

Necrotizing enterocolitis

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Abstract

Necrotizing enterocolitis (NEC) is a neonatal surgical emergency with potentially devastating consequences. Preterm infants of very low birth weight are most at risk with several genetic and environmental risk factors identified. The local microbial environment plays a key role in early life to help reduce the risk of NEC. Breast milk has also shown to be protective. The disease is characterized by infection, inflammation and ischaemia of the bowel affecting focal, segmental or the entire length of bowel. The diagnosis is made clinically with the support of biochemical and radiological features. Emerging new biomarkers are being exploited to identify patients at risk. Bowel perforation is the most widely accepted indication for surgery. However, when conservative management fails, surgery is indicated with the aim of resecting necrotic bowel and preserving intestinal length. Complications include strictures, stoma morbidity, short-bowel syndrome and poor neurodevelopmental outcomes. Preventative strategies include early suspicion and appropriate management as well as encouraging the use of breast milk. The use of probiotics is controversial but has gained support for usage.

Keywords Aetiology; anastomosis; necrotizing enterocolitis; neurodevelopmental outcomes; pathogenesis; peritoneal drainage; probiotics; stoma

Definition

Necrotizing enterocolitis (NEC) is the most common surgical emergency seen in the neonatal setting. It is characterized by varying degrees of inflammation, ischaemia and infection of the bowel culminating in necrosis with or without perforation of the affected length of intestine.

Aetiology

The aetiology of NEC is multifactorial with a predilection towards preterm neonates.¹ Prematurity with its associated low birth weight is the most widely recognized risk factor for this condition. An inverse relationship between the incidence of NEC and birth weight has also been demonstrated in large multicentre studies.² Up to 85% of affected infants are premature with those less than 28 weeks gestation and extremely low birth weight (<1000 g) most at risk.³

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In 90% of cases, NEC develops in infants that have commenced feeds.³ This resulted in the practice of slowly establishing feeds (<20 ml/kg/day increments) amongst preterm infants. However, in a recently published Cochrane review, no significant difference was found between slower or faster advancement of feeds.⁴ Individual components of enteral feeds have been extensively investigated with short chain fatty acids potentially implicated.⁵

The local microbial environment within the gut lumen also has a role to play. In utero, the gut is sterile but is colonized within 1 week by anaerobic bacteria of a healthy breast fed infant.⁵ This process is often hindered in a premature infant resulting in an imbalance of flora in favour of pathogenic organisms that weaken the immune system and mucosal defences. There is strong emerging evidence in the literature of the role of probiotics in the prevention of NEC in an attempt to restore this balance.⁶ In a recent systematic review and meta-analysis, *Bifidobacterium* has been found to be safe and have a potentially beneficial effect and in preventing NEC.⁷

Other risk factors that have been suggested include the presence and/or treatment of a patent ductus arteriosus with non-steroidal anti-inflammatory drugs, transfusion with packed red cells and the use of antacids.⁵

Epidemiology

NEC affects approximately 5% of preterm neonates equating to 3000 infants in the UK each year.⁵ The true incidence is however unknown due to several cases of suspected early NEC that is initially managed in the same way. Amongst very low birth weight infants, the incidence varies worldwide with a 1–2% rate in Japan to a 28% rate in Hong Kong.³ NEC also accounts for 1–7% of all NICU admissions.³ Over a 1-year period, the prevalence of NEC within level 2 and 3 units was reported to be 2% in 2010 within the UK.⁸

Pathogenesis and pathology

The exact mechanism for the development of NEC remains unclear. NEC is characterized by inflammation, infection and ischaemia of the bowel mucosa with necrosis as the most severe complication. It has never been reported in sterile intestine and this points towards a significant role played by the microbial environment.

Preterm hospitalized infants are exposed to several environmental risk factors that alter the composition of flora in the intestine. However, healthy breast fed infants have a predominance of *Bifidobacteria*, which are believed to be protective and have led to the use of probiotics in trials to help reduce the risk of NEC.^{7,9} Breastfeeding is also associated with a reduced risk of NEC compared to formula⁹ due to protection inferred from secretory IgA, antimicrobial proteins and fatty acids.

The lining of the mucosa is usually compromised first and this is immature in preterm infants. Epidermal growth factors responsible for intestinal growth and maturation are also implicated with increasing concentrations found in the amniotic fluid with gestational age.⁹

Ischaemic mucosal injury is also seen in histological specimens of NEC. Localized neuroendocrine factors including

endothelin and nitric oxide regulate the microcirculation and have been shown in animal models to be dysfunctional in NEC.⁹ Pro-inflammatory mediators, platelets activating factor and cyclooxygenase are also important factors in the cascade of inflammation seen as part of the pathology.⁹

As a unifying concept, it is accepted that NEC occurs in ‘at-risk’ intestine of a vulnerable preterm infant. Altered bacterial colonization in the NICU setting and interaction between enterocytes and immune cells triggers an inflammatory cascade and ischaemia causing mucosal injury.³

The terminal ileum is most commonly affected, due to the watershed blood supply, followed by the colon. NEC can affect either a single or multiple segments of bowel. If more than 75% of the gut is affected the disease is classified as being NEC totalis, which accounts for a fifth of all surgically treated cases.³ Histologically, oedema, haemorrhage, necrosis and pneumatosis are all seen to varying extents depending on severity. In the congenital heart disease cohort of patients who have an increased risk of NEC, a recent study has identified the colon to be more commonly affected as compared with a non-cardiac premature group.¹⁰

Diagnosis

NEC is often first suspected in infants demonstrating temperature instability, bradycardia, apnoea, lethargy and irritability. Initially it is difficult to separate this from neonatal sepsis. Abdominal distension, tenderness, abdominal wall erythema/bruising and rectal bleeding may also be seen in association with high bilious aspirates (Figure 1). In early cases, these features may be subtle but can progress rapidly in fulminant cases. In male infants, scrotal bruising may signify intestinal perforation.

The most common biochemical anomalies seen are neutropaenia, elevated C-reactive protein, thrombocytopenia and metabolic acidosis. Thrombocytopenia is usually seen as a consequence of gram-negative sepsis and platelet binding by endotoxin. In a recent study, inflammatory regulators such as Resistin-like molecule β (RELM β) combined with thrombocytopenia have been found to be reliable biomarkers for the early diagnosis of NEC.¹¹

Imaging plays a key role in the diagnosis of NEC with plain abdominal radiography employed most often. The most common features to look for are non-specific bowel distension, fixed



Figure 1 Abdominal wall erythema and bruising.

loop(s) of bowel, pneumatosis intestinalis, portal venous gas and pneumoperitoneum (Figure 2).

Ultrasonography is also increasingly being used to assess the viability of bowel as well as pneumatosis in equivocal cases. There is an increasing drive to help identify the ‘at-risk’ infant early that will benefit from surgical management or conversely facilitate the decision making process in terminally ill infants.¹²

In 1978, Bell introduced a classification system to grade the severity of the disease based on examination findings, biochemical markers and imaging (Table 1).¹³ Objectively, classifying the severity provides a means of stratifying the population being treated and enables outcome comparison.

Differential diagnosis

The differential diagnosis includes neonatal sepsis with or without an ileus, intestinal malrotation with volvulus and hypoplastic left heart syndrome. In all suspected cases of NEC, the general advice is to initiate gut rest, start nutritional support and consider broad-spectrum intravenous antibiotics before further diagnostic tests become available to confirm or refute the diagnosis.

Management

The early stages of NEC are commonly referred to as ‘medical’, and require conservative management. This involves resting the gut, aspirating and replacing gastric contents, broad-spectrum intravenous antibiotics and parenteral nutrition. The most commonly used antibiotic regime involves using a penicillin, aminoglycoside and anaerobic cover. The length of treatment administered varies between centres, but is usually between 10 and 14 days.^{1,3} Between 20% and 40% of infants will, however, fail medical management and require surgery.

The only definitive indication for surgery is a pneumoperitoneum; however, there are several other relative indications that make the timing of surgery more controversial. These

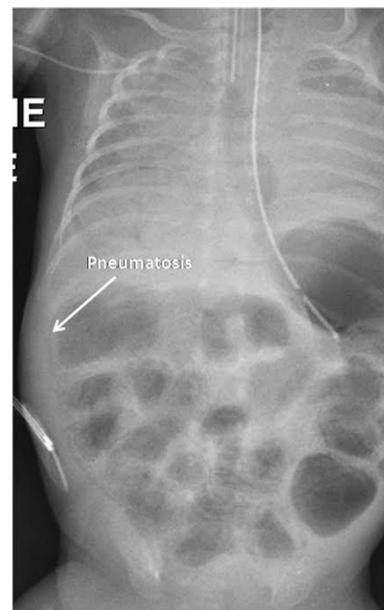


Figure 2 Pneumatosis on plain abdominal radiography.

include a palpable abdominal mass, fixed bowel loop, portal venous gas and failure to progress despite maximal medical therapy. Earlier recognition and intervention in the latter case may potentially improve outcomes. However, despite extensive research in the field, there are no universally accepted criteria that help inform us of this.

The mainstay of surgery is to remove gangrenous bowel and preserve intestinal length. The type of surgery undertaken is dependent on its indication.

If a pneumoperitoneum is confirmed, two main options are available: insertion of a peritoneal drain versus a laparotomy with or without a bowel resection, anastomosis or stoma. The former is often used as a salvage procedure when faced with a tense pneumoperitoneum compromising ventilation. Once the infant is stabilized, definitive surgery can be conducted. In 2015, a survey conducted amongst European surgeons revealed 27% would use primary peritoneal lavage as the definitive procedure in extremely low birth weight infants.¹⁴ This is an acceptable means of management of infants that are critically unwell and would not tolerate a laparotomy either in theatre or in NICU.

Another controversial aspect of surgical management is the need for a bowel resection and anastomosis versus an

enterostomy. In extremely unstable patients, a diverting enterostomy without bowel resection can be performed as an emergency. However, in stable patients with focal NEC, a primary bowel resection with an anastomosis will avoid the morbidity of a stoma as well as the need for further reversal surgery and its complications. In the few limited studies performed, no significant difference in outcomes has been reported between these two approaches.¹⁵

In extensive multi-focal NEC, another option is to perform a ‘clip-and-drop’ technique in which necrotic segments are excised and the ends of the bowel sealed. A re-look laparotomy is then performed 24–48 hours later to assess the viability of the remaining bowel at which time bowel continuity can be restored with or without any enterostomy. A high diverting jejunostomy can also be fashioned as a temporary means in unstable patients with extensive disease.^{1,3}

Laparoscopy has also been described in the context of NEC. Up to 20% of patients in a systematic review of 44 patients did not require further surgery following laparoscopy. Authors were either able to exclude NEC macroscopically or diagnosed NEC totalis in which more than 75% of the bowel was affected and further surgery was deemed futile.¹⁶ Patients that can tolerate laparoscopy are likely to be self-selected and therefore its true role remains to be proven in larger scale studies.

Modified Bell’s classification of NEC¹³

Stage	Systemic signs	Intestinal signs	Radiographic signs
I: Suspected NEC	Temperature instability, apnoea, bradycardia	Elevated gastric residuals, mild abdominal distension, occult blood in stool	Normal or mild ileus
IIA: Mild NEC	Similar to stage I	Prominent abdominal distension ± tenderness, absent bowel sounds, grossly bloody stools	Ileus, dilated bowel loops with focal pneumatosis
IIB: Moderate NEC	Mild acidosis and thrombocytopenia	Abdominal wall oedema and tenderness ± palpable mass	Extensive pneumatosis, early ascites, ±PVG
IIIA: Advanced NEC	Respiratory and metabolic acidosis, mechanical ventilation, hypotension, oliguria, DIC	Worsening wall oedema and erythema with induration	Prominent ascites, persistent bowel loop, no free air
IIIB: Advanced NEC	Vital sign and laboratory evidence of deterioration, shock	Evidence of perforation	Pneumoperitoneum

Table 1

Complications

Complications are related to the inflammatory nature of the disease or a consequence of surgery.

Intestinal strictures are well recognized with an incidence ranging between 9% and 36%.³ The most common site affected is the colon followed by the terminal ileum. In patients managed medically, presenting features include failure to thrive and intermittent obstruction. Patients who have undergone surgery can also develop strictures and common practice is to perform a contrast study to assess the distal bowel prior to restoring continuity. The stricture most often requires a resection and anastomosis but can in some cases be treated with balloon dilatation.

Short-bowel syndrome affects those infants who have undergone significant bowel resection affecting up to a quarter of these cases.³ Prolonged parenteral nutrition is often needed prior to also considering bowel lengthening procedures or a transplant. Cholestatic liver disease is seen in infants receiving such treatment and can be difficult to treat along with central venous line infections.

Recurrent NEC is seen in approximately 5% of cases and is managed in the same way as discussed above.

Stoma related complications include fluid and electrolyte losses, prolapse, retraction, stenosis and herniae. In extremely symptomatic cases, early stoma closure is warranted and can be safely performed within a few weeks after surgery.

Prognosis

Despite several advances in specialized neonatal intensive care, the mortality from NEC remains high between 20% and 40%. Reported rates are even higher in extremely low birth weight infants. More recently, there has been an emphasis in the literature on neurodevelopmental outcomes following general anaesthesia and surgery. Specifically in the case of NEC, poor

outcomes have been noted in up to 50% of cases, particularly in more severe cases or those undergoing surgery.^{17–19}

Prevention

Breast milk is strongly recommended in all cases and has been shown to reduce the risk of all major neonatal infections including meningitis.³ More recently, there has been an emphasis on the use of probiotics, which promotes colonization of the gut with favourable flora. There is however a lack of robust data on the exact regimens to be used and which population of preterm infants are most likely to benefit from the various strains currently available.²⁰ ◆

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