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Objectives

After completing this article, readers should be able to:

1. List the major risk factor for developing necrotizing enterocolitis (NEC).
2. Describe the presenting symptoms and physical findings of NEC.
3. Describe the initial steps in stabilizing an infant who has NEC.
4. Delineate the current recommendations for surgical intervention in NEC.

Introduction

Necrotizing enterocolitis (NEC) is the most common intestinal emergency in the preterm infant, occurring in 1% to 5% of patients admitted to the neonatal intensive care unit (NICU) and in 1 to 3 per 1,000 live births. Data from the National Center for Health Statistics and individual institutions suggest an incidence of 1,200 to 9,600 cases per year in the United States that result in more than 2,600 deaths annually.

The incidence of NEC correlates strongly with the degree of prematurity. Only a handful of patients were reported as having NEC in the 1960s when very low-birthweight (VLBW) infants did not survive long enough to acquire the disease. The incidence of NEC is lower in countries that have decreased rates of prematurity. The routine use of both antenatal steroids and prophylactic surfactant has resulted in the survival of greater numbers of VLBW babies, and these extremely preterm infants present the greatest challenge in the clinical management of NEC.

Over the past decade, advances in neonatal management have decreased the mortality and morbidity associated with most conditions of prematurity, as demonstrated by a recent report of the incidence of chronic lung disease during the postsurfactant administration years of 1996 to 1998. VLBW patients who had birthweights of 801 to 900 g had only a 25% incidence of chronic lung disease; the incidence was only 15% among those weighing 901 to 1,000 g. In comparison, a study in 1975 of mechanically ventilated VLBW patients reported survival in only 32%, all of whom had bronchopulmonary dysplasia. In contrast, during this same period, the mortality rate of patients who had perforated NEC remained largely unchanged, ranging from 35% to 50%. Infants who survive have a high prevalence of adverse intestinal sequelae, including short bowel syndrome and total parenteral nutrition-induced cholestasis. Additionally, a multicenter cohort study found a strong association between NEC and adverse neurodevelopmental outcomes.

Diagnosis

Clinical Findings

Infants who have NEC usually display specific gastrointestinal signs. Early presenting signs are abdominal distention (70% to 98%), feeding intolerance with increased gastric residuals (>70%), emesis (>70%), gross blood per rectum (25% to 63%), occult gastrointestinal bleeding (22% to 59%), and occasionally diarrhea (4% to 26%). As the disease progresses, abdominal findings become more severe. Patients may develop marked abdominal distention due to increased intestinal dilation and ascites. Abdominal wall erythema may be caused by necrotic bowel loops abutting the thin abdominal wall. When the intestine is perforated, the abdomen may develop a bluish cast as intraperitoneal meconium is seen through the abdominal wall.

Early systemic signs among patients who have NEC are typically nonspecific; they are

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similar to those seen with other causes of deterioration and sepsis. Initially, patients may exhibit only lethargy and temperature instability. This is followed by worsening cardiorespiratory function that ranges from episodes of apnea and bradycardia to severe cardiovascular decomposition. The signs of ileus due to systemic sepsis may be difficult to distinguish from NEC, but the initial management is the same for both conditions.

Most cases of NEC are associated with prematurity, although 10% of affected patients are term infants. These infants have an earlier onset of NEC than do preterm infants, and the disease can be fulminant.

Laboratory Findings

A patient who has NEC can present with an abnormal white blood cell count. It may be elevated, but more commonly it is depressed. A severely low white blood cell count ($<1.5 \times 10^9$/L [<1,500 cells/cu mm]) has been reported in 37% of cases. It results from both decreased production and increased utilization of leukocytes. Some authors have shown an association between leukopenia and gram-negative bacteremia in NEC. Thrombocytopenia is also common, seen in up to 87% of patients. In addition, patients may develop other coagulation abnormalities, including prolongation of prothrombin time and hypofibrinogenemia. Glucose instability (hypoglycemia or hyperglycemia), metabolic acidosis, and electrolyte imbalance may occur. Some patients have elevated C-reactive protein levels. Because no unique infectious agents have been incriminated in NEC, bacteriologic and fungal cultures may prove helpful but not conclusive.

Radiology

Radiographic imaging is essential for diagnosing suspected NEC. Plain anteroposterior abdominal and left lateral recumbent radiographs are the studies of choice. These allow the clinician an excellent view of the intestinal gas pattern and the ability to identify free abdominal air. Intestinal ileus is the most common early finding. Other early findings include dilation and thickening of bowel loops with air-fluid levels on the decubitus view. The pathognomonic radiographic finding in NEC is intramural gas (pneumatosis intestinalis) (Fig. 1). The gas is present between the subserosal and muscularis layers of the bowel (Fig. 2). Pneumatosis is caused by hydrogen production from pathogenic bacteria. Two radiographic patterns of pneumatosis are described. The cystic pattern results from bubbles of air in the submucosa and can mimic fecal material in the large bowel. The linear pattern is formed by coalesced air bubbles and courses parallel to the bowel lumen.

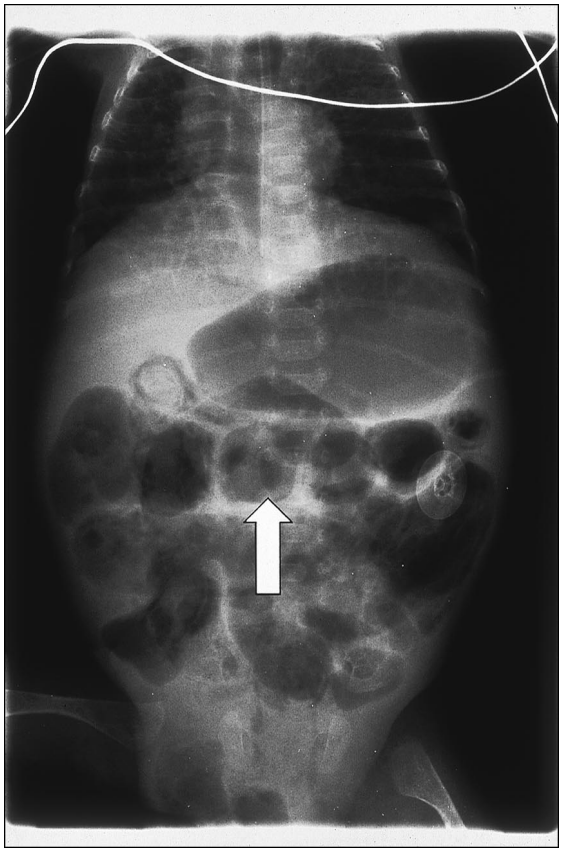

Figure 1. A plain anteroposterior radiograph demonstrating pneumatosis. Note the extensive cystic pneumatosis (arrow) as well as linear pneumatosis in the right upper quadrant.

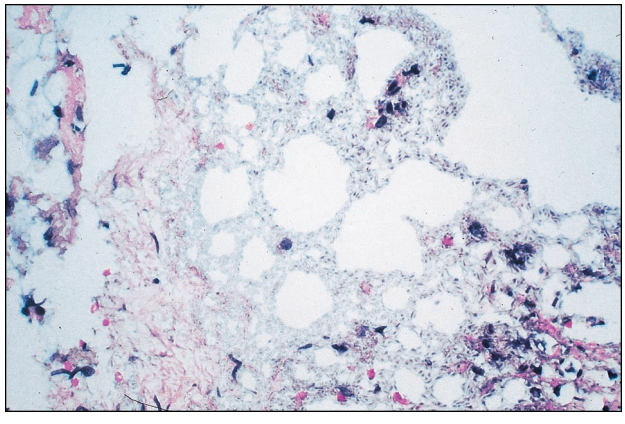

Figure 2. Photomicrograph of intestine with NEC. The cystic areas below the severely disrupted mucosal layer are pockets of hydrogen gas that present radiographically as pneumatosis.

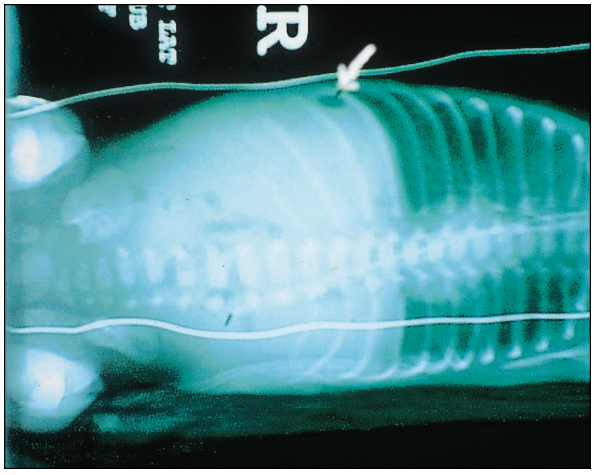

Figure 3. A left lateral decubitus radiograph demonstrating free air (arrow) between the body wall and the liver. A dependent radiographic view is required to visualize this small amount of free air.

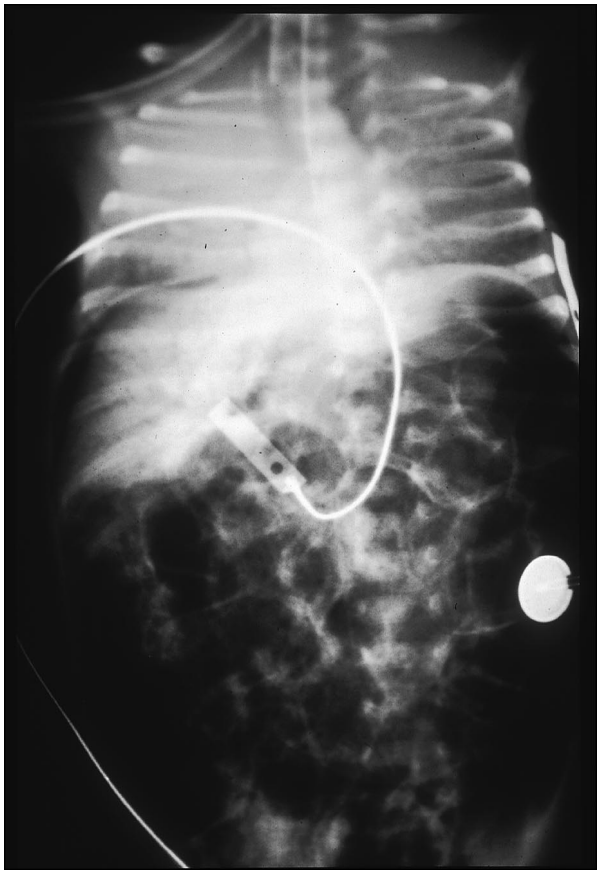

Figure 4. An anteroposterior radiograph showing extensive free air. This so-called "football sign" is a dramatic but uncommon finding in perforated NEC.

The most serious complications of NEC are intestinal necrosis and perforation, which occur in up to one third of patients. Identifying the development of a perforation can be challenging. When free air is seen on abdominal radiographs, the diagnosis is clear. Pneumoperitoneum is the only absolute indication for surgical intervention. Free air is best visualized on a dependent radiograph (left lateral decubitus or cross table lateral). The air migrates to the nondependent portion of the abdomen and is seen between the body wall and hepatic silhouette (Fig. 3). Less commonly, the pneumoperitoneum can be seen as a large central collection of free air on an anteroposterior abdominal film. This so-called "football sign" occurs when free abdominal air outlines the falciform ligament and umbilical arteries (Fig. 4).

Some patients who have NEC and perforation or necrosis will not manifest radiographic evidence of free air. Free air is the only absolute indication for surgery, but other findings may suggest the need for surgical intervention. When intramural air in the bowel is absorbed into the mesenteric venous circulation, it may result in the phenomenon termed portal venous gas (PVG). Some have argued that the gas is actually in the hepatic lymphatics rather than the portal vein. PVG appears as thin, linear, air-dense areas overlying the liver. PVG with extensive pneumatosis is a poor prognostic sign, but PVG alone or with little pneumatosis is seen frequently among patients who eventually recover without surgical intervention.

Occasionally, patients who have NEC have radiographic evidence of a fixed or persistent dilated loop of bowel. In the original report of this finding, loops that remained unchanged for 24 to 36 hours were associated with transmural necrosis. Some reports have shown an association between fixed loops and pan-necrosis, although almost 50% of these patients recover without operation. NEC can present as a distended, gasless abdomen, and it can cause ascites. Increased intraperitoneal fluid can appear as a dense peripheral shadow surrounding gas-filled bowel loops in the center of the abdomen on plain radiographic studies. The finding of ascites with PVG has been associated with high mortality.

Some authors have used other modes of imaging to diagnose NEC and assist in the decision for surgical intervention. The use of ultrasonography, contrast radiography, and even magnetic resonance imaging has been reported anecdotally, but their utility has not been established. These studies never should delay otherwise indicated medical or surgical management.

Table 1. Modified Bell Staging Criteria for NEC*

Stage	Systemic Signs	Intestinal Signs	Radiographic Signs
I: Suspected NEC	Temperature instability, apnea, bradycardia	Elevated gastric residuals, mild abdominal distention, occult blood in stool	Normal or mild ileus
IIA: Mild NEC	Similar to Stage I	Prominent abdominal distention ± tenderness, absent bowel sounds, grossly bloody stools	Ileus, dilated bowel loops with focal pneumatosis
IIB: Moderate NEC	Mild acidosis and thrombocytopenia	Abdominal wall edema and tenderness ± palpable mass	Extensive pneumatosis, early ascites, ± PVG
IIIA: Advanced NEC	Respiratory and metabolic acidosis, mechanical ventilation, hypotension, oliguria, DIC	Worsening wall edema and erythema with induration	Prominent ascites, persistent bowel loop, no free air
IIIB: Advanced NEC	Vital sign and laboratory evidence of deterioration, shock	Evidence of perforation	Pneumoperitoneum

PVG=portal venous gas, DIC=disseminated intravascular coagulopathy
*Reprinted with permission from Kleigman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of disease. *Curr Probl Pediatr*. 1987;17:213.

NEC Staging

In 1973, Bell et al first attempted to categorize NEC by presentation and severity. These criteria were modified in 1978 to include therapeutic and prognostic aspects of the disease (Table 1). Although staging of NEC would appear to be helpful in determining appropriate treatment, each patient's condition supersedes category guidelines.

Differential Diagnosis

Sepsis with ileus, in both term and preterm patients, can mimic NEC. Both present with systemic signs of infection and abdominal distention. The absence of pneumatosis on plain radiographs argues against NEC, but does not rule it out. Fortunately, the treatment for both conditions is similar: bowel rest, antibiotic administration, and supportive care. In VLBW infants, inspissated meconium syndrome results in distended intestinal loops. However, these babies typically present with obstructive signs without evidence of sepsis. Isolated gastric perforation can result in pneumoperitoneum. Gastric perforation may be associated with administration of indomethacin or corticosteroids. Iatrogenic gastric perforation from feeding tubes occurs rarely. Although patients who have gastric perforation present with pneumoperitoneum, they are not as systemically ill as patients who have NEC. Patients who have Hirschsprung enterocolitis or severe gastroenteritis may present with pneumatosis.

Clinical Management

Medical Management

Most patients who have NEC are treated nonoperatively. The maxim of ABCs (airway, breathing, and circulation) holds in these infants. Most require some mechanical ventilatory support. If necessary, tracheal intubation is preferred to continuous positive airway pressure to prevent aerophagia and subsequent greater bowel distention. Peripheral arterial access should be established for accurate measurement of systemic blood pressure and arterial blood gases. Many patients will be hypovolemic and require fluid resuscitation and correction of acid-base imbalance. The acidemia in NEC is often mixed, with a respiratory component from hypoventilation as well as a metabolic contribution from hypoperfusion. Initially, isotonic crystalloid fluid (0.9% sodium chloride or lactated Ringer solution) is recommended, but colloid use may become necessary following capillary leak and subsequent hypoalbuminemia with third space fluid accumulation. If there is evidence of coagulopathy, administration of platelets, fresh-frozen plasma, or cryoprecipitate may be indicated. Sodium bicarbonate should be given in severe metabolic acidosis. Dopamine and epinephrine infusions may be necessary when hypoperfusion does not respond to fluid administration.

After obtaining blood cultures, broad-spectrum antimicrobial therapy appropriate to cover bowel flora should be initiated. Ampicillin and gentamicin are possible choices, but the common use of these antibiotics in the NICU typically results in the development of resistant organisms. Because NEC usually is acquired in the

NICU, antibiotic therapy may be guided by patterns of resistance in the individual unit. In addition, VLBW infants are at risk for bacteremia from coagulase-negative *Staphylococcus*. Accordingly, empiric treatment with vancomycin and a third-generation cephalosporin is appropriate. Because anaerobic flora can be acquired as early as 1 week of age, a third agent to cover these organisms may be warranted. The severity of the disease and the need for long-term coverage with broad-spectrum antibiotics places patients who have NEC at risk for fungal sepsis. Amphotericin, administered either empirically or following proven culture, may be necessary later in the course of treatment.

Discontinuation of enteral feeding and gastric decompression with a large-bore (10 or 12 French) orogastric tube should be facilitated. Although fraught with imprecision, serial measurements of the abdominal girth are warranted. More important is serial examination by the same examiner. Frequent abdominal radiographs are needed to monitor disease progression.

Antimicrobial therapy and bowel rest should be continued for 7 to 14 days, depending on the severity of the episode. At the end of this period, it is important to increase feedings gradually over many days. Some patients who appear to respond successfully to medical treatment will manifest increased gastric residuals, abdominal distention, and bilious emesis as enteral feeds are advanced. This scenario suggests the development of intestinal strictures. Strictures occur in areas of the intestine that suffered ischemia without full-thickness necrosis. These areas heal by scarring, and contraction of the scar leads to stricture. Strictures may occur anywhere in the intestine, but the most common site is at the junction of the descending and sigmoid colon. Radiographic studies reveal evidence of a partial bowel obstruction, with intestinal dilatation on the anteroposterior view and air-fluid levels on the dependent view. High suspicion of stricture warrants bowel rest until 6 weeks after the initial diagnosis of NEC to allow complete fibrous healing. A contrast enema should be performed at the completion of this period. If results of a lower gastrointestinal study are normal, an upper gastrointestinal contrast study is indicated. If a stricture is identified, it should be resected surgically.

Surgical Management

Even with aggressive and appropriate medical management, 34% to 50% of patients who have NEC require surgical intervention. The operation of choice in patients weighing greater than 1,500 g is laparotomy with resection of frankly necrotic bowel. In some cases, there is a well-defined segment of dead bowel, with the remainder of the intestine appearing normal. In others, disease may be patchy, involving multiple segments of the intestine, or large areas of intestine may be of questionable viability. The surgeon must resect all of the necrotic intestine yet avoid removing intestine that ultimately could prove viable. A portion of viable intestine is used to create an enterostomy and mucous fistula. Once evidence of bowel function returns, enteral feeds are introduced slowly. The period of time to bowel reanastomosis varies; 6 weeks is the minimal waiting period.

Primary resection and anastomosis of an isolated perforation has been reported anecdotally, but this procedure is not widely accepted. When multiple segments of bowel are affected, the surgeon traditionally is forced to create multiple stomas. An alternative technique is the so-called "patch, drain, and wait" approach. Each perforation is sutured closed, Penrose drains are placed in the lower abdominal quadrant, and parenteral nutrition is continued. For patients who have pan-necrosis with extensive involvement, the appropriate surgical management is unclear. Resection of affected bowel results in severe short bowel syndrome. Because of the poor outcomes seen in these patients, some surgeons support the practice of foregoing any treatment.

For patients weighing fewer than 1,500 g, the best operative management is not known. Historically, the surgical management of VLBW neonates who had perforated NEC was the same as that for larger babies: laparotomy, resection, and stoma creation. However, applying classic surgical techniques in these very small babies may increase mortality and morbidity. In 1977, Ein and colleagues reported the use of primary peritoneal drainage (PPD) for perforation in VLBW infants. PPD involved making a right lower quadrant incision, irrigating the peritoneal cavity, and placing a small Penrose drain in the abdomen. The authors treated five patients weighing 760 to 1,600 g who were described as septic and unstable. Surprisingly, three of these five "moribund" babies survived. One of the three developed an intestinal stricture that was repaired electively 6 weeks later. The two infants who did not survive died of causes unrelated to NEC, and their gastrointestinal tracts were intact at autopsy. The success of PPD in this anecdotal report was impressive compared with the 35% to 55% mortality associated with conventional surgical treatment, but the technique was widely criticized in the pediatric surgical community. This led to a comment from the authors that PPD should be used only as a temporizing procedure in the "sickest" preterm infants

Table 2. Type of Operation, Gestational Age (GA), Birthweight (BW), and Survival With Perforated NEC: Published Data*

	PPD				LAP			
Author	n	GA(wk)†	BW(g)†	Survival	n	GA(wk)†	BW(g)†	Survival
Cheu	51	29	1,158	18 (35%)	41	32	1,875	31 (76%)
Takamatsu	4	27	808	4 (100%)	—	—	—	—
Morgan	29	27	994	23 (79%)	20	32	1,854	18 (90%)
Azarow	44	28	1,100	27 (61%)	42	31	1,700	24 (57%)
Snyder	12	29	1,134	3 (25%)	91	31	1,628	52 (57%)
Lessin	9	25	615	6 (67%)	—	—	—	—
Ahmed	23	27	910	10 (43%)	22	35	2,271	19 (86%)
Rovin	18	28	1,118	16 (89%)	10	29	1,274	9 (90%)
Downard	24	26	794	19 (79%)	9	30	1,510	7 (78%)
Dimmitt	17	25	677	7 (41%)	9	26	807	5 (56%)
Total	231	27 (0.5)	931 (63.2)	133 (58%)	244	31 (0.9)	1,615 (155)	165 (68%)

PPD=primary peritoneal drainage, LAP=laparotomy, †Means (standard error of the means)
*Reprinted with permission from Moss RL, Dimmitt RA, Henry MC, et al. A meta-analysis of peritoneal drainage and laparotomy in perforated necrotizing enterocolitis. *J Pediatr Surg.* in press.

to stabilize the baby until formal laparotomy could be performed safely.

As experience with PPD increased, many babies treated with this "temporizing" procedure did not appear to need a subsequent laparotomy. The institution originating the procedure reported their updated experience in 1980, describing 15 patients who underwent PPD with the intention of proceeding to laparotomy in 24 to 48 hours. Forty percent of these patients improved so markedly that laparotomy was not performed, and they recovered completely without further intervention.

PPD has never been investigated in a controlled or comparative trial with laparotomy. In fact, every center using PPD reports selection bias in patient assignment. A recent review of the published experience for perforated NEC revealed that patients undergoing PPD were significantly smaller and more preterm than those undergoing laparotomy (Table 2). Using techniques of meta-analysis, these data were pooled. Because of the marked selection bias and the lack of published information explaining why patients were assigned to PPD versus laparotomy, the effectiveness of the two techniques could not be determined. The principle investigators from each institution employed PPD in patients who had a greater expected mortality. The fact that this "sicker" group of patients did better than predicted raises the question of whether PPD may be superior to laparotomy. To answer this question, a multicenter, randomized, controlled clinical trial is currently accruing patients. Results of this trial may determine the best treatment for this severe disease of preterm infants.

Long-term Outcome

In addition to post-NEC intestinal strictures, patients who undergo surgical intervention for NEC have a high probability of long-term adverse outcomes. The most common intestinal complication is short bowel syndrome (25%). In this condition, the amount of remaining intestine is not sufficient to provide adequate absorption of enteral nutrients and fluid. This syndrome occurs in up to 25% of patients postoperatively. Because the bowel is not functional, the patient is dependent on parenteral nutrition. The most serious sequela of prolonged parenteral nutrition is parenteral nutrition-associated cholestasis with resultant cirrhosis and liver failure. A study in 1986 reported cholestasis in 20 of 60 patients undergoing surgical intervention for NEC. Twelve of these 20 patients ultimately died from liver failure. Recurrent central venous catheter sepsis is also common. A few centers have reported anecdotal success with combined small bowel/liver transplantation, but the mortality rate of small infants undergoing this procedure remains unacceptably high.

As many as 50% of patients who survive NEC develop neurodevelopmental delay. Although NEC is not believed to be directly causative, any condition that results in prolonged hospitalization has been shown to place neonates at risk. In a matched cohort study, no difference in the Bailey Scales of Infant Development was seen among patients surviving severe NEC compared with patients who had similar hospital stays without NEC.

Summary

Despite tremendous advancements in neonatal and pediatric surgical management, the mortality and morbidity associated with NEC, especially in VLBW patients, remains great. Most patients present with specific gastrointestinal symptoms and nonspecific signs of sepsis. The most serious complication is intestinal perforation, requiring surgical intervention. The preferred operation for VLBW patients is currently being investigated in a randomized clinical trial.

Ultimately, the answer to improved outcomes for VLBW infants is prevention of NEC. This will require a better understanding of the developmental biology of the preterm intestine and the pathogenesis of the disease. As demonstrated in the accompanying paper by Caplan, these are active areas of current research.

Suggested Reading

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NeoReviews Quiz

5. The incidence of necrotizing enterocolitis (NEC) is higher among infants hospitalized in the neonatal intensive care unit (NICU) than among infants in the general population. Of the following, this increase in the incidence of NEC is *most* likely to be by a factor of:

   A. 2.
   B. 5.
   C. 10.
   D. 50.
   E. 100.

6. Infants who have NEC typically manifest gastrointestinal and other signs and symptoms. Of the following, the *most* common early manifestation of NEC is:

   A. Abdominal distension.
   B. Abdominal wall erythema.
   C. Diarrhea.
   D. Gastric residuals.
   E. Gastrointestinal bleeding.

7. Results of laboratory studies are often abnormal for infants who have NEC. Of the following, the *most* common laboratory finding in early NEC is:

   A. Coagulopathy.
   B. Glucose instability.
   C. Leukocytosis.
   D. Metabolic acidosis.
   E. Thrombocytopenia.

8. A 2-week-old infant, who weighted 750 g at birth, has recurrent apnea and bradycardia, unstable body temperature, and grossly bloody stools. His abdomen is distended and tender, and bowel sounds are absent. Abdominal radiography reveals dilated loops of bowel and focal pneumatosis intestinalis. This description of NEC is *most* consistent with Bell staging of:

   A. I.
   B. IIA.
   C. IIB.
   D. IIIA.
   E. IIIB.

9. Early diagnosis and treatment of NEC is associated with a favorable outcome. Of the following, the *most* accurate statement regarding the treatment of NEC in its early stages is that:

   A. Amphotericin B is the antimicrobial of choice because of prevalent fungal sepsis.
   B. Cryoprecipitate treatment for coagulopathy often is warranted.
   C. Dopamine infusion frequently is necessary for the treatment of poor perfusion.
   D. Endotracheal intubation is preferred to continuous positive airway pressure for ventilatory support.
   E. Most patients need exploratory laparotomy or primary peritoneal drainage.

10. Ischemic necrosis of the gut associated with NEC often results in gastrointestinal strictures at one or more sites. Of the following, the *most* common site for such a stricture is the junction between the:

    A. Ascending and transverse colon.
    B. Descending and sigmoid colon.
    C. Duodenum and jejunum.
    D. Ileum and cecum.
    E. Jejunum and ileum.

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