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ReviewArticle

Necrotizing Enterocolitis: Review Literature

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Neonatal necrotizing enterocolitis:

Neonatal necrotizing enterocolitis (NEC) is a term used to describe a common and often devastating gastrointestinal disorder of the newborn. Neonatal NEC is characterized by some degree of necrosis of the gastrointestinal tract, which can lead to sepsis and death. Because the underlying clinical circumstances are not uniform, NEC may represent a syndrome, with common findings and a variety of etiologies.

Epidemiology:

Although this acute gastrointestinal disorder was first described in the German literature in 1825, first case series were published in 1838 and 1891[1]. From the Database of Buro of Health Policy and Strategy, Ministry of Public Health, Thailand, the incidence of NEC in 2005 was 3.71:1,000 live births[2]. It is estimated that NEC occurs in 1% to 5% of neonatal intensive care unit admissions. Of 11,072 infants who survived for at least 12 hours, 787 (7.1%) developed NEC (11.5% of infants 401-750 g, 9.1% of infants 751-1,000 g, 6.0% of infants 1,001-1,250 g, and 3.9% of infants 1,251-1,500 g)[3].

Characteristics of affected newborns:

NEC usually has its onset in the first 2 weeks of life, but the disease has been reported as early as the first day of life and as late as 3 months of age. Approximately 10% of patients in whom NEC develops are not premature but are full term infants. 30% of NEC infants are born small for their gestational age (SGA). Preterm infants tend to develop NEC later (mean age 13 days), whereas the onset of symptoms of NEC in full term infants is earlier (mean age 5 days). Multivariate analysis showed that low birth weight was the most important risk factor for NEC[4]. Other factors that were associated with an increased risk of NEC were exposure to antenatal glucocorticoids, vaginal delivery, need for mechanical ventilator support, exposure to both glucocorticoids and indomethacin during the first week of life, absence of an umbilical arterial catheter, and low a measurement of a newborn's response to birth and life outside the womb (APGAR) score at 5 minutes[4]. Infants born with intra-uterine-growth retardation are at a several-fold increased risk. Maternal cocaine abuse and exchange transfusion have been accused as initiating factors. Antibiotic administration following preterm premature rupture of membranes is associated with a prolongation of pregnancy and a reduction of NEC. Calcium channel blockers reduced the frequency of NEC compared to betamimetics. There were no statistically significant effects of early introduction of lipids on NEC. There is an increased risk of NEC and bowel perforation in premature infants with PDA receiving indomethacin. The average time interval from the first dose of indomethacin to the manifestation of a bowel perforation has been reported to be 10 days. There is no sex preference for the development of NEC. Incidence of recurrent NEC was 6% with a mean interval of 37 days from onset of first NEC[5].

Pathogenesis:

It is currently believed that the disease involves four factors. 1. Hypoxic-ischemia-reperfusion injury, 2. Enteral alimentation, 3. Bacteria, and 4. Compromised gut barrier.

1. Hypoxic-ischemia-reperfusion injury: Ischemia occurs in NEC and accounts for necrosis, but the mechanism remains unresolved. Diving reflex, stressed homeostatic control by local tissues need for oxygen, vasoconstriction in the intestinal circulation in response to changes in venous pressure, and splanchnic hypoperfusion caused by various perinatal insults were considered as the causes of ischemia. The most commonly affected part of the intestine is the ileocecal region, followed by the colon. Remoteness of ileocolic artery branches from the main blood supply may in part explain this susceptibility of localization. Intraluminal pressure greater than the blood pressure caused compression on the microcirculation and was an important pathogenetic factor of NEC[9].
2. Enteral feeding: Approximately 90% of infants who develop NEC do so after being fed. The median interval between the onset of enteral feeding and NEC was 5 days[6]. Breast milk plays a role in passive immunity of the neonatal intestine. In a British multicenter study, NEC was rare among infants born at more than 30 weeks gestation whose diet included breastmilk; it was 20 times more common in those fed formula only. Infants who received donor human milk were three times less likely to develop NEC than infants who received formula milk. There was no evidence of an effect of early enteral feeding and the rate of advancement on NEC in very low birth weight (VLBW) infants on full parenteral nutrition. Trophic feedings had a 16% increase in NEC compared to no feedings.[7] There was no significant difference in the incidence of NEC for infants fed by continuous versus intermittent bolus tube feeds[8]. Standardized

feeding regimens may provide the single most important global tool to prevent/minimize NEC in preterm neonates[12].

3. Bacteria: NEC does not occur before the colonization of the intestine by bacteria. Bacterial-epithelial interactions lead to local release of inflammatory mediators such as LPS, IFN-γ, and TNF-α by IEL and LP lymphocytes, which led to local overproduction of NO and $ONOO^-$, that may induce enterocyte apoptosis or necrosis and inhibited epithelial restitution. Decreased commensal bacteria by abnormal bacterial colonization may cause reduced barrier function, reduced digestive ability, reduced angiogenesis, and reduced anti-inflammatory activity by modulating NF-κB signalling pathway[11]. Oral antibiotics reduced the incidence of NEC in low birth weight infants[10]. However, Co-amoxiclav was associated with an increased risk of neonatal NEC. Probiotic supplementation reduced both the incidence and severity of NEC. Rotavirus associated with NEC and recurrent NEC have been reported. Many evidences supported inflammatory mediators as pathogenesis of NEC; the Carrier state of IL-4ra mutant allele might be associated with a lower risk of NEC in VLBW infants, Dietary polyunsaturated fatty acid (PUFA) reduces the incidence of NEC, and TNF-α antibody has an attenuating effect on experimental NEC in rats, and arginine supplementation in premature infants reduced the incidence of all stages of NEC.
4. Compromized gut barrier: The preterm infant's gut barrier is immature. The intestinal distention that is frequently observed in premature infants as a consequence of peristaltic disorders increases the damaging effects of hypoxia-reoxygenation in the gut. Preterm infants have insufficient pancreatic enzymes and a low level of gastric acid secretions, that have antibacterial properties. Intestinal functions such as selective permeability, and control of bidirectional fluid flow tend to be underdeveloped due to immature intestinal epithelia (under 26 weeks)[11]. Therefore, pathogens or toxins might not be efficiently washed from the intestinal lumen. Preterm infants might also have immature goblet cells[11]. The mucous layer hampers direct microbial-epithelial binding. Maturational agents such as glutamine and dexamethasone can attenuate the local intestinal inflammatory damage in experimental NEC, although early postnatal corticosteroids administration alone did not decrease the incidence of NEC[13]. The evidence does not support the administration of oral or intravenous immunoglobulin for the prevention of NEC[14]. There are no randomized controlled trials of oral IgA alone for the prevention of NEC[14]. Heparin-binding epidermal growth factor reduced the incidence and severity of NEC in a neonatal rat model, with simultaneous preservation of gut barrier integrity, in part by decreasing apoptosis.

Although the exact pathophysiology of NEC is still unknown, research studies suggest a multifactored process that requires certain preconditions such as feeding, bacterial colonization, immature mucosa. In summary, NEC may develop when virulent microorganisms meet a susceptible host.

Pathology:

As for the macroscopic appearance, a continuous segment of intestine is affected in approximately half of the infants with NEC, while in the other half discontinuous disease is present. The most commonly affected part of the intestine is the ileocecal region, followed by the colon. Terminal ileal involvement occurs in 60% to 75% of patients. Rectal involvement is rare but has been reported. Perforated bowel necrosis presented in 76% of surgically treated cases[6]. Pan-involvement accounted for 19% of surgically treated cases of NEC. There was no significant difference between infants with birth weights <1,000 g. or >1,000 g. for the rate of panintestinal lesion at initial surgery[6]. Microscopic findings show coaggulative necrosis of superficial mucosa in 89% of infants. Reparative changes, including epithelial regeneration, granulation of tissue and fibrosis are commonly found. An absence of immunoreactive VIP and NOS in the plexus submucosus and within the circular muscle layer was reported.

Clinical presentation:

The most common presenting signs and symptoms of an infant with neonatal NEC is abdominal distension. Other common findings are digestive hematochezia, lethargy, hypothermia, apnea and poor peripheral circulation. Vomiting and digestive hematochezia were found in infants with a body weight of <1,000 g., more often than in those with a body weight >1,000 g.[6] Blood in the stool is frequent but seldom massive. Palpable bowel loops and crepitus may be present. Edema and erythema of the abdominal wall present in approximately 18% of patients[6]. Increased respiratory support during the 24 hours before any direct sign of intestinal dysfunction was given in 70%

TABLE 1. Clinical staging system for acute NEC. (Bell, Ternberg et al. 1978)

Stage	Clinical findings	Radiographic findings	Treatment	Survival (%)
1	Mild	Mild ileus	Medical	100
Suspected	abdominal		including	
NEC	distension		work-up for	
	Poor feeding		sepsis	
	Vomiting			
2	The above,	Significant ileus	Medical	96
Definite NEC	plus marked	Pneumatosis		
	abdominal	intestinalis		
	distension	Portal vein gas		
	GI bleeding			
3	The above,	The above, plus	Surgical	50
Advanced	plus	pneumoperitoneum		
NED	deterioration of			
	vital signs			
	Septic shock			

TABLE 2. Probability analysis of various indications for operation in NEC (%).

Indication	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Prevalence
Pneumoperitoneum	48	100	100	52	31
Portal venous gas	24	100	100	43	16
Fixed loop (x-ray)	12.5	100	100	46	7
Fixed abdominal mass	12.5	100	100	46	7
Erythema of abdomen	8	100	100	45	5
Positive paracentesis*	87	100	97	60	72
Severe pneumatosis	31	94	91	43	20
Clinical deterioration	39	89	78	59	25
Platelet count <105	38	83	73	54	28
Severe GI hemorrhage	12	83	50	42	14
Abdominal tenderness	29	72	58	43	29
Gasless abdomen/ascites	0	94	0	41	2

* Positive paracentesis was defined as brown fluid and/or bacteria noted on gram stain.

of infants with NEC. A clinical staging system of NEC was developed in 1978 with the purpose of early recognition of this disease and as an indicator for the need of operative intervention[15]. (Table 1)

Laboratory findings:

Infants with NEC usually have neutropenia. The total leukocyte count may be elevated, but it is generally low. Neutrophil counts less than 6,000 cells/mm^3 are most commonly associated with concomitant gram-negative septicemia. A persistent metabolic acidosis, decreasing platelet, and increasing blood glucose level on several successive days might predict a developing NEC, and leukocyte values above $30x10^9$/L, pH less than 7.25, and a blood glucose rise by 1.5 mmol/L or more within 24 hours predict NEC with intestinal perforation. Initial platelet counts and their products of non-survivors were both significantly lower than in survivors, whereas neutrophils were not different. Low Log_{10}platelet products was significantly associated with greater extent of disease. Hyperglycemia is common in infants with NEC admitted to the ICU and is associated with an increase in late mortality and longer intensive care stay. Aggressive glycemic control may improve the outcome in this group of infants. Stool tests for occult blood are not useful as diagnostic or screening tools. Serial C-reactive protein can be used to distinguish Bell's stage I NEC from ileus or benign pneumatosis. Persistent high C-reactive protein indicated developing complications such as stricture or abscess, or the need for surgical intervention.

Radiological findings:

The plain radiographs should include supine and lateral decubitus views. Intestinal distension is the most common radiographic finding. Dilated intestinal loops on serial x-rays was found in 25% of NEC and pneumatosis intestinalis presented in 68%[6]. The simple presence of pneumatosis intestinalis does not indicate poor outcome. Extensive pneumatosis may be present with minimal signs; it often responds promptly to medical management. Pneumoperitoneum had a 100% specificity for intestinal gangrene. However, 12-50% of infants with intestinal gangrene had no pneumoperitoneum[16]. The incidence of portal vein gas in NEC was 33% and occurred less in preterm infants. The presence of portal vein gas does not increase the risk of mortality among infants with NEC. NEC patients more commonly had pneumatosis and portal vein air on preoperative abdominal radiographs, and less commonly had pneumoperitoneum compared to isolated intestinal perforation[20].

Management:

Conservative management

In the absence of intestinal gangrene or perforation, the mainstay of treatment for the patient with NEC is supportive. The goals of medical treatment are to stabilize the infant and prevent progression of an early form of NEC to the more advanced stage of the disease. The GI tract is decompressed, and intravenous fluid resuscitation is initiated. Duration of bowel rest is 72 hours in stage 1 NEC (70) and 7-14 days in NEC stage 2. Typical antibiotic regimen includes triple combinations; penicillin or ampicillin, aminoglycosides and an agent against anaerobic organisms. With the recent reports of patients with positive stool, and blood cultures for coagulase-negative staphylococci, some groups now treat patients with a combination of vancomycin and gentamicin or vancomycin and a third generation cephalosporin. Close clinical observation consists of frequent physical examination, two-view abdominal radiography performed every 6 to 8 hours, serum platelet and leukocyte counts, and blood gas analysis. Feeding is initiated when the patient is clinically well and return of bowel function has been established.

Surgical management

Ideally, operation should be timed to coincide with the advent of intestinal gangrene, rather than occurrence of perforation. In one study, the patients who underwent surgery in acute phase NEC had median time intervals between the diagnosis of NEC and surgery of 2 days[6]. The cardinal principles of operation for NEC are

1. Excision of the gangrenous bowel
2. Exteriorization of the marginally-viable ends
3. Preservation of as much intestinal length as possible and
4. Make every effort to preserve the IC valve

Indications for operative treatment:

In an attempt to identify characteristics that may serve as predictors of intestinal gangrene, Kosloske reviewed 12 criteria used as indications for surgery and stratified these criteria according to sensitivity, specificity, positive/negative predictive value, and prevalence as Table 2[16]. Currently the only absolute indication for surgery is pneumoperitoneum. Relative indications include a positive paracentesis, palpable abdominal mass, abdominal wall erythema,

portal venous gas, fixed intestinal loop, and clinical deterioration despite maximal medical therapy. Laparoscopy performed in the ICU can provide information regarding intestinal viability which can guide further surgical management.

Massive intestinal resection leaving less than 30 cm. of viable intestine should not be done. There is still controversy between ostomy construction and primary intestinal anastomosis. An analysis of 173 infants with advanced NEC found no advantage for primary anastomosis in selected patients with NEC, and observed that a decision for primary anastomosis may actually jeopardize the survival of an infant who should be expected to live. Another study, however, found that resection and anastomosis, rather than stoma, is an acceptable option in the surgical management of preterm neonates with isolated intestinal perforation or NEC. In a comparative study of Mikulicz enterostomy and double end enterostomy, no difference was found between the two methods in the rate of wound or stomal complications. The use of peritoneal drainage under local anesthesia was introduced in 1977. The mortality rate in extremely low birth weight infants (<1,000 g.) with this technique was 54% compared to 84%[17]. Recent studies showed that the type of operation performed for perforated NEC did not influence survival in preterm and extremely low birth weight (ELBW) infants. In the presence of clinical indication of necrotic gut or metabolic derangement, laparotomy is a better choice. Peritoneal drainage is less morbid and should be considered for isolated intestinal perforation or sudden intraperitoneal free air detected. Rescue laparotomy must be considered when peritoneal drainage fails. 35% of initial drain patients required laparotomy[20]. One study, however, found that infants with severe gut injury whose management includes debridement are more likely to survive and to incur less infectious morbidity.

Results of treatment:

Survival rate has improved from 20-27% in 1955-1966 to 70%-85% in 2006[11]. In-hospital mortality in extremely low birth weight infants was recently reported as high as 49%[20]. Pan-involvement (NEC totalis) accounted for 52% mortality rate among premature and 93% among micropremature infants. There was not a survival difference between initial laparotomy and initial drainage. A significant difference in mortality rates was seen between infants >37 weeks of age (22%) and those <32 weeks (53%). Preoperative use of vasopressor and high frequency oscillator ventilation were reported as poor prognostic factors[20]. Mortality from medical treatments were lower compared to surgical treatment in almost all series. 35% of complications related to the stoma or wound. Combined stomal/wound complication rate in NEC infants with gestational age >28 weeks are significantly lower (29%:47%)[18]. Infants with longer intestinal resection had greater requirements for parenteral nutrition and had lower survival[11,20]. Cholestasis jaundice was found in 26.5% of infants. A significantly lower cholestasis rate was found in continuous extracorporeal stool transport (CEST). One or more strictures form in 9%-36% of the survivors of acute NEC. Single stricture was found in 70% of all strictures[6]. Stricture formation is more frequent after non-operative treatment and the rate is increasing. Barium enema is recommended as a screening procedure for infants who recovered from NEC. In 27% of the patients, the diagnosis of secondary stenosis was made by contrast enema prior to clinical symptoms[6]. The most common site of involvement has been the colon (80%) especially in splenic flexure and terminal ileum (15%). If the study demonstrates a stricture in a symptomatic patient, elective resection with anastomosis is usually indicated. Successful dilation of focal strictures under fluoroscopy using a balloon catheter has been reported with good results. Recurrent NEC was found in 6%, without association with the type or timing of enteral feeding or the anatomical site or method of management of the original attack[5]. Medical treatment is successful in 67.9%[5] of infants. Surgical NEC showed the greatest risk for intraventricular hemorrhage progression. NEC and thrombocytopenia also appear to be risk factors for IVH progression. NEC is associated with a significantly worse neurodevelopmental outcome than prematurity alone. Presence of advanced NEC and the need for surgery increases the risk of neurological impairment[19]. Infants with IC valve resection had more incidence of gastrointestinal dysfunction (frequent stools, diarrhea, need for medication) as compared to infants without IC valve resection. However, growth was similar between infants with or without an IC valve resection.

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