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NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS: PATHOGENESIS, EARLY DIAGNOSIS, SURGICAL MANAGEMENT, AND PREVENTION

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Abstract

Necrotizing enterocolitis (NEC) is one of the most serious gastrointestinal emergencies affecting premature and very-low-birth-weight infants. It is characterized by intestinal inflammation and varying degrees of intestinal ischemia, necrosis, and, in severe cases, intestinal perforation. NEC remains an important cause of morbidity and mortality in neonatal intensive care units, particularly among extremely premature infants. Its pathogenesis is multifactorial and involves immature intestinal barrier function, abnormal intestinal microbiota, dysregulated inflammatory responses, impaired intestinal perfusion, and interactions with enteral nutrition. Clinical manifestations range from feeding intolerance and abdominal distension to systemic instability, metabolic acidosis, hypotension, intestinal perforation, and septic shock. Early diagnosis requires careful clinical observation combined with laboratory assessment and abdominal imaging. Abdominal radiography remains an important diagnostic method, while ultrasonography is increasingly used for assessment of bowel wall perfusion, thickness, peristalsis, and free fluid. Management depends on disease severity and includes bowel rest, gastric decompression, intravenous fluids, nutritional support, antimicrobial therapy, respiratory and cardiovascular stabilization, and close monitoring. Surgical intervention is indicated in intestinal perforation and selected cases of progressive or severe disease. Surgical strategies include peritoneal drainage and laparotomy with resection of necrotic bowel. Prevention focuses on human milk feeding, standardized feeding protocols, avoidance of unnecessary antibiotic exposure, optimization of perinatal care, and prevention of prematurity. Advances in neonatal intensive care, microbiome research, biomarkers, intestinal ultrasonography, and precision medicine may improve early diagnosis and outcomes in the future.

Keywords: necrotizing enterocolitis, premature infants, neonatal intensive care, intestinal necrosis, preterm birth, neonatal surgery, abdominal ultrasound, human milk, prevention, intestinal microbiome.

Introduction

Necrotizing enterocolitis is a severe inflammatory and ischemic disease of the gastrointestinal tract that predominantly affects premature and low-birth-weight infants. It is one of the most feared gastrointestinal complications in neonatal intensive care because progression can be rapid and may result in intestinal necrosis, perforation, sepsis, multiorgan dysfunction, and death. Survivors of severe NEC may experience prolonged hospitalization and important long-term complications, including intestinal strictures, short bowel syndrome, impaired growth, feeding difficulties, and neurodevelopmental problems.

The incidence of NEC is strongly associated with gestational age and birth weight. The most vulnerable population consists of extremely premature infants whose intestinal barrier, immune system, vascular regulation, and intestinal microbiome are still immature. Although NEC may occur in relatively mature newborns, the disease is particularly important among very-low-birth-weight and extremely-low-birth-weight infants.

NEC is not considered a disease caused by a single microorganism or a single pathological mechanism. Instead, it results from the interaction of intestinal immaturity, abnormal bacterial colonization, excessive inflammatory activation, impaired intestinal perfusion, and additional environmental or clinical factors. This multifactorial nature explains why prevention and treatment require a comprehensive neonatal strategy rather than a single intervention.

Pathogenesis

The pathogenesis of NEC begins with the developmental immaturity of the premature intestine. In a healthy newborn, the intestinal mucosa provides an important barrier between the external environment and the systemic circulation. In premature infants, this barrier is structurally and functionally immature. Tight junctions between epithelial cells are less developed, mucosal defense mechanisms are weaker, and the ability to regulate inflammatory responses is limited. Consequently, bacteria and bacterial products may interact more easily with the intestinal immune system.

The intestinal microbiome is another important component of NEC pathogenesis. Premature infants frequently experience abnormal bacterial colonization because of hospitalization, antibiotic exposure, cesarean delivery, delayed enteral feeding, and exposure to the neonatal intensive care environment. Reduced microbial diversity and increased abundance of potentially pathogenic organisms may contribute to intestinal inflammation. Importantly, NEC is not simply an infectious disease; rather, abnormal microbial colonization interacts with an immature immune system and intestinal barrier.

Inflammation plays a central role in disease progression. Recognition of bacterial components by intestinal immune receptors can activate inflammatory pathways and lead to the release of cytokines and other mediators. Excessive inflammation damages the intestinal epithelium, increases vascular permeability, and promotes tissue injury. Intestinal ischemia and impaired microvascular regulation can further aggravate mucosal damage and eventually lead to necrosis.

Enteral nutrition also interacts with these mechanisms. Human milk is associated with a lower risk of NEC compared with exclusive formula feeding, whereas rapid or poorly tolerated feeding in a vulnerable infant may contribute to intestinal stress. However, NEC should not be considered simply a complication of feeding. The disease reflects a complex interaction between prematurity, intestinal development, microbiota, immune regulation, perfusion, and nutrition.

Risk Factors

Prematurity and low birth weight are the most important risk factors for NEC. The risk increases as gestational age and birth weight decrease. Other factors that may contribute include respiratory instability, episodes of hypoxia or hypotension, impaired intestinal perfusion, congenital heart disease, patent ductus arteriosus, severe infection, anemia, and prolonged antibiotic exposure.

The type of enteral nutrition is also clinically important. Human milk, particularly mother's own milk, is associated with a lower risk of NEC. Donor human milk may provide an important alternative when the mother's own milk is unavailable. Formula feeding, especially in highly vulnerable premature infants, is associated with a greater risk compared with human milk feeding.

A history of significant neonatal infection, hemodynamic instability, and exposure to multiple medical interventions may further increase susceptibility. Nevertheless, risk factors should not be interpreted independently because NEC usually develops through the interaction of multiple physiological and environmental factors.

Clinical Manifestations and Early Recognition

Early recognition is essential because NEC may progress rapidly. Initial clinical manifestations are often nonspecific and may resemble other neonatal conditions. Feeding intolerance is common and may present as increased gastric residuals, vomiting, abdominal distension, or reduced tolerance of enteral nutrition. Changes in stool, including occult or gross blood, may occur.

As disease progresses, abdominal findings become more prominent. The infant may develop increasing abdominal distension, abdominal discoloration, tenderness, decreased bowel sounds, and signs of intestinal obstruction or perforation. Systemic manifestations may include temperature instability, apnea, bradycardia, lethargy, hypotension, poor perfusion, metabolic acidosis, thrombocytopenia, and respiratory deterioration.

The combination of gastrointestinal and systemic deterioration should raise immediate concern for NEC. However, none of these findings alone is sufficiently specific. Careful serial assessment is therefore essential, particularly in extremely premature infants.

Diagnosis

Diagnosis is based on the combination of clinical findings, laboratory investigations, and imaging. Serial abdominal examination remains fundamental. Laboratory abnormalities may include metabolic acidosis, thrombocytopenia, leukopenia or leukocytosis, elevated inflammatory markers, electrolyte abnormalities, and evidence of systemic infection. Severe thrombocytopenia and worsening metabolic acidosis may indicate advanced disease, although laboratory findings are not diagnostic by themselves.

Abdominal radiography remains an important imaging modality. Findings may include dilated bowel loops, bowel wall thickening, pneumatosis intestinalis, portal venous gas, and pneumoperitoneum. Pneumatosis intestinalis is an important radiological feature because it indicates gas within the intestinal wall and strongly supports the diagnosis in the appropriate clinical context. Pneumoperitoneum is particularly important because it suggests intestinal perforation and generally represents an indication for surgical evaluation.

Abdominal ultrasonography has become increasingly important in modern NEC assessment. Doppler ultrasound can provide information about intestinal wall perfusion, bowel wall thickness, peristalsis, free fluid, and the presence of complex intra-abdominal findings. Ultrasound may

identify changes that are difficult to appreciate on conventional radiography and can be repeated without radiation exposure. Its value depends on operator expertise and institutional experience.

Differential Diagnosis

Several neonatal disorders can resemble NEC. Important differential diagnoses include spontaneous intestinal perforation, sepsis with ileus, feeding intolerance related to prematurity, intestinal obstruction, Hirschsprung-associated enterocolitis, volvulus, congenital gastrointestinal anomalies, and milk protein-related intestinal disease.

Spontaneous intestinal perforation is particularly important because it can occur in extremely premature infants and may present with abdominal distension and free intraperitoneal air. Unlike NEC, spontaneous intestinal perforation may initially involve a focal perforation with relatively limited surrounding intestinal inflammation. Distinguishing these conditions can be difficult, and clinical evolution and imaging findings must be considered together.

Medical Management

Once NEC is suspected, enteral feeding is generally discontinued and the intestine is rested. Gastric decompression using an orogastric or nasogastric tube may be required. Intravenous fluids are administered according to the infant's cardiovascular and metabolic condition, and careful monitoring of electrolytes, glucose, acid-base status, urine output, and perfusion is necessary.

Broad-spectrum antimicrobial therapy is commonly initiated when NEC is suspected because bacterial translocation and systemic infection are major concerns. Antimicrobial selection and duration should follow local neonatal protocols and the clinical severity of the disease. Blood cultures should be obtained when feasible before antibiotics are started, but treatment should not be unnecessarily delayed in an unstable infant.

Nutritional management is particularly important. When enteral nutrition cannot be safely provided, parenteral nutrition is used to maintain adequate energy and protein intake. Once clinical and radiological findings improve, enteral feeding can be cautiously reintroduced according to the infant's condition and institutional protocol. Human milk is generally preferred because of its nutritional and protective properties.

Respiratory and cardiovascular support may be necessary in severe NEC. Mechanical ventilation, treatment of hypotension, blood products, correction of metabolic abnormalities, and management of associated sepsis may all be required. Continuous monitoring in a neonatal intensive care unit is essential.

Surgical Management

Surgical consultation should occur early in infants with severe or progressive NEC. The clearest indication for surgery is intestinal perforation, usually suggested by pneumoperitoneum. Other indications may include clinical deterioration despite maximal medical treatment, persistent metabolic acidosis, worsening abdominal findings, suspected intestinal necrosis, and other evidence of progressive disease.

Traditional surgical treatment involves exploratory laparotomy. Necrotic or perforated segments of intestine are identified and removed, while viable bowel is preserved whenever possible. The extent of intestinal resection is carefully considered because excessive removal can result in short bowel syndrome and long-term nutritional dependence.

Peritoneal drainage is another surgical approach, particularly in extremely premature infants who may be too unstable to tolerate laparotomy. A drain can decompress the abdomen and provide temporary or definitive treatment in selected patients. However, the role of primary

peritoneal drainage compared with laparotomy remains dependent on patient characteristics, surgical expertise, and institutional protocols.

The major surgical challenge is balancing removal of nonviable intestine with preservation of sufficient functional bowel. Extensive resection may save the infant's life but can result in short bowel syndrome, prolonged parenteral nutrition, intestinal failure, and complications associated with central venous access.

Postoperative Care

Postoperative management is complex and requires prolonged multidisciplinary care. Respiratory support may be necessary, while fluid and electrolyte disturbances must be carefully corrected. Parenteral nutrition is frequently required until intestinal function returns sufficiently to permit enteral feeding.

The surgical team must monitor for complications such as recurrent intestinal necrosis, anastomotic leakage, wound infection, abdominal compartment problems, sepsis, and postoperative obstruction. Intestinal strictures may develop weeks after NEC and can present later with feeding intolerance, vomiting, abdominal distension, or intestinal obstruction.

Children who undergo extensive intestinal resection require long-term monitoring for intestinal failure and nutritional deficiencies. Some may require prolonged parenteral nutrition, while others gradually achieve full enteral independence.

Prevention

Prevention is one of the most important aspects of NEC management because treatment of advanced disease remains difficult. Prevention begins with reducing the risk of extreme prematurity. Appropriate antenatal care, prevention of preterm birth, antenatal corticosteroid therapy when indicated, and timely transfer of high-risk pregnancies to specialized centers can improve neonatal outcomes.

Human milk feeding is one of the strongest evidence-based preventive strategies. Mother's own milk is preferred whenever possible, while donor human milk may be used when maternal milk is unavailable. Human milk contains immunological, nutritional, and bioactive components that support intestinal maturation and may reduce the risk of NEC.

Standardized feeding protocols are also important. Controlled advancement of enteral nutrition, careful monitoring of feeding tolerance, and avoidance of unnecessary interruptions may improve consistency of neonatal care. Feeding strategies should be individualized according to gestational age, birth weight, clinical stability, and associated conditions.

Antibiotic stewardship is another important preventive strategy. Unnecessary or prolonged exposure to broad-spectrum antibiotics can alter the intestinal microbiome and may increase the risk of NEC and other complications. Antibiotics should therefore be used when clinically indicated and reviewed regularly.

Probiotic supplementation has been investigated extensively as a possible preventive strategy. Some studies suggest potential benefits in reducing NEC in selected premature populations, but results vary according to probiotic strains, preparations, dosing, and patient populations. Therefore, probiotic policies should be based on local guidelines, product quality, and institutional safety considerations.

Long-Term Outcomes

NEC can have consequences extending far beyond the neonatal period. Survivors of severe disease may experience growth failure, feeding problems, intestinal strictures, short bowel syndrome, and intestinal failure. Children who required prolonged intensive care may also be at increased risk of neurodevelopmental impairment.

Growth monitoring is particularly important because inadequate nutrition during critical periods of development can affect both physical and neurological outcomes. Weight, length or height, head circumference, micronutrient status, and feeding ability should be assessed regularly.

Neurodevelopmental follow-up is also necessary, especially in extremely premature infants and those who experienced severe systemic illness. Developmental screening should include motor, cognitive, language, behavioral, and social domains. Early intervention can improve functional outcomes when developmental difficulties are identified.

Children with extensive intestinal disease may require long-term gastroenterology and nutrition support. Those with short bowel syndrome may develop complications related to malabsorption, micronutrient deficiency, liver disease associated with parenteral nutrition, and recurrent catheter-related infections.

Future Perspectives

The future of NEC management is increasingly focused on earlier diagnosis and individualized risk prediction. Biomarkers capable of identifying intestinal injury before severe clinical manifestations become apparent are being investigated. Potential approaches include inflammatory markers, intestinal injury proteins, circulating microRNAs, metabolomic profiles, and microbiome-based signatures.

Artificial intelligence may also contribute to early recognition by analyzing clinical parameters, laboratory results, abdominal imaging, and continuous physiological monitoring. A predictive model capable of identifying infants at high risk before irreversible intestinal injury develops could potentially allow earlier intervention.

Research into the neonatal intestinal microbiome is another important area. Understanding the relationship between microbial communities, intestinal maturation, immune responses, and nutrition may lead to more precise preventive strategies. Future treatments may involve targeted microbial therapies, optimized probiotics, prebiotics, or microbiome-derived interventions.

Advances in regenerative medicine may eventually provide new approaches for infants who develop extensive intestinal damage. Tissue engineering and intestinal stem-cell research are being investigated as potential strategies for restoring intestinal function, although these approaches remain experimental.

Conclusion

Necrotizing enterocolitis remains one of the most serious gastrointestinal diseases affecting premature infants. Its development is associated with intestinal immaturity, abnormal microbial colonization, excessive inflammatory responses, impaired intestinal perfusion, and multiple neonatal risk factors. Because early clinical manifestations may be nonspecific, rapid recognition and repeated assessment are essential.

Diagnosis requires integration of clinical findings, laboratory abnormalities, abdominal radiography, and increasingly abdominal ultrasonography. Once NEC is suspected, bowel rest, gastric decompression, antimicrobial therapy, nutritional support, and intensive monitoring are central components of treatment. Surgical intervention is essential in intestinal perforation and may be required in selected infants with progressive disease. The preservation of viable bowel is particularly important because extensive intestinal resection can result in short bowel syndrome and lifelong nutritional complications.

Prevention remains a major priority. Prevention of prematurity, human milk feeding, standardized feeding strategies, appropriate antibiotic use, and high-quality neonatal intensive care can reduce the risk and severity of NEC. Future advances in biomarkers, microbiome research, artificial intelligence, precision medicine, and regenerative therapy may allow earlier identification of high-risk infants and more individualized treatment. Ultimately, successful management of NEC requires not only survival of the newborn but also long-term attention to nutrition, growth, neurodevelopment, intestinal function, and quality of life.

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