International Journal of Medical Science and Clinical Research Studies

ISSN (print): 2767-8326, ISSN (online): 2767-8342

Volume 04 Issue 12 December 2024

Page No: 2484-2497

DOI: https://doi.org/10.47191/ijmscrs/v4-i12-52, Impact Factor: 7.949

Necrotizing Enterocolitis: A Literature Review of Basic Concepts, Diagnosis and Treatment Options

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ABSTRACT

Necrotizing enterocolitis (NEC) is a severe inflammatory bowel condition that causes intestinal tissue ischemia in premature newborns, mainly due to their underdeveloped intestinal and immune systems. NEC develops through both maternal and infant-related factors, including weak immune defenses, reduced transfer of maternal immunity, and various molecular factors such as epigenetics and blood vessel development. Feeding problems are the earliest sign, often accompanied by breathing pauses, slow heart rate, and unstable body temperature. Initial treatment is focused on bowel rest, nutritional support, and antibiotics. Surgery becomes necessary in about 30% of cases, especially in younger patients. Preventing NEC is crucial for reducing complications, medical costs, and long-term developmental problems that affect both quality of life and healthcare resources.

KEYWORDS: Necrotizing enterocolitis, premature newborns, bowel rest, antibiotics, surgery, complications.

ARTICLE DETAILS

Published On:
25 December 2024

Available on:
https://ijmscr.org/

INTRODUCTION.

Necrotizing enterocolitis (NEC) is an inflammatory bowel disease associated with high levels of inflammation and intestinal necrosis involving the Ileum, jejunum, and colon. This disease affects preterm newborns due to the intestinal and immune system's prematurity, with multifactorial characteristics. NEC is considered a life-threatening surgical condition that affects premature newborns. **(1, 2)**

The gastrointestinal system undergoes dynamic, biochemical, structural, and functional changes to accomplish its functions in nutrition, immunity, and self-repair. The immature bowel faces many challenges, such as acquiring the ability to digest and absorb nutrients to maintain somatic and brain growth, and the development of a symbiotic relationship with the microbiome to prevent disease. The successful adaptation of the neonatal gut is critical for survival. **(3)**

In twelve high-income countries, the reported rates for NEC in preterm newborns of 32 weeks of gestation is calculated at 2% to 7%; in infants weighing less than 1000 g, the rate is 5 - 22%. Approximately 2% to 5% of admissions to the Neonatal Intensive Care Unit (NICU) can be attributed to NEC, with up to 85% of those cases occurring in premature newborns; late preterm newborns contribute 7% to 15%. **(2)**

In The United States, out of 480,000 preterm newborns every year, it is estimated that NEC affects close to 9,000; with the most premature or lowest weight newborns presenting a greater risk, approximately 7% of very low birth weight newborns develop NEC, with a high mortality rate of up to

40 to 50%. Whereas in Mexico, the incidence reports range between 10% to 19.2%. **(4, 5, 6, 7)**

The global incidence of NEC varies between 0.3 to 2.4 newborns for every 1,000 births, with up to 70% of cases occurring in preterm neonates born before 36 weeks of gestation. **(8)**

Lately, there have been great improvements in neonatal intensive care, reducing mortality and thus increasing the incidence of NEC. **(9)**

Infant formula-based nutrition and bacterial exposure, without a history of perinatal asphyxia, do not result as the sole injury mechanism for the development of NEC, with perinatal asphyxia having a crucial role in the development of NEC. **(10)**

In a literature review carried out in Latin America in 2023, it was determined that there are maternal and prenatal risk factors for the development of NEC, which included premature rupture of membranes (PROM), preeclampsia, maternal HIV, and gestational diabetes. As for the perinatal and labor risks, prematurity was determined as the main risk factor; other risk factors were low birthweight, low gestational age, and cesarean delivery. Early neonatal and postnatal risk factors included respiratory distress syndrome, pneumonia, mechanical ventilation, neonatal asphyxia, anemia, red blood cell transfusion, neonatal sepsis, congenital heart disease, patent ductus arteriosus, antibiotic therapy, feeding with infant formula and prolonged parenteral feeding, low Apgar scores, oxidative stress and the use of central umbilical catheters. **(11)**

Preeclampsia, PROM, perinatal asphyxia, prematurity (28-32 WG), and low birth weight are considered the main risk factors for the development of NEC. Newborns are known to have weak metabolic and immune function, with inadequate circulatory regulation that increases susceptibility to infections and complications. **(11, 12)**

The usage of an umbilical arterial catheter with a duration greater than 5 days has been significantly associated with an increase in the risk for NEC, most likely secondary to the release of the microthrombi, vasospasm of splanchnic blood vessels, and reduction in the diameter of the abdominal aorta's lumen due to the presence of the catheter, which can lead to diminished blood flow. **(13)**

The exposure to HIV during fetal life, as well as the use of zidovudine, can contribute to the development of NEC due to secondary effects that could favor the colonization of opportunistic microorganisms and other gastrointestinal effects, such as hypoperistalsis and intestinal pseudo-obstruction, predominantly when the administration of the drugs is enteral. **(14)**

In a meta-analysis conducted in China in which a total of 52 studies were included, out of which 48 were cases and controls, and 4 were cohort studies; it was determined that the main risk factors for NEC were: gestational diabetes, PROM, low birthweight, small for gestational age, septicemia, blood transfusion, congenital heart disease, respiratory distress syndrome, premature birth, and pneumonia. On the other hand, the protective factors to reduce the risk of neonates developing NEC were breastfeeding, probiotic intake, and the administration of prenatal glucocorticoids. **(15)**

PATHOPHYSIOLOGY

The pathophysiology of NEC is highly complex since it involves multiple factors, from both the mother and the newborn. The risk of developing the disease cannot be attributed to a singular factor. Various factors contribute to the physiology of NEC, some of these include the immature host with dysfunction and poor maturation of innate and adaptive immune defense mechanisms, a significant reduction in the adaptive immune system transferred by the mother, and molecular considerations such as epigenetic factors, regulatory elements, microvasculature, and nucleotide polymorphisms, which all play a critical role in the development of NEC. **(16, 17)**

Perinatal asphyxia plays an important role, influenced by various intrauterine environmental factors and fetal birth processes. Any condition affecting blood flow or gas exchange between the mother and fetus can lead to hypoxia and, eventually, perinatal asphyxia. The risk is heightened in low-birth-weight neonates and mothers with preeclampsia or eclampsia. **(18, 19)**

Premature newborns with very low birth weight are highly susceptible to postnatal asphyxia because of their underdeveloped respiratory and neurological systems, which limits their ability to initiate and maintain breathing at birth. This does not allow for an effective gaseous exchange to take place, often leading to intensive resuscitation or mechanical ventilation. Exposure to low oxygen concentrations triggers blood flow redistribution to vital organs like the brain, myocardium, and adrenal glands, at the expense of reduced flow to organs such as the kidneys and intestines, this triggers a strong vasoconstriction of the mesenteric blood vessels, which in turn causes hypoxia and ischemia of intestinal epithelial cells, and, in severe cases causing degeneration and necrosis, culminating in NEC. **(20, 21)**

In comparison with full-term neonates, the microflora of preterm neonates is characterized by a delay in colonization and limited microbial diversity, with diminished levels of commensal anaerobic bacteria and increased levels of facultative anaerobic bacteria with pathogenic potential. This, in addition to the environmental factors seen in hospital settings, greatly influences intestinal bacterial colonization. **(22)**

Intestinal microbiota can be altered by antibiotic use, the absence of breastfeeding, parenteral nutrition, and invasive procedures; these are strongly associated with an incomplete microbial barrier in the intestinal mucosa, which plays a critical role in the pathogenesis of NEC and early-onset neonatal sepsis. Moreover, prolonged antibiotic exposure for

more than 10 days has been linked to a two- to three-fold increased risk of developing NEC. **(23, 24, 25)**

The abnormal pattern of intestinal bacterial colonization, characterized by disrupted bacterial homeostasis (dysbiosis), results in bacterial over-reactivity, accompanied by an abundance of pro-inflammatory interleukin-producing cells in the intestinal mucosa of preterm newborns with risk factors, contributing to excessive intestinal inflammation and bacterial invasion. As the disease progresses, the tissue shows signs of ischemia, followed by necrosis and finally perforation, which can range from micro-perforation to overt perforation. Micro perforations can lead to pneumatosis intestinalis, the presence of gas within the intestinal walls. **(4, 26)**

Intestinal immaturity is a key factor in which pathogenic and commensal bacteria penetrate the mucus layer to interact with pattern recognition receptors (PRRs) on epithelial cells and trigger an immune response. The most common PRR in the intestines is Toll-like receptor 4 (TLR4), which is expressed at higher levels in the intestines of preterm neonates. **(27)**

TLR4 belongs to a family of pattern-recognition receptors expressed by the immune system. They have an essential role in recognizing pathogen-associated molecules, such as lipopolysaccharides from gram-negative microorganisms. TLR4 activation is associated with endothelial damage, inflammation, inhibition of enterocyte proliferation, reduced intestinal microcirculation, and intestinal ischemia. **(28, 29)**

The role of intestinal blood flow is crucial, and it is modulated primarily by vasodilators and vasoconstrictors, with nitric oxide (NO) acting as a vasodilator and endothelin-1 (ET-1) as a vasoconstrictor. Preterm newborns exhibit significantly reduced levels of arginine, a precursor of nitric oxide, resulting in limited capacity to regulate intestinal blood flow. which in turn leads to an insufficient blood supply thus causing hypoxia, ischemic areas in the intestine, and a cascade of inflammatory events that result in intestinal injury. **(29, 30)**

The caloric requirements necessary to maintain fetal growth trajectories after birth in preterm newborns cannot be met through breastfeeding alone, requiring external fortification. However, these fortifiers increase osmolarity, which, combined with the immature intestinal mucosa and slow small intestine peristalsis, leads to inadequate digestion, causing the intestine to retain food residues that, upon fermentation, create an environment conducive to bacterial overgrowth, further damaging intestinal mucosa. **(11, 31)**

Feeding with hyperosmolar formula exerts excessive digestive stress and increases oxygen consumption in the immature intestine, significantly increasing the expression of hypoxia markers (GLUT-1 and PHD-1). This effect, associated with osmolarity or high caloric density, compromises the intestinal mucosa, exclusively in preterm neonates with immature intestinal microvasculature and limited ability to regulate blood flow. In contrast, breastfeeding does not cause such damage or elevate hypoxia markers. This demonstrates that hyperosmolar formula feeding induces mucosal hypoxia and ischemia, significantly increasing the risk of developing NEC. **(29)**

CLINICAL PRESENTATION

Clinical manifestations of NEC include non-specific systemic and abdominal findings including abdominal distension, bilious vomiting, biliary drainage through enteral feeding tubes, gastric residue, erythema of the abdominal wall, diminished bowel sounds, crackles, induration; and as the ischemic disease progresses, bloody stools and perforation of the gastrointestinal tract with free peritoneal fluid and free gas in the abdominal cavity are found. Abnormal physiological parameters can also be present, such as apnea, bradycardia, hemodynamic changes, thermal instability, respiratory failure, and cyanosis. The most frequent sign is a sudden change in the patient's feeding tolerance. **(8, 32, 33, 34, 35)**

The symptom onset can vary between preterm and full-term neonates, being inversely related to the number of weeks of life, showing a later onset in preterm neonates. Typically, the first symptoms in preterm newborns appear 2 or 3 weeks after birth, on the other hand, full-term newborns symptoms can manifest themselves during the first week of life; this is probably related to the slower progress in enteral feeding seen in the more premature patients and with a critical developmental window of greater susceptibility that coincides with deregulated intestinal or systemic immune responses and exaggerated inflammatory responses to bacteria or pathogens. Furthermore, there is an association of presentation in full-term neonates linked to congenital malformations and genetic diseases, with a lower prevalence when compared to appearance in preterm newborns. **(36, 37, 38)**

The severity of the disease is inversely proportional to the gestational age and birth weight. NEC can progress rapidly, from the initial symptoms to a fully established disease that can lead to death in the first 24-48 hours of symptom onset, therefore it is critical to make the diagnosis during the early stages. **(39, 40)**

DIFFERENTIAL DIAGNOSES

The absence of a clear definition, diffuse diagnostic criteria and lack of available biomarkers have conditioned for numerous intestinal diseases to be diagnosed as NEC, for this reason, a reevaluation of the different forms of intestinal injury and dysfunction in neonates is necessary, which can distinguish between differential diagnoses. **(41)**

Spontaneous intestinal perforation (SIP), also known as focal intestinal perforation (FIP), is an abdominal pathology that is found in an isolated manner and that does not precede pneumatosis intestinalis and gas in the portal vein, as it is described in the classic form of NEC. Both presentations manifest with abdominal distension and free air in the abdominal cavity, and the surgical treatment is the same for both cases, consisting of the placement of peritoneal

drainage. This entity has a different etiology than NEC, with focal intestinal perforation (FIP) being found earlier, using the age of onset to differentiate between NEC and FIP, with a cut-off point of 14 days. Classifying the onset before 14 days of age as FIP, and after 14 days as NEC, nevertheless, both pathologies can be found before and after the cut-off point, therefore relevant history and other variables must be considered to discern between both etiologies. **(41, 42)**

Congenital heart disease increases the prevalence of NEC, finding a prevalence of 3.7% with significant variation between different diseases of cardiac origin, most frequently associated with hypoplastic left heart syndrome, truncus arteriosus, single ventricle defects, and interrupted aortic arch, and less frequently seen in transposition of the great arteries. **(43)**

The bowel injury is secondary to mesenteric hypoperfusion, hypoxia-induced inflammation, and surgical stress-inducing factors. The gravity of the ischemic lesion associated with congenital heart disease can vary from ileus to enteritis and cardiac NEC. Cardiac NEC is an entity that is found with a higher incidence in full-term babies, with involvement in the most distal regions of the intestine. **(34)**

Food protein-induced enterocolitis syndrome (FPIES) is a rare non-IgE-mediated food allergy that typically occurs in preterm neonates with symptoms resembling NEC, including rectal bleeding, irritability, abdominal pain, occasional vomiting, an eczema-like rash, and pneumatosis intestinalis. There are no specific diagnostic tests available. Thrombocytopenia and elevated C-reactive protein are more commonly found in NEC compared to FPIES. FPIES follows a benign course, and the diagnosis is based on the resolution of symptoms after eliminating milk from the diet. Cow's milk protein allergy and intolerance can be classified based on the presence of IgE, non-IgE, or T-cell-mediated mechanisms, with the severity of adverse food reactions ranging from mild gastrointestinal symptoms to severe sepsis-like episodes. **(44, 45, 46)**

Hirschsprung's disease is a congenital disorder defined by the absence of ganglion cells in Meissner's submucosal plexus and Auerbach's myenteric plexus in the terminal rectum, extending proximally to a variable distance. This happens because of the interruption of the migration and differentiation process of neural crest cells within the enteric nervous system during gestation, resulting in an aganglionic intestinal segment with impaired relaxation, leading to intestinal obstruction and inflammation. **(47)**

Enterocolitis associated with Hirschsprung's disease is a potentially life-threatening complication with a variable clinical presentation which ranges from fever, lethargy, abdominal distension, and explosive diarrhea to intestinal perforation. This can occur secondary to increased intraluminal pressure, transmural inflammation, and vascular events leading to ischemia and subsequent perforation. Unlike classic NEC, which typically occurs in preterm neonates with risk factors, the occurrence of this entity in full-term newborns is associated with congenital malformations or disorders, such as those previously mentioned. **(48)**

DIAGNOSIS

In 1978 Dr. Martin Bell proposed the clinical staging criteria for NEC, which was later modified in 1986 by Dr. Walsh and Dr. Kliegman. They expanded Bell's staging criteria to include additional severity stages, designed to categorize the disease into three stages based on severity and to guide clinical management. The criteria consist of radiographic, clinical, and laboratory findings. **(37, 49)**

The modified Bell classification categorizes NEC into three stages based on severity. Stage I represents suspected disease and is subdivided into IA and IB. Stage IA includes mild systemic signs such as apnea, bradycardia, temperature instability, and lethargy, along with mild intestinal signs like abdominal distension, bilious gastric residuals, and occult blood in the stool, with radiographic findings being normal or nonspecific. Stage IB adds visible blood in the stool to these signs. Stage II represents confirmed disease and is divided into IIA and IIB. Stage IIA exhibits moderate systemic signs, and intestinal findings such as abdominal tenderness and diminished bowel sounds, as well as specific radiographic findings including intestinal dilation, ileus, and pneumatosis intestinalis. Stage IIB includes the signs of IIA along with analytical abnormalities such as metabolic acidosis, leukopenia, and thrombocytopenia, additional abdominal findings like cellulitis, and radiographic evidence of portal venous gas can manifest themselves too. Stage III signifies advanced disease and can also be divided into IIIA and IIIB. Stage IIIA consists of a non-perforated intestine with severe systemic involvement, with hypotension, clear signs of shock, clinical signs of peritonitis, radiographic findings of ascites, and laboratory abnormalities such as metabolic and respiratory acidosis, leukopenia, neutropenia, thrombocytopenia, disseminated intravascular coagulation, and elevated C-reactive protein. Stage IIIB includes all the findings of IIIA but adds intestinal perforation, with radiographic evidence of severe findings such as pneumoperitoneum. **(50, 51)**

The identification of potential early biomarkers as diagnostic tools enhances and increases the accuracy of diagnosis in high-risk populations, providing an opportunity for early intervention and significantly mitigating the disease. **(52, 53)**

Biomarkers can be classified into hematological indices, such as total white blood cell count, absolute neutrophil count, platelet count, and immature-to-total white blood cell ratio; acute-phase reactants, including C-reactive protein, procalcitonin, platelet-activating factor, and hepcidin; and immunological markers, such as cytokines, chemokines, adhesion molecules, intracellular signaling molecules, and growth factors. **(54)**

Various biochemical alterations can be observed, including an increase or decrease in white blood cell count, thrombocytopenia, metabolic acidosis, glucose instability,

and elevated C-reactive protein levels. However, none of these laboratory parameters demonstrate precise sensitivity and specificity. The severity of thrombocytopenia has been correlated with the clinical stages of Bell. **(55, 56)**

Epidermal growth factors play a crucial role in the development of the gastrointestinal tract. Their levels are significantly reduced in the saliva and serum of patients with NEC compared to healthy individuals, while urinary levels show no significant difference. **(56)**

Fatty acid-binding proteins (FABPs) are small intracellular proteins that increase under conditions of inflammation and ischemia. They are in gastric epithelial cells and the intestinal mucosa and are released into the bloodstream following enterocyte injury or death and they can be measured in plasma (I-FABPp) and urine (I-FABPu). Significantly higher concentrations of I-FABPp and I-FABPu have been observed six hours after the suspicion of NEC compared to healthy neonates. **(57, 58)**

There is a statistically significant increase in serum concentrations of I-FABPp corresponding to the severity and progression of the disease, with a diagnostic cutoff value greater than 131.8 ng/mL, offering 90% sensitivity and 100% specificity. Since NEC is a progressive disease, consecutive measurements are recommended to provide detailed information about the disease course rather than relying on a single measurement at the onset of symptoms. **(59)**

Blood lactate is an important marker that reflects tissue hypoxia as well as low perfusion. It is significantly associated with hospital mortality, showing a mortality increase of up to 40-45% for every 1 mmol/L increase in lactic acid levels. It is used as a predictor of poor outcomes, with values linked to severe NEC, both at the onset of the disease and during its progression. **(60, 61)**

The most used nonspecific biomarker is C-reactive protein (CRP). Nevertheless, it has proven to have limitations, including low specificity and a delayed increase of 12-24 hours after the onset of NEC. CRP levels may also be elevated due to other inflammatory causes, making it unable to distinguish between NEC and sepsis. **(62)**

Non-invasive fecal markers have been used as a diagnostic tool and for monitoring the progression of the disease, however, the difficulty in obtaining stool samples from neonates suffering from ileus secondary to NEC exhibits a significant drawback. **(63)**

The quantitative increase of fecal calprotectin, a non-invasive fecal marker, is correlated with an increase in leukocytes within the intestinal barrier, and with migration of granulocytes into the intestinal lumen. Higher levels have been observed in preterm neonates compared to term neonates, associated with an early NEC diagnosis and prediction of the severity of the disease, with sensibility and specificity rates of up to 76%-100% and 39%-96.4% respectively; nonetheless, as calprotectin is a nonspecific inflammatory marker for NEC, a combined approach with other biomarkers and laboratory analyses could improve its specificity. **(64, 65)**

A scoring system has been developed to assist in the differential diagnosis between NEC and spontaneous intestinal perforation (SIP), This system considers the presence of abdominal distension, ileus, and/or bloody stools, along with at least two of the following criteria: pneumatosis and/or portal air detected via X-ray or abdominal ultrasound, persistent platelet consumption (platelet count <150,000 for three days following diagnosis), and onset after the tenth day of life. These findings are more consistent with NEC than with SIP. **(66)**

IMAGING STUDIES

Various clinical staging systems for NEC incorporate abdominal radiographic findings. In Bell stage I (suspected NEC), radiographs typically show nonspecific signs such as mild intestinal dilation or ileus. Stage II (definitive NEC) requires more specific features like pneumatosis intestinalis and/or gas in the portal vein. Finally, Bell stage III (advanced NEC) includes findings such as pneumoperitoneum or free air. **(67)**

Supine abdominal radiographs are the cornerstone of NEC diagnosis. Common findings include asymmetrically dilated intestinal loops, intestinal wall edema, pneumatosis intestinalis, gas in the portal vein, pneumoperitoneum, and air on both sides of the intestine (Rigler's sign). For follow-up, supine and lateral projections are recommended during the first 48 hours, as most perforations occur in this period. If perforation is clinically suspected but not initially evident on a supine abdominal radiograph, additional views such as left lateral decubitus or supine horizontal beam imaging improve sensitivity. Severe imaging findings, such as pneumoperitoneum, gas in the portal vein, and seroperitoneum, are more common in patients with a fulminant disease course. **(67, 68, 69)**

The primary limitations of Bell's staging criteria include the low diagnostic accuracy of radiographs and the nonspecific symptoms in preterm infants, with no radiographic changes evident in the early stages of the disease. Radiographs have low sensitivity for detecting pneumatosis (44%), portal venous gas (13%), and free intraperitoneal air (52%), though specificity ranges from 92% to 100%. **(70, 71)**

All these limitations impede early clinical interventions aimed at risk reduction and possible prevention of NEC. As a result, new algorithms incorporating additional clinical variables for diagnosing and assessing NEC have recently gained traction. Promising modalities such as ultrasound and near-infrared spectroscopy (NIRS) are increasingly utilized in neonatal intensive care units. **(72)**

Near-infrared spectroscopy (NIRS) allows for monitoring regional oxygen saturation and calculating oxygen extraction in tissues. By monitoring splanchnic circulation, NIRS can detect hypoxic-ischemic injuries that traditional hemodynamic examinations are not able to identify. It is

considered a non-invasive tool for identifying preterm infants at risk for NEC development. In early NEC, intestinal oxygen saturation levels decrease, with more pronounced reductions observed in severe cases compared to mild-to-moderate cases. **(73, 25)**

Ultrasound offers diagnostic capabilities beyond radiographs, such as detecting peristalsis and blood flow, with higher sensitivity and specificity. It supports initial diagnosis and patient monitoring. Early findings include intestinal distension, hypervascularity, and echogenic mucosa. As the disease progresses, intestinal wall thickening (ranging from 2.5–2.7 mm) is commonly observed. In advanced stages, the intestinal wall thins, the lumen dilates, and blood flow may become undetectable. **(35, 74)**

The main limitations include challenges in evaluating deeper structures due to intestinal gas. High-frequency ventilation may also cause vibratory motion, creating interference, especially when assessing intestinal perfusion and peristalsis. Reduced intestinal perfusion can be observed in patients with low cardiac output or those receiving vasoconstrictive medications; however, these findings should not be interpreted as indicative of primary intestinal pathology. **(75)**

Another alternative radiological method is abdominal computed tomography, which has demonstrated sensitivity, specificity, positive predictive value, and negative predictive value of up to 100%. However, instability, the difficulty of mobilizing the patient, and the high levels of ionizing radiation involved, result in the contraindication of this method in daily practice. **(76)**

BACTERIOLOGY

Microorganisms associated with NEC are challenging to isolate through blood cultures, with positive results in only 25% of cases. The most identified pathogens include *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Clostridium perfringens, and Pseudomonas aeruginosa*. **(77)**

In a 2019 study with a 5-year follow-up, 1163 fecal metagenomes from 31 preterm neonates who developed NEC and 126 preterm neonates without NEC were analyzed, averaging 7.2 samples per neonate. The intestinal microbiome of all neonates was dominated by Proteobacteria. The study found an increase in Enterobacteriaceae and a deficiency in Actinobacteria and Bacteroides. *Klebsiella pneumoniae* was the most strongly associated bacterium with NEC, detected in 52% of samples before NEC diagnosis compared to 23% in controls. Additionally, a daily increase in bacterial replication was observed three days before and up to the diagnosis, potentially contributing to the disease's onset. **(78)**

TREATMENT

The choice of treatment can be challenging due to the wide range of conditions resembling NEC, such as intestinal perforation, ischemic intestinal necrosis, protein intolerance-associated enterocolitis, and congenital gastrointestinal tract malformations. **(79)**

Early treatment is crucial to prevent devastating consequences, through conservative approaches such as fasting, parenteral nutrition, fluid resuscitation, antibiotic regimens, and maintaining acid-base balance. However, some cases require surgical intervention. Most neonates are managed with conservative treatment, but approximately 30% progress to requiring surgery. Newborns diagnosed at a younger postnatal age are more likely to require surgical treatment. **(80, 81, 82)**

The management of NEC depends on the severity of the disease, which is defined by the modified Bell staging criteria. Treatment decisions are guided by the extent of disease, the surgeon's preference, and the physiological state of the newborn. **(83)**

Antibiotics are a cornerstone of NEC treatment, with broad-spectrum regimens recommended to target both aerobic and anaerobic bacteria. Although no specific microorganism has been definitively linked to NEC, common protocols include ampicillin or vancomycin for gram-positive coverage, combined with aminoglycosides such as amikacin or gentamicin, or cephalosporins like cefotaxime for gram-negative bacteria. In the setting of confirmed intestinal perforation, metronidazole is used for anaerobic coverage**.** Antibiotic selection is tailored to disease severity, with most NEC treatment regimens based on ampicillin and aminoglycosides, which act synergistically. Adjustments to antibiotic therapy are made based on blood culture results. The duration of antibiotic treatment is also determined by Bell staging criteria, with Stage Ia requiring 48–72 hours of treatment followed by clinical reassessment, Stage Ib-II requiring a 10-day course, and Stage III potentially requiring more than 10 days of therapy depending on the progression of the disease and the patient’s clinical condition. **(84, 85, 86)**

Nutritional management of NEC begins with intestinal rest, during which non-nutritive sucking may be initiated to promote intestinal motility and mesenteric blood flow. Enteral nutrition should be resumed as soon as NEC is resolved to mitigate the adverse effects of prolonged gastrointestinal rest and parenteral nutrition, such as an increased risk of sepsis, cholestasis, growth impairment, neurocognitive deficits, and extended hospital stays. Following recovery from conservative or less severe surgical NEC, an initial enteral feeding volume of 10–20 ml/kg/day is recommended, with evidence showing that advancing by 20 ml/kg/day is generally well-tolerated without negative outcomes. However, caution should be exercised based on the severity of the disease and the extent of surgical resection. Bolus feeding is thought to better stimulate intestinal adaptation than continuous infusion. However, continuous feeding provides a slower administration of nutrients, which may improve absorption and feeding tolerance, particularly in infants with short bowel syndrome. **(87)**

Neonates with NEC should begin early parenteral nutrition to maintain a positive nutrient balance, support weight gain, and facilitate tissue repair. Parenteral nutrition should be discontinued once the inflammatory process resolves and enteral feeding becomes sufficient to meet the neonate's nutritional needs, thus reducing the risk of complications. **(88)**

While the only absolute indication for surgery is radiologic evidence of intestinal perforation, manifesting as pneumoperitoneum on abdominal X-rays, emerging evidence suggests that early surgical intervention based on ultrasound findings—such as intestinal wall thickening and deficient intestinal peristalsis—can significantly improve therapeutic outcomes and reduce mortality and complications, even before perforation occurs. **(35, 76, 89, 90)**

The main surgical goal is to minimize contamination by controlling intestinal perforation and resecting nonviable bowel segments. Several surgical approaches exist, including peritoneal drainage, laparotomy with or without bowel resection, and the formation of either a stoma or a primary anastomosis. **(91)**

COMPLICATIONS

Out of the neonates who survive, approximately 50% will develop long-term complications, and around 10% of these will experience late-onset gastrointestinal problems. Meanwhile, the remaining 50% will not have any long-term sequelae. **(92)**

In a 20-year follow-up study of neonates who had NEC (68% Bell stage I, 25% stage II, and 7% stage III), compared with neonates of the same gestational age, birth weight, and birthdate, it was found that weight gain was significantly lower in those who experienced NEC in comparison with the control group. No significant differences in height were observed. **(93)**

NEC is associated with a higher incidence of neurodevelopmental impairment. Among neonates requiring surgery, greater neurological compromise was observed compared to those treated conservatively, reflecting multifactorial impacts, including inflammatory responses, hemodynamic changes in the brain, hypotension, reduced cerebral blood flow, hypoxia, and ischemia. Neurodevelopmental impairment remains a significant concern, with an overall rate of 56% among survivors at 18 to 22 months of corrected age. This impairment is characterized by moderate to severe cerebral palsy, severe bilateral visual impairment (vision below 20/200), or permanent hearing loss. **(94, 95)**

The most frequent gastrointestinal complications include adhesions in 10% of cases and short bowel syndrome (SBS), which is considered the most common cause of intestinal failure. SBS is characterized by a reduction in intestinal function and/or mass below the minimum required to sustain growth, hydration, and electrolyte balance, with a 26% occurrence rate secondary to NEC. **(96)**

The type of treatment serves as a significant prognostic factor, with higher morbidity and mortality observed in patients who underwent surgical intervention compared to those managed with conservative treatment. **(97)**

PREVENTION

Since the pathogenesis of NEC is multifactorial, multiple interventions have been studied for its prevention. These include optimal feeding strategies that prioritize human milk, microbial optimization approaches (probiotics, prebiotics, and symbiotics), immunomodulatory strategies, and nutritional strategies. **(98)**

In a retrospective study examining the impact of mixed feeding with different proportions of breast milk and formula, 303 very low birth weight neonates were included, each following a different feeding plan for two weeks. They were divided into three groups: one group was fed with a higher proportion (greater than 54%) of breast milk, a second group with a lower proportion (less than 54%) of breast milk, and a third group was exclusively fed formula. This study found a significantly higher NEC incidence in the last two groups in comparison with the group fed with a higher proportion of breast milk, concluding that a higher intake of breast milk was more effective than a lower intake in preventing NEC due to bioactive components that shape intestinal immune development and promote healthy intestinal colonization, thus preventing intestinal inflammation and providing strong protection against the development of NEC. Breastfeeding was considered the most effective preventive strategy. **(99, 100)**

The protective effect of breastfeeding has been linked to an enzyme called PAF-acetylhydrolase (PAF-AH-102) that works by inhibiting the platelet-activating factor involved in the inflammatory process, possibly providing a protective effect depending on the amount of breast milk received by the preterm-infant. A meta-analysis found that the risk of NEC was reduced by nearly half with human breast milk feeding, whether from the mother or a donor, compared to formula feeding. **(101, 102)**

Historically, it was believed that delaying the initiation of enteral feeding would minimize the incidence of NEC. However, no higher incidence of NEC has been found when early trophic feeding (within the first 96 hours of birth) is started and continued for one week, compared to fasting and starting enteral feeding at seven or more days of life in very preterm neonates (<32 weeks) or very low birthweight neonates (<1500 grams). **(103)**

In a 2019 meta-analysis that included neonates between 28-36 weeks of gestational age and weighing between 1000-1500 grams, the safety of starting total enteral feedings at 80 ml/kg/day was compared to starting enteral feedings at the conventional volume of 20 ml/kg/day, supplemented with intravenous fluids. No difference was found in the incidence of NEC or feeding intolerance when total early enteral feedings were initiated. **(104, 105)**

A meta-analysis concluded that, for infants with very low birthweight, a faster advancement of feeding (30 to 40 ml/kg/day compared to 15 to 24 ml/kg/day) did not increase the risk of NEC and showed benefits in recovering birthweight and shortening hospital stay. However, the use of this practice should be individualized for newborns with risk factors. **(106, 107)**

Probiotics may positively contribute to modulating immune responses such as inflammation, improving the function of the intestinal mucosal barrier, modulating host gene expression, and preventing colonization by pathogenic bacteria. Probiotics are not routinely administered in all centers, but where they are used, they are started as soon as possible once the patient receives enteral nutrition. **(108, 109)**

Moderate to high-certainty evidence shows the superiority of combinations of one or more Lactobacillus spp. and one or more Bifidobacterium spp. over alternative single and multiple probiotic treatments. The two combinations of Bacillus spp. and Enterococcus spp., and Bifidobacterium spp. and S. salivarius thermophilus, may provide a greater reduction in the development of NEC, with low to very low evidence certainty. A large, high-quality trial in Australia determined that the probiotic combination with Bifidobacterium infantis, Streptococcus thermophilus, and B. lactis demonstrated a reduction in the risk of NEC. **(110, 111)**

The use of antenatal steroids for preterm birth reduces perinatal death, neonatal death, and the most severe events associated with prematurity, including necrotizing enterocolitis. It has the potential effect of accelerating intestinal maturation, evidenced by decreased bacterial translocation, greater absorption of macromolecules, a protective effect against intestinal injury and severity, reduced intestinal barrier permeability, and lower levels of inflammatory cytokines, thus decreasing the incidence of gastrointestinal disorders. Antenatal steroids are considered by the World Health Organization as essential to decrease neonatal mortality, efficiently used in preterm birth at 24-34 weeks, with the possibility of using betamethasone or dexamethasone. **(112, 113, 114)**

CONCLUSION

With recent advancements in medicine and the care of critically ill preterm neonates, there has been an increase in survival rates, alongside a significant rise in gastrointestinal diseases.

Necrotizing enterocolitis (NEC) is a disease-specific to newborns, characterized by an inflammatory process and intestinal injury of multifactorial origin. Its primary contributing factors include periods of hypoxia and asphyxia, gastrointestinal inflammatory mediators, enteral feeding, bacterial colonization, and immaturity of the gastrointestinal barrier, with prenatal, perinatal, and postnatal risk factors—prematurity and low birth weight being the most prominent. NEC is considered a severe condition where the most vulnerable population, identified with risk factors, requires careful monitoring.

This disease presents with nonspecific clinical signs and lacks pathognomonic symptoms, making complementary studies such as imaging and laboratory tests essential for early detection, accurate diagnosis, and timely medical intervention. New techniques and promising biomarkers have been introduced; however, an ideal biomarker that combines high specificity, sensitivity, low cost, and non-invasive characteristics capable of differentiating NEC from similar pathologies is still lacking. Future research is needed to determine its usefulness in everyday clinical practice. This area holds great potential for the development of new molecular techniques that could positively impact the prediction, diagnosis, timely treatment, and, consequently, prognosis, reducing short- and long-term sequelae.

Overdiagnosis leads to the interruption of enteral feeding, with the administration of prolonged courses of antibiotics and parenteral nutrition, and medical practices that, while necessary, are not benign.

NEC is a potentially fatal disease, with increased morbidity and mortality in patients who undergo surgical treatment. Various variables affect outcomes, including birth weight, hemodynamic status, comorbidities, available resources, intraoperative findings, and the attending physician's preferences.

It is crucial to implement preventive measures to reduce the incidence of NEC, lessen the economic burden on healthcare systems, decrease severe complications, shorten hospitalization times, and avoid long-term sequelae and even death. Long-term complications and neurodevelopmental sequelae are associated with poor quality of life and a significant increase in financial resource utilization.

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