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Necrotizing enterocolitis

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Key points
Necrotizing enterocolitis (NEC), with its high mortality and significant long-term morbidity, is the most serious and challenging disease of preterm infants.

The most common predisposing factors to NEC are prematurity, gut ischaemia, an immature immune system, and infection.

Approximately one-third of infants with NEC require surgical intervention.

Neonates who require surgical intervention for NEC have a higher mortality than those who receive medical treatment only.

Perioperative fluid management of infants during surgery for NEC poses considerable challenges for the anaesthetist.

Necrotizing enterocolitis (NEC) is the most common gastrointestinal (GI) emergency in neonatal intensive care units (NICUs), making it one of the leading causes of long-term disability in preterm infants. NEC is called ‘the disease of survivors’ as it is characteristically manifest in preterm infants, who have survived other immediate life-threatening complications associated with their very low birth weights (<1500 g), such as respiratory distress syndrome and congenital cardiac anomalies.¹

Clinical presentation
NEC presents with both GI and systemic signs usually within 3–10 days of preterm birth, although the presentation can be delayed. Typically, a preterm neonate would develop NEC after its first enteral feed when the intestinal lumen first becomes colonized with bacteria. The most common presentation of NEC is intolerance to enteral feeding, abdominal tenderness and distension, bloody diarrhoea, lethargy (evident by reduced spontaneous motor activity), respiratory distress, shock, and body temperature instability.

Diagnosis
Radiological and laboratory tests may provide evidence in support of the initial clinical diagnosis of NEC. For example:

(i) Plain X-rays (supine and decubitus) may be used to determine the presence of hepatic venous gas, free intraperitoneal air, dilated bowel loops, ascites, and asymmetric bowel gas patterns along with pneumatosis intestinalis.

(ii) Ultrasound with Doppler (to demonstrate the absence of mesenteric blood flow) may be used to confirm the presence of the necrotic bowel and portal venous gas.

Laboratory findings help to support the diagnosis but are not diagnostic on their own. A typical presentation of sepsis with thrombocytopenia, neutropenia, metabolic acidosis, and coagulopathy is seen in NEC but will need to be differentiated from other causes of a similar clinical picture in the newborn, for example, congenital bowel strictures/perforation, malrotation, intussusception, pseudomembranous colitis, and meconium ileus. Haemorrhagic disease of the newborn may also cause diagnostic confusion as although the neonate is not septic, bleeding through the GI tract can mimic NEC.²

Persistently high levels of C-reactive protein signify the progression of NEC. Bell’s stages³ of NEC may also be used to categorize the severity of NEC based on the above symptoms and signs and by the results of laboratory investigations (Table 1). High levels of C-reactive protein may also indicate stricture or abscess formation and may therefore be useful in deciding the requirement and timing of surgery.⁴

Pathophysiology
The pathophysiology of NEC is generally poorly understood. Predisposing risk factors for ischaemic bowel injury in NEC are perinatal asphyxia, umbilical artery cannulation, polycythemia, exchange blood transfusion, respiratory distress syndrome, and cyanotic congenital heart disease. The antenatal diagnosis of reduced diastolic blood flow in the fetal aorta by Doppler velocimetry is associated with increased incidence of NEC.⁴ Indomethacin, the most commonly used agent for pharmacological closure of patent ductus arteriosus, is known to cause hypoperfusion of the brain, kidney, and gut.⁵ Hence, the use of indomethacin may be implicated as an important contributing factor leading to NEC in preterm infants.⁶

Fetal hypoxia and perinatal asphyxia reduce intestinal motility in preterm infants. The distal ileum and the proximal colon which are located at the watershed areas of perfusion by the superior and inferior mesenteric arteries are the most commonly affected bowel segments in neonates with NEC. Hypoxic ischaemic injury acts similarly to the ‘diving reflex’ whereby blood flow is preferentially diverted away from...
the non-vital organs such as the gut towards the central organs, for example, the heart and brain. This type of ischaemic gut injury leads to NEC and is typically seen in infants with cyanotic congenital heart disease and in infants having undergone open-heart surgery (owing to the reduced gut blood flow during cardiopulmonary bypass). NEC also presents in infants who have been exposed to maternally ingested cocaine during the antenatal period which in turn leads to hypoxic vasoconstriction of the bowel vasculature.

A newborn infant has extremely low intestinal vascular resistance due to the increased production of nitric oxide (NO) which is required to optimally maintain gut perfusion. Consequently, reduced endothelial production of NO caused by endothelial dysfunction (possibly due to hypoxic injury) can predispose preterm babies to NEC.

From 26 weeks onwards, fetal bowel mucosa develops secretory and absorptive functions. The secretory functions include chloride and water secretion to flush away toxins and pathogenic organisms. However, in preterm neonates, immature bowel endothelium lacks this secretory function. In addition, the absence of adequate number of goblet cells (associated with protective mucin production) along with an underdeveloped immune system [in particular, secretory immunoglobulin A (IgA) deficiency in the terminal ileum and colon] also contribute towards bacterial translocation across the intestinal lumen.

NEC may develop due to bacterial or viral infection, for example, Escherichia coli, Enterobacter, Pseudomonas aeruginosa, and Clostridium perfringens, and viruses, for example, coronavirus, rotavirus, and enterovirus. Bacterial endotoxins can initiate the production of inflammatory mediators such as cytokines, tumour necrosis factor, and platelet-activating factor leading to a pro-inflammatory response in the gut flora similar to that seen in NEC. Intra-luminal fermentation of undigested lactose from milk feeds by the normal or pathogenic gut flora leads to the production of gas (raising intra-abdominal pressure) and subsequent intestinal intra-cellular acidosis due to decreased gut perfusion. The intra-luminal gas produced in the gut can be absorbed by the intestinal wall leading to the typical appearance on plain X-ray films of intra-mural air known as pneumatosis intestinalis (Fig. 1). Intra-vascular absorption of this gas can be seen on plain X-rays within portal venous vessels (Fig. 2). Pneumatosis intestinalis and portal venous gas are pathognomonic of a diagnosis of NEC.

Full-term neonates that develop NEC often have an associated cyanotic or congenital heart lesion. The outcome for infants with congenital heart disease who develop NEC is better than for infants who develop NEC without congenital heart disease. Putative associations of NEC with gastroschisis and total parental nutrition-induced cholestatic jaundice have also been seen.

Antenatal steroids and patent ductus arteriosus surgery are statistically significant predictors of NEC in infants with birth weight from 400 to 1000 g. The hypothesis is that antenatal steroids

| Table 1 Bell’s stages of NEC |
|--------------------------------|
| **Stage I** (suspected disease): mild systemic signs (apnoea, bradycardia, temperature instability), mild GIT signs (abdominal distension, large gastric aspirates, bloody stools), non-specific or normal radiological signs |
| **Stage II** (definite disease): mild systemic signs with additional GI signs (absent bowel sounds, abdominal tenderness), specific radiological signs (dilated loops of intestines, pneumatosis intestinalis or portal venous air), abnormal laboratory investigations (e.g. metabolic acidosis, thrombocytopenia) |
| **Stage III** (advanced disease): severe systemic illness (with haemodynamic instability), additional GI signs (gross abdominal distension, peritonitis), severe radiological signs (pneumoperitoneum), additional laboratory findings (e.g. metabolic and respiratory acidosis, disseminated intravascular coagulopathy) |

![Fig 1 Abdominal radiograph in an infant with NEC demonstrating pneumatosis intestinalis (intra-mural air) and gut perforation (evident by gas situated anterior to the liver in this supine film).](image1)

![Fig 2 Abdominal radiograph in an infant with NEC demonstrating portal venous gas and gut perforation.](image2)
help the extremely premature infant to survive respiratory distress syndrome in the first few days of life, only to present with NEC later.

Early enteral feeding in preterm neonates is also implicated as an important contributor to the development of NEC; however, NEC can also develop in term neonates who have never been enterally fed.\(^1\)

**Epidemiology**

More than 90% of infants diagnosed with NEC are preterm. The morbidity and mortality in NEC are inversely proportional to the infant’s post-conceptional age and birth weight.\(^2\) NEC typically occurs after commencing enteral nutrition. Infants fed on breast milk have 3–10 times lesser incidence of NEC than those fed formula milk. The host defence factors in breast milk such as IgA, lymphocytes, macrophages, lactoferrins, complement, lysozymes, and antioxidants impart protection against NEC. The frequency of NEC ranges between 1% and 5% of all NICU admissions or 0.5–5 patients per 1000 live births and 7% of very low-birth-weight infants (<1500 g). The incidence is higher in male infants and mortality is greater in the Afro-Caribbean population. NEC is the most serious and challenging disease in preterm infants with a mortality rate of 20–40% in North America.\(^2\) The mortality is higher (~50%) for infants requiring surgical intervention and is related to the severity of the disease and postoperative complications.\(^2\)

**Prevention**

Feeding exclusively with human milk and conservative enteral feeding practices, especially in high-risk infants, can reduce the incidence of NEC; however, antenatal steroids, IgA and arginine supplementation, erythropoietin, oral antibiotics, and probiotics have questionable efficacy in preventing the disease.\(^5\)

**Management**

**Medical management of NEC**

On clinical suspicion of NEC, the neonate should be given bowel rest, bowel decompression (intermittent naso-gastric tube suction), and broad-spectrum antibiotics (after blood/stool cultures have been obtained). Although NEC is suspected to be associated with bacterial growth in the gut and hence in blood (bacterial translocation), only one-third to half of the newborns developing NEC have a positive blood culture.\(^6\) Treatment with antibiotics is continued for 10–14 days. In cases with pneumoperitoneum, the antibiotic regimen should ensure adequate cover for anaerobic organisms. The usual antibiotic combination prescribed at our institute are cephalosporins, aminoglycosides, and metronidazole. Supportive care including inotropic therapy for hemodynamic instability, ventilation for respiratory compromise, and blood products to correct anaemia and coagulation abnormalities play an important role in the intensive care management of these cases. Third space losses due to bowel oedema and metabolic acidosis necessitate careful fluid and electrolyte monitoring. The physician’s clinical judgement should guide the duration of the medical management for Bell’s stage I cases, while for Bell’s stage III cases, in addition to the supportive treatment outlined above, there is a need for the physician to consider surgical intervention.

**Surgical management of NEC**

Approximately 20–40% of infants with NEC require surgery. Surgical intervention is indicated by the presence of bowel perforation, gangrenous bowel, and pneumoperitoneum and also by laboratory findings of persistent and severe haematological changes and the radiological signs of generalized intestinal distension.

Surgery usually involves resection of the gangrenous bowel and enterostomy formation. The mortality rate for NEC has decreased from 80% to 20% over the last three decades due to earlier diagnosis and better intensive care. NEC is associated with a morbidity rate of 10–30% related to post-NEC complications, in particular intestinal stricture (10–40% incidence) and short gut syndrome (25% incidence if more than 70% of small bowel is resected). The preservation of the terminal ileum and ileo-caecval valve are important surgical considerations for survival.\(^1\) Intraoperative liver haemorrhage is a known lethal complication of NEC surgery and is especially seen in infants with lower preoperative mean arterial pressure and in those requiring larger fluid resuscitation before operation.\(^1\)

**Anaesthetic management of NEC**

The infant should be pre-optimized wherever possible before surgery; however, a critically ill infant may require life-saving operative treatment while resuscitation is in progress. A very unstable infant with NEC, for example, requiring high-frequency jet ventilation might necessitate the surgical intervention to be performed on the NICU itself, although this option should only be considered in extreme circumstances, as sterility of the surgical field in this situation is questionable. After an initial urgent intervention such as the insertion of an abdominal drain, subsequent operative procedures can be carried out in the operating theatre when the baby is more stable. Primary peritoneal drainage is a useful adjunctive therapy before definitive surgery, especially in very low-birth-weight infants.\(^10\)

NEC babies often require large volumes of i.v. fluid (Ringer’s lactate, 5% albumin, and hydroxyl-ethyl starch are the most commonly used fluids at our institute) along with appropriate maintenance fluids to maintain normoglycaemia. Frequently, severely ill infants with NEC require inotropic support to maintain adequate perfusion pressures. The assessment of intra-vascular blood volume and blood loss is a real challenge. High infusion rates of 20 ml kg\(^{-1}\) h\(^{-1}\) together with boluses of 5% albumin may be required as replacement fluid to maintain adequate circulating...
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volume. A good urine output (>2 ml kg⁻¹ h⁻¹) may reflect an adequate perfusion pressure and hence correlate with an increased survival from an episode of severe NEC. Blood loss needs to be replaced with blood, fresh-frozen plasma (FFP), and albumin. Coagulopathy as indicated by constant oozing at the surgical field requires platelets and FFP transfusion.

Standard routine monitoring (pulse oximeter, ECG, end-tidal CO₂, and non-invasive arterial pressure) is used, while central venous pressure and invasive arterial pressure monitoring (an umbilical artery catheter or a peripheral arterial line) are helpful but not mandatory. At times, in our experience, the infant with the distended abdomen is peripherally shut down and the anaesthetist has to compromise on monitoring the infant and start the surgical procedure with peripheral lines only. Almost all infants are intubated and ventilated before operation at our institute. The patients presenting with NEC for surgery are usually very sick and poikilothermic. Accordingly, body temperature monitoring and active warming measures, including a warm theatre, a forced-air blanket, and warmed i.v. fluids, are essential. Addition of a heated humidifier within the breathing system also helps to reduce heat loss.

Preterm babies undergoing surgery show an increased neuroendocrine response. Induction with a high dose of opioid (e.g. fentanyl 10 µg kg⁻¹ body weight or an equivalent dose of remifentanil or sufentanil) helps to avoid postoperative catabolism and substrate mobilization caused by the systemic stress response. This is worthwhile as the surgical stress response lasts longer in preterm infants than in full-term babies and adults. Moreover if the neonates have been in the NICU for a long time before operation, then they might require higher doses of opioids intraoperatively due to opioid tolerance. Nitrous oxide is contraindicated as it worsens bowel distension. The use of volatile anaesthetic agents, although not contraindicated, may not be required as the neonates are usually receiving opioid and benzodiazepine infusions as part of their intensive care sedation regimen.

Ethical issues

Good medical practice requires an obligation on the part of the physician to keep parents and carers well informed at all stages of treatment, including the decision to withhold or withdraw treatment. This sensitive issue needs to be managed with care and empathy, keeping in mind the right to life of every child but avoiding futile and potentially inhumane invasive procedures which may well be the case in a very premature infant with severe NEC.

Declaration of interest

None declared.

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Please see multiple choice questions 1–4.