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Research Progress on High-Risk Factors of NEC

Hao He, Jianhong Liu, Xiaoqian Yi, Xiaofang Zhu

Department of Neonatology, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
Email: 314226634@qq.com

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Abstract

Necrotizing enterocolitis (NEC) in newborns is one of the life-threatening diseases. With the continuous advancement of perinatal medicine and neonatal intensive care technology, NEC has been on the rise year by year. The etiology of NEC is not yet clear, and it may be the result of multiple risk factors working together, such as premature birth, infection, formula feeding, ischemia, hypoxia, dysbiosis of intestinal flora, and immune damage. Additionally, recent reports have documented factors such as immunoglobulin treatment for hemolytic jaundice, blood transfusion therapy, and rapid achievement of adequate feeding. This article comprehensively analyzes the current research progress on high-risk factors of NEC, and provides a reference for future prevention, diagnosis, and treatment directions.

Keywords

NICU, NEC, Preterm, High Risk Factor

1. Introduction

Neonatal necrotizing enterocolitis (NEC) is a serious life-threatening disease in newborns. It is characterized by intestinal injury, systemic inflammation and multisystem organ failure. In severe preterm newborns, NEC often occurs in the fourth week of life. In neonates born close to term, the onset of the disease usually occurs in the first week of life. The lower the birth weight, the greater the risk of NEC [1]. According to the NICHD in the United States, the incidence of NEC in live births is 0.3 to 2.4 per 1000 live births; 70% of these births are preterm; approximately 1/2 of patients require surgical intervention; and morbidity and mortality account for 20% to 30% of morbidity. Clinical manifestations of NEC are variable and can range from subtle progression to severe. Manifestations may include temperature fluctuations, lethargy, episodes of apnea, bradycardia, hypotension, and poor glucose homeostasis. Early symptoms of NEC can be easily

confused with sepsis. Complicated gastrointestinal symptoms may include bloating, bloody stools, gastric retention, or vomiting. Physical examination may reveal significant abdominal distension and tenderness. In more severe cases, an abdominal mass may be palpable, indicating the presence of fixed intestinal collaterals. Laboratory tests, however, are not significantly specific and include thrombocytopenia, metabolic acidosis (including elevated lactate levels), neutropenia, increased white blood cell counts, and elevated ultrasensitive C-reactive protein and calcitoninogen [1].

There are many risk factors affecting NEC, with preterm labor, low birth weight, infections, and formula feeding usually considered to be the main risk factors [2]. However, in recent years, as the perinatal mortality rate of low-birth-weight infants continues to decrease, the incidence of NEC has gradually increased. National and international studies have found that an increasing number of risk factors have an impact on the occurrence of NEC. And there may be differences in NEC risk factors between very preterm and near-preterm infants [3].

2. Prenatal High-Risk Factors

2.1. The Impact of Premature Birth on NEC

Preterm birth is the greatest risk factor for NEC, especially in very preterm infants and those with very low birth weights. NEC is more likely to occur because of the immaturity of the immune defense system, including intestinal motility, digestion, intestinal barrier function, and intestinal immunomodulation. The adaptive immune system usually plays an important role in regulating innate immunity. However, all preterm infants are born with an immature adaptive immune system, which is more likely to lead to intestinal inflammatory responses [4]. In recent years, an increasing number of studies have suggested that there may be differences in risk factors and pathogenesis between very preterm and near-preterm infants.

2.2. The Impact of Intrauterine Growth Retardation (IUGR) on NEC

Bowel dysfunction is a major source of neonatal morbidity and mortality. Recent studies have shown that infants with developmental delays are at higher risk for abnormal prenatal Doppler flow velocities. NEC is more likely to occur when fetal descending aortic or umbilical artery blood flow velocity slows down during diastole [5]. It has been shown that preterm infants with intrauterine growth retardation have a significant difference in the loss or reversal of umbilical artery end-diastolic flow and are 2.13 times more likely to develop NEC than normal [6]. The possible reason for this is the redistribution of blood flow to ensure the supply of vital organs, leading to intestinal ischemic-hypoxic injury and clinical manifestations of delayed attainment of adequate feeding, feeding intolerance and NEC.

2.3. Impact of Meconium Contamination on NEC

There has been controversy about whether the uterus is sterile prior to delivery

[7]. If the uterus is in a sterile environment, the meconium will also be sterile. However, studies have shown the presence of microbial DNA in the meconium of healthy infants [8]. The route of transmission of microorganisms in the meconium is unknown and may be acquired through maternal intestinal transit or in certain types of circulating antigen-presenting cells [9]. The gut microbiota may be present during the development of the mucosal immune system. These microorganisms may also play a role in innate immunity by modulating the fetal inflammatory response. It is well known that the intestinal mucosa is highly immunoreactive during fetal life and can cause severe inflammatory responses when the fetus is re-exposed to inflammatory mediators after birth. Therefore, intrauterine meconium contamination has an impact on the development of postnatal NEC.

2.4. The Effect of Chorioamnionitis on NEC

Most preterm deliveries are associated with chorioamnionitis (an inflammation of the placenta and fetal membranes). It can be diagnosed after delivery by histologic examination of the placenta. Chorioamnionitis can lead to postpartum inflammation, including sepsis and congenital pneumonia, but the association with NEC is unknown. Several studies have reported an association between chorioamnionitis and NEC, suggesting an increased risk of NEC in newborns [10].

3. High Risk Factors during Childbirth

3.1. The Impact of Cesarean Section on NEC

Approximately 60% of very preterm births are born via cesarean section. Normal infant intestinal colonization occurs during vaginal delivery, due to direct exposure to maternal vaginal and intestinal flora. In contrast, during cesarean delivery the fetus does not pass through the birth canal, which results in a less diverse gut flora, and the dominant flora may be more susceptible to NEC. Cesarean delivery has been shown to be positively associated with the development of NEC in <31W preterm infants. However, there was no difference between elective and natural deliveries [11].

3.2. The Impact of Neonatal Asphyxia on NEC

During labor asphyxia and hypoxia, the body's protective reflex (diving reflex) is elicited, redistributing blood to ensure blood supply to vital airways such as the brain and heart. Blood supply to the gastrointestinal tract is drastically reduced and mesenteric arterial blood flow is slowed down; hypoxia also leads to the release of free radicals and disruption of local NO synthesis homeostasis, which makes it more likely to cause organ damage.

4. Postpartum High-Risk Factors

4.1. The Impact of Anemia on NEC

Anemia reduces intestinal perfusion and impairs oxygen delivery, leading to

intestinal hypoxia and mucosal damage [12]. In addition, anemia disrupts the normal intestinal vascular autoregulatory system and is more likely to cause intestinal ischemic injury [13]. Studies have shown that anemic intestinal mucosa has an inflammatory state with macrophage infiltration. Anemia increases the risk of NEC. In addition to anemia, red blood cell transfusion (RBCT) may also be involved in the worsening of NEC. During RBCT, blood flows into the intestinal tract, resulting in a sudden increase in blood viscosity and exacerbating intestinal damage [12]. During storage, the affinity of erythrocytes for oxygen increases, leading to a leftward shift in the oxygen ionization curve of the receptor, making the receptor more susceptible to ischemia and hypoxia [14]. More importantly, the biological activity of nitric oxide in erythrocytes is rapidly lost during storage, which impairs the ability of erythrocytes to diastole hypoxic blood vessels, leading to intestinal vasoconstriction and ischemic injury [15].

4.2. The Impact of Gastrointestinal Food Allergies on NEC

Gastrointestinal food allergy (FA) in children mostly occurs between 1 and 6 months after birth [16]. However, in recent years, the incidence of neonatal FA has been increasing year by year. Neonatal FA may require clinical differentiation from NEC, and the development of necrotizing enterocolitis (NEC) from neonatal FA is extremely rare. However, the role of FA as a risk factor for NEC is unknown. Early diagnosis and targeted treatment of patients with FA is difficult, and the initial strategy is to repeat a detailed clinical examination and conservative treatment. However, if FA progresses to NEC, the decision to perform exploratory open surgery remains a clinical dilemma. There are case reports of neonatal FA still requiring open surgical treatment due to secondary NEC. Moreover, it has been suggested that FA has the risk of affecting NEC [17].

4.3. Impact of Patent Ductus Arteriosus (PDA) on NEC

More than 30% of very low birth weight infants have PDA, and the percentage of PDA in preterm infants under 29 weeks can be as high as 60% [18]. PDA is also one of the risk factors for NEC. Its pathogenesis is due to the shunting of cardiac diastolic blood through the pulmonary artery conduit, resulting in reduced mesenteric artery blood flow and a low perfusion state of the intestine, leading to intestinal ischemia and hypoxic injury. Studies have shown that PDA increases the risk of NEC. However, there is no difference in the incidence of NEC between PDA with and without indomethacin [19].

4.4. The Impact of Acid Suppression Therapy on NEC

Acid suppression therapy has a negative impact on the gut microbiota of preterm infants [20]. Acid suppression therapy not only reduces microbial diversity but also increases bacterial species associated with NEC such as Aspergillus phylum [21]. In preterm infants, gastric acid inhibitors have an increased risk of NEC. Some early clinical studies abroad have also shown the benefits of enteral

supplementation with hydrochloric acid (HCl) [20]. Although HCl therapy is not currently recommended for prophylaxis. If one is alert to neonatal necrotizing small bowel colitis NEC, acid suppression therapy should be avoided.

4.5. The Impact of Probiotics on NEC

Probiotics may modulate innate adaptive immune pathways by upregulating cytoprotective genes, downregulating pro-inflammatory genes, producing short-chain fatty acids, and supporting barrier function and maturation. Probiotics have been shown to have a beneficial effect on the incidence of NEC in preterm infants. However, safety concerns remain regarding probiotic strain selection, dosage, and age of initiation (including bacterial probiotic strains and dosage). Nevertheless, most foreign medical organizations continue to support the use of probiotic supplements in clinical practice to reduce the risk of NEC.

4.6. The Impact of Breastfeeding and Formula Feeding on NEC

Breastfeeding has been shown to reduce the risk of NEC [22]. During pregnancy, the mother transfers immunoglobulin G (IgG) through the placenta. After birth, placental IgG transfer is interrupted and immune function is maintained primarily through IgG in breast milk [23]. Breast milk contains antimicrobial and anti-inflammatory factors that provide protection and promote intestinal maturation in newborns [24]. Oligosaccharides in breast milk are indigestible and promote the growth of the gut microbiota [25]. Casein in breast milk promotes the production of stimulatory mucins that help protect the intestinal barrier [26]. Triglycerides in breast milk have been shown to have antiviral effects [27]. In addition, breast milk contains bioactive proteins such as lactoferrin, which has antibacterial and antifungal activity, and lysozyme, which has antimicrobial activity. Together, these two proteins can destroy Gram-negative bacteria [28]. A meta-analysis evaluated randomized or semi-randomized controlled trials comparing formula-feeding of preterm infants with donor breastfeeding of preterm infants in terms of growth and development. Although formula-fed infants had better growth, there were no differences in neurodevelopmental outcomes or growth after hospital discharge; however, formula feeding increased the risk of NEC with a risk ratio of 2.77 [29].

4.7. Effects of Long-Term Broad-Spectrum Antibiotics on NEC

Prolonged use of broad-spectrum antibiotics leads to a reduction in gut microbial diversity, promotes the growth of pathogenic bacteria, and may trigger an inflammatory response in the gut. In culture-negative infants, exposure to antibiotics for more than 10 days leads to a nearly threefold increase in the risk of NEC [30]. In addition, one study showed that substituting ceftazidime for gentamicin during the first three weeks of life was associated with a higher risk of death. Based on the evidence from these studies, not only is the administration of empiric antimicrobials limited to 48 hours, but clinically feasible narrow-spectrum drugs may also

be used if blood cultures are negative and the infant is clinically stable [31].

4.8. The Impact of Congenital Heart Disease on NEC

Congenital left ventricular dysfunction can occur in neonates at full-term gestation but may also occur in preterm infants secondary to cardiac-induced ischemic intestinal necrosis, with the colon being the most common site of involvement. Underdeveloped left heart syndrome, truncus arteriosus, aortic arch obstruction and aortopulmonary artery can lead to most cardiogenic ischemic intestinal necrosis [32]. Several case reports have shown an association between supraventricular tachycardia and necrotizing small bowel colitis. Supraventricular tachycardia may lead to ischemic and hypoxic changes in the bowel, which progresses to NEC. however, some studies have shown no association between necrotizing small bowel colitis and supraventricular tachycardia. Further multicenter studies are needed to test whether there is a significant association between supraventricular

Table 1. High risk and etiopathogenesis of NEC.

	Etiopathogenesis
Prenatal risk factors:	
Preterm birth	Immature intestinal peristalsis, digestive function, intestinal barrier function, and intestinal immune regulation
Intrauterine growth retardation	Redistribution of blood flow to ensure supply to vital organs leads to intestinal ischemia and hypoxic injury
Meconium contamination	Causes an intense inflammatory response in the intestinal tract
Chorioamnionitis	Leads to postnatal inflammation including sepsis, congenital pneumonia
High risk factors during childbirth:	
Cesarean section	Influence on the diversity of intestinal flora
Neonatal asphyxia	Protective reflex (diving reflex), blood redistribution leading to intestinal ischemia and hypoxia
Postpartum high-risk factors :	
Anemic	Decreased intestinal blood perfusion; anemic intestinal mucosa has an inflammatory state with macrophage infiltration
Patent ductus arteriosus	Blood shunts away through the pulmonary artery conduit, leading to a state of intestinal hypoperfusion
Acid suppression therapy	Decreased microbial diversity and also increased NEC-associated bacterial species
No probiotics used	Probiotics have up-regulated cytoprotective genes and down-regulated pro-inflammatory genes to promote intestinal barrier function and maturation
Non-breastfeeding	Breast milk contains antimicrobial and anti-inflammatory factors that protect and promote the maturation of the newborn's intestinal tract
Long-term broad-spectrum antibiotics	Leads to a decrease in gut microbial diversity and promotes the growth of pathogenic bacteria
Congenital heart disease	Causes cardiogenic ischemic intestinal necrosis

tachycardia and the development of necrotizing small bowel colitis [33]. Cyanotic congenital heart disease is characterized by coarctation of the aorta, pulmonary atresia, and transposition of the great arteries. Treatment is prostaglandin infusion, umbilical vein catheterization, cardiac surgery and percutaneous interventional catheterization. Some studies have shown a higher frequency of NEC in infants undergoing palliative surgery or prolonged prostaglandin withdrawal compared to infants with complete surgical repair [34].

Although NEC has received increased attention and focus from NICU physicians in recent years, it remains unavoidable. Incorporating parental perspectives into the diagnosis and treatment of the disease may become an important driver of progression. Early on, parents often lack awareness of the risk factors and prognosis associated with NEC. It is only when a child is actually diagnosed that parents truly understand NEC and its severity. This lack of information and diagnostic uncertainty creates a tremendous amount of stress for families. Once NEC occurs, the inability to improve the prognosis creates a strong sense of helplessness, dissatisfaction, and frustration among the patient's family and clinicians. Grading the high-risk of NEC (**Table 1**) would facilitate the diagnosis and treatment of NEC in infants. Thus, early identification of high-risk factors allows for rapid intervention before disease onset. The participation and full cooperation of the patient's family members will facilitate research on high-risk NEC and will help to promote the development of NEC diagnosis and treatment and its integration into clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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