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REVIEW ARTICLE

Pathophysiology and Current Management of Necrotizing Enterocolitis

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Abstract Necrotizing enterocolitis (NEC), an inflammatory bowel necrosis of preterm infants, is the most common gastrointestinal emergency and a major cause of morbidity and mortality in these infants. In this article, the authors review the pathophysiology and clinical presentation of NEC and provide a critical appraisal of the evidence supporting various prophylactic and therapeutic strategies. A literature search was performed using the databases PubMed, EMBASE, and Scopus. Current pathophysiological models of NEC suggest that the disease occurs when mucosal injury in the preterm intestine results in translocation of luminal bacteria across the epithelial barrier, triggering an exaggerated and damaging local inflammatory response. Medical management of NEC is largely supportive and likely does not modify the etiopathogenesis of this disease. Antenatal steroids, human milk feedings, adoption of standardized feeding regimens, and probiotics hold promise for prevention of NEC. Future research should focus on early recognition that occurs well before the onset of intestinal necrosis, and prevention of this disease.

Keywords NEC · Pathophysiology · Treatment

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Introduction

Necrotizing enterocolitis (NEC) is an inflammatory bowel necrosis of premature infants and is a major cause of morbidity and mortality in neonatal intensive care units throughout the world [1]. In this article, the authors review the pathophysiology and clinical manifestations of NEC, and discuss the quality of evidence and strength of recommendations for the clinical management of NEC. A literature search was performed using the databases PubMed, EMBASE, and Scopus. To avoid bias in identification of existing studies, keywords were carefully short-listed prior to the actual search from anecdotal experience and from PubMed's Medical Subject Heading (MeSH) thesaurus.

Incidence

The incidence of NEC has been estimated in population studies to be approximately 1 to 3 per 1,000 live births. In the United States, multicentric studies from the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development have reported the incidence of NEC as 7–11 % [2–4]. Similar figures (7.4 %) have been reported from the Vermont Oxford Network, which included data from 71,808 very low birth weight (VLBW) infants during a study period 2005–2006 [5]. Studies from Europe show lower incidence, ranging between 3 and 5.8 % [6, 7]. The Canadian Neonatal Network documented that 5.1 % of infants born earlier than 33 wk gestation developed NEC during 2003–2008 in a cohort of 16,669 infants [8]. The incidence of NEC varies significantly between

nurseries, occurring at a stable endemic rate in each center that is punctuated by outbreaks [3].

Pathophysiology

Although the etiopathogenesis of NEC remains unclear, current evidence supports a complex, multi-factorial model of disease (Fig. 1). In the following section, the authors summarize this information on factors that may predispose the developing intestine to NEC.

Prematurity

More than 90 % of all cases of NEC occur in premature infants [9]. The incidence and severity of NEC rise in inverse relationship to gestational maturity, presumably related to immaturity of gut motility, digestion, perfusion, barrier function and immune defense.

Genetic Factors

Although the rate of NEC in identical twins is higher than the general population, the influence of genetic factors is small. Bhandari et al. reported NEC in either one or both of the twins in 9 (14 %) of 63 pairs of monozygotic twins and in 29 (15 %) of 189 pairs of dizygotic twins [10]. After controlling for covariates, the genetic factors were not significant. NEC has been associated with single nucleotide polymorphisms (SNPs) in the IL-4 receptor (+1902G; protective), IL-18 (-607A; increased severity), vascular endothelial growth factor (+450C; increased risk), and carbamoyl-phosphate synthetase 1 (T450N; increased risk) [11].

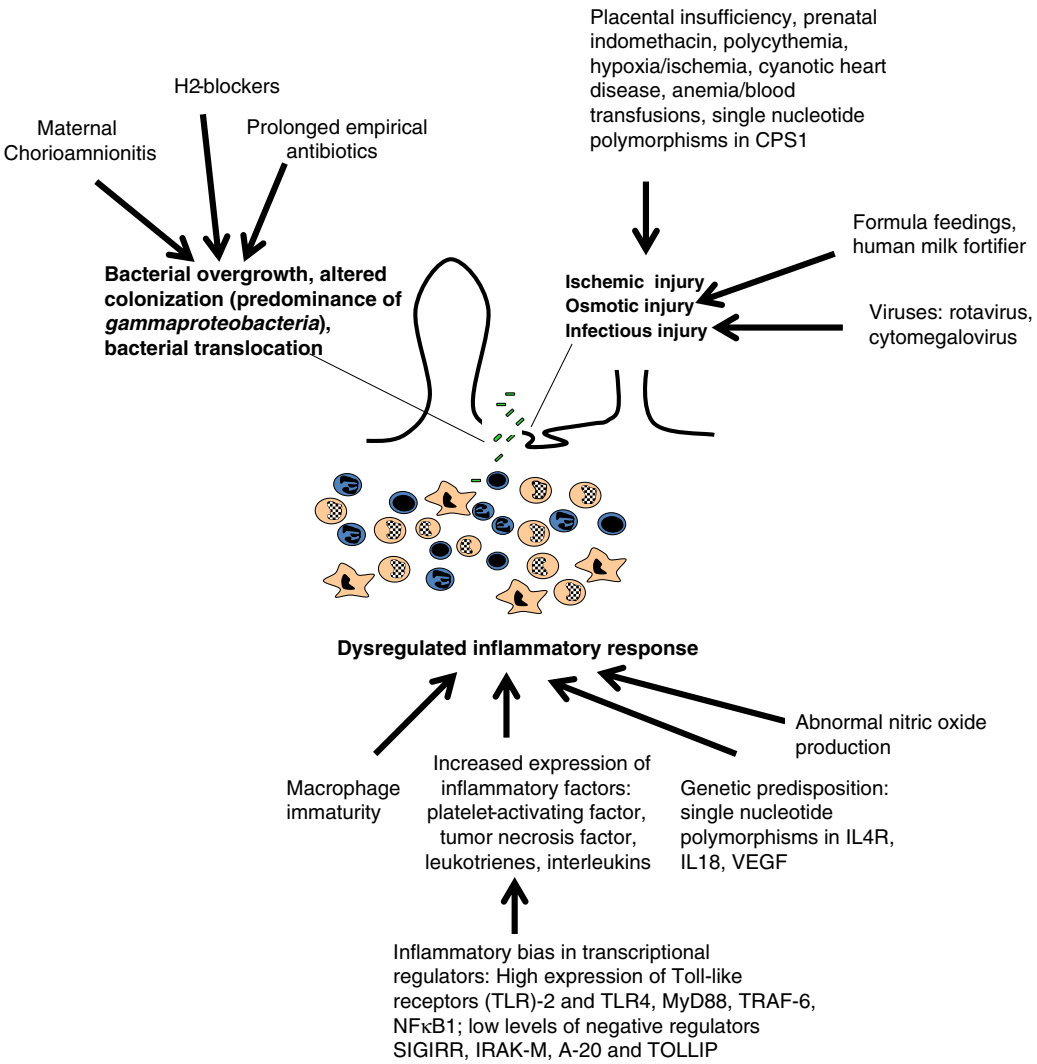

Fig. 1 Schematic summarizing pathophysiology of NEC. Current evidence indicates that in premature infants, mucosal injury results in bacterial translocation, triggering an exaggerated and damaging mucosal inflammatory response

Enteral Feedings

Although NEC can occur in neonates who have never been fed, 90–95 % of cases occur in infants with a history of recent volume advancement or re-initiation of enteral feedings. The introduction of feedings may cause osmotic damage to the mucosa, may alter blood flow and/or motility, and promote bacterial overgrowth in the gut lumen. Formula-fed infants are at higher risk of NEC than exclusively breast-fed infants, which has been attributed to a lack of immunoprotective factors in formula and abnormal bacterial colonization. However, despite these data, clinical trials have failed to show an association of NEC with aggressive increase in feeding volumes. Most studies indicate that early, low-volume feedings are not only safe, but may also reduce other morbidities associated with prematurity [12, 13].

Mucosal Injury

Histopathologically, NEC is characterized by coagulative necrosis, mucosal edema, ulceration, focal hemorrhages, and leukocyte infiltration. The prominence of coagulative necrosis in NEC indicates that ischemic events may play a role in NEC. However, ischemic events are recorded only in a minority of preterm infants with NEC. In contrast, NEC in full-term neonates is associated with congenital heart disease, recorded hypoxic–ischemic events, and polycythemia, factors that may plausibly result in gut hypoperfusion [14]. In growth-restricted fetuses, placental insufficiency and abnormal Doppler flow in the umbilical artery have been associated with NEC [15–19]. Dorling et al. reviewed 14 independent case series of fetuses with absence/reversal of umbilical arterial Doppler flow and showed increased odds of NEC compared with controls (odds ratio: 2.13, 95 % CI 1.49 to 3.03) [20]. The absence or reversal of diastolic blood flow in the umbilical artery is presumably associated with decreased splanchnic perfusion and ischemic intestinal injury,

Inflammatory Response

During NEC, mucosal injury results in bacterial translocation and a severe, unregulated inflammatory response [21]. Emerging evidence indicates that the activation of Toll-like receptors is an important event, which triggers the activation of the transcription factor nuclear factor-kappa B (NF-κB) [22]. Increased expression of tumor necrosis factor and platelet activating factor (PAF) propagate mucosal injury, which triggers a cascade of inflammatory mediators including IL-1β, IL-6, IL-8, IL-10, IL-12, and IL-18 [23]. Activation of the complement and coagulation cascades, cytokines, reactive oxygen species and nitric oxide further amplify the mucosal injury [23].

Bacterial Translocation

NEC always occurs after the postnatal bacterial colonization of the gut mucosa; intestinal injury *in utero* prior to colonization may cause strictures or atresia, but not NEC [24]. In tissue sections of NEC, bacterial overgrowth, and *pneumatosis intestinalis*, the accumulation of gaseous products of bacterial fermentation in the bowel wall, are readily evident. The pathogenic role of bacteria in NEC is also supported by evidence that enteral antibiotics can reduce the incidence of NEC [25].

Cases of NEC are often clustered in time and space in NICUs, which has led to suggestions that NEC may be caused by a transmissible agent. However, most studies have failed to consistently implicate a single agent. Cultures of blood and other sterile fluids from infants with NEC usually yield microorganisms that typically colonize critically-ill preterm infants and the NICU microenvironment [26]. However, some recent studies suggest that early colonization with specific *Enterobacteriaceae* and *Clostridia* may predict later development of NEC [27]. Cronobacter is another emerging Gram-negative pathogen associated with NEC [28]. Using PCR-based methods, Wang et al. demonstrated that infants who developed NEC had lower bacterial diversity and bacterial dysbiosis with abundant gammaproteobacteria (which include *Enterobacteriaceae and Pseudomonadaceae*) but decreased Firmicutes [29]. The role of bacterial flora in NEC remains an issue of scientific debate. The oligoclonality of gut microbiota and the disproportionate representation of coliforms may be related to broad-spectrum antibiotics, delayed or interrupted feedings, and exposure to the selected multi-drug resistant nursery flora. In a recent analysis, empirical antibiotic treatment for ≥ 4 d in the presence of sterile body fluid cultures was associated with increased risk of NEC (odds ratio 1.34, 95 % CI: 1.04–1.73) [30].

Maternal Chorioamnionitis

Several studies have shown an important association between clinical chorioamnionitis and NEC (odds ratio 1.24; 95 % CI, 1.01–1.52; $p=0.04$). The association between histological chorioamnionitis with fetal involvement is also significant (OR, 3.29; 95 % CI, 1.87–5.78; $p\leq 0.0001$) [31].

Red Cell Transfusions

A number of retrospective studies in the last 8 y suggest that red cell transfusions are temporally-associated with NEC in preterm infants [32]. In meta-analysis, Mohamed and Shah [33] confirmed increased risk of NEC within a 48 h period after red blood cell (RBC) transfusion (pooled odds ratio 3.91, CI: 2.97–5.14). RBC transfusions can dampen the normal postprandial increase in mesenteric blood flow in premature

infants, particularly in those with a birth weight < 1,250 g [34].

Pathology

The disease is commonly localized to the ileo-colic region, although the colon may be frequently involved in term infants. In some extremely-low-birth-weight (ELBW) infants as well as in some advanced cases, there might be total gut necrosis ('*NEC totalis*'). Lesions are characterized by coagulation necrosis, bacterial overgrowth, *pneumatosis intestinalis*, inflammation, and, depending on the age of the lesions, reparative changes.

Clinical Features

The presenting signs of NEC are protean and may be insidious in onset or sudden and catastrophic. NEC characteristically presents by 2 wk of age, but the onset may be as late as 3 mo of age in some infants [9]. Age of onset is typically inversely related to gestational age. Presenting signs include tachycardia, apnea, lethargy and temperature instability. Related gastrointestinal signs may include feeding intolerance, increased pre-feed residuals or delayed gastric emptying, emesis, abdominal distention and/or tenderness, and ileus with decreased bowel sounds. Grossly bloody stools are seen in approximately 25 % of infants. The spectrum of illness ranging from mild disease to severe NEC is commonly staged by using the modified Bell's criteria (Table 1) [35]. Characteristically, NEC follows an initial, early stage of systemic inflammatory response, followed by a 'definite' stage of localized peritonitis and finally an advanced stage of diffuse peritonitis.

NEC in full-term infants: Approximately 10 % of infants with NEC are born at full-term. Unlike preterm infants, most term infants develop NEC within the first week (median 2 d) and often have colonic involvement [14]. NEC in term infants is usually 'secondary,' associated with birth asphyxia, polycythemia, congenital heart disease, rotavirus infections, Hirschsprung's disease, and during withdrawl from maternal opioid narcotics [14]. Overall, the outcome is generally better than in preterm neonates.

Diagnosis

A very high index of suspicion in diagnosing at-risk infants is crucial. Most clinical antecedents prior to Bell stage III NEC are non-specific for gastrointestinal pathology and may not provide sufficient time to the

Table 1 Modified Bell's staging criteria for necrotizing enterocolitis (NEC)

Stage	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics×3 d
IB Suspected	Same as above	Grossly bloody stool	Same as above	Same as IA
IIA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics×7 to 10 d
IIB Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites	NPO, antibiotics×14 d
IIIA Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites	NPO, antibiotics×14 d, fluid resuscitation, inotropic support, ventilator therapy, paracentesis
IIIB Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum	Same as IIA, plus surgery

DIC Disseminated intravascular coagulation; *NPO* "Nil per os" or nothing by mouth

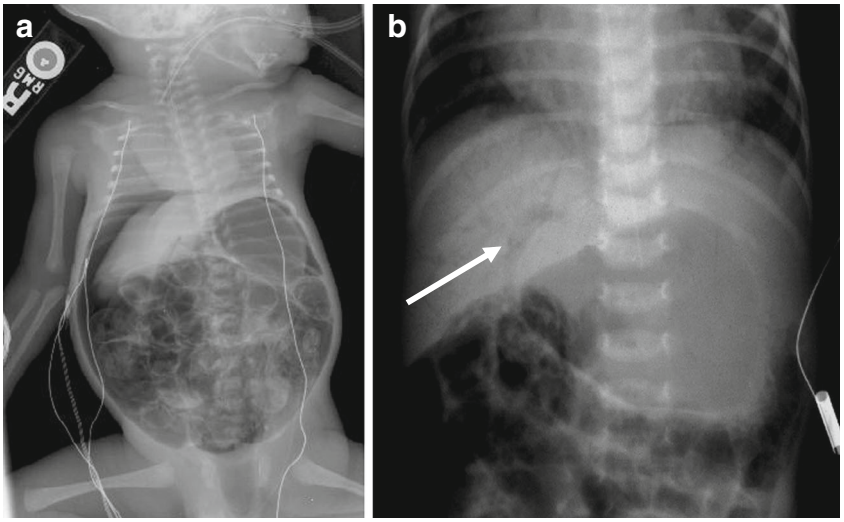

Fig. 2 **a** Abdominal radiograph showing *pneumatosis intestinalis* and pneumoperitoneum. **b** Portal venous gas (*arrow*)

clinician for early institution of treatment measures. Christensen et al. reviewed the records from 118 patients with Stage III NEC [36]. The earliest recognized antecedents were non-specific for NEC, including apnea/bradycardia, skin mottling and irritability, which were first noted 2.8±2.1, 4.5±3.1 and 5.4±3.7 (mean ± standard deviation) h, respectively, prior to the diagnosis of NEC. The most commonly identified gastrointestinal antecedents were blood in the stools, increased abdominal girth and elevated pre-feeding gastric residuals or emesis identified 2.0±1.9, 2.8±3.1, and 4.9±4.0 h before NEC was recognized.

Radiographic features are the mainstay of definitive diagnosis of NEC. The pathognomonic signs for NEC are *pneumatosis intestinalis* (Fig. 2a) and portal venous gas (Fig. 2b). Sonographic detection of portal air can also help in early diagnosis. Serial radiographs are clinically invaluable in following the progression of disease, particularly in the first 2 d after the onset of NEC [37].

Most patients with NEC develop leukocytosis and neutrophilia, although neutropenia can occur in advanced disease due to the migration of neutrophils into the peritoneal cavity. Some patients with transfusion-associated NEC may show eosinophilia. Blood cultures may grow organisms typically associated with late-onset sepsis. Thrombocytopenia may occur in stage II and III and patients with advanced NEC may have evidence of disseminated intravascular coagulation.

Prevention

The levels of evidence and strength of recommendations are summarized in Table 2. A summary of various preventive strategies is provided in Table 3.

Treatment

Medical Management

Rapid initiation of therapy is necessary for suspected as well as proven cases of NEC. There is no definitive treatment for established NEC, therefore treatment is directed at supportive

Table 2 Levels of evidence and recommendations for clinical use based on the guidelines developed by the US preventive services task force

Levels of evidence	
I	Evidence obtained from at least 1 properly designed randomized, controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case–control analytic studies,
II-3	Preferably from >1 center or research group
	Evidence obtained from multiple time series with or without the intervention; dramatic results in uncontrolled trials might also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Levels of recommendations for clinical use	
A	Good scientific evidence suggests that the benefits substantially outweigh the potential risks
B	At least fair scientific evidence suggests that the benefits outweigh the potential risks
C	At least fair scientific evidence suggests that there are benefits provided, but the balance between benefits and risks are too close for making general recommendations
D	At least fair scientific evidence suggests that the risks outweigh potential benefits
I	Scientific evidence is lacking, of poor quality, or conflicting, such that the risk/benefit balance cannot be assessed

Table 3 Prevention of NEC

Therapeutic intervention	Current status	Evidence level	Recommendation level
Prevention			
Antenatal corticosteroids	Small beneficial effect of antenatal steroids for reducing risk of NEC; relative risk (RR) 0.46 [95 % confidence interval (CI) 0.29 to 0.74] [48].	I	A
Minimal enteral (Trophic) feedings	Infants receiving trophic feedings take less time to tolerate full enteral feeds and have a shorter duration of hospital stay, without an effect on the incidence of NEC [13].	I	C
Delayed introduction or slow advancement of feedings	Delayed introduction or slow advancement of enteral feeding volumes does not prevent NEC in VLBW infants [12, 49].	I	D
Development of a standardized feeding regimen in the NICU	Despite significant heterogeneity, data from 6 studies showed a significant reduction in NEC (RR 0.13 (95 % CI 0.03 to 0.50) [50].	I	A
Breast milk	Strong evidence favoring the use of human milk to reduce the risk of NEC in premature infants. Effect extends to banked donor human milk (RR 0.21, 95 % CI 0.06 to 0.76) [51].	I	A
Oral immunoglobins	Data from available trials do not support oral administration of immunoglobulin for the prevention of NEC [52].	I	D
Enteral antibiotics	Enteral antibiotic treatment leads to a small reduction in NEC risk [RR 0.47 (0.28, 0.78); number needed to treat 10 (6, 25)]. There was a statistically significant reduction in NEC-related deaths [RR 0.32 (0.10, 0.96); number needed to treat 14 (8, 100)]. However, concerns about increase in antimicrobial-resistant intestinal microbiota precludes routine use of this therapy [25].	I	D
Amino acid supplementation	The supplementation of *L*-arginine, a substrate for NO production, appeared promising in small cohorts in reducing NEC but the data are insufficient to support a practice recommendation. Similarly, glutamine promotes gut barrier function in animal studies but data are insufficient at present to support supplemental administration of glutamine [53] to reduce the risk of NEC.	I	C
Recombinant cytokines and growth factors	Epidermal growth factor (EGF) has shown promise in preclinical studies [54]. In early clinical studies, enteral administration of a synthetic amniotic fluid-like solution containing erythropoietin and granulocyte-colony stimulating factor showed an encouraging safety/efficacy profile [55].	III	I
Probiotics	Probiotics may reduce the risk of severe NEC. A number of clinical trials have been conducted to address this issue. Despite robust cohort sizes, some of these trials are limited by variability in enrollment criteria (such as birth weight and gestational age), baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics, and feeding regimens. In a meta-analysis of data from 16 eligible trials randomizing 2,842 infants, enteral probiotics were shown to significantly reduce the incidence of severe NEC (stage II or more) (typical RR 0.35, 95 % CI 0.24 to 0.52) and mortality (typical RR 0.40, 95 % CI 0.27 to 0.60). There was no evidence of significant reduction of nosocomial sepsis (typical RR 0.90, 95 % CI 0.76 to 1.07). Although existing trials have not reported any cases of systemic infection with the probiotics supplemental organism, concerns for the safety of these formulations in ELBW infants have prevented widespread use of probiotics. [56]. There are also unresolved questions regarding optimal choice of agent(s) and dose.	I	C
Prebiotics	Showed promise in preclinical studies but no effect in human clinical trials [57].	I	D
Oral lactoferrin	Insufficient data to support the use of lactoferrin.	NA	NA

care and prevention of further injury with cessation of feeding, nasogastric decompression and administration of intravenous fluids. Infants are usually made *nil per os* (NPO) for a variable period of time, depending on the severity of disease. Parenteral antibiotics are widely used for the treatment of NEC, but there is surprisingly sparse evidence guiding the choice of antimicrobial agent and duration of therapy. One study comparing alternative treatment regimens, that included 90 infants with definite NEC, treated 46 cases with ampicillin and gentamicin, while another 44 cases received cefotaxime and vancomycin. Infants ≥ 2,200 g birthweight had similar outcomes with either regimen. Smaller infants given cefotaxime and vancomycin had a lower risk of culture-positive peritonitis, were less likely to die or develop thrombocytopenia. These data suggest that carefully chosen antibiotic regimens can improve the outcome of NEC [38]. Antibiotic coverage for anaerobes should be considered for infants with stage III NEC.

Surgical Management

Approximately 20–40 % of patients with pneumatosis intestinalis will require surgical management. Indications for surgery include evidence of perforation seen on abdominal radiographs or positive abdominal paracentesis (stool or organism on Gram stain from peritoneal fluid). Failure of medical management, a single fixed bowel loop on radiographs, abdominal wall erythema or a palpable mass are all relative indications for surgery. In rare cases, the entire intestine can be involved, precluding surgical intervention. Ideally, surgery should be performed after the development of bowel necrosis, but before perforation and peritonitis occurs.

In unstable premature infants with perforated NEC, peritoneal drainage (PD) can be cautiously considered as an alternative to exploratory laparotomy (LAP), although the best surgical approach in these infants remains unresolved. In the NECSTEPS trial, there was no significant difference in 90 d survival, dependence on parenteral nutrition, or length of hospital stay in 117 VLBW infants randomly assigned to PD or LAP [39]. However, other studies have raised important concerns about the routine use of PD. In the NET trial, 69 ELBW patients were randomized to PD or LAP and no significant differences were noted in survival, hospital length of stay, ventilator dependence, or need for parenteral nutrition [40]. However, PD was effective as a definitive treatment in only 4/35 (11 %) surviving neonates, the rest either required a delayed laparotomy (26/34, 74 %) or died. In a recent prospective multicenter study, PD has also been associated with increased risk of death or neurodevelopmental impairment [41]. A meta-analysis of 3 prospective observational studies and 2 RCTs suggested a significant excess mortality of 55 % associated with PD [42]. There is a need for better identification of patients who are less likely to tolerate LAP and may benefit from PD as a temporizing strategy.

Prognosis

Mortality rates range between 20 and 50 %. Approximately 27–63 % of affected infants may require surgery [11, 43] and as many as 50 % infants may die in the post-operative period [43]. Subacute complications include strictures (9–36 %), recurrent NEC (5 %), dysmotility, malabsorption, short bowel syndrome, and cholestatic liver disease [44, 45]. Severe NEC has been associated with growth delay that can persist beyond infancy into childhood and poor neurodevelopmental outcome [46, 47].

Conclusions

Despite advancements in neonatal intensive care, NEC remains a devastating condition for many infants. Although the etiology of NEC remains unclear, current evidence indicates that antenatal steroids, human milk feedings, adoption of standardized feeding regimens, and probiotics hold promise for prevention of NEC. Current medical management of NEC is largely supportive and likely does not modify the etiopathogenesis of this disease. Controversies remain regarding optimal surgical management for this condition. Future research should focus on early recognition that occurs well before the onset of intestinal necrosis, and prevention of this disease.

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