Necrotizing Enterocolitis

66

Stephanie C. Papillon, Scott S. Short, and Henri R. Ford

Contents

Abstract

Necrotizing enterocolitis (NEC) is the predominant intestinal inflammatory disorder affecting the newborn infant. Risk factors for NEC include prematurity, formula feeding, and bacterial colonization of the gastrointestinal

S. C. Papillon (✉) · S. S. Short · H. R. Ford
Division of Pediatric Surgery, Children's Hospital Los Angeles, Los Angeles, CA, USA
e-mail: spapillon@huhosp.org; dr.scottshort@gmail.com; HFord@chla.usc.edu

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(GI) tract. The number of neonates at risk of developing NEC continues to rise due to recent advances in neonatology that have resulted in increased survival of extremely premature infants. Clinical features of NEC are often nonspecific and include evidence of physiologic instability, feeding intolerance, abdominal distention, and hematochezia. A cluster of key clinical and radiographic findings, known as the Bell staging system, has been used to characterize disease severity. Despite aggressive management strategies, morbidity and mortality from NEC remain high. Thus, this vexing disease will likely remain a major contributor to healthcare costs and may, one day, become the leading cause of death among premature infants. Optimal preventive strategies are needed to avert the devastating consequences of NEC.

Keywords
Necrotizing enterocolitis · Short bowel syndrome · Ostomy, prematurity · Low birth weight infants · Peritoneal drainage · Total parenteral nutrition

Introduction

Epidemiology of Necrotizing Enterocolitis Worldwide

NEC is predominantly a disease of the premature neonate. The majority of patients diagnosed with NEC are less than 32 weeks of gestation. Data from population-based studies worldwide estimate the incidence of NEC to be 0.72–1.8 per 1000 live births (Dominguez et al. 2014). The incidence is highest in extremely low birth weight infants (ELBW) weighing less than 1000 g, likely reflecting the degree of prematurity (Patel et al. 2016; Sylvester et al. 2012; Holman et al. 2006; Llanos et al. 2002; Sankaran et al. 2004; Guthrie et al. 2003; Christensen and Gordon 2010). NEC decreases proportionally as birth weight increases, and a drastic decline occurs after 35 weeks gestation (Llanos et al. 2002; Hunter et al. 2008; Sylvester et al. 2012).

The incidence of NEC has been increasing worldwide as a result of a steady rise in the rate of high-risk pregnancies and recent advances in neonatology that have resulted in the survival of significant numbers of extremely low birth weight infants (Heida et al. 2017; Schlager et al. 2012; Ahle et al. 2013). Thus, the need to understand this disease has never been more imperative.

Pathogenesis

Risk Factors

Early studies by Santulli and colleagues suggested that NEC develops in a susceptible or premature host as a result of various insults to the gastrointestinal tract inflicted by ischemia, enteral feeding, and pathogenic bacteria (Mizrahi et al. 1965; Santulli et al. 1975). Our current understanding of the pathogenesis of NEC suggests that immaturity of the gastrointestinal tract in the preterm neonate, combined with these insults, accounts for the cascade of events that lead to NEC. The immature intestine is characterized by poor microcirculatory regulation, impaired integrity of the epithelial barrier, and various immune deficiencies, including decreased production of mucin, defensins, and secretory IgA, to name a few, which impair the host's ability to restrict the transmucosal passage of pathogenic bacteria and toxins. In addition, the dysfunctional motility and reduced digestive capacity of the premature intestine further predispose to the accumulation of toxins or noxious substances that may contribute to or exacerbate mucosal injury (Neu and Pammi 2017; Niño et al. 2016; Dominguez et al. 2014; Sylvester et al. 2012). Although a normal intestinal microbiota could mitigate such mucosal injury, the premature neonate suffers from abnormal microbial colonization of the gastrointestinal tract. Thus, breakdown of the epithelial barrier is further exacerbated by loss of the vigorous and complex interaction between the mucosa and intestinal microbiota, which results in an inappropriate, exuberant inflammatory response to commensal and pathogenic bacteria. The inflammatory mediators released lead to further epithelial injury, exaggerated systemic inflammation, and the resulting adverse sequelae characteristic of NEC. The mechanisms that predispose the immature intestine to injury must be further defined in order to prevent or treat NEC in the premature neonate (Llanos et al. 2002).

Mechanisms of Intestinal Mucosal Injury

Various studies describe some of the mechanisms by which mucosal injury occurs in NEC (Nadler et al. 2000; Sodhi et al. 2010). These studies have established a role for mediators such as nitric oxide, which is made in large quantities during inflammatory conditions by the inducible isoform of nitric oxide synthase (iNOS), and toll-like receptor 4 (TLR4) in the pathogenesis of NEC. These mediators are not only elevated in neonates with NEC but also have been localized to regions of mucosal injury and have been shown to inhibit pathways necessary for restoration or repair of the damaged intestinal epithelium (Ford 2006; Afrazi et al. 2011; Sodhi et al. 2010). Inhibiting the activation of these mediators can not only reverse the inflammatory changes noted in the intestinal epithelium in experimental models of NEC but can also restore reparative pathways such as epithelial restitution through enterocyte migration and proliferation (Sodhi et al. 2010). Interplay between these pro-inflammatory mediators and others such as platelet-activating factor (PAF) has been demonstrated and could represent putative pathways essential for the development of NEC (Soliman et al. 2010). Despite these observations, the sequence of events that lead to NEC have yet to be established. Nonetheless, targeted inhibition of these mediators may ultimately lead to new therapeutic approaches to prevent or attenuate NEC.

Histopathologic Findings

NEC can occur anywhere along the gastrointestinal tract but most commonly affects the small intestine (Hackam et al. 2015). Morphological analysis of resected, diseased intestine and autopsy specimens has historically shaped much of our understanding of the pathogenesis of tissue injury in NEC. On gross morphology, the bowel appears distended with patchy or diffuse areas of gray to dark discoloration. Focal lesions occur as commonly as multisegmental disease (Nadler et al. 2001; Dominguez et al. 2014). Examination of the mucosa may reveal a hemorrhagic and friable surface. Predominant histologic findings range from acute and chronic inflammatory changes to frank necrosis or perforation. These include bowel wall edema, submucosal gas, as well as neutrophilic and lymphocytic infiltrates, which may reflect in part the acuity or chronicity of the disease (Fig. 1). Subserosal or submucosal gas, a product of bacterial fermentation also known as pneumatosis intestinalis, may also be visible and lends support to the infectious nature of NEC. Rapidly progressing injury to the bowel is suggested by necrosis in the absence of inflammation, also known as coagulation necrosis, while more gradual progression is suggested by the presence of chronic inflammatory changes (Gould 1997; Ballance et al. 1990). Coagulation necrosis is often, although not exclusively, the result of ischemia. Coagulation necrosis may be limited to the mucosa; however, advanced disease may ultimately result in transmural involvement and perforation. Necrosis may be accompanied by hemorrhage and intramural thrombi. Reparative

Fig. 1 Diffuse patchy necrosis in a patient with NEC totalis. Subserosal gas can be seen

changes and granulation tissue have also been observed along with active injury. These findings suggest that the acute injury characteristic of NEC probably occurred prior to the clinical manifestations that required resection of the diseased intestine (Ballance et al. 1990). Patients with transmural inflammation that do not undergo resection may subsequently develop regions of submucosal fibrosis that can manifest clinically as intestinal strictures.

Risk Factors for NEC in the Full-Term Infant

Fewer than 10% of patients who develop NEC are full term. While the pattern of mucosal injury reflects that of preterm infants, full-term infants differ clinically from their premature counterparts and, in this population, NEC "may be initiated by different perinatal factors" (Ostlie et al. 2003). Most studies suggest that congenital heart disease (CHD) is the most significant predisposing risk factor for NEC in the full-term infant (Ostlie et al. 2003). Infants with CHD develop intestinal ischemia due to reduced blood flow to the intestine, which may result in mucosal injury and bacterial invasion, which in turn incites the inflammatory cascade that leads to NEC.

Clinical Features

Presentation

At initial presentation, infants who develop NEC often exhibit nonspecific systemic signs that may prompt a workup for sepsis. Symptoms specific to the gastrointestinal tract are present in over 70% of patients and include feeding intolerance manifested by high gastric residuals or frank vomiting, abdominal distention, and gross or occult blood in the stool, which is seen in up to 60% of patients (Sylvester et al. 2012). These symptoms may present postoperatively following the initial stages of cardiac repair for CHD in the full-term infant. As NEC progresses, patients may develop worsening abdominal distention,

Fig. 2 Abdominal distention and extensive abdominal wall erythema in a patient with NEC totalis

abdominal wall discoloration, or erythema (Fig. 2). Within hours, patients can rapidly deteriorate and develop peritonitis with signs of cardiovascular collapse. The diagnosis is often established by radiographic imaging. Standard imaging consists of plain abdominal radiographs. Initial findings may be nonspecific such as dilated loops of intestine and a bowel gas pattern consistent with ileus. Pneumatosis intestinalis is the most common finding observed in patients with NEC (Dominguez et al. 2014). Portal venous gas is another potential finding that is associated with pan-involvement and an unfavorable outcome. The NEC staging system, originally developed by Bell et al., combines the clinical symptoms with radiographic findings and has been used to classify severity of disease and guide therapy.

Laboratory Findings

Laboratory data, although universally used, have not proven to be specific or reliable indicators for the diagnosis of NEC. Metabolic acidosis, leukopenia, and thrombocytopenia are common findings in patients with NEC (Sylvester et al. 2012; Dominguez et al. 2014). Thrombocytopenia that occurs rapidly has been associated with a poor prognosis (Sylvester et al. 2012; Dominguez et al. 2014). Studies have investigated potential indices predictive of NEC that may also serve as prognostic indicators; however, no inflammatory marker has emerged as highly sensitive and specific (Dominguez et al. 2014).

Associated Comorbidities

Several retrospective studies have reported a high prevalence of NEC in patients who underwent abdominal wall closure for gastroschisis (Oldham et al. 1988; Amoury 1989; Mollitt and Golladay 1982; Jayanthi et al. 1998). The patients described were often managed nonoperatively; however, recurrence was commonly observed (Oldham et al. 1988). NEC was significantly more common in patients with severe gastrointestinal dysfunction, a characteristic of the premature gastrointestinal tract.

Management

Nonoperative

Patients with NEC are initially managed with supportive care. Upon clinical suspicion of NEC, feeds are withheld and the gastrointestinal tract is decompressed using an orogastric tube. Intravenous fluid resuscitation is initiated. Laboratory data including a chemistry panel, complete blood count with differential blood gas, and C-reactive protein (CRP) are obtained. Broad spectrum intravenous antibiotics are initiated once blood and urine are sent for culture. Close clinical observation with serial abdominal examinations as well as serial abdominal radiographs are used to monitor disease progression. Clinical improvement is expected to occur within the first 72 h (Brunicardi et al. 2015). For patients who stabilize and show improvement, antibiotic therapy is continued for 1–2 weeks.

Operative Indication and Technique

Up to 20–40% of patients with NEC will require surgical intervention (Dominguez et al. 2014; Sylvester et al. 2012). Over the past decades, indications for operation have evolved as practitioners have sought to identify patients just prior to perforation; however, pneumoperitoneum remains the only consistent and definitive indication for surgical intervention. Relative indications for surgery include failure to respond to optimal medical therapy, as evidenced by worsening clinical status, abdominal wall erythema, or the presence of a persistent intestinal loop on serial abdominal radiographs. The goal of surgery is to resect gangrenous bowel while minimizing the risk of short bowel syndrome. The operation is largely determined by the extent of disease found at laparotomy (Hansen et al. 2016). The entire length of the gastrointestinal tract is examined and frankly necrotic bowel is resected. Where intestinal viability is questionable, a second look laparotomy may be warranted. The standard surgical approach to the patient with NEC is resection of gangrenous or perforated bowel with creation of a proximal ostomy. Traditionally, enterostomy creation has been accepted as the safest approach because primary anastomosis may be tenuous in a septic infant (Pierro 2005). For selected stable patients with localized disease, resection with primary anastomosis may obviate the need for a second operation as well as some of the morbidity associated with ostomy creation (Sylvester et al. 2012; Pierro 2005). In the past, multiple stoma creation had been advocated for patients with multifocal disease; however, this approach can lead to short bowel syndrome by sacrificing viable intestine; therefore, it has been abandoned.

The “clip and drop back technique,” which consists of resection of all necrotic bowel leaving the remaining clipped segments within the abdominal cavity without creating ostomies or anastomoses, has been advocated for patients with extensive multifocal disease. The viable segments are then re-anastomosed at a second operation 48–72 h later. Delayed re-exploration has been proposed in a yet more controversial technique, the "patch, drain, and wait." This approach involves irrigation of the abdominal cavity, primary approximation of intestinal perforations, placement of a Stamm gastrostomy, and insertion of two Penrose drains beneath the diaphragm that course along the lateral aspect of the peritoneal cavity and exit from the lower quadrants for continued peritoneal drainage (Moore 2000). Postoperatively patients are kept on long-term parenteral nutrition (TPN). The drains are left in place until the drainage ceases and patients are tolerating enteral feeds. The authors advocate postponing a second operation during the 2-week period immediately postoperatively, and in cases where return of bowel function does not occur, reoperation may occur as late as 2 months.

In the 1970s, peritoneal drainage was proposed as a temporizing measure for the critically ill very low birth weight (VLBW) patient, weighing less than 1500 g, with perforated NEC. The procedure is typically performed under local anesthesia at the bedside. The major components involve copious irrigation of the abdominal cavity and placement of a Penrose drain in the lower quadrant or bilateral lower quadrants allowing for decompression and removal of fecal contamination. Peritoneal drainage is widely viewed as initial treatment, and its use as definitive treatment remains controversial. There have been two randomized controlled trials investigating the use of peritoneal drainage versus laparotomy in VLBW infants with perforated NEC to determine any survival advantage. In the first multicenter trial, 117 VLBW infants were randomized to either treatment with 55 undergoing drainage and 62 undergoing laparotomy (Moss et al. 2006). The investigators did not observe any significant differences in 90-day mortality. Similarly, no significant differences were observed in secondary outcome measures that included TPN dependency and length of hospital stay at 90 days postoperatively. In the second international multicenter randomized controlled trial (Rees et al. 2008), 35 patients were randomized to peritoneal drainage and 34 to laparotomy. There were no significant differences in mortality or in secondary outcome measures that included length of stay and gastrointestinal and respiratory outcomes at 1 and 6 months postoperatively between the two groups. Seventy-four percent of the patients who underwent drainage subsequently required laparotomy for deteriorating clinical status. The authors concluded that peritoneal drainage is not "a safe alternative to laparotomy and is not an effective temporizing measure." While neither randomized trial detected differences in primary nor secondary outcomes, each included a mixed population of patients with focal intestinal perforation and NEC, and the studies did not meet the minimum number of required participants for appropriate statistical power perhaps limiting the ability to observe differences.

Outcomes

Overall

NEC is associated with a high morbidity and mortality. Overall outcome is affected by the degree of prematurity and extent of disease. Over the past decades, survival for NEC has shown steady improvement. This observation has been most notable in VLBW infants and is likely related to advances in supportive care. NEC has a relatively low recurrence rate. Up to one third of patients with NEC will develop intestinal strictures. Strictures occur more frequently in patients with medically treated NEC (Sylvester et al. 2012). Suspected patients should undergo contrast enema and surgical resection.

Postoperative Outcomes

Postoperative complications occur in up to 40% of neonates who undergo surgical therapy for NEC. These include anastomotic leak, stoma complications such as prolapse or necrosis, and injury to the liver (Sato et al. 2011). Other complications include intestinal strictures, sepsis, and short gut syndrome (Horwitz et al. 1995; Blakely et al. 2005). While mortality shows stepwise progression with decreasing gestational age, Horwitz et al. found the overall number of complications to be relatively stable across all age groups (Horwitz et al. 1995).

Long-Term Outcomes

Gastrointestinal

The most devastating complication of NEC is intestinal failure due to inadequate residual small bowel (short gut). Nearly one quarter of patients undergoing surgical resection for NEC will develop short bowel, and NEC is among the leading causes of intestinal failure in the neonatal population. The absence of the ileocecal valve does not always predict the likelihood of failure of intestinal adaptation in patients with inadequate small bowel length (Duro et al. 2010). The patient's gestational age at the time of small bowel resection is an important prognostic indicator of the risk of intestinal failure because an increase in small bowel length typically occurs during the third trimester (Goulet and Ruemmele 2006).

Neurodevelopmental Outcome

NEC has been found to be an independent risk factor for adverse neurodevelopmental outcomes. Analysis at 7 years for children included in the ORACLE Children Group, a randomized study investigating the use of broad-spectrum antibiotics in preterm premature rupture of membranes, found increased risk of any functional impairment in children with a history of NEC (Pike et al. 2012). In a multicenter retrospective study, ELBW infants who required surgery for NEC were found to have a significantly increased prevalence of neurodevelopmental and neuromotor or neurosensory deficits including cerebral palsy, blindness, and deafness (Hintz et al. 2005).

Conclusions and Future Directions

NEC remains a vexing problem for both neonatologists and pediatric surgeons. The most devastating impact of this disease is its direct effect on patients and their families. NEC is also a major contributor to healthcare costs, and the economic burden persists beyond the initial hospitalization period. A retrospective cohort study found significantly higher healthcare costs for patients with both medical and surgical NEC compared with matched controls. These differences persisted through the first 3 years of life for patients with surgical NEC (Ganapathy et al. 2013). Thus, for the practitioner caring for these patients and their families, there is an urgent need to optimize current management and develop preventive strategies.

Although numerous studies have identified putative risk factors for NEC, preventive approaches are limited. Animal models have demonstrated a protective role for growth factors such as EGF and HB-EGF, which can promote intestinal restitution, and for inhibitors of pro-inflammatory mediators. Studies in human infants have shown a beneficial role for probiotics and prebiotics in reducing the incidence of NEC and producing a fecal microbial composition that resembles that of their breastfed counterparts (AlFaleh and Anabrees 2014). However, there is insufficient evidence to recommend these interventions at this time. Restrictive feeding strategies have not shown any advantage. Corticosteroid administration has also been investigated as a therapeutic adjunct in NEC because of its ability to induce maturation of immature organs. The impact of corticosteroids on the developing intestine was first explored in the 1960s and was subsequently shown to accelerate the maturation of the mucosal barrier (Israel et al. 1990). Randomized trials have demonstrated that steroids can reduce the number of patients who develop NEC as well as the severity of disease (Bauer et al. 1984; Halac et al. 1990). However, the direct impact of steroids on the gastrointestinal tract and their long-term effects on the developing intestine are not well defined. While antenatal steroids show benefit, the use of postnatal steroids is cautioned since long-term outcomes will require further study (LeFlore et al. 2002). Breast milk is the only intervention that is recommended for the preterm infant by the American Academy of Pediatrics to prevent or reduce the incidence of

NEC. Clinical trials have demonstrated the ability of breast milk to reduce the incidence of NEC and its associated mortality and morbidity among preterm infants, including improved neurodevelopmental outcomes. As studies on NEC continue, identifying the child at risk, advocating for the use of breast milk, and providing aggressive care will be key in managing this perplexing problem.

Cross-References

- ▶ Gastroschisis
- ▶ Nutrition in Infants and Children
- ▶ Sepsis
- ▶ Specific Risks for the Preterm Infant
- ▶ Stomas of Small and Large Intestine

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