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NECROTIZING ENTEROCOLITIS AND INFECTION

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Necrotizing enterocolitis (NEC) is an important complication of prematurity in infants who survive the first week of life.[30,31] It is clinically indistinguishable from sepsis neonatorum in its early stages. Typically gastrointestinal tract manifestations such as abdominal distention, ileus, and gastrointestinal tract bleeding predominate. The clinical diagnosis of NEC depends on criteria initially proposed by Bell and coworkers (Table 1),[6] and is confirmed radiologically by the presence of pneumatosis intestinalis or portal venous gas (stage II) or at surgery (stage III) (Figure 1).

Necrotizing enterocolitis usually involves the distal small intestine and proximal colon. Its symptoms include bland necrosis, mucosal edema, and hemorrhage. Typically there is little inflammation and no evidence of bacterial invasion in tissue specimens obtained early in the course of the clinical disease.[8,45] In contrast to other diseases causing bland bowel necrosis, lesions from infants with NEC also include submucosal or subserosal collections of gas.[2] The source of the gas has received little study, but it may be the product of bacterial fermentation.[19] Attention has focused on the frequent finding of uninvolved mucosa in various stages of repair, suggesting that multiple previous episodes of subclinical mucosal damage typically occur in infants in whom NEC develops.[2]

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Table 1. CLINICAL STAGING OF NECROTIZING ENTEROCOLITIS BY BELL'S CRITERIA

Stage	Clinical	Radiograph	Treatment
I. Suspect NEC	Abdominal distention Poor feeding Vomiting	Ileus	Medical
II. Definite NEC	All of the above Gastrointestinal bleeding	Pneumatosis intestinalis Portal vein gas	Medical
III. Advanced NEC	All of the above Septic shock	All of the above Pneumoperitoneum	Medical and surgical

NEC = necrotizing enterocolitis.
Data From Bell MJ: Perforation of the gastrointestinal tract and peritonitis in the neonate. Surg Gynecol Obstet 160:20, 1985.

CAUSES OF NECROTIZING ENTEROCOLITIS

The cause and pathogenesis of NEC are unknown. In the 1970s, when NEC was recognized as a frequent complication among increasingly premature infants, a classic triad of risk factors was identified as essential for NEC development.[45] This triad included (1) intestinal damage from an ischemic or hypoxic insult, (2) the presence of bacteria, and (3) metabolic substrate for bacteria, such as infant feedings. In the ensuing 20 years, improved neonatal survival caused a shift in the age spectrum of NEC away

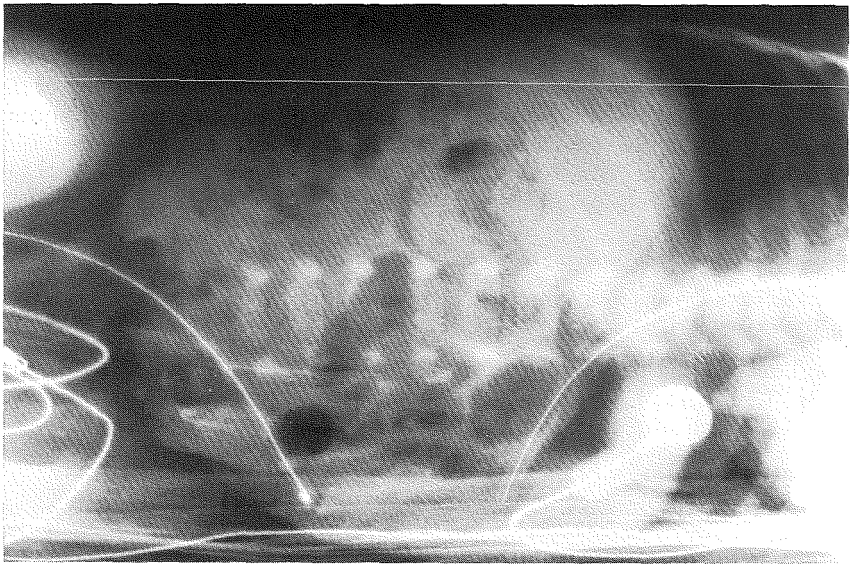

Figure 1. Abdominal radiograph of an infant with pneumatosis intestinalis and necrotizing enterocolitis.

from asphyxiated infants toward seemingly healthy "growers" in the second or later weeks of life.[56] Although ischemic or hypoxic insults still cause NEC in some infants, careful epidemiologic studies have not defined risk factors for a damaged infant other than general immaturity or prematurity.[32,55,57] Evidence supporting the necessity of enteral feeding and infection is only circumstantial. Whether the pathogenesis of NEC requires an infectious pathogen is a critical question.

Infection as a Cause of NEC

If Bell's criteria are used for diagnosis of medical (stage II) NEC, then a bacterial cause is necessary by definition. Necrotizing enterocolitis that is not proved surgically (stage III) is defined radiologically by the presence of pneumatosis intestinalis (stage II). Because the origin of the intramural gas is presumed to be bacterial fermentation, both gas-producing bacteria and a substrate (milk) are required for pneumatosis intestinalis to occur. Both therefore must be present to fulfill the clinical case definition. Whether bacteria or other infectious agents are necessary for causality (Figure 2A), or whether the bacteria (with feedings) generate an epiphenomenon that is useful to clinicians as a serendipitous diagnostic test, is an important question (Figure 2B). In the latter case, a cryptic insult such as local hypoperfusion has already damaged the intestine (subclinical NEC). The injured bowel is detected in enterally fed infants by the abnormal localization of fermented products of the colonizing bowel flora. Necrotizing enterocolitis in unfed infants usually does not show pneumatosis intestinalis.[2]

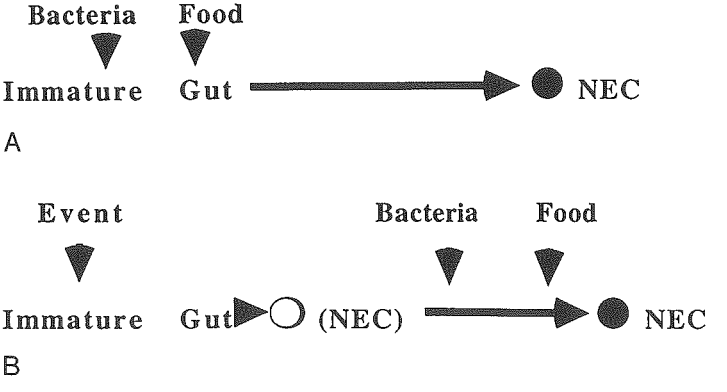

Figure 2. Two hypothetical series of events leading to clinical NEC as defined by Bell's criteria. *A,* Bacteria and a food substrate interact with an immature intestine to damage the gut, producing pneumatosis and clinical NEC *(closed circle). B,* An event (such as local hypoperfusion) damages an immature gut to produce subclinical NEC *(open circle).* Bacteria then ferment a food substrate, producing pneumatosis and leading to the diagnosis of clinical NEC *(closed circle).*

Several lines of evidence have been used to support the thesis that infection is necessary for NEC development.[29,42] This evidence includes the isolation of infectious agents from infants with NEC, epidemiologic characteristics of outbreaks suggestive of an infectious process, and decreased incidence of NEC resulting from preventive interventions.

Frequently NEC is complicated by bacteremia or peritonitis.[29] Early reports implicating some bacteria were tempered when recovered organisms were those that normally colonize the intestinal tracts of premature infants. Such colonizing organisms include aerobes (coagulase-negative staphylococci), facultative anaerobes (Enterobacteriaceae and enterococci), and strict anaerobes (Bacteroides, Clostridium bifidobacterium).[9,34,53] An enrichment of certain colonizing bacteria in cohorts of symptomatic infants has been reported during outbreaks of NEC, but considerable overlap with the flora content of unaffected infants usually exists.[5,21,24,25,41,44] Overgrowth of a single predominant stool organism has been implicated in NEC development.[7,27,41] Whether this overgrowth precedes NEC or is a reflection of a compromised enteric luminal environment is unknown. The link between fecal isolates and ileocecal microbiology also is tenuous. When interpreting the isolation of stool flora organisms, it is often impossible to distinguish opportunistic from true pathogens.

Necrotizing enterocolitis also has been reported in severely ill neonates with systemic bacterial, viral, or fungal diseases.[1,25,35,40] Whether these NEC episodes should be considered the direct local consequence of NEC-producing organisms or whether NEC occurs as a result of other mechanisms in a severely stressed neonate is not clear. Sepsis may be similar to hypoxia/asphyxia in precipitating a subset of NEC cases.

It is remarkable that NEC has not been associated with most well-known enteric pathogens.[42] In the few instances in which enteropathogens (Salmonella, enterotoxigenic *Escherichia coli,* rotavirus) were identified in outbreaks among neonates, the clinical presentation was that of diarrhea.[15,44,54] Among these stressed infants, NEC develops in some. The anatomic distribution of NEC in these cases does not necessarily correlate with the predilection for small or large intestine of pathogens such as enterotoxigenic *E. coli* or rotaviruses.[15,43] The diarrhea that occurred in these outbreaks was often bloody, which is atypical for the pathogenesis of disease produced by enterotoxigenic *E. coli,* rotavirus, and coronavirus.[12,15,43]

Bacterial toxins have been proposed repeatedly as causes of NEC. There are many confounders in elucidating their importance in the pathogenesis of NEC. Most bacteria produce toxins that are measurable in vitro. In contrast, known potent toxins, such as *Clostridium difficile* toxins, are isolated commonly in vivo in asymptomatic infants.[16] Other toxins, such as staphylococcal delta toxin, have no effect at the negative redox potential of the colon.[47] The potential role of toxins elaborated by colonizing enteric flora has been reviewed.[46]

Infections, whether systemic or localized to the intestinal tract, precipitate NEC in a subset of affected infants. In this sense infection, like hypoxia/asphyxia, is a severe stress on the infant. Whether a local enteric infection is necessary for the development of NEC is still unclear.

Table 2. INFECTIOUS AGENTS ASSOCIATED WITH NECROTIZING ENTEROCOLITIS

Enteropathogenic Viruses
Rotavirus[43]
Coronavirus[12]
Enteropathogenic and Toxin-producing Bacteria
Coagulase-negative staphylococcus[48]
Salmonella[54]
Enterotoxigenic *Escherichia coli*[15]
Clostridium difficile[42]
Other Bacteria
Escherichia coli[52]
Klebsiella[29]
Enterobacter[41]
Pseudomonas aeruginosa[24]
Clostridium butyricum[26]
Clostridium perfringens[34]
Generalized Sepsis Syndromes
Staphylococcus aureus[40]
Klebsiella[25]
Enterovirus[35]
Torulopsis[1]

Epidemiologic Proof of an Infectious Cause

The most compelling evidence for an infectious cause of NEC is found in reports of temporal or geographic outbreaks.[29,42] Many pathogens have been reported, but a unifying pathogen or pathophysiologic mechanism has not been identified (Table 2). Because NEC, like pneumonia, is a clinical syndrome, this should not be surprising. Many organisms cause pneumonia, and many organisms may precipitate NEC. Most of the reported outbreaks have been incomplete in the inclusion of unaffected, concurrent controls and in examining all known bacterial, toxin, and viral causes. In most outbreaks, a definite pathogen has not been identified.[10] Therefore, an unrecognized enteric agent may still be responsible for NEC development.

Many investigators postulate that an immature intestine is the primary risk factor. If this is true, then the pathophysiology of epidemic NEC may be distinct from that of endemic NEC. In epidemic NEC, diarrhea also develops in many caregivers.[10,22] The history of staff illness is usually not volunteered and caregivers must be questioned specifically. Illness among hospital staff implies circulation of an enteropathogen that infects adults and neonates. Prompt use of cohorting and other infection-control practices has been reported to stop outbreaks of NEC,[10] but proof is uncertain. Given the nature of epidemics, it is difficult to determine when the cessation of an outbreak is random or when it is the result of infection-control measures.[33]

PROPHYLAXIS OF NECROTIZING ENTEROCOLITIS

The hypothesis that NEC is an infectious disease can be tested by strategies to prevent infections (primary prophylaxis) or their spread (sec-

ondary prophylaxis or infection control.) The efficacy of such interventions is equivocal. Several very small trials of oral antibiotic prophylaxis have been reported, with a protective effect shown in most of them.[11,17,23,38] This may reflect a tendency toward publication of studies with positive results. Enthusiasm for this approach has waned because of concern about the selection of resistant organisms.[11,14,17] Furthermore bacterial colonization is beneficial and necessary for proper enteric and immunologic development and for efficient caloric absorption.[28]

Since the 1960s, neonatologists have reported that human milk offers protection against NEC.[39] Animal models substantiate these opinions,[3] although the microbiology of the intestines of most small animal models is substantially different than that of human infants.[51] Although human milk is protective against infectious diarrhea, it has been difficult to substantiate a similar protective effect against NEC in human trials.[29,36,37] Perhaps because of this, use of human milk in neonatal units has declined.[36] Even when postulating a protective effect of breast milk, it is not clear whether this effect would be due to potential antimicrobial factors in human milk or to other factors such as Bifidobacterium colonizing factor, endogenous growth factors for the immature intestine, or differences in substrate composition of human milk and artificial milk formulas.[29]

Oral administration of immune globulin has been reported to be effective in preventing NEC, presumably because of its antimicrobial properties,[18] but more studies are needed to support this observation. A protective effect may be more difficult to show in centers with low NEC rates.

NEC AS A CAUSE OF INFECTION

Although it is still unclear whether infections are necessary causes of NEC, NEC must be treated as an infectious disease. It occurs clinically as a sepsis syndrome and frequently is complicated by bacteremia or peritonitis, which require antibiotic treatment. Empiric antibiotic coverage of infants with NEC should be based on organisms prevalent in a particular nursery, especially coliforms, coagulase-negative staphylococci, and enterococci. There are differences among neonatal centers about whether to treat anaerobic infections empirically,[4,13,20,49,50] but little data in the literature support or refute either practice. Intra-abdominal abscesses are the primary complication of anaerobic contamination of the peritoneum. Abscesses do occur as complications of NEC but are infrequent.[4,50] Some nurseries do not routinely provide coverage for anaerobes because increased strictures associated with use of clindamycin has been reported.[20]

Because NEC does occur in outbreaks, and often when caregivers are also ill, strict cohorting of infants and nursery staff is very important. Although the role of specific pathogens as a cause of NEC is debated in the literature, prompt implementation of infection-control procedures may curtail an outbreak and protect infants from this devastating syndrome.

FUTURE DIRECTIONS

The North American criteria for NEC are still those proposed by Bell and coworkers.[6] Standardization of the definition has been valuable in refining the medical and surgical approaches to treating NEC and in the careful epidemiologic studies that rejected many of the early putative risk factors for this illness. Nevertheless, 20 years have past since NEC was first described and the cause remains unclear. Bell and coworkers' criteria assert that NEC is caused by feedings and bacteria. The pathologic findings of regenerating mucosa suggest that damage may occur much earlier and is clinically silent. In the search for the cause of NEC, it may be worthwhile to propose and test other definitions of NEC and pre-NEC for use as clinical research tools. These may allow us to escape the circularity of the current definition and identify new risk factors.

Appropriate bacterial colonization and fermentation are essential for proper intestinal function and for efficient use of dietary intake.[28] Empiric antimicrobial coverage has evolved without trials in many institutions as the importance of newer pathogens (such as coagulase-negative staphylococci) has been recognized and as new drugs (such as third-generation cephalosporins) have emerged.[38] As use of quinolones and other anaerobe-sparing antibiotics is applied to pediatric patients, controlled trials of these agents as gut-sparing, empiric therapy for neonatal sepsis should be considered.

During outbreaks, increased attention should be paid to illness among nurses, physicians, and other staff. In searching for the specific cause of an outbreak, it may be easier and as useful to obtain microbiologic or serologic samples from ill 60-kg NICU staff as from 1.0-kg infants. Isolation of recently identified enteric agents (for example, Norwalk, caliciviruses, and astroviruses) may be possible through careful use of polymerase chain reaction, newer immunologic reagents, and other diagnostic methods.

Ultimately the only clear risk factor for most cases of NEC is prematurity. Prevention of prematurity is the most effective means to prevent NEC.

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