature infant with feeding intolerance, an acute drop in peripheral blood monocyte concentrations compared with the last presymptomatic blood counts may be an early indicator of NEC.

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INTRODUCTION

Necrotizing enterocolitis (NEC) is a devastating inflammatory condition of the gastrointestinal disease that afflicts 4% to 11% of very low birth weight infants and is a leading cause of morbidity and mortality in this population.[1–3] The pathogenesis of NEC is complex and is not well understood. Clinical studies associate NEC with diverse prenatal and postnatal factors, such as placental insufficiency, prolonged/premature rupture of membranes, chorioamnionitis, gut ischemia, altered bacterial colonization, viral infections of the gastrointestinal tract, bacterial overgrowth, and red blood cell (RBC) transfusions.[1,2] Although a unifying mechanism may not be readily evident in all the risk factors of NEC, some of these conditions presumably alter/disrupt the intestinal epithelial barrier to allow bacterial translocation from the lumen into the subepithelial lamina propria, where these bacteria or their products trigger an exaggerated, damaging mucosal inflammatory reaction.[1,4] In severe intestinal injury, bacterial products and/or the inflammatory mediators may spill into the bloodstream, causing a systemic inflammatory response and multiorgan dysfunction.[5] In this article, we review the immunologic aspects of the pathogenesis of NEC and its hematological manifestations. A literature search was performed using the databases PubMed, EMBASE, and Scopus. To minimize bias, keywords from PubMed's Medical Subject Heading (MeSH) thesaurus were shortlisted before the actual search and combined with text words likely to be used in titles and abstracts.

IMMUNOLOGIC ASPECTS OF NECROTIZING ENTEROCOLITIS

Mucosal Sensitivity to Bacterial Products in the Premature Intestine

Several lines of evidence indicate that luminal bacteria play a central pathophysiological role in NEC: (1) bacterial overgrowth, and *pneumatosis intestinalis*, the accumulation of gaseous products of bacterial fermentation in the bowel wall, are prominent histopathological findings in NEC; (2) ischemic intestinal injury in the sterile in utero microenvironment may cause strictures or atresia, whereas similar insults after postnatal bacterial colonization may increase the risk of NEC[6]; (3) enteral antibiotics can reduce the incidence of NEC and NEC-related mortality.[7] Although specific bacterial species have not been causally associated with NEC, infants who go on to develop NEC often display a microbial imbalance ("dysbiosis") with abnormal abundance of gammaproteobacteria (Enterobacteriaceae and Pseudomonadaceae) and *Clostridia*, but with fewer Firmicutes, the dominant Gram-positive bacterial phylum in infants who do not develop NEC.[8,9] Gammaproteobacteria express lipopolysaccharides and other products that have unique microbial-associated molecular patterns, which engage with the Toll-like receptors (TLRs) on mucosal cells to activate downstream inflammatory signaling. As discussed in the following section, the developing intestine is at risk of inflammatory injury because of 2 major factors: (1) the epithelium and mucosal immune cells in the developing intestine are uniquely sensitive to bacterial products, and (2) a paucity of adaptive mechanisms that normally limit the interaction of luminal bacteria with the mucosa.

Intestinal Epithelium

Fetal intestinal epithelial cells (IECs) express a variety of innate response receptors and display a "hyperactive" TLR-activated transcriptional program, which manifests with exaggerated expression of cytokines and inflammatory mediators.[10–15] This epithelial sensitivity to bacterial products correlates with high levels of expression of TLR2, TLR4, downstream adaptors such as the myeloid differentiation primary response gene 88, and tumor necrosis factor receptor-associated factor 6, and the