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Necrotizing Enterocolitis: A Continuing Problem in the Neonate

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Necrotizing enterocolitis (NEC) is a syndrome of diverse etiologies with a significant mortality rate affecting mostly prematurely born stressed infants. Now recognized as a discrete entity, it had been poorly defined because other conditions seem to represent the same entity. A number of risk factors have been identified that appear to "trigger" NEC, though these have been questioned because they have been present just as frequently in premature and older infants who did not develop NEC as in those that did. Recently, maternal cocaine use has been added to the suspected risk factors. A steady improvement in the survival of babies with NEC has been due largely to a high index of suspicion of the disease and early, aggressive medical management.

Necrotizing enterocolitis (NEC) is a syndrome of diverse etiologies with a significant mortality rate. It was first reported as a discrete entity in 1964 [1], with the first surgical experience published in 1967 [2]. For many years it has been a poorly defined entity, with some of the previous reports of functional ileus, intraabdominal abscess, spontaneous perforation of the ileum, appendicitis, neonatal necrotizing colitis with perforation, ischemic enterocolitis, and neonatal gut infarction seeming to represent the same entity.

Incidence

Necrotizing enterocolitis appears both sporadically and in clusters. In a prospective study an incidence of 2.4 per 1000 live births was derived, representing 2.1% of all admissions to neonatal intensive care units (ICUs) in 12 centers [3].

Clinical Presentation

Necrotizing enterocolitis presents a spectrum of illness that varies from a mild case that proceeds through recovery without sequelae to a severe form of disease characterized by intestinal necrosis, perforation, peritonitis, sepsis, and death. Clinical findings include abdominal distension, high gastric residuals, bile emesis, diarrhea, hematochezia, apnea, lethargy, and pallor or mottling [1–6].

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Gestational Age and Birth Weight

The disease most commonly affects prematurely born infants in whom one or more stress factors can be identified. In a review of 123 patients with NEC, the mean gestational age was found to be 31 weeks, with an average birth weight of 1460 g. Only 7.3% were term infants [7]. The clinical presentation in term infants has been characterized elsewhere [8]. Although the usual onset of NEC occurs during the first 1 to 2 weeks of life, onset during the first day of life has been reported [9].

Risk Factors

A number of risk (stress) factors have been identified that appear to "trigger" NEC: asphyxia, hypoxia, apnea, pulmonary disease, hypotension, hypovolemic shock, breech delivery, twin births, jaundice, maternal vaginal bleeding, hyperosmolar feedings, neonatal anemia, bacteremia, viremia [2–9], cold stress [10], hyperviscosity syndrome [11], use of umbilical artery and vein catheters (and catheter plasticizers) [12], exchange transfusions [13], and specific pharmacologic agents and drugs. Although generally accepted, the concept of "risk factors" has been questioned, as they have been present just as frequently in premature infants who did not develop NEC as in those that did [14, 15].

Pathology

The mucosa consists of the most metabolically active cells in the intestine, and their injury or death results in disruption, ulceration, and loss of the protective mucosal (epithelial) barrier of the gut [2, 16, 17].

Intramural air (pneumatosis intestinalis) is a pathologic as well as a radiologic hallmark of NEC. It may involve the submucosa or the subserosal layers of the gut and can be seen at times at celiotomy. Coalescence of subserosal pneumatosis may produce visible preperforative blebs (Fig. 1).

The process is characterized by "skip" areas, with the most common sites of involvement being in the ileum and the proximal colon. Gangrenous but intact intestine may also be seen, and areas of fresh intramural hemorrhage can be confused with gangrenous intestine [16, 17] (Fig. 1A). Full-thickness

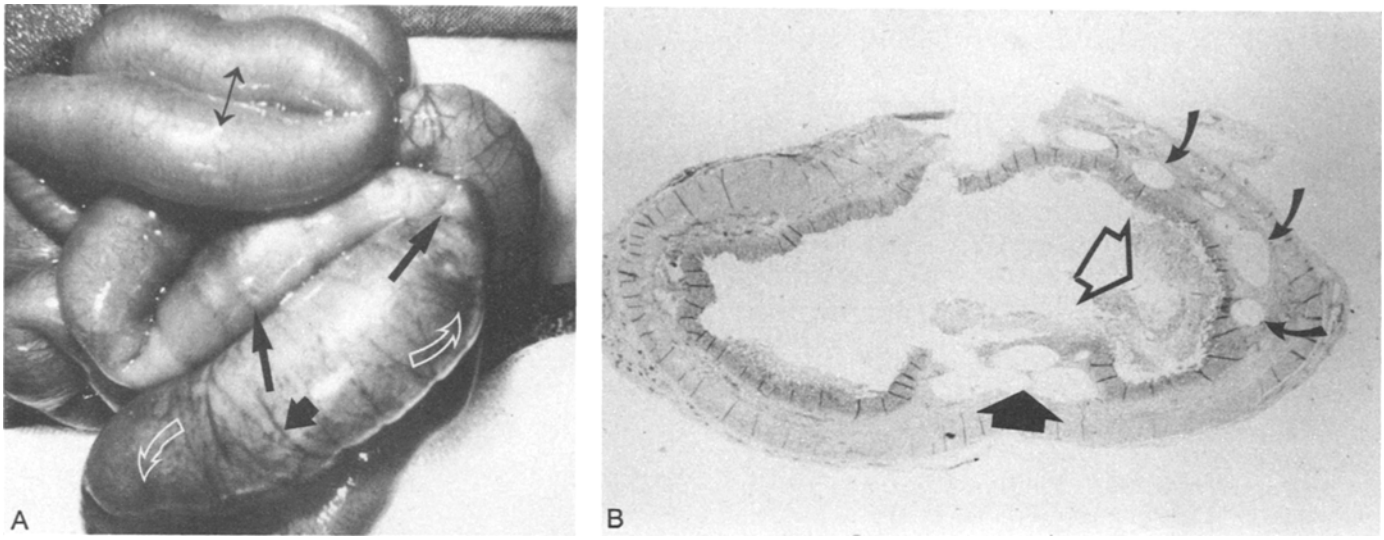


Fig. 1. Surgical pathology of NEC: gross and microscopic findings. **A.** The surgical pathology of necrotizing enterocolitis is variable and encompasses a spectrum of changes such as seen in this infant. The upper loops of intestine appear normal (connected arrows) with only mild dilatation and serosal injection. The lower segments are obviously diseased and, although intact, are marginally viable with irregular dilatation of thin-walled intestine showing subserosal "blebs" of pneumatosis intestinalis (long black arrows indicate two blebs with several blebs in between that are not marked). Grossly involved intestine contained hemorrhagic fluid and showed dull, brown-green surfaces. Dark areas (white curved arrows) correspond to intramural hemorrhages. Intramural vessels appeared thrombosed in the involved segment (wide black single arrow) and congested elsewhere. (Reprinted with permission of the publisher [5].) **B.** Full-mount photomicrograph of resected specimen seen in **A** shows the histologic appearance of submucosal "blebs" of pneumatosis (curved and wide black arrows). The mucosa has essentially sloughed following extensive ulceration. There is limited inflammatory reaction around the submucosal "blebs." The lumen of the gut is partly covered by a shaggy, fibrinous pseudomembrane consisting chiefly of fibrin and leukocytes (open arrow). (Hematoxylin-eosin, × 5) (Courtesy of Dr. Eugene C. Beatty, Department of Pathology, The Children's Mercy Hospital, Kansas City, Missouri.)

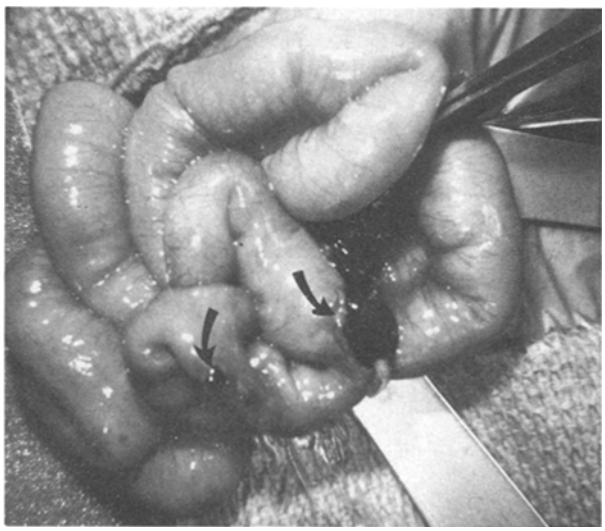


Fig. 2. Surgical pathology of NEC: localized perforations. Intestinal perforation(s) may be single or multiple and usually occur in the ileum or proximal colon along the antimesenteric side of the intestine. In this infant there is a uniform appearance of loops of ileum showing moderate dilatation and serosal injection. A few peristaltic contractions are seen. There are two localized perforations (black arrows) with early meconium spillage. Although there was minimal contamination, the segment was resected and double enterostomies constructed rather than performing a primary anastomosis. The infant was maintained on total parenteral nutrition (TPN) and underwent subsequent anastomosis with good outcome.

necrosis results in single or multiple perforation(s), which occur on the antimesenteric aspect of the intestine (Fig. 2).

Pathophysiology and Pathogenesis

The pathogenesis of NEC is unknown. The most widely held theory is that of perinatal stress(es) leading to activation of the potent defense mechanism of selective circulatory ischemia. This disorder was first noted in neonates with spontaneous gastrointestinal perforations and led to the concept that sustained stress induces a selective circulatory ischemia similar to that found in diving mammals and birds, with shunting of blood away from the mesenteric circulation to the more critical vascular beds of the heart and brain [18, 19]. Selective circulatory ischemia and reperfusion with intramural hemorrhages have been demonstrated experimentally [20]. The findings of multiple small-vessel thrombi at the periphery of intestinal lesions has suggested a localized Shwartzman reaction secondary to the formation of endotoxins by gram-negative bacteria acting on an intestinal wall previously sensitized to these substances [2]. Ultrastructurally, platelet-capillary thrombi have been found consistently in the gut of animals stressed by hypoxia as well as hemorrhagic shock [21]. Clinical pathologic findings have been well summarized elsewhere [22].

Microbiology

In neonates there is an intricate balance of gut organisms that may change with types of feeding, use of antibiotics, gut motility, and other factors.

There is a long list of organisms associated with NEC that may be separated into two general groups with considerable overlapping: (1) those associated with nonepidemic NEC; and (2) those associated with epidemic outbreaks, or clusters, of the disease [23]. *Escherichia coli*, *Klebsiella*, *Staphylococcus aureus*, *Pseudomonas*, *Enterococcus*, *Clostridium*, *Bacteroides*, α-streptococcus, *Aerobacter aerogenes*, and *Proteus* have been listed in the former group and *E. coli*, *Klebsiella*, *Pseudomonas*, *Salmonella*, and *Clostridium* have been reported in the latter group [23]. Temporal variations in the epidemiology of NEC can be correlated with increased retrieval of specific organisms from affected infants [24]. In some instances where a specific pathogen cannot be identified, strains of ordinary bacteria with altered physiology may be pathogenetic. For example, in one study enterotoxigenic *E. coli* or heat-labile enterotoxin (or both) were retrieved from the feces of infants during an outbreak of NEC [25].

Clostridia

The role of clostridia in NEC has been reported in humans [26], compared with gas gangrene of the bowel [27], and related to a necrotizing enteritis in Papuan highlanders of New Guinea [28]. The presence of clostridia has been related to the severity of NEC based on cultures of blood and peritoneal fluid [29]. Infants with negative cultures survived with medical therapy alone, whereas babies with positive cultures required operative treatment. In those infected with *Clostridium perfringens*, the disease was fulminant with extensive pneumatosis intestinalis, gangrene, perforation, and death [29]. *Clostridium butyricum* has also been found during an outbreak of NEC [30]; and although the role of clostridial toxins is uncertain, an association of toxigenic *C. butyricum* and NEC has been reported [31]. In addition, an etiologic role of *Clostridium difficile* has been documented in an outbreak of NEC by the detecting *C. difficile* cytotoxin in the stools of 12 of 13 affected infants and isolating the organism in 8 (61.5%) [32].

Coagulase-Negative Staphylococci

Coagulase-negative staphylococci were definitively identified as pathogens in 1966 [33]. More recently, coagulase-negative staphylococci have been recognized as pathogens in pediatric patients [34], especially in neonatal ICUs. Although commonly associated with central venous catheters, persistent bacteremia in the absence of such catheters has been described in low-birth-weight neonates, characterized by persistent coagulase-negative staphylococcal bacteremia, thrombocytopenia, and abdominal distension. This syndrome may represent a new clinical entity [35] in contrast to cases of full-blown NEC where *Staphylococcus epidermidis* was the single most frequent organism recovered from those infants who expired [36]. Some strains have been reported to produce a cytotoxin capable of inducing intestinal necrosis experimentally [37].

Enterococci and Sepsis

The relation of NEC to neonatal sepsis has been noted in 56 infants with Lancefield group D streptococcal (enterococcal) sepsis in whom NEC developed in 12. It was late in onset (> 7 days), and the mortality rate was 17% [38].

Viruses

One of the earliest reports of a viral etiology for NEC involved a patient with a fatal coxsackie B2 infection [39]. In addition, the association of coronavirus was studied in two Parisian hospitals. Stools were examined using electron microscopy; and in a group of 32 infants with clinical manifestations of NEC, pleomorphic enveloped particles consistent with coronavirus were found in 23 (72%) [40].

The role of rotaviruses in the pathogenesis of NEC is unclear. In one study rotavirus was documented in 11 of 15 symptomatic infants compared with 8 rotavirus infections in 147 asymptomatic or minimally symptomatic babies ($p < 0.0001$). Cofactors and viral recombination may be mechanisms for the evolution of virulence in a nursery [41].

Pharmacologic Agents

An increased occurrence of NEC has been found with the use of certain pharmacologic agents, both clinically and experimentally.

Xanthines

One of the earliest such associations involved xanthine derivatives (theophylline and intravenous aminophylline) used for the treatment of neonatal apnea [42, 43]. Statistical analysis, however, did not support this link [44]. In an ischemia model aminophylline-treated rat intestine was examined using scanning electron microscopy. There was a striking overgrowth of bacteria on the mucosa that appeared to extend into the mucosal cell surface. This finding was consistent with the known effects of methylxanthines (aminophylline) on the slowing of gastrointestinal motility with stasis, bacterial overgrowth, and invasion of an intestinal wall damaged by one or more mechanisms [45].

Vitamin E

Vitamin E has been used to reduce the incidence of serious sequelae of retrolental fibroplasia; however, its use has been associated with an increased incidence of NEC using an oral hyperosmolar preparation. To reduce serious eye sequelae and the risk of NEC, either parenteral vitamin E or a low osmolar oral preparation should be used [46].

Prostaglandins and Indomethacin

Prostaglandins are unsaturated fatty acids derived from arachidonic acid; they are acted on by the enzyme prostaglandin synthetase to form a variety of compounds. The specific prostaglandin E_1 (PGE_1) is a powerful vasodilator of the splanchnic bed and results in increased superior mesenteric artery flow. PGE_1 is frequently used to maintain patency of the ductus arteriosus in patients with heart lesions characterized by low pulmonary blood flow. Prostaglandins also appear to have a direct cytoprotective effect on the intestine [47].

Indomethacin, by contrast, is a nonsteroidal antiinflammatory drug (NSAID) that inhibits prostaglandin synthesis by blocking prostaglandin synthetase, thereby causing intense vasoconstriction. This effect has been used to produce pharmacologic closure of the patent ductus arteriosus in premature infants in congestive heart failure. An increased incidence of NEC and gastrointestinal perforation has been seen in infants so treated [48] and appears related to a reduction in mesenteric blood flow and an increase in mesenteric vascular resistance [47]. The use of indomethacin requires careful monitoring for intestinal complications [47, 48].

Surfactant

Deficiency of pulmonary surfactant is the chief cause of the respiratory distress syndrome (RDS) in premature infants. This syndrome is characterized by reduced lung volumes and seriously impaired lung compliance. Although mechanical ventilation has reduced mortality rates, bronchopulmonary dysplasia develops in many of these patients. The relation of surfactant replacement and NEC has been examined in three clinical trials with varying results [49–51]. In one study [49] using single-dose surfactant replacement, the incidence of NEC was increased, whereas in the other single-dose study [50] and the double-dose "rescue" study [51] there was no difference when comparing infants receiving intratracheal surfactant versus controls. Unfortunately, improvement in ventilation, compliance, and gas exchange did not significantly reduce the incidence of NEC.

Ischemia, Reperfusion Injury, Toxic Oxygen Radicals, Toxic Radical Scavengers

The role of ischemia, reperfusion, and toxic oxygen radicals in producing tissue injury has been elucidated [52], reviewed [53], and examined with a view toward specific therapeutic interventions [54, 55]. In general, 98% of molecular oxygen is completely reduced to water during the process of respiration. The other 2% is converted to potentially toxic "free radicals" with enhanced chemical reactivity because of a single, unpaired electron in the radicals' outer shells. Oxygen-free radicals are active during postischemic (reperfusion) tissue damage. In addition to the superoxide radical (O_2^-), other cytotoxic species of oxygen are the hydroxyl radical (HO^-) and hydrogen peroxide (H_2O_2) derived from superoxide. The main cytotoxic action of superoxide is most likely due to lipid peroxidation of cell membranes resulting in membrane fragmentation and loss of cellular integrity [52, 53]. Ischemia is now recognized to cause increased capillary permeability and to enhance production of superoxide radicals from "leaky" sites in the mitrochondrial electron transport chain. The major source of superoxide in postischemic tissues appears to be the enzyme xanthine oxidase. It is synthesized as xanthine dehydrogenase but is converted to xanthine oxidase. Unlike its precursor, xanthine oxidase can use molecular oxygen delivered during reperfusion to produce superoxide, H_2O_2, or both [52, 53].

Elucidation of some of these biochemical events has led to evaluation of the protective effects of free-radical anion scavengers [54, 55]. The enzyme superoxide dismutase was postulated to be a free-radical scavenger that could block the effects of the toxic oxygen forms by destroying the superoxide free radical (O_2^-) [52]. Superoxide dismutase, administered intraluminally and parenterally, has a protective effect on ischemic injury to the newborn rabbit ileum [56].

Another mechanism of reducing production of superoxide is by inhibition of xanthine oxidase by the xanthine oxidase inhibitor allopurinol. This agent blocks or diminishes conversion of the substrates hypoxanthine and xanthine into uric acid and superoxide (O_2^-). Experimentally, the use of low-dose enteral allopurinol has proved beneficial to survival and has reduced mucosal damage in rats subjected to mesenteric ischemia [57]. Both agents have shown effective scavenger function in the cat small intestine [58]. In addition to mucosal cell injury, endothelial cell injury in oxidant-induced organ damage can result in loss of vascular cell integrity and cellular leak [59]. Further studies will, hopefully, result in the development of agents that are effective in reducing or eliminating oxidant cellular injury.

Cocaine

Cocaine is an amino alcohol that has widespread cardiovascular effects related to an increased circulating level of catecholamines. Cocaine prevents the reuptake of the neurotransmitters epinephrine, norepinephrine, and serotonin by receptors at nerve terminals, thereby prolonging the activity of these vasoactive amines near the receptors of the effector organs. In addition to stimulating the central nervous system, cocaine stimulates the sympathetic nervous system and may cause generalized vasoconstriction. The cardiovascular effects on the cardiac output of infants of mothers who abused cocaine has been studied [60]. Although a definite casual relation between the presence of fetal and postnatal cocaine and NEC is uncertain, it has been found in four relatively large infants with no other known risk factors for NEC [61]. There are several possible mechanisms for cocaine-induced gastrointestinal ischemia, and they have been reviewed elsewhere [62]. In one study 10 infants born to cocaine abusers showed a 2.38-fold increase in risk of developing NEC compared to controls matched for race, sex, and birth weight. A greater percentage of the cocaine-positive infants with NEC required operation (70% versus 42% of controls), and their mortality was significantly higher (50% versus 23%) [63].

In our experience [62, 64], 8.6% (69/794) of infants admitted to our neonatal ICU were tested positive for cocaine metabolites. The overall incidence of NEC was 3.2% (26 of 794). Thirty-eight percent (10 of 26) of the infants with NEC had documented antenatal or intrapartum cocaine exposure. Their gestational ages were greater and the onset of disease earlier than in non-cocaine-exposed infants developing NEC. Others reporting on their experiences from large urban centers have shown no increase [65] in the incidence of NEC in cocaine-positive babies, whereas others [66] have noted a significant increase in very low birth weight (< 800 g) infants exposed to cocaine. Although these results are somewhat conflicting, maternal cocaine use should probably be considered a "new" risk factor for NEC.

NEC Following Operations in Neonates and Infants

Necrotizing enterocolitis following operation was initially reported in three patients who had undergone correction of complex congenital heart defects [67, 68]. The first report of NEC occurring as a postoperative complication following operations for a variety of anomalies during the neonatal period was from The Children's Mercy Hospital in 1980 [69]. This subject deserves some emphasis, as the occurrence of NEC in the postoperative setting is not widely recognized, and delays in treatment can result in a fatal outcome. In addition, it introduces specific anomalies as "new" risk factors and adds information about the pathogenesis of NEC. Two anomalies merit comment as "new" risk factors with suggested mechanisms for "triggering" NEC.

With "apple-peel" intestinal atresia, the intestinal circulation is precarious, based as it is on retrograde flow from the right colic artery. Any significant shift in the circulatory pattern (e.g., dehydration from any cause) could result in a low flow state in the intestinal microcirculation and trigger the cascade of events leading to a virulent and fatal course of NEC. Extensive gut necrosis was found within hours of onset of symptoms in our two infants with "apple-peel" atresia [69].

Three of our original nine patients developed NEC following operative correction of gastroschisis; one survived. In the second series of patients reported with postoperative NEC, 7 of 11 infants were born with gastroschisis; five survived [70].

The high incidence of NEC following repair of gastroschisis was examined in 10 of 54 (18.5%) babies with gastroschisis who developed NEC [71]. A mean 2.1 episodes of NEC occurred per patient. All but one of these infants were treated successfully nonoperatively; 8 of the 10 survived [71].

In an effort to explain the association of gastroschisis and NEC, we postulated that the intestinal wall in gastroschisis may be predisposed to NEC because of a higher than normal tissue pressure (requiring a higher perfusion pressure for an adequate microcirculation) due to: (1) the thickened "peel" that invests the prolapsed gut; and (2) increased intraluminal pressure due to kinks and partial intestinal obstruction [69]. The investing "peel" has been found to be mainly collagen of varying thickness [72]. Subtle changes in an infant's blood volume (e.g., dehydration, fever, hyperosmolar feedings) could lead to selective circulatory shunting away from a gut having a high intramural pressure, with hypoperfusion of the involved intestine resulting in the onset of NEC. The occurrence of multiple late-onset episodes of NEC and episodes of a "benign" nature may be related to thickness, extent, distribution, and persistence of the "peel." Reversal of the process could occur relatively quickly by early intervention with restitution of adequate perfusion to these areas [73].

Imaging and NEC

Plain Roentgenographic Findings

The radiologic findings of NEC have been well defined [1, 2, 4, 5, 74–76] and critically evaluated in our series [77]. In order of decreasing frequency, the main radiographic features included (1) intestinal distension; (2) intramural gas (pneumatosis intestinalis); (3) ascites; (4) free peritoneal air (pneumoperitoneum); (5) gas in the portal vein; (6) static intestinal loop; (7) diminishing bowel gas and asymmetric loops; and (8) toxic dilatation of the colon. The most common of these findings are illustrated with commentary (Figs. 3–6).

Therapy

Since the first reports during the 1960s there has been steady improvement in the survival of babies with NEC. This improvement has been due largely to a high index of suspicion of the disease and early, aggressive medical management.

As soon as a diagnosis of NEC is considered, feedings are discontinued and a nasogastric tube is inserted for decompression. Umbilical catheters are removed whenever possible, and intravenous fluids are administered. Total parenteral nutrition is begun early [22].

Broad-spectrum parenteral antibiotics are administered using a penicillin and an aminoglycoside. Coverage against anaerobic organisms is also used in some centers (clindamycin, metronidazole). Antibiotics are adjusted according to sensitivities for specific isolates from blood, stomach, stool, peritoneal fluid, tracheobronchial secretions, cerebrospinal fluid, central venous catheters, or other sites.

In those babies who show a good clinical and radiologic response (reduced abdominal distension, clearing of pneumatosis intestinalis if present, reduced gastric drainage, and disappearance of blood in the stools), treatment is continued for approximately 10 days. The nasogastric tube may be removed earlier, but feedings are withheld until approximately 2 weeks have elapsed. Feedings are then started with hyposmolar formula and are slowly advanced to formula that supplies adequate calories.

In infants who show progression of NEC, a minimum of 3 weeks of parenteral nutrition using a central venous catheter or peripheral veins has been arbitrarily selected to allow for healing of involved areas of intestine. Enteral feedings containing intestinal trophic components such as the amino acid glutamine may be of use for restoring the functional integrity of the gut [90].

Indications for Surgical Management

Review of the early surgical experience with NEC led to the conclusion that pneumoperitoneum was the most clear-cut indication for operation [2]. When free air is not demonstrable initially, roentgenograms should be repeated at 6- to 12-hour intervals until the clinical picture is resolved.

Since 1967 increasing experience in various centers has resulted in a broadening of indications for operation. These indications have been reviewed elsewhere [5]. Variable survival rates have been seen in babies operated on for increasing signs of sepsis, evidence of peritonitis, or when the general condition of the infant seemed worse on sequential examinations [4, 5].

Additional clinical findings suggesting operative intervention include the following:

1. An *abdominal mass* indicates an intraperitoneal abscess following an undetected perforation or an aggregate of coalesced, infarcted loops of intestine [5].

2. *Inflammatory changes in the abdominal wall*, such as induration, edema, or cellulitis, have been recognized as omi-

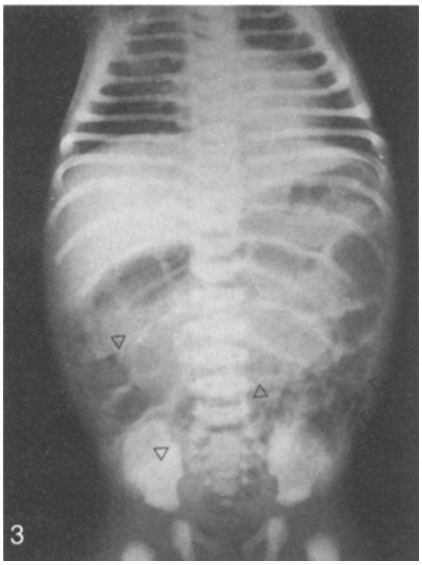
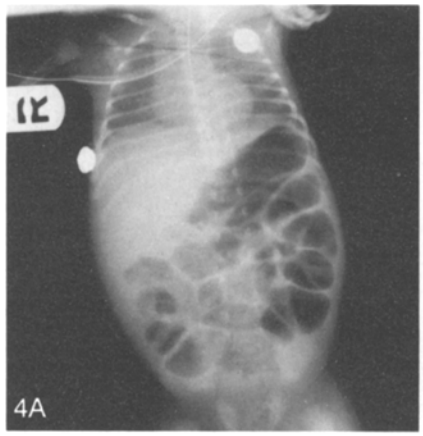
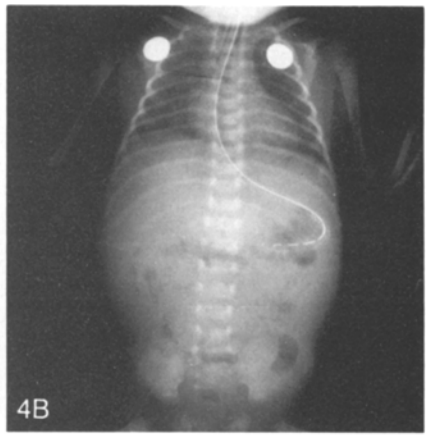
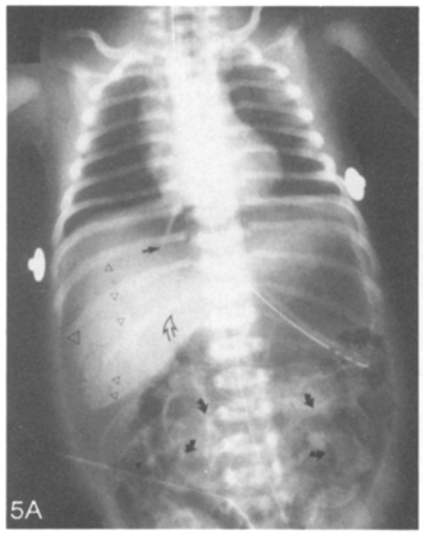


Fig. 3. Intestinal distension and intramural air (pneumatosis intestinalis). Intestinal distension in the form of multiple, dilated loops of small bowel such as seen here was most common; as an isolated finding it most often suggests intestinal obstruction. It is usually associated with other roentgenographic findings [75–77]. Intramural air (pneumatosis intestinalis) is also present in this roentgenogram. It is often subtle and appears as small cystic or "bubbly" extraluminal collections of air. The "bubbly" pattern can be misinterpreted as stool mixed with air. The terminal ileum and right colon are most commonly involved. Here cystic pneumatosis is present in several right-sided and central intestinal loops (open triangles). Linear pneumatosis appears as strips of intramural air in the wall of the intestine. A short strip is seen adjacent to the left lateral lower abdominal wall (open diamonds). With "pneumatosis coli" the colon is mainly involved by linear pneumatosis (with little or no small bowel dilatation or intramural air) and the clinical course is relatively benign [78]. The intramural gas in NEC patients is produced by intestinal bacteria, with hydrogen predominating in the blebs. Extensive pneumatosis is usually associated with a high mortality rate [79].







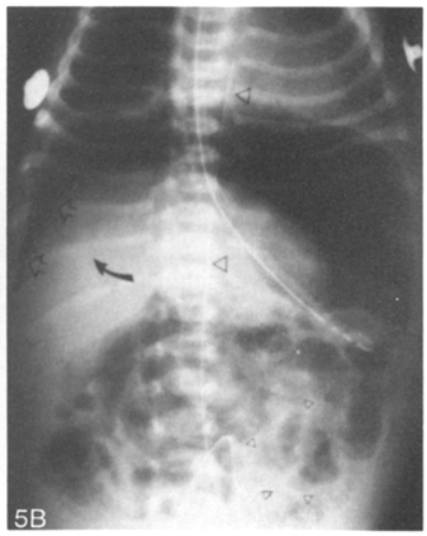
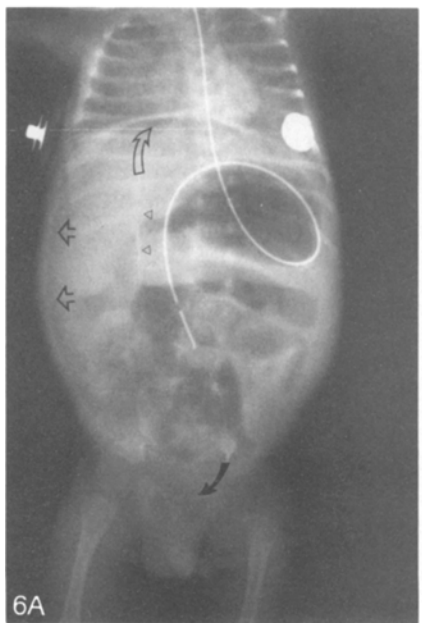
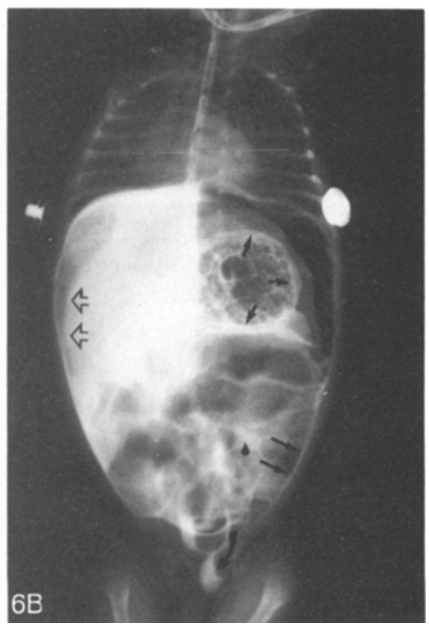


Fig. 4. Ascites (free peritoneal fluid). Appearance of ascites either on initial roentgenographic examination or subsequent studies is a grave sign [76] suggesting bacterial peritonitis secondary to intestinal perforation or translocation of organisms through a structurally intact but severely damaged intestine. The intestine may be preperforative. **A.** In this 1842-g baby, abdominal distension with emesis and bradycardia suggested a diagnosis of NEC. Initial roentgenograms showed intestinal dilatation and a mild degree of "bubbly" pneumatosis in the right mid-abdomen and right lower quadrant. The abdomen is distended and the flanks bulged by air-filled loops of gut. **B.** Eight hours later the appearance of ascites was obvious. Although the intestinal dilatation has disappeared, the flanks remain bulged, now by free peritoneal fluid rather than distended, air-filled, intestinal loops. This sudden appearance of ascites suggests serious intestinal damage and perhaps gangrene. Four of our five patients with ascites died [77]. (**A, B**: Reprinted with permission of the publisher [5].)





nous signs reflecting an underlying abscess, peritonitis, or gangrenous intestine [5, 22].

Laboratory Findings. Coagulation disturbances such as prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT) [91], sudden thrombocytopenia [92], and development of severe hyponatremia [93] suggest nonviable gut, as does severe acidosis that is unremitting despite vigorous medical therapy [91–93].

Abdominal Paracentesis. Paracentesis and lavage with examination and culture of peritoneal fluid has been used for evaluating infants with NEC for operation [94, 95]. In a relatively large experience, full-thickness necrosis was present and operation was indicated when: (1) the fluid was brown and cloudy; (2) the Gram stain showed extracellular bacteria; (3) many leukocytes were present; and (4) the differential white blood cell count showed more than 80% neutrophils. Although there is some reluctance to use this technique, the reported complication rate is low [94, 95].

All of the above indications are weighted variably in different institutions. The value of the various indications was examined in a detailed review of 61 infants with NEC [96]. Indications for operation verified by this study were (1) pneumoperitoneum; (2) paracentesis findings indicating intestinal gangrene; (3) erythema of the abdominal wall; (4) a fixed abdominal mass; and (5) a persistently dilated loop of intestine seen on serial roentgenograms.

Operative indications that proved to be invalid were (1) clinical deterioration; (2) persistent abdominal tenderness; (3) lower gastrointestinal hemorrhage; (4) the radiographic finding of a gasless abdomen with ascites; and (5) severe thrombocytopenia. Twenty-four infants were operated on. It is of interest that the mortality rate for those infants operated on after free intestinal perforation had occurred was 64% in contrast to 30% for those infants operated on for intestinal gangrene without perforation [96].

Operative Management

Once operative intervention is decided on, the procedure selected should be determined by the surgical pathology [97]. A variety of operations have been used, with the primary aim being resection of obviously necrotic or perforated intestine. The ileocecal valve should be preserved, if possible, to avoid serious intestinal fluid losses and malabsorption, which usually follow loss of the ileocecal "throttle." Extensive resection of questionably viable intestine can be avoided by performing a "second look" operation in approximately 24 hours. During

Fig. 5. Multiple roentgenographic findings in NEC: pneumatosis intestinalis, free peritoneal air (pneumoperitoneum), intrahepatic portal vein gas. **A.** Multiple findings were seen in this term infant admitted moribund at 2 days of age. Pneumatosis intestinalis is present in both sides of the abdomen (small curved black arrows). Gas in the liver is shown within a prominent vessel (curved open arrow) with the smaller arborizing pattern of vessels corresponding to the direction of portal flow to branches of intrahepatic veins and lymphatics extending out to the periphery of the liver (small open triangles). Death, which frequently occurs despite vigorous medical therapy in babies with this sign, is thought to be secondary to overwhelming septicemia due to gram-negative bacteria. Intrahepatic portal vein gas is an ominous sign. It occurred in four of our patients, all of whom died [77]. Pneumoperitoneum is also seen in this supine film, with free air outlining the right hepatic lobe (large open triangle). The falciform ligament of the liver is also seen outlined by air on either side (straight black arrow), which produces the "football sign," where the falciform ligament represents the "stitching" of a football. Pneumoperitoneum varies from small amounts of free air seen only on erect or decubitus views to massive amounts of free air. It is sometimes difficult to detect, and a significant false-negative rate has been reported [80]. Note that the volume of free air is fairly large and the right lobe of the liver is well outlined by air (large open triangle). (Reprinted with permission of the publisher [5].) **B.** Massive pneumoperitoneum. In cases where pneumoperitoneum is not obvious, it can usually be demonstrated if the infant can tolerate the erect or decubitus position. Massive pneumoperitoneum is seen here in the erect roentgenogram of the patient illustrated in **A**. The lateral edge of the right lobe of the liver (open arrows) is clearly outlined by free peritoneal air. Pneumatosis (small open triangles) and gas in the liver (curved black arrow) confirm the origin of the pneumoperitoneum as being secondary to NEC with perforation. An umbilical artery catheter (large open triangles) is positioned in the descending aorta above the diaphragm. At operation the colon was largely necrotic with multiple perforations, and much of the small intestine was nonviable. She died shortly after operation. The static intestinal loop is a less common finding and suggests intestinal ischemia with hypoperistalsis. Diminishing bowel gas with asymmetric dilatation of intestinal loops also signifies ischemia, altered gut motility, and stasis, leading to asymmetric dilatation of loops of intestine. Both are serious prognostic findings. Toxic dilatation of the colon occurred in only one of our patients [77]. Although it can mimic an obstruction proximal to a stricture, the dilatation occurs in diseased but unobstructed colon and seems to be the newborn counterpart of the toxic dilatation of ulcerative colitis [75].

Fig. 6. Use of contrast agents. In some cases where pneumatosis is absent and plain roentgen findings are nonspecific, contrast studies using barium [81] or a water-soluble, nonionic agent such as metrizamide may be indicated to differentiate NEC from other diagnostic possibilities (e.g., malrotation, volvulus [82], or aganglionic megacolon [2]). Metrizamide is isotonic with blood and does not cause the significant fluxes of fluid associated with hyperosmolar agents [83]. It can be helpful in cases of pneumoperitoneum where the exact source of several possible sources [84] is uncertain. For example, it is especially useful in ventilated infants who develop pneumoperitoneum without obvious pneumatosis intestinalis or intraperitoneal air-fluid levels. In such patients the pneumoperitoneum may be secondary to severe pulmonary disease [85–88] rather than to a gastric [89] or intestinal perforation. Demonstration of an intact gastrointestinal tract by orally administered contrast can spare such critically ill patients unnecessary laparotomy, or confirm the need for exploration. **A.** Roentgenogram of this small infant showed findings characteristic of the idiopathic respiratory distress syndrome. Sudden deterioration and abdominal distension suggested the massive pneumoperitoneum documented here. Air is seen under the right diaphragm (curved open arrow) outlining the right hepatic lobe (open arrows), and the falciform ligament (small triangles). Air is also present in the left scrotal area (curved black arrow). Intestinal dilatation is evident, but pneumatosis intestinalis is not definitely seen, raising the possibility of pneumoperitoneum secondary to a gastric perforation; however, the nasogastric tube in the air-filled stomach suggested gastric integrity. Absence of extraintestinal (intraperitoneal) air-fluid levels in this erect film lead to the additional diagnostic possibility of pneumoperitoneum secondary to chronic pulmonary disease without a perforated viscus [85–88]. **B.** To establish the presence or absence of a perforated viscus, water-soluble contrast was instilled into the nasogastric tube and a roentgenogram obtained with the infant's right side down. The intact stomach is clearly outlined (small black arrows). Spillage into the peritoneal cavity occurred from an intestinal perforation. Contrast outlines the right lobe of the liver (open arrows) and has entered a patent left processus vaginalis (curved black arrow). The left lateral parietal peritoneum is well outlined (longer black arrows). An ileal perforation as a result of NEC was found. (**A, B**: Reprinted with permission from the publisher [5].)

this interval full supportive treatment is given, and at reexploration the appearance of the intestine may have improved significantly [98]. This point is especially true in some of the dark necrotic-appearing segments that are the result of extensive interstitial hemorrhages rather than actual gangrene (Fig. 1A).

Following resection, the safest method for managing the remaining viable intestine is by exteriorizing the transected ends as separated enterostomies. Primary anastomosis can be considered in cases in which there is localized disease with no distal involvement, with a recent or walled-off perforation, or in cases where a high jejunal stoma would be required [99, 100]. Intestinal diversion has been reported in three infants with extensive involvement of the small and large intestine (without definite necrosis) and resulted in recovery [101].

Open drainage of the peritoneal cavity via a lower quadrant incision has been used successfully in selected, tiny, critically ill patients. Exploration is not carried out; rather, a soft rubber drain is placed through the incision to serve as a path of egress for intestinal contents, air, and peritoneal fluid. It can be done in an isolette; and if no improvement occurs, repeat drainage or a formal laparotomy may be considered. Closure has occurred spontaneously with nothing further required to reestablish alimentary continuity, or a stricture may develop and require later resection [102].

It again bears emphasis that access for total parenteral nutrition is required whatever operative approach is selected. A central venous line can be placed at the time of operation.

Late Sequelae

The natural history of NEC includes the development of strictures of the intestine in approximately 20% to 25% of infants [103–106] surviving either medical [107] or surgical [103, 104, 108] treatment. Strictures have been well described [17] and found in the ileum and colon [22]. They may require resection.

Contrast studies should be done on recovered infants who develop signs of intestinal obstruction [105–107]. Symptoms can begin 3 to 12 weeks after NEC [106–108]. Contrast studies of the intestine distal to an enterostomy should be done prior to closure [104–106]. Prospective evaluation of contrast studies during the early recovery period of NEC have proved helpful in evaluating these patients for the development of strictures [108].

The distribution of ischemic strictures has been detailed. In 20 of 175 neonates with previous NEC, there were 26 strictures: 7 in the small bowel and 19 in the colon [107].

Results

In 1967 the overall survival rate in the first large series of patients so analyzed was 24% [2]. In 1975 a review of 64 patients with NEC (including the original 25 babies reported in 1967) revealed an overall survival rate of 22% [22]. In these infants the diagnosis was established by rigid criteria, with the disease being unequivocal in all and, in most, far advanced.

When evaluating patients in the spectrum of NEC, the concept of clinical staging has proved useful. In a significant number of cases studied, the results correlated with the severity (stage) of the disease and therapeutic decisions that were based on staging [109].

In a detailed report of outcomes of 302 patients with NEC-changing trends were analyzed by comparing infants managed during an early period (1972–1982, n = 176) with those from a more recent period (1983–1990, n = 126). The total number of patients requiring surgical intervention was 184, with a similar operative incidence in both groups. The overall survival improved from 58% (1972–1982) to 82% (1983–1990). Operative survival rate also improved from 51% to 75%. Long-term survival was 75% overall with 65% long-term survival for surgical patients in the 1983–1990 era [110]. Fungal sepsis has been identified as a significant factor in the mortality of surgically treated infants with NEC [111].

In general, better results are achievable when low-birthweight stressed infants are considered as "candidates" for NEC and treated medically before the diagnosis is established. The process is thus hopefully interrupted before progression to an advanced stage that requires operative intervention [4–6, 22]. In a 10-year period, we had 134 cases of NEC so managed, with a 20% rate of operative intervention [112].

Résumé

L'entérite nécrosante regroupe un ensemble de syndromes d'étiologies diverses comprenant des cas de pronostic favorable comme un ileus ou un syndrome appendiculaire reversibles mais aussi des cas d'infarctus massif avec perforation et péritonite, de pronostic redoutable. La pathogénèse n'est pas connue mais il semble que différents facteurs de "stress périnataux" peuvent être incriminés. Les rôles respectifs des clostridia, des staphylocoques coagulase-négatifs et des entérocoques sont importants à connaître. Le rôle des agents pharmacologiquement actifs, tel les xanthines, la vitamine E, les prostaglandines, le surfactant, les radicaux libres toxiques et la cocaïne (chez la mère) sont aussi à considérer. L'amélioration du pronostic est à rapprocher de l'augmentation de la fréquence avec laquelle le diagnostic est évoqué. La présence d'air dans les parois intestinales est un signe pathognomonique. En cas de pneumopéritoine, de signes de gangrène à la ponction lavage diagnostique, un érythème de la paroi abdominale, une masse abdominale ou la persistence d'une anse intestinale dilatée sur les clichés de l'abdomen sans préparation successifs sont autant d'indications à la chirurgie. Le chirurgien se doit d'être aussi conservateur'intervention que raisonable, l'intestin viable doit être extériorisé en stomie dans la plupart des cas. Une relaparotomie (pour voir) est souvent nécessaire. L'alimentation parentérale associée est impérative. Avec une telle attitude, la survie a augmenté de 24% en 1967 à plus de 70% en 1984. Vingt à 25% des enfants développeront des sténoses, entre 3 et 12 semaines après le début de la maladie, certaines nécessitant des résections ultérieures.

Resumen

La enterocolitis necrotizante es un síndrome de etiologías diversas que se caracteriza por una significativa tasa de mortalidad. Fue descrito por primera vez como entidad definida en 1964 y la primera experiencia quirúrgica fue publicada en 1967. Por muchos años permaneció como una entidad no bien

definida; su incidencia, en un estudio prospectivo fue de 2.1% de las admisiones a unidades de cuidado intensivo neonatal en 12 centros. Se presenta con un cuadro variado que va desde los casos leves que se recuperan sin secuelas, hasta la necrosis intestinal con perforación, peritonitis, sepsis y muerte. Se presenta con mayor frecuencia en los prematuros con factores de riesgo de estrés; la neumatosis intestinal es una caracterítica patológica y radiológica. Su patogénesis no ha sido establecida. En el presente artículo se revisa la microbiología, el papel de los agentes farmacológicos como factor etiológico, igual que de diversos agentes humorales, con énfasis en la isquemia, la lesión de reperfusión y los radicales tóxicos de oxígeno. Se ha informado un mayor riesgo de enterocolitis necrotizante en madres que abusan de la cocaína. Se revisa el uso de imágenes diagnósticas y plantean las indicaciones para intervención quirúrgica, así como el tipo de operación, cuyo propósito es la resección del intestino isquémico o perforado.

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