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Current Status of Necrotizing Enterocolitis

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Diagnosis and epidemiology

Necrotizing enterocolitis (NEC) is one of the most common and catastrophic causes of gastrointestinal (GI) morbidity and mortality in infants, typically affecting those of lower birth weight and prematurity. In 1969, Stevenson was one of the first to describe early diagnosis and surgical management of NEC in 21 infants.[1] He suggested the aggressive use of a 2-staged technique consisting of a midabdominal transverse incision and resection of necrotic or acutely inflamed bowel followed by a second look laparotomy within a few days after the initial operation. Since that time, multidisciplinary efforts have continued to elucidate the pathophysiology, diagnosis, and treatment of this devastating disease.

Traditionally, Bell's criteria have been employed in defining and staging NEC in infants based on clinical, systemic, and radiographic signs.[2] The 3 stages were originally designed to help clinicians determine need for surgery in neonates but have become the most commonly used criteria for defining and staging NEC (Table 1). These criteria, however, have been widely criticized after it was determined that Bell's stage I definitions led to over-diagnosing patients with NEC. The Vermont Oxford Network has also established a less ambiguous classification system for defining the disease and requires 1 clinical and 1 radiographic finding.[3] These clinical findings include bilious emesis or gastric aspirate, abdominal distention, or gross blood in the stool, while radiographic findings include pneumatosis intestinalis, pneumoperitoneum, or portal venous gas, and correspond to Bell's stage II or higher.

Alternatively, a "two out of three" rule has been described recently as an algorithm that could replace Bell's staging in defining preterm NEC.[4] This rule defined preterm NEC as infants having clinical symptoms including abdominal distention, ileus, and/or bloody stools and at least 2 of the following criteria: pneumatosis or portal venous gas on abdominal radiograph, persistent platelet consumption (platelet count $<150{,}000/mm^3$), and postmenstrual age at disease onset

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Table 1
Modified Bell's criteria for the diagnosis of necrotizing enterocolitis (NEC).

Stage	Classification	Abdominal signs	Systemic signs	Radiographic signs
IA	Suspected NEC	Abdominal distention, emesis, heme-positive stool	Temperature instability, bradycardia, lethargy	Normal or mild intestinal dilation
IB	Suspected NEC	Same as above, plus grossly positive stool	Same as above	Same as above
IIA	Definite NEC, mild	Same as above, plus absent bowel sounds with or without abdominal tenderness	Same as above	Same as above, plus pneumatosis intestinalis
IIB	Definite NEC, moderate	Same as above, plus definite tenderness, with or without abdominal cellulitis or RLQ mass	Same as above, plus metabolic acidosis and thrombocytopenia	Same as above, plus ascites
IIIA	Advanced NEC	Same as above, plus signs of peritonitis, marked distention and tenderness	Same as above, plus hypotension, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulopathy, neutropenia	Same as above
IIIB	Advanced NEC, perforated or necrotic bowel	Same as above	Same as above	Same as above, plus pneumoperitoneum

RLQ, right lower quadrant

consistent with NEC rather than spontaneous intestinal perforation (SIP). Infants known to have SIP, complex congenital anomalies, greater than 36 weeks' gestation, and those fed less than 80 mL/kg/day were excluded from a diagnosis of preterm NEC.

The advancement of mechanical ventilator support along with treatment of pulmonary immaturity has led to significant improvement in survival of premature infants; this, in turn, has increased the incidence of infants diagnosed with and treated for NEC.[5] The true incidence of NEC in children remains unknown and has been controversial due to inconsistencies in the diagnosis and definition of the disease.[6] For proven NEC, or infants with Bell's stage II-III, the rate of disease has been estimated between 1 and 3 per 1000 births.[7] Historically, there has been a greater preponderance of NEC affecting very low birth weight (VLBW) infants, with an inverse relationship between the disease and birth weight.[8,9] In a cohort of 71,808 VLBW infants, NEC incidence was evaluated in 4 different birth-weight categories in increments of 250 g. Infants with a birth-weight between 501 and 750 g had a 12% incidence of developing NEC; there was a decrement in incidence of approximately 3% for each 250 g increase in birth-weight category (Fig 1). Although the incidence of NEC was historically 7% to 9% in VLBW neonates, there has been a downward trend in rates of NEC over the last decade, with an incidence of 4.9% in 2014, likely related to the advancements in prevention discussed in this review.[8-10]

It is important to recognize that NEC appears to be an umbrella diagnosis encompassing multiple underlying pathologies in a variety of clinical populations with different implications for prevention and treatment. NEC is classically associated with premature, low birth-weight infants. Term, normal birth-weight infants with NEC are less likely to require intervention and have a lower mortality rate. Major congenital anomalies have been identified in nearly one half of infants with a birth-weight greater than 2500 g who are diagnosed with NEC.[11]

Congenital heart disease (CHD) in particular has been associated with NEC development in full term, normal birth-weight infants.[12] The impaired regional allocation of blood flow after enteral feeds may perpetuate diminished intestinal blood flow and lead to NEC development in infants with CHD.[13] Low flow states and the use of vasoactive medications also contribute to the

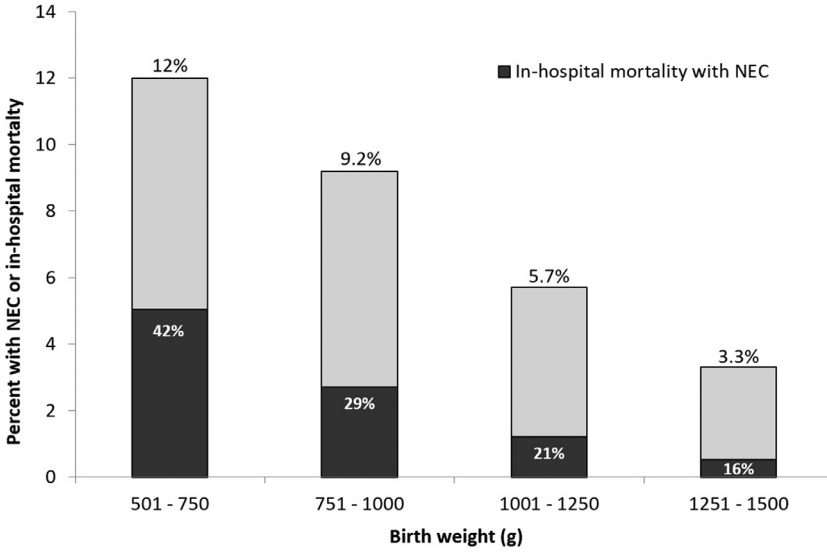

Fig. 1. Incidence of necrotizing enterocolitis (NEC) by birth weight categories among very low birth weight infants (n = 71,808) in the Vermont Oxford Network database 2005-2006, adapted from Fitzgibbons and colleagues.[8]

different perinatal factors that lead to a diagnosis of NEC in these infants.[14] Finally, the mortality of infants with both CHD and NEC appears to be substantially higher than with each diagnosis alone, perhaps indicating that this represents a more severe form of the disease.[15]

Gastroschisis also appears to be associated with an increased risk of NEC,[16] however these infants less frequently require surgery and the rate of mortality is lower than expected, at approximately 12%. This indicates that NEC in gastroschisis may represent a less clinically severe pathology. Finally, SIP and NEC share many similar presenting features, but they appear to represent 2 distinct clinical pathologies with different prognosis and management. Although it is important to distinguish SIP from NEC, this is often challenging to do without laparotomy.

Pathophysiology

The pathogenesis of NEC remains ambiguous, although it is currently believed to be multifactorial and affected by 3 primary factors: intestinal immaturity, microbial dysbiosis, and formula feeding.[5] Prematurity has been identified as a primary risk factor for NEC[17] and is attributed to an immature mucosal barrier and immune response. Although a genetic predisposition for NEC has remained ambiguous, there are studies to suggest a familial predisposition for NEC based on comparison of rates between monozygotic and dizygotic twins.[18] Infant related factors contributing to NEC development also include low Apgar scores, need for mechanical ventilation, presence of other congenital anomalies, and pharmacologic interventions including prolonged empirical antibiotic use, H_2 blockers, and indomethacin.[15,19-21] Maternal risk factors for NEC in the infant include illicit drug abuse, chorioamnionitis, and HIV-positive status.[19,22]

Prematurity

The intestinal epithelium is a complex network that provides a physical barrier between the luminal environment and the body through the presence of enterocytes, tight junctions, goblet cells, and pattern recognition receptors. Enterocytes, or intestinal epithelial cells, make up approximately 80% of the intestinal epithelium and are connected by tight junction to maintain

the integrity of the small intestinal mucosa.[23] Enterocyte immaturity affects tight junctions, particularly through interactions with occludins and claudins leading to increased permeability, bacterial invasion, and translocation.[24] Enterocytes also play an important role in identifying antigens through toll-like receptors, eliciting an immune response.[25] Cytokines are released by the intestinal epithelium in reaction to bacterial invasion, further perpetuating tight junction permeability and translocation of bacteria.[26] Lipopolysaccharide, an endotoxin found in bacterial membranes, also promotes the release of inflammatory cytokines like TNF-a, interferon-y, IL-6, and IL-8 by enterocytes, which in turn leads to the overproduction of nitric oxide. Increased levels of nitric oxide are associated with intestinal epithelial apoptosis, decreased epithelial cell proliferation, and migration.[27]

Goblet cells are responsible for mucus production and play an important role in the maintenance of the gut barrier. These cells are found along the crypts and secrete mucus composed of glycoproteins called mucin, which are responsible for promoting intestinal immune homeostasis by allowing the passage of commensal bacterial antigens from the intestinal lumen to intestinal dendritic cells.[28] In addition, the product of the gene MUC2 is responsible for regulating the morphology of goblet cells and the production of mucin. Decreased expression of MUC2 may be an important risk factor for NEC development in premature infants, since the production of mucin plays a key role in regulating gut barrier integrity.

Pattern recognition receptors are able to sense pathogenic molecules released during the process of inflammation.[29] Toll like receptors (TLRs) are transmembrane receptors that initiate an immune response within enterocytes against bacterial invasion.[29] These TLRs, specifically toll like receptor-4 (TLR4) have been implicated in the development of NEC. Both premature murine and human intestines have a higher level of TLR4 expression compared to their full term controls.[30] High levels of TLR4 activation in enterocytes lead to increased activation of inflammatory cytokines, reduced proliferation and migration of enterocytes, increased apoptosis, epithelial breakdown, and bacterial translocation.

Microbial dysbiosis

The notion that bacterial colonization and dysbiosis predisposes an infant to NEC is based on studies conducted approximately 50 years ago on more than 100 infants with NEC suggesting a predilection for gram-negative bacteria, particularly *Escherichia coli*.[31] NEC has not been observed in utero, and is associated with exposure to antibiotics, furthering the belief that there is a causal relationship between gut bacteria and the disease.[32,33] The presence of pneumatosis intestinalis on radiography, possibly representing submucosal gas produced by bacterial fermentation,[34] also affirms the role of bacterial colonization in NEC pathogenesis. Studies have demonstrated that *Clostridial* species may account for the pneumatosis intestinalis seen on radiography in infants with NEC.[34,35] However, it has not been established that *Clostridial* species themselves are the single pathogens associated with NEC. Many now suggest that NEC may result not due to single microbial colonization and infection, but due to secondary inflammation in response to microbial dysbiosis related to multiple organisms.[36]

Stool colonization studies have demonstrated that microbial dysbiosis contributes to mucosal injury and initiation of an inflammatory response promoting intestinal permeability in premature infants with NEC.[37] Recent data have shown an overrepresentation of gram-negative, pathogenic bacilli and decreased amounts of commensal, obligate anaerobes in stool cultures of premature infants with NEC when compared to their control counterparts.[38] Meta-analyses suggest the abundance of *Proteobacteria* precedes the diagnosis of NEC and triggers the inflammatory cascade through the expression of TLR4.[39] Alteration of the intestinal microbiome from commensal to pathogenic bacteria within preterm infants with NEC has also been described.[40] Studies using 16S rRNA sequencing showed the succession of bacterial classes from *Proteobacteria* to *Clostridia* in these NEC infants.

Formula feeding

Infant formulas that are currently available are largely designed to resemble human milk composition in terms of calorie provision and nutrients needed for appropriate growth. However, these formulas do not provide other components of human milk that contribute to boosting immune function and maintaining mucosal integrity and function of the GI tract.[41] Formula feeding is associated with a higher intestinal pH when compared to human milk, which does not favor the growth of commensal bacteria. The mucus coating of the small bowel is also affected by formula feeding, with higher rates of disruption and increased permeability within bowel enterocytes when an infant is formula fed.[42] Increased intestinal stasis associated with formula feeding also contributes to increased intestinal permeability. Finally, formula feeding also decreases the stimulation of the mucosal defense system and leads to increased immune activation and release of proinflammatory cytokines to foreign antigens.[42,43]

Prevention of NEC

Human milk feeding

Large amounts of data support the concept of human milk feeding and the reduction of NEC incidence and severity.[20,44] Human milk, when compared to formula feeding in preterm infants, is likely protective against NEC due to components reducing overall inflammation.[45] Human milk provides mucosal immune components, oligosaccharides, secretory immunoglobulin A (IgA), and lactoferrin that decrease intestinal permeability and alter bacterial flora to prevent an inflammatory cascade and NEC development. Human milk is associated with lower intestinal pH compared to formula, favoring the growth of commensal bacteria. A meta-analysis of 343 infants showed that those receiving human milk were 3 times less likely to develop NEC when compared to those who were formula fed.[46] The role of banked donor breast milk in prevention of NEC is less clear. Most donated milk is from mothers of term infants and the milk undergoes processing and pasteurization that may alter its composition.[47] Although studies have demonstrated benefit from donor breast milk compared to synthetic formula feeding,[48] mothers' own milk is likely superior due to factors that are incompletely elucidated.

It is important to note that although human milk feeding is important in preventing NEC in preterm infants, feeding related factors including rate of advancement, timing of initial feeds, and trophic feeding do not seem to contribute to the development of NEC. Although 1 trial found that infants fed at 20 cc/kg/day were more likely to develop NEC than those fed at 10 cc/kg/day,[49] other studies evaluating slow versus fast feeding advancement found faster feeding advancements were safe without an increased risk of NEC.[50] Delaying feeds in preterm infants is not a recommended strategy for the prevention of NEC, as delayed feeds have been shown to result in delayed gut development, increased central catheter days, and increased risk of central line associated bloodstream infections.[49] In addition, delayed enteral feeding has been associated with more severe NEC.[51] Conflicting reports also exist regarding trophic feeding, with some clinical data suggesting a decreased risk of NEC with the use of trophic feeding for the first few days of life while others have shown delayed time to full enteral feeding without a decreased risk of NEC.[50,52,53]

Colostrum

Colostrum, due to its higher concentration of proteins and immunoactive components, has been proposed to have potential to prevent NEC.[45] Studies on oral colostrum administration in preterm infants and the development of the immune system have been contradictory. One group demonstrated the safe administration of colostrum in extremely low birth weight (ELBW)

infants with improved overall growth in 36 weeks.[54] Another randomized controlled trial showed an increase in salivary secretory IgA and decreased hospital length of stay.[55] Other randomized controlled trials, however, have not shown an impact on immune peptides and intestinal microbiota.[56] Further studies are needed to determine the efficacy of colostrum in improving innate immune function and potentially preventing NEC development.

Probiotics

Probiotics have been proposed as a means to prevent NEC in infants. The exact mechanism by which probiotics may exert a protective effect in these infants remains ambiguous, however it has been demonstrated that probiotics may provide commensal bacteria to improve intestinal barrier function, modulate proinflammatory cytokines, and regulate the innate immune response.[57] The use of probiotics, in a meta-analysis by the Cochrane Review, showed that probiotic use was associated with a 49% reduction in NEC incidence and an overall reduction in mortality of VLBW infants.[58] However, studies have also associated probiotic use with fungemia, bacteremia, and sepsis with postulated transmigration of the probiotic bacteria across inflamed intestinal mucosa into the bloodstream.[59] Finally, a large number of different probiotic organisms and products are available, making studies of different probiotic therapies difficult to compare. Although probiotic use may be an adjunct in preventing NEC in preterm infants, large, randomized prospective trials are needed to determine the long-term effects and overall value in prevention and treatment of NEC.

Prebiotics

Prebiotics are supplements containing a nondigestible food stimulating the growth and activity of indigenous bacteria without carrying the same infectious risk of probiotics. Oligosaccharides, a component found in human milk, are a prebiotic that may play a strategic role in preventing NEC. Galacto- and fructo-oligosaccharide administration has been shown to increase short chain fatty acid production, thereby decreasing bowel pH, increasing intestinal motility, and improving mucosal barrier integrity.[60,61] Oligosaccharides also serve as a nutritional substrate for commensal bacteria, including *Bifidobacterium*, and influence the innate intestinal microbiome.[61]

Oligosaccharides also play a role in inhibiting pathogenic bacterial adherence to the GI mucosa, further protecting an infant from infection.[61] The supplementation of oligosaccharides may lead to increased levels of fucosylated oligosaccharides and contribute to added immune benefits for the infant. Although sialylated galacto-oligosaccharides and fucosyllactose were shown to reduce NEC in animal models, other human milk oligosaccharides were found to be significantly elevated in infants with NEC.[62] There is the potential for prebiotic administration to decrease the rate of NEC in preterm neonates.[63] However, supplementation with this particular human milk component has not been widely recommended, and investigation into the role of isolated oligosaccharide administration in preventing NEC is further warranted.

Lactoferrin

Components within human milk, including lactoferrin, have been shown to have protective properties that prevent NEC development. Lactoferrin, a protein found in human milk, is known for its antimicrobial properties. Animal studies have shown that lactoferrin interferes with triggering of the inflammatory cascade, therefore preventing intestinal inflammation and NEC development.[64] This may occur through competition with lipopolysaccharides for TLR-4 binding,

thereby inhibiting the release of proinflammatory cytokines.[65] Trials that have evaluated lactoferrin supplementation in infants have shown mixed results. A Cochrane review of lactoferrin administration in preterm infants concluded that the quality of evidence to reduce the incidence of NEC was marginal.[66]

Red blood cell transfusion

Packed red blood cell transfusion is a debated topic in infants with NEC. Several studies have temporally linked packed red blood cell transfusion and the development of NEC,[67,68] whereas others have shown no definitive relationship.[69,70] In infants receiving transfusions within the 48 hours prior to the onset of NEC, disease is associated with higher incidence of surgical intervention and higher mortality.[71] The possible pathophysiological mechanisms are not clear, although alterations in mesenteric perfusion in individuals receiving enteral feeding during transfusion have been suggested.[72] Other groups have proposed that disease is related not to transfusion itself, but to the underlying anemia.[73] Given the potential risks of worsening intestinal ischemia by feeding during transfusion, several groups have recommended holding feeds during packed red blood cell infusion. One study showed a decrease in the incidence of NEC in VLBW infants after initiation of a peritransfusion protocol that holds feeds before, during, and after transfusion.[74] However, since this was not a concurrent study it is possible this benefit could be attributed to improving care overall. A randomized controlled trial is currently being performed in the UK, titled the Withholding Enteral Feeds Around Transfusion trial (ISRCTN62501859) in order to further evaluate this issue.

Presentation and diagnosis

NEC manifests as a spectrum of disease, ranging from subtle, clinical findings to septic shock, perforation, and need for emergent surgery.[6] Generally, preterm infants developing NEC present with feeding intolerance. This is demonstrated through GI symptoms including abdominal distention, bilious emesis or aspirates, diarrhea, or bloody stools.[75] Infants may also manifest altered physiology including bradycardia, apnea, hypotension, and temperature volatility.[2,76] These hemodynamic changes are usually associated with the insidious progression of NEC, while advanced stages are associated with peritonitis, acidosis, disseminated intravascular coagulopathy, and septic shock.[77,78]

Physical assessment is crucial in NEC diagnosis, as this may guide a clinician's therapeutic decision making. Early findings may be notable for abdominal distention and tenderness, while infants with advanced disease may present with abdominal wall discoloration and edema (Fig 2). Timing in the presentation of NEC appears to be bimodal based on an infant's gestational age.[79] The median onset of NEC for infants with a gestational age of less than 26 weeks has been shown to be at around 3 weeks of age, whereas disease onset is generally shorter at around 10 days for infants with a gestational age greater than 31 weeks.[80]

Abdominal radiography remains the standard imaging modality used to diagnose NEC and determine the need for surgical intervention, although definitive diagnosis is only made through surgical inspection of the abdomen or postmortem pathologic confirmation of intestinal inflammation and necrosis. The hallmark finding of NEC is pneumatosis intestinalis, or gas within the intestinal wall (Fig 3). However, bowel wall thickening, paucity of gas, and portal venous gas are other imaging findings associated with NEC.[81] Fixed bowel loops, also called sentinel loops, can be suggestive of necrotic bowel without pneumatosis when noted on plain film.[82] Pneumoperitoneum seen on radiography requires urgent surgical intervention. The "football sign" is one of the classic radiographic findings of pneumoperitoneum seen on supine radiography. It is important to consider taking these films in both a supine and left lateral decubitus or cross-table configuration to easily detect pneumoperitoneum, especially for free air overlying the liver. In

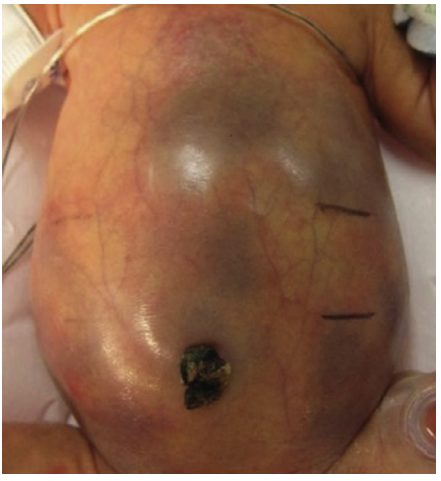

Fig. 2. Abdominal wall discoloration in an infant with necrotizing enterocolitis.

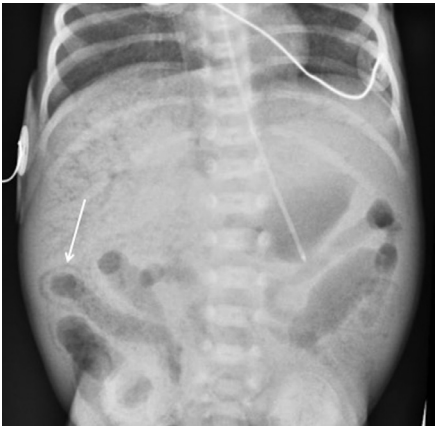

Fig. 3. Pneumatosis intestinalis on abdominal radiography.

infants with feeding intolerance and suspected or confirmed NEC, radiographs are usually obtained serially every 6-12 hours to follow the progression of the disease.

An abdominal assessment scale was recently proposed to standardize the diagnosis of NEC based upon positive radiographic findings. The scoring system based these positive findings on plain film and gave a score ranging from 0 to 10, with 0 representing normal bowel gas patterns and 10 representing the presence of pneumoperitoneum.[83] However, it is important to note there is significant interobserver variability in interpretation of radiographic signs of NEC.

Ultrasonography is increasingly playing a role in the evaluation of the disease due to its capacity to provide images in real time and assess the presence of peristalsis, thickness of the intestinal wall, presence of fluid in the peritoneal cavity, and potentially altered blood flow.[84] It has been argued that ultrasound may be beneficial in early, suspected NEC in infants with presumed feeding intolerance due to its ability to detect abnormal bowel wall echogenicity, subtle pneumatosis otherwise not seen on radiography, and initial increase in intestinal wall vascularity (Fig 4).[85,86] Ultrasound has also been shown to be more sensitive for the detection of portal venous gas.[87] A meta-analysis of 9 studies including 462 patients with NEC showed that the use of abdominal ultrasound had overall low sensitivity but high specificity in detecting bowel wall

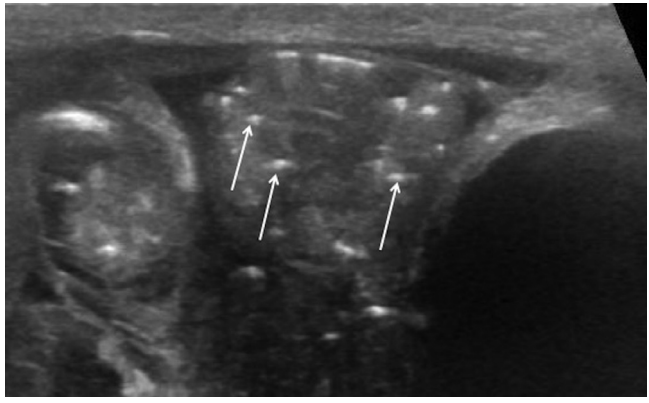

Fig. 4. Pneumatosis on ultrasonography as noted by hyperechoic spots within the intestinal wall (white arrows).

thinning, absent peristalsis, portal venous gas, pneumatosis, and free air.[88] Although ultrasound may confirm the diagnosis of NEC, it has not been demonstrated to be a superior diagnostic modality to plain radiography. It is becoming an important adjunct to abdominal radiographs in diagnosing and following the progression of NEC, but further studies are warranted to examine its efficacy in this population.

Near-infrared spectroscopy (NIRS) is a noninvasive method of measuring local abdominal tissue oxygenation as a marker of bowel perfusion. Decreased NIRS readings have been identified in piglets who developed NEC compared to healthy controls.[89] NIRS has also been used to show an increase in mesenteric oxygenation during enteral feedings.[72] Further advances in this technology could result in a non-invasive test that allows for early detection of intestinal ischemia.

Although laboratory tests are not used to confirm the diagnosis of NEC, blood tests and biomarkers may support its diagnosis, stage severity, and aid NEC management. The presence of metabolic acidosis and increasing serum glucose in preterm infants with NEC has been understood to support diagnosis of the disease.[90,91] An absolute neutrophil count of less than 1500 cells/μL on a complete blood count has been associated with a poor prognosis in infants with NEC.[92] Thrombocytopenia and declining platelet counts over time correlate with NEC and worsening disease, whereas increasing platelet counts over time may conversely indicate clinical improvement.[93]

Due to the relative nonspecificity of current clinical and radiographic tests, potential biomarkers have been assessed in their value for the evaluation of NEC and its progression. Proinflammatory cytokines and acute-phase reactants like TNFa, IL-6, IL-8, and C-reactive protein also show promise in diagnosing NEC and may even predict the need for surgical intervention.[94] Organ specific biomarkers indicating enterocyte injury and intestinal barrier dysfunction implicated in the diagnosis of NEC include fecal calprotectin, claudin-3, and intestinal fatty acid binding protein.[95,96] Fecal calprotectin is a marker of intestinal inflammation and has been shown to differentiate Bell's stage II NEC from systemic illness/Bell's stage III NEC with approximately 76% sensitivity and 92% specificity.[97] In infants who developed bowel perforation, fecal calprotectin was found to be significantly higher than those who did not.[98] The use of this biomarker, however, is limited due to its interindividual variability and typically less frequent bowel movements in infants with NEC.[99]

Intestinal-fatty acid binding protein (I-FABP) is a cytosolic protein located in mature enterocytes and villi that is released into the bloodstream after cell disruption and excreted into the urine.[100] In a prospective trial, I-FABP levels were significantly higher in both plasma and urine for those with NEC with cutoff values of 9 ng/mL in plasma and 218 ng/mL in urine.[101] Serial plasma and urinary I-FABP measurements also accurately predicted worsening versus improvement of NEC in these infants. Another study showed I-FABP levels, when taken at birth and at

the start of feeding, were elevated in infants who would go on to develop NEC when compared to their healthy counterparts, suggesting that the biomarker may help in predicting NEC development in patients.[102]

A survey amongst pediatric surgeons concluded that the most commonly used biochemical tests in the diagnosis and progression of NEC include platelet count, C-reactive protein, white blood cell count, and lactate level.[103] Most surgeons currently do not use fecal calprotectin, interleukin levels, or I-FABP to routinely aid in clinical decision making. Strategies to utilize these biomarkers in predicting NEC severity need to be validated but are promising in identifying infants both at risk for developing NEC and assessing those requiring future surgical intervention for perforation or bowel necrosis.

Medical management of necrotizing enterocolitis

Once the diagnosis of NEC is suspected clinically, medical management should be initiated promptly. Medical therapy includes supportive care with broad spectrum empiric antibiotics, bowel rest with gastric decompression, initiation of parenteral nutrition (PN), fluid resuscitation, correction of any hematologic/metabolic derangements, and cardiovascular and respiratory support, as needed. Data suggest that approximately 60% to 80% of patients may recover with these non-invasive strategies alone.[104]

Empiric antibiotic therapy

Due to concerns that microbial dysbiosis plays a role in pathogenesis and early reports of bacteremia in up to 30% of NEC patients, intravenous broad spectrum antibiotics remain a mainstay of care.[17] However, there are no current consensus guidelines regarding a specific antibiotic regimen or duration of therapy for NEC. The most common bacterial species isolated in samples from infants with NEC include *Clostridia*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter, Pseudomonas*, *Clostridium difficile,* and *Staphylococcus epidermidis.*[37,105] Coverage of both gram-positive and gram-negative organisms is recommended (eg., ampicillin and gentamicin).[35,106] Vancomycin has been recommended in place of ampicillin in centers with a high prevalence of methicillin resistant *Staphylococcus aureus* (MRSA). Amikacin may be used in lieu of ampicillin in centers with high levels of ampicillin resistance.[107] Piperacillin-tazobactam is becoming more frequently used in neonatal care because it lacks the ototoxic and nephrotoxic side effects of gentamicin.[108] In addition, its broad spectrum coverage has allowed it to be used as a single agent in infants with suspected NEC. Fungal coverage is not routinely recommended but should be considered in patients with positive fungal cultures or in those who continue to decline clinically despite broad spectrum antibiotics.[109]

The addition of concomitant anaerobic coverage in these patients remains controversial. In an early study, infants randomized to ampicillin plus gentamicin were compared to infants randomized to ampicillin, gentamicin, and clindamycin therapy.[110] There was no significant difference in mortality; however, there was a significantly increased rate of intestinal stricture in the cohort receiving clindamycin.

More recent studies have attempted to evaluate the benefits of anaerobic coverage while also investigating the potential risk of stricture. A prospective, case controlled study of VLBW infants found no mortality benefit in patients with medical NEC who received anaerobic coverage, but did identify a lower mortality rate in infants with surgical NEC.[111] Notably, an increased rate of stricture was identified in patients treated with anaerobic coverage; however, this was only significant in patients with surgical NEC. Infants receiving anaerobic coverage were more likely to be ventilated and on inotropic support, indicating that anaerobic overage may be beneficial in more severe disease. Other studies have shown lower rates of mortality, complications, and need for surgery in patients treated with anaerobic antibiotics; however, these were performed in small or non-concurrent patient populations.[112]

The optimal length of antibiotic treatment in patients with NEC is currently debated. Although early antibiotic treatment is a mainstay of sepsis management, multiple groups have shown significant adverse effects of antibiotic exposure in neonates including risk of sepsis, NEC, bronchopulmonary dysplasia, and death.[33] Typically, a 10 to 14 day course is considered standard of care in the absence of intra-abdominal abscess formation. The WHO Guidelines for the Management of Common Childhood Illnesses recommend ampicillin, gentamicin, and metronidazole for 10 days in infants with medical NEC.[106] At present, further studies are needed to determine the optimal antibiotic regimen and duration in patients with NEC. Gram-positive and gram-negative coverage should be provided to all patients, with specific regimens tailored to institutional antibiograms. Infants with more severe disease may benefit from the addition of an anaerobic agent. Treatment duration should be titrated to the clinical status of the individual patient. Given the adverse effects of antibiotics in the neonate, early discontinuation in patients with mild disease should be considered.

Feeding and parenteral nutrition

Once a diagnosis of NEC is suspected, the infant should be placed on bowel rest and initiated on PN. A naso- or orogastric tube is inserted to provide bowel decompression. The duration of bowel rest is typically based on the severity of disease, need for operative intervention, and clinical judgment.

Several studies have shown no increase in mortality or NEC recurrence with early feeding regimens (defined as 5-7 days).[113,114] Two retrospective studies have shown a significant increase in time to full enteral feeds and an increased rate of central line associated bloodstream infections (CLABSIs) in patients who received delayed feeding.[87,114] Although current data suggest that earlier feeding may not lead to increased mortality or recurrence of NEC and may reduce the hospital length of stay and the number of CLABSIs, common practice involves NPO duration of 7 to 14 days based on disease severity. Large randomized studies are needed to clarify the optimal timing to resume feeds after NEC.

Resuscitation and ventilatory support

Fluid resuscitation is initiated to optimize intravascular volume status and organ perfusion after NEC is suspected. Standard markers of tissue perfusion and urine output are used to assess the adequacy of resuscitation. Inotropes should be used as needed.

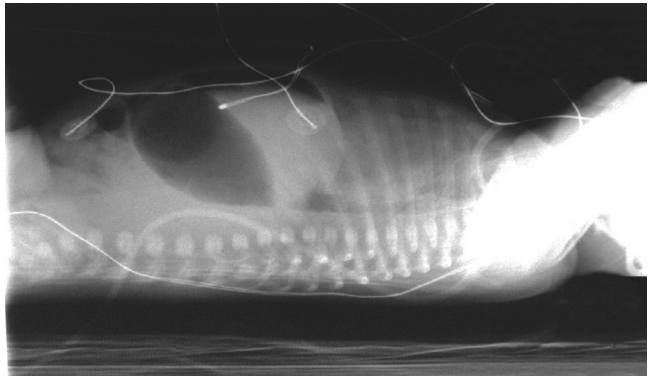

Fig. 5. Pneumoperitoneum on as seen on cross-table abdominal radiography.

Due to the overrepresentation of premature infants in the cohort of patients affected with NEC, concurrent pulmonary disease is common. Infants with NEC tend to experience a systemic inflammatory response resulting in third spacing and higher fluid resuscitation requirement. This manifests as severe inflammatory lung disease, more severe than lung disease in premature infants without NEC.[115,116] Many infants require mechanical ventilation during this time.[91] Abdominal distention may become severe enough to affect pulmonary mechanics, further necessitating mechanical ventilation.

Although there is no consensus regarding the optimal strategies for ventilatory support in infants with NEC, avoidance of modalities that may cause worsening abdominal distention, such as continuous positive airway pressure, is a common practice. Several studies have shown an increased risk of NEC in patients receiving continuous positive airway pressure.[116,117] In contradiction, however, a study of the use of early nasal continuous positive airway pressure in premature infants did not show a higher incidence of NEC.[115]

Monitoring response to therapy

Serial physical examination, laboratory testing, and radiographic imaging should be performed to evaluate the clinical status. If the patient demonstrates signs of worsening abdominal compromise, surgical consultation is required.

Close attention should be paid to changes in the physical examination, as NEC may progress rapidly. Increasing abdominal distention, abdominal wall erythema, and tenderness to palpation are all concerning findings that should prompt further evaluation.

Laboratory values should be monitored every 12-24 hours, including complete blood count, platelet count, metabolic panels, and acid base studies (including pH and lactate). Worsening thrombocytopenia, acidosis, or hyperglycemia are all concerning for disease progression. Normalization of these values after treatment suggests a positive response to medical therapy. Persistent abnormality or worsening of these studies are concerning.

Serial abdominal imaging should also be obtained to assess bowel viability. Depending on the clinical severity of the patient's presentation, radiographs should be obtained every 6 to 24 hours.

Surgical management

Indications for operative intervention

Approximately 25% to 50% of infants with NEC will ultimately require surgery. The only absolute indication for surgical intervention in infants with NEC is bowel perforation. Perforation is typically manifested by the presence of pneumoperitoneum on the abdominal radiograph (Fig 5); however, the rate of infants with perforation without radiographic signs of pneumoperitoneum may be as high as 25% to 50%.[118,119] The presence of bile, purulence, or stool in the peritoneal fluid after paracentesis is also an indication of perforation, although paracentesis is infrequently performed. Lastly, many clinicians consider clinical deterioration in a patient receiving maximal medical therapy to be an indication for operative intervention.

The optimal timing of surgical intervention in infants with NEC is theoretically after the development of irreversible bowel necrosis but prior to perforation. This avoids the stress of major surgery in infants who will recover with medical management alone but allows for intervention prior to the development of peritoneal sepsis. Although no definitive markers of bowel necrosis have been identified, radiographic signs, laboratory abnormalities, and several physical examination findings have been linked to more severe disease and may be considered relative indications for surgical intervention.

Several studies have linked portal venous gas to disease severity and higher rates of morality[77,118-120] (Fig 6). Additionally, infants with portal venous gas, particularly ELBW infants, have

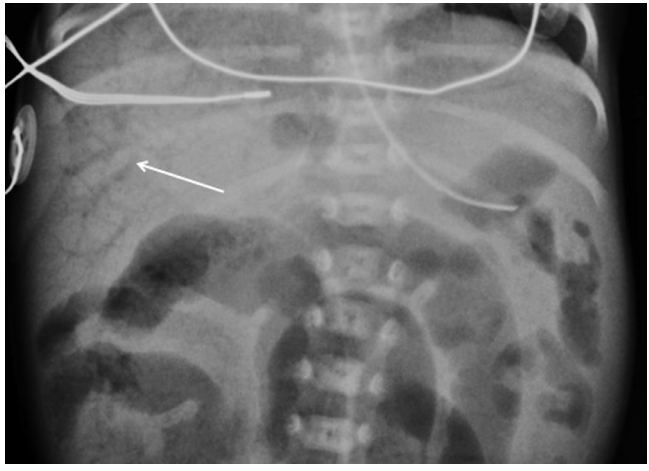

Fig. 6. Portal venous gas on abdominal radiography (white arrow).

been found to have a higher rate of NEC totalis (defined as >75%-80% bowel necrosis).[77,121,122] It is also theorized that radiographic signs of perforation and bowel necrosis develop later in ELBW infants, potentially leading to delays in treatment.[122,123] Although portal venous gas has been associated with higher rates of NEC totalis and the need for surgical intervention in the ELBW neonate, there is still a percentage of patients with findings of portal venous gas on radiography who survive with medical management alone. Therefore, the overall clinical scenario should dictate whether operative intervention is appropriate.

Additional radiographic signs that should prompt surgical consideration include a fixed bowel loop on radiography and a gasless abdomen. A fixed loop has been associated with a higher rate of surgical intervention and higher mortality rate.[120,124] This represents another concerning imaging finding that should prompt close clinical observation and serial radiologic evaluation. Several groups have evaluated the prognostic role of ultrasonography in NEC and need for surgical intervention. Absent bowel perfusion by Doppler, thinning of the bowel wall (less than 1 mm), and echogenic ascites have been associated with perforation.[85]

Metabolic acidosis, hyperglycemia, neutropenia, and thrombocytopenia have been associated with more severe disease. Persistent metabolic acidosis, defined as a pH less than 7.2, has been shown to be a predictor of the need for operative intervention.[91] Acidosis has also been associated with higher mortality rates.[77] Thrombocytopenia and declining platelet counts over time correlate with NEC and worsening disease, whereas increasing platelet counts over time may indicate clinical improvement.[90] Premature infants tend to have frequent episodes of hypoglycemia and this derangement has not been associated with NEC.[91] Persistent hyperglycemia has been associated with the development of NEC, worsening severity, and increased mortality rate.[91,125]

Physical examination findings concerning for perforation include abdominal wall erythema or discoloration, crepitus, and a palpable abdominal mass. Although these findings are highly specific for infants with perforated NEC, they occur in less than 10% of patients.[118] The presence of 1 or more of these findings should prompt consideration for operative intervention.

Several groups have attempted to create predictive models to identify patients who will require surgical intervention. A panel of 7 laboratory derangements that were associated with worse prognosis in infants with NEC has been proposed.[126,127] These markers include positive blood culture, acidosis (pH<7.25), bandemia, hyponatremia, thrombocytopenia (<50,000/mm^3), hypotension/pressor requirement, and absolute neutrophil count <2,000/mm^3. Three or more panel derangements were associated with advanced disease and need for surgical intervention. In an uncontrolled trial at a single institution, use of the panel was associated with significant improvement in outcomes, including mortality rate and enteral feed tolerance.[127]

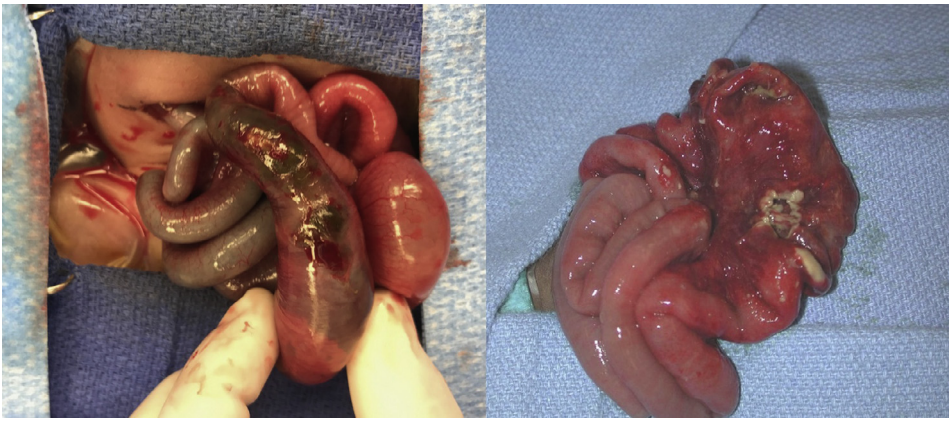

Fig. 7. Exploratory laparotomy with necrotic bowel and perforation in an infant with necrotizing enterocolitis.

In summary, there are no current, definitive guidelines for surgical intervention in patients with NEC without clear evidence of perforation. As such, individual treatment plans should be guided by a multidisciplinary team of neonatologists, anesthesiologists, and surgeons. Findings such as portal venous gas, fixed abdominal loop, and worsening metabolic derangements are not absolute indications for surgery but should prompt operative consideration.

Operative considerations

Regardless of operative technique, several principles and considerations apply to all patients with NEC. In the operating room, gastric decompression should be continued and general anesthesia induced. Anesthesia in preterm and term neonates differs in important ways from that in the older patient. The physiologic immaturity of neonates is characterized by limited pulmonary and cardiac reserve, high metabolic rate, increased temperature sensitivity, and varied responses to medication.[128] In patients with NEC, in particular, intraoperative anesthesia is often made challenging by the patient's extreme prematurity with associated respiratory failure, hemodynamic instability, acidosis, and coagulopathy. Abdominal distention can decrease functional residual capacity and complicate intubation and ventilation. Intraoperative fluid requirements may be considerable due to third-spacing and potential bleeding. If inotropes are required, dopamine has been shown to improve intestinal perfusion and is preferred.[128]

Once the decision has been made to proceed with laparotomy, the operative goals are to remove all gangrenous bowel, if possible (Fig 7). Because the neonatal abdomen is round, a supraumbilical transverse incision should be made. This allows for good access to the entire abdomen and easier closure.[129] Careful tissue handling in the premature infant is important and should be employed. The fragility of the neonatal liver cannot be overstated and liver manipulation should be minimized to avoid subcapsular hematoma and catastrophic liver hemorrhage, which is associated with a high mortality rate. In patients who require significant small bowel resection, placement of an enteral feeding tube should be considered. Bowel length should always be measured during operation to guide future management should the patient develop short bowel syndrome. Typical operative management during laparotomy involves resection of necrotic bowel followed by proximal diversion with an enterostomy. There has been a trend toward using different strategies to limit bowel resection including primary anastomosis at the time of initial operation, multiple look laparotomies to salvage marginal

bowel, and utilization of new techniques such as the "clip and drop-back" or "patch drain, and wait" models.

Enterostomy vs primary anastomosis

Laparotomy with resection of necrotic bowel and enterostomy, with or without a mucus fistula, has long been considered to be the safest option for infants with NEC.[130] These infants tend to be systemically ill with gross abdominal contamination, an environment that is traditionally considered hostile for anastomotic healing and high risk for leak. Enterostomy diverts the fecal stream and allows for resolution of peritonitis before re-establishing continuity.

Several groups have advocated for primary anastomosis during the initial operation as an attempt to avoid stoma complications and the need for additional operations. Studies in the 1970s to 1980s reported reasonable overall survival rates in selected infants with primary anastomoses.[131,132] In contrast, another report argued that infants who underwent primary anastomoses had increased mortality risk with multiple anastomotic leaks discovered at the time of autopsy.[133]

More recently, studies have demonstrated no difference in mortality rate between infants receiving primary anastomosis and those receiving enterostomy,[134-136] although patients offered primary anastomosis tended to be healthier. Several groups included VLBW or ELBW infants, indicating there may be a role for primary anastomosis in selected low birth weight infants.[125,136] However, as was to be expected, a recent meta-analysis could offer no recommendations on this matter due to study heterogeneity.[137]

Primary anastomosis may be an appropriate option in some infants, particularly those with focal necrosis or SIP. Careful analysis of the condition of the bowel as well as the patient's overall clinical status should be considered in any patient when deciding which surgical technique to use. Further prospective studies in larger patient populations are required to determine the safety and efficacy of primary anastomosis with appropriate patient selection.

Proximal diverting ostomy

In infants with severe and widespread disease, multiple bowel-preserving techniques have been proposed. A proximal diverting ostomy in infants with diffuse disease may be considered, with resection of necrotic bowel and primary distal anastomoses or evaluation of bowel at a second-look laparotomy. This technique was first reported in 3 infants with NEC. All infants recovered and on reoperation it was possible to salvage bowel that would otherwise have been resected.[138] However, proximal jejunostomies are associated with more complications than more distal enterostomies, with rates reported as high as 83%.[130]

Clip and drop-back technique

The "clip and drop-back" technique was proposed in infants with diffuse disease in an attempt to maximize bowel preservation and avoid proximal diversion.[139] In this technique, the grossly nonviable bowel is resected, and the ends of the remaining bowel are clipped, tied, or stapled closed. The bowel is replaced in the abdomen, and a second look is performed 48-72 hours later. When feasible, intestinal continuity is restored without enterostomy. If further necrotic bowel is identified during the second look, the process is repeated, and a third look is planned. This technique has the advantage of controlling leakage of bowel contents while allowing the patient to medically stabilize. Although success has been reported by several groups with this technique, the studies evaluated small cohorts without controls.[140,141] The clip and drop-back technique may be an option for clinically unstable patients with multifocal disease.

Patch, drain, and wait technique

An alternative technique called "patch, drain, and wait" has also been proposed.[142] In this approach, no bowel is resected at initial laparotomy. Using multiple different closure techniques, including primary approximation and omental patching, all perforations are repaired. Penrose drains are placed in the upper abdominal quadrants and exit via stab incisions in the lower quadrants, with the goal of draining fecal material. Further laparotomy is delayed for at least 14 days and drains remain in place until all fecal egress has stopped. Using this technique, the authors reported that 70% of patients did not require a second operation. Notably, they reported 2 cases of NEC totalis with total small bowel and colonic involvement. No patches were performed in these infants and operative intervention consisted solely of washout and drain placement. On second look laparotomy viable bowel was found in both cases and intestinal continuity was able to be restored. This technique is not commonly used in clinical practice.

Primary peritoneal drainage vs laparotomy

The optimal surgical treatment option for VLBW infants is highly controversial. In the 1970s, Ein and colleagues described their success using primary peritoneal drainage (PPD) in ELBW infants with perforation who were felt to be too unstable to undergo laparotomy, with the goal of stabilizing the patient until laparotomy could be performed.[143] Under local anesthesia, a small incision is made in the right lower quadrant (or where the majority of free air is visualized on imaging). Cultures of peritoneal fluid are taken and the abdomen is irrigated with saline until clear, although this last step is omitted by some groups. A flexible ¼ inch Penrose drain is passed through the incision into the abdomen. The use of PPD aims to remove stool and purulent peritoneal fluid from the abdomen in an attempt to mitigate the sepsis response. Additionally, by removing gas and liquid from the abdomen, distention decreases, urine output increases, and ventilation improves transiently.[144]

In their initial evaluation of 5 infants who received PPD, Ein and colleagues found that 3 of the infants survived without further operative intervention. The authors revisited their experience with 15 patients in 1980 and found no survival difference between infants receiving PPD and those receiving laparotomy. Interestingly, they again identified a cohort of infants that did not require subsequent laparotomy.[145]

Over time PPD has gained popularity among surgeons not only as a temporizing measure but also as a definitive therapy in some situations. Studies regarding the use of PPD in NEC have, however, been contradictory. Although some studies have reported similar or improved mortality with PPD,[146-149] others showed higher mortality rates.[150-152] Infants undergoing PPD generally had a lower birth weight, younger gestational age, and were clinically sicker. In some studies initially showing higher mortality after PPD, when infants were matched for gestational age and birth weight, or when limited to ELBW infants, the survival between PPD and laparotomy was no longer significantly different.[150,151] A large prospective database review identified PPD as an independent predictor of mortality.[153] The percentage of patients who survived following PPD and did not require secondary laparotomy was reported to range from 27% to 67%.[147-149,152,154] Interestingly, 1 group identified a cohort of infants who improved clinically several days after drainage and went on to survive.[148]

It is important to note that several of these studies report an increased rate of complications in patients undergoing PPD,[148,151,152,154] including the initial 1980 review, which noted an increase in the number of strictures.[145]

Several more recent studies evaluating prospectively collected information in large data sets showed a significantly higher mortality rate associated with PPD.[150,155] A prospective cohort study from the Vermont Oxford Network (VON) evaluated mortality in VLBW infants undergoing PPD and/or laparotomy [9]. The mortality rate in infants undergoing PPD alone was found to be significantly higher than those undergoing laparotomy (50% vs 31%). There was no statistically

significant difference between patients who underwent PPD followed by laparotomy and those who underwent laparotomy alone; 27% of infants receiving PPD survived without requiring an additional operation. This indicates that this group is likely dichotomous. Since there is no reliable way to distinguish SIP from NEC without laparotomy, the infants that survive after PPD alone likely have minimal NEC or SIP.

Two randomized controlled trials have been performed in an attempt to clarify the optimal treatment regimen for low birth weight infants with NEC. The Necrotizing Enterocolitis Study Towards Evidence-based Pediatric Surgery (NECSTEPS) trial in North America was published in 2006[156] and the Necrotizing Enterocolitis Trial (NET) in Europe was published in 2008.[157] Both trials were multicenter studies, with NECSTEPS involving 14 US and Canadian centers and NET involving 31 centers in 13 countries. NECSTEPS included infants weighing less than 1500 g at birth and NET included infants weighing less than 1000 g at birth. The trials differed in their technique and operative decision making. Infants undergoing PPD in the NECSTEPS trial received irrigation as part of the drainage procedure, whereas infants in the NET trial did not. Perhaps most importantly, post-PPD laparotomy was discouraged in the NECSTEPS trial, although it was allowed for patients who continued to clinically deteriorate. Only 5 patients (9%) in the PPD group underwent laparotomy in the acute period, although it should be noted that 16 infants required delayed laparotomy for stricture, obstruction, or enteral intolerance. The NET trial allowed for laparotomy if patients developed clinical deterioration as soon as 12 hours after drainage and 26 infants (74%) underwent laparotomy at a median of 2.5 days postdrainage. The effect of this protocol difference is that PPD was treated as a definitive therapy in the NECSTEPS trial, whereas it was treated as a bridge to laparotomy in the NET trial. PPD alone was used in 33% of infants in the NECSTEPS trial and in only 11% of infants in the NET trial.

The primary outcome for both groups was mortality rate. The NECSTEPS trial evaluated mortality rate at 90 days and the NET trial at 1 and 6 months. Both groups found no statistically significant difference in mortality rate between patients who underwent PPD compared to those who underwent laparotomy. Both trials were analyzed using an intention to treat approach such that infants who received laparotomy after PPD were included in the PPD group. Secondary outcomes including rates of PN-dependence, length of hospital stay, and respiratory outcomes were not significantly different in both trials. A substantial portion of infants were excluded at the discretion of the clinician in both trials (30 patients in the NECSTEPS trial and 20 in the NET trial). When these infants were considered separately in the NECSTEPS trial the outcomes were consistent with prior retrospective studies and showed that premature, lower weight infants were offered drainage, whereas the older, higher weight infants underwent laparotomy. When these groups were compared to each other, patients who underwent PPD had a significantly higher survival rate than infants who underwent laparotomy (41.4% vs 14.9%, respectively).

It should be noted that both trials closed prior to reaching their goal enrollment and both groups of authors caution that this increases the risk for missing clinically significant outcomes. Neither group evaluated cost or neurodevelopmental outcomes after PPD compared to laparotomy, 2 topics of great interest to clinicians. The Necrotizing Enterocolitis Surgery Trial is currently underway to evaluate both mortality rate after PPD versus laparotomy and neurodevelopmental outcomes (NCT01029353). A meta-analysis of both randomized controlled trials found no significant difference in survival between infants receiving PPD compared to those receiving laparotomy. However, given the small sample size clinically significant differences between the 2 groups could easily have been missed.[158]

In almost all studies, a subset of patients survives after PPD alone, without the need for salvage laparotomy. This suggests that infants receiving PPD represent a dichotomous group. Those who do not survive to laparotomy likely represent infants with significant, diffuse bowel necrosis, whereas those who clinically improve may represent a more physiologically stable group of infants, possibly those with minimal NEC or SIP. Further studies evaluating the role of PPD in VLBW infants should focus on the differences in outcomes between infants who are very ill at the time of PPD compared to those who are more stable.

Complications

Complication rates after surgical management of NEC have been estimated to be as high as 50% to 70%.[151,159] These include recurrence, stricture, wound infections, stoma complications, and short bowel syndrome.

Recurrent NEC is reported to occur in approximately 5% to 10% of patients.[160,161] It can occur in patients who had either surgical or medical NEC. The disease recurs on average 1 month after the initial episode, although it may occur as far out as 5 months.[160] The overall mortality rate for recurrent NEC is similar to the morality rate for a first-time episode[162] and is managed in the same way.

The rate of stricture after NEC has been reported to be as high as 40%.[130,163] Structure formation occurs as a result of the healing process of necrotic intestinal tissue, and as a result stricture can occur in patients after either medical or surgical NEC. The incidence of stricture is higher in infants after surgical treatment compared to medical treatment. On average, strictures occur approximately 1 month after the initial episode of NEC.[164] The most common site of stricture is in the colon (84%), followed by the ileum (16%).[164] Multiple strictures may manifest in up to 50% of infants.

Some studies have shown a higher incidence of stricture in infants with surgical NEC after proximal diverting enterostomy compared to primary anastomosis.[164] Infants with stricture frequently present with abdominal distention, vomiting, and feeding intolerance. Strictures may also be found in asymptomatic patients on pre-operative upper GI contrast studies or barium enemas. Surgical resection is typically necessary in patients with symptomatic strictures. Asymptomatic strictures frequently do not require treatment.

In patients with enterostomy, stoma complications may affect up to 68% of patients.[130] These complications include strictures requiring ostomy revision, retraction, parastomal hernia, prolapse, and intussusception.[130] Patients can also have difficulty achieving adequate enteral nutrition due to high stoma output.[165] Most of these complications are repaired at the time of stoma takedown.

Postoperative wound complications in infants with NEC include surgical site infection (SSI), wound dehiscence, and herniation. SSI rates after operative intervention for NEC are widely variable, with rates ranging from 4% to 23%.[159,161,166,167] Higher rates of SSI have been seen in lower gestational age infants.[168] Postoperative intra-abdominal abscess formation has been reported at 2.3% to 11%.[151,167]

Short bowel syndrome occurs when the intestine has insufficient absorptive capacity to support growth and may result from extensive intestinal resection or in infants without bowel resection due to poor absorptive function of diseased bowel.[129] Multiple definitions of short bowel syndrome are found in the literature; it is commonly described as prolonged PN dependence with definitions varying from 30 to 90 days.[169] Although there have recently been substantial improvements in outcomes for patients with short bowel syndrome over the past several decades, the associated comorbidities remain significant. Intestinal failure associated liver disease, CLABSI, vitamin deficiencies, and metabolic bone disease affect many patients with short bowel syndrome. Short bowel syndrome in infants with NEC has been reported to be as high as 25%.[104,166] The incidence of short bowel syndrome increases with decreasing gestational age.[170] Infants with short bowel syndrome secondary to NEC have been shown to be more likely to wean from PN than infants with short bowel syndrome secondary to other diagnoses.[171] Management in a multidisciplinary short bowel clinic can help optimize outcomes in these patients.[169,172]

Spontaneous intestinal perforation

It is important to distinguish NEC from SIP, an isolated perforation of less than 2 centimeters without diffuse bowel pathology. Initially thought to be a variant of NEC, SIP is now gener-

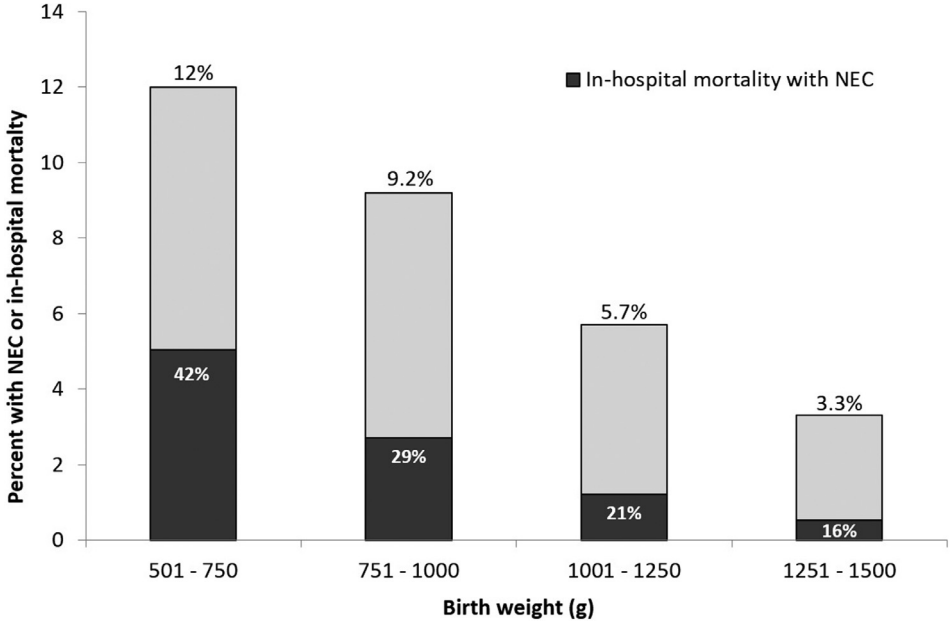

Fig. 8. Mortality in extremely low birth weight infants with necrotizing enterocolitis (NEC) by birth weight category in the Vermont Oxford Network database between 2005 and 2006, adapted from Hong and colleagues.[192]

ally recognized as a distinct clinical entity.[173] The diffuse inflammation and ischemia seen on histopathology in infants with NEC is absent in SIP.[174,175] Attenuation of the muscularis propria adjacent to the area of perforation has been described in a cohort of infants with SIP, although the pathologic consequences of this are unclear.[174] Perforation almost uniformly occurs on the antimesenteric border of the terminal ileum.[174,175] Early postnatal glucocorticoids and indomethacin have both been linked to SIP.[175,176] An infectious component has also been suggested as *Candida* and *Staphylococcus epidermidis* are frequently isolated from peritoneal cultures in infants with SIP.[177,178]

SIP and NEC share many similar presenting features. Both manifest primarily in premature infants,[153] however infants with SIP tend to have lower birth weights.[177] SIP tends to manifest earlier in life than NEC (median age 7 vs 15 days).[179] Infants with SIP present with acute onset abdominal distention, typically without abdominal erythema or crepitus. Isolated, blue-black discoloration of the abdomen is commonly seen in SIP but is rarely seen in NEC.[173] This discoloration represents extravasation of meconium from perforated bowel and may extend into the groin or scrotum due to a patent processus vaginalis. Radiographically, infants with SIP typically lack signs of diffuse bowel necrosis including pneumatosis and portal venous gas.[173] Laboratory changes in SIP are nonspecific and rarely useful in making a diagnosis.[174] The severe hemodynamic changes that often accompany NEC may be less common in infants with SIP, at least early in the course.[180] Conclusive diagnosis typically requires laparotomy.[153]

Treatment consists of prompt operative intervention. Both PPD and laparotomy have been used in patients with SIP. It is unclear which operative intervention is optimal based on current literature.[153,155] If laparotomy is performed, the patient may receive primary repair, undergo resection followed by primary anastomosis, or division of the intestine and proximal diversion with an enterostomy.

Investigation into clinical outcomes for infants with SIP is difficult due to limitations in definitive diagnosis. In infants with laparotomy-confirmed SIP, the mortality rate is lower than in those with laparotomy-confirmed NEC (19% vs 38%).[153,181] A retrospective, single center review found that mental and psychomotor development were higher at 1 year adjusted age in infants

with SIP compared to those with NEC. MRI has found that white matter injury, a significant cause of brain injury in premature infants, is less severe in infants with SIP than infants with NEC.[182]

NEC totalis

NEC totalis is a term used to describe panintestinal necrosis, involving more than 75% to 80% bowel compromise.[121,122] Morbidity and mortality rates are significant in infants with this disease and nearly all patients that survive develop short bowel syndrome. Historically, when pannecrosis was identified at index laparotomy no resection was performed and comfort measures were offered. With the success of formal multidisciplinary teams specializing in management of short bowel syndrome, improvements in PN management, and options for intestinal and multivisceral transplant, these patients have increasingly demonstrated long-term survival. Despite these limited successes, NEC totalis carries a grim prognosis and a candid discussion with the family regarding overall goals of care in the setting of other comorbidities may be appropriate. A recent survey of pediatric surgeons and neonatologists found significant variability in clinician recommendations regarding comfort care in infants with NEC who had limited viable bowel.[183] Up to 73% of providers recommended comfort care in premature infants with NEC, despite survival rates of greater than 90% in infants with intestinal failure.

Outcomes

Mortality

Despite recent medical advances, mortality from NEC remains significant, contributing significantly to neonatal deaths.[184] The reported overall mortality rate from NEC has varied highly in the literature. Rates have been reported to be anywhere from approximately 10% to 40%.[9,19,185,186] A review of the National Inpatient Sample and Kids' Inpatient Database showed a higher mortality rate in VLBW infants compared to LBW infants.[187]

An evaluation of mortality in infants with NEC by birth weight category using the Vermont Oxford Network database identified an overall mortality rate of 28%.[9] Consistent with prior results, the mortality rate was higher in infants requiring surgery compared to those managed medically (35% vs 21%). Overall mortality was found to increase as birth weight decreased. When outcomes were broken down by 250 g birth weight categories, the mortality rate in patients with medical NEC decreased as birth weight increased for each incremental increase in birth weight. However, the mortality rate in infants with surgical NEC plateaued at approximately 30% in infants weighing 750 g and more. Thus, the difference in mortality rate between medical and surgical NEC was most pronounced at the highest birth weights (Fig 8). It is important to note that infants who require surgery tend to be clinically more unstable with more significant comorbidities. When accounting for these risk factors, surgical NEC remained an independent predictor of death.

For infants with NEC weighing more than 2500 g, the overall mortality rate was 11%[120]. When infants with major congenital anomalies were excluded, the mortality rate was 5%. Congenital heart defects, chromosomal abnormalities, other congenital malformations, surgical NEC, and sepsis were all found to be predictors of mortality. Although the mortality rate is lower in infants over 2500 g than in VLBW infants, it remains substantial.

Growth

Infants with NEC are at high risk for nutritional deficiencies due to prolonged periods of bowel rest, bowel dysfunction, stricture or obstruction, and surgical resection which can lead to

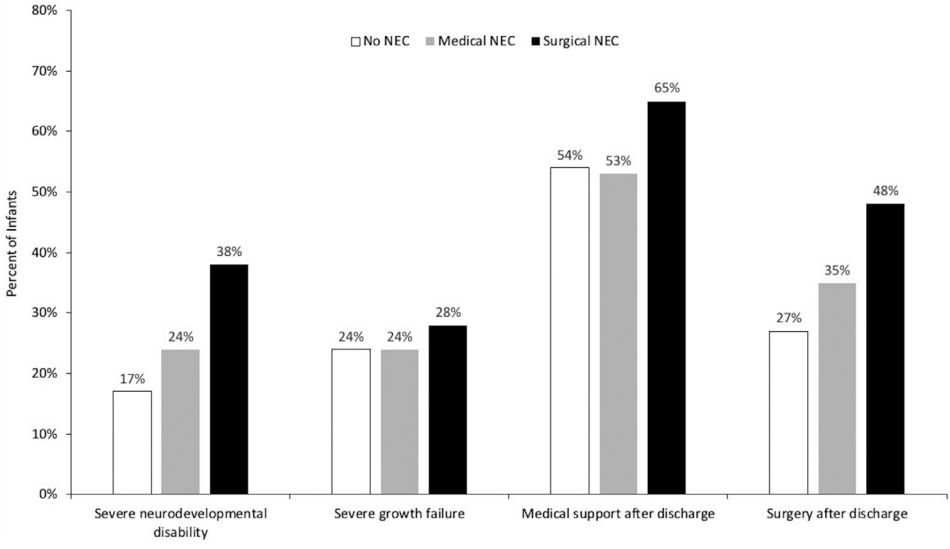

Fig. 9. Long-term outcomes in extremely low birth weight infants with necrotizing enterocolitis (NEC) at 18-24 month follow-up in the Vermont Oxford Network database from 1999 to 2012, adapted from Fullerton and colleagues.[196]

short bowel syndrome. Studies have found conflicting results regarding growth delay in survivors of NEC. Some have shown comparable growth rates between infants with NEC and those without,[188,189] whereas others have shown significant growth delay in infants with surgical NEC.[190]

A large, multicenter analysis of 2948 ELBW infants from 1995 to 1998 using the NICHD Neonatal Research Network database evaluated infants at 18 to 22 months after discharge.[191] Infants with surgical NEC but not medical NEC were found to have significantly higher rates of growth delay when compared to infants without NEC. Growth delay was defined as less than tenth percentile weight for age.

A more recent review of 3137 ELBW infants enrolled in the VON database between 2006 and 2017 evaluated growth failure at discharge vs 18 to 24 months follow-up.[192] In this study, severe growth failure was defined as less than third percentile weight for age. Of infants with surgical NEC, 25% required gastrostomy or nasogastric tube feedings at the time of discharge. Eight percent were rehospitalized for failure to thrive or nutritional problems prior to follow-up and 48% required surgery after discharge. Severe growth failure at discharge was highest in patients with surgical NEC, at 61%, compared to 56% with medical NEC and 36% without NEC (Fig 9). At follow-up, there was no significant difference between any of these groups, although approximately one quarter of infants had persistent severe growth failure. Infants with surgical NEC overall had the longest initial length of stay. The authors hypothesized that the more stringent cutoff for growth failure in addition to the improvements in medical care in the decades since the prior study explained the differences in results.

Impaired growth and nutrition in the neonatal period have significant long-term consequences, including impaired neurodevelopmental outcomes.[193] Close follow-up and nutritional evaluation are necessary to ensure adequate growth in infants who survive NEC.

Neurodevelopmental outcomes

ELBW infants are known to be at risk for significantly worse neurodevelopmental outcomes than their peers with normal birth weights.[194] Given the prolonged and complex hospitalizations and preponderance of ELBW infants in the population of patients with NEC, these infants are

at high risk for poor neurodevelopmental outcomes. A number of studies have demonstrated poor neurodevelopmental outcomes in infants with NEC.[166,195] Two groups have performed large database studies to compare the rates of neurodevelopmental impairment in VLBW and ELBW infants with NEC compared to those without NEC.

An evaluation of VLBW infants with a history of NEC from the NICHD Neonatal Research Network database demonstrated significantly worse neurodevelopmental outcomes in infants with a history of surgical NEC.[191] Neurodevelopmental outcomes were measured using the Bayley Scales of Infant and Toddler Development (BSID-II or BSID-III). Neurodevelopmental impairment, defined as BSID scale Mental Developmental Index or Psychomotor Developmental Index (PDI) <70 (2 standard deviations below the mean), was significantly higher in infants with surgical NEC compared to those without NEC (57% vs 40%). There was no difference in those with medical NEC.

A review of infants enrolled in the VON cohort evaluated neurodevelopmental outcomes in ELBW infants with a history of NEC at 18-24 month follow-up.[196] Again, the BISD model was used to determine neurodevelopmental outcomes. The incidence of cerebral palsy, deafness, and blindness were all significantly higher in infants with surgical NEC compared to infants without a history of NEC. There was no significant difference between infants with medical NEC and those without NEC. Severe disability was defined as 1 or more of the following: bilateral blindness, hearing loss requiring amplification, inability to walk 10 steps without support, cerebral palsy or a BSID Mental Developmental Index or Psychomotor Developmental Index of less than 70. Severe disability was present in 38% of those with surgical NEC compared to 17% of those without NEC (Fig 9). An additional 19% had moderate disability.

It is unclear why infants with surgical NEC would have worse neurologic outcomes. Damage to the infant brain can be caused by multiple factors, including hypotension, acidosis, and anesthesia.[197] NEC has been shown to cause a substantial inflammatory response, which includes the release of cytokines and other inflammatory markers. Chemical mediators such as TNF-alpha, IL-6, PAF, and nitrous oxide have all been shown to contribute to brain white matter injury.[198] Higher levels of multiple cytokines have been identified in infants with NEC as well as a higher rate of developmental delay.[199] Intestinal perforation has also been independently associated with poor neurologic outcome.[200] It is possible that less invasive procedures, such as peritoneal drainage, would result in a decreased inflammatory response and may minimize neurologic damage. Ongoing studies to assess the difference in neurodevelopmental outcomes between infants receiving PPD and laparotomy will help guide treatment of infants with surgical NEC.

Given the high rates of neurodevelopmental impairment in infants with NEC, neurodevelopmental evaluation should be included in follow-up to help identify and support affected infants early in their childhood. Further studies will help define at risk infants and may identify ways to minimize poor outcomes.

Healthcare burden after discharge

Several groups have evaluated healthcare needs in infants with NEC after discharge. ELBW infants with NEC have high postdischarge needs that contribute to the overall healthcare burden of this disease.[192,196] In an evaluation of infants with NEC in the VON cohort, 39% to 54% of ELBW infants required at least 1 hospitalization in the 18 to 22 months after discharge. Infants with surgical NEC were more likely to require admission than those with medical NEC. The most common reason for hospitalization in all groups was respiratory. Infants with surgical NEC were also more likely to require further surgery; 48% underwent additional procedures. Significant numbers of infants in both groups required medical support after discharge with cardiopulmonary monitors and supplemental oxygen being the most common (Fig 9). Of infants with surgical NEC, 25% required tube feedings at the time of discharge and 8% were readmitted for nutritional problems or failure to thrive.

Conclusion

Despite improvements in medical care, NEC is the most common cause of GI pathology in preterm infants and continues to have devastating consequences. Further studies directed at clarifying the pathophysiology, options for prevention and treatment, as well as the nutritional and neurodevelopmental outcomes of NEC are needed to guide care for these complex patients.

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