Necrotizing enterocolitis (NEC) is the most common life threatening surgical and medical emergency affecting the gastrointestinal tract encountered in the neonatal intensive care unit. NEC occurs in 2–5% of all preterm infants although the majority of cases develop in infants less than 36 weeks of gestational age. It has been noted that infants born at earlier gestational age, develop NEC at a later chronological age. The average age of onset of disease is 20.2 days for infants born less than 30 weeks of gestation whereas disease onset is reduced to 13.8 days for infants born at 31–33 weeks and 5.4 days for infants born after 34 weeks of gestation.

Epidemiological studies have identified multiple risk factors for NEC, although a history of hypoxia, asphyxia and the introduction of enteral feeding are characteristically associated with premature infants that develop NEC. Despite its predilection for premature infants, NEC has also been described in term infants particularly those with cyanotic heart disease. There is no clear evidence to suggest that geographical origin, ethnicity or gender alter the incidence of NEC.

NEC is characterized by intestinal inflammation accompanied by epithelial barrier disruption, bacterial overgrowth and submucosal invasion. In its most severe form, NEC is characterized by full-thickness destruction of the intestinal wall leading to intestinal perforation, peritonitis, sepsis and death. Although the overall mortality for patients with NEC ranges from 10% to 50%, it approaches 100% in infants with the most severe form of the disease, characteristically the smallest and most premature infants. Moreover, infants that recover from NEC may still require prolonged hospitalisation.
due to complications from disease, such as intestinal obstruction due to scarring, short bowel syndrome and complete intestinal failure further impacting long-term survival, growth and development.

### 44.2 Etiology

Epidemiological studies have identified multiple perinatal factors that increase an infant’s risk for the development of NEC, although prematurity and a history of hypoxia, asphyxia and the introduction of formula feeding are characteristic of infants that develop NEC. Three main factors are however required for the development of disease including immaturity, bacterial colonization, and enteral feeding. Figure 44.1 summarizes the pathogenic sequences and factors contributing to the development of NEC.

#### 44.2.1 Immature Intestinal Barrier

The intestinal epithelium is a primary barrier between the inside of the body and the external environment. As such, the intrinsic function of this epithelial layer is to protect the host. The mucosal defence system can be divided into two categories: non-immunologic and immunologic defence mechanisms. Non-immunologic mechanisms include peristalsis, gastric acidity, proteolytic enzyme activity, mucin production and semi-permeable intestinal barrier function provided by tight junctions between the epithelial cells lining the gut. Peristalsis is the progressive wave of contraction and relaxation of the intestine. In full-term infants and adults, migrating motor complexes propagate these waves along the intestine. In humans migrating complexes are not present until approximately 34 weeks of gestation, which may contribute to intestinal stasis in premature infants, thereby altering the microbial ecosystem. Gastric acidity is thought to be a first line defence against bacterial passage into the proximal intestine. The premature human infant’s gastric pH is initially high and then decreases towards mature levels with increasing age and ultimately reaching a pH < 4. Permeability is an important factor in the ability of bacteria to translocate, causing systemic infection, and the premature infant intestine is more permeable in the first 2 days of life. Mucus production provides a protective viscoelastic layer to the epithelial intestinal lining. In humans, mucus production and composition changes with age, and increases in response to bacterial challenge.

Immunologic defence mechanisms in the gut include both the innate and adaptive immune systems. Cells of the innate immune system include paneth cells, macrophages, polymorphonuclear leukocytes (PMN), dendritic cells, M cells (specialized epithelial cells overlying lymphoid aggregates called Peyer’s patches) and epithelial cells. Paneth cells produce a variety of antibacterial substances including defensins, lysozymes, secretory phospholipase A2, and lectins. While PMN

![Fig. 44.1 Contributing factors in the development of NEC](image-url)
are not regular inhabitants of the healthy intestine, PMN increase in number in response to intestinal injury and their production and function is known to be impaired in the newborn, contributing to the inadequate immature intestinal response. Dendritic cells and M cells function to capture and present antigens from the lumen of the bowel to T and B cells dispersed in the mucosal layer and in lymphoid aggregates along the length of the gut. Cells of the adaptive immune system include T and B lymphocytes and their differentiated effector cell subsets. T lymphocytes differentiate as cytotoxic T cells and are responsible for direct killing of damaged or infected epithelial cells and helper T cells are responsible for enhancing B cell differentiation and the production of plasma cells that secrete immunoglobulin in particular IgA. When compared to the adult, both the number and function of B and T cells is reduced in intestine contributing to defects in the intestinal epithelial barrier.

44.2.2 Role of Bacterial Pathogens and Other Microbes in NEC

NEC occurs in both sporadic and clustered distributions, causing speculation that specific infectious entities may be responsible. A variety of bacterial and viral pathogens have been implicated in the pathogenesis of NEC including Enterobacteriaceae, Clostridia, coagulase negative Staphylococcus and several viral species (Table 44.1).

Despite the fact that no single organism appears to be responsible for NEC the importance of bacteria in the pathogenesis of disease should not be discounted. It is known that NEC does not develop in animal models kept in sterile environments. At birth the intestine is devoid of bacterial flora, but is rapidly colonized by bacteria from the rectovaginal flora of the mother, and bacteria from the surrounding environment. Additionally, colonization by commensal bacteria is required for the normal development and maturation of the newborn intestine. Bacterial-host cross talk has been shown to modulate gut vascular development, and promote immune system development. Abnormal intestinal colonization patterns of neonates admitted to the neonatal intensive care unit may further increase susceptibility to NEC.

Table 44.1 Organisms implicated in necrotizing enterocolitis

| Bacteria                          |
|----------------------------------|
| Enterobacteriaceae species       |
| Escherichia species              |
| Salmonella species               |
| Klebsiella species               |
| Enterobacter species             |
| Clostridium species              |
| Staphylococcus species           |
| Viruses                          |
| Rotavirus                        |
| Echovirus                        |
| Coronavirus                      |
| Torovirus                        |
| Fungus                           |
| ±Candida species                 |

44.2.3 Role of Enteral Feeding

Rapid advancement of formula feeding has been associated with the development of NEC. Breast milk feeding is known to protect against NEC, and premature infants have a reduced incidence of infection when fed human breast milk rather than formula. A prospective multicenter study of preterm infants found almost a tenfold increase in the incidence of NEC in formula-fed infants as compared with those who were fed breast-milk. The positive effects of breast milk are likely due to a variety of potential anti-microbial products including immunoglobulins, oligosaccharides, lactoferrin and glycoproteins with anti-adhesive capacity for bacteria, and cytokines present in breast milk. Additionally breast milk promotes intestinal colonization by probiotic (beneficial) bacteria such as Lactobacillus species and Bifidobacteria species.

44.2.4 Inflammatory Mediators and NEC

A variety of inflammatory chemokines including tumor necrosis factor alpha (TNF-α), nitric oxide (NO), platelet activating factor (PAF), and several cytokines (IL-1, IL-6, IL-8 and IL-10) have been implicated in the pathogenesis of NEC. Elevated plasma levels of TNF-α have been found in infants with NEC, and local upregulation of IL-1, IL-8 and inducible NO synthase (iNOS) has been demonstrated in the intestine of infants with NEC. Nitric oxide plays a paradoxical role in the pathogenesis of NEC. Constitutive low-level
production of NO enhances mucosal blood flow, and promotes local vascular health. However, sustained overproduction of NO due to upregulation of iNOS leads to intestinal damage. The pathologic effects of NO are postulated to be due to the strong oxidant effects of peroxynitrite (ONOO⁻) resulting in enterocyte cell death, and impaired mucosal healing. ONOO⁻ causes enterocyte cell death and impairs mucosal healing. The up-regulation of NO has been demonstrated in areas of intestinal epithelial injury in human infants with NEC. In infants who recover from NEC, iNOS, and NO return to baseline levels.

44.2.4.1 Maternal Factors

Several maternal risk factors increase an infant’s risk of developing NEC, including placental insufficiency and maternal cocaine abuse. These factors may contribute to disease susceptibility by compromising placental blood flow and hence perfusion of vital organs in the foetus.

44.3 Pathology

Several pathological findings are associated with NEC. It is important to note however, that findings are highly variable. The terminal ileum is the most frequently involved site, however NEC may affect any part of the small or large intestine. Pan-necrosis is a highly morbid finding associated with fulminant disease (Fig. 44.2). Pneumatosis intestinalis is a pathognomonic finding in NEC characterized by the presence of air in the intestinal wall (Fig. 44.3). The etiology of pneumatosis intestinalis is thought to be due to bacterial invasion, fermentation and hydrogen production in the intestinal wall.

Histologically, intestinal tissue may demonstrate epithelial layer sloughing, increased apoptotic bodies within epithelial cells, tissue oedema and submucosal air (Fig. 44.4). Evidence of the response of the immune

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**Fig. 44.2** Intraoperative image of pan intestinal necrosis, diagnosed at the time of laparotomy for NEC

**Fig. 44.3** Supine abdominal x-ray in a neonate showing diffuse pneumatosis intestinalis. Arrows indicate signet sign

**Fig. 44.4** Hematoxylin-eosin staining of intestinal tissue harvested from an infant with NEC. Arrows indicate epithelial destruction with submucosal gas collections
system is characterized by neutrophil infiltration and hypertrophy of intestinal lymphoid aggregates. However, ultimately the diagnosis of NEC is based on clinical findings.

44.4 Diagnosis

The assessment of an infant suspected of having NEC starts with a thorough history and physical examination. A typical presentation of NEC would be that of a premature infant advancing on enteral feedings who develops signs of feeding intolerance. These signs may be subtle and first noted by the nursing staff and include abdominal distension, high gastric residuals, and guaiac positive stool. In more advanced cases of disease, infants may present with progressive abdominal distention, evidence of peritonitis, frankly bloody stool and cardio-respiratory failure.

Although prompt diagnosis and intervention are desirable tenants of disease management, there is no clear evidence proving that early diagnosis and interventions alters patient outcome.

44.4.1 Clinical Features

In 1973 Bell et al proposed the NEC grading system, in an attempt to standardize diagnosis, disease severity scoring and, management. A slight modification of Bell’s original criteria is in use today (Table 44.2). The presenting symptoms may vary and include feeding intolerance, abdominal distension, bloody stools, apnoea, lethargy, temperature instability and hypoperfusion. Classically, increased amounts of gastric residual and abdominal distension and visible loops of bowel are noted on physical exam. Occasionally discoloration of the abdomen wall may be present and the palpation of the abdomen may elicit tenderness with guarding. The progression of disease is variable; some infants have minor symptoms that resolve spontaneously over a period of days in response to bowel rest, while others progress over hours with respiratory failure requiring intubation, hypotension requiring fluid resuscitation and inotropic support and/or immediate surgical intervention.

| Table 44.2 Modified Bell’s stages of necrotizing enterocolitis |
|---------------------------------------------------------------|
| **I. Suspected disease**                                      |
| IA.                                                           |
| Mild systemic signs (apnea, bradycardia, temperature instability) |
| Mild intestinal signs (abdominal distention, gastric residuals, occult blood in stool) |
| IB.                                                           |
| Mild systemic signs (apnea, bradycardia, temperature instability) |
| Mild intestinal signs (abdominal distention, gastric residuals, gross blood in stool) |
| Non-specific or normal radiological findings                   |
| **II. Definite disease**                                       |
| IIA.                                                          |
| Mild systemic signs (apnea, bradycardia, temperature instability) |
| Additional intestinal signs (absent bowel sounds, abdominal tenderness) |
| Specific radiologic signs (pneumatosis intestinalis or portal venous air) |
| Laboratory changes (metabolic acidosis, thrombocytopenia)     |
| IIB.                                                          |
| Moderate systemic signs (apnea, bradycardia, temperature instability, mild metabolic acidosis, mild thrombocytopenia) |
| Additional intestinal signs (absent bowel sounds, abdominal tenderness, abdominal mass) |
| **III. Advanced disease**                                      |
| IIIA.                                                         |
| Severe systemic illness (same as IIB with additional hypotension and shock) |
| Intestinal signs (large abdominal distention, abdominal wall discoloration, peritonitis, intestine intact) |
| Severe radiologic signs (definite ascites)                     |
| Progressive laboratory derangements (metabolic acidosis, disseminated intravascular coagulopathy) |
| IIIB.                                                         |
| Severe systemic illness (same as IIIA)                         |
| Intestinal signs (large abdominal distention, abdominal wall discoloration, peritonitis, intestinal perforation) |
| Severe radiologic signs (definite ascites and pneumoperitoneum) |
| Worsening laboratory derangements (metabolic acidosis, disseminated intravascular coagulopathy) |

44.4.2 Laboratory Findings

Common laboratory abnormalities include thrombocytopenia, leukocytosis, electrolytes imbalance, metabolic acidosis, hypoxia, or hypercapnia. Therefore a comprehensive laboratory analysis should be performed in infants with suspected NEC. A patient with NEC may
present with an abnormal white blood cell count (WBC). Although it may be elevated, it is more commonly depressed, and a severely low white blood cell count (<1.5 × 10⁹/l) has been reported in 37% of cases. The granulocytopenia results from decreased production and increased utilization of leukocytes. Thrombocytopenia is also commonly seen in almost 90% of affected individuals. Serial C-reactive protein levels have been shown to be successful in differentiating benign abdominal etiologies such as ileus from NEC. Furthermore, it has been suggested that persistently elevated CRP levels indicate the need for surgical intervention, although this is controversial. NEC is associated with bacteraemia in approximately one third of cases, and thus blood cultures should be obtained prior to administration of antibiotics.

### 44.4.3 Radiological Diagnosis

#### 44.4.4 Abdominal Series X-rays

Serial plain films of the abdomen (anteroposterior radiograph and a left lateral decubitus or cross table lateral film) should be obtained at the first suspicion of disease. Several radiologic findings pathognomonic of NEC can be identified on abdominal x-ray including intramural air (pneumatosis intestinalis), portal vein gas, the “fixed loop sign”, “signet sign”, and in advanced cases pneumoperitoneum.

Portal venous air is noted in approximately 30% of advanced cases, and occurs when intramural air is absorbed into the mesenteric venous circulation (Fig. 44.5). Portal venous air portends a worse prognosis. The finding of a fixed loop is referred to as a “signet sign” and results from a bowel loop that remains unchanged for 24–48 h and is associated with transmural necrosis (Fig. 44.3). Despite some reports indicating an association between fixed loops and pan-necrosis, almost half of patients recover without surgical intervention. Free air can be seen in severe cases of NEC (Fig. 44.6). A large pneumoperitoneum can be seen as a central collection of air on the anteroposterior film, and is an indication for surgical intervention. Pneumoperitoneum in the absence of pneumatosis intestinalis may be more suggestive of focal intestinal perforation (FIP), rather than NEC.

Several common non-specific radiographic findings include a gasless abdomen, non-specific bowel gas patterns and ascites. Ascites has been reported to occur in approximately 10% of infants with NEC.

Computed tomography scans (CT) will reveal findings similar to those seen by X-ray, and is generally unnecessary and therefore not indicated.

#### 44.4.5 Contrast Studies

The use of contrast enemas is contraindicated in the diagnosis of NEC. However, contrast studies may be indicated following recovery from acute disease. In patients with a history of NEC and new intestinal obstruction, contrast studies may localize a stricture secondary to scarring.

#### 44.4.6 Ultrasound

Ultrasound can be useful in the diagnosis of NEC, allowing evaluation of intestinal wall edema, portal gas and free fluid. However ultrasound remains a
notoriously operator-dependent modality and may not be readily available in many centers.

**44.5 Differential Diagnosis**

The variability in the presentation and severity of NEC may mimic different conditions. Both sepsis and ileus can present with signs and symptoms of systemic infection and abdominal distension. Radiologic imaging may help in diagnosis, but often does not definitively rule in NEC unless pneumatosis intestinalis is present. Fortunately the therapy, to be discussed later, is the same for both early NEC and sepsis. Advanced cases of Hirschsprung’s enterocolitis or severe gastroenteritis may present with intramural air. In advanced cases other aetiologies of intra-abdominal catastrophe including volvulus, intussusception, inspissated meconium syndrome and intestinal vascular accident may be mistaken for fulminant NEC.

Focal intestinal perforation is important to consider in the differential of NEC. FIP is a distinct entity often characterized by the lack of signs and symptoms of sepsis. Despite the fact that FIP is typically seen in infants of smaller birth weight and more extreme prematurity, it has a higher survival rate. FIP is also associated with the use of pharmacologic agents including indomethacin and dexamethasone. Furthermore the most commonly associated organism of sepsis in FIP is *Candida* species, which is distinct from the agents associated with sepsis in NEC. It is important to note that infants with FIP who are culture-positive for *Candida* may be more severely ill, than those infants with FIP who are culture-negative.

**44.6 Management**

**44.6.1 Medical Management**

The majority of patients with NEC are treated non-operatively. Prompt resuscitative measures including evaluation of airway, breathing and circulation remain paramount in these patients. Many patients may require ventilator support, and tracheal intubation is preferred to prevent aerophagia and greater intestinal distension. Most patients with NEC will be hypovolemic and will require adequate fluid resuscitation, with intravenous crystalloids. If the patient is affected by coagulopathy then correction with platelets and/or fresh frozen plasma is indicated. States of acidosis should be corrected by optimal ventilation, fluid resuscitation, and if necessary, bicarbonate or Tris[hydroxymethyl]-aminomethane (THAM) administration. The use of inotropic support may be indicated in patients with refractory hypotension despite fluid administration. After blood cultures have been obtained broad-spectrum antibiotics should be started. Currently there is insufficient evidence regarding the choice of a specific antibiotic regimen or duration, although broad-spectrum antibiotics based on patterns of microbial resistance within individual neonatal intensive care units is recommended. The use of antifungal agents should also be considered in severely ill patients. Appropriate antibiotic therapy has been shown to improve the outcome and survival in infants with NEC.

*Fig. 44.6* Lateral decubitus abdominal x-ray of an infant with NEC, demonstrating intestinal free air
All enteric feeds should be stopped and the stomach decompressed with an orogastric tube. Serial measurements of abdominal girth, frequent abdominal exams, and serial abdominal radiographs are obtained to monitor disease progression.

44.6.2 Probiotics

At birth, the intestine lacks bacterial flora, and with time becomes colonized with a variety of bacterial species. As previously mentioned, the microbial flora in the premature hospitalized patient is different from that of a healthy full-term infant. Typically, full-term infants have a predominance of favourable gram-positive organisms including Lactobacilli and Bifidobacteria, whereas premature infants are largely colonized by Enterococcus and gram negative organisms. The administration of exogenous probiotics may protect against NEC by altering the intestinal ecosystem from colonization by potentially harmful microflora to a more favourable or beneficial environment. Clinical trials investigating the potential benefit of probiotics have produced mixed results. A randomised prospective study by Bin-num et al found an absolute risk reduction of 12% in the incidence of NEC, and a decline in disease severity after daily feeding supplementation with probiotics. In a prospective study by Lin et al the overall patient mortality was lower after probiotic administration, with a lower incidence of NEC following probiotic therapy (1.1% vs. 5.3%). However, a similarly designed study revealed no benefit. Currently the role of probiotic therapy remains an area of investigation.

44.6.3 Surgical Management

Despite appropriate and timely medical management, over a third of patients with NEC require surgical intervention. In infants with a birth weight greater than 1,500 g laparotomy with resection of affected intestine is the preferred approach. In some cases the intestine is necrotic in only a single segment; while in others, the disease pattern is more complex involving multiple segments with intervening areas of questionable viability, or the entire extent of the small and large bowel (Fig. 44.2). The standard of care is to remove all necrotic areas, taking great care to preserve any bowel that appears viable. After resecting the necrotic regions, an area of viable intestine is used to create an ostomy with or without a mucus fistula. There are occasional reports of resection of isolated perforation with primary reanastomosis of the remaining intestine, however this is not a widely accepted approach. In patients who are found to have multiple areas of questionable intestinal viability, a “second-look” procedure may be planned to reevaluate the bowel in 24–36 h prior to the formation of an enterostomy. In the past, if at the time of surgery many segments of intestine were found to be involved, the creation of multiple stomas was typically practiced. However, this strategy may result in the sacrifice of potentially viable intestine, hence some surgeons advocate the “patch, drain and wait” approach. In this case each perforation is sutured closed, penrose drains are placed and parenteral support is continued. In cases of pan-necrosis surgical therapy is often associated with extremely poor outcomes and intervention may be foregone.

In patients weighing less than 1,500 g the optimal choice of surgical intervention has been more controversial. Laparotomy with intestinal resection in very-low-birth weight infants is associated with a very high morbidity and mortality, and poor neurodevelopmental outcomes. Ein et al in 1977 reported a series of extremely low birth weight patients treated with a peritoneal-drainage procedure. They reported that three survived, two of which did not require a subsequent operation. It was postulated that peritoneal drainage allowed a release of intra-abdominal pressure, drainage of infection, and time for further medical optimisation and stabilisation. Despite remaining somewhat controversial, this approach was adopted for years by many surgeons as both a temporising measure and a definitive therapeutic approach to Bell stage III disease in extremely low birth weight patients. Moss et al. published a multi-institutional, randomised, controlled trial in 2006, comparing primary peritoneal drainage with laparotomy and bowel resection in infants less than 1,500 g. They found no statistical difference in survival, dependence on parenteral nutrition or length of hospital stay. Hence, while peritoneal drainage may have an important role in the surgical management of extremely low birth weight infants, careful individual
assessment of each patient and consultation between medical and surgical personnel is required for determining an optimal treatment strategy.

In patients who improve after laparotomy with ostomy formation, re-establishing intestinal continuity within 6 weeks, assuming adequate bowel length, remains an optimal course of action.

44.7 Complications

44.7.1 Strictures

The most serious complications of acute NEC include intestinal necrosis and perforation, which may occur in up to one third of patients. However, some patients who initially appear to respond well to medical management develop gastric residuals associated with abdominal distension and bilious emesis upon resuming enteral feedings. This scenario is suggestive of the presence of intestinal strictures, which form in areas of partial intestinal necrosis or ischemia with healing, causing tissue contraction and scarring. The most commonly affected site is at the junction of the descending and sigmoid colon. Radiographic imaging may confirm bowel obstruction, with a transition zone and air-fluid levels. If a stricture is suspected a contrast enema (or an upper gastrointestinal study) should be performed to assess intestinal patency. If a stricture is demonstrated, surgical resection is indicated at this time. Intestinal strictures develop in approximately one third of patients with a history of NEC.

44.7.2 Short Bowel Syndrome

In addition to intestinal strictures, nearly 25% of patients with a history of NEC and surgical intervention develop short bowel syndrome. The intestine of a full-term neonate is approximately 250 cm, when a large segment or multiple segments of bowel is (are) resected, the amount of remaining intestine may not be sufficient to adequately absorb nutrients and fluids. The patient is then reliant upon intravenous nutrition, and is exposed to the risks of long-term parenteral support including line sepsis, cholestasis, cirrhosis and liver failure. Some success in survivors with short bowel syndrome has been reported after small bowel transplant.

44.7.3 Neurodevelopmental Delay

Neurodevelopmental delay continues to be a significant issue in survivors of NEC, as many as 50% of infants are affected. In a recent study, Blakely et al. found that patients with NEC who underwent laparotomy instead of peritoneal drainage had a lower risk of future developmental delay. Prior investigations suggested that neurodevelopmental delay was more related to prematurity and prolonged hospital stay, rather than NEC itself. However, Blakely et al controlled for the confounding factors of prematurity and severity of disease in their study. More investigation into this area is warranted.

Further Reading

Blakely ML, Tyson JE, Lally KP et al (2006) Laparotomy versus peritoneal drainage for necrotizing enterocolitis or isolated intestinal perforation in extremely low birth weight infants: Outcomes through 18 months adjusted age. Pediatr 117:e680–e687
Ford HR (2006) Mechanism of nitric oxide-mediated intestinal barrier failure: Insight into the pathogenesis of necrotizing enterocolitis. J Pediatr Surg 41:294–299
Hackam DJ, Upperman JS, Grishin A, Ford HR (2005) Disordered enterocyte signaling and intestinal barrier dysfunction in the pathogenesis of necrotizing enterocolitis. Semin Pediatr Surg 14:49–57
Lin P, Stoll B (2006) Necrotising enterocolitis. Lancet 368: 1271–1283
Moss RL, DKimmit RA, Barnhart DC, et al (2006) Laparotomy versus peritoneal drainage for necrotizing enterocolitis and perforation. N Engl J Med 354:2225–2234
Puri P, Höllwarth M (2006) Pediatric Surgery. Springer, Berlin, Heidelberg
Strober W (2006) Immunology: Unraveling gut inflammation. Science 313:1052–1054