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Seminars in Perinatology

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Necrotizing: A historical perspective

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ARTICLE INFO

Keywords:
NEC
human milk
microbiome
intestinal ischemia

ABSTRACT

Necrotizing enterocolitis is a devastating disease afflicting premature infants, though after 50 years of investigation, the pathophysiology remains elusive. This report describes the possible etiologic factors from a historical perspective, and outlines the importance of human milk, intestinal blood flow, and intestinal blood flow changes from a developmental perspective over the last 40-50 years

Introduction

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease that primarily afflicts premature infants and results in significant morbidity and mortality. The understanding of this unique condition has grown slowly over the past 50 years; though the basic tenets were established over 40 years ago when astute clinicians identified the increased risk in preterm infants having previously been fed, a role for intestinal bacteria, and a contribution from gut ischemia. At that time, it was suggested that endotoxin initiated an inflammatory response that resulted in the perpetuation of severe disease, though the specific factors involved in this cascade had not yet been elucidated. This review will highlight the historical perspective on the clinical features of NEC, as well as identify components of enteral feedings, intestinal blood flow, and bacterial factors that have influenced our understanding, preventive approaches, and treatment for this complex condition.

Clinical features

In the early 1900s, several cases were reported of neonatal intestinal perforation without obstruction, with varying inclusion of stenosis, bands, adhesions, and atresias.[1] These were suspected to result from infection, and surgery was suggested with antibiotic (sulfanilamide) therapy to follow. In the 1940s, additional cases of "severe infectious enteritis" were identified, and Willi[2] described 62 cases and recommended the discontinuation of oral feedings while providing intravenous fluid resuscitation. In 1952, Schmid and Quaiser coined the term "necrotizing enterocolitis" to describe 85 infants who died in the first few months of life with intestinal necrosis, and while they searched for offending bacteria, no consistent infectious etiology was identified.[3,4] It should be noted that the vast majority of patients that were diagnosed with NEC at this time were full-term or near-term infants, and as more and more patients were observed with NEC, most had episodes of perinatal or post-natal asphyxia stress. In the 1960s and 1970s additional cases of NEC were observed, and as neonatal units became skilled in caring for slightly younger premature infants, the incidence of NEC continued to rise. During this time, the onset of NEC occurred early, with the median at 7 days of life (though with a wide range), the most common day at 3 days (the mode), and over time, this has changed dramatically.[5,6] A CDC report described 21 cases per 1000 NICU admissions, with a mortality rate of 40.5% and calculated 7600 cases per year in the United States.[7] A survey by Brown and Sweet[8] identified 23.8 cases per 1000 NICU admissions, with a mortality rate of 29.7% and predicted 3480 cases per year in the United States. Accumulating evidence from animal studies reinforced the importance of altered intestinal blood flow in

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http://dx.doi.org/10.1053/j.semperi.2016.09.012
0146-0005/

the pathogenesis of NEC, and a "multifactorial theory" was proposed that included the key risk factors of prematurity, altered intestinal blood flow, bacterial colonization, and enteral feeding. While much remained to be discovered, by the 1970s, the framework for our current understanding of NEC was already established.

Impact of enteral feeding

From the early days, physicians and scientists hypothesized that enteral feedings could initiate or perpetuate intestinal injury observed in patients with NEC. Some of the early writings suggested cessation of enteral feedings in patients with gastrointestinal symptoms to treat or prevent NEC. Subsequent observations revealed that the vast majority of patients with NEC had received enteral feedings.[9] Small studies in the 1970s suggested that hyperosmolar feedings could contribute to mucosal injury and yet, into the 1980s, high osmolar formula preparations were no longer utilized.[10] Nonetheless, today we continue to add multiple supplements and medications into the enteral feedings for premature infants, and these are known to dramatically increase the osmolality of the material.[11] It has been suggested that this increased osmolarity is measurable in vitro, yet when the feedings reach the intestinal tract, the in vivo osmolarity has decreased to normal ranges after equilibration has occurred following osmosis, facilitated diffusion, and active transport of chemical compounds. For these reasons, it seems unlikely that hyperosmolar stress contributes significantly to the development of NEC in recent years.

In the 1960s and 1970s, when NEC was occurring in neonates that were less premature than many who currently develop the disease, it was reasoned that increased feeding volumes and caloric strength might contribute to the initiation of the disease. Brown and Sweet[8] at Mount Sinai Hospital in New York published a lengthy description of a strict enteral feeding regimen that significantly reduced the development of NEC in their experience. Using this protocol, they described a 4-year cohort, including 2557 infants with 932 low birth weight (74% weighed between 1500 and 2500 g), and only 1 developed clinical evidence of NEC. In contrast, during the previous 3 years, they observed 14 cases of NEC amongst 1745 low birth weight infants, and concluded that alteration of the feeding protocol would be necessary to reduce the risk of disease. Although no statistical comparisons were performed in the original report, using Fisher's exact test, the reduced incidence of NEC was statistically significant with a $p = 0.026$. In addition, the investigators concluded that the reduction of disease was so impactful, that a prospective randomized trial could not be performed, since ethically it would not be appropriate to expose babies any further to the risk of "aggressive" feedings. They hypothesized that it would be impossible to eliminate episodes of bowel ischemia that also may contribute to NEC, so that careful, strict feeding regimens would be a rational approach to prevent the disease. The regimen was based on personal observations over several years, and infants that experienced perinatal distress were made NPO for the first 5–7 days. Thereafter, babies began on water, advanced to half strength formula/milk, and after 1 week, advanced further to full strength formula/milk supplementation. In addition, they began on low-feeding volumes, and advanced slowly over the next 10–14 days to full-volume feedings, with typical increases of less than 10 ml/kg/day during this period. For any babies that developed significant symptoms or signs, including apnea and bradycardia, emesis, abdominal distention, or bloody stools, feedings were held for another week, and the protocol was then resumed as previously followed. This protocol worked well for these physician–investigators, and additional neonatal units adapted the protocol and described a significant reduction in cases of NEC. Nonetheless, as more premature infants with lower gestational ages and more extremely low birth weight infants were surviving the initial neonatal experience over the ensuing years, more and more patients were developing symptoms and signs of NEC. Into the current millenium, epidemiologic observations demonstrated that approximately 7–10% of babies born weighing less than 1500 g developed disease, with significantly higher rates in babies born weighing less than 1000 g.[12] During this time, there seemed to be less confidence that a strict and careful feeding regimen could limit or reduce the prevalence of NEC.

To better understand if altered feeding volumes could influence the initiation of NEC, a few randomized controlled trials were performed to clarify this conundrum. Based on the limited evidence, a meta-analysis was done that included 4 such trials, and concluded that compared to baseline feeding volume advancement (15–20 ml/kg/day), rapid advancement (30–35 ml/kg/day) did not increase the statistical risk of developing NEC, and faster feeding volumes allowed for more rapid weight gain and discharge.[13] Of interest, a study did demonstrate a statistically higher risk of NEC using more aggressive feeding schedules, and yet, no clear conclusions should be reached by the current data available.[14] In the "old" days, even before Brown and Sweet, rapid feeding advancements were even "more rapid", particularly for larger preterm infants around 2000–2500 g (approaching advancements of 50 ml/kg/day), and these regimens have not been prospectively studied for safety or efficacy. Therefore, neonatologists and dieticians should remain cautious but consistent in choosing feeding volumes, particularly for the highest-risk infants.

Role of human milk

It was suggested in the 1960s and 1970s that human milk could reduce the risk for NEC. Despite this contention, many cases of NEC were described in patients who received human milk either refrigerated, frozen, or pasteurized. A large, prospective trial compared human milk vs. infant formula in the United Kingdom and found that human milk resulted in lower rates of NEC compared to those receiving formula preparations at each gestational age strata.[15] For the patients that were prospectively randomized between human milk and formula, though the incidence of NEC was lower in the human milk fed group, the $p > 0.05$, and to date, for ethical reasons, there has not been another prospective, randomized trial comparing the 2 types of enteral feeding. Subsequent cohort and case–control studies have suggested human milk feedings lower the risk for NEC, with a range of reduction

from 2-fold to as much as 6-fold. Of interest, recent information demonstrates a dose–response relationship between total volume of human milk consumed with lower incidence of NEC or death.[16] Furthermore, in cases where mother's milk is unavailable, donor milk has been advocated, although there are no definitive trials to date demonstrating a reduced incidence of NEC using this strategy compared to cow's milk-based formula.[17] In support of these data, there have been many biochemical and animal studies in the last 50 years identifying key factors in human milk that might contribute to gut immunoprotection against NEC.[18] These include immunoglobulins (particularly IgA), growth factors, lysozyme, lactoferrin, polyunsaturated fatty acids, oligosaccharides, PAF-acetylhydrolase, cytokines, and even beneficial bacteria.[19–24] More recently, it has been suggested in some studies that the fortification added to human milk might contribute to the initiation of intestinal injury observed in NEC.[25] This hypothesis contends that cow's milk protein, which is present in bovine-based human milk fortifiers, can initiate an inflammatory response in the intestine thereby resulting in gut injury. Although difficult to prove, in vitro studies evaluating peripheral blood mononuclear cells collected from NEC patients produced more inflammatory cytokines compared to pbmc's collected from premature infants without NEC.[26] Interestingly, human milk contains multiple cow's milk proteins at varying concentrations, particularly in lactating women who consume dairy in their diet, so the true impact of cow's milk protein on the NEC cascade remains speculative. Further studies are needed to clarify the importance of cow's milk exposure on the initiation of NEC.

Role of ischemia and associated vascular factors

In the 1960s and 1970s it was hypothesized that significant perturbations in intestinal blood flow resulted in NEC. Touloukian et al.[27] developed animal models to mimic neonatal human conditions, and demonstrated that severe gut ischemia in rodents and dogs caused intestinal injury similar to the NEC. They described situations resembling the "dive reflex" where blood flow was diverted away from the intestine, allowing for sustained perfusion to the brain and heart, but ultimately resulting in intestinal injury. Additional studies showed that reperfusion injury was necessary for inflammatory necrosis of the intestine to occur,[28] and in a provocative clinical trial, it was shown that early PDA ligation could reduce the risk of NEC in extremely low birth weight infants.[29] Furthermore, it has been suggested that indwelling umbilical arterial catheters could compromise mesenteric blood flow and contribute to NEC, though prospective trials have not proven this hypothesis.[30,31]

Studies in the 1980s and 1990s by Nowicki et al.[32–35] identified unique alterations in neonatal intestinal blood flow autoregulation that might contribute to NEC, and additional work pinpointed key mediators in the cascade, including nitric oxide, endothelin, and many others. With the curious pathological findings of skip lesions that are characteristic of NEC cases particularly in the ELBW population, recent research efforts have focused on understanding perturbations in the intestinal microcirculation in these fragile infants, and these may ultimately help explain the unique pathology of this poorly understood condition.

Recent reports have suggested a temporal association between packed red blood cell transfusions and NEC in a significant number of cases. These studies describe the onset of disease within 48 h following the transfusion, and suggest a particularly aggressive form of NEC.[36–38] It is hypothesized that severe anemia may compromise intestinal blood flow and therefore initiate pathologic changes leading to intestinal necrosis. Nonetheless, conflicting reports have shown no association between NEC and transfusion, and it remains controversial whether this transfusion-associated NEC is a real entity in preterm infants.[39]

Role of bacteria

Bacteria have long been implicated as a critical factor in the initiation of NEC, and in fact, it was originally suspected that bacteria solely caused the disease in the 1940s and 1950s, even before the entity was identified and named. By the 1970s and 1980s, epidemics of NEC were described from various NICU's and were associated with a single bacterial pathogen, yet in most cases, the disease occurred sporadically without any specific offending bacteria.[40] In most cases of NEC, accompanying blood cultures remained negative, with only 30% of these cultures turning positive in large cohorts. By the 1990's, increasing evidence suggested that the microbiome of the preterm gut differed significantly from that of the full-term infant.[41] With the advent of non-culture based technology utilizing DNA approaches to better identify the microbiome in the 21st century, a wealth of knowledge has accumulated regarding the microbiome, and although several studies suggest alterations in gut flora in preterm patients with NEC, this topic will be described in detail in a subsequent articles.[42–44] Nonetheless, it is becoming clearer that NEC occurs in high-risk premature infants who harbor an altered intestinal microbiome and respond with an exaggerated pro-inflammatory signaling response.[45,46] Several reports identify alterations in anti-inflammatory down-regulation of the inflammatory response in preterm infants, and it is suggested that exaggerated pro-inflammatory signaling contributes to the intestinal necrosis unique in this population.[47–49] To that end, prospective trials have demonstrated a reduction in NEC in patients on preventive antibiotics and large numbers of trials have described a reduction in NEC using preventive probiotics.[50,51] These innovative approaches will be explored in depth in subsequent articles.

In summary, the understanding of neonatal NEC has evolved over the past 50 years, though the current state-of-the-art in 2016 fails to clearly define specific determinants that initiate the disease. As such, preventive approaches and efficacious treatments do not adequately control the incidence or untoward outcome of this complex and overwhelming condition.

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