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REVIEW ARTICLE

Necrotizing Enterocolitis: Old Problem with New Hope

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The incidence of necrotizing enterocolitis (NEC) and mortality rate associated with this disease are not decreasing despite more than three decades of intensive research investigation and advances in neonatal intensive care. Although the etiology of NEC is not clearly elucidated, the most accepted hypothesis at present is that enteral feeding in the presence of intestinal hypoxia-ischemia-reperfusion, and colonization with pathogens provokes an inappropriately accentuated inflammatory response by the immature intestinal epithelial cells of the preterm neonate. However, delayed colonization of commensal flora with dysbiotic flora with a predominance of pathologic microorganisms plays a fundamental role in the pathogenesis of NEC. Recent studies have further identified that NEC infants have less diverse flora compared to age-matched controls without NEC. Increased gastric residual volume may be an early sign of NEC. An absolute neutrophil count of $<1.5 \times 10^9$/L and platelets below 100×10^9/L are associated with an increased risk for mortality and gastrointestinal morbidity. Nonspecific supportive medical management should be initiated promptly. Sudden changes in vital signs such as tachycardia or impending shock may indicate perforation. A recent meta-analysis investigating using probiotics for prevention of NEC with a total of 2176 preterm very low birth weight infants found a success rate of just 1/25. Careful monitoring of the residual volume, and of serious changes in hemograms and vital signs may help in early diagnosis and prediction of when to perform medical or early surgical intervention. In term of prevention, administration of oral probiotics containing *Bifidobacterium* and *Lactobacillus* is a simple and safe method that attempts to early establish of commensal flora balance to inhibit pathogenic flora and an inflammatory response.

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1. Introduction

Necrotizing enterocolitis (NEC), an acute inflammatory necrosis of the intestinal tract, is the most common acquired gastrointestinal and surgical emergency for preterm very low-birth weight (VLBW) infants in the neonatal intensive care unit (NICU).[1] Despite more than three decades of intensive research investigation, little progress has been made in the prevention and treatment of NEC; in fact, despite advances in NICU care throughout the world, the incidence and mortality associated with this disease is not decreasing.[2,3]

2. Epidemiology

The incidence of NEC is inversely proportional to birth weight (BW), with NEC affecting 11.5% of infants weighing 401 to 750 g, 9% of infants weighing 751 to 1000 g, 6% of infants weighing 1001 to 1250 g, and 4% of infants weighing 1251 to 1500 g.[4] Two sets of national data showed that the incidence of NEC was relatively low in Taiwan (about 7%)[5,6]; however, since fatality is a competing variable for NEC, true incidence might be underestimated because the mortality rate for VLBW infants was higher in Taiwan than in the USA.

3. Etiology and pathogenesis

NEC is a complex disease and the etiology has not been clearly elucidated. Multiple factors appear to contribute to the pathogenesis:immaturity of multiple intestinal functions includes gastrointestinal dysmotility, impaired digestive capacity, altered regulation of intestinal blood flow, barrier dysfunction, altered anti-inflammatory control, and impaired host defense. It has been shown in experimental systems that feeding, intestinal ischemia, and bacteria could cause mucosal injury,[7–9] and in preterm infants with an altered pattern of bacterial colonization,[10] provoke an inappropriate accentuated proinflammatory response that results in inflammatory necrosis of the bowel,[11] and in some cases, the systemic inflammatory response syndrome.[12,13]

It has been suggested that an unfavorable balance between commensal and pathogenic bacteria is present in the VLBW intestinal tract, and that this triggers a series of cellular events that results in the pathogenesis of NEC.[14,15] More recent studies using high-throughput molecular techniques have identified differences in the diversity of organisms present, and in one report it appeared that NEC patients had lower diversity compared to age-matched controls without NEC.[16]

Commensal bacteria can regulate the expression of genes important for barrier function, digestion, and angiogenesis.[17] *In vitro* studies have demonstrated that many species of commensal bacteria have the ability to dampen the inflammatory response through inhibition of the transcription factor nuclear factor kappa-B (NF-kB).[18,19] Endotoxin is known to bind to and activate Toll-like receptor 4 (TLR4), and TLR4 mRNA expression has been documented in fetal human intestine[20] and is increased in formula-fed and hypoxia-stressed rats.[21] When lipopolysaccharide binds to TLR4, a series of chaperone and signal transduction molecules are activated, which result in NF-kB translocation from cytoplasm to the nucleus where this important transcription factor activates the gene expression of multiple proinflammatory cytokines.[22] Following the activation of proinflammatory gene expression, multiple changes occur in neonatal intestine, including accentuated apoptosis of epithelial cells, perturbation of tight junctional proteins and complexes, increased mucosal permeability, bacterial translocation, alterations of vascular tone and microcirculation, and additional neutrophil infiltration and accumulation.[23–27] Thus,dysbiotic flora with a predominance of pathologic microorganisms plays a fundamental role in the pathology of NEC; animal studies have shown that severe NEC could not be induced without the pathologic flora.[28] It is likely that the balance of pro- and anti-inflammatory signaling is critical in maintaining intestinal homeostasis. Nonetheless, it is hypothesized that the immature intestine responds to injury with excessive inflammation and that this contributes to the final common pathway in the pathogenesis of NEC.[29,30] Many pro- and anti-inflammatory mediators are involved in the pathogenesis of NEC based on animal or human studies. Proinflammatory compounds that are up regulated in NEC include platelet activating factor, tumor necrosis factor, nitric oxide, interleukins (IL), such as IL-1β, IL-6, IL-8, IL-12, and IL-18, and endothelin-1, leukotrienes, thromboxanes, and oxygen-free radicals.[31–39] Several anti-inflammatory compounds down regulate intestinal inflammation and these include prostacyclin, nitric oxide, several growth factors such as epidermal growth factor, heparin-binding epidermal growth factor, and insulin-like growth factor, erythropoietin, IL-11, glutamine, and arginine.[40–45] In addition, animal studies have shown that neonates have an impaired ability to prevent NF-kB from entering the nucleus in intestinal epithelial cells and activating the production of multiple downstream proinflammatory mediators.[17–19] In summary, these results suggest that the neonatal balance of the inflammatory response may be weighted towards the proinflammatory side and more likely to result in the pathologic outcome of NEC.

4. Diagnosis

Diagnosis of NEC is suspected when the characteristic clinical features of abdominal distention, increased gastric residual volume or frank emesis, and rectal bleeding are present, and is confirmed by abdominal radiographic evidence of pneumatosis intestinalis or portal venous air. Increased residual gastric volume might be an early sign of NEC. Radiological findings vary by gestational age; intramural gas was detected in infants of $\geq$37 weeks' gestational age with NEC, but was only present in 29% of those of $\leq$26 weeks' gestational age.[46] Abdominal ultrasonography is a newer technique to aid in the diagnosis of NEC[47] and may be more sensitive than abdominal radiography in detecting bowel necrosis and alterations in bowel wall perfusion as confirmed at laparotomy.[48] The sonographic findings include central echogenic focus of bowel wall and a hypoechoic rim (the pseudo-kidney sign) that indicate necrotic bowel and imminent perforation. Ultrasonography also can