Clinical features and diagnosis of necrotizing enterocolitis in newborns

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INTRODUCTION — Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in the newborn infant. It is a disorder characterized by ischemic necrosis of the intestinal mucosa, which is associated with inflammation, invasion of enteric gas forming organisms, and dissection of gas into the muscularis and portal venous system [1]. Although early recognition and aggressive treatment of this disorder has improved clinical outcomes, NEC accounts for substantial long-term morbidity in survivors of neonatal intensive care, particularly in premature very low birth weight infants (birth weight below 1500 g).

The clinical features and diagnosis of NEC are reviewed here. The pathology, pathogenesis, management, and prevention of this disorder are discussed separately. (See "Pathology and pathogenesis of necrotizing enterocolitis in newborns" and "Management of necrotizing enterocolitis in newborns" and "Prevention of necrotizing enterocolitis in newborns".)

EPIDEMIOLOGY — NEC occurs in 1 to 3 per 1000 live births and 1.0 to 7.7 percent of admissions to neonatal intensive care units (NICUs) [2].

The incidence decreases with increasing gestational age and birth weight (BW), and is about 6 to 7 percent in infants with very low birth weight (VLBW) infants (BW less than 1500 g) [3-5].

This was illustrated in one study of VLBW infants born between 1999 and 2001 from the National Institute of Child Health and Human Development (NICHD) neonatal network cohort [3]. The overall rate of NEC was about 7 percent. Rates were inversely related to BW as follows:

- BW between 401 to 750 g — 11.5 percent
- BW between 751 to 1000 g — 9 percent
- BW between 1001 to 1250 g — 6 percent
- BW between 1251 to 1500 g — 4 percent

Although unadjusted rates of NEC varied among the 362 NICUs, there were no significant differences when risk was adjusted for confounding variables. However, one limitation of this study is that it most likely included infants with spontaneous intestinal perforation, which may alter these rates. (See "Spontaneous intestinal perforation of the newborn".)
Males and females are affected equally. NEC affects black and white infants more than Hispanic infants, but the racial patterns reflect the populations served by neonatal centers. Although seasonal variation does not occur, NEC sometimes occurs in clusters and is associated with epidemics.

Reported mortality rates range from 15 to 30 percent and also are inversely related to gestational age and birth weight [6]. The estimated yearly infant death rate in the United States from 1979 to 1992 was 12.4 deaths per 100,000 live births. The death rate from NEC was highest in black VLBW male infants.

**Term infants** — Although the majority of infants with NEC are born prematurely, approximately 13 percent of cases occur in term infants [7]. Term infants who develop NEC typically have a preexisting illness [8-10]. This was illustrated by the following two studies:

- In one report, predisposing conditions were identified in 16 of 26 term infants with NEC [9]. Among these, 6 had congenital heart disease and 10 had other disorders, including sepsis, seizures, hypoglycemia, severe intrauterine growth restriction, hypercoagulable state, gastroschisis, and congenital herpes infection.
- In the second study, a preexisting condition was found in all 30 infants greater than 36 weeks gestation with NEC cared for in a regional multiple-center health care system from 2001 to 2006 [10]. Diagnoses included congenital heart disease (n=8), respiratory distress (n=8), sepsis (n=4), birth anoxia (n =4), and polycythemia (n=2). None of the patients were exclusively breastfed. (See "Pathology and pathogenesis of necrotizing enterocolitis in newborns", section on 'Human milk'.)

**CLINICAL PRESENTATION** — The majority of premature infants who develop NEC are healthy, feeding well, and growing [11]. A change in feeding tolerance with gastric retention is a frequent early sign. The timing of the onset of symptoms varies and appears to be inversely related to gestational age [12].

The clinical presentation of NEC consists of systemic and abdominal signs.

- Systemic signs are nonspecific and include apnea, respiratory failure, lethargy, poor feeding, or temperature instability. Hypotension resulting from septic shock may be present in the most severe cases. Twenty to 30 percent of infants with NEC have associated bacteremia, which may contribute to these findings [13].
- Abdominal signs include distention, gastric retention (residual milk in the stomach before a feeding), tenderness, vomiting, diarrhea, rectal bleeding (hematochezia), and bilious drainage from enteral feeding tubes [14,15].

**Bell staging criteria** — The Bell staging criteria provide a uniform definition of NEC based upon the severity of systemic, intestinal, and radiographic findings and is the most commonly used criteria in practice (table 1) [1,16]. These definitions are useful in comparing cases and studies;,
however, treatment is directed at the clinical signs rather than the particular stage of NEC. Each advancing stage includes the characteristics of the previous stage plus additional findings due to increasing severity of the disease.

- Stage I, or suspected NEC, is characterized by nonspecific systemic signs, such as temperature instability, apnea, and lethargy. Abdominal signs include increased gastric residuals, abdominal distention, emesis, and heme-positive stool. Abdominal radiographs may be normal or show dilation of the bowel consistent with mild ileus. Although therapy does not change, stage I cases are further divided by the absence (stage IA) or presence of grossly bloody stools (stage IB).
- Stage II, or proven NEC, encompasses the signs of stage I plus absent bowel sounds with or without abdominal tenderness. Abdominal tenderness is present, and some infants have cellulitis of the abdominal wall or a mass in the right lower quadrant. Infants with stage IIA are mildly ill, whereas those with stage IIB NEC are moderately ill and also have mild metabolic acidosis and thrombocytopenia. Abdominal radiograph findings include intestinal dilation, ileus, pneumatosis intestinalis, and ascites. (See 'Abdominal radiography' below.)
- Stage III, or advanced NEC, is the most severe form. In stage IIIA, the bowel is intact, whereas stage IIIB is characterized by bowel perforation visualized as a pneumoperitoneum on the abdominal radiograph. Infants with advanced NEC are critically ill. In addition to the signs of less severe stages, they typically have hypotension, bradycardia, severe apnea, and signs of peritonitis (eg, abdominal distention and marked tenderness). Laboratory signs include a combined respiratory and metabolic acidosis, neutropenia, and disseminated intravascular coagulation (DIC).

In about one-third of cases, NEC is suspected but not confirmed (stage I), and symptoms resolve gradually in these infants. In 25 to 40 percent of cases, the progression of NEC is fulminant with signs of peritonitis and sepsis, and the rapid development of DIC and shock (stage III).

**DIAGNOSIS** — The diagnosis of NEC is based on the presence of the characteristic clinical features of abdominal distention and rectal bleeding (heme-positive or grossly bloody stools), and the abdominal radiographic finding of pneumatosis intestinalis.

Assessment of infants with suspected NEC includes abdominal imaging, blood studies, stool analysis, and sepsis evaluation. Although the results of this evaluation often are nonspecific, certain findings are supportive of the diagnosis of NEC, and in the case of abdominal imaging (ie, pneumatosis intestinalis), may be diagnostic.

**Radiographic studies**

**Abdominal radiography** — Abdominal radiographs confirm the diagnosis of NEC and follow the progression of the disease. Of note, although abdominal radiography is usually useful in making the diagnosis of NEC, when there are equivocal radiographic findings, treatment decisions should be based upon clinical suspicion.

Abdominal radiographs are obtained in the supine position [17]. In infants with more advanced illness in whom pneumoperitoneum is suspected, films also are taken in the supine cross-table
lateral view or in the lateral decubitus position with the left side down to detect free air in the abdomen. After the initial evaluation, we obtain serial radiographs to follow the course of the disease, usually every 8 to 12 hours during the first few days or until the infant improves.

The following characteristic radiographic features are seen in the majority of infants with suspected NEC (picture 1) [15].

- An abnormal gas pattern with dilated loops of bowel that is consistent with ileus, and is typically seen in the early stages of NEC.
- Pneumatosis intestinalis, the hallmark of NEC, appears as bubbles of gas in the small bowel wall, and is seen in most patients with stages II and III NEC [18].
- Pneumoperitoneum typically appears when bowel perforation occurs in patients with IIIB NEC. A substantial amount of intraperitoneal air may result in the "football" sign on a supine radiograph. This sign consists of a large hypolucent area in the central abdomen with markings from the falciform ligament.
- Sentinel loops, a loop of bowel that remains in fixed position, is suggestive of necrotic bowel and/or perforation in the absence of pneumatosis intestinalis.

Portal venous gas had been thought to be a predictor of poor outcome and an indication for surgical intervention. However, subsequent data, do NOT support these assumptions. This was illustrated in a prospective study of 194 infants with NEC treated at a single center from 1991 to 2003 [19]. There was NO difference in survival rates between those patients with PVG and those without (17 versus 20 percent) [19]. Of the infants with PVG, those who were treated medically had a higher survival rate than those treated surgically (91 versus 74 percent).

Radiological findings may vary by gestational age. This was illustrated in one observational series of 202 infants with NEC [20]. Although intramural gas was detected in all infants ≥37 weeks gestation with NEC, it was only present in 29 percent of those ≤26 weeks gestation. In addition, portal venous gas was more common in infants ≥37 weeks compared to those ≤26 weeks gestation (47 versus 10 percent). Thus, abdominal radiography may not be as helpful in the most immature infants. Particularly in these infants, treatment decisions should be based upon clinical suspicion as confirmatory radiographic findings may not be present.

Abdominal ultrasonography — Although we currently rely on radiographs, abdominal ultrasonography has been increasingly used in the diagnosis of NEC [21,22]. The sonographic appearance of bowel wall with a central echogenic focus and a hypoechoic rim (the pseudo-kidney sign) may indicate necrotic bowel and imminent perforation. Ultrasonography also can detect intermittent gas bubbles in liver parenchyma and the portal venous system that are not detected by radiographs. Free gas and focal fluid collections are associated with more severe NEC [22].

Color Doppler ultrasonography has also been used to diagnose NEC. In a small study, color Doppler ultrasonography was more sensitive than abdominal radiography in detecting bowel necrosis and
alterations in bowel wall perfusion as confirmed at laparotomy [23]. Additional studies are needed to determine what is the optimal radiologic modality to confirm NEC in at risk infants in all settings.

**Contrast enema** — Contrast enemas are NOT recommended if NEC is suspected, as it may result in bowel perforation with extravasation of contrast material into the peritoneum.

**LABORATORY EVALUATION**

**Blood tests** — Although blood tests are not used in the diagnostic and staging criteria for NEC, laboratory findings may support the diagnosis and aid in the management of infants with NEC. In particular, low platelet count, metabolic acidosis, and an increasing serum glucose are associated with NEC [24,25].

- **Complete blood count** — A complete blood count and differential are performed when NEC is suspected. Alterations in the white blood count are nonspecific, although an absolute neutrophil count of less than 1500/microL is associated with a poor prognosis [1]. Thrombocytopenia is a frequent finding and can result in significant bleeding. In the early course of NEC, declining platelet counts correlate with necrotic bowel and worsening disease, whereas a subsequent rise in platelet counts often signals improvement [24].
- **Coagulation studies** — Coagulation studies are not ordered routinely but should be obtained if the infant has thrombocytopenia or bleeding, because disseminated intravascular coagulation (DIC) is a frequent finding in infants with severe NEC. DIC is confirmed by a decreased platelet count, prolonged prothrombin and partial thromboplastin times, decreased serum factor V and fibrinogen concentrations, and increased fibrin split products (D-dimer). (See "Disseminated intravascular coagulation in infants and children").
- **Serum chemistries** — Serum electrolytes, blood urea nitrogen, creatinine, and pH are routinely measured. An arterial blood gas analysis is performed in infants with signs of respiratory compromise. Electrolyte abnormalities often are nonspecific. However, persistence of hyponatremia (serum sodium levels of less than 130 meq/L), increasing glucose levels, and metabolic acidosis are suggestive of necrotic bowel or sepsis [25].
- **Other nonspecific findings** in infants with NEC include increased levels of C-reactive protein [26], lysosomal acid hydrolase, and alpha-1-acid glycoprotein (orosomucoid).

**Sepsis evaluation** — A sepsis evaluation is performed when NEC is suspected because 20 to 30 percent of patients will be bacteremic. Culture results may be used in guiding antibiotic therapy. (See "Management of necrotizing enterocolitis in newborns", section on 'Antibiotic therapy'.) Blood, stool, and, if indicated, cerebrospinal fluid cultures are obtained. Cultures of the stool typically reveal enteric flora. If Clostridium difficile is suspected, specific cultures and assays for its toxins are performed. (See "Clostridium difficile infection in children: Approach to diagnosis"). Stool is cultured for viral or fungal organisms if these infectious agents are suspected.

A diagnostic abdominal paracentesis occasionally is performed to obtain fluid for culture and Gram stain in infants with severe ascites or when peritonitis is suspected because of progressive clinical
deterioration and an unchanging radiographic bowel gas pattern. In these cases, the identification of enteric organisms in the peritoneal fluid supports the diagnosis of peritonitis from intestinal perforation and helps guide appropriate antibiotic coverage [27].

Other tests — In an infant suspected of having NEC, stool may be positive for occult blood. A positive finding may increase the diagnostic suspicion, but it is not specific for the disease, as occult blood in stool is commonly found in premature infants. In a survey of infants <1800 g, 58 percent of infants had at least one positive occult blood in stool test over a six week period [28].

Other stool tests have been studied but are not performed routinely. As an example, many infants with NEC have carbohydrate malabsorption, reflected by the presence of reducing substances in the stool or a positive breath hydrogen test [29,30]. In one study, breath hydrogen excretion increased 8 to 28 hours before clinical signs of NEC were detected [29].

Other nonspecific findings in infants with NEC include increased levels of stool alpha-1 antitrypsin, and urinary D-lactate (a carbohydrate fermentation metabolite produced by enteric microflora).

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of NEC includes other conditions that cause rectal bleeding, abdominal distension, gastric retention, or intestinal perforation. In addition, infants with sepsis can have an ileus that is difficult to distinguish from early signs of NEC.

- Pneumatosis coli is a rare and benign form of NEC that affects premature infants [31]. Affected infants typically have gastric retention and vomiting, apnea and lethargy, mild abdominal distention, and bloody stools. In contrast to typical NEC, intramural bowel gas occurs in the colon rather than in the small bowel. Infants recover within three days without sequelae [32].
- Pathogenic organisms, including Campylobacter, C difficile, Salmonella, and Shigella, sometimes cause infectious enterocolitis. These organisms are identified by stool cultures, although their causative role in NEC is uncertain.
- Anatomic or functional conditions that cause intestinal obstruction can result in enterocolitis. These disorders include Hirschsprung disease, ileal atresia, volvulus, meconium ileus, and intussusception.
- Spontaneous intestinal perforation of the newborn is a single intestinal perforation that is typically found at the terminal ileum. It also occurs primarily in very low birth weight (VLBW) infants (birth weight <1500 g) similar to NEC. It is distinguished from NEC by the clinical findings of hypotension, and abdominal distension with the classical bluish discoloration of the abdominal wall in the absence of abdominal wall erythema, crepitus, and induration commonly seen in NEC, and the absence of NEC radiographic findings of pneumatosis intestinalis, transient thickening of the intestinal wall, and fixed dilated small bowel loops. (See "Spontaneous intestinal perforation of the newborn").
- Anal fissures can result in rectal bleeding. This condition usually is benign, although the diagnosis of NEC must be strongly considered in any premature infant who has occult or gross blood in the stools.
• Neonatal appendicitis is a rare disorder with high morbidity and mortality, most likely due to a delay in diagnosis [33]. The presentation may be the same to NEC and the diagnosis may be made only at laparotomy.

**Diagnostic guidelines** — New guidelines in premature infants with BW <1250 g have been proposed to distinguish four of the acquired neonatal intestinal diseases (ANID) from one another [34].

- Ischemic NEC is characterized by increased abdominal distension, radiologic evidence of pneumatosis, bloody stools, mild acidosis and disseminated coagulopathy, and onset is most common with rapid advances of enteral feeds. Congenital heart disease, polycythemia, growth restriction, or hypoxic-ischemic event are risk factors associated with ischemic NEC.
- Viral enteritis of infancy is characterized by frequent and sometimes bloody stools, abdominal distention, and secondary sepsis. There may be a clustering of cases within a single unit. Common pathogens include rotavirus and enterovirus.
- Cow's milk protein allergy is rare in preterm infants and rarely occurs before six weeks of age. It is characterized by abdominal distention, increased stooling, which may progress to bloody stools, and in severe cases, pneumatosis may be present. (See "Food protein-induced proctitis/colitis, enteropathy, and enterocolitis of infancy".)
- Spontaneous intestinal perforation, as discussed above, is not associated with pneumatosis, occurs within the first week of life, and is independent of feeding. (See "Spontaneous intestinal perforation of the newborn".)

**SUMMARY AND RECOMMENDATIONS**

- Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in the newborn infant [1]. It occurs in 1 to 3 per 1000 live births. The incidence decreases with increasing gestational age and birth weight (BW), and is about 6 to 7 percent in infants with very low birth weight infants (BW less than 1500 g). Term infants who develop NEC usually have a preexisting illness, such as congenital heart disease or sepsis. (See 'Epidemiology' above.)
- NEC primarily occurs in healthy, growing, and feeding premature infants. It presents with both nonspecific systemic signs (eg, apnea, respiratory failure, poor feeding, lethargy, or temperature instability) and abdominal signs (eg, distension, gastric retention, tenderness, vomiting, rectal bleeding, and diarrhea). (See 'Clinical presentation' above.)
- The Bell staging criteria defines the different stages of NEC based upon the severity of clinical findings (table 1). (See 'Bell staging criteria' above.)
- The diagnosis of NEC is based upon the presence of the characteristic clinical features of abdominal distention and rectal bleeding (hematochezia), and the abdominal radiographic finding of pneumatosis intestinalis. At times, radiographic findings may be equivocal and treatment decision should be based upon clinical suspicion and findings. (See 'Diagnosis' above.)
Results of laboratory evaluation, including blood studies and stool analysis, are nonspecific but may be supportive of the diagnosis of NEC. In particular, low platelet count, metabolic acidosis, and a heme-positive stool are associated with NEC. (See 'Laboratory evaluation' above.)

The differential diagnosis of NEC includes other conditions that cause rectal bleeding, abdominal distension, or intestinal perforation. These include spontaneous intestinal perforation of the newborn, infectious enterocolitis, and the usually benign diagnoses of pneumatosis coli and anal fissures. NEC is differentiated from these conditions by the abdominal radiographic finding of pneumatosis intestinalis. (See 'Differential diagnosis' above.)

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