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Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in neonatal intensive care units (NICUs) around the world. Advances in perinatal and neonatal care have contributed to a growing population of premature infants at risk for NEC. It is now the most common newborn surgical emergency, with a mortality rate that far exceeds that of any other gastrointestinal (GI) condition requiring surgical intervention. Despite extensive research, the precise cause and pathogenesis remain elusive.

**HISTORY**

In 1888, Paltauf described five patients who died of overwhelming peritonitis, the cause being suggestive of NEC in three of them. Despite this report, many credit Generisch with publishing the first report of NEC in 1891, but on careful review of his description of the findings, it almost certainly was a case of meconium peritonitis rather than NEC.

In 1939, Thelander reported 16 cases of perforation of the stomach, 30 of the duodenum, and 39 of the small and large intestines. Many of the patients who had intestinal perforations probably had NEC. The first report of a successfully treated infant with a localized ileal perforation as a result of NEC is attributed to Agerty et al. in 1943. In 1953, Schmid and Quaiser first used the term necrotizing enterocolitis. In 1959, Rossier and colleagues described 15 infants, 14 of whom died of ulcerative-necrotic enterocolitis of the premature.

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low gestational age and birth weight being at particular risk. It is estimated that only 7% to 13% of all NEC cases occur in full-term infants.27,221,311 The advent of early surfactant therapy and improved methods of mechanical ventilation has resulted in significant improvement in the survival of low- and extremely low-birth-weight infants.51,113 As a result, an increasing population of tiny infants is now at risk for the development of NEC. In the future, NEC may surpass respiratory distress syndrome as the principal cause of death in premature infants.141

**EPIDEMIOLOGY AND PATHOGENESIS**

**Epidemiology**

**Age and Maturity**

NEC is predominantly a disease of premature low-birth-weight infants rather than those who are small for gestational age. Kliegman and Fanaroff142 reported that the mean gestational age of 123 patients with NEC was 31 weeks (average birth weight, 1460 g). Only 7.3% of the patients were full-term and 10.5% were small for gestational age. Infants with extremely low birth weight (<1000 g) and those 28 weeks’ gestational age or less are at greatest risk.115,254 In a large multicenter prospective study involving 4438 infants weighing between 501 and 1500 g, Lemons et al.174 demonstrated an inverse relationship between the incidence of NEC and birth weight. The incidence of NEC was highest in infants weighing between 501 and 750 g (14%) and declined with increasing weight: 751 to 1000 g (9%), 1001 to 1250 g (5%), 1251 to 1500 g (3%).

Tesdale et al.268 reported an inverse relationship between the age at onset of NEC and gestational age. Infants in whom NEC developed in the first week of life were more mature (average gestational age, 36.1 weeks) than those in whom NEC developed after 1 week of age (average gestational age, 33.4 weeks). Complications were more common and the mortality rate was higher in patients with early-onset disease. Ostlie et al.221 demonstrated a similar inverse relationship between gestational age and the onset of NEC. Full-term (≥38 weeks) infants had a significantly earlier onset of NEC (4.9 days) than did preterm (<38 weeks) infants (13 days). Similarly, Martinez-Tallo et al.187 also demonstrated an earlier onset of NEC (3.3 days) in infants with a birth weight greater than 2000 g.

Wilson et al.310 calculated the birth weight–specific, weekly attack rate in patients with NEC. The risk period for NEC decreased as birth weight increased. They found a consistent pattern of sharply declining risk with attainment of age equivalent to 35 to 36 weeks’ gestation. It was suggested that functional maturation of the GI tract may play a principal role in determining the risk for NEC. The preterm GI tract has decreased gastric acid production and lower levels of protective mucus,19,213 increased mucosal permeability,292 and an absence of normal coordinated peristaltic activity until around 34 to 35 weeks’ gestation.19,213

**Feedings**

NEC develops in approximately 90% of infants after being fed, whereas it develops in only 10% or less before feedings are initiated.144,147,157,185,281 In 1978, Brown and Sweet135 proposed that aggressive feeding protocols contributed to the pathogenesis of NEC. They found that before they changed to a slowly progressive feeding regimen in July 1974, 14 cases of NEC occurred in 1745 low-birth-weight infants. From July 1974 to June 1978, when a cautious approach to feeding was practiced, only 1 case developed in 932 low-birth-weight infants and 2557 total patients admitted to the NICU. In a longitudinal cohort study reviewing the incidence of NEC for a 3-year period before and after implementing a “standardized feeding schedule” for infants weighing between 1250 and 2500 g and less than 35 weeks’ gestation, Kamitsuka et al.152 reported an 84% reduction in the risk for NEC. Other studies have also suggested an association between an increase in the incidence of NEC and advancement of formula feedings at rates greater than 20 kcal/kg/day.5,9,165,291,313 Despite these reports, however, randomized trials have failed to demonstrate any difference in the incidence of NEC related to fast versus slow, early versus delayed, or continuous versus intermittent bolus feedings.136,137,258,245 In a randomized trial involving 185 VLBW infants in which slow (15-mL/kg/day increments; 10-day schedule to full feeding) and fast (35-mL/kg/day increments; 5-day schedule to full feeding) feeding advancements were compared, Rayyis et al.243 demonstrated no significant difference in the incidence of NEC (13% versus 9%), perforation (4% versus 2%), and mortality (2% versus 3%) in both groups. In a review of randomized trials comparing continuous versus intermittent bolus tube feeding for premature infants weighing less than 1500 g, Premji and Chessell238 could find no significant differences in the incidence of NEC between the two groups.

In a recent randomized trial investigating the incidence of NEC in VLBW infants assigned to receive either minimal-volume feeding (20 mL/kg/day) for 10 days before advancing to full-volume feeding or a standard feeding advancement protocol (starting at 20 mL/kg and increasing by 20 mL/kg/day to full-volume feeding), Berseth et al.21 reported a significantly lower incidence of NEC in the minimal-volume group than in the standard group (1.4% versus 10%). The difference in the risk for NEC was so great that the study was closed early. The prolonged use of “trophic feeding” volumes is thought to trigger maturation of GI function. This study reinforces previous studies that gut stimulation protocols are beneficial to VLBW infants71 and that initiation of a minimal-volume feeding protocol for 7 to 10 days followed by modest advancement of feeding may greatly reduce the incidence of NEC.258

**Hyperosmolar Formulas and Medications**

The osmolarity and composition of enteral feedings have also been associated with an increase in the incidence of NEC. Formulas with high osmolarity have been shown to increase the incidence of NEC in infants and
cause intestinal mucosal injury in animal models. De Lemos et al.65 demonstrated intestinal lesions resembling NEC in newborn goats that were fed a hyperosmolar formula. Book et al.29 prospectively studied 16 preterm infants fed either an elemental (650 mOsm/kg of body weight) or a milk (350 mOsm/kg) formula and found that NEC developed in 85% of the infants fed the elemental diet and 25% of the infants fed the milk formula. Grantmyre and associates96 described one patient in whom fatal NEC developed after a Renografin-76 (osmolality, 1900 mOsm/kg) enema was administered for the treatment of meconium ileus.

Many oral medications, such as vitamin preparations, use hyperosmolar vehicles that could potentially lead to mucosal injury in the bowel. Willis et al.309 reported a significantly higher incidence of NEC in infants fed undiluted calcium lactate (osmolality, 1700 mOsm/kg) than in infants fed no calcium or those fed calcium lactate diluted with water or formula. White and Harkavy306 reported that many oral medications commonly used in the intensive care nursery have very high osmolality, even when mixed with formula, and that it is usually the vehicle rather than the medication itself that is responsible for the high osmolality. Finer et al.82 reported a 13.4% incidence of NEC in preterm infants receiving an oral hyperosmolar vitamin E preparation as compared with a 5.7% incidence in infants who were given a parenteral preparation of vitamin E. The proposed mechanism of injury from the introduction of hyperosmolar solution into the GI tract, though not proved clinically, has been a reduction in intestinal mucosal blood flow secondary to rapid fluid shifts from the intravascular space into the bowel lumen.108,252,255 How relevant this mechanism of intestinal injury in the development of NEC is in the clinical setting is unknown.

**Pharmacologic Agents**

Xanthine derivatives (e.g., theophylline, aminophylline), which are known to slow intestinal motility and produce oxygen free radicals during their metabolism to uric acid, have been reported to be associated with NEC. In 1980, Williams307 and Robinson et al.248 described three patients in whom NEC developed after receiving oral and intravenous xanthines for apnea of prematurity. In animal experiments, Cronin et al.59 demonstrated alterations in GI blood flow and oxygen delivery after aminophylline administration in newborn lambs that may result in depletion of the GI oxygen reserve and mucosal injury. Despite these earlier reports, subsequent results in large patient studies have failed to confirm this association.63,112

Administration of large doses of vitamin E to premature infants has been linked to an increase in NEC.124 Vitamin E is given to reduce the incidence of adverse sequelae of retinopathy in premature infants and has been shown to interfere with intracellular killing of bacteria by leukocytes. The increased incidence of NEC, however, has been noted only after oral administration of hyperosmolar preparations and not after intramuscular administration.82

Indomethacin blocks prostaglandin synthetase and causes vasoconstriction. This effect has been exploited to close the patent ductus arteriosus (PDA) in premature infants with congestive heart failure. GI perforation and NEC have been noted in low-birth-weight infants treated with high-dose indomethacin.7,98,162 It has been postulated that indomethacin increases mesenteric vascular resistance and reduces mesenteric blood flow by 16% to 20%.99 Norton et al.215 demonstrated that the use of indomethacin as a tocolytic agent was associated with an increased incidence of NEC in babies delivered before 30 weeks’ gestational age (mean age at delivery, 27.6 weeks); however, indomethacin did not increase the incidence of NEC in babies born after 32 weeks’ gestation. In a retrospective study involving 252 premature infants with symptomatic PDA treated with intravenous indomethacin, Grosfeld et al.97 found a 35% incidence of NEC. In contrast, two randomized controlled trials involving more than 500 low-birth-weight premature infants receiving early low-dose indomethacin versus placebo for closure of PDA demonstrated no difference in the subsequent incidence of NEC.89,183 Indomethacin by itself may not be enough to cause NEC; however, in the setting of hypoxia, heart failure, or sepsis, its adverse GI effects contribute to the development of NEC in VLBW infants.156

**Cocaine**

Cocaine has very potent vasoconstrictive properties, and with the dramatic increase in its abuse since the 1980s, it has been implicated as a risk factor for NEC.235,260,286 In addition to its vasoconstrictive effects, cocaine has also been shown to block the reuptake of catecholamines at nerve terminals, thereby resulting in increased circulating levels of catecholamines in pregnant women.312 Prenatal cocaine exposure has been associated with many adverse perinatal events, including stillbirths, abruptio placentae, intrauterine growth retardation, preterm delivery, sudden infant death syndrome, and maternal hypertension.16,70,125 The proposed mechanism involves increased uterine vascular resistance, decreased uterine blood flow, and chronic placental insufficiency with accompanying fetal hypoxemia, hypertension, and tachycardia.37,110,202

Despite these concerns, there have been few studies investigating the vascular and inflammatory effects of cocaine on the neonatal GI tract. Studies in pregnant rats exposed to cocaine demonstrated severe inflammatory changes in the uterus, placenta, and GI tract of the embryos.37 Newborn piglets receiving high doses of cocaine had a prolonged increase in mesenteric vascular resistance and a decrease in mesenteric blood flow by Doppler evaluation.110 In a study using radiolabeling techniques in which pregnant and nonpregnant rats were compared, exposure to cocaine resulted in a significant dose-dependent decrease in perfusion of the uterus, placenta, and fetus in the pregnant group but no change in perfusion of the uterus in the nonpregnant animals.138

In retrospective studies involving infants with confirmed NEC, several differences have been reported between infants with and without prenatal exposure to cocaine. Czyrko et al.61 noted a significantly greater need for surgical intervention (72.7% versus 38%), higher incidence of massive intestinal gangrene (34% versus 12%), and higher mortality (54.5% versus 18%) in infants with prenatal...
cocaine exposure than in those without exposure. Case-controlled analysis matching for race, sex, and birth weight demonstrated a 2.5-fold increased risk for the development of NEC in the cocaine-exposed group versus the nonexposed group. Lopez et al.\textsuperscript{178} reported a 12\% incidence of NEC in infants exposed to cocaine as compared with 3\% in nonexposed babies. In addition, NEC developed in a significantly greater number of infants within the first 7 days of life in the cocaine-exposed group. In a retrospective cohort study of infants with a birth weight between 750 and 1500 g, Hand et al.\textsuperscript{106} compared 48 infants prenatally exposed to only cocaine with 101 infants who had no drug exposure. There was no significant difference in the incidence of NEC between the two groups.

Despite the well-known adverse effects of cocaine, it is difficult to establish a definite causal relationship with NEC. Mothers who abuse cocaine during pregnancy report an ill-defined duration and extent of use, may have used it at a remote time before delivery, and may not have had adequate prenatal care. In addition, maternal cocaine use may be associated with the use of other recreational drugs, alcohol, and tobacco, and thus these mothers are at higher risk for having a baby who is premature or small for gestational age, or both.

Cytokines and Growth Factors

Cytokines and growth factors play a critical role in mediating the proliferation, maturation, chemotaxis, and activation of hematopoietic and immune-related cells. It is recognized that cytokines and growth factors have important effects on a number of cells from various tissues, including those in the GI tract (Table 92-1). Intestinal cells are exposed to cytokines secreted by intestinal endothelial cells, by mucosal fibroblasts, and by enterocytes themselves.\textsuperscript{172,214,224,226,316} Epidermal growth factor (EGF) is known to be an important trophic factor for the developing GI tract. EGF receptors have been demonstrated throughout the fetal and neonatal intestine.\textsuperscript{50,57,129,184} EGF is secreted into the gut lumen primarily by the salivary glands and Brunner glands of the duodenum and has been shown to be present in high concentration in human breast milk.\textsuperscript{233,244} Significantly reduced levels of salivary and serum EGF have been demonstrated in premature infants in whom NEC developed versus age-matched controls.\textsuperscript{111,267} Inactivation of the EGF receptor in knockout mice has been shown to result in a hemorrhagic enteritis that is histologically similar to NEC.\textsuperscript{191} In studies using a neonatal rat model of NEC that involved exposure to asphyxia and cold stress, enterally administered supplements of EGF have been shown to significantly decrease the incidence and severity of NEC in rat pups,\textsuperscript{72} thus suggesting that this protective effect may be mediated by down-regulation of the proinflammatory cytokine interleukin-18 (IL-18) and increased production of the anti-inflammatory cytokine IL-10.\textsuperscript{103} Fagbemi et al.\textsuperscript{80} investigated the association of NEC with EGF receptors in the intestinal mucosa of preterm infants undergoing resection for severe NEC and confirmed the presence of intact EGF receptors located on the basolateral membrane of enterocytes.

Erythropoietin (Epo) is a growth factor produced by the kidneys that regulates red blood cell production in response to anemia. Since development of the recombinant protein, rEpo has become widely used in the NICU.\textsuperscript{127,218} Epo has been found in human breast milk, and functional Epo receptors have been demonstrated in fetal and neonatal small intestine, thus suggesting a possible role in GI development.\textsuperscript{128,130,149} In a retrospective study comparing 260 VLBW infants who received rEpo with 233 matched controls, Ledbetter and Juul\textsuperscript{171} demonstrated a significantly lower incidence of NEC in

### Table 92-1: Cytokines and Growth Factors with Important Effects in the Gastrointestinal Tract

| Cytokine | Hematopoietic Effects | Proinflammatory | Anti-inflammatory | Protective Effects in the Gut | Trophic Effects in Enterocytes |
|----------|-----------------------|----------------|------------------|-------------------------------|-------------------------------|
| EGF      |                       | No             | Yes              | Yes                           | Yes                           |
| Epo      |                      | No             | No               | No                            | Yes                           |
| IL-1     | Acute phase response  | Yes            | No               | Unknown                       | Yes                           |
| IL-2     | T-, B-, and NK-cell growth and activation | Yes | No | Yes | Unknown |
| IL-3     | Proliferation and differentiation of early heme cells | Yes | No | Unknown | Yes |
| IL-4     | T- and B-cell and macrophage regulation | Yes | Yes | Yes | Unknown |
| IL-10    | Decreases macrophage activation | No | Yes | Yes | Unknown |
| IL-11    | Increases megakaryocyte and macrophage production | No | Yes | Yes | Yes |
| IL-15    | T-, B., and NK-cell activation | Yes | Unknown | Unknown | Yes |
| NO       | Regulates platelet aggregation and adhesion, regulates leukocyte-endothelial interactions | Yes | Yes | Yes | No |

EGF, epidermal growth factor; Epo, erythropoietin; IL, interleukin; NK, natural killer; NO, nitric oxide.

Data modified from Ledbetter DJ, Juul SE: Necrotizing enterocolitis and hematopoietic cytokines. Clin Perinatol 2000;27:697.
the rEpo group (4.6%) than in the control group (10.8%). Studies in neonatal rats given rEpo enterally have demonstrated a dose-dependent increase in intestinal mucosal villus surface area and increased cellular proliferation, thus suggesting a role of rEpo as a trophic factor in the developing small intestine.\(^{128}\) In a neonatal rat model of NEC involving exposure to hypoxia and reoxygenation, pretreatment with intraperitoneal injections of rEpo resulted in significantly decreased mucosal inflammation and necrosis, which was thought to be mediated by decreased production of nitric oxide (NO).\(^{163}\)

Cytokines are endogenous mediators of the inflammatory cascade. Proinflammatory and anti-inflammatory cytokine production is tightly regulated by complex feedback mechanisms to maintain homeostasis.\(^{280,297}\) Overproduction of either may have significant untoward effects. Overproduction of proinflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, tumor necrosis factor-\(\alpha\) [TNF-\(\alpha\)], interferon-\(\gamma\), platelet-activating factor [PAF]) may lead to shock, multiorgan failure, and death.\(^{188,232}\) Overproduction of anti-inflammatory cytokines (IL-4, IL-10, IL-11) may result in excessive suppression of immune function.\(^{280,283}\) A number of different inflammatory mediators have been implicated in the pathogenesis of NEC.\(^{47,107}\)

In vitro studies comparing the response of mature human intestinal cell lines and fetal intestinal cell lines to inflammatory stimulation by TNF-\(\alpha\), IL-1\(\beta\), or lipopolysaccharide (LPS) demonstrated an exaggerated secretion of IL-8 by the fetal cells.\(^{56,210}\) Pretreatment of cells with Epo inhibited TNF-\(\alpha\)-induced IL-8 secretion to control levels. In a study evaluating serial serum levels of two proinflammatory cytokines (IL-1\(\beta\), IL-8) and two anti-inflammatory cytokines (IL-1 receptor antagonist [IL-ra], IL-10) in infants with NEC, Edelson et al.\(^{73}\) demonstrated significantly higher levels of IL-8 and IL-10 in infants with severe NEC from the onset of disease through 24 hours than in infants with less severe NEC. They noted that counter-regulatory mediators in premature infants are secreted in appropriate concentrations, are released later after the onset of disease, and may be useful as a marker of more severe disease. Nadler et al.\(^{289}\) investigated the pattern of cytokine expression in infants undergoing resection for severe NEC and infants undergoing intestinal resection for other inflammatory conditions. Significant up-regulation of IL-8 mRNA was seen in the specimens from infants with NEC as compared with controls. In addition, they noted significant up-regulation of IL-11 mRNA in infants with NEC and found an inverse correlation between IL-11 expression and the likelihood of pan-necrosis, thus suggesting that IL-11 secretion may be an adaptive response to limit the extent of intestinal damage. Several of the interleukins (IL-4, IL-10, IL-11) have been shown to have a protective or trophic role in the GI tract. IL-4 has been demonstrated to possess cytoprotective effects in human intestinal epithelial cells by reducing bacterial translocation, increasing leukocyte superoxide production, and inducing decay-accelerating factor, which protects the host from the attack of autologous complement activation.\(^{10,208}\) IL-10 is known to be a potent anti-inflammatory cytokine that inhibits the production of proinflammatory cytokines.\(^{108}\) In a neonatal rat hypoxia-reoxygenation model of NEC, recombinant IL-10 administered subcutaneously was found to significantly attenuate the extent of intestinal injury when compared with control animals, thus suggesting a protective effect of its anti-inflammatory properties.\(^{222}\) IL-11 has been shown to be a pleiotropic cytokine that promotes epithelial regeneration and enhances adaptation after bowel resection.\(^{177}\) Subcutaneous administration of recombinant IL-11 in rats undergoing placement of a defunctionalized (Thiry-Vella) loop of intestine or massive small bowel resection has resulted in prevention of mucosal atrophy in the defunctionalized loop and enhanced mucosal adaptation and absorptive function in the remaining intestine after resection.\(^{6,58}\)

A tremendous amount of investigation has been performed to define the role of NO in the pathogenesis of a number of different inflammatory processes. There is evidence to support a possible dichotomous function of NO as both a beneficial and a detrimental molecule, especially with regard to the GI tract.\(^{159,161}\) NO is produced from arginine by three isoforms of nitric oxide synthase (NOS). NOS-1 (neuronal, nNOS) and NOS-3 (endothelial, eNOS) are constitutively present at low levels in the small intestine. NOS-2 (inducible, iNOS) is a form that can be induced in response to inflammatory cytokines.\(^{5,211}\) The constitutive forms of NOS and constitutive levels of NO have been demonstrated to modulate a number of important functions in the GI tract, including maintenance of mucosal integrity, regulation of mucosal permeability and blood flow, regulation of motility, and inhibition of leukocyte adhesion and activation.\(^{6,18,90,198,279}\)

Inhibition of NO synthesis in a variety of animal models of intestinal injury induced by ischemia-reperfusion, LPS, or PAF has resulted in marked exacerbation of mucosal injury.\(^{41,117,158,181,193,239}\) Administration of exogenous sources of NO, including L-arginine, sodium nitroprusside, and nitroglycerin, greatly attenuates these detrimental effects.\(^{3,69,95,228}\) In a prospective study of 53 premature infants, Zamora et al.\(^{217}\) demonstrated a significantly lower plasma arginine level at the time of diagnosis in infants in whom NEC developed than in controls. In a randomized prospective placebo-controlled study of VLBW infants assigned to receive either daily oral or parenteral L-arginine supplements (261 mg/kg) or placebo for the first 28 days of life, Amin et al.\(^{8}\) found a significantly lower incidence of NEC in the supplement group (6.7%) than in the control group (27.3%). Throughout the study, the group that received arginine supplementation had significantly higher mean plasma arginine levels than the control group did. Interestingly, in both groups the infants in whom NEC developed had significantly lower plasma arginine levels at the time of diagnosis than their respective peers did. It is not known whether the decreased arginine levels represent increased utilization for NO production, consumption for the synthesis of other proteins, or decreased enteral absorption. This study suggests the possible benefits of arginine supplementation and potentially other NO donors in the prevention of NEC.

The inducible form of NO synthase (NOS-2, iNOS) is known to be up-regulated in response to inflammatory cytokines. Within several hours of stimulation, NOS-2...
expression and activity within the intestinal epithelium increase up to 15-fold and result in the production of large amounts of NO. Although the low levels of NO produced by the constitutive isozymes of NOS may play a homeostatic role in the GI tract, sustained release of NO as a result of up-regulation of NOS-2 has been suggested to have deleterious effects by inducing cellular injury and failure of the mucosal barrier. This is thought to occur by the reaction of excess NO with superoxide (O$_2^-$) to produce peroxynitrite (ONOO$^-$), which is a potent reactive nitrogen intermediate that may trigger cytotoxic processes, including lipid peroxidation and DNA damage. In a prospective study investigating NOS-2 expression in the intestine of infants undergoing resection for NEC, Ford et al. demonstrated marked up-regulation of NOS-2 gene expression in the intestinal epithelium and increased apoptosis of enterocytes in the apical villi. In addition, increased levels of nitrotyrosine residues were detected in the apical villi, thus suggesting that the mucosal injury and increased apoptosis were mediated through the formation of NO and peroxynitrite. In a neonatal rat hypoxia model of NEC, Caplan et al. have shown that the mucosal injury and increased apoptosis were mediated through the formation of NO and peroxynitrite. In a neonatal rat hypoxia model of NEC, Nadler et al. demonstrated a significantly higher incidence of NEC, NOS-2 expression, and enterocyte apoptosis and decreased IL-12 mRNA in the formula-fed group than in the breast milk-fed group. The decreased IL-12 expression is thought to be mediated by NO and theorized to contribute to intestinal injury by attenuating bacterial clearance.

PAF, an endogenous phospholipid inflammatory mediator, has been shown to play an important role in the pathophysiology of intestinal injury in animal and human studies. PAF has diverse biologic effects, including mesenteric vasoconstriction, capillary leakage, increased intestinal mucosal permeability, and neutrophil and platelet activation. Clinically, increased PAF levels have been demonstrated in formula-fed premature infants, as well as those in whom NEC developed. In a neonatal rat model of NEC, Caplan et al. have shown that intestinal PAF concentrations, intestinal phospholipase A2 (PAF-synthesizing enzyme) mRNA expression, and intestinal PAF receptor mRNA expression are elevated. In other animal experiments, exogenous PAF administration results in severe bowel necrosis; endogenous intestinal production of PAF is up-regulated in response to various stimuli, including LPS, hypoxia, and TNF-α. PAF acetylhydrolase (PAF-degrading enzyme), reduces the risk for NEC. In human studies, PAF acetylhydrolase activity has been demonstrated to be present in human breast milk; it has been shown to be decreased in neonates, with levels approaching adult enzyme activity at around 6 weeks of life, and has been found to be deficient in infants with NEC. In a prospective study of 164 infants at risk for NEC, Rabinowitz et al. monitored serial plasma levels of PAF and PAF-related lipids (PAF-LL) to investigate the changes that occur with NEC. There was a significantly higher peak in PAF-LL levels in infants in whom NEC developed than in controls. In addition, rising PAF-LL levels were positively correlated with progression of the severity of NEC; these levels returned to baseline levels during recovery.

TNF-α has many proinflammatory effects, including neutrophil activation, induction of leukocyte and endothelial adhesion molecules, and induction of other cytokines, such as PAF. TNF-α has been demonstrated to produce profound hypotension and severe intestinal necrosis similar to NEC in animals. This effect has been shown to be mediated by PAF and attenuated by PAF receptor antagonists.

LPS (endotoxin) is a bacterial product that has the capacity to produce potent inflammatory responses through the induction of various proinflammatory cytokines such as PAF and TNF. Systemic injection of LPS has been shown to produce hypotension, shock, and severe intestinal necrosis. It has been used in animal models of NEC to reliably generate intestinal injury that resembles NEC. LPS-induced intestinal injury has been demonstrated to be mediated by PAF and TNF-α and can be prevented with PAF antagonists.

Cyclooxygenase (COX) catalyzes the rate-limiting step of arachidonic acid metabolism into prostanoids, leukotrienes, and thromboxanes. Two isoforms of the COX enzyme have been identified. COX-1 is constitutively expressed in many tissues, including the GI tract. COX-2 is the inducible form that is expressed in inflammatory conditions of the GI tract such as inflammatory bowel disease. Proinflammatory cytokines (IL-1, IL-6, TNF-α), as well as the proinflammatory transcription factor nuclear factor-κB (NF-κB), have been shown to increase COX-2 expression. NF-κB is an important protein in the activation of a number of inflammatory mediators and cytokines. A marked increase in COX-2 expression has been demonstrated in intestine resected from infants with severe NEC. To elucidate the mechanisms involved in COX-2 expression in NEC, Chung et al. demonstrated a coordinated induction of NF-κB activation and COX-2 expression during the early phase of the injurious event.

Pathogenesis

Despite many years of extensive investigation and identification of several risk factors, the pathogenesis of NEC remains elusive. The etiology is probably multifactorial and involves some combination of mucosal compromise, pathogenic bacteria, and feedings that in a susceptible host result in bowel injury and an inflammatory cascade. Of the risk factors, prematurity is the most consistent and important. Another important risk factor involves enteral feeding of formula. Commercially available formulas lack many of the beneficial properties present in breast milk. These protective agents include gut trophic hormones, factors that induce intestinal maturation, factors that enhance colonization by nonvirulent bacteria, anti-inflammatory mediators, vitamins and other antioxidants, and components that provide cellular and humoral immunity.

Evidence for an Impaired Gut Barrier

The preterm GI tract is characterized by an immaturity of cellular and humoral immunity, increased...
permeability, reduced gastric acid secretion, reduced concentration of proteolytic enzymes, incomplete innervation and decreased motility, and immaturity of the intestinal epithelium and microvilli. Decreased barrier function is evident in otherwise healthy preterm infants by their ability to systemically absorb and deliver undigested macromolecules, whole bacteria, and LPS. Compromise of the intestinal epithelial mucosal barrier appears to be the first event leading to activation of the inflammatory cascade.

Reduced mucosal blood flow leading to cellular hypoxia and injury is one of the most frequently cited etiologic factors for NEC. Touloukian emphasized the high incidence of perinatal physiologic stressors that may primarily or secondarily cause intestinal ischemia. Chief among these factors are hypoxic and hypotensive episodes, exchange transfusions through the umbilical vein, umbilical artery catheters, cardiovascular lesions, and serum hyperviscosity. An atavistic “diving reflex” in which blood is preferentially diverted away from the splanchnic circulation in order to maintain adequate perfusion of the heart and brain has been hypothesized to occur during these episodes. During periods of low blood flow and subsequent reperfusion, Parks et al. found that a reaction between xanthine oxidase, hypoxanthine, and molecular oxygen results in a burst of superoxide radical production. These free radicals may cause damage to cellular and mitochondrial membranes and alter the permeability of the intestinal mucosal barrier. Although animal studies provide support for this theory, clinical correlation has been lacking, and prospective clinical trials have not been able to consistently establish an association between a hypoxic event and the development of NEC.

Extensive investigation into the critical role of various inflammatory mediators in the pathogenesis of NEC has been conducted. Studies in animal models and human specimens have identified PAF, LPS, NO, and TNF-α as potential mediators of the disease. The effects of LPS and TNF-α have been shown to be mediated by PAF. Increased mucosal permeability and susceptibility allowing translocation of bacteria or bacterial toxin and activation of the inflammatory cascade are thought to be the critical steps leading to the final collapse of intestinal epithelial integrity.

Very little is known about the early chain of events that occur at the onset of tissue damage. Recent studies have suggested that the disruption in the intestinal mucosal barrier results from accelerated apoptosis. All of the key mediators identified in NEC (PAF, NO, LPS, TNF-α) have been shown to cause apoptosis of intestinal epithelial cells. In a neonatal rat model of NEC involving formula-fed animals exposed to hypoxia and cold stress and mother-fed controls, Jilling et al. demonstrated a marked increase in apoptosis in the epithelial layer of the NEC group in comparison to controls, although the mechanism was undetermined. The accelerated apoptosis was shown to precede gross morphologic changes in the intestinal epithelium. Administration of a pan-caspase inhibitor to inhibit intestinal apoptosis resulted in a significantly reduced rate of epithelial apoptosis, as well as a decreased incidence of NEC, thus suggesting that apoptosis was the underlying cause of the subsequent mucosal damage ultimately leading to NEC.

Sustained overproduction of NO because of up-regulation of NOS-2 in the GI tract in response to an inflammatory stimulus has been suggested to induce cellular injury and disruption of the intestinal epithelial barrier by production of the potent oxidant peroxynitrite. Ford et al. demonstrated up-regulation of NOS-2 and NO in the intestinal wall of infants with NEC and increased apoptosis of enterocytes mediated by the peroxynitrite. This accelerated apoptosis is thought to result in a “bare area” at the villus tip representing a break in the intestinal mucosal barrier where bacteria may attach, translocate, and initiate an inflammatory cascade. In addition, peroxynitrite has also been shown to inhibit the proliferation of intestinal epithelial cells in rat models of NEC. The data suggest that in conditions associated with sustained overproduction of NO or peroxynitrite (e.g., NEC), intestinal epithelial barrier dysfunction may result from an imbalance caused by accelerated epithelial injury and blunted tissue repair mechanisms.

Role of Infectious Agents

The type of feeding and pattern of intestinal colonization may determine the risk for development of NEC. Breastfeeding infants become colonized predominantly with bifidobacteria (gram-positive bacteria), which help control the growth of gram-negative bacteria. In contrast, formula-fed infants become colonized predominantly by coliforms, enterococci, and Bacteroides species.

The importance of bacteria in the pathogenesis of NEC is supported by the following evidence: (1) NEC occurs in episodic, epidemic waves, affected patients were related in place and time or had the same infectious agent, and the initiation of infection control measures has been shown to stop epidemics; (2) during clustered occurrences, the identical microorganisms can be isolated from both afflicted babies and their caretakers; (3) NEC can occur in infants with no known risk factors; (4) NEC can develop several weeks or months after a perinatal insult, when the GI tract is fully colonized and has had sufficient time to recover from any perinatal insult; (5) administration of large doses of vitamin E (interferes with intracellular killing of bacteria by leukocytes) to premature infants has been linked with an increase in the incidence of NEC; (6) an NEC-like disease occurs in vulnerable hosts after the ingestion of Clostridium species; (7) lesions resembling NEC can be reproduced experimentally with the administration of LPS; (8) endotoxia is demonstrated in 80% of those with NEC and positive blood cultures for gram-negative bacteria; and (9) pneumatosis intestinalis is a common radiographic finding and represents submucosal gas collections produced by bacterial fermentation.

UNIFYING HYPOTHESIS FOR NECROTIZING ENTEROCOLITIS

The following common clinical scenario supports a unified hypothesis for the pathogenesis of NEC. A premature infant is admitted to the NICU, usually for treatment of...
respiratory distress, and is exposed to the potentially pathogenic nosocomial flora. The infant may experience intermittent episodes of apnea and bradycardia. The broad-spectrum antibiotics that are routinely administered eliminate the infant’s anaerobic flora, which normally functions as a barrier to colonization and overgrowth of potentially pathogenic gram-negative organisms. Instead of breast milk, formula feedings are usually administered. Formula provides substrate for bacterial growth and contains none of the protective factors present in breast milk. Poor peristalsis of the GI tract permits overgrowth by pathogenic bacteria. Depending on the quantity and virulence of the microorganisms and the presence or absence of mucosal damage, bacteria may breach the mucosal barrier. Because of deficiencies in both specific and nonspecific immune defenses, bacterial killing is ineffective. Either through episodes of decreased perfusion and reperfusion or through mild infection, the mucosal barrier is damaged. Proinflammatory cytokines are induced and result in initiation of the inflammatory cascade. This cascade leads to increased mucosal permeability, which in turn causes further damage to the mucosa and bowel wall. More bacteria and bacterial by-products invade through the mucosal breaks, and progressive bowel damage results in full-thickness necrosis and perforation.

PATHOLOGY

NEC may involve single (50%) or multiple (discontinuous) segments of intestine, most commonly in the terminal ileum, followed by the colon. Involvement of both the large and small intestine occurs in 44% of cases. Pan-involvement (pan-necrosis, NEC totalis) is a fulminant form of NEC characterized by necrosis of at least 75% of the gut, and it accounts for 19% of all cases of surgically treated NEC and most of the deaths.

At surgery, the gross appearance of NEC is fairly constant. The bowel is markedly distended with patchy areas of thinning. The serosal surfaces are typically red to gray and may be covered by a fibrinous exudate. With frank gangrene, the serosal surface is black. Suberosal gas collections are frequently encountered. The mucosal surface may be ulcerated with wide areas of epithelial sloughing. Bloody peritoneal fluid is seen when bowel necrosis is present, and brown and turbid fluid is seen when perforation has occurred.

Bowel inflammation is nearly ubiquitous in NEC (Fig. 92–1A). The degree and nature, however, vary from one area to another. Acute and chronic inflammatory changes coexist in 60% of cases. The most common microscopic lesion is bland or coagulation necrosis of the superficial mucosa (89%). Edema and hemorrhage of the submucosa follow complete mucosal necrosis (Fig. 92–1B). Pneumatosis intestinalis is initially seen in the submucosa and later in the muscularis and subserosa. Bacteria in the bowel lumen and wall are present in up to 40% of cases and are occasionally found in gas cysts. Transmural necrosis, characterized by hyaline eosinophilia and loss of nuclear detail in the muscular layers, is present in advanced disease. Epithelial regeneration, formation of granulation tissue, and early fibrosis are often present.

This suggests a suppurative process lasting at least a few days. Granulation tissue with mucosal and submucosal fibrosis may be seen adjacent to areas of active mucosal and submucosal necrosis and may account, in part, for late stricture formation. Thrombi are sometimes noted in small mesenteric vessels and in small arterioles of the submucosa. Small-vessel thrombosis within necrotic tissue is considered a secondary change. Large-vessel thrombosis is a relatively rare finding at autopsy.

DIAGNOSIS

Clinical Features

NEC is commonly heralded by nonspecific clinical findings that simply represent physiologic instability.
These findings include lethargy, temperature instability, recurrent apnea, bradycardia, hypoglycemia, and shock. More specific symptoms related to the GI tract include abdominal distention (70% to 98%), blood per rectum (79% to 86%), high gastric residuals after feeding (>70%), vomiting (>70%), and diarrhea (4% to 26%). Gross blood in the stool is present in 25% to 63% of cases and occult blood in 22% to 59%. Rectal bleeding is seldom massive.

Because the spectrum of disease severity varies, physical examination may initially demonstrate only subtle abdominal distention and minimal tenderness. As the disease progresses, abdominal palpation may elicit tenderness and demonstrate palpable bowel loops, a fixed or mobile mass, or abdominal wall crepitus. Edema and erythema of the abdominal wall as a result of the underlying peritonitis are present initially in approximately 4% of cases, but are more common later in the course of the disease. In males, there may be discoloration of the scrotum, indicative of perforation. In a small subset of patients, the disease is rapidly progressive and the initial manifestation is heralded by florid clinical findings and death within 24 hours.

**Laboratory Findings**

Infants with NEC usually have neutropenia, thrombocytopenia, and metabolic acidosis. The total leukocyte count may be elevated, but it is generally low. In one study, 37% of infants had absolute neutrophil counts less than 1500 cells/mm³. The infants with the lowest counts in this study had the worst prognosis. Neutrophil counts less than 6000 cells/mm³ are most commonly associated with concomitant gram-negative sepsis.

Thrombocytopenia is nearly universally present and seems to be associated with gram-negative sepsis and platelet binding by endotoxin. The incidence of thrombocytopenia in NEC is 65% to 90%, essentially unchanged from the earliest reports from the 1970s. O'Neill demonstrated that in a cohort of 40 infants who underwent surgery for NEC, 95% had platelet counts less than 150,000 cells/mm³. Rowe et al. found that platelet counts less than 150,000 cells/mm³ were present in patients who had positive cultures for gram-negative organisms. The nadir platelet count during the course of the disease was noted to be lower in patients with more severe disease and in those who died.

Metabolic acidosis is very common (40% to 85% of patients with NEC) and is believed to result from hypovolemia and sepsis. It is not a specific indicator of intestinal necrosis. Stool samples are commonly positive for occult blood and reducing substances. Book et al. reasoned that intestinal mucosal damage from NEC leads to carbohydrate malabsorption. Poorly digested carbohydrates pass into the colon where they are fermented and excreted in stool. The authors tested the stool of formula-fed infants for reducing substances with Clinitest tablets and found that 71% of formula-fed infants in whom NEC developed had greater than 2+ reducing substances in their stool. Colonic bacterial fermentation increases the local production of d-lactate, which is absorbed and excreted by the kidneys. Garcia et al. could show elevated urinary d-lactate levels in infants with NEC but not in control infants. With recovery from NEC or administration of enteral antibiotics, d-lactate excretion decreased. Similarly, hydrogen excretion in the breath is elevated when fermentation is increased. This test is helpful in ruling out NEC. A negative result on a breath hydrogen test is 99% accurate in ruling out NEC.

C-reactive protein (CRP), an acute phase reactant, has been measured in an attempt to correlate its level with the presence, absence, or resolution of the disease. CRP may serve as an early indicator of NEC when its level rises more than 10 mg/L within 48 hours of the suspected diagnosis (reported sensitivity, 92%; specificity, 81%). Failure of CRP to return to normal within 10 days was an indicator of abscess, stricture, or sepsis.

**MICROBIOLOGY**

It has proved extremely difficult to identify common offending infectious agents. Organisms recovered from the blood and stool of patients with NEC vary depending on the GI tract flora, the nosocomial flora, the site cultured, and the duration of previous antibiotic therapy. It is unclear whether the bacteria cultured represent pathogens causing NEC or, instead, secondary opportunistic invaders selected by the antibiotic regimen. Furthermore, lack of sufficiently matched controls and complete bacteriology data on other patients in similar environments makes study of the microbiology of NEC difficult.

**Bacteriology**

Bacteriologic data for NEC have primarily been based on cultures obtained from the blood, stool, and peritoneal cavity. Blood cultures are positive in 30% to 35% of patients. Cultures commonly grow Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus aureus, Staphylococcus epidermidis, enterococci, Clostridium perfringens, and Pseudomonas aeruginosa. K. pneumoniae and E. coli cause the majority of positive blood cultures. The organisms most frequently cultured from stool specimens are E. coli, K. pneumoniae, Enterococcus cloacae, P. aeruginosa, Salmonella species, coagulase-negative staphylococci (S. epidermidis), C. perfringens, Clostridium difficile, and Clostridium butyricum. Peritoneal cultures most commonly grow Klebsiella species, E. coli, coagulase-negative staphylococci, Enterobacter species, and yeast.

**Fungal Cultures**

In contrast to bacteria, no data implicate a fungus as an initiating organism in the pathogenesis of NEC. Fungi are believed to be secondary invaders. In 1991, the National Institute of Child Health and Human Development Neonatal Research Network study of NEC reported that 5% to 17% of blood cultures were positive for fungus.
In 1993, Karlowicz reported an increase in fungal peritonitis from 7% in 1980 to 1989 to 35% in 1989 to 1991 at the same institution. Fungal septicemia with Candida species has been implicated in many late NEC deaths. Colonization was found in 20%; the first positive culture was obtained a mean of 22 ± 8.9 days after surgery. Eight patients (27%) had fungal sepsis: seven with Candida species and one with Torulopsis species. The first positive fungal culture was obtained 16.5 ± 7.0 days after surgery. Fungal sepsis was diagnosed before death in only four of the eight patients.

**Bacterial Toxins**

Mucosal injury may be mediated by toxin in some cases of NEC. Toxins produced by C. difficile, C. butyricum, and E. coli have been isolated from stool samples during epidemics. Studies by Scheifele et al. have demonstrated that a delta toxin is elaborated from coagulase-negative staphylococci and is present in the stool of 56% of coagulase-negative staphylococcal cases of NEC. This toxin is rarely found in patients colonized with coagulase-negative staphylococci without NEC.

**Clustered Epidemics**

In most large series, sporadic cases have been followed by the sudden appearance of a cluster of a relatively large number of cases. In many of the epidemics, no specific pathogen has been identified. Book et al., as part of an ongoing nosocomial infection surveillance program, prospectively studied 74 infants in whom NEC developed between 1972 and 1977. Six temporally and geographically related clusters of cases of NEC occurred, and no specific organisms were isolated. During these episodes, nursery personnel experienced concomitant acute GI illnesses. Implementation of infection control measures was associated with a significant decrease in the rate of NEC. Similar epidemics without specific pathogens were noted at Rainbow Babies and Children’s Hospital in 1972, 1973, 1974, 1975, and 1978. At the Children’s Hospital of Philadelphia, 11 sporadic cases of NEC occurred, but no pathogen was identified in the stools of infants in the nursery. Van Acker et al. reported an outbreak of NEC in 12 infants over a 2-month period associated with Enterobacter sakazakii. This pathogen was found to be a contaminant of the powdered milk formula that was used in the NICU. Other epidemic outbreaks have identified E. coli, Salmonella species, C. difficile, rotavirus, and a coronavirus-like organism.

**IMAGING**

Plain abdominal radiograph demonstrating extensive pneumatosis intestinalis (cystic and linear) and an arborizing pattern of air over the liver shadow representing gas dispersed within the radicles of the portal venous system.

Figure 92–2

**Figure 92–2**

**Bowel Distention**

Multiple gas-filled loops of intestine are the earliest and most common radiologic finding in patients with NEC (55% to 100% of cases). As fluid and air accumulate, air-fluid levels are visible on the decubitus view. The degree of dilatation and the distribution of bowel loops are related to the clinical severity and progression of the disease. In some cases, nonspecific intestinal dilatation precedes clinical symptoms suggestive of NEC by several hours.

**Pneumatosis Intestinalis**

Demonstration of pneumatosis intestinalis (intramural gas) in the appropriate clinical setting is diagnostic of NEC. The air mainly comprises hydrogen, a by-product of bacterial metabolism. The frequency of pneumatosis intestinalis ranges from 19% to 98%, although it may be absent in up to 14% of patients with NEC (even severe disease). Conversely, extensive pneumatosis may be present with minimal signs; it often responds promptly to medical management.
than a late finding. It is most frequently noted when infants have been fed (84%), in contrast to unfed babies (14%). Pneumatosis intestinalis is not specific for NEC and has been noted in infants with enterocolitis of Hirschsprung’s disease, inspissated milk syndrome, pyloric stenosis, severe diarrhea, carbohydrate intolerance, and other disorders.

Two forms of pneumatosis intestinalis are recognized radiographically: cystic and linear. The cystic form has a granular or foamy appearance and represents gas in the submucosa. It is often confused with fecal material in the large intestine. Linear pneumatosis consists of small bubbles collected within the muscularis and subserosa to form a thin linear or curvilinear gas pattern outlining the wall of a segment of the intestine.

**Portal Vein Gas**

Portal vein gas appears as linear branching radiolucencies overlying the liver and often extending to its periphery. It represents gas dispersed through the fine radicles of the portal venous system. The presence of portal vein gas is fleeting, which perhaps accounts for the low reported incidence of 10% to 30%. In most series, the presence of portal vein gas is associated with a poor prognosis. In cases with pan-involvement, the gas is present in 61% of patients. The genesis of portal vein gas may involve accumulation of gas in the bowel wall as a result of bacterial invasion, dissection into the venous system, and migration to the radicles of the portal vein. Alternatively, it may represent the action of gas-forming bacteria within the portal venous system.

**Pneumoperitoneum**

Free air in the peritoneal cavity associated with perforation of the intestine can be demonstrated in 12% to 30% of patients. It is best noted on the left lateral decubitus or cross-table lateral view. Upright radiography is unnecessary. A supine view of the abdomen can demonstrate free air by outlining the falciform ligament (“football sign”), the umbilical artery, or urachal remnants or by revealing the “double wall” sign. This sign refers to visualization of air on both sides of the wall (lumen and peritoneal cavity). In patients who have intestinal perforation proved by surgery, radiographic evidence shows free air in only 63%, thus demonstrating that perforation can occur in a surprisingly high number of patients without evidence of free air.

One must keep in mind that pneumoperitoneum may occur without intestinal perforation from mechanical ventilation for severe lung disease. In this clinical situation, barotrauma may produce alveolar rupture with air dissection into the abdomen through the mediastinum. The patient’s signs, symptoms, and laboratory findings will often differentiate the cause of the air. If one is unsure, abdominal paracentesis may be performed and any aspirated fluid analyzed. If there is no ascites, a water-soluble contrast study via the gastric tube may be performed to rule out gastric perforation.

**Intraperitoneal Fluid**

Several plain radiographic findings suggest free fluid in the peritoneal cavity that is amenable to paracentesis: (1) a grossly distended abdomen devoid of gas, (2) gas-filled loops of bowel in the center of the abdomen surrounded by opacity out to the flanks, (3) increased haziness within the abdomen, and (4) separation of bowel loops. These findings have been reported in 11% of cases. Both ascites and portal vein gas are radiographic findings associated with high mortality rates. Twenty-one percent of patients with surgically proven intestinal perforation have ascites. However, 16% of all patients with proven intestinal perforation have neither ascites nor free air on plain radiographs.

**Persistent Dilated Loops**

The “persistent dilated loop sign” is a plain radiographic finding that was described by Wexler in a study of five babies with NEC in whom a single loop or several loops of dilated bowel remained unchanged in position and configuration for 24 to 36 hours. Full-thickness necrosis subsequently developed in these patients. This finding, however, does not always indicate bowel necrosis. Leonard et al. found a persistent loop in 33% of 21 patients with proven NEC. Fifty-seven percent of infants with a persistent loop had necrotic intestine at surgery or autopsy, but necrosis never developed in 43% and they recovered with nonoperative treatment.

**Contrast Studies**

Radiopaque contrast studies of the upper GI tract may occasionally be useful to improve diagnostic accuracy in patients with equivocal clinical and radiologic signs of NEC. However, overdiagnosis by contrast radiography is possible and may lead to unwarranted treatment. Careful attention to the type of contrast agent used for the study is critical. Barium should never be used because extravasation of a barium and stool mixture through a perforation may intensify the peritonitis. Unlike barium, water-soluble contrast agents are absorbed by both the bowel and the peritoneal cavity. The practical implication of this absorption is a transient (6 to 12 hours) increase in urinary specific gravity. Historically, water-soluble agents were hyperosmolar and caused dangerously large intraluminal fluid shifts, especially in premature patients. Current water-soluble agents are nonionic, have much lower osmolarity, and produce excellent opacification of the GI tract. NEC is suspected when intestinal contrast enhancement demonstrates bowel wall loops separated by edematous walls, an irregular mucosa with ill-defined margins, mucosal ulceration, bowel wall spiculation, or pneumatosis intestinalis. The examination may be performed at the bedside.

Though advocated by some, contrast enemas should not be performed because of the risk for rectosigmoid perforation. Unless there is colonic disease or reflux of
contrast into a diseased distal ileum, the contrast enema will not be diagnostic of NEC. It may, in fact, overdiagnose NEC because contrast enemas have been shown to produce pneumatosis and transient portal venous air. Unlike the bedside upper GI series, contrast enema must be performed with simultaneous fluoroscopy, which necessitates transfer of the critically ill neonate to the radiology suite. In an infant who has recently completed a course of therapy for NEC but signs of partial small bowel obstruction or blood-tinged stools develop, contrast enemas are very useful in identifying strictures.

**Ultrasonography**

Ultrasonography (US) has been used to identify necrotic bowel, intraperitoneal fluid, and portal venous air. Theoretically, US may have significant value if it can identify patients who require surgery in a more sensitive and timely manner than is possible with conventional clinical and radiographic methods.

Abnormal bowel loops on US are characterized by a hypoechoic rim with a central echogenic focus ("target sign"). Pericholecystic hyperchogenicity, believed to represent either pericholecystic venous gas or extension of the foamy inflammatory infiltrate of NEC into the pericholecystic space, was described by Avni et al.

The use of US for the diagnosis of NEC is most applicable to patients with questionable clinical and radiologic findings or to localize intra-abdominal fluid for paracentesis.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is a noninvasive modality that has recently been used to identify infants with ischemic bowel secondary to NEC. Although MRI is capable of demonstrating the cardinal findings of NEC, the need to use this study is limited at most.

**CLASSIFICATION**

To select the appropriate treatment (nonoperative versus operative) and to determine the impact of therapy on survival and late outcome, it is essential that investigators use comparable criteria for classifying the stages of NEC. Several classification schemes have been proposed. In 1978, Bell et al. introduced the now most commonly used classification, a three-stage system (suspected, definite, and advanced) that categorizes patients by historical factors, GI manifestations, radiologic findings, and systemic signs (Table 92-2). The Bell staging criteria have been modified; the three stages are still used, but subsets are included in an effort to identify specific prognostic factors. Infants with stage I disease have features suggestive of NEC, patients with stage II disease have definitive NEC without an indication for surgical intervention, and patients with stage III disease have advanced NEC with evidence of bowel necrosis or perforation.

**TABLE 92–2 Necrotizing Enterocolitis Staging System**

| Stage I (Suspected) | Stage II (Definite) | Stage III (Advanced) |
|---------------------|---------------------|----------------------|
| Any one or more historical factors producing perinatal stress | Any one or more historical factors | Any one or more historical factors |
| Systemic manifestations—temperature instability, lethargy, apnea, bradycardia | Above signs and symptoms plus persistent occult or gross gastrointestinal bleeding, marked abdominal distention | Above signs and symptoms plus deterioration of vital signs, evidence of septic shock, or marked gastrointestinal hemorrhage |
| Gastrointestinal manifestations—poor feeding, increasing regurgitation, abdominal distention, emesis (may be bilious or test positive for occult blood), mild abdominal distention, occult blood in stool (no fistula) | Abdominal radiographs showing distention with mild ileus | Abdominal radiographs showing pneumoperitoneum in addition to the findings listed for stage II |

From Bell MJ, Ternberg JL, Feigin RD, et al: Neonatal necrotizing enterocolitis: Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1.

**MANAGEMENT**

**Nonoperative**

In the absence of intestinal necrosis or perforation, the mainstay of treatment for patients with NEC is supportive. Feedings are stopped, the GI tract is decompressed through a sump gastric tube, and intravenous fluid resuscitation is initiated. A complete blood count, platelet count, blood gas analysis, and CRP and serum electrolyte levels are obtained. Blood and urine samples are sent for culture, and broad-spectrum intravenous antibiotic therapy is initiated. Until recently, most antibiotic regimens included a penicillin, an aminoglycoside, and an agent effective against anaerobic organisms. It seems logical that coverage for anaerobic organisms be included because these infants are usually 1 to 2 weeks old, but in carefully performed studies, anaerobes are sparse. To date, no controlled study has shown the efficacy of this therapy. The antibiotic regimen is best tailored not only to the most common organisms found with NEC but also to the nosocomial nursery flora. Because of recent reports of patients with stool and blood cultures positive for coagulase-negative staphylococci, some groups now empirically treat patients with a combination of vancomycin and gentamicin or vancomycin and a third-generation cephalosporin. The incidence of fungal sepsis in infants who die of NEC is high, so a strong index of suspicion must be maintained and empirical antifungal therapy should be considered if the patient continues to be symptomatic without an obvious bacterial cause.
Close clinical observation consists of frequent physical examination, two-view abdominal radiography performed every 6 to 8 hours, serum platelet and leukocyte counts, and blood gas analysis.

Once feedings resume, stools are tested for reducing substances and occult blood. Feedings are discontinued if the result of either test becomes positive. Patients with definite disease of moderate severity (Bell stage II) are treated by bowel rest, decompression, and antibiotic therapy for at least 7 to 14 days. A central venous catheter may be placed for total parenteral nutrition. If the patient is clinically well, small amounts of diluted formula may be restarted. The infant is constantly and carefully monitored for abdominal distention, vomiting, or nonspecific signs or symptoms of NEC. Feedings are progressed slowly to goal volumes while avoiding the use of concentrated formulas or large-volume feeding. Infants who have undergone surgery receive 1 to 2 weeks of postoperative intravenous antibiotics. Feedings are initiated when the patient is clinically well and return of bowel function has been established.

**Indications for Surgery**

The principal goals of surgical intervention in the setting of NEC are to remove gangrenous bowel and preserve intestinal length. Ideally, surgery should not be undertaken until gangrene is present but be performed before perforation occurs. Unfortunately, no combination of clinical examination or adjunct testing has been shown to have high sensitivity for intestinal gangrene. Thus, there remains controversy regarding the indications for surgery, the most appropriate timing of intervention, and the optimal surgical treatment strategy. The most widely accepted indication for surgery is the presence of pneumoperitoneum. In an attempt to identify characteristics that may serve as predictors of intestinal gangrene, Kosloske reviewed 12 criteria used as indications for surgery in 147 patients with NEC and stratified these criteria according to sensitivity, specificity, positive/negative predictive value, and prevalence. The “best” indicators (specificity and positive predictive value [PPV] approaching 100%, prevalence >10%) were pneumoperitoneum, positive paracentesis (aspiration of >0.5 mL brown or yellow fluid containing bacteria on Gram stain), and portal venous gas. “Good” indicators (specificity and PPV approaching 100%, prevalence <10%) were a fixed intestinal loop, erythema of the abdominal wall, and a palpable abdominal mass. A “fair” indicator (specificity of 91%, PPV of 94%, prevalence of 20%) was “severe” pneumatosis intestinalis as graded by a radiographic system. “Poorer” indicators were clinical deterioration (PPV of 78%), platelet count lower than 100,000/mm³ (PPV of 50%), abdominal tenderness (PPV of 58%), severe GI hemorrhage (PPV of 50%), and gasless abdomen with ascites (0%). Unfortunately, none of the indicators had sensitivity greater than 48%. Currently, the only absolute indication for surgery is pneumoperitoneum. Relative indications include a positive paracentesis, palpable abdominal mass, abdominal wall erythema, portal venous gas, fixed intestinal loop, and clinical deterioration despite maximal medical therapy.

**Pneumoperitoneum**

Infants in whom pneumoperitoneum develops during nonoperative treatment should undergo either laparotomy or peritoneal drain placement. Unfortunately, pneumoperitoneum is not always demonstrable in neonates with gut perforation, with one study reporting that only 63% of infants with perforation demonstrated free air.

**Paracentesis**

A positive result on paracentesis, defined as free-flowing aspiration of more than 0.5 mL of brown or yellow-brown fluid that contains bacteria on gram stain, is highly specific for intestinal necrosis. A negative result on paracentesis is rare with intestinal necrosis but can occur when a localized, walled-off perforation is present or a segment of bowel is injured but not perforated. There is no absolute indication for paracentesis. Kosloske recommends abdominal paracentesis for patients with extensive pneumatosis intestinalis or for those who do not improve with nonoperative management. If no peritoneal fluid is aspirated, peritoneal lavage is performed by instilling up to 30 mL/kg of normal saline solution into the peritoneal cavity, turning the patient from side to side, and then withdrawing the fluid. Ricketts and Jerles reported a greater than 70% survival rate when a positive result on abdominal paracentesis was used as the indication for surgery in 51% of their patients; three false negatives occurred. They performed paracentesis when there was erythema and edema of the abdominal wall, portal vein gas, a fixed and dilated loop on sequential abdominal radiography, a fixed and tender abdominal mass, or persistent clinical deterioration. The indications used for paracentesis in this report are considered indications for surgery by many surgeons.

**Portal Venous Gas**

To determine the significance of portal vein gas in relation to the presence and extent of bowel necrosis and mortality, Kurckchubasche et al. reviewed the experience of Children’s Hospital of Pittsburgh, as well as the world literature. Of the 616 patients collected, 118 (19%) had portal vein gas on plain radiography. Of these 118 patients, 102 underwent surgery, usually 24 hours after the radiographic appearance of portal vein gas. All 102 patients had full-thickness bowel necrosis, and 52% had necrosis of more than 75% of the length of the entire small intestine. The overall surgical mortality rate for patients with portal vein gas was 52%, and more than 90% of those with pan-involvement died. Of the 15 patients who had portal vein gas and did not undergo surgery, bowel necrosis requiring surgery developed in 6 (40%), and 5 of the 6 died. In a separate study, Rowe et al. suggested that intestinal necrosis will develop in more than 90% of infants with portal venous gas, with pan-involvement developing in 52%. More recently, in a review of 40 infants with NEC and portal venous gas, Mollik et al. reported a 54% overall operative mortality and pan-involvement in 25%. 

Fixed Persistent Intestinal Loop

A fixed dilated intestinal loop is defined by persistent location and configuration for more than 24 hours. Approximately half the patients recover without an operation.\(^{250}\) Laparoscopy has been used to assess two patients with dilated intestinal loops.\(^{251}\) NEC was confirmed in one case and ruled out in the other.

Clinical Deterioration

There are many criteria for operating on children who show continued clinical deterioration despite adequate supportive therapy,\(^ {245}\) but none by themselves are absolute indications. These criteria include abdominal wall erythema, peritonitis on physical examination, persistent/increasing acidosis, and persistent/progressive thrombocytopenia.

Ascites

As mentioned, pneumoperitoneum may not always be evident with intestinal perforation. A gasless abdomen, suggestive of a fluid-filled abdominal cavity, may be the only indication of perforation. Frey et al.\(^ {85}\) reported that in 21% of infants with intestinal perforation, the only radiographic evidence was ascites. They noted that radiographs are imprecise and that evidence of ascites in the appropriate clinical setting of NEC mandates paracentesis for further evaluation.

Operative Management

Advanced disease requiring surgical intervention develops in up to 50% of infants with NEC.\(^ {36,151}\) Because of the lack of quality prospective randomized trials, the optimal surgical treatment strategy for NEC remains controversial. The goals of surgery are to remove gangrenous bowel and preserve intestinal length. Within this context, a number of different options exist, but most agree that the surgical approach should be determined by the extent of intestinal involvement.

The patient’s general condition should be optimized before surgery with aggressive ventilatory support, treatment of shock, administration of broad-spectrum antibiotics, and correction of anemia and coagulopathy. Ideally, a minimum urine output of 1 mL/kg/hr and an age-appropriate mean arterial pressure should be achieved. Operative procedures may be performed in the NICU under appropriate conditions without an increase in complications.\(^ {87}\)

Primary Peritoneal Drainage

Treatment of intestinal perforation in VLBW infants remains controversial. In 1977, Ein et al.\(^ {77}\) reported the use of peritoneal drainage (PD) as a means of stabilizing and improving the systemic status of premature infants with perforation before laparotomy. Since then, primary treatment with PD has been used in a variety of settings, and some investigators have suggested that it may serve as definitive therapy.\(^ {14,66,93,176,203}\) In a prospective study involving 44 infants treated with PD as primary management for advanced NEC, Demestre et al.\(^ {66}\) reported 28 patients (63.6%) treated with PD only and 16 patients (36.4%) who required laparotomy after PD. The survival rate after PD only was 64%, although 86% demonstrated improvement after drainage. After PD, 54% of infants required delayed surgery. Morgan et al.\(^ {203}\) used PD as primary treatment of NEC and perforation for infants weighing less than 1500 g and for unstable babies heavier than 1500 g. They reported a 79% survival rate after PD, with 17 of 25 (73.9%) survivors requiring no other operative intervention. Moss et al.\(^ {205}\) recently performed a meta-analysis of PD versus laparotomy for perforated NEC and reviewed 10 published studies on this topic. Because of the marked bias in treatment assignment, with a greater proportion of smaller babies undergoing PD versus laparotomy, the authors were unable to determine the relative merits of PD. Currently, most surgeons propose PD as the initial treatment in VLBW infants with perforated NEC to allow resuscitation and stabilization before definitive laparotomy. In an attempt to address this issue, two multicenter prospective randomized controlled trials are currently in progress to compare PD with primary laparotomy in premature infants less than 1000 g (A. Pierro: NET trial) or less than 1500 g (R.L. Moss: NECSTEPS trial).

Laparotomy

At laparotomy, the extent of NEC may be classified as focal, multifocal, or pan-intestinal (<25% viable bowel). Depending on the disease and patient characteristics at the time of surgery, a number of different surgical options may be undertaken, including resection with enterostomy, resection with anastomosis, proximal enterostomy, the “clip and drop” technique, and the “patch, drain, and wait” technique. The abdomen is entered via a right transverse supraumbilical incision with precautions taken to not injure the liver. Samples of peritoneal fluid may be harvested for culture of aerobic, anaerobic, and fungal organisms. The entire GI tract is systematically examined to assess the extent of disease and viability of the bowel. At the conclusion of the procedure, one should record the length of viable intestine remaining and note the presence or absence of the ileocecal valve.

A rarely cited complication of laparotomy for NEC is spontaneous intraoperative liver hemorrhage from injury caused by retractors or finger dissection. VanderKolk et al.\(^ {286}\) reported this complication in 11.8% of operations for NEC over a 5-year period. The mean gestational age of those with liver hemorrhage was 28 weeks (mean weight, 1262 g). Only one of these patients survived. The authors identified low mean preoperative arterial pressure and high preoperative fluid administration over the preceding 24 hours as significant predisposing factors. This complication occurred shortly after the abdomen was opened and the intestine was eviscerated. Liver congestion was followed by subcapsular hematoma and then free rupture.
**Focal Disease**

When a single area of bowel is necrotic or perforated, only limited resection is necessary. Creation of a proximal enterostomy and distal mucus fistula has been the standard of care. We prefer to exteriorize the stomas through the wound (either juxtaposed or separated) because (1) the mesentery is often thick and foreshortened, thus making passage of the stoma and its blood supply through the abdominal wall difficult, (2) stoma closure is facilitated, and (3) the incidence of wound complications is not increased in comparison to stomas at remote locations. The enterostomy is created by suturing the intestine to the fascia with interrupted sutures. About 2 cm of bowel is left protruding from the abdominal wall, and no attempt is made to use sutures to “mature” the end of the intestine. If stoma viability is in question after surgery, a small portion of the full thickness of the intestine is excised at the bedside and the cut ends are observed for bleeding.

Resection with primary anastomosis for isolated disease may be performed in carefully selected patients. Proponents of primary anastomosis cite the high morbidity associated with enterostomies in infants and no need for a second operation. To safely perform this technique, the following criteria must be met: (1) a sharply localized, usually proximal segment of disease, (2) undamaged appearance of the remaining intestine, and (3) good overall patient condition without evidence of rapidly progressive sepsis or coagulopathy.

**Multisegmental Disease (>50% Viable)**

If the patient has multiple areas of necrosis separated by viable bowel, several options are available. Historically, the surgeon excises each diseased segment individually and creates multiple stomas rather than performing a massive resection. Conversely, a single high stoma (proximal jejunum) may be created and the distal bowel “spliced” together, thereby avoiding multiple stomas. A proximal jejunostomy can cause significant fluid and electrolyte loss and peristomal skin complications, although aggressive skin care with measurement and replacement of the stoma losses can avoid these potential complications. Anastomotic strictures are not uncommon and are addressed at the time of jejunostomy closure. Resection plus anastomosis has also gained increased acceptance as a valid treatment option for severe NEC and for multifocal disease. In a study involving 46 infants with multifocal NEC, Fasoli et al. reported a higher survival rate after resection and primary anastomosis (85%) versus enterostomy (50%).

Moore described a controversial approach termed the “patch, drain, and wait” procedure in 1989. The principles of this potentially bowel length–preserving method are transverse single-layer suture approximation of perforations (patch), insertion of two Penrose drains that exit in the lower quadrants (drain), and a commitment to long-term parenteral nutrition (wait). The Penrose drains capture fecal fistulas and function as de facto enterostomies as the peritoneal cavity is rapidly obliterated by adhesions. This procedure does not address the issue of ongoing sepsis because necrotic bowel is not resected, the general peritoneal cavity is difficult to drain, and the thin-walled perforated bowel often cannot handle suture.

Vaughan et al. described a promising novel technique aimed at avoiding multiple enterostomies, circumventing the complications of a high jejunostomy, and preserving bowel length. The authors performed the “clip and drop back” technique in three patients with NEC. In this procedure, the obviously necrotic bowel is removed, and the cut ends are closed with titanium clips or staples. Re-exploration is performed 4 to 72 hours later, the clips are removed, and all segments are reanastomosed without any stomas. In one of the three patients, re-resection was required during the second-look operation, the bowel ends were clipped again, and a successful primary anastomosis was performed during a third operation. Follow-up for this very small series was 6 months to 7 years with no anastomotic complications or delayed reoperations.

**Pan-involvement (NEC Totalis, <25% Viable)**

Pan-involvement develops in 19% of patients; it poses an enormous treatment problem and is a highly controversial management issue. The overriding consideration is to spare as much intestine as possible. Treatment options include resection of all necrotic bowel with placement of proximal or multiple stomas or proximal diversion without bowel resection, with plans for a second-look procedure. The decision to forego any treatment is supported by studies that demonstrate a 42% to 100% mortality rate in patients with pan-involvement, with almost all survivors left with short-bowel syndrome. The mortality rate is nearly 100% for infants who weigh less than 1000 g.

Diverting the intestinal stream by high proximal jejunostomy (without bowel resection) may facilitate healing of injured bowel through distal intestinal decompression, a reduction in its metabolic demands, and a decrease in the number of bacteria and possibly their by-products. This technique was initially reported by Martin and Neblett and involves performing a high jejunostomy without resection, with plans for a second-look operation after 6 to 8 weeks. In a series of 10 patients with pan-involvement, Sugarman and Kiely reported 8 infants surviving to undergo a second procedure. Resection of necrotic segments plus anastomosis was performed successfully, but the long-term survival rate was only 50%.

**Stoma Closure and Complications**

There is neither an ideal weight and age nor a universally agreed upon time at which intestinal continuity should be restored. The principal determinants are time since surgery, weight gain, and stoma output. In general, the enterostomy may be safely closed anytime after 4 weeks since the last operation; the risk period for strictures; attempted closure at less than 4 weeks after surgery may be met with a peritoneal cavity that is obliterated by vascular adhesions and resolving inflammation. Before enterostomy closure, patency of the distal end of the bowel
should be confirmed by either a retrograde or antegrade contrast study. A study by Musemeche et al. examined the complication rate after stomas were closed less than 3 months after surgery, 3 to 5 months after surgery, and more than 5 months after surgery; no differences were found. They also noted no difference in complications between patients who underwent closure at a body weight less than 2.5 kg, 2.5 to 5.0 kg, or greater than 5.0 kg.

Although enterostomy in neonates may be lifesaving, it is also a major cause of morbidity. In recent studies, enterostomies in newborns had an associated complication rate ranging from 34% to 68%. Complications included wound infections, wound dehiscence, stoma stenosis requiring revision, incisional hernia, parastomal hernia, prolapse or intussusception, and small bowel obstruction.

**SURVIVAL**

Over the past decades, the survival of infants with NEC has progressively improved (Table 92-3). This improvement has been attributed to earlier diagnosis and more effective supportive treatment for premature infants. Effective supportive treatment includes improved ventilatory strategies, surfactant therapy, total parenteral nutrition, improved understanding of the pathophysiology and management of critically ill newborns, and advancements in pediatric anesthesia. The increased survival has been most noticeable in infants who weigh less than 1000 g and are less than 28 weeks’ gestational age. In a recent review of 754 premature infants born between 22 and 25 weeks’ gestation, the overall survival rate was 63%, with a range of 14% at 22 weeks’ gestation to 76% at 25 weeks’ gestation. Mortality was still significantly higher in VLBW infants than larger patients. This is highlighted by studies that examined the outcome of VLBW infants in comparison to “standard” premature infants (>1000 g) with pan-involvement NEC. Snyder et al. found that infants weighing less than 1000 g are more likely to require surgery (51% versus 34%) and to eventually have pan-involvement (10% versus 4%) than infants greater than 1000 g. Pan-involvement was associated with 100% mortality in both groups. In a retrospective study of 70 infants weighing less than 1000 g with perforated NEC, Erhlich et al. demonstrated that infant survival was independent of the type of surgical treatment (PD versus laparotomy), but instead was inversely related to the number of comorbid conditions associated with the patient.

We do not believe that the differences in mortality rates between series are attributable to differences in the effectiveness of the treatment programs used. In different groups of patients, the disease varies from predominantly localized disease to extensive necrosis. The patient population differs between the various series. The mortality rate can vary considerably, depending on birth weight, coexisting disease, virulence of the disease process, and whether the patient is in-born locally versus transferred. The precarious state of patients at risk for NEC is emphasized by the fact that in one series that compared patients who had NEC with matched controls, the mortality rate in the controls was 33%.

**COMPLICATIONS**

**Gastrointestinal**

**Intestinal Strictures**

The first clinical and radiologic description of intestinal stricture after recovery from acute NEC was reported in 1968 by Rabinowitz et al. The reported overall incidence varies from 9% to 36% and stricture formation is more frequent after nonoperative treatment. The incidence of strictures after NEC is increasing as the mortality rate from the disease decreases. Strictures result from fibrotic healing of an area of severe ischemic injury. Regardless of whether the stricture follows operative or nonoperative therapy, the most common site of

| Authors                          | Years of Review | Patients (N) | Medically Treated | Surgically Treated |
|----------------------------------|-----------------|--------------|------------------|------------------|
| Touloukian                        | 1955-1966       | 25           | 20               | 27               |
| Wilson et al.                     | 1958-1968       | 16           | 14               | 13               |
| Dudgeon et al.                    | 1970-1972       | 63           | 59               | 26               |
| O’Neill                           | 1970-1974       | 52           | 69               | 60               |
| Philippart and Rector             | 1974-1976       | 73           | 73               | 81               |
| Grosfeld et al.                   | 1972-1982       | 176          | 68               | 51               |
| Ricketts and Jerles               | 1980-1988       | 100          | —                | 70               |
| Grosfeld et al.                   | 1983-1990       | 126          | 95               | 75               |
| Lemelle et al.                    | 1985-1990       | 331          | 82               | 65               |
| Snyder et al.                     | 1971-1996       | 266          | —                | 68               |
| Ehrlich et al.                    | 1991-1998       | 70           | —                | 75               |
| Guthrie et al.                    | 1998-2000       | 390          | 95               | 77               |

Adapted from Rowe MI: Necrotizing enterocolitis. In Welch KJ, Randolph JG, Ravitch MM, et al (eds): Pediatric Surgery, 4th ed. Chicago, Year Book, 1986.
involvement has been the colon (80%). The next most common site is the terminal ileum (15%). Sixty percent of colonic strictures involve the left colon, and the most common colonic site is the splenic flexure (21%). Most patients have single strictures, but multiple strictures can occur (15%). An intestinal stricture should be suspected after nonoperative management of NEC in an infant with failure to thrive, rectal bleeding, or bowel obstruction. These signs and symptoms occur in 50% of patients with strictures and should be evaluated with a contrast enema. If the study demonstrates a stricture in a symptomatic patient, elective resection with anastomosis is usually indicated.

Intestinal Malabsorption and Short-Bowel Syndrome

Malabsorption may result from a variety of factors, including decreased bowel length, decreased mucosal absorptive area, enzyme depletion, gut hypermotility, hypersecretion of gastric acid, bacterial overgrowth, decreased intestinal transit time, vitamin B₁₂ deficiency, and bile salt deficiency. Short-bowel syndrome (see Chapter 86) is the most serious long-term GI complication associated with surgically treated NEC. It occurs in up to 23% of NEC survivors who undergo surgical resection.

Cholestatic Liver Disease

Cholestatic liver disease results from a number of factors, but primarily from prolonged administration of total parenteral nutrition. It is characterized by direct hyperbilirubinemia, hepatomegaly, and elevated aminotransferase levels. Although the condition is multifactorial, the most important contributing factor is probably prolonged fasting. It has been shown that the most effective treatment is establishment of early, small-volume enteral feeding, concomitant with the administration of total parenteral nutrition, which aids in bowel adaptation by conferring a trophic effect on the intestinal mucosa and by stimulating bile flow.

Recurrent Necrotizing Enterocolitis

NEC can recur after operative and nonoperative management. The incidence is 4% to 6%. No consistent association has been noted between recurrent NEC and the type or timing of enteral feeding, the anatomic site, or the method of initial management. More than 70% of patients were successfully treated nonoperatively for recurrence by Stringer et al.

Anastomotic Ulceration

A late complication that may occur many years after resection for NEC is the development of anastomotic ulceration. Sondheimer et al. reported six children who underwent ileocolonic resection and anastomosis in the neonatal period in whom lower GI bleeding developed at 5 to 13 years of age. Anastomotic ulceration was diagnosed by colonoscopy, and treatment entailed ulcer resection in five of six patients. Recurrence of marginal ulcers developed in four of five patients who underwent resection. Histologic examination revealed shallow ulcers penetrating only to the muscularis. The cause of the ulcers is unknown.

Neurodevelopmental Complications

The length of hospitalization of infants has been strongly associated with developmental progress at 1 to 2 years of age. This probably reflects the adverse effects of medical and social factors on the developing brain. It is recommended that developmental screening be performed every 4 months during the first year and every 6 months during the second year because long-term follow-up data suggest that normal premature infants and survivors of severe NEC remain at high risk for neurologic developmental morbidity.

Approximately 50% of infants surviving NEC are neurodevelopmentally normal. Historically, it was believed that any adverse neurodevelopmental outcome in a patient treated for NEC was due to underlying prematurity and comorbid conditions rather than the NEC itself, but recent evaluations of surviving infants contest this assumption. Vohr et al. studied the neurodevelopmental, neurosensory, and functional outcomes of 1151 extremely low-birth-weight (401 to 1000 g) survivors at 18 to 22 months’ corrected age and reported significant deficits in neurologic development (25%), a Bayley II Mental Developmental Index less than 70 (37%), a Psychomotor Development Index less than 70 (29%), vision impairment (9%), and hearing impairment (11%). NEC was specifically associated as a risk factor for both an abnormal neurologic examination and a low Bayley Psychomotor Development Index. In a study assessing the effect of NEC on neurodevelopment, Sonntag et al. compared VLBW infants with NEC with matched infants without NEC at 12 and 20 months’ corrected age. Despite normal somatic growth in infants with NEC not complicated by short-bowel syndrome, the authors demonstrated significant neurodevelopmental delay at both 12 and 20 months of age. Fifty-five percent of infants with NEC were noted to be severely retarded versus only 22.5% of infants without NEC.

Prevention

Attempts to reduce the incidence of or prevent NEC must consider the probable pathogenesis of the disease and some of the putative perinatal risk factors. Investigations into preventive measures for NEC, including limiting the nosocomial spread of microorganisms, augmenting host defense, decreasing bacterial colonization and overgrowth in the GI tract, providing factors that enhance intestinal maturation, and attenuating the inflammatory cascade, may be useful. Infection control measures, breast-feeding, cautious feeding of sick premature babies, immunoglobulin supplementation of feedings, corticosteroid therapy, administration of growth factors, and use of inflammatory mediator antagonists are some of the preventive strategies that have been studied.
Infection Control Measures

Adoption of infection control measures in the nursery may limit the incidence and restrict the spread of infections, thereby potentially eliminating the epidemic waves of NEC. The traditional prophylaxis for nosocomial epidemics includes strict hand washing with a germicidal agent, long-sleeved gown and gloves, separate diaper and laundry bags for each patient, cohorting and isolation of confirmed cases, and separate rooms and nurses for confirmed cases (without cross-covering). It has been demonstrated that the initiation of infection control measures stops epidemics of NEC.31,109 During clustered occurrences, identical microorganisms can be isolated from both the afflicted neonates and their caretakers.

Augmentation of Host Defense

Oral Immunoglobulin Preparations

The protective immunoglobulins, principally IgA, are deficient in the premature gut. In the absence of breastfeeding, there are only trace amounts of secretory IgA and gut-associated IgG and IgM. Secretory IgA acts as an “antiseptic paint” by binding bacteria and preventing their attachment to the intestinal mucosa. Eibl et al.76 demonstrated that enteral administration of an IgG-IgA preparation decreases the incidence of NEC. Their randomized trial involved feeding 179 high-risk infants weighing 800 to 2000 g a human preparation of IgG and IgA with their formula, whereas controls received formula alone. Neither group received breast milk. No cases of NEC developed in the immunoglobulin group, but 6 cases developed in the 91 controls. In a recent study in rabbits, Dickinson et al.67 demonstrated that IgA supplementation in feedings prevented bacterial translocation by enhancing gut mucosal barrier functions. This effect was not seen with IgG or lactoferrin. In a randomized double-blind controlled trial, enteral IgG supplementation in infants failed to reduce the incidence of NEC.170

Maternal Glucocorticoid Administration

Glucocorticoids have been shown to accelerate mucosal cell maturation and improve gut barrier function. The action is mediated by glycosylation on the intestinal surface, which impairs bacterial attachment. Glucocorticoids have also been shown to down-regulate the inflammatory response by stimulating the enzymatic degradation of PAF.274 These observations have been made experimentally and clinically.76,101 Bauer et al.20 retrospectively noted a significant reduction in the incidence of NEC in babies born to mothers who received antenatal glucocorticoids for fetal pulmonary maturation as compared with controls (2% versus 7%). This large, multicenter, placebo-controlled trial was well controlled for many potentially confounding variables. Halac et al.101 conducted a randomized, controlled trial of prenatal glucocorticoid administration to mothers in preterm labor. The control mothers received placebo, but their infants received an immediate postnatal course of high-dose dexamethasone for 7 days. The rate of NEC within and between groups significantly decreased after prenatal and postnatal steroid treatment. Although postnatal therapy did not decrease the incidence as effectively as prenatal therapy did, it improved the clinical outcome of NEC; however, many potentially confounding factors were not assessed in this study. Confirmatory prospective data and assessment of potential postnatal toxicity are needed.

Breast Milk

Breast milk decreases the risk for a number of neonatal infections, including lower respiratory tract illness, otitis media, bacteremia, meningitis, and NEC.34 Human milk provides an array of humoral and cellular anti-infectious factors, growth factors, and probiotics, as well as essential vitamins and nutrients. Milk factors include IgA, macrophages, lymphocytes, components of the complement system, lactoferrin, lysozyme, transferrin, interferon, EGF, alpha fetoprotein, erythropoietin, the probiotics Bifidobacterium infantis and Lactobacillus acidophilus, PAF acetylhydrolase, and several inflammatory mediators. Strong evidence exists for the protective role of secretory IgA, the main immune component of the enteromammary axis. Breast milk also inhibits the growth of E. coli by providing an acidic environment, promoting competitive growth of Lactobacillus bifidus, and binding iron (an essential element for the growth of E. coli).17

Because invasion by infectious agents seems to be a prime factor in the pathogenesis of NEC, breast milk appears to be ideally suited to protect the infant against the disease. Administration of breast milk prevents experimental NEC.17,65 Formula-fed babies have four to six times the incidence of NEC as breast-fed infants do.179

Feeding Practices

There is little disagreement that NEC is more common in fed infants and that bacterial overgrowth is facilitated by the substrate provided by formula. Although the potential benefit of careful regulation of feeding to prevent NEC is widely accepted, randomized trials have failed to demonstrate any difference in the incidence of NEC related to fast versus slow, early versus delayed, or continuous versus intermittent bolus feeding.136,157,166,220,258,243

Low-birth-weight infants and infants with illnesses or prenatal problems are not fed for 7 to 10 days. Nutrition is provided parenterally. If no symptoms suggestive of NEC develop, feedings are cautiously begun. The type, concentration, and rate of increase are not universally accepted, although most clinicians begin with a hypocaloric formula at a slow rate. Feedings are withheld and the infant is evaluated if gastric residuals increase or any clinical findings potentially associated with NEC develop.

Methods to Decrease Intestinal Bacterial Colonization and Overgrowth

Administration of Probiotics

Probiotic bacteria are defined as “live microbial supplements that colonize the intestine to provide benefit to
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the host. The use of anaerobic bacterial supplementation in the treatment or prevention of GI disease has been well described. There has been increasing interest in using probiotics for the prevention of NEC. Bifidobacteria are gram-positive anaerobic bacteria that predominantly colonize the gut in healthy breast-feeding neonates but are much less prevalent in the intestinal tract of premature infants at highest risk for NEC. Preliminary investigations in a neonatal rat model of NEC using probiotic supplementation have demonstrated a significant reduction in the incidence of NEC. Future human clinical trials are needed.

**Enteral Antibiotics**

Nonabsorbable broad-spectrum antibiotics that inhibit bacterial growth have been administered in an effort to prevent NEC. The use of an enteral aminoglycoside (e.g., kanamycin or gentamicin) has been proposed as a means to decrease the incidence of perforation during nonoperative treatment. However, randomized, controlled studies found no difference in the clinical course, complications, or mortality rate between infants who received the antibiotic and those who did not. In addition, oral aminoglycosides may be absorbed across the damaged gut, which can lead to increased serum levels and thereby potentially contribute to drug toxicity. Resistant strains of bacteria emerged after treatment with enteral kanamycin and there is the omnipresent risk for promotion of the growth of fungal species. In a recent randomized placebo-controlled study of oral vancomycin in preventing NEC in preterm infants, Siu et al. reported a 50% reduction in the incidence of NEC in the vancomycin group in comparison to controls. The available studies do not support the routine administration of enteral antibiotics to all high-risk premature infants, many of whom have poor intestinal motility. Effectiveness has not been proved, and resistant organisms may develop. Administering specific antibiotics to infants may be indicated in nurseries in which an outbreak of NEC is associated with a specific organism.

**Acidification of Formula**

Carrion and Egan conducted a small prospective double-blinded study in which feedings given to premature infants were acidified with HCl to a pH of 2.5 to 5.5. Acidification of feedings significantly decreased the rate of gastric bacterial colonization in infants with a gastric pH less than 4.0. They also found a significantly lower incidence of NEC in infants given acidified feedings than in controls.

**Inflammatory Mediator Antagonists**

The effects of PAF are mediated by receptors, and many compounds that function as receptor antagonists or enzymes that degrade these proteins have been described. Animal experiments using PAF antagonists (WEB 2086, WEB 2170, SRI 63-441) or PAF-degrading enzyme (PAF acetylhydrolase) have demonstrated the capacity to prevent bowel injury produced by the administration of endotoxin or hypoxia in rats. PAF acetylhydrolase is also known to be present in breast milk. Despite promising results in animal models, no human trials using PAF antagonists or degrading enzyme in the treatment of NEC have been reported.

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