Necrotizing Enterocolitis: The Future

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Abstract

Progress in our understanding of the pathophysiology, prevention and treatment of necrotizing enterocolitis (NEC) has been hampered for many reasons. Included among these is the fact that what we are calling “NEC” is likely to represent different disease processes, which need to be delineated before evaluating individual pathogenic mechanisms and attempting to develop predictive and diagnostic biomarkers. Treatment is also likely to be hampered because not all of the different entities called “NEC” will respond to the same regimen. In this review, some of these entities will be discussed in more detail, with suggestions for refining our approach toward improving methods for their diagnosis, prevention and treatment.

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Introduction

Necrotizing enterocolitis (NEC) is a disease seen primarily in preterm infants [1]. In some ways, NEC is a by-product of the successes experienced in neonatology wherein babies of low gestational age who would not have survived 30–40 years ago are now surviving. NEC has emerged as one of the most destructive diseases occurring

in neonatal intensive care. In addition to extremely high morbidity and mortality and high costs, long-term complications include strictures and adhesions of the intestine, cholestasis, short bowel syndrome, failure to thrive, and neurodevelopmental delay [2]. Unfortunately, not much progress has been made in its treatment or prevention [3]. When examining the literature, one might consider NEC to be a single, homogeneous entity, but it is becoming clear that NEC is several different diseases or endotypes [4]. In this review, the pathophysiology of some of these entities and how they differ from the more classic form of NEC will be summarized. A better understanding of these differences is critical to our ability to diagnose these entities early with the development of appropriate predictive and diagnostic biomarkers for the individual diseases. In addition to improved diagnosis, individualized preventative and treatment strategies can be improved. I will then briefly summarize the pathophysiology of each of these entities, raising some questions and commenting on how we might best proceed in the future in terms of improving our understanding, preventing and treating these entities we now call “NEC.”

Why So Many Studies and So Little Progress?

Over the past several decades, there seems to have been very little progress in our prevention or treatment of the disease we call “NEC” [3, 5]. One argument that can be made is that we are seeing a much greater survival of ex-

tremely preterm infants, who are also known to have a higher incidence of this disease [6]. Another argument is that we do not have a clear definition of this disease and the criteria used 40 years ago probably do not fit clearly into the present-day neonatal intensive care unit (NICU) care. For example, Bell's staging criteria developed in the late 1970s include 3 different stages. Stage 1 describes feeding intolerance, abdominal distension, respiratory instability and several other nonspecific signs that are seen in most extremely low birthweight infants in the NICU. Although many of the recent observational retrospective studies have avoided including these infants in their data, and state that only stage 2 or 3 are included, problems still remain. Stage 2 relies on clinical signs and radiographic criteria which may not be highly specific but are frequently interpreted as NEC. For example, abdominal radiographic reports state there is a localized "bubbly" appearance, which may or may not correlate with clinical symptoms or other laboratory values. The bubbly appearance may be confused with stool in a normal intestine, primarily the colon. A follow-up film 6 h later is recommended to observe changes in position in the case of stool. If this radiographic finding persists on repeat radiographs taken within the first 24–48 h after the first film, and if this corresponds with clinical signs such as abdominal distension and elevated inflammatory markers, it is likely that this represents disease. However, this finding is often recorded on the discharge summary as "NEC." Other radiographic markers such as crescentic appearance of air in the abdominal wall and/or portal venous gas, or free intraperitoneal air (best evidenced on left lateral decubitus radiographs) are more serious findings and are likely to portend severe disease [7]. Evidence of free air in the peritoneal cavity, as mentioned, usually portends significant disease. However, this is not specific for NEC and can represent spontaneous intestinal perforation (SIP) or another entity that is not classic NEC. If no laparotomy is done and only a peritoneal drain is placed as is now common practice, this may be entered into the patient record as "NEC." Thus, the use of Bell's criteria based on purely clinical and radiographic evidence has significant limitations.

More recently, abdominal ultrasound has been used for the diagnosis of NEC and some authors highly recommend it partly because of its sensitivity to detect pneumatosis [8–10]. However, there are still questions about sensitivity and specificity of this technique based on the fact that it needs to be evaluated against a "gold standard" which we likely do not have with the exception of intestinal necrosis seen at surgery or autopsy. Although this technique shows promise, routine use may not yet be in-

dicated without prospective, well-designed and validated studies [11].

There are other reasons underlying our lack of progress with NEC. As previously mentioned, NEC has been considered a homogeneous entity, but with different pathways contributing to its development [12]. This is in some ways similar to considering all cases of diabetes as one disease. However, it is now clear that diabetes is heterogeneous consisting of not only type 1 and 2 disease but also different endotypes within type 1 diabetes [13]. Similar to diabetes, even though NEC is considered under a homogeneous umbrella, there are several different entities seen in neonates that can lead to similar symptomatology [4]; however, they require more personalized approaches for prevention and treatment.

In order to make progress in the understanding, therapy and prevention of the entities that we call "NEC," we will first need to summarize some of the shared features as well as features that differentiate these entities. We need to underscore the fact that many of the common highly regarded databases available to evaluate "NEC" are flawed and these shortcomings need to be recognized whenever retrospective evaluations using these datasets are undertaken.

Diseases Commonly Diagnosed as NEC

Spontaneous Intestinal Perforation

At one time thought to be a form of NEC [14], SIPs began to be recognized as a separate entity approximately 40 years ago [15–17]. A major differentiating factor is that SIP is found most commonly as an isolated perforation in the terminal ileum in an antimesenteric location, with the remaining bowel appearing grossly normal [18]. Although the pathophysiology of SIP remains poorly understood, it is clearly a different disease to NEC [19]. The perforation in SIP has minimal surrounding necrosis or neutrophil infiltrate. The average age of onset of SIP is usually earlier than that of the more classic form of NEC. Although the use of individual agents does not appear to increase risk, the combined use of nonsteroidal anti-inflammatory agents such as indomethacin and ibuprofen and postnatal corticosteroids have been shown to significantly increase risk [20]. Pneumatosis intestinalis and portal venous gas usually do not precede SIP as often seen in the more classic form of NEC. There are some suggestions that certain biomarkers such as blood levels of inter-alpha inhibitor proteins may be significantly decreased in NEC when compared to SIP and matched con-

trols [21]. However, such studies are difficult to interpret unless we have a “gold standard” diagnosis of NEC and SIP.

Both NEC and SIP may be suggested by the presence of abdominal distension and free air in the abdominal cavity. They are often treated similarly with placement of peritoneal drains [22]. Thus, there is a lack of clarity because it is not known if the bowel has undergone significant necrosis as seen with NEC compared to simply a perforation as seen with SIP. This may never be fully clarified without a definitive laparotomy. Thus, contamination of our datasets between NEC and SIP are likely to occur and often all these intestinal injuries are reported as NEC. The extent to which this causes problems in analyses of these datasets in observational studies is unclear.

Ischemic Intestinal Necrosis

Ischemia of the intestine can result from several forms of congenital heart disease and should be differentiated from classic NEC. This low flow state is seen in full-term neonates but can also occur in preterm infants [23, 24]. With ischemic intestinal necrosis secondary to heart disease, the colon is the most commonly involved site. Hypoplastic left heart syndrome, truncus arteriosus, aortic arch obstruction and aortopulmonary window account for most cases of cardiogenic ischemic intestinal necrosis [25]. I propose that this disease should be classified as an individual entity and not be diagnosed as “NEC.” A more apt diagnostic moniker would be “cardiogenic ischemic necrosis of the intestine.”

Food Protein Intolerance Enterocolitis Syndrome

Primarily recognized as a problem seen outside of the neonatal period during infancy, food protein-induced enterocolitis syndrome (FPIES) can also occur in the neonatal period, presenting with abdominal distension, bloody stools and flank discoloration, which improve after being treated with hydrolyzed formula [26–28]. A cow’s milk challenge and even breast feeding (if the mother is exposed to certain proteins) may result in relapse. FPIES is a non-IgE-mediated disease which remains poorly delineated, especially in neonates. Diagnostic biomarkers for FPIES that may help differentiate this disease from NEC are not yet available but recent case reports suggest that this entity may be underreported in neonates [29]. It is important to differentiate FPIES from NEC because the treatment is different: in FPIES, removal of the offending antigen and symptomatic support may be sufficient, whereas in NEC, the treatment is

more extensive with the use of antibiotics, withholding of feeds and provision of parenteral nutrition for approximately a week.

Congenital Anomalies of the Bowel That Mimic NEC

Patients with Hirschsprung disease may develop inflammatory enterocolitis, an entity that leads to significant morbidity and mortality [30]. The clinical signs of this disease include vomiting, rectal bleeding, loose stools and abdominal distention, making it sometimes difficult to differentiate from classic NEC. Intestinal obstruction due to volvulus, intussusception, and meconium ileus due to cystic fibrosis may also present with signs and symptoms of “NEC” including radiographic features such as pneumatosis intestinalis and should be kept in mind in the differential diagnosis of “NEC.”

“Classic” NEC

NEC can be a rapidly progressive disease often progressing from first symptoms to full-blown disease and death within 24–48 h. As a result, it is important to diagnose it in the earliest stages. Although there is some utility in terms of staging severity of illness, Bell’s criteria developed in the late 1970s can be misleading. This author believes that this staging system is outdated. It is more informative to simply use the terms “medical NEC” to apply to the condition with well-defined clinical symptoms plus radiologic signs (i.e., portal venous gas and definite pneumatosis intestinalis), and “surgical NEC” to apply to definitive intestinal necrosis seen at surgery or autopsy.

Pathophysiology of “Classic” NEC

The following factors are considered important antecedents in the pathophysiology of “classic” NEC.

Intestinal Immaturity and Inflammation

Barrier function, circulatory regulation, motility, digestion and absorption as well as immune defenses are immature in preterm infants. In addition, the balance between effector and tolerizing immune response may not be fully developed [31, 32]. Classic NEC appears to be related to excessive inflammatory responses, with serum cytokines and chemokines, especially IL-8 significantly elevated [33]. Other factors that are elevated and could potentially be used as biomarkers for NEC include claudin 3 (a tight junction protein), intestinal fatty acid-binding protein which is produced by the epithelial cells and fecal calprotectin which is the product of inflammatory cells [32].

Microbial Colonization and Interaction with the Immune System

An imbalance of the usual, healthy microbial ecosystem of the gastrointestinal tract, termed “dysbiosis,” is also thought to contribute to the pathogenesis of NEC [34]. Recently studies using non-culture-based techniques have interrogated the intestinal microbiome prior to the onset of NEC. There appears to be a shift of microbes with an increase in the phylum Proteobacteria and a decrease in the phylum Firmicutes [33]. A highly speculative hypothesis suggests that an exaggerated host inflammatory response causes this microbial shift and may be at least partially responsible for triggering NEC. Further studies are required to address this hypothesis and its possible mechanisms.

Diagnosis

The clinical presentation of what has been termed NEC can be highly variable, with signs and symptoms that are indistinguishable from sepsis. It is the presence of pneumatosis intestinalis and/or portal venous gas or direct visualization of necrotic bowel at the time of surgery that clearly differentiate NEC from fulminant sepsis. Laboratory tests commonly performed when the diagnosis of NEC is suspected include a complete blood cell count, electrolytes and inflammatory markers such as C-reactive protein. These have poor sensitivity, specificity and positive predictive value for the diagnosis of NEC and better biomarkers are clearly required.

Management and Prevention

Once the disease starts, it is difficult to stop. Withholding of enteral feedings, gastric decompression, broad-spectrum antibiotics and parenteral nutrition are mainstays of treatment. It is frequently difficult to decide whether a laparotomy should be performed or a peritoneal drain placed for treatment or as a temporizing measure. There are several strategies that have been utilized in attempts to prevent NEC. The provision of human milk appears to provide the greatest benefit. There are many popular notions not based on clear evidence regarding the prevention of NEC, which include extremely slow initiation of enteral feeds, not feeding preterm infants while they are being given blood transfusions, not feeding infants when they have umbilical arterial or umbilical venous lines in place, and not feeding infants if they are being treated with drugs such as indomethacin, ibuprofen or other vasoactive drugs. In terms of enteral feeding, a recent well-designed clinical trial demonstrated that advancement of feeds between 20 and

30 mL/kg/day does not increase the likelihood of developing NEC compared to infants who have feeds advanced more slowly [35]. Antibiotic use in preterm infants in the first few days after birth is very common and not based on clear evidence. However, data are emerging that dysbiosis may be caused by the use of antibiotics and this can affect the developing immune system and lead to intestinal inflammation and NEC [32]. Studies are currently underway to evaluate this issue.

There has been significant excitement about microbial therapeutics such as pre-, pro-, post- and synbiotics for the prevention of NEC. Although meta-analyses suggest benefit to the routine use of probiotics, they offer little guidance in terms of which probiotics should be used, their dosage, which age group they provide the greatest benefit for, whether they should be used in conjunction with a prebiotics preparation, and how long they should be given. Furthermore, not all probiotics are the same. It is this author’s opinion that these agents should undergo prospective trials with the same rigorous criteria for safety and efficacy as other therapeutic pharmaceutical agents, with regulatory guidance [36].

Disclosure Statement

- 1 Principal Investigator Research Study with Infant Bacterial Therapeutics
- 2 Scientific Advisory Board Medela
- 3 Scientific Advisory Board Astarte

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