Necrotizing Enterocolitis: Treatment Based on Staging Criteria

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Necrotizing enterocolitis (NEC) continues to be the most serious and most frequent gastrointestinal disorder seen in neonatal intensive care units (NICU). The disease is characterized by signs of sepsis in addition to multiple gastrointestinal disturbances ranging from abdominal distention, bilious emesis, and hematochezia to intestinal perforation, peritonitis, and shock. The incidence varies widely from institution to institution and across time periods within the same institution. The usual incidence of NEC is between 1 and 5 per cent of all admissions to a NICU.[17, 48, 66, 80] The incidence of NEC increases in the very low birthweight (less than 1500 gm) infant, in whom it approaches 12 per cent.[51] The reported mortality has ranged widely from 0 to 55.5 per cent.[17] In a 1976 investigation conducted by the Centers for Disease Control, the mortality rate related to NEC was 40 per cent.[80] NEC is therefore a major perinatal public health concern as a significant cause of mortality and morbidity among neonates. Despite extensive research, the etiology or etiologies of NEC continue to elude investigators. This review will focus on the epidemiology, pathogenesis, and treatment of this important newborn gastrointestinal disease. As the spectrum of severity of NEC varies from a mild gastrointestinal disturbance to an acute fulminant disease, specific treatment protocols based on the severity of the presenting clinical manifestations are emphasized.

EPIDEMIOLOGY

NEC is usually a disease of ill premature neonates and develops during their stay in a NICU. In a review of 123 patients with NEC at Rainbow Babies and Childrens Hospital of Cleveland, Ohio, the mean birthweight

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Table 1. *Purported Risk Factors*

1. Prematurity
2. Perinatal asphyxia
3. Respiratory distress syndrome (RDS)
4. Umbilical catheterization
5. Hypothermia
6. Shock
7. Hypoxia
8. Patent ductus arteriosus (PDA)
9. Cyanotic heart disease
10. Polycythemia
11. Thrombocytosis
12. Anemia
13. Exchange transfusion
14. Congenital gastrointestinal anomalies
15. Chronic diarrhea
16. Non-breast milk formula
17. Nasojejunal feedings
18. Hypertonic formula
19. Too much formula—too fast
20. Hospitalization during epidemic
21. Colonization with "necrogenic" bacteria

of affected infants was 1460 gm and the mean gestational age was 31 weeks.[48] Nevertheless, 10 per cent were previously ill term infants who were admitted to the NICU for other reasons prior to the onset of NEC.[48, 69] These term infants had cyanotic heart disease, enteritis, polycythemia, or birth asphyxia. Furthermore, during the past 2 to 3 years, we have become aware of previously healthy full-term infants who developed NEC in level I well-baby nurseries.

Ninety to 95 per cent of patients with NEC have been enterally fed either breast milk, formula, or both.[17, 48, 81] However, NEC has occasionally developed in infants who have never been enterally fed.[64] At our institution, NEC usually begins between day 3 and day 10 of life. The range of day of onset, however, is very wide—from less than 24 hours to as long as 90 days.[48] Recently, Thilo and colleagues[86] reviewed a 6-year experience at Children's Hospital of Denver and reported 13 infants who developed NEC in the first 24 hours of life. These infants were larger and more mature than infants with onset of NEC after the first day of life.

Multiple risk factors have been identified that predispose the infant to NEC. Many of these risk factors are related to neonatal problems that may reduce gastrointestinal blood flow (Table 1). However, most of these purported risk factors are common to all patients in the NICU. Prematurity alone is probably the most significant risk factor, followed by polycythemia (see below).

Some infants develop NEC who have no identifiable risk factors. At our institution, 11.4 per cent did not demonstrate identifiable risk factors other than prematurity.[48] O'Neill et al.[68] reported 5 of 50 (10 per cent) infants with no risk factors; Yu and Tudehope[96] reported that 6 of 44 (13 per cent) infants had no risk factors.

There appear to be at least two distinct epidemiologic classifications of

Table 2. *Initial Signs and Symptoms of Necrotizing Enterocolitis*

SIGNS	PERCENTAGE OF PATIENTS*
Abdominal distention	73
Bloody stool	28
Apnea, bradycardia	26
Abdominal tenderness	21
Retained gastric contents	18
Guaiac-positive stool	17
"Septic appearance"	12
Shock	11
Bilious emesis	11
Acidosis	10
Lethargy	9
Diarrhea	6
Cellulitis of abdominal wall	6
Right lower quadrant mass	2

*Total exceeds 100 per cent, as many patients had more than one sign. (Modified from Kliegman, R. M., and Fanaroff, A. A.: Neonatal necrotizing enterocolitis: A nine-year experience. Epidemiology and uncommon observations. Am. J. Dis. Child., *135*:603, 1981.)

NEC: endemic and epidemic. In many nurseries, there is a low background, or endemic (sporadic) incidence of NEC of zero to two cases a month.[48] Superimposed on the endemic occurrence are epidemics in which a large number of cases are clustered together in space and time.[15, 47] These two types of disease states seem inherently different and may ultimately allow us to better define pathogenetic mechanisms. Indeed, during epidemics, patients tend to have higher birthweights and Apgar scores and later onset of disease, compared with endemic cases of NEC.[66]

Clinical Presentation

Necrotizing enterocolitis may present a wide range of clinical manifestations. The disease may manifest with signs of mild feeding intolerance, including abdominal distention and gastric retention of feedings. In contrast, NEC may also be indistinguishable from neonatal sepsis with apnea, bradycardia, lethargy, temperature instability, peritonitis, and shock.

The diagnosis of NEC is suspected when typical gastrointestinal signs and symptoms predominate. At our institution, the most common initial sign is abdominal distention accompanied by grossly bloody stools.[48] The initial signs and symptoms of 123 consecutive patients are presented in Table 2. It must be appreciated that not every patient will have every symptom and that signs will vary in their time of appearance, according to the severity of the disease process.

Radiographic examinations of the abdomen show nonspecific findings such as an intestinal distention, ileus, and ascites. The two diagnostic radiologic signs, pneumatosis intestinalis (the formation of intramural intestinal gas) or intrahepatic portal venous gas, are needed to confirm the diagnosis (Figs. 1 through 5). More severe disease will result in bowel perforation and pneumoperitoneum (Figs. 6 and 7). Free air rises anteriorly in the supine patient and distributes evenly over the entire abdominal
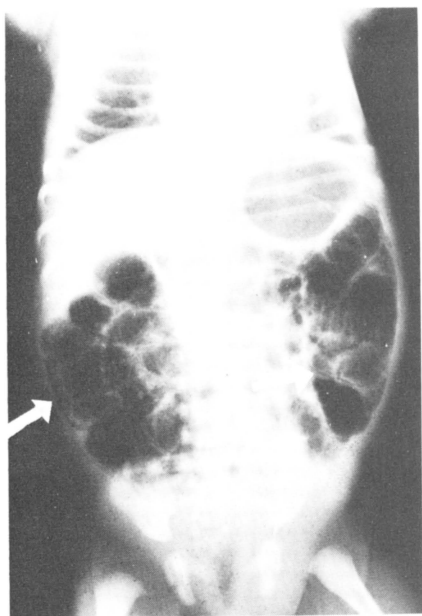
Figure 1. Abdominal radiograph demonstrating marked abdominal distention and the classical linear markings along the bowel surface characteristic of pneumatosis intestinalis (*arrows*).

Figure 2. Patient with necrotizing enterocolitis demonstrating marked distention, a bubbly pattern (*arrow*), and a linear pattern along the bowel contour (*arrowhead*). The bubbly pattern may be pneumatosis intestinalis, or blood or stool mixed with gas, whereas the linear pattern is typical of pneumatosis intestinalis. (Courtesy of Dr. B. Fletcher, Department of Pediatric Radiology, Case Western Reserve University.)
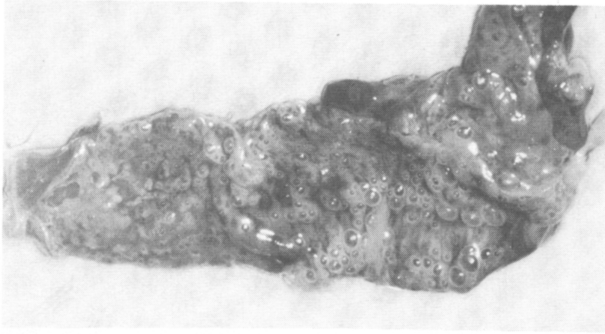
Figure 3. Resected bowel submerged under water immediately in the operating room, demonstrating macroscopic appearance of the gas filled cysts of pneumatosis intestinalis. (Courtesy of Dr. M. Gauderer, Department of Pediatric Surgery, Case Western Reserve University.)

contents. A horizontal beam cross-table lateral radiograph reveals large collections of gas, which are much more difficult to appreciate on the standard "flat plate" examination of the abdomen (Figs. 6 and 7). Pneumatosis intestinalis may be present on only the first or second abdominal films; it is not a consistent observation in each patient.

The intramural gas seen on abdominal roentgenograms is also observed in submucosal cysts noted in surgical pathology or post-mortem specimens
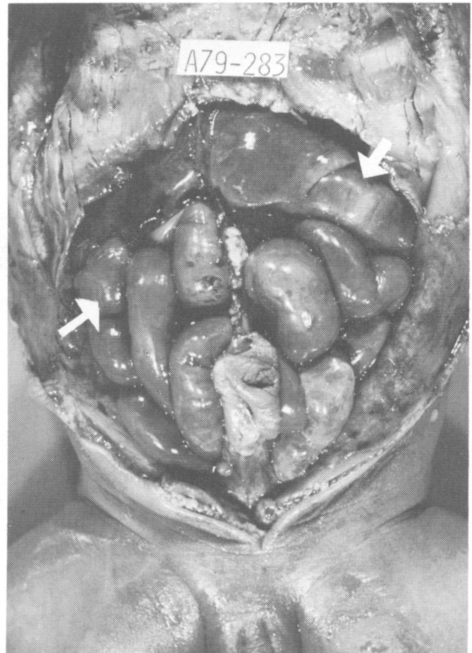

Figure 4. Gross macroscopic appearance of large gas-filled cysts (*arrows*) of pneumatosis intestinalis at autopsy in a patient with NEC. Remaining bowel demonstrates distention, necrosis, gangrene, and hemorrhage. (Courtesy of Dr. B. Dahms, Department of Pediatric Pathology, Case Western Reserve University.)
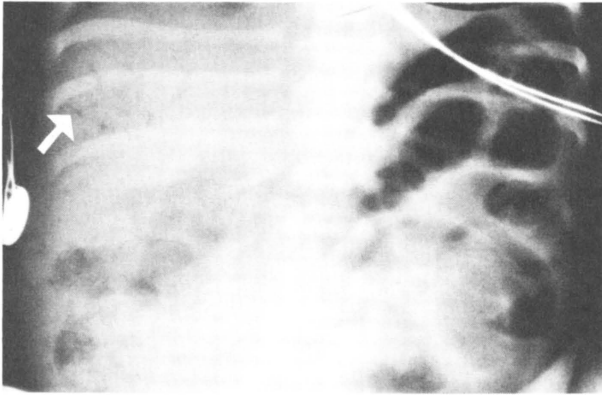
Figure 5. Gas is present in the hepatic portal venous system (*arrow*) in a patient with NEC. (Courtesy of Dr. B. Fletcher, Department of Pediatric Radiology, Case Western Reserve University.)

(see Figs. 3 and 4). Other pathological findings include intramural hemorrhage, transmural gangrene, and mucosal pseudomembrane formation (see Fig. 4).[48] The origin of the intramural gas remains obscure. Engle and coworkers[29] studied the cystic intramural and luminal gas at the time of surgery in 31 patients. They demonstrated that the gas is 30 per cent hydrogen and further demonstrated that enteric bacteria isolated from these patients produced hydrogen only in the presence of a substrate such as milk. Thus, it would seem that a substrate, which is usually formula, must be presented to enteric bacteria in order for intestinal hydrogen gas to be produced.

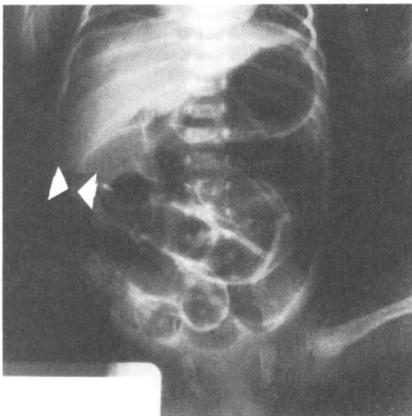At the present time, the diagnosis of NEC is confirmed in the presence

Figure 6. Free gas in the abdomen demonstrated on an anteroposterior film of the abdomen following intestinal perforation. Note visualization of both sides of the bowel wall (between *arrowheads*). (Courtesy of Dr. B. Fletcher, Department of Pediatric Radiology, Case Western Reserve University.)

Figure 7. Cross-table lateral film demonstrating, without a doubt, free gas within the abdomen, over the liver. This is the preferred view to follow infants with NEC who are at risk for intestinal perforation during the first 24 to 72 hours of the acute illness. (Courtesy of Dr. B. Fletcher, Department of Pediatric Radiology, Case Western Reserve University.)

of clinical symptoms plus positive radiographic findings. Pneumatosis intestinalis can be subtle, and much time and discussion are expended in NICUs debating its presence or absence. This sign is often confused with gas mixed with stool or blood. It would be advantageous to have other objective tests to substantiate the diagnosis of NEC. Several methods aimed at detecting increased production of hydrogen gas, although currently not universally available, are worthy of comment. Malin and co-workers[63] reported the incidental finding of echocardiographic evidence of microbubbles in the circulation of an asymptomatic neonate who later developed fulminant NEC and expired. In a subsequent report by Merritt and colleagues,[65] 12 infants with NEC demonstrated a characteristic ultrasonographic pattern of intermittent hepatic parenchymal and portal venous microbubbles of gas. Ultrasonic evidence of abnormal gas was seen in the absence of pneumatosis intestinalis or portal gas on x-ray examination in five patients.[65] Another potential diagnostic tool is the analysis of breath hydrogen excretion. Kirschner et al.[46] have demonstrated increased levels of hydrogen gas in breath samples of infants with NEC. Finally, Garcia and colleagues[33] studied urine samples from nine infants with confirmed NEC for the presence of D-lactate. D-lactate is known to be produced in large quantities by the bacterial enteric flora of ruminates fed excessive amounts of carbohydrates. This group found markedly elevated levels of D-lactate in infants with NEC. Nonetheless, each of these new methods requires much further testing before it can aid the clinician in the diagnosis of infants with NEC.

Staging Based on Clinical Manifestations

As detailed earlier, NEC can manifest within a wide range of severity and within various stages along a continuum of bowel disease. The spectrum

ranges from a slowly evolving and benign form to a course characterized by shock, peritonitis, and fulminant intestinal necrosis. The true nature or clinical course that NEC will follow is usually not known until 24 to 48 hours of onset. Thus, a benign disease that on day 2 of illness manifests with a soft non-tender abdomen in a patient without oliguria, shock, acidosis, neutropenia, or disseminating intravascular coagulation is unlikely to advance to a more serious condition after this time period.

Studies of the pathogenesis and treatment of NEC have been hampered by the failure to define the stage of the disease at the time of diagnosis. In 1978, Bell and colleagues[9] proposed important clinical staging criteria for NEC. The criteria allow accurate comparisons of patients with disease of similar severity. They are also useful in guiding therapeutic decisions. We have modified Bell's staging criteria to include systemic, intestinal, and radiographic signs and to suggest treatment based on added stages and the severity of the illness (Table 3).

Stage I includes infants who are suspected or "rule-out NEC" patients. These infants have mild systemic and gastrointestinal disturbances. Radiologic findings include ileus or mild intestinal dilation, and many infants have normal abdominal findings in this stage. Most infants in this group do not have NEC but have the much more usual feeding intolerance common among low birthweight infants. Nonetheless, during epidemics of documented NEC, the incidence of Stage I NEC also increases in tandem with that of the definitive disease.

In Stage IIA disease, the diagnosis of NEC is confirmed by the presence of pneumatosis intestinalis on abdominal radiographs. The previous nonspecific systemic signs are present in addition to mild abdominal tenderness. The infant is only mildly ill. In Stage IIB, the infant is moderately ill, with acidosis and thrombocytopenia, or hepatic portal venous gas. Cellulitis of the anterior abdominal wall, originating at the umbilicus and extending upward along the subcutaneous route of the umbilical vein, suggests local or early stages of more generalized peritonitis. A right lower quadrant mass suggests intestinal microperforation or a matted inflammatory reaction of bowel or both.

More serious or advanced NEC, classed as Stage III, is marked by clinical instability with progressive deterioration of vital signs, respiratory failure, disseminated intravascular coagulation, and shock. In Stage IIIA, the bowel is intact, whereas in Stage IIIB, intestinal perforation has occurred. Patients who progress to more advanced NEC from Stage I or Stage II usually do so within 24 to 48 hours. Progression from Stage II or IIIA to Stage IIIB with intestinal perforation can be delayed for 5 to 7 days; nonetheless, most patients will have intestinal perforation documented within the first 24 to 48 hours after the onset of NEC. Furthermore, the majority of patients with advanced Stage III NEC present with significant disturbances of vital signs as an acute rapidly fulminant disease within hours; only rarely do patients with less severe disease, such as Stage I or IIA, progress to Stage III.

Through use of staging criteria, an appreciation of the wide range of severity of NEC is obtained. There are many forms of gastrointestinal disease that have been classified within the spectrum of NEC. Leonidas

Table 3. *Modified Bell's Staging Criteria for NEC*

STAGE	SYSTEMIC SIGNS	INTESTINAL SIGNS	RADIOLOGIC SIGNS	TREATMENT
IA—Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated pre-gavage residuals, mild abdominal distention, emesis, guaiac-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics ×3d pending culture
IB—Suspected NEC	Same as above	Bright red blood from rectum	Same as above	Same as above
IIA—Definite NEC Mildly ill	Same as above	Same as above, *plus* absent bowel sounds, +/− abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics ×7–10d if exam is normal in 24–48 hours
IIB—Definite NEC Moderately ill	Same as above, *plus* mild metabolic acidosis, mild thrombocytopenia	Same as above, *plus* absent bowel sounds, definite abdominal tenderness, +/− abdominal cellulitis or right lower quadrant mass	Same as IIA, *plus* portal vein gas, +/− ascites	NPO, antibiotics ×14d NaHCO$_3$ for acidosis
IIIA—Advanced NEC Severely ill, bowel intact	Same as IIB, *plus* hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia	Same as above, *plus* signs of generalized peritonitis, marked tenderness, and distention of abdomen	Same as IIB, *plus* definite ascites	Same as above, *plus* 200 + ml/kg fluids, inotropic agents, ventilation therapy, paracentesis
IIIB—Advanced NEC Severely ill, bowel perforated	Same as IIIA	Same as IIIA	Same as IIB, *plus* pneumoperitoneum	Same as above, *plus* surgical intervention

and Hall[61] described seven infants with what they termed *neonatal pneumatosis coli*. All infants had mild systemic signs, grossly bloody stools, and pneumatosis intestinalis limited to the colon. All responded rapidly to standard medical therapy. The authors labeled this as a mild form of NEC and emphasized an excellent prognosis. These infants fulfill criteria for Stage IIA. Richmond and Mikity[73] have also described a similar group of seven infants with what they labeled "benign necrotizing enterocolitis." Again, these infants generally had mild systemic and gastrointestinal symptoms and signs. Nonetheless, their abdominal radiographs showed surprisingly extensive pneumatosis intestinalis. Five of the seven infants had pneumatosis intestinalis limited to the colon; two infants also had portal venous air. Again, the prognosis for "benign NEC" was excellent.

This benign end of the spectrum of disease, which is clinically and radiologically identical to NEC, is expanded in a report by Powell[70] of two infants with bloody diarrhea associated with pneumatosis intestinalis. Both infants developed symptoms while being fed a standard cow's milk protein formula. After standard treatment for NEC, the patients improved, but NEC recurred whenever challenged with a cow's milk or soy-based formula. Aziz[6] described another term infant with a presentation similar to that reported by Powell. Peripheral blood eosinophilia or specific mucosal biopsy findings may be helpful to identify an immunologic component in this group of patients. The number of term infants included in this category of NEC emphasizes the need to include the diagnosis of NEC in the differential diagnosis of bloody diarrhea in previously well full-term newborns with presumed milk allergy.

PATHOGENESIS

Presently, there is no universal acceptance of a unifying theory of the pathogenesis of NEC. Early theories that invoked perinatal gastrointestinal injury due to local bowel ischemia and secondary bacterial invasion did not always consider a multifactorial etiology for NEC. In addition, newer investigations that include unaffected control patients have documented that many of the traditional perinatal ischemic risk factors exist equally in affected and unaffected infants.[32, 50, 85, 96] In addition, NEC is well documented in infants without any purported ischemic risk factors.[48, 68, 96]

It is hypothesized that NEC is the final common response of the immature gastrointestinal system to potentially multiple injurious factors. In addition, the final mucosal pathology may be the result of simultaneous events that produce synergistic damage.[49, 53] Mechanisms of mucosal injury that have been implicated to be important in the pathogenesis of NEC include gastrointestinal and immunologic immaturity, ischemia, colonization by and subsequent invasiveness of pathogenic enteric bacteria, isolated intestinal bacterial overgrowth, excess bacterial substrate, and immunologic injury from milk protein allergy.

Gastrointestinal Immaturity

The gastrointestinal system of the premature infant must undergo marked alterations during the transition after birth. The fetus receives a

continuous transplacental "parenteral" supply of metabolic substrates in utero. Cutting the umbilical cord requires a rapid and smooth transition to enteral feeding to ensure adequate postnatal growth. Much of this adaptation seems to require a local intestinal factor or stimulus and not a specific gestational age; even a very premature infant can thrive on enteral feedings many weeks "too soon" in terms of biologic maturity. There is increasing evidence that enteral feedings may be the critical element that initiates functional postnatal intestinal maturation via the release of gut peptide hormones.[5] Knowledge of the processes controlling maturation are nonetheless incomplete. There is evidence, however, that levels of important potentially trophic gastrointestinal hormones are different in unfed infants, infants given bolus feedings, and continuously enterally fed infants.[4, 62] Whether prolonged periods without enteral feedings or the artificial nature of timed bolus nasogastric feedings in an immature infant contributes to the pathogenesis of NEC is presently unknown.

Two other factors may contribute to the vulnerability of the premature infant's gastrointestinal mucosa to injury. Robertson and co-workers[75] studied serum levels of beta-lactoglobulin, which is a macroglobulin constituting the major whey protein in cow's milk. They found decreasing amounts of this protein in serum with increasing gestational age. They postulated that premature infants have increased gastrointestinal absorption of macromolecules due to incomplete gut closure. This might predispose the less mature infant to develop local or systemic sensitization to milk proteins.

Poor local immunologic function may also compromise the immature bowel. At birth, the human intestinal mucosa has no secretory IgA, the major gastrointestinal immunoprotective antibody.[35] Human breast milk contains many immuno-active components, including sIgA, leukocytes, lysozyme, and lactobacillus growth factors. All of these are thought to be protective against gastrointestinal infection; indeed, the incidence of neonatal sepsis and diarrhea has been suggested to be lower among breast milk fed infants.[40, 49] These observations, combined with experiments in an animal model of NEC in which fresh breast milk protected newborn rats from a disease similar to NEC, led many investigators to hope that human milk feedings might be equally protective in human neonates. Unfortunately, this has not been demonstrated in the premature human; NEC is well documented in neonates exclusively fed human milk.[31, 51, 67, 72, 96]

Enteral Feeding

Perhaps more so than in any other area, conflicting opinions exist regarding the relationship of enteral feeding practices and the development of NEC. Ninety to 95 per cent of all infants who develop NEC have been enterally fed.[17, 48, 51, 66, 80, 81] Although hyperosmolar elemental formulas[13] and possibly hyperosmolar medications[92] have been associated with gastrointestinal mucosal injury and, subsequently, an increased incidence of NEC, other proposed theories of the role of oral feedings in the pathogenesis of NEC have not been proved.

One hypothesis of the relationship of enteral feedings and the etiology of NEC holds that the volume and absolute rate of enteral feedings contribute to NEC. Brown and Sweet[16] advocate a cautious feeding schedule

to prevent the development of this disease based on retrospective review of their experience. These neonatologists propose that a 1000-gm infant should be fed slowly and not be advanced to full enteral feeding until 2 weeks into the feeding protocol. Distention, hematest positive stools, or apnea warrants stopping enteral feedings for various periods of time. The risk of such a cautious approach is that of limiting enteral feedings at the time that may be critical to the postnatal adaptation of the intestine. Furthermore, there is a paucity of prospective studies related to feeding practices and the development of NEC. In the only prospective, randomized trial, Book and associates[14] demonstrated that two rates of formula volume increments (10 ml/kg/day vs. 20 ml/kg/day), designed to reach a reasonable maximum of 140 ml/kg/day, did not result in differences in the incidence of NEC. Goldman[34] reported in a retrospective uncontrolled study that an increased incidence of NEC occurred during a period when large absolute feeding volumes (greater than 150 ml/kg/day) or large increments in volume (greater than 60 ml/kg/day) were introduced into his nursery. Furthermore, Anderson and colleagues[3] retrospectively compared 19 infants with endemic NEC to 38 controls matched by birthweight and the time of admission. They found a highly significant difference in the daily increment of enteral feedings; patients with NEC had their feedings increased by a mean of 28 ml/kg/day, whereas on the same day, the control infants had their feedings increased by 17 ml/kg/day. The present issue of "how much is too much?" remains unresolved, but caution should be taken in that large increments of formula may stress the immature bowel.

The mechanism by which excess feeding may contribute to the development of NEC also remains obscure. Many researchers postulate that excess formula may be malabsorbed and pass to the colon where it may serve as a substrate for the colonic bacterial flora.[17, 48, 49, 53] Fermentation ensues with the production of hydrogen gas. Hydrogen was identified by Engel and colleagues[29] as the primary gas in the cysts of pneumatosis intestinalis. It would therefore seem that bacterial fermentation of formula-derived carbohydrates is a major component of the pathogenesis of necrotizing enterocolitis.

Ischemia, and subsequent damage to the gastrointestinal mucosa, has long been hypothesized as a factor in the pathogenesis of NEC. Touloukian and colleagues[88] developed an ischemic model of NEC in newborn piglets. They linked the "diving reflex," well documented during submersion in marine mammals, to the response during neonatal systemic hypoxia. During this reflex, the brain and heart are selectively perfused while blood is shunted away from other vascular beds, including the intestines. Factors implicated in the hypoxia-ischemic pathogenesis of NEC are many of the events commonly seen in high-risk premature infants: perinatal asphyxia, respiratory distress syndrome, hypothermia, hypotension, umbilical vessel catheterization, patent ductus arteriosus, and exchange transfusion (see Table 1). Nonetheless, these risk factors are often present among many infants in a NICU, and NEC does not develop in the majority of these infants. Furthermore, when studies compared control infants matched for gestational age with patients with NEC, few risk factors were consistently

identified.[32, 50, 85, 93, 96] In addition, NEC has been observed among premature infants without identifiable risk factors.[48, 68, 96]

Umbilical arterial catheterization has been implicated as a potentially ischemic event that might predispose to NEC.[13, 14, 19, 44, 60, 93] Large vessel thromboemboli have been a rare and inconsistent pathologic finding in patients dying with NEC.[34, 45] If the arterial catheter is indeed a factor, infants with catheters above the orifices of the mesenteric arteries should be at a higher risk than those with lower lying catheters. In a prospective trial of 341 infants randomized to high or low umbilical arterial catheter, the incidences of NEC in patients with catheters above and below the mesenteric arteries were similar.[52]

Neonatal polycythemia has been consistently demonstrated in controlled studies to be a risk factor for NEC.[12, 58, 93] It is unclear whether the hyperviscosity accompanying polycythemia results in sluggish gastrointestinal blood flow or whether the partial exchange transfusion used to treat polycythemia is the etiology of the ischemia. Work by LeBlanc and associates[59] in newborn dogs suggests that the hyperviscosity rather than the exchange transfusion is the cause.

The Role of Bacteria

Evidence has accumulated to support the hypothesis that NEC, at least in some cases, is a contagious disease.[15, 47, 76] The evidence can be divided into four categories: (1) epidemics of NEC, (2) association of outbreaks with specific bacterial pathogens, (3) interruption of epidemics by infection control measures, and (4) prevention of NEC with oral antibiotics.

Epidemics of NEC have been observed in most NICUs. The list of specific enteric pathogens associated with these outbreaks of NEC is rapidly increasing. Pathogens implicated thus far include: *Escherichia coli*,[25, 83] *Klebsiella*,[42, 74] *Enterobacter*,[71] *Pseudomonas*,[41, 89] *Salmonella*,[84] *Clostridia* species,[20, 30, 38, 43] *Coronavirus*,[21, 79] *Rotavirus*,[77] and enteroviruses.[55] Nonetheless, in most cases, no single enteric pathogen has been consistently isolated from each epidemic of NEC.[2] Confounding the issue are asymptomatic carriers who have also been reported during epidemics. Thus, it would seem that bacteria or viruses alone may not be sufficient to result in disease. Furthermore, most epidemics of NEC have not had any enteric virus of bacteria isolated from affected infants.[2] Nevertheless, epidemics have been terminated by routine infection control procedures such as cohorting of nurses and patients, strict isolation, and handwashing.[15, 47] Other investigators have reported a reduction in the incidence of NEC (prevention) in babies treated with oral aminoglycosides.[7, 28, 36]

Lawrence and associates[56] proposed that because of the sterile NICU environment and liberal use of broad-spectrum antibiotics, there may be a delay in the normal bacterial colonization of the neonatal intestine. Under these circumstances, they suggested that colonization with only one or a few species may alter the intestinal flora. It was postulated that the lack of competition among normal members of the gastrointestinal flora might contribute to the initiation of NEC. Yale and Balish,[94] in studies with germ free and monocolonized animals, have demonstrated a spectrum of bacterial

virulence, with certain strains inherently more virulent than others. In their studies, *Clostridium perfringens* was lethal in 99 per cent of animals, and *E. coli* was lethal in 77 per cent. Kosloske[53] went on to further postulate that elaboration of excessive amounts of bacterial toxin may be the critical initiator of intestinal necrois.

The most intriguing group of bacteria implicated as a pathogen in NEC are the clostridia organisms. These are obligate anaerobes with a propensity to infect ischemic tissue; they also produce hydrogen gas and enteric toxins. There are naturally occurring clostridial diseases in animals and humans that result in gastrointestinal disease with striking similarities to NEC. Pulpy kidney disease is seen in newborn lambs exposed to an increased carbohydrate load. The disease is characterized by intestinal dilatation, bloody stools, and, frequently, death; it is due to *C. perfringens* Type B enterotoxin.[26] There are also models for clostridia enterotoxin–mediated disease in humans. Highlanders of New Guinea contract a disease similar to NEC whenever a period of relative starvation is followed by a pig feast. These victims develop NEC characterized by abdominal distention, bloody diarrhea, and shock. Pathologic examination of clinical specimens reveals areas of submucosal and subserosal cellulitis, and gangrene. Pigbel is due to *C. perfringens* Type C enterotoxin and can be prevented by immunization with clostridial toxoid.[57] The analogies between these diseases and neonatal NEC are obvious and have fueled the search for clostridia organisms as primary pathogens in NEC. However, certain clostridia and clostridia toxins appear to be present in the normal flora of the neonatal gastrointestinal tract.[23, 82] Therefore, their role as primary pathogens has been challenged.[23, 26, 56, 57, 82, 87, 91]

Summary of Pathogeneses

A unifying theory of necrotizing enterocolitis must explain the development of disease in the enterally fed, high-risk neonate and in the apparently healthy term infant or in the unfed infant. It seems likely that what we identify as necrotizing enterocolitis represents one of a limited number of potential final reponses that the immature gastrointestinal tract may express after one or more unrelated stresses. It is appropriate to assume that because there are many stressful factors, there may also be a wide range of the severity of bowel injury and, therefore, a continuous spectrum of disease. Perhaps in benign forms of disease, the mucosa is exposed to a low inoculum of one injurious agent; whereas in the more severely affected infants, multiple stresses interact to synergistically produce more serious damage. Figure 8 is a diagram of the interaction of implicated agents. The relative contribution of each factor in any given case can only be speculative at the present time.

TREATMENT

Treatment must be instituted when signs suggestive of NEC appear, rather than being delayed until the diagnosis is confirmed by radiologic criteria. Current practice rests on the triad of prompt recognition, aggressive
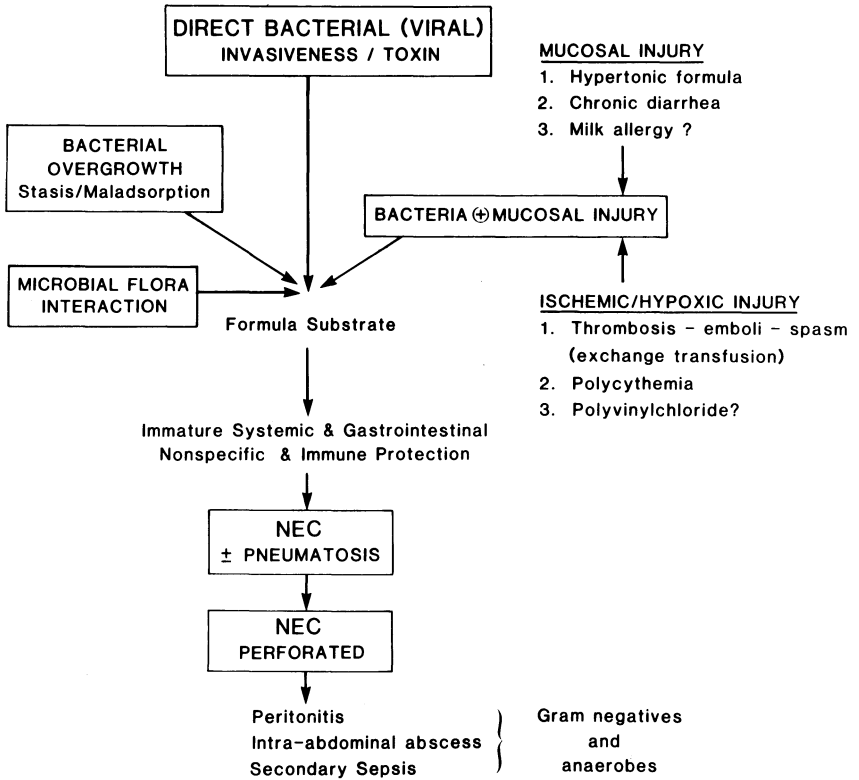
Figure 8. Proposed pathways for the development of necrotizing enterocolitis (NEC). Disease may be initiated by direct bacterial action or by bacteria acting together with malabsorption, abnormal microfloral environments, or mucosal injury. Local mucosal injury from intraluminal factors or systemically-induced ischemia may also contribute. These factors then act, in the presence of formula, as a microbial substrate (in an immunologically immature intestine) to progress further to necrotizing enterocolitis. (From Kliegman, R. M., and Fanaroff, A. A.: Necrotizing enterocolitis. N. Engl. J. Med., *310*:1093, 1984; with permission.)

monitoring, and early treatment in an effort to minimize the severity of the disease and prevent complications. Use of the staging criteria will be helpful in guiding therapeutic decisions.

As stressed earlier, the initial manifestations of NEC may be identical to those of neonatal sepsis. Therefore, all patients suspected of having NEC must be evaluated for sepsis, with a complete blood cell count, white blood cell count, differential and platelet counts, arterial blood gas measurements, and blood, stool, urine, and cerebrospinal fluid (CSF) cultures. Once NEC is documented, cross-table lateral abdominal radiographs should be taken every 6 hours during the acute period. Enteral feedings are discontinued, and the stomach is decompressed with a nasogastric tube. Parenteral antibiotics with broad-spectrum coverage against the common enteral flora in each individual nursery are instituted. In our nursery, mezlocillin, 150 mg/kg/day divided into doses given every 12 hours, and gentamicin, 2.5

Table 4. *Infectious Disease Control Measures for Necrotizing Enterocolitis*

1. Strict handwashing with Betadine or other germicidal agent.
2. Long-sleeve gowns and gloves at bedside of each patient.
3. Separate diaper and laundry bags for each patient. Handwashing after each diaper change.
4. Grouping and isolation of confirmed cases. Separate room and separate nurses for confirmed cases.
5. Personnel or visitors with gastrointestinal symptoms are excluded from the nursery.
6. Above measures to continue for 1 week after symptoms have cleared, or a minimum of 10 days, after symptoms have cleared.

Modified from Pediatr. Clin. North Am., 26:327, 1979.

mg/kg/dose every 8 to 12 hours, are used. Peak and trough gentamicin levels must be monitored as well as blood urea nitrogen (BUN) and creatinine. Other nurseries use parenteral clindamycin, 15 to 40 mg/kg/day divided every 6 to 8 hours, in addition to gentamicin. Because epidemics of NEC are well documented, infectious disease control measures such as those in Table 4 must be instituted. In addition to systemic antibiotics, enteric antibiotics have been used during the acute phase of NEC to avoid intestinal perforation.[8] However, recent evidence suggests that they do not prevent gastrointestinal perforation or alter the course of the disease. Furthermore, enteral gentamicin may even increase serum gentamicin levels and therefore is not indicated.[39]

Patients with Stage I, or suspected, NEC may benefit from bowel rest and antibiotic therapy for 72 hours pending culture reports and signs of clinical deterioration. At the end of this time, if symptoms have not progressed and the adominal radiographs remain negative, feeding may be reinstituted (see Table 3).

Cases of Stage III NEC will require longer periods of therapy (see Table 3). Most NICUs treat with approximately 2 weeks of bowel rest and intravenous antibiotics. Milder documented cases (Stage IIA) will be adequately treated with a shorter course; cases reported in the literature with mild NEC (benign NEC) have been treated for 3 to 10 days with both bowel rest and antibiotics.[61, 73] Unfortunately, there are no prospective controlled studies to guide us in the management of milder cases of NEC. We prefer to treat patients with Stage IIa NEC for 7 to 10 days (see Table 3). These patients have minimal systemic and abdominal signs and usually have normal results on clinical examinations and laboratory data within 24 to 48 hours of the onset of illness. During the period of bowel rest, maintenance nutritional needs can be met with peripheral intravenous alimentation.

The critically ill neonate with advanced Stage III NEC may develop a septic shock–like state. Edema of the intestine and, in some cases, peritonitis with ascites lead to tremendous third-space fluid losses. In neonatal animal models with septic shock, fluid volumes of 100 per cent of total blood volume were required to restore cardiac output.[11] In our nursery, these critically ill infants have required as much as 200 to 300 ml/kg/day above maintenance fluid requirements. Such large fluid infusions seem excessive but are often necessary to restore and maintain intravascular

volume. End points in fluid resuscitation are normalization of heart rate, blood pressure, and urine output, and reversal of metabolic acidosis as adequate tissue perfusion is restored. Buntain et al.[18] have reported the use of transcutaneous oxygen ($TcPO_2$) measurements as an adjunct to fluid therapy.[18] Adequate fluid resuscitation improves tissue perfusion, and because $TcPO_2$ measurement depends in part on tissue perfusion as the perfusion improves, the $TcPO_2$ should also improve. Buntain et al. found that a ratio of $TcPO_2/PaO_2$ equal to 0.7 correlates with survival. In their study, there were no survivors in the group receiving less than 150 ml/kg/24 hours. Fluids commonly used include saline, lactated Ringer's solution, and albumin. We prefer fresh frozen plasma and, if anemia is present, packed red blood cells. If anuria or oliguria is present, excessive fluid replacement may result in pulmonary edema; monitoring of central venous pressure and respiratory status may avoid this complication.

Inotropic drugs and pressor agents may be needed in addition to volume replacement, but they should not take the place of fluids. Dopamine may be very beneficial if it improves cardiac output, but, in high doses, it may reduce mesenteric blood flow and should be used cautiously (5 to 15 µg/kg/minute). If further inotropic support is needed, dobutamine may be added (5 to 10 µg/kg/minute) and increased as required. If metabolic acidosis is severe, a bicarbonate infusion may be beneficial.

Many neonates will develop thrombocytopenia and neutropenia in Stage III NEC. Margination of white cells rather than bone marrow neutrophil depletion produces neutropenia in NEC but may not require white cell transfusions as suggested in other cases of neutropenia associated with neonatal sepsis.[22] In addition, platelet transfusions are not indicated in the presence of thrombocytopenia unless thrombocytopenia is severe ($<10,000/mm^3$) or there is clinical evidence of systemic bleeding or massive gastrointestinal bleeding.

Currently, the only recognized absolute indication for surgery is intestinal perforation. It would be ideal to be able to select those infants with gangrenous bowel and proceed to surgery prior to perforation. Kosloske and Goldthorn[54] have advocated paracentesis and lavage as a method to select these patients. In their series, 36 infants with NEC underwent paracentesis; brown peritoneal fluid or bacteria was noted in 26. All 26 infants had gangrenous bowel resected at exploratory laparotomy. Ten infants had a negative paracentesis; four were subsequently taken to the operating room and were found to have necrotic bowel. It remains to be seen whether this technique will be useful in all Stage III patients in other neonatal centers.

During laparotomy, the surgeon is often faced with the difficult task of discerning necrotic bowel from hemorrhagic and dark bowel that is potentially viable. If a short segment of involved bowel is identified, it may be resected, and the remaining bowel may be reanastomosed at that time. More generalized involvement is usually treated with resection and enterostomy. However, if the entire bowel is gangrenous, the surgeon may decide not to perform resection at that time. Rather than creating a short bowel syndrome and a child incapable of sustaining life on enteral nutrition,
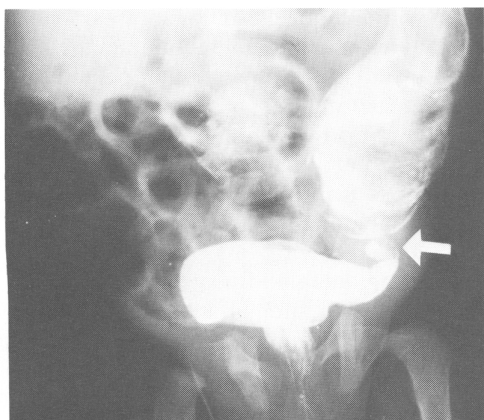
Figure 9. Barium enema in a patient presenting with abdominal distention, obstipation, and vomiting 4 weeks after the onset of NEC and 2 weeks after the reinstitution of formula feeding. A stricture was noted (*arrow*) and was subsequently resected. (Courtesy of Dr. B. Fletcher, Department of Pediatric Radiology, Case Western Reserve University.)

a second-look operation 48 hours later may permit better definition of viable bowel.

Following the acute phase of NEC, survivors enter a variable period of convalescence. It is prudent to reinstate feedings after NEC at small volumes of dilute formula and to increase to full calories by mouth over 7 to 14 days. Carbohydrate malabsorption may occur. A non–lactose-containing formula may be helpful to improve absorption in these patients. In very severe cases of malabsorption, one may also see malabsorption of simple sugars.

SEQUELAE

Mortality from classical NEC (predominantly Stage III) varies between 20 and 40 per cent. Morbidity is more difficult to assess. Strictures of the small or large intestine or both occur in approximately 10 to 22 per cent of survivors of NEC (Fig. 9).[24] Obstipation, hematochezia, vomiting, and abdominal distention are signs of stricture. Strictures, which are caused by formation of cicatricial scarring, become symptomatic 2 to 8 weeks after the acute illness. In addition, nonobstructing strictures are probably a common cause of gastrointestinal bleeding after NEC. Some of these patients have persistent melena and may require repeated blood transfusions. Post-NEC bleeding due to strictures may be due to a local, small area of active disease remaining at the base of the stricture. Strictures associated with post-NEC bleeding do not necessarily present with intestinal obstruction. Resection is not indicated for bleeding alone. Until we can predict those infants who will develop obstructive strictures, it may be necessary to screen all infants who survive Stage II or III NEC with a barium enema examination. Alternatively, one could observe the patient very carefully and educate the parents as to the signs of gastrointestinal obstruction. It is worthy to note that all strictures identified by routine barium enema examination do not

go on to obstruct. This observation further complicates the decision to perform routine x-ray studies in asymptomatic infants.

Infants who required surgical resection during the acute phase of NEC have a prolonged recovery phase. There is a gradual period of intestinal adaptation that occurs over a period of months to years. During this period, malabsorption is very common. Nonetheless, survival after extensive resection is possible. In general, if more than 70 per cent of the intestine is removed, serious nutritional consequences will predominate. Preservation of the terminal ileum and the ileocecal valve also appears to be an important determinant of successful enteric alimentation and survival. The ileum contains the majority of active transport sites for nutrient absorption, especially of fat, vitamin B_{12} and bile salts.[87] Furthermore, in both humans and experimental animals, the ileum has the greatest potential for adaptation. Patients with excessively short bowel may benefit from bowel lengthening procedures.[27]

Infants with ileostomy are at high risk for potentially life-threatening salt and water losses precipitated by otherwise minor gastrointestinal illnesses.[78, 95] Early closure of the ileostomy terminates these episodes.[78] It is prudent to initiate reanastomosis of the bowel at the earliest time possible, preferably before the infant is discharged from the NICU.

Infants with resected bowel are also at risk for late onset bacterial sepsis. Thirty-eight per cent of infants requiring bowel resection at Rainbow Babies and Childrens Hospital developed bacterial sepsis, which occurred at a mean onset of 17 weeks after surgery.[90] The presence of a central venous catheter increased this risk. Many of the causative organisms were those traditionally associated with "catheter sepsis": S. aureus, S. epidermidis, and Candida species. However, in 12 of 27 episodes (44 per cent), Enterobacteraciae were recovered. Meticulous catheter care, early catheter removal, and successful enteric alimentation may reduce the incidence of post-resection sepsis.

The long-term growth and neurodevelopment of survivors of NEC are very encouraging.[1, 37] After the prolonged hospitalizations required for the care of these infants, minor but transient developmental delays are frequent. The overall developmental morbidity is no higher than that due to prematurity, respiratory distress syndrome, or other problems present prior to the onset of necrotizing enterocolitis.

GOALS FOR THE FUTURE

It is obvious that we are far from a consensus on the etiology or etiologies of NEC. It is likely that NEC may be more than one disease process. Future studies must clearly differentiate patients with different severities of illness, perhaps by using staging criteria and classification.[49] We can then begin to investigate and define the pathogenesis of NEC. Once the pathology is understood, we can identify those infants at risk and possibly prevent NEC.

General pediatricians need to be aware of this serious gastrointestinal

disease of the newborn. Increasingly, we are seeing transferred from newborn nurseries infants with fulminant NEC or the long-term sequelae of NEC. Furthermore, graduates of the NICU who are reverse transported back to level II nurseries remain at risk for NEC.

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