# Part 1. Current Controversies in the Understanding of Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC) has widespread implications for neonates. While mostly affecting preterm neonates, full-term neonates, especially those with congenital heart disease, are also at risk. Although the exact pathogenesis of NEC remains elusive, three major factors, a pathogenic organism, enteral feedings, and bowel compromise, coalesce in at-risk neonates to produce bowel injury. Initiation of the inflammatory cascade likely serves as a common pathway for the disorder.

Clinical signs and symptoms range from mild feeding intolerance with abdominal distension to catastrophic disease with bowel perforation, peritonitis, and cardiovascular collapse. Vigilant assessment of at-risk neonates is crucial. When conservative medical management fails to halt injury, surgical intervention is often needed. Strategies to decrease the incidence and ultimately prevent NEC loom on the horizon, such as exclusive use of human breastmilk for enteral feedings and administration of probiotics.

Necrotizing enterocolitis (NEC) is an acquired condition of diffuse necrotic injury to the mucosal and submucosal layers of the bowel. It is the most serious gastrointestinal (GI) disorder that occurs during the neonatal period.[1-3] The entire GI tract, from the stomach to the anus, is susceptible. The distal small gut and proximal colon are involved most frequently.[1] The lesions may be diffuse and contiguous or patchy and more focal in nature. Systemic signs and symptoms accompany GI injury.

Neonatal NEC initially was described in case reports of GI perforations in 1825 and 1891. In 1888, 5 deaths after long-segment bowel necrosis and multiple perforations were reported.[3,4] Credit for naming the disorder was given to Schmid and Quaiser in 1953 and then Rossier in 1959.[3-5] It was not until the mid-1960s that an in-depth delineation of this disorder, including clinical and radiographic findings, was published by Berdon[6] and then Mizrahi[7] and their respective colleagues.

Despite numerous case reports, decades of clinical experience, and multiple research studies examining this condition, a complete understanding of NEC remains unclear. Part 1 of this series provides a comprehensive review of current discoveries and ongoing controversies surrounding this disorder. The definition, incidence, and staging are discussed. Risk factors and differences in the presentation of NEC in preterm and full-term infants are compared and contrasted. The interaction between mucosal injury, infection, enteral feedings, and prematurity is presented, along with important clinical considerations. Part 2 of the series will address the diagnosis of this disorder, outline key controversies in the medical and surgical management, and examine the prognosis and outcome of affected infants. The nursing care of infants with NEC will be presented along with a discussion of novel prevention strategies.

NEC is best defined along a continuum from suspected cases to infants with advanced disease. Suspected cases present with nonspecific signs and may reflect feeding intolerance, sepsis, or GI bleeding caused by stress or other factors.[8] In 1978, Bell et al presented a system for the uniform clinical staging of neonates with NEC.[9] Later, other authors expanded these stages to include systemic, GI, and radiographic features[10,11] ( ). Use of a staging system with consistent disease definitions improves the clinician's ability to compare cases and interpret research findings more accurately.[2]

**Table 1.**

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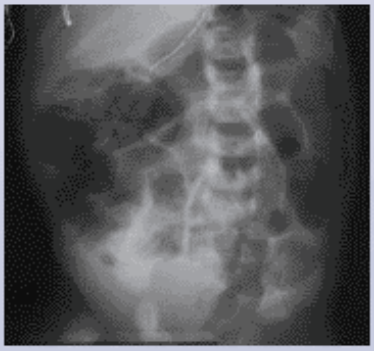
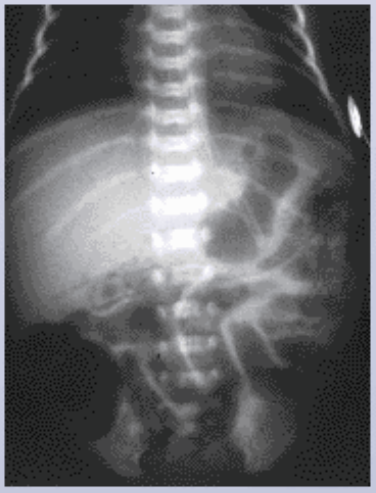
## Stages of NEC[1,8-10]

| Classification | Stage I<br>Suspected NEC | Stage II<br>Proven or Definite NEC | Stage III<br>Advanced NEC |
|---|---|---|---|
| Systemic signs | • Temperature instability<br>• Apnea<br>• Bradycardia<br>• Cyanosis<br>• Lethargy<br>• Glucose instability<br>• Mimics signs of infection | • Stage I signs plus<br>• Possible mild metabolic acidosis<br>• Mild thrombocytopenia<br>• Poor perfusion | • Stage I and II signs plus<br>• Signs of shock<br>• Rapid deterioration of vital signs<br>• Mixed acidosis<br>• Respiratory compromise<br>• Hypotension<br>• DIC<br>• Neutropenia |
| GI signs | • Increased NG residuals<br>• Abdominal distension<br>• Vomiting (may be billious)<br>• Ileus<br>• Possible abdominal tenderness<br>• Occult or frank blood in stools | • Stage I signs plus<br>• Absent bowel sounds<br>• Abdominal tenderness<br>• Possible abdominal cellulitis or RLQ mass | • Stage I and II signs plus<br>• Peritonitis<br>• Marked abdominal tenderness & distension |
| Classic radiographic signs | • Normal<br>• Possible mild GI dilation (dilated loops of bowel) | • Intestinal dilation<br>• Fixed dilated loops of bowel<br>• Pneumatosis intestinalis<br>• Ascites<br>• Possible portal venous gas | • Likely pneumoperitoneum |

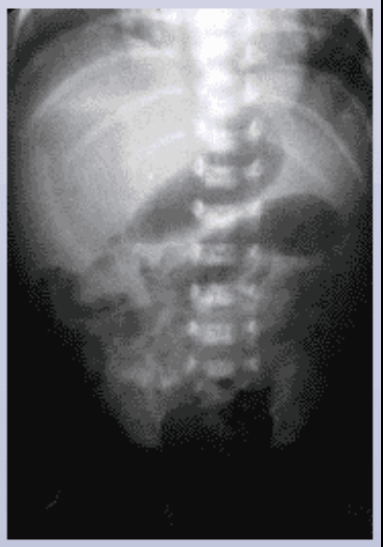
Sample radiographs



Stage I



Pneumatosis



Pneumoperitoneum with free air

NOTE. Clinical manifestations and radiographic features of various stages of neonatal NEC.
Abbreviations: GI, gastrointestinal; NEC, necrotizing enterocolitis; NG, nasogastric; RLQ, right lower quadrant; DIC, disseminated intravascular coagulation.

Source: Adv Neonatal Care © 2003 W. B. Saunders

The incidence of NEC varies. It is stated most often as 1% to 7% of all neonatal intensive care unit (NICU) admissions, or 1 to 3 per 1,000 live births, and it occurs equally in males and females.[1-4] Most published reports calculate NEC incidence

for an individual institution over a specified time. That information is then expressed as a percentage of all NICU admissions with NEC. Further extrapolation is often made to the number of cases per 1,000 live births at the institution. The mortality rate for NEC is estimated to be 11.5 to 12.3 per 100,000 infant deaths, greatly exceeding that of other GI surgical disorders.[4]

Institutional, regional, and gestational age variations in prevalence exist. Preterm infants account for 70% to 90% of total NEC cases, the more preterm the infant the higher the risk.[2,3] By 36 weeks of gestation, there is a sharp decrease in incidence, supporting the hypothesis that GI maturation plays an important role in the development of NEC.[1,2,4]

In 2001, the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported (from a data set of 14 centers) an overall incidence of proven NEC of 7% in very low-birth-weight infants (VLBW) (401 to 1,500 g).[12] The incidence increased to 15% for infants between 501 to 600 g. Although the survival of the smallest preterm neonates has improved over time, NEC-related morbidity remains unchanged.

A report from Australia suggests that NEC incidence in preterm neonates born at <29 weeks gestation is higher in hospitals with in-house surgical facilities compared with hospitals without these resources, despite statistically similar mortality rates.[13] The Vermont Oxford Network database examined information for close to 20,000 neonates (501 to 1,500 g) from 196 hospitals, to find that the presence of intrauterine growth restriction increased the risk of NEC.[14] The true incidence of NEC may be clouded by institutional practices or differences in specific patient and gestational age characteristics.

Historically, the frequency of NEC evolved with the establishment of NICUs in the 1960s. The disease continued to escalate as neonatal care improved and the survival and absolute number of pre-term neonates increased.[4,8] Countries with low rates of preterm births (eg, Japan, Sweden) have a correspondingly low prevalence of NEC.[4] highlights risk factors for NEC. Prematurity is the major risk.

**Table 2.**

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## Risk Factors for NEC[1-4,8,15,54-58]

| Preterm Neonates | Full-Term Neonates |
|---|---|
| • GI immaturity | • Congenital heart disease |
| • Immature host defense mechanisms | • Other coexisting conditions such as hypothyroidism, Down syndrome, small bowel atresia, or gastroschisis |
| • Aggressive enteral feedings | |
| • PDA | |
| • Indomethacin therapy | • Polycythemia |
| • Mucosal injury (eg, hypoxic-ischemic insults) | • Conditions compromising GI oxygenation and/or blood flow (eg, SVT) |
| • Presence of bacteria within GI lumen | • Exchange transfusion |
| • Nursery/NICU overcrowding | • Perinatal "stress" |
| | • Aggressive enteral feedings |

NOTE. Comparison of proposed risk factors for NEC in preterm and full-term neonates. Identification of specific variables remains controversial.
Abbreviations: GI, gastrointestinal; PDA, patent ductus arteriosus; NICU, neonatal intensive care unit; SVT, supraventricular tachycardia.

Source: Adv Neonatal Care © 2003 W. B. Saunders

The specific vulnerabilities of the preterm infant's GI tract to NEC, although not completely understood, are likely related to an immature GI mucosal barrier and immune response, along with impaired circulatory dynamics from hypoxic-ischemic insults.[8] Premature infants may experience vasoconstriction, hypotension, and thrombosis leading to decreased GI perfusion and GI mucosal injury.[3] Indwelling umbilical artery catheters (UAC) may decrease blood vessel diameter and flow, leading to GI ischemia.[4] The potential for UAC-induced arterial spasm or microemboli formation is a well-documented risk of therapy. Small emboli may cause visible blanching or cyanosis of a neonate's lower extremity. However, decreased GI perfusion may be clinically silent, until clinical symptoms of NEC appear.

Preterm infants commonly have a patent ductus arteriosus (PDA) with its inherent left-to-right shunt, diminishing blood flow to the mesenteric vascular bed.[13] Treatment of the PDA with indomethacin, a highly effective, potent vasoconstrictor, is associated with numerous adverse effects including GI bleeding, isolated ileal perforation, and NEC.[15]

The efficacy of indomethacin therapy and the risk of NEC were evaluated by retrospective data analysis of 250 preterm neonates with echocardiogram-confirmed PDA who were treated with indomethacin.[15] Closure of the PDA was achieved in 89% of cases. Ninety infants developed NEC, with 34 of these requiring surgical intervention. NEC was associated with younger gestational age ($P < 0.04$), lower birth weight ($P < 0.001$), and prolonged ventilator support ($P < 0.02$).

The authors then compared these infants with a matched control group without PDA or indomethacin therapy.[15] The incidence of NEC in control infants was 13.7% compared with 35% in the study group ($P < 0.02$). The need for surgical

intervention and mortality was similar between groups. Perforation rates in the control group were 12.3% compared with 30% in those treated with indomethacin ($P < 0.05$). A 16% decrease in mesenteric blood flow was observed after indomethacin administration.[15] This was of concern because GI hypoperfusion with resultant mucosal hypoxia is implicated in gastric perforation and NEC. Ischemia and ulceration may follow hypoperfusion, allowing for bacterial invasion, the setup for NEC.

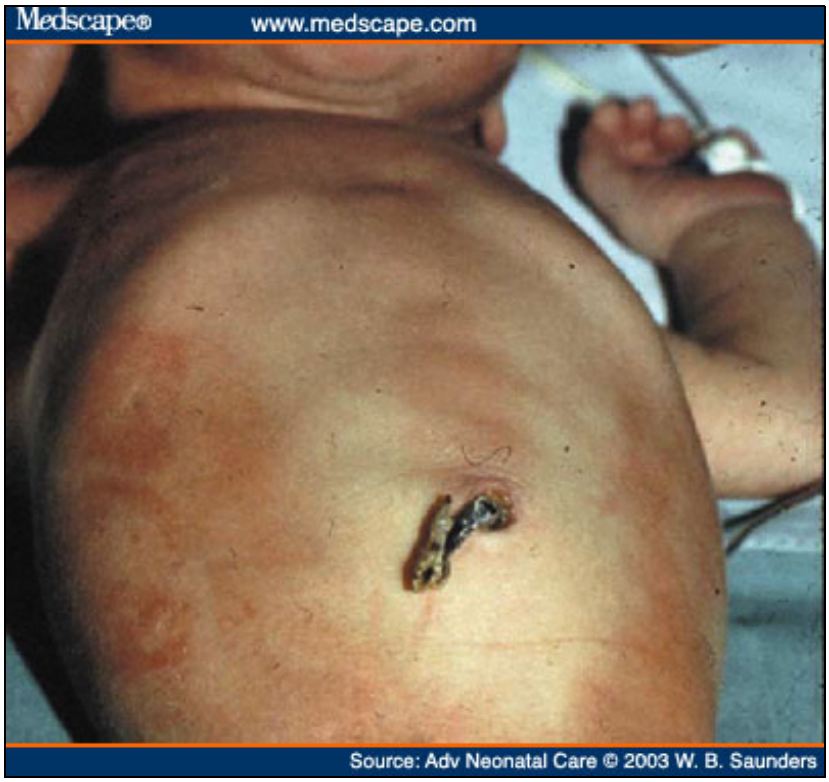
In summary, caregivers must be aware of both the risks of an untreated PDA and those associated with treatment. Both the left-to-right shunt and mesenteric steal associated with PDA and the acute decreased blood flow associated with indomethacin increase the preterm infant's risk for NEC.

The age of onset of NEC varies inversely with birth weight and gestation; NEC in VLBW neonates occurs later than in older and larger infants.[1,2] For infants <30 weeks gestation, the mean age at diagnosis is approximately 20 days.[2] Those ≥34 weeks have an onset of approximately 5 days. See Sidebar 1 for a discussion of NEC in full-term neonates.

Symptoms of NEC may be sudden and profound or insidious and subtle. An insidious onset is more common in growing preterm neonates.[11] The clinical presentation and diagnosis of NEC are based on well-defined staging criteria.[8-10] Stage I is nonspecific and mirrors other processes such as feeding intolerance, infection, or GI bleeding. Gross blood in the stool is a common finding associated with NEC, with an incidence of 25% to 63%.[4]

No single laboratory feature is diagnostic of NEC. Neutropenia, caused by sequestration of neutrophils in the peritoneal fluid, is more common than an elevated white blood cell count.[4] The worst prognosis is associated with infants who have the lowest neutrophil counts, progressively lower absolute neutrophil counts, and persistent thrombocytopenia.[8]

Abdominal distension and feeding intolerance are initial clinical indicators of NEC.[11] Abdominal distension progresses as gas builds up in the bowel. Continued abdominal distension further compromises GI blood flow (Fig 1).




Example of neonatal abdominal distension. Note abdominal wall erythema, seen here in a neonate with NEC. Photograph courtesy of Francois I. Luks, MD, Division of Pediatric Surgery, Hasbro Children's Hospital and Brown University School of Medicine, Providence, RI. Reprinted with permission (http://bms.brown.edu/pedisurg/).

Identifying pathologic abdominal distension in tiny preterm neonates is challenging because of their size, inherently weak abdominal musculature, the presence of medical equipment, and coexisting disease states and therapies. Despite the

imperative for developmentally sensitive care, there is no replacement for serial physical assessment by the bedside care provider. Clinicians must consider numerous causes of abdominal distension unrelated to NEC; inadvertant distension from nasal continuous positive airway pressure is a frequent culprit.

A common practice in the NICU is to measure gastric residual (GR) before nasogastric (NG) feedings. This is a theoretic, albeit indirect, measure of feeding intolerance. Although incorporated in GI signs of stage I NEC, there is little published evidence to support the predictive value of GR. No uniform or concise definition of normal GR has been evaluated and tested. Further, the relationship between GR and feeding intolerance in tiny preterm neonates has not been established.

On a practical level, NG tubes that are placed too high (in the lower esophagus or upper segment of the stomach) may fail to measure existing residual accurately. Conversely, tubes placed too deeply may be in the jejunum. Both the diameter of the syringe used to aspirate GI contents and the nature and size of the NG tube may have an impact on the volume aspirated. The negative pressure generated during aspiration may move the lumen of the tube against the stomach wall, precluding the return of gastric contents.

A recent randomized, controlled multicenter trial assessed GR in 99 infants with birth weights <1,000 g (mean gestation, 26 weeks; mean birth weight, 820 g) who were receiving breastmilk or formula.[16] Bolus gavage feedings of 12 mL/kg were initiated at 48 hours of age. Infants were fed every 2 hours and, if tolerated, the volume was advanced by 12 mL/kg every 24 hours. GR was assessed before each feeding. Study protocol dictated that a GR of 2 mL was acceptable for neonates ≤750 g, and 3 mL was accepted for neonates weighing 751 to 1,000 g. Five infants developed NEC with clinical diagnosis of absent bowel sounds, abdominial tenderness, and pneumatosis intestinalis. The mean GR in these 5 neonates was 1.2 mL and did not predict NEC. GR volume or color did not have a significant effect on feeding volumes in the study. In the absence of other clinical manifestations, green GR at <2 to 3 mL was not a significant finding for feeding intolerance and NEC in this population. The authors state that in an ongoing trial in neonates with birth weights up to 1,500 g, the authors accepted GR up to 5 mL/kg. It is important to note that bilious GR may be indicative of other forms of GI obstruction, such as duodenal atresia or malrotation, requiring further urgent evaluation.

Although neonatal stool patterns are not formally included in the clinical staging of NEC, they are often the focus of clinical discussions. A retrospective chart review compared stool patterns in infants with and without at least stage II NEC (n = 68; mean gestational age, 29 weeks).[17] Those infants who developed NEC passed their first stool approximately 14 hours after the first feeding as compared with non-NEC controls, who first passed stool 13 hours before the first feeding ($P$ = 0.008). Further research evaluating stool patterns is needed. Documentation of stool patterns may be helpful in identifying infants at risk for NEC.

A useful clinical marker might facilitate the early differentiation of neonates who are at low risk for NEC (eg, stage I), avoiding the prolonged cessation of enteral feedings and the use of unneeded laboratory tests, radiographs, and antimicrobial agents. Various investigations have evaluated the use of a number of potential clinical markers, including the following[3,4,18,19]:

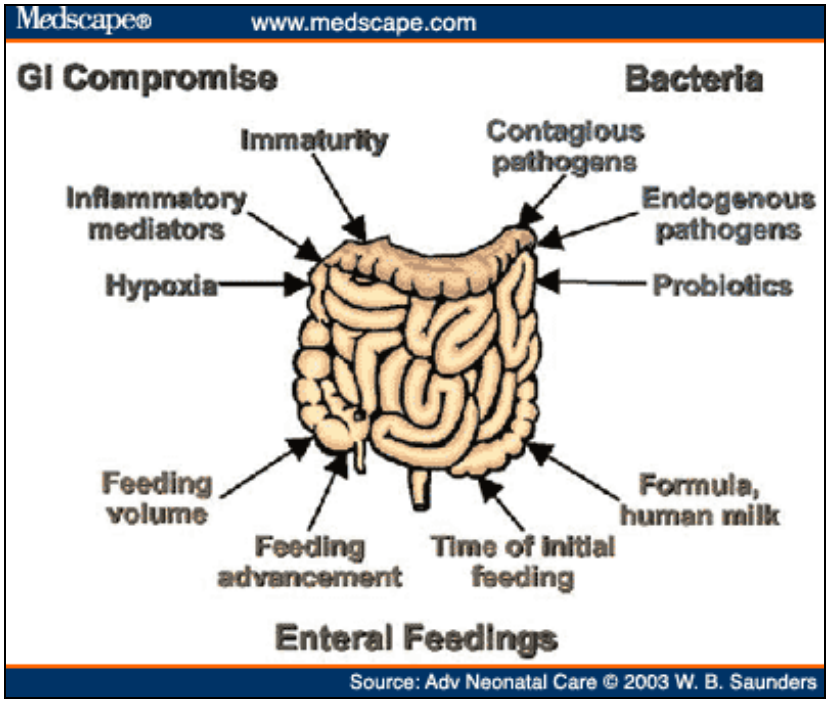
- GI tonometry (measurement of intramucosal pH by equilibration with a fluid-filled balloon)
- Urinary D-lactate levels
- Exhaled breath hydrogen
- Endotoxin elevations in stool
- Plasma intestinal fatty acid binding protein

Although investigations continue, widespread clinical application of these markers is limited.

Glutamine and arginine, amino acids known to be essential fuel for GI muscle cells, have been found to be decreased for at least 10 days before clinical recognition of NEC.[20] It is unclear if this is a marker of disease or a contributing factor in pathogenesis. Low arginine levels may result in insufficient nitric oxide, a compound synthesized through the arginine pathways, which is needed for bowel vasodilatation and repair. In adult populations with multisystem failure, dietary

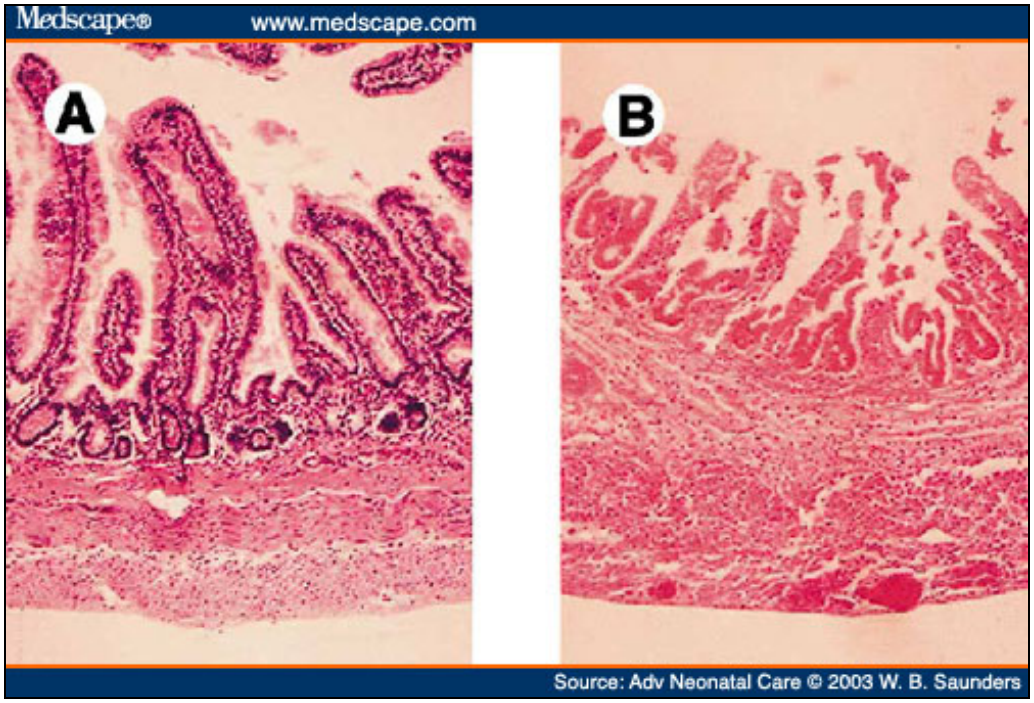
augmentation with increased arginine has proven beneficial.[20] Further research is needed to determine if neonatal parallels exist.

The precise pathogenesis of NEC is elusive. For a brief review of GI anatomy and physiology, see Sidebar 2. As early as 1975, the triad of GI mucosal injury, presence of bacteria in the gut, and introduction of a metabolic substrate (eg, feedings) was proposed as the etiology of bowel necrosis[3] (Fig 2). Ongoing investigation of the role of ischemic mucosal injury in NEC has now progressed to the molecular level.




Pathogenesis of NEC. Three major factors play a role in the development of NEC: enteral feedings, GI compromise, and bacterial invasion.

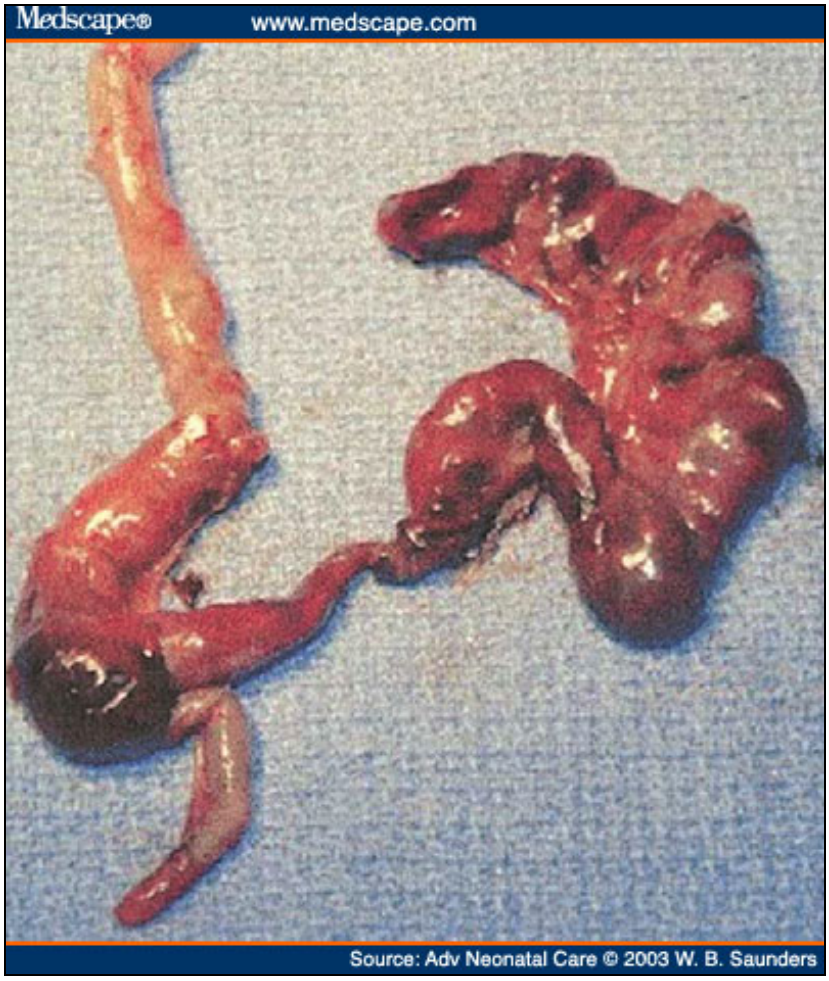
Histologic findings in NEC include GI mucosal ulceration and edema, hemorrhage, vascular congestion, and in advanced cases, full-thickness coagulation necrosis with perforation; all of these findings are consistent with ischemia.[1,4,8,21] Early mucosal lesions lead to marked broadening of the mucosal villi, with advanced NEC causing bleeding and sloughing of surface epithelium. Hydrogen gas pockets, produced by gas-forming organisms, arise in the submucosa and subserosa. Severe necrosis may completely obliterate the villi (Fig 3A and B).




Microscopic images of (A) normal bowel and (B) characteristic findings of NEC, which illustrates hemorrhagic necrosis, beginning in the mucosa and extending to the muscular bowel wall, where the potential for perforation exists. NEC frequently involves the terminal ileum. Reprinted with permission from WebPath, courtesy of Edward C. Klatt, MD, Florida State University College of Medicine, Tallahassee, FL (http://medlib.med.utah.edu/WebPath).

Maternal cocaine use during pregnancy may result in vasoconstriction and GI ischemia from cocaine's

-adrenergic action, predisposing infants to NEC.[22] An increased incidence of surgical NEC, mortality, and massive GI gangrene has been found in cocaine-exposed infants (Fig 4). There were no differences in rates of perinatal asphyxia, hypotension, or UAC placement.




Example of necrosis of right colon and ileum from a neonate with NEC. Photograph courtesy of Francois I. Luks, MD, Division of Pediatric Surgery, Hasbro Children's Hospital and Brown University School of Medicine, Providence, RI. Reprinted with permission (http://bms.brown.edu/pedisurg/).

Conflicting evidence exists regarding the role of maternal preeclampsia and NEC. Because preeclampsia exposes the fetus to a chronic reduction in uteroplacental blood flow, the potential for decreased GI perfusion exists. A recent study (n = 242) measured umbilical artery end-diastolic flow in 41 neonates who developed NEC.[23] Contrary to historical data, no association between absent end-diastolic flow with or without abnormal fetal heart rate patterns at birth and the incidence of definitive NEC was found.[24,25]

During a sustained underwater dive with suboptimal cardiac output, certain mammals demonstrate an autonomically mediated diving reflex, resulting in redistribution of blood flow away from the GI tract and toward vital organs. In 1969, Lloyd proposed a similar phenomena in asphyxiated neonates as a major factor in the development of NEC.[26] Correspondingly, the most common sites for NEC, the distal ileum and proximal colon, lie between watershed areas of the superior and inferior mesenteric arteries.[21] These watershed areas represent potential zones of decreased perfusion during ischemia.

Recent information weakens the connection between bowel ischemia, NEC, and the diving reflex postulate. Although the relationship seems rational, the underlying premise is false. Lloyd's theory was that decreased GI blood flow impaired local tissue oxygenation, leading to bowel necrosis. In most cases, however, decreased GI blood flow leads to microvasculature compensation, preserving tissue oxygenation.[21] Only severe ischemia disrupts the process.

Current evidence suggests that although asphyxic events impair GI perfusion, the damage is transient and not great enough to cause GI necrosis without some additional factors.[21] Hypoxic and ischemic damage to the bowel may actually be a secondary event aggravated by components such as inflammatory mediators, immature GI vascular control, and chemical irritation.[8]

Epidemiologic case control studies suggest that hypoxic-ischemic insults are not primary risk factors in the development of NEC. Prematurity is the only independent risk factor consistently identified.[2,3,8] Additionally, many cases of NEC occur in convalescing preterm neonates with no known antecedent hypoxic-ischemic stressors (eg, low Apgar scores, mechanical ventilation, umbilical catheters, significant apnea).[3,8] Further research is needed to answer questions regarding the association of ischemia and NEC.

The impact of inflammatory mediators on a variety of disease processes is under intense investigation because of their influence on regional blood supply, capillary permeability, and leukocyte migration.[27] Inflammatory mediators are likely to be a component of GI mucosal injury's role in the development of NEC.[4,27] Inflammatory cytokines, proteins produced by macrophages in response to infection, worsen any hypoxic cellular damage.

The cytokines interleukin-6 (IL-6), produced in response to circulating bacteria, and tumor necrosis factor (TNF), a key mediator in septic shock, have been examined in neonates with NEC.[28] Although TNF did not differ between groups, IL-6 levels were elevated in neonates with bacterial sepsis and NEC compared with those with isolated bacterial sepsis or those with NEC without bacteremia.[28] The majority of infants with NEC have negative blood cultures; thus, testing for IL-6 elevations, which measures a systemic response to severe bowel injury, may not be clinically useful.[29]

Elevations in the proinflammatory cytokines IL-8 and IL-10 have correlated significantly with both NEC severity and time after onset of symptoms.[29] This test may have the potential to help differentiate between infants likely to recover from NEC with little intervention from those at risk for severe disease.[29]

Another inflammatory mediator implicated in the pathogenesis of NEC is platelet activating factor (PAF), an endogenous phospholipid messenger. PAF levels were measured in 164 at-risk neonates with a mean gestation of 30 weeks before onset and during progression of NEC.[30] Higher PAF levels were found in 11 infants who developed NEC.

Immaturity of GI mucosal defense mechanisms against invading organisms may play a role in the pathogenesis of NEC ( ). Lysozyme (muramidase), a bactericidal enzyme, appears early in fetal life and is secreted in the bowel by Paneth cells in the small intestine. Delay in Paneth cell maturation may impair production of lysozyme and defensins, both potent antimicrobial factors.

**Table 3.**

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**Components of GI Immaturity Implicated in Pathogenesis of NEC[8]**

| Immunologic Factors | Luminal Factors | Immature GI Mucosal Barrier Factors |
|---|---|---|
| • Decreased secretory IgA | • Decreased gastric $H^+$ ion output | • Mucin blanket composition |
| • Decreased GI T lymphocytes | • Decreased proteolytic enzyme activity | • Microvillus properties |
| • Limited antibody response | • Decreased motility | • Microvillus composition |
| | | • Increased permeability to bacteria |

Abbreviations: GI, gastrointestinal; IgA, immunoglobulin A.

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Lysozyme deficiency was evaluated by comparing infants with small bowel mucosa (n = 10 infants with NEC; mean gestational age, 31.3 weeks) with control infants.[31] All control samples stained positive for lysozyme. However, no lysozyme was found in 9 of 10 NEC samples, strongly indicating an absence of lysozyme in the GI mucosa of preterm and term neonates with NEC. A delay in GI maturation is suggested as a contributing factor in NEC; the potential to use Paneth cell inducers as prophylaxis against NEC has been proposed.[31]

Another component believed to contribute to GI immaturity is enteric human defensins. Defensins are a family of antibiotic peptides with a broad range of antibiotic activity, found in circulating neutrophils and epithelial cells of the bowel. Low levels of human defensin 5 (HD5) are present in the neonatal bowel at 24 weeks of gestation; amounts increase as gestation

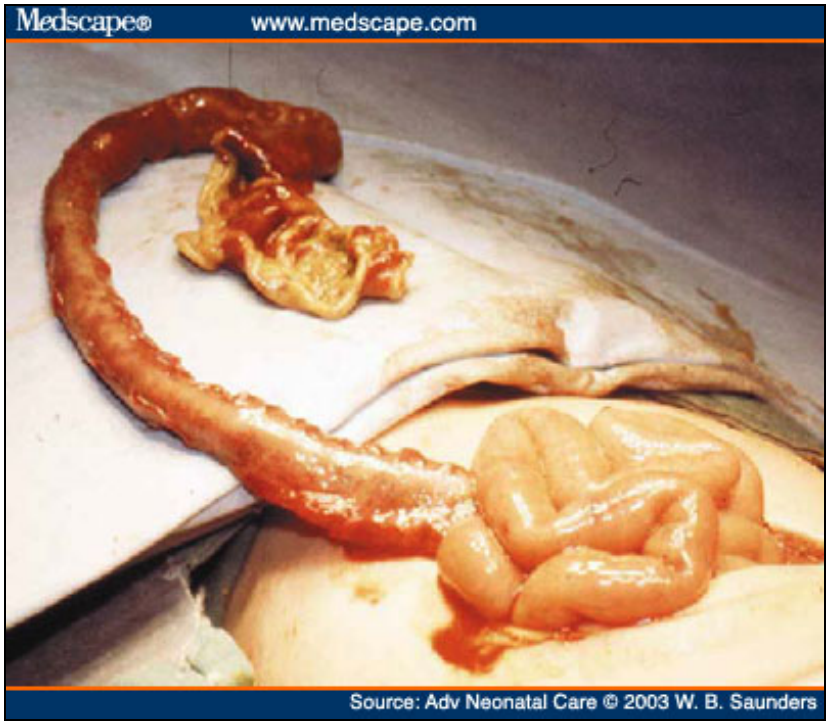
continues.[32] Elevated levels of messenger RNA HD5 in NEC GI mucosal tissue samples were found in 6 infants with NEC, compared with controls.[32] The process of NEC is proposed as a trigger for messenger RNA HD5 production, indicating a role for this GI defensin in the pathophysiology of the NEC.[32]

Epidermal growth factor (EGF) appears to be important during GI development and mucosal repair.[33] Salivary glands are a major source of EGF production. Preterm neonates have low levels of EGF, which increase with gestational age. The use of exogenous EGF administration to salvage neonates who are terminally ill with NEC has been suggested.[33]

A recent analysis compared EGF levels in saliva, serum, and urine in premature infants with and without NEC.[33] EGF levels were significantly lower in saliva and serum of the NEC group, who were also more preterm, supporting EGF as a possible factor in the pathogenesis of NEC. Future development of clinically useful markers of EGF levels may guide practice. The potential for exogenous EGF administration as an NEC prevention measure calls for further exploration and testing.

In the GI tract, the T lymphocyte C-KIT plays an important role in local immunity; C-KIT numbers increase with inflammation. C-KIT cells monitor alterations in cell membranes infected by bacteria or virus, and destroy the invading organism. Because invading organisms or normal GI bacterial flora extend into the bowel lumen in 40% of NEC cases, the role of C-KIT warrants exploration.[34] Postmortem specimens from 9 neonates with proven NEC were compared with agematched control specimens.[34] Controls displayed normal distribution of C-KIT cells in the GI submucosa. Infants with NEC had significantly fewer C-KIT cells, despite the presence of local inflammation. Lower CKIT numbers may impair local gut immunity, allowing for bacteria, even normal flora, to overgrow, initiating the inflammatory cascade leading to NEC.

NEC rarely occurs in utero, suggesting that bacterial colonization is associated with the disease.[8,35] The absence of NEC in the sterile in utero bowel and in stillborn infants strengthens the role of infection in its pathogenesis.[35,36] Others assert that by definition (via NEC staging criteria), bacteria are a necessary ingredient in the disease process.[37] The radiographic hallmark of NEC, pneumatosis intestinalis, signifies intramural gas, which is believed to be a result of hydrogen gas produced during the bacterial fermentation of enteral feedings[36] (Fig 5). Although rare, infants who were never fed and develop NEC seldom have pneumatosis.[37]




Example of gross pneumatosis intestinalis in a neonate with NEC. GI narrowing is also seen. Photograph courtesy of Francois I. Luks, MD, Division of Pediatric Surgery, Hasbro Children's Hospital and Brown University School of Medicine, Providence, RI. Reprinted with permission (http://bms.brown.edu/pedisurg/).

Breath hydrogen levels increase before the clinical onset of NEC.[36] Increased urinary D-lactate excretion in neonates with NEC is probably a result of increased bacterial activity.[36] Many believe that the systemic illness associated with NEC results from bacterial toxins or from strains of organisms that are high carbohydrate fermenters, leading to the lowering of bowel pH with resultant injury.[38]

Most NEC occurs sporadically; however, case clustering has been reported.[1] Clustered cases tend to affect larger infants and those with better Apgar scores and fewer perinatal complications, and are associated with decreased case-mortality rates.[2] Case clusters are often associated with nonspecific GI disturbances among other neonates and the NICU staff, leading many to speculate that these outbreaks are infectious in origin.[4]

Although NEC clusters or epidemics may provide persuasive evidence for the role of infection in pathogenesis, a unifying pathogen remains elusive.[37-39] A variety of organisms, including Enterobacteriaceae, *Clostridia*, coagulase-negative staphylococci, *Escherichia coli*, and *Klebsiella*, have been associated with NEC. Even during outbreaks, typically no single pathogen is implicated.

Case reports of NEC caused by nosocomially acquired echovirus have been published.[40] Overcrowding is associated with outbreaks, supporting the hypothesis of an infectious agent with a higher attack rate during crowding.[2] It also reflects an increase in NICU census, resulting in a greater number of at-risk neonates.

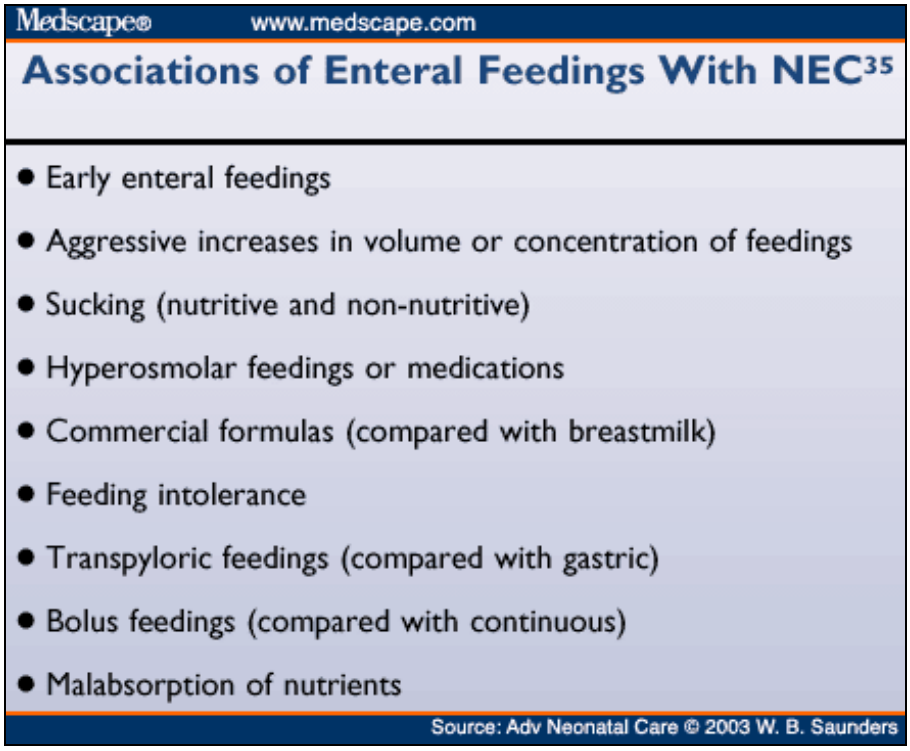
Despite the failure to establish a direct relationship between a specific microbe and NEC, the presence of bacteria appears crucial for the development of NEC.[36-38] Many organisms isolated from stool, blood, or peritoneal fluid in neonates with NEC are also commonly found in the bowel. Exposure to broad-spectrum antibiotics shortly after birth may markedly alter the GI flora. This could result in an intestinal environment with large numbers of bacteria more conducive to the development of NEC.

The microflora of the duodenum of VLBW infants is initially sterile or contains gram-positive organisms. Colonization changes with time[36]; gram-negative organisms, primarily *E. coli*, *Klebsiella*, and *Enterobacter* species, appear once enteral feedings are started, and predominate after 15 days of age.[36] The high incidence of Enterobacteriaceae may be related to decreased secretion of gastric acid, the normal line of defense against small bowel colonization. Limited GI motility and bowel stasis common in premature infants may also contribute. Thus, functional GI immaturity in the presence of gram-negative organisms may trigger the inflammatory process, resulting in tissue injury and ultimately NEC.[41]

Translocation is the ability of bacteria to cross bowel mucosal epithelium and enter the lymphatic system or bloodstream. Strains of *E. coli* not previously recognized as pathogenic are able to translocate across mucosal cell layers.[41] The exact mechanisms responsible are ambiguous, but likely do not involve initial tissue injury. The ability of bacteria to cross epithelial cell layer is a crucial first step in the cascade of events leading to NEC.[41] It is unclear whether bacteria and substrate interact in the immature GI tract to damage the bowel or if stressors damage the immature GI tract to produce an environment in which bacteria proliferate in the presence of available substrate.

The GI tract is an active organ in utero. The fetus swallows amniotic fluid composed of nutrients, growth factors, and immunoglobulins.[8] Although occasionally NEC occurs in neonates who have never been fed, more frequently it occurs in preterm infants on enteral feedings. Aggressive feeding advancement, often defined as greater than 20 kcal/kg/d, has been implicated.[8] See for feeding factors that have potential associations with NEC.

**Table 4.**




The delay of enteral feedings in sick preterm neonates may decrease the normal GI functional adaptation, resulting in subsequent feeding intolerance. Delayed feedings and/or starvation are associated with the following[35,42-44]:

- Fewer mucosal antibody cells due to limited exposure to gut antigens
- Reduction in the local immune response to foreign organisms
- Decreased enzyme levels (eg, disaccharidases)
- Damage to mucosal barriers
- Increased susceptibility to infections
- Morphologic injury
- Decreased secretion of immunoglobulin A (IgA)
- Bacterial overgrowth

Early enteral feedings have been proposed to avoid the anatomic and physiologic alternations associated with delayed enteral feedings.[35,42] A recent systematic review of the literature found few randomized studies addressing the role of early or minimal enteral feedings in preterm neonates.[43,44] Based on the limited results available, early feedings had no significant effect on weight gain, NEC, mortality, and age at discharge. Although no increase in NEC was found with early feedings, it remains unclear if early or delayed feedings are of benefit in high-risk neonates.[43]

Others have proposed the use of minimal enteral feedings or subnutritional feedings in premature infants. A meta-analysis of minimal enteral feedings showed an overall decrease in days to full enteral feedings, total days that feedings were held, and total length of stay in the hospital, with no perceptible effect on NEC.[44] The reviewers concluded that the evidence for benefit of minimal enteral feedings was not convincing because of the small number of available studies and limitations of study methods.[44]

The relationship between the rate of advancement of feedings and NEC remains controversial. Although some retrospective case control studies suggest that rapid advancement of feedings is linked to NEC,[45-47] a recently published prospective randomized controlled trial provides contrary evidence.[48] A total of 185 neonates with birth weights 501 to 1,500 g

(gestational age ≤34 weeks) were randomized according to weight stratification into 2 groups. The fast group started feedings at 35 mL/kg/d with incremental advancements of 35 mL/kg/d (5-day schedule to full feedings). The slow group had feedings started at 20 mL/kg/d with advancements of 15 mL/kg/d (10-day schedule to full feedings). Both groups received a 20-cal/oz commercial formula initially and were advanced to a 24-cal/oz product when full feedings were reached (160 mL/kg/d).

No difference in the incidence of NEC (stage ≥II), intestinal perforation, mortality from NEC, age at NEC diagnosis, or feeding intolerance between groups was found.[48] The study incidence did not differ significantly from historical data from the same NICU. Although birth weight in the fast group was regained more rapidly, this did not translate to earlier discharge from the hospital. A small sample size leading to a type II error (failure to reject a false null hypothesis) existed in this study, warranting cautious interpretation. Feeding increments >35 mL/kg/d do have the potential to alter the risk for NEC and require further study.

The incidence of NEC before and after introduction of a standardized feeding protocol was recently reported.[5] Before standardization, the incidence of NEC was 4.8% (n = 477 infants 1,250 to 2,500 g). After introduction of the standardized protocol, the incidence declined to 1.1% (n = 467 matched cohorts). The protocol consisted of feedings of 3 to 4 mL, initiated at 24 to 72 hours after birth, and advanced by no more than 20 mL/kg/d. The exclusive use of breast-milk was approximately 35% in the standardized group compared with 20.5% in the nonprotocol group ($P$ = 0.002).

Multivariate analysis confirmed that the change in feeding protocols was an independent variable for the decreased incidence of NEC.[5] The risk of NEC decreased by 60% in neonates fed only breastmilk, although this did not reach statistical significance. Encouraging mothers to provide breastmilk for the baby's initial feedings, even if they do not wish to continue breastfeeding during infancy, is essential. Not only does this foster active participation in care and decision making, but it also may lessen the risk of NEC.

Breastmilk feedings are associated with a decrease in NEC in premature infants. The unique immunologic properties of breastmilk, such as secretory IgA, specific macrophages and lymphocytes, presence of nonpathogenic bacteria such as bifidobacteria, and secretory molecules with antibacterial properties, may all contribute to this protective effect.[49-51] Preterm infants are born before transport of most antibodies across the placenta. Because specific IgG production is delayed in newborns, and 33% of VLBW neonates have substantial hypogammaglobulinemia, the IgA content of breastmilk may be an important facet of GI mucosal protection.[3]

Breastmilk promotes the growth of bifidobacteria, which produce acetic and lactic acid that in turn inhibits the growth of many pathogenic, gram-negative organisms.[50,51] VLBW infants have a delay in the establishment of GI bifidobacteria.[50,51] This delay appears related to decreased intake of human milk.

There are a limited number of experimental studies evaluating the incidence of NEC in breastfed infants. However, they consistently report a decreased incidence of NEC. In a study of 40 neonates, 15 who were fed frozen breastmilk and then developed NEC were compared with 25 formula-fed neonates who subsequently developed NEC.[52] Those fed breastmilk were smaller, more premature, had a greater degree of perinatal stress, and required more ventilator support than their formula-fed peers. The authors concluded that frozen breastmilk did not fully protect the neonates from NEC. However, because the formula-fed neonates were at decreased risk for NEC because of their increased maturity and being less stressed, breastmilk did potentially provide some protection against NEC.

A multicenter trial provides additional evidence that breastmilk provides protection against NEC.[53] Neonates in the study were divided into groups fed only formula, those receiving formula and expressed breastmilk and those supplied with only breastmilk. The lowest incidence of NEC (1.2%) was in the group given only breastmilk, compared with 7.2% and 2.5%, respectively, in the other groups, suggesting a protective effect of breastmilk.

Various associations have been suggested between enteral feedings and the development of NEC ( ). Consensus on a cause and effect relationship and the practical aspects of feeding preterm neonates is lacking. In a review of available information, LaGamma and Browne summarize clinical criteria for gut readiness to help answer the question of when to start and when to discontinue feedings[35] ( ).

**Table 4.**

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## Associations of Enteral Feedings With NEC[35]

- Early enteral feedings
- Aggressive increases in volume or concentration of feedings
- Sucking (nutritive and non-nutritive)
- Hyperosmolar feedings or medications
- Commercial formulas (compared with breastmilk)
- Feeding intolerance
- Transpyloric feedings (compared with gastric)
- Bolus feedings (compared with continuous)
- Malabsorption of nutrients

Source: Adv Neonatal Care © 2003 W. B. Saunders

**Table 5.**

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## Clinical Criteria to Help Guide Enteral Feeding Practices

| Indications of Readiness to Feed[35] | Indications to Consider Discontinuing Feedings[35] |
|---|---|
| • Absence of abdominal distension | • Presence of abdominal distension |
| • Benign abdominal examination (eg, soft, nontender, no masses) | • Gastric residual volumes of 50% or more of a previous feeding |
| • No bilious emesis or nasogastric aspirate | • Decreased bowel sounds |
| • Presence of normal bowel sounds | • Occult or gross blood in the stools |
| • Stool passage* | • Respiratory or cardiovascular instability |
| • No evidence of gastrointestinal bleeding | • Bilious vomiting or nasogastric drainage |
| • Respiratory, cardiovascular, and hematologic stability during mechanical ventilation | |

*Most ELBW neonates pass stool by 1 week of life.

Source: Adv Neonatal Care © 2003 W. B. Saunders

NEC prevention strategies targeted at issues of GI maturation, enteral nutrition, mucosal immunity, inflammatory mediators, and infectious agents require further study. Bedside clinicians must be alert for signs and symptoms of NEC because preterm neonates and selected full-term neonates are at high risk. Important clinical guidelines include the following:

- Encourage all mothers to initially provide breastmilk for their preterm neonates, even if the mother does not wish to continue breast-feeding.
- Educate all staff about NEC clinical staging criteria to increase awareness of subtle disease signs.
- When on rounds, discuss risk factors and time frames for NEC development.

- Evaluate any untoward GI findings (eg, abdominal distension, feeding intolerance).
- Keep abreast of evidence-based correlates for detection or prevention of NEC.
- Establish unit-based feeding protocols based on current evidence.

True reductions in the incidence of NEC likely depend on limiting preterm births. Health care providers having close contact with infants at risk for NEC play a vital role in recognition and management of this potentially debilitating disease.

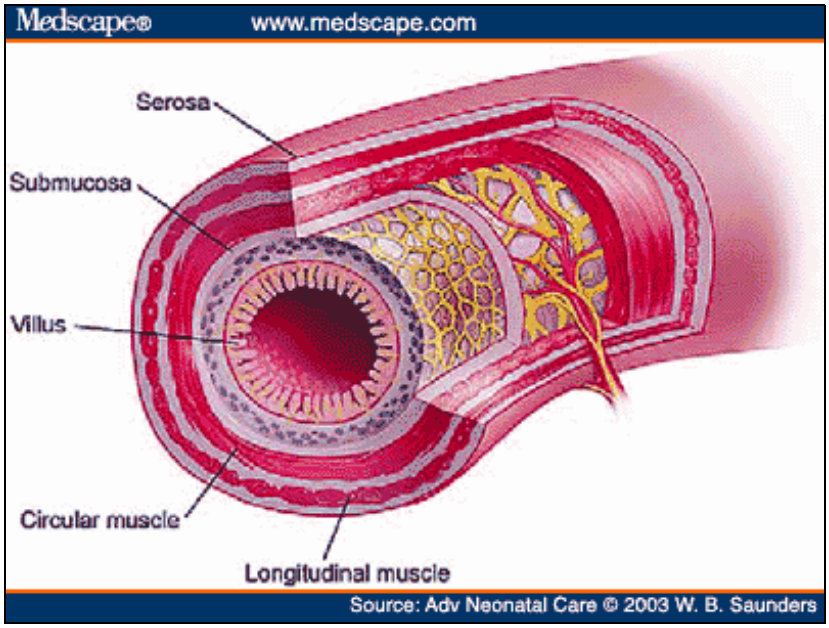
NEC is rare in full-term infants. Over a 25-year period in one institution, only 23 of 226 cases of NEC occurred in full-term infants.[4] NEC is described as a different disease in the full-term infant, with direct injury to the GI mucosa playing an important role.[2,54] Congenital heart disease (CHD), hypothyroidism, Down syndrome, small bowel atresia, and gastroschisis are often present in full-term infants with NEC.[54-58]

Neonates with CHD have a 10-fold increased risk for the development of NEC.[54] Recent review of a database including 643 neonates with CHD admitted over a 4-year period reported NEC in 21 (3.3%).[54] Thirteen infants presented with NEC before surgical intervention for CHD. The majority (10 of 21) had hypoplastic left heart syndrome, with an overall NEC incidence of 7.6% among neonates with this complex lesion.

Alterations in mesenteric blood flow make infants with CHD vulnerable to NEC.[54] Neonates with many forms of CHD (eg, hypoplastic left heart syndrome, coarctation of the aorta, truncus arteriosus) have a widened pulse pressure and low diastolic pressure leading to retrograde diastolic flow in the descending aorta with the potential for mesenteric ischemia.[57] Surgical intervention requiring cardiopulmonary bypass adds to the potential for low perfusion states leading to mesenteric ischemia.[56]

There are minor variations in the clinical presentation of NEC between preterm and full-term infants.[4,58] In full-term infants, the age of onset of symptoms tends to be earlier and occurs more rapidly, with signs and symptoms as early as the first day of life.[2] Thrombocytopenia and acidosis are not outstanding features in these infants when compared with the preterm infant.[4] There may be fewer systemic manifestations, and pneumatosis intestinalis occurs less frequently. The mortality rate for NEC is also lower in the full-term infant.

Approximately 85% of fluids ingested and those secreted by the GI tract on a daily basis are absorbed via the small intestine. During fetal development, the small intestine undergoes several invaginations, where the small bowel becomes ensheathed. The result is formation of multiple villi and microvilli. Intestinal villi, with their branching projections and folds, increase the surface area for absorption tremendously. With a combination of the villi and microvilli in the small intestine, it is estimated there is an absorptive surface equal to that of a tennis court in adults.



The villus is the functional unit of the small intestine, specifically designed for its important role of absorption of nutrients. Located over the entire surface of the small intestine, the villus can be found from about the common bile duct to the ileocecal valve. A single layer of columnar epithelium containing capillaries and lymphatic vessels lines the villus. Each epithelial cell has a characteristic brush border area containing as many as 1,000 microvilli in adults. The brush border protrudes into the GI chyme.

There are 3 layers of smooth muscle in the small intestine. One is circular and the other 2 run longitudinally. The wall of the small intestine is lined by mucosa, or mucous membrane and serosa, or serous membrane. The mucosal layer contains the villi. The serosa continues onto the mesentery, the peritoneal fold that encircles most of the small intestine and connects it to the posterior abdominal wall. Nerve fibers, lymphatic, and blood vessels are located in the mesentery.

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