Necrotizing enterocolitis

Nigel Hall, Agostino Pierro

Necrotizing enterocolitis is the principal cause of surgical referral in preterm neonates and the most common gastrointestinal emergency among infants. Its pathophysiology is unclear and it carries high levels of mortality and morbidity. This article provides an overview of necrotizing enterocolitis including risk factors, preventative strategies and medical and surgical management.

Necrotizing enterocolitis (NEC) is a disease characterized by diffuse or focal necrosis of the ileum and/or colon. There is a spectrum of clinical and pathological manifestations. In the least severe cases there may be mild inflammation of the intestinal wall in a baby with mild abdominal distension and minimal systemic upset. The most severely affected cases, however, may show evidence of full thickness intestinal necrosis with perforation, respiratory and cardiovascular collapse, multi-system organ failure and in some cases death.

While primarily a disease of infants born prematurely, it is also observed in term infants, particularly those with co-existing morbidities and recognized risk factors such as congenital heart disease. The reported incidence varies from 1 to 5 per 1000 live births and there is a strong association with low birthweight and prematurity such that the incidence is as high as 5% in infants less than 1000g and more than 90% of affected infants are born prematurely (Kliegman and Fanaroff, 1984; Holman et al, 1989).

PATHOGENESIS AND RISK FACTORS

Several theories and mechanisms of injury have been proposed to explain the aetiology of NEC. However, despite over 30 years of research the aetiology remains unclear and no single mechanism at present can account for the pathogenesis in all cases. The interaction of multiple aetiologies is likely to be responsible in the majority of cases. A number of risk factors have been shown to be associated with NEC and others implicated by strong association. Intestinal immaturity of premature infants is thought to be central to the pathogenesis, although the precise nature of this immaturity and the mechanisms by which disease ensues are unclear.

Peripartum events

There are several risk factors related to pre- and perinatal events which are associated with NEC. Absent or reversed end diastolic blood flow in the umbilical artery has been reported as a predisposing factor (Malcolm et al, 1991). In addition there is an association with maternal eclampsia, fetal distress, premature rupture of membranes and delivery by caesarean section. In the immediate postnatal period risk factors include asphyxia, hypothermia, respiratory distress syndrome, apnoeic episodes, cyanotic congenital heart disease, persistent fetal circulation, persistent ductus arteriosus and sepsis.

Feeding regimen

The majority of infants who develop NEC have been fed enterally. There is often pressure to provide feeds of increased calorific density in order to meet the metabolic requirements of the premature neonate necessary for growth. Such hyperosmolar feeds may cause mucosal damage in the pre-existing immature intestine and may cause NEC. Breast milk appears to offer some protection against NEC, probably as a result of its immunologically active components (immunoglobulin, cytokines and complement proteins; Buescher, 1994).

Altered blood supply

NEC has been associated with a number of predisposing factors which are believed to result in intestinal vascular insufficiency and subsequent selective mesenteric ischaemia. The causes of this vascular insufficiency include pre- and perinatal stress, umbilical catheterization, exchange transfusion, congenital cardiac disease and indomethacin treatment. This results in the loss of the protective mucosal barrier, autodigestion and presents an opportunity for bacterial invasion. Bacterial proliferation leads to toxin release, gas production and intestinal necrosis.

Mr Nigel Hall is Clinical Research Fellow and **Professor Agostino Pierro** is Professor of Paediatric Surgery in the Department of Paediatric Surgery, The Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, University College London, London WC1N 1EH

Correspondence to: Professor A Pierro

In addition to these associations, evidence for a vascular component in the aetiology of NEC comes from an experimental animal model in which a disease like NEC is observed following an intestinal ischaemia reperfusion injury (Vejchapipat et al, 2002).

Bacterial involvement

While the precise role of bacterial agents in the development of NEC is unclear, there are a number of factors which suggest their involvement. Occasionally NEC is seen to occur in clusters in which a higher than expected number of cases are observed in one centre. Identical organisms are grown from babies within these clusters and the initiation of infection control measures has been shown to control such outbreaks (Rotbart and Levin, 1983). Bacterial involvement in the pathogenesis of NEC is also implicated by association; endotoxaemia (Scheifele et al, 1985) and positive blood cultures are common in infants with NEC and the gastrointestinal pneumatosis found in NEC contains 30% hydrogen, a gas produced solely by bacterial metabolism (Engel, 1973). Furthermore, in experimental animals an NEC-like illness can be induced by ingestion of *Clostridium* species (Lawrence et al, 1982) and administration of bacterial endotoxin (Caplan et al, 1990).

PREVENTION

Over recent years a number of investigators have attempted to prevent NEC by a number of mechanisms. Given that the aetiology of this disease is multifactorial any intervention improving one of the recognized risk factors may be expected to decrease the incidence of NEC. Eibl et al (1988) showed that administration of preparation containing immunoglobulins IgG and IgA decreases the incidence of NEC but a review by the Cochrane collaboration of the use of oral immunoglobulin for preventing NEC in low birthweight neonates revealed that there was no evidence to support the administration of oral immunoglobulin for the prevention of NEC (Foster and Cole, 2003). A review of the use of enteral antibiotics for preventing NEC (Bury and Tudehope, 2003) did suggest that they reduce the incidence of NEC in low birthweight infants. However, there were concerns about adverse effects, particularly those related to the development of resistant bacteria and antibiotics are not routinely used for this indication.

The role of bacteria in the pathogenesis of NEC has also led investigators to determine the effect of probiotics on the incidence on NEC. While Hoyos (1999) found a reduction in the incidence of NEC and mortality in infants who received probiotic bacteria, their control group was historical and the study not randomized. Dani et al (2002) conducted a prospective double-blind placebo-controlled study of 7 days' administration of *Lactobacillus* and found no reduction in the incidence of NEC.

Other novel agents have been suggested for the prevention of NEC including recombinant erythropoietin (Ledbetter and Juul, 2000) and arginine (Amin et al, 2002). While both of these agents resulted in a reduction in incidence of NEC when compared to controls, the mechanism of action of each is unclear and may be attributable to other secondary effects. Further studies of these and other agents may be warranted.

There is little doubt that one of the most important preventative measures is that of feeding with breast milk. Feeding with formula milk significantly increases the risk of developing NEC. This has been reviewed by McGuire and Anthony (2003) who found a threefold reduction in incidence of NEC in infants fed with donor breast milk compared with those fed formula milk and a fourfold reduction in the presence of confirmed NEC. The authors' current practice is to encourage feeding of neonates at risk of NEC with maternal expressed breast milk wherever possible and not contraindicated.

DIAGNOSIS

Infants with NEC usually display specific gastrointestinal signs. In the early stages of the disease abdominal distension with or without tenderness (*Figure 1*), feeding intolerance with increased gastric residuals, vomiting and occult blood in the stools may all be present. These findings may become more severe as the disease progresses to include ascites, abdominal wall oedema and bluish discoloration. In addition to these gastrointestinal signs, generalized non-specific signs indicative of systemic deterioration or sepsis may be present including temperature instability, tachycardia, hypotension and respiratory distress

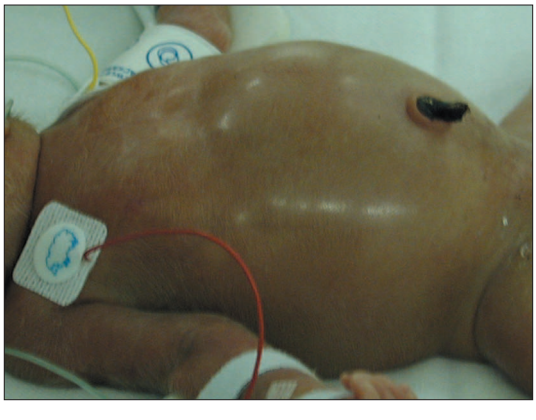


Figure 1. Typical appearance of abdominal distension in an infant with necrotizing enterocolitis (NEC). Note the 'shiny' appearance of the abdominal skin suggestive of abdominal wall oedema and the slight bluish discoloration commonly observed in infants with severe NEC.

often requiring ventilatory support. There are no defining laboratory parameters of use although an abnormal white cell count (raised or depressed), thrombocytopenia (Ververidis et al, 2001), metabolic acidosis, glucose instability and elevated C-reactive protein levels are common findings.

Radiographic imaging is essential in the diagnosis of NEC. The pathognomonic radiological finding is that of pneumatosis intestinalis (*Figure 2*) representing intramural gas from pathogenic bacteria. When this gas becomes absorbed into the mesenteric circulation it may result in the presence of portal venous gas on the abdominal radiograph. This is seen as a narrow, linear air-dense area in the hepatic region. The most significant radiological finding is that of intestinal perforation. Free gas may be seen in the subhepatic space and hepatorenal fossa when it is visible as a triangular gas shadow obviously not in continuation with the intra-intestinal gas.

Rigler's sign, in which there is clear visualization of the outer as well as the inner wall of a loop of bowel, is also a valuable indication of free intraperitoneal gas. The football sign (free gas outlining the falciform ligament and umbilical arteries) unequivocally indicates pneumoperitoneum. In many cases the identification of perforation is challenging and a lateral decubitus radiograph may be useful (*Figure 3*). There are cases in which intestinal perforation may be represented by a completely gasless abdomen and it is not unusual to find a sealed perforation at laparotomy in the absence of free air on the abdominal radiograph. A small proportion of neonates with NEC present with a palpable abdominal mass. This may be a result of matted loops of bowel around an area of gangrene or perforation. An abdominal ultrasound scan may be helpful for diagnosis in these cases.

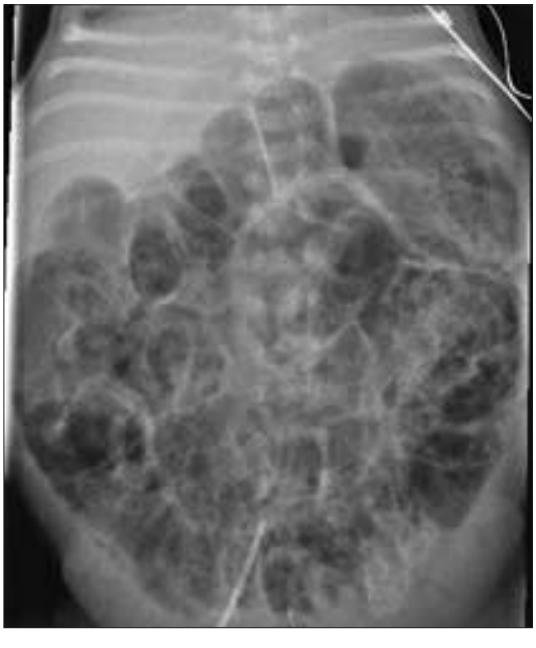


Figure 2. Plain abdominal radiograph of an infant with necrotizing enterocolitis showing intestinal dilatation and extensive pneumatosis intestinalis.

STAGING

To select the appropriate treatment and to determine the effectiveness of therapy on survival and outcome it is necessary for investigators to use comparative criteria for classifying the different stages of NEC. The most commonly used classification system is that proposed by Bell in 1978, which has subsequently been modified by Walsh and Kliegman (1986) (*Table 1*). There are three stages of NEC which are further sub-divided depending on the presence or absence of particular prognostic factors. Infants with stage I disease have features suggestive of NEC and are often treated as having NEC until they either develop stage II disease or their symptoms resolve. Stage II is confirmed NEC and stage III advanced NEC suggestive of intestinal necrosis.

CLINICAL MANAGEMENT

Medical management

Most infants with NEC are treated non-surgically although they may require intensive medical management. Adequate resuscitation is essential and most require some form of ventilatory assistance. Correction of hypovolaemia and correction of acid–base imbalance are almost always required and inotropic support of the cardiovascular system is not uncommon. Correction of thrombocytopenia and coagulopathy may be indicated. Before the administration of blood products the authors recommend testing the infant for T-cryptantigen activation, a finding more common in infants with severe NEC (Hall et al, 2002), and using appropriate blood products to avoid the potentially fatal complication of haemolysis.

Figure 3. Left lateral decubitus abdominal radiograph of an infant with perforated necrotizing enterocolitis showing intestinal dilatation and pockets of free intraperitoneal air (marked by arrows).

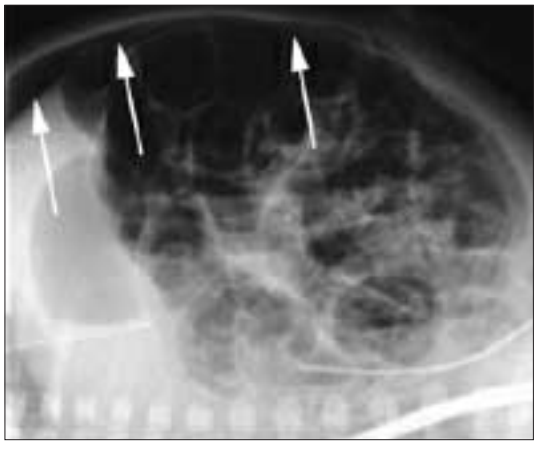


TABLE 1.
Modified Bell staging of necrotizing enterocolitis (NEC)

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

DIC = disseminated intravascular coagulopathy; PVG = portal venous gas. From Walsh and Kliegman (1986)

In patients with stage I NEC, the intestine should be rested by means of discontinuation of enteral feeds and decompressed with a large bore nasogastric tube. Broad spectrum antibiotics should be administered to cover bowel microbes and altered appropriately in light of culture results. Serial clinical and radiological examination is of extreme importance to detect any evidence of perforation or other indication for surgical intervention. In the absence of such indication, medical management should continue for at least 7 days depending on severity of illness. The authors' preferred approach is to rest the bowel for at least 10 days and to administer intravenous antibiotics for 7 days. Following this feeds may be slowly reintroduced over many days while particular attention is paid to detecting feeding intolerance suggestive of a repeat episode of NEC or intestinal stricture. From the time of diagnosis to re-establishment of full enteral feeds it is essential to maintain nutritional input adequate for tissue healing and repair, and organic growth with total parenteral nutrition (TPN).

Surgical management

Despite aggressive medical treatment, a proportion of infants with NEC require surgical intervention in the acute stage. Perforation of the gastrointestinal tract is the only absolute indication for surgical intervention in acute NEC and although other cases may benefit from surgery, the indications are less well defined. The continued deterioration of an infant despite maximal medical support over a period of 12–24 hours may warrant surgical intervention and portal venous gas on the abdominal radiograph has been proposed as an indication for surgery (Molik et al, 2001) although this is not universally accepted.

The choice of surgical procedure for acute NEC is contentious. The traditional approach to infants with NEC requiring surgery has been to perform a laparotomy, resect all areas of necrotic intestine and exteriorize the bowel to allow adequate time for healing and growth before restoring intestinal continuity at a later stage. However, in 1975 Marshall described the use of percutaneous peritoneal drainage before laparotomy, as a way to stabilize and improve the systemic status of premature infants with intestinal perforation secondary to NEC. Initially it was hoped that the drainage of air and stools from a child too unstable for a laparotomy would relieve symptoms of abdominal compartment syndrome and infection, to better tolerate the subsequent laparotomy. Two years later, Ein et al (1977) reported the use of peritoneal drainage without laparotomy (primary peritoneal drainage) in the management of newborn infants with complicated NEC. Since then peritoneal drainage has been used in a number of settings, with varying outcomes. A meta-analysis of peritoneal drainage *vs* laparotomy for perforated NEC (Moss et al, 2001) failed to show any superiority of one approach over the other and two randomized controlled trials concerning this issue are currently in progress.

There are a number of options available to the surgeon undertaking laparotomy for NEC. The decision of which to use is based on intraoperative findings, overall clinical condition of the infant and experience. Resection of affected segments and creation of one or more stomas may be complicated by nutritional and metabolic derangements associated with stomas and is followed by a need for further surgery to restore intestinal continuity. Resection and primary anastomosis avoids such hazards and this approach has gained popularity in recent years, having been first proposed by Kiesewetter et al in 1979. If multiple segments of bowel are involved, the 'clip and drop' technique may be used in which gangrenous bowel is resected, the ends of the remaining intestine clipped and returned to the abdomen. A 'second look' laparotomy and definitive procedure is performed after 48 hours. The advantages of this are

a potentially shorter anaesthetic in a critically ill infant and the salvage of as much bowel length as possible. In the presence of pan-necrosis the appropriate management is unclear and because of poor outcomes in many of these patients, many surgeons would forego further treatment. The authors' recommended surgical management of NEC is illustrated in *Figure 4*.

COMPLICATIONS

Intestinal strictures

Rabinowitz et al (1968) reported the first clinical and radiological description of intestinal stricture after recovery from acute NEC. This stricture was inflammatory in aetiology resulting from contracted scar tissue in an area of severely ischaemic intestine. The reported incidence of inflammatory strictures varies but is more common following non-operative treatment. The most common site is the colon followed by terminal ileum and strictures are usually single although multiple cases have been reported. With the advent of resection and primary anastomosis as surgical management of NEC, anastomotic strictures have also been encountered. Strictures should be suspected in an infant who fails to thrive, shows evidence of recurrence of NEC or intestinal obstruction following medical or surgical management. Most surgeons advocate the routine use of gastrointestinal study to identify strictures in infants treated with enterostomy before closure of the stoma. In most cases strictures, including anastomotic ones, are treated by resection and primary anastomosis.

Nutritional and metabolic problems

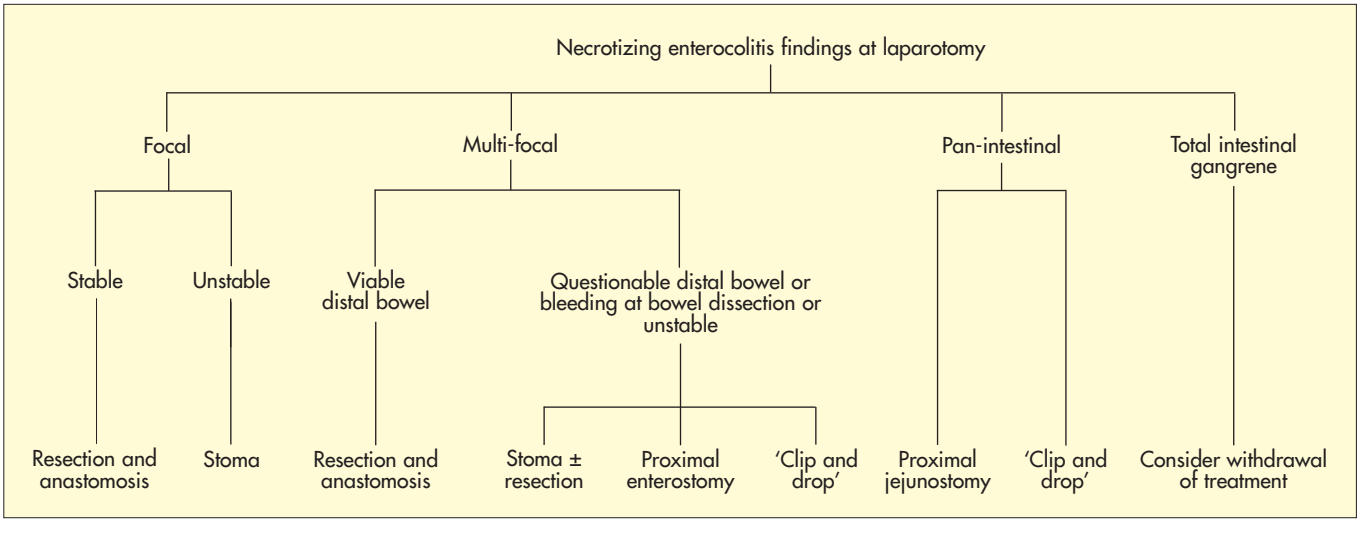
Malabsorption may result from a variety of factors including gut dysmotility, enzyme deficiency, abnormal intestinal mucosa, bacterial overgrowth, decreased bowel length and vitamin B_{12} deficiency as a result of ileal resection. Short bowel syndrome is the most serious gastrointestinal complication associated with NEC and great efforts are taken to avoid resection of more bowel length than is absolutely necessary. Supporters of resection and primary anastomosis cite this as one of the advantages over stoma formation and multiple primary anastomoses have been reported for the preservation of bowel length. In infants with pan-intestinal NEC and inadequate length of viable bowel to sustain life, withdrawal of treatment is preferred by many surgeons over a lifelong commitment to TPN dependence.

TPN-related complications are commonly encountered in infants with NEC and include sepsis, suppression of the immune response and impairment of liver function. Introduction of enteral feeds after 10 days from the onset of disease is emphasized to minimize the incidence of these complications.

OUTCOME

Survival rates following NEC vary from 60% to 80% for infants treated medically and this falls to 53% (Snyder et al, 1997) for those requiring surgical intervention. Overall survival rate in the authors' unit is 70% (Fasoli et al, 1999). Limited information concerning the long-term follow up of infants with NEC is available. At least 10% of patients have gastrointestinal sequelae including short bowel and malabsorption syndromes (Stevenson et al, 1980). The neurodevelopmental outcome following NEC has been addressed by a number of authors. Approximately 50% of survivors of NEC are neurologically normal in long-term follow up and there do not appear to be any adverse neurodevelopmental outcomes

Figure 4. The authors' recommended surgical management of necrotizing enterocolitis.



attributable to NEC specifically over and above any effect of prematurity and low birthweight (Stevenson et al, 1980).

CONCLUSIONS

Despite the advances in medical management and surgical techniques in recent years, the morbidity and mortality associated with NEC remains high. Most infants are premature, of low birthweight and have serious co-existing conditions which may adversely affect their outcome. Infants with NEC usually present with specific gastrointestinal problems and non-specific signs of sepsis. While medical management may be sufficient for some cases, about one third will require surgery.

It is unlikely that improved outcomes for NEC will be seen until the pathogenesis of this devastating disease and the response of the developing premature neonate are better understood. These are areas of active research and will hopefully result in agents or techniques of clinical therapeutic benefit. While we currently strive towards decreasing morbidity and improving survival for the current generation of affected neonates, prevention must be the goal for those of the future. HM

Conflict of interest: none.

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KEY POINTS

- Necrotizing enterocolitis is the commonest cause of surgical referral in preterm neonates.
- Despite many years of research the exact aetiology and pathogenesis remain unclear.
- Medical management consists of aggressive resuscitation, intensive care therapy, intestinal rest and intravenous antibiotics for at least 7 days.
- Frequent re-evaluation to identify those infants requiring surgical intervention is essential.
- Surgery is aimed at resection of gangrenous intestine and restoration of intestinal continuity.
- Further research is required to investigate the precise causes of this disease in order to improve the management and outcome of these infants.