

Article

Necrotizing Enterocolitis in Preterm Infants

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Abstract: Necrotizing enterocolitis (NEC) is one of the most serious gastrointestinal emergencies affecting preterm infants, particularly those born at very low birth weight. It is characterized by intestinal inflammation and varying degrees of intestinal wall injury, which may progress to necrosis, perforation, systemic infection, and multiorgan dysfunction. Despite advances in neonatal intensive care, NEC remains an important cause of morbidity and mortality among premature newborns. Its pathogenesis is multifactorial and involves intestinal immaturity, dysregulated immune responses, alterations in the gut microbiota, impaired intestinal barrier function, and feeding-related factors. Established risk factors include extreme prematurity, low birth weight, formula feeding, and compromised intestinal perfusion. Early recognition is essential because the initial clinical manifestations, including feeding intolerance, abdominal distension, vomiting, bloody stools, apnea, and temperature instability, may be nonspecific. Diagnosis is based on clinical assessment, laboratory investigations, and imaging, particularly abdominal radiography and, where available, intestinal ultrasonography. Management depends on disease severity and generally includes cessation of enteral feeding, gastric decompression, intravenous fluid and nutritional support, antimicrobial therapy, and close monitoring. Surgical intervention may be necessary in cases of intestinal perforation, necrosis, or clinical deterioration despite intensive medical treatment. Human milk feeding, standardized feeding protocols, infection prevention, and careful monitoring of high-risk infants are important preventive strategies. This review summarizes the current understanding of the epidemiology, pathogenesis, risk factors, clinical presentation, diagnosis, treatment, and prevention of necrotizing enterocolitis in preterm infants.

Keywords: Necrotizing enterocolitis; preterm infants; prematurity; very low birth weight; neonatal intensive care; intestinal inflammation; human milk; neonatal morbidity; intestinal microbiota; neonatal surgery.

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1. Introduction

Necrotizing enterocolitis (NEC) is a severe inflammatory disease of the gastrointestinal tract that predominantly affects premature infants. It is associated with substantial neonatal morbidity and mortality and represents a major challenge in neonatal intensive care. The disease is characterized by intestinal mucosal injury that can progress to transmural necrosis, intestinal perforation, peritonitis, and systemic inflammatory complications. Although NEC can occur in term newborns, its incidence is substantially higher among infants born prematurely, particularly those with extremely low birth weight.[1]

The clinical significance of NEC is related not only to its acute complications but also to its potential long-term consequences. Survivors, especially those requiring surgical intervention or experiencing extensive intestinal injury, may develop intestinal strictures, short bowel syndrome, feeding difficulties, growth impairment, and neurodevelopmental

complications. These outcomes can increase the need for prolonged hospitalization, specialized nutritional support, and long-term multidisciplinary follow-up. Consequently, NEC places a considerable burden on healthcare systems and the families of affected infants.

The pathogenesis of NEC is complex and remains incompletely understood. Current evidence suggests that the disease develops through interactions among intestinal immaturity, abnormal microbial colonization, excessive inflammatory responses, impaired epithelial barrier function, and disturbances in intestinal microcirculation. In preterm infants, the gastrointestinal tract has limited digestive, immunological, and barrier capabilities. These developmental vulnerabilities may increase susceptibility to injury when combined with microbial exposure and enteral feeding. Human milk is associated with a lower risk of NEC than formula feeding, although the mechanisms underlying this protective effect are multifaceted and include immunological, nutritional, and microbiome-related factors.[2]

Several clinical factors influence the likelihood of developing NEC and the severity of its progression. Gestational age and birth weight are among the most important determinants, while feeding practices, hemodynamic instability, infection, and other neonatal complications may further modify individual risk. Nevertheless, NEC is a heterogeneous condition, and no single risk factor or mechanism adequately explains all cases. This heterogeneity complicates early prediction, prevention, and the development of universally effective therapeutic strategies.

Early diagnosis remains a central component of clinical management. Initial manifestations may include feeding intolerance, abdominal distension, bilious vomiting, bloody stools, lethargy, apnea, and temperature instability. However these findings are not specific to NEC and may overlap with other neonatal conditions, including sepsis and intestinal obstruction. Abdominal radiography remains a key diagnostic method, particularly for identifying pneumatosis intestinalis and portal venous gas. Intestinal ultrasonography can provide additional information about bowel wall thickness, perfusion, peristalsis, and the presence of complex intra-abdominal fluid collections. Timely assessment is essential because clinical deterioration may occur rapidly in severe cases.[3]

Treatment is determined by the clinical stage and extent of intestinal injury. Conservative management generally involves discontinuation of enteral feeding, gastric decompression, intravenous fluid administration, parenteral nutrition, broad-spectrum antimicrobial therapy, and repeated clinical and radiological assessment. Surgical consultation is required when intestinal perforation, progressive necrosis, or deterioration despite medical treatment is suspected. Since established NEC can progress unpredictably, identifying infants at increased risk and implementing effective preventive measures remain important priorities in neonatal medicine.

Prevention strategies focus on improving feeding practices, promoting human milk feeding, implementing standardized clinical protocols, and reducing avoidable intestinal and systemic stressors. Donor human milk may be an important alternative when the mother's own milk is unavailable. Probiotic supplementation has also been investigated as a preventive intervention, but its implementation requires consideration of product-specific evidence, safety, quality control, and local clinical guidelines.[4]

The aim of this review is to examine the current evidence on the epidemiology, risk factors, pathophysiological mechanisms, clinical manifestations, diagnostic approaches, treatment, and prevention of necrotizing enterocolitis in preterm infants, with particular emphasis on opportunities to improve early recognition and clinical outcomes.

A literature search on necrotizing enterocolitis (NEC) in preterm infants should focus on the epidemiology, pathophysiology, risk factors, diagnostic approaches, treatment, and prevention of the disease. The principal databases for identifying relevant publications include PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library. PubMed provides access to biomedical literature, while Scopus and Web

of Science facilitate multidisciplinary citation tracking. The Table 1. Cochrane Library is particularly useful for identifying systematic reviews of clinical interventions.[5]

Table 1. Key publications identified through scientific databases[6]

Authors and year	Study type	Main contribution
Hu et al. (2024)	Clinical review	Epidemiology, diagnosis, prevention, and management
Roberts et al. (2024)	Narrative review	Pathophysiology, treatment, and prevention
Colarelli et al. (2024)	Clinical review	Prevention strategies and clinical management
Zhao et al. (2024)	Systematic review and meta-analysis	Factors associated with NEC in premature infants
Sharif et al. (2023)	Cochrane systematic review	Benefits and uncertainties of probiotics
Chen et al. (2024)	Network meta-analysis	Comparative preventive interventions

The publications above are indexed in PubMed; their full bibliographic records and abstracts can be accessed through the links in the references below.

2. Materials and Methods

This study employed a comprehensive analytical approach to examine necrotizing enterocolitis (NEC) in preterm infants, focusing on its clinical characteristics, risk factors, diagnostic methods, and management strategies. The methodology was based on the analysis and synthesis of scientific literature, clinical guidelines, and published research addressing the pathogenesis, early diagnosis, treatment, and prevention of NEC in premature newborns. Particular attention was paid to the relationship between gestational age, birth weight, feeding practices, intestinal immaturity, and the development and severity of the disease.

The literature analysis focused on preterm infants born before 37 weeks of gestation, with particular emphasis on extremely and very preterm newborns, who are at increased risk of developing NEC. The principal variables considered included gestational age, birth weight, postnatal age at disease onset, type of feeding, clinical manifestations, laboratory parameters, radiological findings, disease severity, treatment outcomes, and associated complications. Clinical manifestations such as abdominal distension, feeding intolerance, bilious vomiting or gastric residuals, bloody stools, and systemic signs of infection were considered in the context of the differential diagnosis of NEC.

Diagnostic assessment was examined with reference to established clinical and radiological criteria, including the modified Bell staging system. The analysis considered the role of abdominal radiography in identifying characteristic findings, such as pneumatosis intestinalis, portal venous gas, and pneumoperitoneum, as well as the potential contribution of abdominal ultrasonography to the assessment of intestinal wall abnormalities, perfusion, and free fluid. Laboratory indicators, including complete blood count, platelet count, inflammatory markers, blood gas analysis, and metabolic parameters, were reviewed as supportive tools for evaluating disease progression and systemic complications. These indicators were not considered individually sufficient to establish or exclude the diagnosis.

The management component examined the principles of conservative and surgical treatment according to disease severity. Conservative management was considered in relation to bowel rest, gastric decompression when indicated, intravenous fluid and nutritional support, antimicrobial therapy according to clinical protocols, and continuous monitoring of vital signs and abdominal findings. Surgical intervention was reviewed in the context of intestinal perforation, suspected intestinal necrosis, or clinical deterioration

despite medical treatment. Preventive approaches, including human milk feeding, appropriate advancement of enteral nutrition, infection prevention, and careful monitoring of high-risk infants, were also included in the analysis.

The collected information was organized thematically and compared across the selected publications to identify consistent findings, differences in clinical recommendations, and areas requiring further investigation. A descriptive and comparative approach was used to synthesize the evidence concerning risk factors, diagnostic accuracy, treatment options, and clinical outcomes. As this methodology is based on published literature rather than newly collected patient data, the findings should be interpreted as a synthesis of existing evidence and not as the results of an independent clinical trial or a statistical analysis of a newly recruited patient cohort.

3. Results and discussion

Figure 1. Epidemiological characteristics of necrotizing enterocolitis in preterm infants. Necrotizing enterocolitis (NEC) remains one of the most severe gastrointestinal complications in premature infants, particularly those with very low birth weight. The literature indicates that the risk of NEC increases as gestational age and birth weight decrease. This association reflects the structural and functional immaturity of the intestinal barrier, underdeveloped immune responses, and limited capacity to regulate microbial colonization.[7]

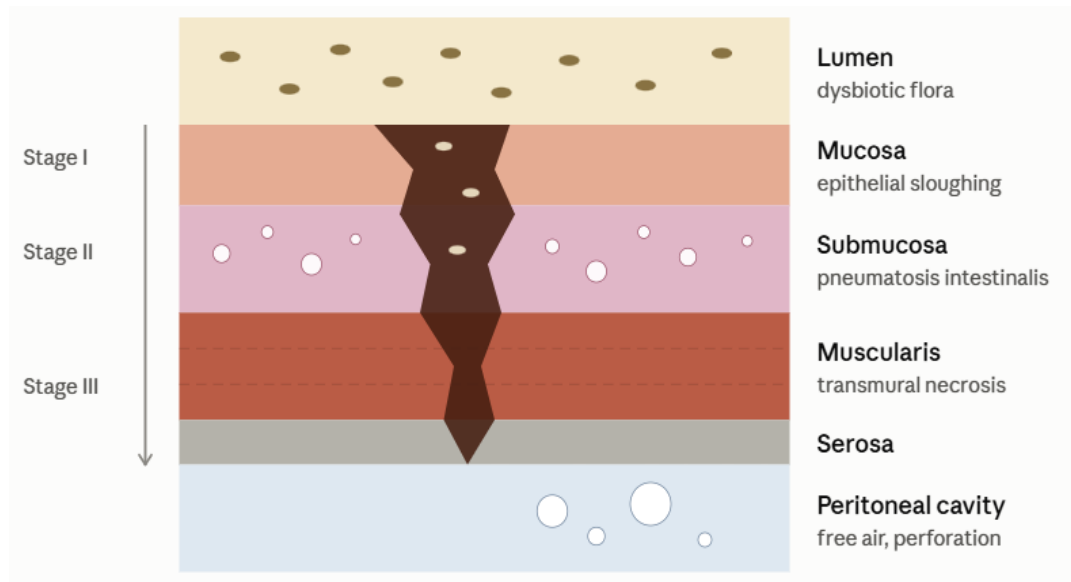


Figure 1. Fugure Depth of injury in necrotising enterocolitis a stratified schematic of the preterm bowel wall, Bell stages I-III[8]

The results of published studies indicate substantial variation in NEC incidence across neonatal intensive care units. Such differences may be explained by variations in the gestational age and birth-weight distributions of study populations, diagnostic criteria, feeding practices, and availability of specialized neonatal care. Consequently, comparisons between institutions require standardized case definitions and clearly defined denominators. The reviewed evidence suggests that NEC develops through interactions between neonatal vulnerability and environmental or clinical exposures.[9]

Table 2. Major Risk Factors for Necrotizing Enterocolitis in Preterm Infants, Their Potential Mechanisms, and Clinical Significance[10]

Risk factor	Potential mechanism	Clinical significance
Extreme prematurity	Immature intestinal barrier and immune regulation	Major underlying susceptibility
Very low birth weight	Greater physiological and developmental immaturity	Increased risk of severe disease

Risk factor	Potential mechanism	Clinical significance
Formula feeding	Differences in protective bioactive components compared with human milk	Human milk is generally preferred for prevention
Intestinal dysbiosis	Altered microbial communities and inflammatory signaling	Potential contributor to intestinal injury
Intestinal hypoperfusion	Reduced oxygen and nutrient delivery to intestinal tissues	May contribute to tissue injury
Systemic infection and inflammation	Dysregulated inflammatory responses	May complicate the clinical course

These findings support a multifactorial model rather than a single-cause explanation. Prematurity is a major nonmodifiable risk factor, whereas nutritional practices and some aspects of neonatal care represent potentially modifiable factors. Nevertheless, the presence of an individual risk factor does not establish that NEC will develop, and associations reported in observational studies should not automatically be interpreted as causal relationships.[11]

The reviewed literature identifies abdominal distension, feeding intolerance, bloody stools, apnea, and systemic instability among the clinical manifestations that should raise suspicion of NEC. However, these findings are not specific enough to establish the diagnosis independently.

Abdominal radiography remains important for identifying pneumatosis intestinalis, a characteristic finding in NEC, and for detecting pneumoperitoneum when intestinal perforation occurs. Intestinal ultrasonography can provide complementary information regarding bowel-wall thickness, perfusion, peristalsis, and intra-abdominal fluid.

The principal diagnostic challenge is recognizing disease before irreversible intestinal injury develops. Laboratory indicators of inflammation, thrombocytopenia, metabolic acidosis, and other systemic abnormalities may support clinical assessment, but none should be considered independently diagnostic. Serial examination and integration of clinical, laboratory, and imaging findings are therefore essential.[12]

The evidence supports human milk feeding as a central preventive strategy in preterm infants. Mother's own milk is preferred, while pasteurized donor human milk is an important alternative when maternal milk is insufficient or unavailable. Standardized feeding protocols and careful monitoring can also improve consistency of neonatal care.

Probiotics have been investigated extensively, but their effectiveness and safety depend on the specific strains, products, patient populations, and clinical setting. Evidence is less certain for extremely preterm infants and those with extremely low birth weight. Therefore, probiotic supplementation should be guided by current clinical recommendations and local safety protocols rather than applied indiscriminately.[13]

Other preventive measures include appropriate antimicrobial stewardship, infection prevention, and consistent monitoring of infants with multiple risk factors. The literature does not support the assumption that one intervention can eliminate NEC risk; prevention is more appropriately understood as a coordinated clinical strategy.

The selected studies contribute complementary evidence to the understanding of NEC. Clinical reviews explain the biological mechanisms and practical challenges of diagnosis, systematic reviews identify recurring risk factors, and randomized-trial syntheses assess the effectiveness of preventive interventions.

Three conclusions emerge from this evidence:

1. Biological vulnerability is central. Intestinal immaturity in preterm infants creates susceptibility to inflammatory injury, but additional microbial, nutritional, and clinical factors influence disease development.[14]

2. Prevention is more established than early prediction. Human milk feeding and standardized neonatal care are important preventive measures, whereas reliable prediction before clinical deterioration remains challenging.
3. Evidence must be interpreted according to population and intervention. Findings from broader preterm populations may not apply equally to extremely preterm infants, and the results of one probiotic preparation cannot automatically be generalized to another.

These conclusions are consistent with the broader literature on NEC pathophysiology, prevention, and clinical management[15]

4. Conclusion

Necrotizing enterocolitis (NEC) remains a major cause of morbidity and mortality among preterm infants, particularly those with very low birth weight and extreme prematurity. The literature reviewed in this article demonstrates that NEC is a multifactorial disease arising from the interaction of intestinal immaturity, dysregulated immune responses, alterations in the gut microbiota, impaired intestinal barrier function, and nutritional and clinical factors. Although the precise mechanisms underlying disease development remain incompletely understood, the interaction between developmental vulnerability and environmental exposures appears to play a central role in its pathogenesis.

Early recognition and timely intervention are essential for reducing the risk of severe intestinal injury and systemic complications. Clinical assessment, laboratory investigations, abdominal radiography, and intestinal ultrasonography provide complementary information for diagnosis and disease monitoring. However, the nonspecific nature of early symptoms and the absence of a universally reliable early predictive biomarker continue to present significant clinical challenges.

Prevention remains a central priority in neonatal care. Feeding with mother's own milk, the use of donor human milk when appropriate, standardized feeding protocols, infection prevention, and responsible antimicrobial use may contribute to reducing NEC risk. Probiotic supplementation may offer additional benefits in selected populations, but its use requires careful consideration of product-specific evidence, safety, and current clinical guidelines, particularly in extremely preterm and extremely low-birth-weight infants.

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