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In Brief

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Necrotizing enterocolitis (NEC) is a devastating disease of the newborn GI tract that typically affects preterm infants. NEC is characterized by diffuse inflammatory necrosis of the bowel and is a leading cause of mortality and long-term morbidity in affected infants. Advancements in neonatal care have led to increased survival of premature neonates, which has corresponded with an increased number of infants diagnosed with NEC. Despite recent medical advances, the mortality rate for infants with NEC has not changed significantly. There is a critical role for both medical and surgical management of this disease, but prevention will most likely have the largest impact on survival of premature infants with NEC.

The incidence of NEC is approximately 1 to 3 per 1000 births, although estimates are limited by inconsistent definitions of NEC in the literature. The incidence is highest in very low birth weight (VLBW) infants, with rates as high as 12% in infants weighing 501 to 750 g. Overall, the incidence is inversely proportional to birth weight and gestational age.

The pathogenesis of NEC remains unclear but is likely multifactorial. Prematurity is the primary risk factor for NEC, attributed to an immature mucosal barrier and immune response. Prematurity causes disruption of enterocyte tight junctions, resulting in increased mucosal permeability. Mucus secretion is also defective and compromises this normal protective intestinal barrier. Impaired motility in the premature gut predisposes to stasis and bacterial overgrowth and hence is also potentially deleterious.

Microbial dysbiosis has been implicated in the etiology of NEC. Stool colonization studies have shown an over-representation of pathogenic gram-negative bacteria in affected infants. These pathogenic bacteria may trigger an inflammatory cascade through activation of TLR4, resulting in the massive inflammatory response seen in NEC. Finally, formula feeding lacks the immunoprotective components of human milk and may result in a proinflammatory state, further predisposing to NEC.

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Significant research has been devoted to identifying methods to prevent or minimize the severity of NEC. Human milk has been shown to have immunoprotective properties. Feeding-related factors including timing of initial feeds, trophic feeding, and rate of feed advancement have not been shown definitively to contribute to disease development. Delaying feeds in preterm infants results in delayed gut development and increased risk of central line associated bloodstream infections. Probiotic use has been shown to decrease both the incidence of NEC in VLBW infants and reduce the overall mortality rate in some studies. However, probiotics have also been associated with bacteremia and sepsis, possibly due to bacterial translocation across compromised bowel. Another problematic factor is that no consensus has emerged about which specific probiotic formulation is beneficial. Large, randomized trials are needed to determine the long-term effects of probiotics and their value in preventing NEC.

The roles for lactoferrin, a human milk protein, and human milk oligosaccharides in the prevention of NEC are unclear. Some trials show a decreased incidence of NEC; however, further investigation into lactoferrin and human milk oligosaccharides is warranted.

Packed red blood cell transfusion has also been implicated in the development of NEC, although several authors suggest this may be due to underlying anemia and not transfusion itself. Regardless, withholding feeds during transfusion has been proposed as a method to prevent NEC. Although some successes have been identified with withholding feeds, and many neonatal units make this part of the standard practice, larger studies are needed to demonstrate a clear benefit.

The clinical presentation of NEC may range from isolated feeding intolerance to septic shock, intestinal perforation, and need for emergency surgery. Early physical examination findings include abdominal distention and tenderness, progressing to abdominal wall erythema and edema. Pneumatosis intestinalis is the radiographic hallmark of NEC. Other radiographic signs include portal venous gas, fixed bowel loops, and pneumoperitoneum. Ultrasonography is emerging as a diagnostic tool for the detection of early changes in bowel perfusion.

Laboratory findings may include metabolic acidosis, hyperglycemia, neutropenia, and thrombocytopenia. Research into biomarkers of NEC have identified fecal calprotectin and intestinal-fatty acid binding protein as potential indicators of disease, but additional validating studies are still required to allow for routine clinical use.

It is important to distinguish NEC from spontaneous intestinal perforation, which is characterized by focal perforation without the diffuse inflammatory necrosis seen in NEC. Moreover, spontaneous intestinal perforation often manifests as acute onset of abdominal distention and pneumoperitoneum without pneumatosis on radiography, and portends a different prognosis than surgical NEC.

Medical management of NEC includes supportive care with empiric antibiotics, bowel rest with gastric decompression, parenteral nutrition, correction of metabolic and hematologic derangements, and cardiorespiratory support.

There is no consensus regarding a specific antibiotic regimen or duration in affected infants. Coverage for gram-positive and gram-negative organisms (eg, ampicillin and gentamicin) is commonly employed. Anaerobic coverage has been associated with increased stricture rate. However, more recent data show improved outcomes in patients with surgical NEC receiving anaerobic coverage. Some institutions use piperacillin-tazobactam alone in the treatment of NEC due to its broad coverage and lack of ototoxic and nephrotoxic side effects. A 10 to 14 day course of antibiotics is commonly used, although minimizing antibiotic exposure in infants with mild disease may be appropriate.

The duration of bowel rest may last up to 7 to 14 days. Several studies have shown no increase in mortality rate or disease recurrence with early feeding regimens (defined as 5-7 days). Large randomized studies are needed to further clarify optimal timing for resumption of feeds.

Infants with NEC frequently require ventilatory support. Although there is no consensus regarding optimal ventilation strategies, modalities that may worsen abdominal distention, such as continuous positive airway pressure (CPAP), are frequently avoided. Serial physical examination, laboratory testing, and imaging should be used to monitor the response to therapy as worsening clinical factors may indicate the need for surgical intervention.

Approximately 25%-50% of infants with NEC will ultimately require surgery. The only absolute indication for operative intervention is perforation, demonstrated by pneumoperitoneum on the abdominal radiograph. In infants without clear evidence of perforation, the following radiographic and physiologic findings may indicate severe disease: portal venous gas or a persistent fixed bowel loop on radiography; metabolic acidosis, hyperglycemia, neutropenia and thrombocytopenia on laboratory evaluation; abdominal wall erythema or greenish discoloration, crepitus or palpable abdominal mass on physical examination. Predictive models using common laboratory values have shown promise and are an area of active research.

Anesthesia in infants with NEC is often made challenging by underlying extreme prematurity and sepsis. In addition, abdominal distention may make mechanical ventilation difficult.

Intraoperatively, the fragile tissue of the premature infant warrants careful handling and damage to the liver should be avoided because this can cause catastrophic hemorrhage. Typical operative management during laparotomy involves expeditious resection of necrotic bowel followed by proximal diversion with an enterostomy. There has been a recent trend toward bowel-preserving techniques. In infants with significant small bowel resection, central access for parenteral nutrition and feeding tube placement for enteral feeding should be considered.

Primary anastomosis at initial laparotomy may be appropriate in a subset of patients, particularly those with focal necrosis or isolated intestinal perforation. Minimal resection of only grossly nonviable bowel followed by second-look laparotomy, termed the “clip and drop-back” technique, may be a good option for infants with multifocal disease. Others have suggested the “patch, drain, and wait” technique which involves approximation or patching of any perforations without bowel resection; this is followed by drainage over a period of at least 14 days.

NEC totalis is a term used to describe greater than 75%-80% necrosis of the bowel. This condition has historically been associated with a very grim prognosis, although recent advances in the care of ultra-short bowel syndrome (SBS) have resulted in long-term survival. Withdrawal of care may be appropriate in certain clinical contexts.

The most highly debated aspect of the surgical care of these patients is the role of primary peritoneal drainage (PPD) vs laparotomy. PPD can be performed under local anesthesia and was initially described as a bridge to laparotomy in extremely low birth weight (ELBW) infants who were felt to be too unstable for major surgery. Thereafter, several small case series identified a group of infants receiving PPD who survived without requiring further intervention, implying that PPD may serve as a definitive therapy in some situations. Early retrospective and large, prospective, multicenter studies were unable to show the superiority of either technique, although patient selection and inadequate power may have limited their capacity to do so. To date, 2 randomized controlled trials have been performed, each showing similar outcomes between PPD and laparotomy. A third randomized controlled trial is currently ongoing in order to further clarify this issue.

The complication rate with surgical intervention has been reported to be as high as 50%. Recurrent NEC, intestinal stricture, and stoma complications are among the most common complications. Surgical site infections and intra-abdominal abscess rates are highly variable in this population. SBS occurs when the intestine has insufficient absorptive capacity to support homeostasis and growth. Rates of SBS in infants with NEC have been reported upward of 25%. This may result from extensive resection or from diminished function in previously diseased bowel. Children with SBS due to NEC have been shown to be more likely to completely wean from parenteral nutrition than children who have SBS due to other etiologies. Management in a multidisciplinary intestinal failure center can help optimize the outcomes in these patients. Complications also occur in patients managed without operative intervention, particularly stricture formation, which has been reported to occur in up to 30% of infants with medical NEC.

The overall mortality rate with NEC has been reported between 10% and 40%. The mortality rate in infants with surgical NEC is higher than in those with medically managed NEC. The overall mortality rate also increases with decreasing birth weight. Although the mortality rate for infants with medical NEC improves with each incremental increase in birth weight, the mortality rate for infants with surgical NEC plateaus around 30% in infants weighing 750 g or more.

Large babies (>2500 g) with NEC have a lower mortality rate of 5% to 10%, implying the disease is different in this population.

Treated infants are at high risk for nutritional deficiencies after hospital discharge. Although several early studies showed higher rates of growth failure in infants with surgical NEC but not infants with medical NEC, more recent studies suggest no difference in rates of growth failure at approximately 2 years. Close nutritional monitoring is necessary to ensure adequate growth in survivors of NEC.

Infants with surgical NEC have significantly worse neurodevelopmental outcomes when compared to age-matched controls without NEC or with medical NEC. Severe neurodevelopmental disability is seen in up to 38% of neonates with surgical NEC. A substantial healthcare burden after discharge has been identified in survivors of NEC, particularly those requiring surgical intervention.

NEC remains 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, and the nutritional and neurodevelopmental outcomes of NEC are needed to guide the care for these complex patients.