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## **Necrotizing enterocolitis: Pathophysiology, prevention and treatment**

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### **Abstract**

Necrotizing enterocolitis (NEC) is the most common acute abdomen in a newborn kid, according to neonatologists. It is the leading cause of mortality and morbidity in neonatal intensive care units. Gut necrosis of various lengths and depths is seen, with intestinal perforation occurring in up to one-third of affected newborns. Prenatal and neonatal treatment advancements resulted in the survival of preterm babies who were in danger of NEC. NEC is the most common surgical emergency in newborns, with a higher fatality rate than other gastrointestinal disorders requiring surgical treatment. Despite much research, the exact aetiology and pathophysiology of the disease remain unclear. The history, epidemiology, aetiology, and risk factors, pathophysiology, prevention, and treatment modalities of necrotizing enterocolitis are all included in this study.

**Keywords:** necrotizing enterocolitis, pathophysiology, prevention, treatment

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### **Introduction**

#### **History**

Paltauf was the first to recognize occurrences of this condition in 1888, but Schmid and Quaiser coined the name "necrotizing enterocolitis" in 1953<sup>[1]</sup>. Early surgical intervention was used to treat NEC in the 1960s; however, patients diagnosed early enough in the 1970s may be cured without surgery<sup>[2-3]</sup>. The number of premature births has increased dramatically in recent decades, owing to two factors: <sup>[1]</sup> the increased use of caesarian sections before 34 weeks of pregnancy for therapeutic reasons, and <sup>[2]</sup> the fact that, in the modern era of neonatal intensive care units (NICUs) and surfactant therapy, most premature babies can overcook<sup>[1]</sup>.

#### **Epidemiology**

NEC mostly affects preterm, low birth weight newborns rather than those who are tiny for gestational age<sup>[3]</sup>, and it has been reported in both sporadic instances and nosocomial epidemics. The rate of occurrence differs across nations and between various areas within the same country. It has been estimated that it accounts for 1–7.7% of all NICU hospitalizations in the United States, or one to three per 1000 live births, or around 10% of VLBW newborns. In Japan, the prevalence of VLBW babies has risen to 1–2%. Only 5–25% of all instances of NEC occur in full-term newborns<sup>[9]</sup>, demonstrating the link between preterm and NEC<sup>[1]</sup>.

Although overall infant mortality has decreased, NEC-related death still accounts for 10–30% of all NEC cases in different centres. On the other hand, during the last decade, the surgical death rate for this ailment has fallen from over 70% to between 20% and 50%, demonstrating the progress made in this sector. Surgical intervention is required in around 20–40% of newborns with NEC, and it has been found that those who need this therapy the most are those with the earliest gestational age and birth weight. Furthermore, according to the modified Bell's

classification, the severity of NEC, as well as mortality, are inversely linked to birth weight and gestational age, with a report of 100% fatality in babies with birth weights less than 1000 g and gestational ages less than 28 weeks<sup>[1]</sup>. According to some sources, the total death rate of NEC is likely to be about 30%, with surgical NEC having a much greater mortality rate than medical NEC<sup>[4]</sup>.

In the past, survivors of NEC had normal neurocognitive development as they grew older, but more recently, there has been a rise in the prevalence of mental retardation. In addition, data from a study conducted for the National Institute of Child Health and Human Development revealed that NEC is an independent risk factor for a guarded prognosis on the neurodevelopmental outcome of children born at a very low birth weight<sup>[1]</sup>. Despite several studies aimed at identifying risk factors for NEC, prematurity appears to be the only consistently demonstrated association. Some regions have higher reported rates of the disease than others, and urban areas may be more significantly affected than rural ones<sup>[4]</sup>.

Though NEC is a relatively rare disease, its economic burden is substantial. The median length of hospital stay (LOS) for deficient birth weight neonates is between 2 and 3 months. The addition of a diagnosis of successfully treated medical NEC increases that by 20 days, and treatment with surgery increases LOS by 60 days<sup>[4]</sup>.

#### **Aetiology**

Although much study has been done on the aetiology of this terrible illness, it has yet to be understood entirely. It's most likely a complex condition caused by a variety of causes<sup>[4, 5]</sup>. Birth asphyxia, polycythemia, umbilical vessel catheterization, congenital heart disease, blood transfusions, exchange transfusions, early and rapid feeding, hyperosmolar formulas, maternal cocaine use, neonatal medications, hypoalbuminemia, symptomatic or subclinical perinatal infection, respiratory

distress syndrome, and hypoxic-ischaemic oedema are among the most common risk factors <sup>[4]</sup>.

Congenital heart disease, neonatal hypoxia, hypoglycemia, polycythemia, respiratory distress, prolonged diarrhoea, maternal preeclampsia, cow's milk protein intolerance, and antic rhesus incompatibility are potential risk factors for the development of NEC in full-term newborns <sup>[4]</sup>.

### Pathophysiology

The origins and pathogenesis of NEC are currently being discussed. NEC is assumed to be the consequence of a complex mix of factors, including prematurity, that produce mucosal damage, leading to ischemia and necrosis in the intestine. Mucosal injury may be caused by infection, intraluminal substances, immature immunity, the release of vasoconstrictors, and inflammatory mediators. The loss of mucosal integrity in severe instances of NEC allows bacteria and their toxins to get through the gut wall and into the bloodstream, resulting in a broad inflammatory response and overwhelming sepsis. The inflammatory process in NEC causes the increased blood flow in the affected intestinal segment. Bacteria break the mucosal barrier, causing intramural gas to form as a consequence of metabolic by-products. As NEC progresses, platelet-activating factor, produced by inflammatory cells and bacteria, propagates the inflammatory cascade, which includes cytokines and complement, culminating in severe transmural involvement. The tissue's microvasculature ultimately gets impaired, resulting in ischemic changes. Finally, necrosis occurs in the nonperfused gut wall, which may be strong enough to produce sloughing, resulting in intestinal wall weakness and eventually perforation <sup>[6]</sup>.

### Clinical Diagnosis

Nonspecific clinical findings that merely signify physiological instability are often used to diagnose NEC <sup>[3]</sup>. When distinctive radiologic signs are seen in the proper clinical situation, it is usually diagnosed. NEC is most often associated with feeding intolerance, resulting in vomiting, excessive gastric residuals, and abdominal distention. Apnea, bradycardia, lethargy, and temperature instability are examples of early indicators that are less precise. Hematochezia or occult faecal blood are further possibilities. A history of rapid increases in ventilatory needs during the outset of the NEC may also be elicited by the surgeon, indicating higher metabolic demands mixed with increasing intra-abdominal pressure. The most frequent exam finding is abdominal distention. Bowel loops protruding through the skin may be seen under the skin. Changes in skin tone should be noticed. Through thin, soft tissue, the dusky color of the abdominal wall may reflect the underlying color of the bowel or faeces. Peritonitis with inflammation transmitted via the wall may cause erythema. Bowel loops that may be felt are usually cause for worry. A fixed abdominal mass and erythema of the abdominal wall are substantially predictive of NEC when present. These characteristics, however, are seen in just 10% of people with NEC. Signs and symptoms, as well as radiologic evidence, are used to confirm the diagnosis of NEC. These results have been included in Bell's suggested clinical staging system, which assists in characterizing the severity of illness <sup>[4, 7]</sup>. A thorough physical examination, laboratory testing, and specific imaging modalities are part of the first assessment of a newborn suspected of having

NEC <sup>[8]</sup>.

### Laboratory evaluation

Laboratory tests aren't used to diagnose NEC, although they may help determine the infant's systemic sickness severity. Neutropenia, thrombocytopenia, and metabolic acidosis are common in infants with NEC. The level of metabolic acidosis may be a reflection of bowel and whole-body perfusion. You may have leukocytosis or leukopenia. Worsening thrombocytopenia, notably a sharp decline, might be a warning indicator <sup>[3, 4]</sup>.

For the proper administration of antibiotics, blood and peritoneal cultures and susceptibility tests are required, and the findings vary depending on the situation, such as sporadic vs epidemic instances, VLBW versus full-term newborns, and so on <sup>[1]</sup>.

In NEC, the number of serum acute-phase proteins and cytokines are increased. In preterm newborns with NEC, elevated IL-6, IL-10, and C-reactive protein (CRP) levels have been reported, with the most significant amounts of IL-10 identified in those who did not survive. The beginning of NEC may be accompanied by a rapid increase in CRP, and some prospective evidence suggests that this shift may distinguish NEC from other GI illnesses. More critically, the failure of CRP to normalize is linked to a variety of problems, including abscesses, strictures, and sepsis <sup>[4]</sup>.

Faecal calprotectin is an inflammatory marker in the faeces that has been demonstrated to distinguish restricted NEC from NEC with systemic disease (Bell III) with a sensitivity of 76 % and specificity of 92 %. Infants with suspected NEC who developed perforation had higher amounts of a comparable faecal protein than those who did not <sup>[4]</sup>.

### Imaging

#### Radiography

The defining radiologic finding in NEC is pneumatosis intestinalis, which may be observed on plain film. Pneumatosis is often the critical finding that establishes the diagnosis due to the lack of specificity of the standard indications, symptoms, and laboratory data. Pneumatosis intestinalis, on the other hand, is not a particular finding and has been shown in a variety of disorders such as Hirschsprung's disease with enterocolitis, pyloric stenosis, and carbohydrate intolerance. Dilated bowel loops or a lack of bowel gas may be seen in the early stages of NEC (Bell I). Pneumatosis may be accompanied by portal venous gas, which is typically seen as a wrong indication. Other radiographic abnormalities include intestine ascites and pneumoperitoneum in the context of intestinal perforation (free gas within the peritoneal cavity). Other than pneumoperitoneum, radiographs of babies with localized perforation may show none of these symptoms. A "fixed loop" of the bowel, or successive plain films showing a dilated loop in the exact location, might indicate a nonfunctioning section that has to be evaluated for necrosis. A fixed loop is considered a clear surgical indication by some surgeons <sup>[4, 7, 8]</sup>.

#### Ultrasound

Since around 2005, there has been a trend toward using abdominal ultrasound (US) with Doppler imaging of the GI tract to identify more subtle findings such as abdominal fluid, hyperemia, decreased blood flow to the gut, and pneumatosis intestinalis, all of which may not be well seen on plain abdomen radiographs, making the US more sensitive than explicit films for

the diagnosis of NEC. Furthermore, the US may detect bowel peristalsis, wall thickening, echogenicity, and pneumoperitoneum. Based on many studies, it has a better capacity to see tiny air or fluid collections and describe the intestinal wall more thoroughly. Although the US seems to help define a prognosis, it is still not generally utilized as an effective technique for diagnosing NEC or determining therapy options [4, 9].

### Other Imaging Modalities

In assessing babies with acute NEC, computed tomography and contrasted fluoroscopy have no apparent relevance. Magnetic resonance imaging (MRI) is a non-invasive technique that has recently been utilized to detect babies with NEC-related ischemic bowel disease. Although MRI may be used to demonstrate the key features of NEC, its value is limited. Recently, near-infrared spectroscopy (NIRS) has emerged as a promising method for assessing intestinal perfusion in newborns. NIRS is a non-invasive technique for measuring tissue haemoglobin oxygen saturation [4, 9].

### Classification

Scientists must adopt matching criteria for defining the phases of NEC in order to pick the proper treatment (nonoperative vs operative) and establish the effect of therapy on survival and late outcomes. There have been many categorization systems developed. Bell's three-stage categorization approach (suspected, definite, and progressed) was created in 1978, and it categorizes patients based on history variables, GI symptoms, radiologic findings, and systemic indicators. The Bell staging criteria have been tweaked; the three stages are still in place, but subcategories have been added to help pinpoint particular prognostic markers. Patients with stage I illness have NEC-like symptoms, patients with stage II disease have definite NEC without the need for surgery, and patients with stage III disease have progressed NEC with intestinal necrosis or perforation [9].

**Table 1:** Modified Bell Classification for NEC [2]

Stage	Clinical Findings	Radiographic Findings	Gastrointestinal Findings
Stage I	Apnea, bradycardia, and temperature instability	Normal gas pattern or mild ileus	Mild abdominal distention, stool occult blood, gastric residuals
Stage IIA	Apnea, bradycardia, and temperature instability	Ileus with dilated bowel loops and focal pneumatosis	Moderate abdominal distention, hematochezia, absent bowel sounds
Stage IIB	Metabolic acidosis and thrombocytopenia	Widespread pneumatosis, portal venous gas, ascites	Abdominal tenderness and oedema
Stage IIIA	Mixed acidosis, coagulopathy, hypotension, oliguria	Moderate to severely dilated bowel loops, ascites, no free air	Abdominal wall oedema, erythema, and induration
Stage IIIB	Shock, worsening vital signs and laboratory values	Pneumoperitoneum	Bowel perforation

### Management

#### Medical Management

Individuals with NEC who do not have intestinal necrosis or perforation are treated with supportive treatment. The gastrointestinal system is decompressed by a gastric sump tube,

and intravenous fluid resuscitation commences. A complete blood count, platelet count, blood gas analysis, and CRP are all assessed, and a total blood count, platelet count, blood gas analysis, and CRP. Blood and urine cultures are sent in, and broad-spectrum intravenous antibiotic therapy begins. Most antibiotic regimens included penicillin, an aminoglycoside, and an anaerobic organism-killing medication until recently. The efficacy of this regimen has yet to be shown in a controlled study. The antibiotic regimen should be tailored to the nosocomial nursery flora as well as the most common organisms identified by NEC. Based on recent reports of coagulase-negative staphylococci in their stool and blood cultures, several organizations are now treating patients with a combination of vancomycin and gentamicin or vancomycin and a third-generation cephalosporin. Because fungal sepsis is prevalent in newborns who die of NEC, a strong index of suspicion is required, and empirical antifungal therapy should be considered if the patient's clinical course is prolonged [9].

Like with any sick patient, Cardiopulmonary care focuses on supplying oxygen via proper resuscitation with fluids and blood products, sufficient oxygenation and ventilation, and, if required, vasopressor support. In NEC treatment, no unique supporting method has yet evolved. In these infants, close clinical and radiographic surveillance by neonatology and surgical services, as well as continual reevaluation for operational indications, is critical [4].

#### Surgical Management Indications

Intestinal perforation or clinical worsening despite maximum medicinal therapy is surgical grounds for NEC [10]. Up to 52 per cent of VLBW infants with NEC are operated on. Although some babies with medical NEC gain surgical indications while being monitored, many need surgery at the time of presentation [4]. Paracentesis has been utilized in the diagnostic algorithm for NEC in addition to the sole unequivocal indication for surgery in NEC, which is pneumoperitoneum on an abdominal radiograph. A positive tap for enteric contents in the abdomen is also a strong justification for surgery [4].

Surgical reasons for NEC include intestinal perforation or clinical deterioration after maximal medicinal treatment [10]. Operation is performed on up to 52% of VLBW newborns with NEC. Although some newborns with medical NEC develop surgical indications while being followed, many babies with medical NEC need surgery right once [4]. In addition to the single clear indication for surgery in NEC, which is pneumoperitoneum on an abdominal radiograph, paracentesis has been used in the diagnostic algorithm for NEC. A positive abdominal tap for intestinal contents is also considered a good indication for surgery [4].

Due to a scarcity of high-quality prospective randomized studies, NEC's best surgical treatment plan remained a point of contention until recently. The surgical objective is to remove the gangrenous bowel while preserving the length of the intestine. There are a variety of surgical techniques available in this situation, but most agree that the level of intestinal involvement should choose the surgical strategy. Before surgery, the patient's general state should be improved with solid ventilatory support, shock therapy, broad-spectrum antibiotics, and anaemia and coagulopathy

correction. Under the right circumstances, surgical operations may be done in the NICU without increasing the risk of problems [9].

### Prevention

Our failure to find the optimum therapy for NEC and the disease's high fatality rate highlight the need for better preventative methods. Even though various interventions have been examined, feeding preterm neonates human breast milk remains the most effective strategy in preventing NEC. Other preventative measures include exogenous prophylactic steroids, prophylactic antibiotics, and enteral IgA supplementation, strengthening the intestinal host defence. The most recent intense research about prevention has come from probiotics [4, 11-12].

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