Necrotizing Enterocolitis

Fawn C. Lewis and Daniel A. Bambini

Incidence
The incidence of necrotizing enterocolitis (NEC) in the United States is 1-3 cases per thousand live births, or 25,000 cases per year. NEC is the most serious and frequent disorder of low-birth-weight infants with an incidence of approximately 6% in infants below 1500 g. NEC is primarily, but not exclusively, a disease of premature infants born in nations with well-developed neonatal intensive care systems. Among the most developed countries, the incidence of NEC is unequal with the United States, Canada, United Kingdom, and Australia having the highest rates of disease. NEC is rare in Switzerland, Scandinavia, and Japan.

Etiology
There is no single identified cause of necrotizing enterocolitis. Currently, there are three main factors that are present and seem to contribute to the development and progression of NEC in infants:

1. intestinal ischemia (thrombotic, embolic, or selective as in the diving reflex),
2. bacterial colonization of the intestine, and
3. substrates in the gut lumen.

Prematurity is the major predisposing factor to NEC development. Premature newborns have immature guts in which the gastrointestinal barrier defense mechanisms are limited by inadequate production of mucus, complement, immunoglobulins (i.e., IgA, IgM), and poor phagocyte function. Exposure to antibiotics, pathogenic bacteria, and formula feeds create a luminal environment suitable for bacterial overgrowth. With intestinal ischemia, bacteria breach the mucosal layer and NEC begins. Many additional factors may contribute to the development of NEC (Table 64.1).

Classification
Necrotizing enterocolitis follows a variable clinical course. The stages of NEC are commonly classified as outlined in Table 64.2. However, clinical distinction between each stage is often difficult.
Pathology/Pathophysiology

NEC can involve any segment of the intestine, but the most commonly affected region is the ileocecal area (45%) supplied by the most distal branches of the superior mesenteric artery. Isolated small intestinal involvement is noted in 30% of cases. NEC is limited to the colon in 25% of cases, and the splenic flexure is the most common site of colonic involvement. Pan-necrosis (involvement of more than 75% of the bowel) occurs in 14-30% of cases. NEC occurs as a single continuous lesion in only about half of cases.

Grossly, the affected bowel is distended. The intestinal wall is thinned with hemorrhagic or graying areas. Subserosal or intravascular gas is observed in 50% of cases. White colored bowel indicates areas of nonperfusion. Histologically, coagulation

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Table 64.1. NEC associated factors or conditions

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<th>Condition</th>
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<tr>
<td>Umbilical catheters</td>
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<td>Hypotension</td>
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<td>Enteral feeds</td>
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<tr>
<td>Pneumonia</td>
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<tr>
<td>Maternal cocaine use</td>
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<tr>
<td>Hyperosmolar formula feedings</td>
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<tr>
<td>Vasoconstrictive medical therapy (indomethacin)</td>
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<td>Patent ductus arteriosus</td>
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Table 64.2. Clinical classification of NEC and survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Findings</th>
<th>Radiographic Findings</th>
<th>Treatment</th>
<th>Survival</th>
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<tr>
<td>I: Suspected NEC</td>
<td>Emesis, mild distention, intolerance to feeds</td>
<td>Ileus pattern</td>
<td>medical evaluation, treat for NEC, sepsis evaluation</td>
<td>100%</td>
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<td>II: Definite NEC</td>
<td>Bilious emesis or gastric drain output, marked abdominal distention, occult or gross GI hemorrhage</td>
<td>Ileus, pneumatosis intestinalis, portal vein gas</td>
<td>aggressive medical resuscitation and therapy for NEC</td>
<td>96%</td>
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<tr>
<td>III: Advanced NEC</td>
<td>Bilious gastric output, abdominal distention, occult or gross GI hemorrhage, abdominal wall erythema, deterioration of vital signs, septic shock</td>
<td>Ileus, pneumatosis intestinalis, portal vein gas, pneumoperitoneum, ascites</td>
<td>Surgical</td>
<td>50%</td>
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necrosis of the mucosa is the predominant feature. Full or partial thickness involvement of the subserosa and muscular layers is also common. Viable areas of bowel demonstrate features of acute and chronic inflammation. Granulation tissue, fibrosis, and epithelial regeneration are signs of an extended duration of injury and recovery.

Clinical Presentation

Although the clinical presentation can be quite variable, early NEC presents as intestinal ischemia. An ileus is often present producing abdominal distention, tachypnea, lethargy, feeding intolerance, gastric distention, and bilious or nonbilious emesis. Gross or occult blood in the stool is identified in 25-55% of patients. As the disease progresses, clinical indicators of shock and sepsis become evident including temperature instability, increased lethargy, apnea, bradycardia, and oliguria. Increasing oxygen requirement and a need for intubation and mechanical ventilation are also signs of disease progression.

Abdominal exam is notable for distention, diminished bowel sounds, and tenderness. Initially the abdomen is soft but often become firm and increasingly tender with erythema, discoloration, abdominal wall edema, and crepitance. Tympany on abdominal percussion is frequently present in cases with perforation and free intraperitoneal air. Periphera1 perfusion is diminished.

Laboratory testing reveals leukocytosis or leukopenia and thrombocytopenia that occur as a response to gram negative bacterial septicemia. Metabolic acidosis occurs as a result of sepsis as fluid lost into the interstitial space causes intravascular volume depletion and hypoperfusion. Prothrombin (PT) and activated partial thromboplastin time (PTT) are frequently prolonged due to disseminated intravascular coagulopathy (DIC).

Diagnosis

The diagnosis of NEC should be suspected in premature or low birth weight infants with abdominal distention, an increasing need for respiratory support, feeding intolerance, or lethargy. Initial evaluation of an infant suspected of having NEC includes a careful physical exam, laboratory evaluation, and plain abdominal radiographs. On a flat anteroposterior view, bowel distension is the earliest and most common radiographic finding of NEC (Fig. 64.1). Intramural bowel gas (pneumatosis intestinalis) occurs in almost all patients with NEC. However, pneumatosis intestinalis is not a specific finding and has been reported in several other diseases including Hirschsprung’s disease with enterocolitis, pyloric stenosis, and carbohydrate intolerance. Other plain film findings include portal venous gas, pneumoperitoneum, ascites, or fixed and persistently dilated bowel loops. Only 63% infants with intestinal perforationsdue to NEC demonstrate pneumoperitoneum on preoperative abdominal films (Fig. 64.2).

Treatment

As is true for most diseases, the best treatment is prevention. Prenatal care helps to decrease the number of premature births. NEC is rare among infants receiving breast milk, when compared to formula fed infants in the neonatal intensive care unit. The frequency of NEC in babies whose feeding schedule is advanced quickly is not different from that observed in infants whose feedings are advanced more slowly.
Table 64.3. Medical management of NEC

<table>
<thead>
<tr>
<th>Cultures:</th>
<th>Blood cultures are necessary. Urine/sputum/CSF as indicated</th>
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<tr>
<td>Orogastric or nasogastric decompression of stomach.</td>
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<td>Intravenous fluid resuscitation to restore tissue perfusion and renal function</td>
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<td>Antibiotics: synergistic coverage for gram positives and gram negatives, with additional coverage for anaerobes. A penicillin, an amino-glycoside, and either clindamycin or metronidazole are most commonly used.</td>
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<td>Correction of anemia and coagulopathy: transfuse packed red blood cells and platelets. Fresh frozen plasma is used as coagulation parameters indicate.</td>
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<td>Abdominal supine and gravity-dependent (cross-table or left lateral decubitus) radiographs, repeated serially as clinical picture indicates.</td>
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<td>Frequent repeat abdominal exams by the same physician at least every 6 hours until infant stable, then as clinical picture indicates.</td>
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<td>Surgical intervention if the infant worsens, fails to improve on intensive nonsurgical therapy, or for advanced NEC with perforation and gangrene.</td>
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Fig. 64.1. Extensive pneumatosis intestinalis consistent with severe necrotizing enterocolitis.
Medical therapy is instituted immediately once the diagnosis of NEC is suspected (Table 64.3). The goals of medical management include restoration of tissue perfusion, control of infection or sepsis, and careful observation for evidence of gangrene or perforation. An orogastric or nasogastric tube is placed to decompress the stomach and diminish further gastrointestinal distention. Aggressive volume resuscitation with isotonic fluids restores intravascular volume and helps improve organ perfusion as indicated by reversal of hypotension, oliguria, and acidosis. Because ischemic bowel sequesters large amounts of fluid in its walls and lumen, surprisingly large resuscitation volumes are often required.

Systemic antibiotics for control of bacteremia are given, targeting broad coverage of enteric bacteria (i.e., gram-positive, gram-negative, anaerobic). Many centers use ampicillin, gentamicin, combined with metronidazole or clindamycin. In some institutions with a high prevalence of coagulase negative staphylococcus, vancomycin is used to provide broader gram-positive coverage.

After initial resuscitation, surveillance includes serial abdominal exams with serial evaluation for leukopenia, thrombocytopenia, anemia, acidosis, and hypoxia. Abdominal films are repeated when there is a clinical change or increased suspicion.
of gastrointestinal perforation. Indicators of intestinal gangrene or perforation and potential need for operative intervention include:

1. an inability to resuscitate the infant,
2. subsequent deterioration of vital signs and hematologic indices (i.e., thrombocytopenia, leukopenia),
3. septic shock,
4. intestinal hemorrhage,
5. increasing ascites,
6. radiographic evidence of a persistent, fixed, dilated loop of intestine and
7. pneumoperitoneum.

Of these, pneumoperitoneum is probably the only absolute indication for surgical intervention.

The morbidity and mortality of laparotomy in septic, premature neonates is high. The ideal timing of surgical intervention is often difficult to identify during the progressive course of NEC; however, it is important to operate once it is clear that a perforation has occurred. If nonsurgical therapy is ineffective after 4-6 hours of intensive treatment, strong consideration for surgical intervention is warranted.

The main surgical options for an infant with NEC include:

1. peritoneal drainage,
2. laparotomy with resection and stoma(s),
3. laparotomy with resection and primary anastomosis,
4. laparotomy with proximal diversion, or
5. a combination of 1-4.

In cases of severe pan-necrosis, the surgeon (and family) may choose to explore the abdomen and close with no further surgical intervention. In this scenario, surgery is performed to confirm the diagnosis and to allow the provision of comfort care to infants with no chance of survival. The choice of procedure is individualized for each patient based on size, severity of illness, and presence of other comorbid factors (i.e., intraventricular hemorrhage (IVH), etc.). Regardless of the procedure chosen, great care is taken to minimize evaporative heat and water losses during surgery (i.e., warming pads, plastic coverings, warmed fluids, and efforts to keep the intestine inside the abdominal cavity whenever possible).

For laparotomy, the usual incision is a right-sided, transverse supraumbilical incision which allows careful examination of the entire intestine. White-appearing areas often represent full-thickness ischemic necrosis. Transparent areas of bowel indicate areas of mucosal necrosis penetrating through to the muscularis and are at high risk of perforation. Other areas of dull greenish-black or purple discolored intestine may or may not recover. Bowel segments with questionable viability are left in place and a "second look" operation is planned to re-evaluate the integrity of these segments. Frankly necrotic segments require resection. If multiple necrotic segments are resected, the surgeon must decide whether to bring out multiple stomas and/or mucous fistulas or to create distal anastomoses. This decision depends on the clinical status of the patient, the number of bowel segments, the individual bowel segment lengths, the total length of remaining viable bowel, the presence/absence of an ileocecal valve, and the ability of bowel ends to reach the anterior
abdominal wall. The length of the remaining viable intestine, its location, and the
presence or absence of the ileocecal valve are carefully noted in the medical record.
Peritoneal drainage is often performed in infants weighing less than 1000 gm
and in some larger infants who are physiologically unstable. A drain (e.g., penrose)
is placed into the peritoneal cavity usually via a right lower quadrant incision. Some
infants improve with this therapy and do not require emergent laparotomy.
Approximately one third of infants with NEC and weight < 1000 gm treated with
peritoneal drainage require no further surgical intervention. However, subsequent
exploration may be indicated if there is no improvement.
After recovery from a NEC episode, enteral feeding is introduced slowly after
about 10-14 days of medical therapy. Enteral feeds are slowly advanced toward goal
rates and concentration; nutrition is supplemented by intravenous hyperalimentation
(TPN) as needed. After recovery from NEC, 25% of infants develop intestinal stric-
tures resulting from circumferential scarring of nonperforated intestinal segments.
Enteral nutritional goals are frequently not met due to feeding intolerance related to
post-NEC stricture formation. Strictures are usually treated surgically by resection
and primary anastamosis well after the recovery phase and after significant growth
has occurred.
Infants with stomas are allowed to feed and grow well before these stomas are
closed. An arbitrary time or size such as two months or five kilograms is sometimes
used as a goal. Intestinal continuity is restored earlier if:
1. the intestinal segment proximal to the stoma is short causing failure to
   thrive or difficult water and/or salt loss problems, or
2. stomal complications occur (i.e., stenosis, prolapse).
Patients with resections leaving insufficient absorptive intestinal length have short
bowel syndrome (SBS) (Chapter 95) and require long-term TPN. In some of these
infants, SBS is a temporary problem that resolves as intestinal length and diameter
increase with age, but central venous catheter infections and complications (i.e.,
cholestatic liver disease, etc.) are sometimes serious, life-threatening problems.

Outcomes
Overall survival from NEC is improving, especially in those infants weighing
less than 1000 gm. Overall survival has increased from near 50% in the 1980s to
approximately 80% in the 1990s. Early diagnosis and treatment are important. Infants
who progress to intestinal perforations have nearly a 65% perioperative mortality,
whereas infants without perforation at the time of surgery have a 30% mortality.
Survival rates for surgically treated NEC are similar between infants receiving lap-
arotomy and those receiving peritoneal drainage except in very low birth weight
infants (< 1000 gm) in which laparotomy results in only a 22% survival rate com-
pared to a 69% survival rate following peritoneal drainage.
Of infants surviving acute NEC, 25% will develop a late circumferential intesti-
nal stricture. Recurrent NEC occurs in about 6% of infants and typically occurs 3-5
weeks after the first episode. NEC also occurs as an infrequent postoperative com-
plication, most commonly following gastroscisis or myelomeningocele repairs. The
mortality rate of postoperative NEC is 46-67%.
Significant neurological impairment is observed in 15-30% of infants that survive NEC, but this rate is similar to the rate expected in premature hospitalized infants of comparable size without NEC. Other gastrointestinal sequelae include a 10% incidence of short bowel syndrome (SBS) and malabsorption.

**Selected Readings**


