CHAPTER 70
NECROTISING ENTEROCOLITIS

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Introduction

Necrotising enterocolitis (NEC) is a disease of the infant gastrointestinal tract (GIT) most commonly found in premature newborns. Although the aetiology and pathogenesis of the disease is not fully understood, in its most severe cases, NEC rapidly progresses from bacterial invasion of the intestinal wall to full-thickness bowel necrosis, leading to perforation and subsequent peritonitis, sepsis, and possibly death.[1] The elusive nature, unpredictable onset and progression, as well as the fragile nature of the affected patient population, combine to make NEC one of the leading causes of morbidity and mortality in neonatal intensive care units (NICUs) globally.[2,3]

Although technological advances, such as the advent of the modern intensive care unit (ICU), initially yielded fairly dramatic improvements in the survival of patients with NEC,[4,5] the condition is still associated with a sustained high mortality (19–50%), even in developed countries,[6] with little improvement over the last two decades.[7] These advances have been accompanied by a dramatic rise in the cost of treating patients with NEC. As a result, the challenges facing clinicians in First World nations are magnified in developing countries, where medical care is often constricted by dilemmas of triage and allotment of limited resources.

Demographics

Necrotising enterocolitis is the most common cause of death in surgical neonates worldwide.[8] Although the prevalence of NEC varies geographically and temporally, sometimes occurring in clusters or epidemics, the overall incidence in the United States is estimated to be 1–3 cases for every 1,000 live births.[9] Due to improvements in technology and perinatal care and the concomitant increase in survivability of neonates, the incidence of the disease appears to be increasing in Western nations.[10] Interestingly, there appears to be an overall increase in NEC prevalence in developing countries in recent years as well. This may be partly attributed to factors such as the increased survival of very small premature infants, the increasing drug abuse culture, and the high incidence of preterm labour (especially in developing countries), as well as the impact of the HIV epidemic currently sweeping over sub-Saharan Africa, where an increase in severity can probably be anticipated. Accurate statistical analysis of the disease in continental Africa is not feasible because the poor access to antenatal diagnosis, primary health care, transport facilities, and low survival of infants with delayed presentation significantly contribute to the decreased number of recorded admissions with the diagnosis of NEC.[11]

Epidemiology and Incidence

NEC is the most frequent and most lethal disease affecting the GIT of premature infants.[12] The disease appears to display no particular ethnic predilection. Prematurity remains the most consistent risk factor for developing NEC, with incidence and mortality from NEC both inversely related to birth weight and gestational age.[13] Approximately 7–10% of very low birth weight (VLBW) infants (<1,000 g) suffer from NEC, and almost 20% of these newborns experience a period of suspected disease known as an "NEC scare" at some point during their postnatal care.[7,14] Additionally, several reports have suggested that there may be an inverse relationship between gestational age and the age at onset of the disease.[15,16] Snyder et al. have recently reported that VLBW infants developed NEC later than their higher-weight cohorts, which may suggest that birth weight and age at the onset of disease may also be inversely related.[16]

Although the disease does not exclusively affect premature infants, nearly 90% of patients who develop NEC are premature. When NEC does occur in term infants, it is almost always associated with comorbidities that promote intestinal ischaemia (e.g., congenital heart disease, neonatal asphyxia, maternal pre-eclampsia, and diabetes) or causes of intestinal obstruction such as Hirschsprung's disease.

Reported NEC mortality in the United States ranges from 15% to 30%, with smaller infants, infants with more extensive disease, and infants requiring surgery at the greatest risk.[7] Although the mortality rates in industrialised nations have been decreasing over the past 30 years due to early detection, implementation of preventive measures, and upgrading of intensive care support facilities, this success has not been shared by developing countries due to limited resources.[17]

Aetiology/Pathophysiology

Despite extensive research in the field, an adequate understanding of the aetiology and pathophysiology of NEC remains elusive. Current knowledge of the cause and course of NEC has been confined to associated risk factors and recognised patterns of pathophysiologic change. Although any portion of the intestinal tract may be involved, NEC most commonly affects the terminal ileum. Its frequent distribution to the distal ileum and right side of the colon suggests a local vascular component because this area is most removed from the blood supply.

The histologic hallmark of NEC is a "bland infarct," which is characterised by full thickness coagulation (ischaemic) necrosis, a paucity of acute inflammatory cells (neutrophils), and a predominantly lymphocytic infiltrate (Figure 70.1).[18] Santulli and colleagues described a classic triad of pathological events leading to the development of NEC, including (1) intestinal ischaemia, (2) colonisation by pathogenic bacteria, and (3) excess protein substrate in the intestinal lumen.[19] Using this triad, Kosloske et al. hypothesised that quantitative extremes of two out of three of these factors is sufficient to cause NEC.[20]

Mucosal ischaemia arises from a neonatal insult resulting from factors such as a decrease in end diastolic blood flow, foetal distress, cold exposure, asphyxia, hypotension, congenital heart disease, or sepsis. Intestinal ischaemia results in local production of free radicals and initiates a cytokine cascade within the gut wall.

Novel treatments are currently being developed to abrogate the toxic effects of some of the local factors at play in the inflammatory process.[21] As a result of the mucosal damage, bacterial translocation can occur through the intestinal wall, and systemic infection may follow, leading to further ischaemia and necrosis of the bowel wall, progression to perforation, peritonitis, overwhelming septicaemia, and possible multiorgan failure and death.
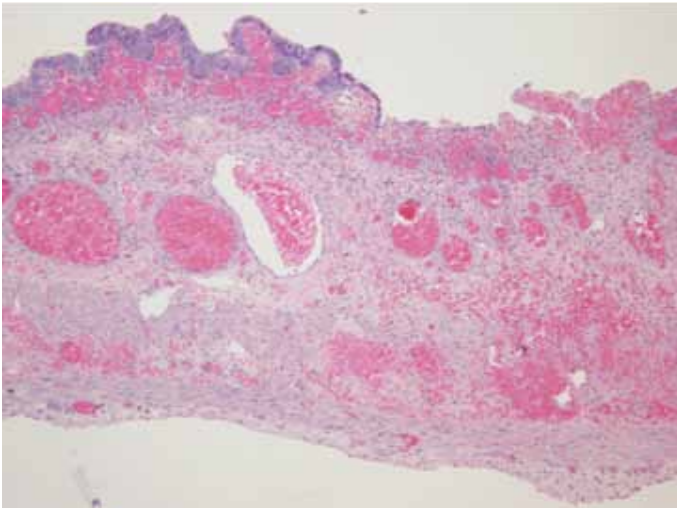
Figure 70.1: Small intestine showing necrosis, haemorrhage and congestion with a focal area of re-epithelisation of the mucosa (right). Original magnification, 20x.
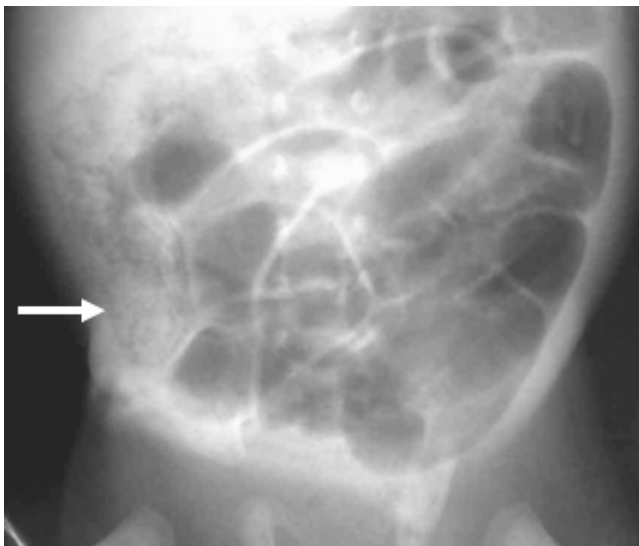

Figure 70.2: Frontal abdominal radiograph showing pneumatosis intestinalis in the right colon (arrow).

Figure 70.3: Segments of small bowel showing hyperaemia and an area of full-thickness necrosis (arrow).

Among the most accepted and consistently recognised risk factors for developing NEC are prematurity and timing and content of gastrointestinal feeding (i.e., formula concentration). Certain aspects of prematurity have been recognised that would appear to place these children at increased risk for NEC development. Among these are immaturity of gastrointestinal motility, digestive ability, circulatory regulation, intestinal barrier function along with abnormal colonisation by pathologic bacteria, and underdeveloped intestinal defense mechanisms.[22] Other risk factors implicated in the pathogenesis of NEC include bacterial infection,[23] the presence of pathogenic bacteria in the ICU (the so-called NEC epidemics), intestinal ischaemia,[24,25] certain pharmacologic agents,[26,27] and a host of inflammatory mediators,[28,29] although their relative contributions remain unclear. Other factors particularly pertinent to developing nations include antenatal factors, such as impaired umbilical artery flow, multiple pregnancy, and maternal infections, including HIV.[30] Nevertheless, despite these numerous recognised associations, no clear pathway of pathogenesis has been identified.

Pathology

NEC usually begins in the mucosal layer of the bowel. Intramural progression may be recognised by the frequent association of pneumatosis intestinalis, which represents bacterial hydrogen gas in the intestinal wall (Figure 70.2). This gas may extend into the vessels and into the portal vein and may be visualised radiographically as portal venous gas. Macroscopically, there is considerable variation in the degree of bowel involvement from a fairly minor inflammatory response of the bowel to full thickness necrosis, which may involve large segments of intestine (Figure 70.3). The terminal ileum and caecum are most commonly affected, but NEC represents a spectrum of disease; in its severest form, it may affect the entire bowel and parts of the stomach (NEC totalis). The affected bowel frequently extends beyond the macroscopic disease seen at surgery.

At surgery, the serosal surface is characterised by patches of full-thickness necrosis, oedema, and subserosal haemorrhages in affected portions of bowel. Pneumatosis intestinalis may be seen and felt in the bowel wall and may extend into the mesentery. Perforation of transmural necrotic patches is common, with subsequent gross contamination and peritonitis. Surgical intervention is required in at least 40% of patients with NEC due to intestinal necrosis with or without perforation. The objectives of surgical management are to remove the necrotic bowel, preserve bowel length, divert the faecal stream if required, and control sepsis.

Clinical Presentation

Infants with acute NEC usually present with both specific gastrointestinal signs as well as nonspecific physiologic signs often indicative of generalised infection. The classic history for a patient with NEC is a premature infant within 2 weeks of delivery who begins to develop feeding intolerance, distention, and/or blood per rectum after the initiation of formula feeds. The most common gastrointestinal signs reported are abdominal distention and blood per rectum. Others include feeding intolerance, bilious emesis, haematemesis, and guaic positive stools. Some of the nonspecific signs include lethargy, temperature and glucose instability, hypotension, and apnoeic spells associated with bradycardia (Table 70.1).

Initial physical exam findings are often subtle, significant only for mild distention and tenderness. As the disease progresses, the abdominal exam often reveals significant tenderness, palpable bowel loops, and an inflammatory mass, along with erythema or oedema of the abdominal wall.

Table 70.1: Specific and nonspecific signs of NEC.

Gastrointestinal signs	Nonspecific physiologic signs
Feeding intolerance	Hypotension
Abdominal distention	Temperature instability
Blood per rectum	Apnoeic spells (with bradycardia)
Bilious emesis	Lethargy
Haematemesis	Glucose instability

Laboratory Testing and Imaging

A complete blood count often demonstrates thrombocytopaenia and may show leukocytosis or, more commonly, leukopaenia.[31] Blood gas analysis (arterial, venous, or capillary) may demonstrate a significant base deficit due to metabolic acidosis associated with hypoperfusion, but is not necessarily indicative of intestinal necrosis. Because the initial history, physical exam, and laboratory findings in patients with NEC are often nonspecific, sepsis from a source other than the GIT is the most common diagnosis that needs to be excluded in cases of suspected NEC. Other diagnoses that may be included are malrotation of the intestines with midgut volvulus, gastroenteritis, Hirschsprung's disease, intestinal atresia, intussusception, and, less commonly, gastro-oesophageal reflux disease.

Plain radiography remains the imaging modality of choice in the diagnosis of NEC. In 70% of cases, the diagnosis is established by the presence of pneumatosis intestinalis on plain abdominal radiograph. Other radiographic findings in infants with NEC include air in the portal vein, a ground-glass appearance suggestive of ascites, pneumoperitoneum (Figure 70.4), and the "fixed-loop" sign, which is the defined as one or several loops of dilated small intestine that remain unchanged in position on x-ray over 24 to 36 hours. The fixed loop sign is suggestive of a nonperistalsing segment of intestine due to necrosis. Whereas contrast studies of the GIT, such as computed tomography (CT) and magnetic resonance imaging (MRI) scans, have not been proven to be clinically useful in the evaluation of patients with NEC,[32–35] a recent study has suggested a possible role for sonography due to its increased ability to detect intraabdominal fluid, bowel wall thickness, and bowel wall perfusion.[36] The resources available in developing countries may limit the applicability of ultrasound in such regions.

Radiologic features commonly associated with NEC include:

• thickened, distended bowel loops;

• pneumatosis intestinalis, or gas in the bowel wall;

• pneumoperitoneum, which indicates intestinal perforation;

• portal venous air (a severe infection that is not an absolute indication

for surgery in its own right as it may be a transient phenomenon);

• constant ("fixed") small bowel loop present on serial x-rays, which indicates necrotic loop of bowel;

• ascites;

• thickening of the abdominal wall due to cellulitis;

• outline of falciform ligament highlighted by intraperitoneal air ("football sign"); and

• outlining of the intestinal wall between two gas lucencies ("Rigler's sign").

Bell Staging System

Based on this initial work-up, patients with a presumed diagnosis of NEC can be classified into one of three clinical stages, as described by Bell et al.[37] (Table 70.2).

Table 70.2: Simplified Bell staging system for NEC..

Stage	NEC involvement	Manifestations	Radiographic signs
I	Infants with mild features suggestive, but not diagnostic, of NEC	Gastrointestinal, includes feeding intolerance, abdominal distention, blood per rectum, etc.; systemic includes temperature instability, lethargy, bradycardia, etc.	Abdominal radiograph with nonspecific ileus pattern
II	Infants with definitive NEC but without indication for surgical intervention	Persistent or marked gastrointestinal or systemic manifestations	Abdominal radiograph with pneumatosis intestinalis
III	Infants with more advanced NEC, defined by intestinal necrosis, signs of clinical deterioration or intestinal perforation	Above signs with deteriorating vital signs, evidence of septic shock or marked gastrointestinal haemorrhage	Above radiographic signs with pneumoperitoneum or other signs suggestive of intestinal necrosis

Source: Kliegman RM, Fanaroff AA. Necrotizing enterocolitis. N Engl J Med 1984; 310:1093–1103.

Differentiation of NEC from Spontaneous Intestinal Perforation

Spontaneous intestinal perforation (SIP) or focal intestinal perforation (FIP) have been reported as disease entities different from NEC. The aetiology, pathophysiology, and best treatment of spontaneous intestinal perforation remain subjects of ongoing research, but the principles for the management of NEC mostly apply. Similar to NEC, FIP presents with the sudden onset of a pneumoperitoneum. However, unlike NEC, FIP often represents a small isolated perforation, which may spontaneously seal without surgery in the very low weight infant (<1,000 g).

Management

Initial management of acute NEC consists primarily of supportive care. If patients are receiving enteral alimentation, the feedings should be discontinued and an orogastric tube should be placed to decompress the stomach. Aggressive intravenous fluid resuscitation is critical in the early phase of NEC to prevent exacerbation of intestinal hypoperfusion, and a catheter may be inserted into the bladder to help monitor urine output and adequacy of resuscitation. Blood and urine cultures should be obtained, and broad-spectrum antibiotics should be adminis-
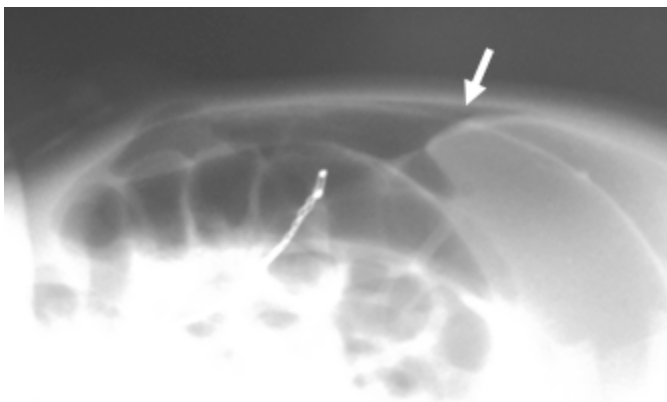

Figure 70.4: Decubitis abdominal radiograph demonstrating pneumoperitoneum (arrow); Rigler's sign is also seen.

tered. Currently, the recommended antibiotic therapy regimen includes ampicillin, gentamicin, and clindamycin or metronidazole to cover gram-positive, gram-negative, and anaerobic bacteria, respectively. In a series reported by Chan et al., several gram-negative bacteria resistant to ampicillin or gentamicin were isolated.[38] Thus, depending on the antimicrobial profile of the institution, different antibiotic strategies may be required to treat the emerging strains of bacteria.

In addition to clinical exams and continued haemodynamic monitoring, disease progression should be monitored by using serial abdominal radiographs, ideally obtained every 6 to 8 hours. Daily and as-needed x-rays may be sufficient, however, if that is all the resources will allow. Imaging protocols should include both vertical and horizontal beam radiographs to ensure adequate sensitivity for signs of disease progression. Many institutions use supine abdominal images along with cross table lateral images, which allow the infants to remain supine, thereby minimising repositioning of the unstable patients.[24] Alternatively, decubitus films often more clearly demonstrate pneumoperitoneum. If repeat radiographs display an unchanged or improving pattern of pneumatosis intestinalis, then expectant management may be continued, provided that the infant remains haemodynamically stable.

Acute Medical Management Summary

In the absence of surgical indications, acute medical management of patients with suspected NEC includes the following:

1. *Resuscitation:* intravenous fluids, nasogastric decompression, careful control of acid-base balance, and correction of electrolyte abnormalities.

2. *Cessation of oral feeds and medications.*

3. *Broad-spectrum antibiotics:* guided by cultures and local microbiological profile.

4. *Management* of thrombocytopaenia and abnormal clotting profile; important due to the potential for cerebral bleeds.

5. *High index of suspicion for complications:* frequent monitoring and reassessment as well as x-ray monitoring in the acute patient to look for pneumoperitoneum (6 to 8 hourly or as clinically indicated).

6. *Early surgical consultation.*

Surgical Indications

Indications for surgical intervention focus on signs of perforation or impending perforation. Development of pneumoperitoneum on abdominal radiograph is considered an absolute indication for surgical intervention. Other signs, such as a fixed loop on abdominal radiographs, an abdominal mass or erythema of the abdominal wall on physical exam, positive paracentesis, or little to no clinical improvement despite optimal medical management, are considered relative indications. Some authors argue that portal venous air on radiography should also mandate surgical intervention due to its associated poor prognosis (70% mortality in some series), although this is not a universally accepted view.[39,40] With the exception of evidence of pneumoperitoneum, the timing and method of surgical intervention must be made based on individual cases.

Exploratory Laparotomy versus Primary Peritoneal Drainage

Although there is a general consensus regarding the factors and relative indications for surgical intervention, in the setting of acute NEC, controversy persists regarding the optimal surgical strategy. Some authors have advocated primary peritoneal drainage alone as definitive therapy for advanced NEC.[41,42] Primary peritoneal drainage is performed by using a 0.5–1–cm incision to evacuate the peritoneum of all faecal and purulent content followed by aggressive irrigation and placement of a drain. Advocates of primary laparotomy argue that many patients with NEC treated initially with peritoneal drainage require subsequent

laparotomy[43,44] and therefore primary laparotomy would minimise the number of surgical interventions in these patients. A recent multicentred, prospective randomised trial comparing laparotomy to primary peritoneal drainage in patients weighing less than 1,500 g with perforated NEC showed no significant difference in survival, dependence on parenteral nutrition, or length of hospital stay.[43] It has also been suggested that peritoneal drainage may be particularly suited to the treatment of infants less than 26 weeks gestational age or who weigh less than 1,000 g because isolated intestinal perforations are more frequently encountered in this patient population.[44] In regions with scarce resources and a shortage of skilled personnel, primary peritoneal drainage may be the best initial option for all NEC patients who meet the criteria for surgical intervention.

Extent of Surgical Intervention

Most authors agree that the extent of surgical intervention should be determined by the degree of bowel involvement encountered at laparotomy. Approximately 50% of infants with acute NEC present with focal disease, and the other 50% present with multiple areas of involvement.[43] Nearly 20% of infants treated surgically for NEC are found to have pan-involvement, which is defined as disease encompassing greater than 75% of the total intestine.[34]

Focal Perforation

Exploratory laparotomy with limited resection and creation of an enterostomy remains the standard of care for infants with NEC found to have a focal perforation. Recently, some authors have advocated intestinal resection with primary anastomosis as an alternative to enterostomy, citing the high morbidity associated with enterostomies in the newborn population.[43,45,46] Additionally, they argue, primary anastomosis affords the possibility of avoiding a second surgery. Advocates of resection and enterostomy creation maintain that the majority of stomal complications are minor and easily managed.[47] Additionally, early ostomy closure has been shown to be well-tolerated in this patient population[48] and therefore does not justify the added risk inherent in primary anastomosis. Cooper et al. reported their experience with primary anastomosis as compared to resection and diversion at the Children's Hospital of Philadelphia.[49] They reported that overall survival for infants who underwent intestinal diversion was 72%, compared to only 48% for patients with primary anastomosis. Postmortem examination of 7 out of the 14 patients who died after primary anastomosis revealed two anastomotic leaks and a gangrenous anastomosis that was easily disrupted during the postmortem exam. The authors of that study concluded that primary anastomosis is not comparable, much less superior, to intestinal diversion.

Principles of Surgery

NEC with pan-involvement carries the highest mortality rates;[50] infants who survive often develop short-bowel syndrome and long-term TPN dependence with associated complications.[1,33] As such, surgical strategies have focused on minimising the extent of bowel resection without compromising patient outcome. One such strategy is primary peritoneal drainage as a temporising measure to allow the infant time to regain haemodynamic stability and perfuse viable bowel, thus saving bowel that may have been resected with initial laparotomy.[51] Some surgeons even suggest that peritoneal drainage may, in fact, serve a definitive therapy for some cases of NEC, particularly for VLBW (<1,000 g) infants.[52,53] Nevertheless, the majority of infants treated with peritoneal drainage require subsequent laparotomy in some series.[54] Currently, peritoneal drainage is considered by many as an initial approach in haemodynamically unstable VLBW infants with NEC to allow resuscitation and stabilisation prior to definitive laparotomy.[46]

When initial laparotomy is employed, the overriding consideration is to spare as much bowel as possible to prevent short bowel syndrome. Aggressive resection of all diseased segments leads to sacrifice of intestine with borderline viability, and creation of multiple ostomies

results in loss of intestinal length at the time of stoma closure. For this reason, a second-look laparotomy after proximal diversion has been proposed as an alternative to initial extensive resection. Weber and Lewis[55] reported their results of 32 infants with acute NEC who underwent operative intervention with resection of only frankly necrotic bowel and proximal diversion. Survival of the 14 infants who met criteria and underwent a second-look surgery was similar to that of the infants who underwent only one procedure. The authors concluded that a second-look strategy results in survival rates similar to a single-stage procedure while potentially sparing intestinal length.

Surgical Indications in Developing Nations

Much of the success over the years in the treatment of NEC has been afforded by supportive care and sophisticated ICUs and therefore has not been manifest in segments of the developing world. Banieghbal and colleagues have suggested the institution of more aggressive surgical protocols in developing nations that do not have modernised intensive care unit capabilities may lead to improved survival in those regions.[17] In their prospective study, conducted at a single institution in Johannesburg, South Africa, 450 neonates with NEC were treated with a more aggressive surgical protocol, and results were compared to prior data collected using the more classic criteria described by Kosloske.[56] The aggressive surgical protocol consisted of:

1. Laparotomy is undertaken in all patients with radiological perforation within 8 hours.

2. Any neonate with peritonitis on clinical exam is actively resuscitated and re-examined in 4–6 hours. Continuing peritonitis is an indication for laparotomy within 4 hours.

3. If the main area of disease is found to be in the ileocolic region, extended colonic resection for all macroscopic disease is performed with ileostomy creation.

4. In the cases of multiple areas of perforation/necrosis, only the most obvious necrotic/perforated bowel is excised with anastomosis or enterostomy, and a second-look laparotomy is performed in 3–4 days. The authors reported an overall decrease in mortality rate from 82% to 48%, with the institution of the more aggressive surgical protocol. Infants with active disease involving a limited length of the terminal ileum and/or colon derived the greatest benefit from the more aggressive protocol. Each individual hospital/region must decide whether this protocol or one using primary peritoneal drainage is suitable for the local resources available.

Postoperative Complications

The overall mortality rate for NEC is 15–30%. Smaller infants, infants with a larger proportion of diseased intestine, and infants undergoing surgery have the highest mortality rates. With improvements in supportive care and monitoring, the survival rate for patients with NEC has been increasing, calling attention to the issue of postoperative complications in those survivors. Overall, infants <28 weeks gestation had a significantly higher complication rate (47%) compared to those further along in gestation (29%).[57] Complications of NEC can be separated into early or predischarge complications and late, usually chronic, complications.

Early Complications

A multiinstitutional observational study reported that 39% of NEC patients who underwent surgery had some type of stomal or wound complication.[57] One multicentred prospective cohort study reported the overall incidence of postoperative intestinal stricture at 10.3% and an intraabdominal abscess occurred in 5.8%, with no difference between the initial laparotomy versus the initial drainage group.[58] Laparotomy was found to have a 7.9% incidence of wound dehiscence as compared to a 1.3% incidence in the initial drainage group. The overall rate of prolonged parental nutrition, defined as lasting >85 days, is 11% and was similar for the drainage and laparotomy groups.

Late Complications

Late, or postdischarge, complications of NEC are often chronic in nature. Infants with stage II or greater NEC are reported to have a significantly higher risk of long-term neurodevelopmental impairment compared to similar infants without NEC.[59] Additionally, surgery for NEC has been shown to be an independent risk factor for physical, psychomotor, and neurodevelopmental impairment compared to VLBW infants without NEC.[60] Although the reason for this increased risk of neurodevelopmental delay is not entirely clear, some studies suggest that increased duration of parenteral nutrition may render the neonate particularly susceptible to this issue.[61] Due to the high risk of preterm infants with NEC developing neurodevelopmental disability, most units now recommend close follow-up for all ≤1,250-gram infants who develop stage II or III (clinical) NEC.

Prevention Strategies

Treatment strategies to reduce the incidence of NEC have targeted some of the perinatal insults believed to contribute to its pathogenesis, such as bacterial colonisation, immaturity of the neonatal defense system, and formula feeding.[62] Some approaches include (1) administration of prophylactic oral antibiotics to decontaminate the gut[63–65]; (2) administration of glucocorticoids to accelerate epithelial cell maturation;[66–68] and (3) administration of human (breast) milk, which is replete with substances that are both immunologically active as well as trophic for the intestinal mucosa.[69,70]

Oral Antibiotics

The use of prophylactic oral antibiotics for the prevention of NEC has met with mixed results. The theory behind the proposed efficacy of antibiotic treatment is that gut decontamination may prevent potential pathogens from invading the bowel wall after mucosal breakdown. Indeed, results of one trial suggested early introduction of such antibiotics as gentamicin and amoxicillin in cases of suspected NEC have been shown to have a protective effect.[71] However, subsequent trials failed to demonstrate a reduced incidence of NEC in patients receiving prophylactic antibiotics.[72] As such, the issue of prophylactic antibiotics in the prevention of NEC remains controversial and is not commonly practiced due to the inherent risks of antibiotic resistance and pseudomembraneous colitis. A new area of study that is being actively researched is administering probiotic bacteria in an effort to prevent pathogenic bacteria from colonising the intestine.[73]

Corticosteroids

A large multicentred trial reported a decreased incidence of NEC in infants of mothers who received prenatal steroids.[57] Similarly, a 12-day course of postnatal steroids reduced the incidence of NEC in newborn infants with respiratory distress syndrome.[74] These results, however, are called into question as a meta-analysis performed by the Cochrane Database of 15 randomised trials of postnatal steroids demonstrated no benefit in the prevention of NEC. Thus, the question of whether steroids should be used in the prevention of NEC remains unresolved.[75]

Human Breast Milk

Studies have shown that neonates fed with human breast milk are 10 times less likely to develop NEC, although the exact mechanism of this protective affect is unknown.[76,77] Possible protective factors present in breast milk include macrophages, neutrophils, lymphocytes, lactoferrin, oligosaccharides, growth factors, and immunoglobulins.[60] In a landmark study by Eibl et al.,[78] supplementation of standard formula with IgA and IgG reduced the incidence of NEC in a cohort of premature infants. Subsequent trials using monomeric IgG supplementation alone showed conflicting results.[79,80] Ultimately, the question regarding the mechanism by which breast milk exerts its protective effect is yet to be elucidated.

Ethical Issues

Many of the ethical issues involved in the treatment of NEC in developing nations relate to the challenge of proper and efficient allocation of scarce resources. The survival rate of the disease often relies on prolonged, intensive, and costly ICU care, so the question arises as to the advisability of expending precious time and money on aggressive interventions only to yield poor survival rates. Additionally, a high percentage of the survivors of NEC in these regions end up with long-term complications that cannot be adequately managed, which leads to further morbidity and mortality. These issues must be evaluated based on the resources of each individual region.

Table 70.3: Evidence-based research.

Title	Laparotomy versus peritoneal drainage for necrotizing enterocolitis and drainage
Authors	Moss RL, Dimmitt RA, Barnhart DC, Sylvester KG, Brown RL, Powell DM, et al.
Institution	Yale University School of Medicine, New Haven, Connecticut, USA; among others
Reference	N Engl J Med 2006; 354(21):2225–2234
Problem	Evaluation of primary peritoneal drainage versus laparotomy in infants with perforated necrotising enterocolitis.
Intervention	Laparotomy, primary peritoneal drainage.
Comparison/ control (quality of evidence)	The population was 117 preterm infants (delivered before 34 weeks of gestation) with birth weights less than 1,500 g and perforated NEC at 15 paediatric centres randomised to undergo primary peritoneal drainage or laparotomy with bowel resection. Postoperative care was standardised. The primary outcome was survival at 90 days postoperatively. Secondary outcomes included dependence on parenteral nutrition 90 days postoperatively and length of hospital stay.
Outcome/ effect	At 90 days postoperatively, there was no significant difference in mortality between the drainage and laparotomy groups (34.5% versus 35.5%, P = 0.92). There was also no significant difference in dependence on parental nutrition (47.2 % versus 40.0%, P = 0.53) or mean length of stay (126±58 days and 116±56 days, respectively; P = 0.43).
Historical significance/ comments	This randomised, prospective trial suggests that treatment with primary peritoneal drainage and laparotomy with bowel resection are comparably efficacious in the treatment of perforated NEC. Mortality in this patient population was found to be ~35%. Although 5 out of the 30 patients (16.7%) in the primary peritoneal drainage group subsequently required laparotomy for clinical deterioration, drainage obviated the need for laparotomy in the remaining infants without any discernible increase in mortality.

Evidence-Based Research

Table 70.3 presents a study that compares primary peritoneal drainage and laparotomy in infants with perforated NEC. Table 70.4 revisits indications for surgery in NEC.

Table 70.4: Evidence-based research

Title	Indications for operation in necrotizing enterocolitis revisited
Authors	Kosloske AM
Institution	Department of Surgery, Ohio State University College of Medicine, Columbus, Ohio, USA: University of New Mexico Hospital, Albuquerque, New Mexico, USA
Reference	J Pediat Surg 1994; 29(5):663–666
Problem	Evaluation of 12 criteria as predictors of intestinal gangrene in patients with necrotising enterocolitis.
Comparison/ control (quality of evidence)	A series of 147 infants treated for NEC was analysed to evaluate the accuracy of 12 proposed findings as indicators of intestinal gangrene. These findings included pneumoperitoneum, portal venous gas, fixed loop, fixed abdominal mass, erythema of abdomen, positive paracentesis, severe pneumatosis, clinical deterioration, low platelet count, severe gastrointestinal haemorrhage, abdominal tenderness, and gasless abdomen/ascites. Operation was performed (usually resection and enterostomy) for evidence of intestinal perforation or gangrene. Intestinal gangrene was documented for all infants by either operation, autopsy, or radiographic findings of pneumoperitoneum or intestinal stricture.
Outcome/ effect	The findings of pneumoperitoneum, portal venous gas, and positive paracentesis each had specificities and positive predictive values approaching 100% with a prevalence greater than 10%. Pneumoperitoneum had a prevalence of 48%. The findings of a "fixed-loop," palpable abdominal mass and erythema of the abdominal wall also had specificities and positive predictive values approaching 100% but had a prevalence below 10%. Severe pneumatosis had a specificity of 91%, and positive predictive value of 94% and a prevalence of 20%. The remaining five findings all had specificities below 90%, positive predictive values below 80%, and prevalence ranging between 2% and 28%.
Historical significance/ comments	Although no single finding is particularly sensitive for intestinal necrosis, the findings of pneumoperitoneum, portal venous gas, positive paracentesis, fixed-loop sign, palpable abdominal mass, and erythema of the abdominal wall all had specificities approaching 100% and may be used as an indication for surgical intervention. Severe pneumatosis was also found to have a fair specificity for intestinal necrosis. The remaining findings had poor specificity and positive predictive value. Although seven of these findings were highly specific for intestinal necrosis, the prevalence of these signs were low. As such, the absence of these findings cannot rule out intestinal necrosis, and the decision for surgical intervention will often rely on clinical judgment of the managing surgeon.

Key Summary Points

1. Necrotising enterocolitis occurs in 1–3 infants per 1,000 live births.

2. Ninety percent of cases occur in premature infants.

3. Mortality rates range between 15% and 30%.

4. The aetiology and pathophysiology of the disease is not well understood.

5. Prematurity as well as timing and content of gastrointestinal feeding are the most consistent risk factors associated with NEC.

6. Human breast milk has been shown to be protective against the development of NEC.

7. NEC presents with both specific gastrointestinal signs of vomiting, distention, and blood per rectum as well as nonspecific signs of haemodynamic instability.

8. Abdominal radiography is the primary imaging tool in establishing the diagnosis of necrotising enterocolitis.

9. Pneumoperitoneum is an absolute indication for surgical intervention; relative indications include a fixed-loop on abdominal radiographs, an abdominal mass or erythema of the abdominal wall on physical exam, positive paracentesis, and whether there is little or no evidence of clinical improvement.

10. Primary peritoneal drainage and laparotomy are comparable treatments for perforated necrotising enterocolitis.

11. Surgical goals focus on resection of frankly necrotic bowel with an effort to preserve intestinal length.

12. Advances in intensive care unit facilities in developed nations have translated into improved survival in patients with NEC.

13. More aggressive surgical protocols may improve survival in developing nations that lack modern intensive care unit facilities.

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