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Review Article

Necrotizing enterocolitis: a complication of prematurity. Its pathogenesis, prevention and management

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Abstract

One of the most severe gastrointestinal illness that occur in newborns is neonatal necrotizing enterocolitis (NEC). This puzzling disease remains a challenge for neonatologists around the globe with uncertain definite etiology along with extremely high mortality and morbidity.

Keywords: Neonatal necrotizing enterocolitis, low birth weight, preterm, complications, managements.

Introduction

NEC typically occurs in premature, formula-fed babies during the second to the fifth week of life. It is characterized by variable damage to the intestinal tract, ranging from mucosal injury to full-thickness necrosis and perforation. The risk is inversely proportional to gestational age and weight at birth. Paltauf first described the condition in 1888 but the term "necrotizing enterocolitis" was used for the first time by Schmid and Quaiser in 1953[1].

Epidemiology

The incidence in the population as a whole is estimated to be between one to three cases per 1000 live births. However, NEC occurs in 2–5% of very low birth weight infants [VLBW] and in 1–8% of neonatal intensive care unit admissions [NICU] [2].

Risk Factors

In regards to NEC etiology, many prospective risk factors have been investigated; however, the definite etiology still eludes contemporary medical research. No single factor may be adequate to precipitate NEC. Low birth weight and prematurity are recognized as one of NEC's most significant risk variables [3].The occurrence of NEC in the exclusively formula-fed group were 6-10 times higher than those for breast milk alone and 3 times higher than those for breast milk and formula mixtures[4].

Anemia is linked to an enhanced danger of developing NEC. Blau et al also found that a trigger for NEC could be a neonatal transfusion of packed red blood cells [5]. Polycythemia is commonly considered as an important risk factor, and current guidelines recommend timely diagnosis and management to prevent unfavorable outcomes [6]. Ververidis et al. in his study concluded that a low platelet count or a sudden drop in platelets was a poor prognostic indicator [7]. While thrombocytosis appears to be a risk factor as it induces a thrombogenicity state that may impede the flow of mesenteric blood, but thrombocytopenia is perhaps more useful as a prognostic indicator.

A risk factor for NEC is dehydration. It increases the blood viscosity when severe, and has been shown to decreases mesenteric perfusion which may therefore precipitate NEC [8]. Hypotension requiring inotropic therapy is regarded as an independent risk factor for NEC within a week of life. The circulatory collapse may affect the gastrointestinal blood flow in the first week of life, leading to a higher incidence of NEC [9].

The level to which umbilical catheterization is possibly a risk factor for the development of necrotizing enterocolitis has conflicting reports. An early study showed impairment in mesenteric blood flow associated with insertion of the umbilical catheter [10]. Other trials, however, have shown the contrary to be true [11].

The evidence of congenital persistent ductus arteriosus [PDA] as a cause of NEC is well established, and several prospective studies have confirmed it. The shunt from left to right that happens in PDA results in reduced mesenteric blood flow velocity. The intestinal mucosa has high metabolic activity and needs about 80% of total blood flow through the intestine. When this is reduced, it increases the vulnerability of the intestinal immune barrier functions.

Perinatal indomethacin exposure has been documented in children with VLBW as a risk factor for intestinal injury [12]. However, other studies have not been able to support these claims [13].

A recent retrospective study found the association of extended use [over five days] of antibiotic therapy and increased threat of NEC [14]. Antibiotic use in premature infants for five days or less has been carefully evaluated in a big RCT, and there was no rise in incidence of NEC between the control and the study group [15]. The isolation of strains of E. coli and Clostridia during the epidemics of NEC along with improvement in attack rate following rigid infection control measures validate the role of infection in the pathogenesis of NEC [16].

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Maternal factors: Chronic fetal hypoxia and IUGR can result from an unfavorable intrauterine situation. This may lead to a diversion of cardiac output from the gut that may precipitate necrotizing enterocolitis. Thirty five % of babies whose mothers had premature rupture of membrane developed NEC, while only 21% of children whose mothers had no PROM developed NEC. Maternal hypertension is a threat factor [17].

Factors Making Premature Infant's Gut Susceptible to NEC

Reduced peristalsis, mucus layer deficiency and abnormal lipid structure in the cell wall make the premature gut more permeable. It is also associated with delayed or altered bacterial colonization and paucity of anaerobic bacteria. Decreased production of gastric acid, reduced concentrations of lactase, inadequate bile acids to form appropriate micelles of bile make the premature infant's gut susceptible to NEC [18].

Pathogenesis

An ischemic or toxic event that causes damage to the immature gastrointestinal mucosa with loss of mucosal integrity is thought to precede the process leading to NEC. The initiation of enteral feedings enables gas-producing bacteria to proliferate and invade the damaged mucosa. This process may lead to necrosis which can cause either perforation of the bowel or sepsis [19].

Pathophysiologic Mediator

Essential elements in modulating the damage that results from NEC are the inflammatory cytokines interleukin 1, 3, 6, tumor necrosis factor [TNF], and platelet activating factor [PAF]. [20]. Ischemia causes free oxygen radicals to accumulate and during the reperfusion phase, there is a burst of superoxide release, which causes further tissue damage [21].

Preventive Strategies

Effect of Human Milk

Secretory IgA, lysozyme, oligosaccharides, polyunsaturated fatty acids, and platelet activating factor (PAF)-acetyl hydrolase are non-nutrient elements of human milk. These elements contribute to the integrity, function, and immunity of GI mucosa against different GI diseases [22]. A decrease in infection-related morbidity in human milk-fed premature infants is well documented.

Cautious Advancement of Feeds

Henderson et al. proposed that trophic feeding and the rate of the advancement of feed volumes are important modifiable risk factors for NEC in premature infants [23]. Standardized slow enteral feeding [SSEF] was associated with a reduced risk of NEC relative to early enteral feeding [24]. Due to initial concerns that NEC may be associated with the rapid advancement of enteral feeding, many clinicians in the past have delayed initiating and slowed the rate of advancement of enteral feeding [25]. Based on the existing evidence, early feeding advances are secure and can be regarded as an option to minimal enteral nutrition in a clinically stable VLBW infant shortly after birth.

Trophic Feeding (Minimal Enteral Nutrition)

Based on the current evidence that the risk of NEC or intolerance to feeding is not increased by minimum enteral nutrition (trophic feeding), it may be regarded a safe option to complete fasting before progressive feeding increments. A minimal enteral feed is usually started within 1–3 days after birth with 15–20 ml/kg/day of enteral milk, given every 2–3 hours and continued for 5–7 days after birth without any advancement [18].

Standardized Feeding Regimens (SFR)

Delayed introduction of progressive feeds was described as an intention to advance feed quantities exceeding trophic feeds [up to 24 ml/kg/day] later than 5–7 days after birth, as compared to progressing feeds at less than four days after birth. It was observed that delayed progression of enteral feedings in preterm infants did not have a significant effect on the risk of NEC. Based on the current evidence, early feeding advances are safe and can be regarded as an option to minimal enteral nutrition in clinically stable VLBW infants soon after birth. Evidence indicates that both slow [15–20 ml/kg/day) and fast [30–35 ml/kg/day] advancement practices are safe and can be used in the preterm infants (especially larger VLBW infants) while advancing minimal enteral nutrition to full feeds [25]. Further study is required to determine the effect of slow versus fast feeding advancement on outcomes in the subset of smaller ELBW infants [<750g].

Relationship of Feeding Intolerance and NEC

Currently there is no evidence-based definition of feeding intolerance. A sudden rise in gastric residuals and abdominal distension may be an early sign of NEC, but are usually non-specific [26]. In the absence of other clinical or radiological evidence of NEC, the stable children may be provided with minimal enteral nutrition (trophic feed) while continuing to re-evaluate the infant at frequent intervals, rather than completely suspending enteral feeding.

Effect of Osmolality of Feeds on NEC

Studies had shown the association of increased incidence of NEC when hyperosmolar formula feedings were given above the currently recommended maximum osmolarity, [450 mOsm/kg] [27]. By adding supplements and other therapeutic additives, there occur a rises in osmolality of enteral feedings which may lead to delayed gastric emptying and risk of NEC.

Lactoferrin Supplementation

Lactoferrin, an antimicrobial glycoprotein present in colostrum and breast milk reduces the risk of NEC and invasive nosocomial infection in VLBW infants [18]. Further large trials are needed to investigate the effect of lactoferrin on the risk of NEC.

Prebiotics, Probiotics and Symbiotic

Oligosaccharides in human breast milk are regarded to be the prototype of prebiotics as they have been shown to promote the development of bifido bacteria and lactobacilli in the neonate breast-fed colon. It was proposed that enteral probiotic administration to premature newborns could prevent infections, prevent NEC and decrease antibiotic use [28]. The intestinal microbiota in preterm children has a low number of species compared to healthy, full-term babies, with typically only three bacterial species found at ten days of age [29]. The author found that in premature neonates, prebiotic-supplemented formula improved stool colony counts of bifidobacteria and lactobacilli [30]. Given current evidence relating to the efficacy of the use of particular prebiotics in preterm children are limited and

does not allow any conclusions to be drawn about the use of prebiotics in clinical exercise.

Markers for diagnosis

It is still challenging to recognize and diagnose early. For many years, scientists have been searching for various biomarkers such as cell surface antigens [neutrophil CD64], calprotectin, gut-specific proteins [intestinal fatty acid binding protein, I-FABP], and intestinal micorbiomes in plasma, urine, and stool samples [31]. To date, however, there is no ideal biomarker for screening, diagnosing NEC or predicting disease severity and guiding therapeutic management.

Signs and symptoms

The cornerstone of effective NEC therapy is based on an accurate diagnosis of the disease, which can generally be determined on the grounds of clinical, radiographic and laboratory information. In premature infants, the onset of NEC is seen during the first several weeks after birth, with the age of onset inversely related to gestational age at birth but onset may occur as late as age 1 month. The typical NEC neonate is a thriving, premature infant, but suddenly develops feeding intolerance, abdominal distension, bloody stools, and signs of sepsis. The modified Bell scoring system, which evaluates the degree of NEC severity as mild [Bell stage I], moderate [Bell stage II] and severe [Bell stage III], has been commonly used for disease stratification.

Diagnostic Considerations

Thrombocytopenia, metabolic acidosis, elevated C-reactive protein, leukopenia, positive blood cultures [30%] is seen in a patient with NEC, but these are non-specific parameters. Bowel wall thickening, persistent bowel loop, and overall gaseous distention are suspicious signs but are not specific. Diagnosis is usually made with findings of pneumatises intestinalis, portal venous gas in abdominal radiographs [32]. Pneumoperitoneum is a sign of intestinal perforation. However, it is seen in only 50–75% of all patients with bowel perforation secondary to NEC [32].

Medical Management

Patients with definitive NEC require medical therapies including bowel rest, gastric decompression, intravenous antibiotics, parenteral nutrition, and blood product transfusion when necessary. To define the ideal timing of surgical intervention, frequent clinical examination, and serial abdominal radiographs are required.

Surgical Management

About 20-40% of neonates with NEC develop advanced disease that requires operative treatment [33]. Surgical NEC is the leading cause of morbidity for preterm infants [32]. Pneumoperitoneum is considered an absolute indication for surgical intervention [32]. Relative indications for emergency surgical interference are clinical deterioration despite supportive care, persistent thrombocytopenia, or neutropenia, positive paracentesis, evidence of peritonitis, and intestinal obstruction [32].

Psychomotor Development

In the short-term follow-up, the ELBW babies with definite NEC [Stage 2 or 3] are at enhanced danger of neurodevelopmental delay influencing specifically psychomotor function. About 40 percent of NEC children were of short stature and in 85 percent mild to severe mental retardation was observed compared to about 50 percent of the controls [34].Failure to thrive in the ELBW population is commonly seen ranging from 40 to 70% of infants below the 10th percentile at follow-up [27, 28]. The etiology of this brain injury is unclear and likely multifactorial. Potential incriminating factors include hypoperfusion at the time of the insult, cytotoxic inflammatory mediator release during the systemic infections, stressful environmental conditions and poor postnatal growth [35].

Conclusions

This article highlights the challenges involved in neonatal intensive care. Necrotising enterocolitis has proved to be an extraordinarily enigmatic and morbid illness, the etiology of which is bound up in a medical literature minefield. There remain many potential risk factors for NEC; however, the extent to which these risk factors are important in the etiology of NEC remains unclear. It seems that no individual factor alone is sufficient to precipitate NEC pointing to a multifactorial etiology. With progressive research and knowledge in the future, we could create targeted therapies for people most vulnerable to NEC.

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