

Necrotizing Enterocolitis

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Abstract. Improvement in survival rates of low birth-weight infants particularly in the neonatal intensive care units of India appears to be accompanied by frequent recognition of Necrotizing enterocolitis (NEC) among early survivors. As the philosophy and practice of advanced care for tiny infants becomes more acceptable and affordable in the country, a steady increase in survival of such infants is predictable. However there is growing concern in India that NEC could become a significant contributor to morbidity and mortality in the future. NEC is currently regarded as the most common acquired gastrointestinal emergency in the newborn period, and the outcome of this disease is universally poor. Improved understanding of the pathophysiology and pathogenesis of this condition is required for formulating optimal principles of prevention and management. [Indian J Pediatr 2001; 68 (9) : 847-853]

Key words : Necrotizing Enterocolitis; LBW infants; Aetiology

HISTORICAL ASPECTS

NEC was initially recognised as a disease primarily affecting premature babies in 1950s and 1960s. The first case with signs and symptoms similar to NEC was described by Genersich in 1891 in a 45 hour old premature infant who died within 24 hours. Since then there have been several case reports. However, it was recognised as a syndrome and described by Mizrahi *et al.* in 1965 in what is referred to as the landmark report.¹

As most of the studies published early on NEC were retrospective in nature, Ryder *et al* conducted a multicentre prospective case control study which was published in 1980.² The results of this study showed that incidence of NEC was 2% of all admissions to the neonatal intensive care units and several factors were found on multivariate analysis to be significantly associated with NEC. Low 5 minute apgar score, patent ductus arteriosus, maternal receipt of anaesthesia during delivery, enteral feeding on 10% dextrose, early gavage feeds and premature rupture of membranes were factors considered significant. Since then several studies have attempted to define the contribution of various aetiological factors precisely and they shall be referred to and discussed later.

EPIDEMIOLOGY

The incidence of NEC as reported from different parts of the world is comparable.^{3,4} There is paucity of published data about the incidence of NEC in India. As expected, fewer cases of full blown NEC are seen in India because only a small proportion of VLBW population survives. A survey conducted by All India Institute of Medical Sciences over 16 Indian NICU's has reported an incidence

of 1.55% in pre-term babies.

PREDISPOSING FACTORS

Prematurity and low birth weight, enteral feeding, gastrointestinal infection and compromised in-utero blood flow are some of the known predisposing factors for NEC. Greater than 90% of infants with NEC are preterm infants with low birth weight and the maturity of the gastrointestinal tract is considered to be an important factor in the aetiology of NEC.⁴

Nearly all infants with NEC have history of enteral feeding.⁵ Rapid increment in feeds of more than 20 ml/kg/day, formula feeding as compared to breastfeeding, and hyperosmolar feeds are factors associated with development of NEC.⁵

Epidemics of NEC are frequently reported from neonatal intensive care units. However, investigation of epidemics with standard techniques have not revealed any microbiological agent in affected infants.

Association between reverse end diastolic flow in umbilical arteries and NEC have been reported. Histopathology of intestines has been characterised by coagulation necrosis indicative of ischaemia.

Aetiology and Pathogenesis

The aetiology of NEC is multifactorial. Figure 1 gives a diagrammatic representation of aetiology and pathogenesis.⁶

I. Prematurity

Preterm infants are at higher risk for NEC because they are vulnerable to tissue damage by toxins, nutrients, circulatory insufficiency, stasis and bacterial proliferation, and translocation of infecting organisms. Deficiency of immunological factors particularly IgA secretory component, and intestinal T-lymphocytes coupled with

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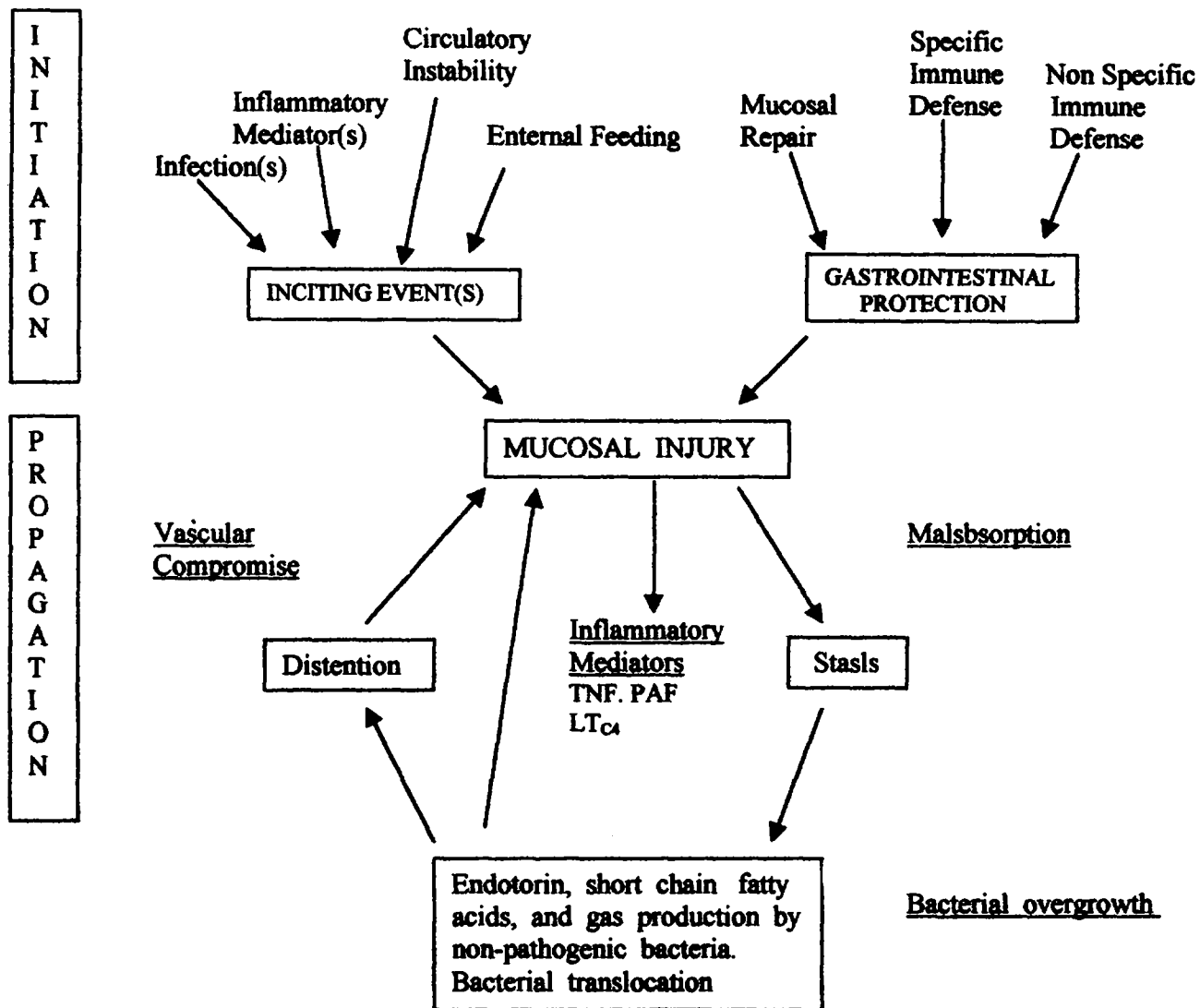


Fig. 1. Pathogenesis of Necrotizing Enterocolitis.

poor antibody response may be contributory.

II. Enteral Feeds

The hypothetical mechanisms by which enteral feeding contributes to the pathogenesis of NEC has been recently discussed by Kliegman *et al.*⁷ Enteral feeding particularly with artificial formula aggravates mucosal injury. Premature intestine has low levels of lactase. Malabsorbed carbohydrates in the presence of microbial flora lead to production of hydrogen and short chain fatty acids. Hydrogen is responsible for pneumatosis and abdominal distension. Fatty acids can be toxic to intestinal epithelium. Malabsorbed casein initiates allergic response leading to intestinal inflammation and injury. Malabsorbed long chain fatty acid particularly oleic acid causes increased permeability and haemorrhagic necrosis. Hypertonic hyperosmolar formulae may cause direct

mucosal injury in the intestines.

Increased oxygen requirement by intestinal epithelium during nutrient absorption may further aggravate tissue hypoxia. Similarly if the infant has not been fed for a long time mucosal atrophy occurs which may predispose to endotoxin and bacterial translocation and subsequent local and systemic inflammation.

How Does Breast Milk Protect ?

Breast milk has been shown to reduce the risk of NEC in preterm infants. The particular properties of breast milk that account for its protective nature are immunological defence factors and non-immunological defence factors. In addition to IgA immune protection is believed to be provided by anti-inflammatory components, namely PAF acetylhydrolase, Vitamin E, B-carotene and ascorbic acid. Human milk lipids may be less toxic to the intestinal

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epithelium. Nutrients such as glutamine and nucleotides enhance gastrointestinal cell metabolism and function. Also breast milk contains many growth factors and hormones that may improve function and maturity.

III. Infectious Agents

Epidemic outbreaks of NEC strongly favours the role of an infectious agent as a causative factor particularly if the same organism is isolated from stool, blood and peritoneal fluid. Organisms commonly associated with NEC are various bacteria like *Klebsiella*, *E. Coli*, *Enterobacter*, *Pseudomonas*, *Clostridia* and *Staph epidermidis*, viruses like Corona Virus, Rota Virus and Entero Virus and sometimes *Candida Albicans* (Fungus) is grown on various cultures.

It is also understood that the cysts of pneumatosis contain methane + CO₂ + hydrogen and bacterial fermentation is the only known source of hydrogen gas. Further evidence is provided by the decreased incidence of NEC following the use of oral antibiotics⁸

Cohen has commented that the gastrointestinal pathology of NEC is consistent with the interaction of epithelial cells with bacterial toxins and one toxin that presents similar pathologic finding is the enterotoxin produced by *C. perfringens* type C, the causative agent of pigbel which is a disease seen in adults and children following a traditional pigfeast.

Enteropathogenic viruses are believed to infect epithelial cells resulting in cell destruction, necrosis and intestinal perforation.

There are, however, some indications that infection is not mandatory for development of NEC. Infectious agents are isolated only in 30 - 35% cases, and there is no uniformity in pathogens isolated. Also same pathogens can be isolated from stools of healthy infants and sick babies with known gastrointestinal infection who do not develop NEC. It is arguable that infection may not be the initiating factor, but a permissive agent in the pathologic cascade leading to NEC.

IV. Circulatory Disturbances

The link between circulatory disturbances and pathogenesis of NEC is based on the understanding that reduced mesenteric blood flow leads to ischaemia which in turn causes hypoxic cell damage and release of inflammatory mediators. These changes are associated with reperfusion followed by release of oxygen free radicals leading to loss of cellular integrity. Although decreased circulation is a significant factor, extensive physiological studies carried out recently dispute ischaemia as being the primary aetiological agent.⁹

Several clinical studies published in the recent times have shown that infants who developed NEC did not have low apgar scores and they showed no concomitant changes of hypoxia and ischaemia in other organs.¹⁰ However, it is interesting to note that all these risk factors are significantly associated with development of NEC in term and near term babies.¹¹

Umbilical artery catheterisation and exchange transfusion have been shown to have an association with development of NEC in term or near term infants.¹² However, studies in Australian populations of preterm infants have not confirmed this relationship.

Explanation

Antenatal circulatory disturbances predispose the gut to damage by various agents. Moreover, these disturbances are associated with IUGR and VLBW and these factors may independently contribute to the development of NEC. The pathological changes are probably a secondary event following mucosal injury. Endothelial injury causes altered nitric oxide production leading to vasoconstriction and ischaemia.

V. Inflammatory Mediators

The final common pathway in the development of NEC is believed to involve mediators like platelet activating factor, endotoxin lipopolysaccharide, tumour necrosis factor and other cytokines, prostaglandins and leukotrienes. This theory has been supported by the fact that administration in experimental animals produced 'NEC' like lesions. Elevated levels of some of these have been documented in babies with 'NEC'.¹³ Antenatal/postnatal glucocorticoids are known to decrease incidence of NEC.¹⁴ Furthermore isolated thrombocytopenia and all the other haematological and circulatory disturbances seen in NEC are also explained on this basis.

Clinical Features

Clinical presentation of NEC may vary from subtle feeding intolerance and change in bowel pattern to catastrophic deterioration in general condition with severe abdominal distension and bloody stools. In general, infants demonstrate *gastrointestinal dysfunction* as reflected by the presence of abdominal distension, vomiting, bilious drainage from feeding tubes or blood stained bowel action, and *systemic illness* as reflected by temperature instability, apnoea, lethargy or hypotension. The age of onset is inversely related to gestational age at birth and preterm infants remain at risk until postconceptual age of 35 to 36 weeks or later. Clinicians must be extremely vigilant in assessing preterm infants for a protracted post natal period.

Staging of NEC (Clinical and Radiological)

Initially proposed by Bell and coworkers¹⁵ and later modified by Walsh and Kliegman,¹⁶ these criteria provide a basis for a strategic plan of management. (Table 1).

Stage 1. (Suspected NEC) is associated with non-specific clinical and radiological signs like temperature instability, mild abdominal distension, dilated bowel loops and bowel wall thickening on X-ray.

Stage 2. (Definite NEC) is characterised by gross blood in stool, mild metabolic acidosis and thrombocytopenia along with radiological finding of intestinal pneumatosis.

TABLE 1. Modified Bell Classification for Necrotizing Enterocolitis

Stage	Classification	Systemic Signs	Intestinal Signs	Radiologic Signs
IA	Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Increased pregavage residuals, midabdominal distention, emesis, guaiac-positive stool	Normal or intestinal dilation, mild ileus
IB	Suspected NEC	Same as above	Bright red blood from rectum	Same as above
IIA	Proven NEC - mildly ill	Same as above	Same as above plus absent bowel sounds, with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Proven NEC - moderately ill	Same as above plus mild metabolic acidosis and mild thrombocytopenia	Same as above plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIB, plus definite ascites
IIIA	Advanced NEC - severely ill, bowel intact	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia	Same as above, plus sign of generalized peritonitis, marked tenderness, and distention of abdomen	Same as IIB, plus definite ascites
IIIB	Advanced NEC - Severely ill, bowel perforated	Same as IIA	Same as IIA	Same as IIB, plus pneumoperitoneum

Typically there is a linear streak of gas within the bowel wall visualized in a single discrete portion of the small intestine. Rarely, it may extended throughout the small and large intestine. Sometimes a bubbly pattern is seen which is similar to that seen in newborn infants who retain meconium in the intestine. This is less specific for NEC than the linear pattern.

Stage 3. (Advanced NEC) is characterised by hypotension, disseminated intravascular coagulation and sometimes signs of generalised peritonitis. Respiratory acidosis may be present due to elevation of diaphragm along with radiological features of intestinal perforation. Typically, free air is visualised on a cross-table lateral or lateral decubitus film.

DIAGNOSIS

Diagnosis is mainly clinical supported by radiological features. Intra mural gas (pneumatosis intestinalis) is the hall mark of diagnosis. However, other radiological features which may be present are :

1. Intestinal distension - Multiple dilated loops of small intestines
2. Fixed intestinal loop - suggestive of intestinal ischaemia. Prone and decubitus position can help to differentiate from normal dilated intestine
3. Diminishing bowel gas - poor motility leads to filling with fluids and reduced gas
4. Intrahepatic portal-venous gas
5. Pneumoperitoneum best seen in lateral decubitus films

No individual laboratory feature is diagnostic of NEC. Laboratory analysis is primarily used to confirm clinical diagnostic impressions and to assess progression of severity of disease. Peripheral haematological studies may reveal abnormally high or low leucocyte counts with a shift towards immature precursors. The classical triad of increasing thrombocytopenia, acidosis and hyponatremia is suggestive of severe NEC likely to progress towards surgical intervention. Thrombocytopenia is probably caused by increased peripheral destruction rather than

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diminished production of platelets. Hyponatremia is usually due to tissue sequestration of sodium. Metabolic acidosis is an indicator of sepsis with decreased tissue perfusion and arterial pH is frequently below 7.20.

A recent study of magnetic resonance imaging (MRI) for non-invasive diagnosis of intestinal necrosis in NEC showed that it is a useful method of confirming necrosis in NEC and may aid the timing of surgical intervention in preterm infants with a clinical diagnosis of NEC.¹⁷

Early Diagnosis : It is extremely important to diagnose this condition as early as possible to limit the morbidity and mortality. This can be achieved by the following :

1. High index of suspicion particularly in preterm babies
 - (a) watch closely for bilious residues,
 - (b) hyperglycemia,
 - (c) metabolic acidosis
 - (d) blood in stools
 - (e) positive stool cultures
 - (f) presence of reducing substances > 2%.
2. Other reported markers are :
 - (a) Iso enzyme CK-BB activity in serum.¹⁸
 - (b) Computerised Tomography examination of urine after enteral administration of iodinated water - soluble contact material.

This diagnostic facility is based on a study carried out in the department of Radiology at University of California, San Francisco. Urine specimens from 22 neonates were obtained 8-12 hours after enteral administration of Iohexol. 12 of these had suspected (n=5) or definite (n=7) NEC. Routine upper gastrointestinal study was conducted on these and 13 control neonates who did not receive Iohexol. The attenuation coefficient of each urine specimen was determined with computerized tomography. The main CT attenuation coefficient in neonates with NEC was significantly higher than that in patients without NEC who underwent upper gastrointestinal study.

Prognosis : The prognosis depends upon the clinical staging and some radiological and haematological parameters. The bad prognostic indicators are depicted in Table 2.

Management of NEC

When the diagnosis of NEC is made, carefully planned medical management should be instituted. Staging of the disease is helpful in designing various components of therapy.

Stage 1. (Suspected NEC)

The infant requires cardiorespiratory monitoring, prompt cessation of enteral feeding and commencement of 2 hourly gastric suction as well as continuous open drainage. Intravenous fluid therapy should be commenced simultaneously. Broad spectrum antibiotics namely ampicillin and Gentamicin along with a loading dose of Metronidazole should be initiated. Close

TABLE 2. Bad Prognostic Indicators

Abdominal	
a.	Peritonitis
b.	Perforation
c.	Pan-NEC (involvement of entire GIT)
Systemic	
a.	Shock and DIC
b.	Acute renal failure
c.	Multi system organ failure
d.	Capillary leak syndrome
e.	Rapid progression of disease
Laboratory	
a.	Progressive thrombocytopenia
b.	Severe acidosis
c.	Electrolyte imbalance
d.	Progressively decreasing absolute neutrophil count
Radiological	
a.	Fixed intestinal loop
b.	Hepatic portal venous gas
c.	Perforation

monitoring for gastric residues, along with abdominal girth measurement and abdominal X-ray should be performed periodically.

If progressive improvement is seen leading to full recovery from symptoms and signs within five days enteral feeding should be introduced gradually.

Stage II (Definite NEC)

When the diagnosis is certain enteral nutrition should be withdrawn until full recovery. The infant requires total parenteral nutrition during that time.

Respiratory function of infants with established NEC becomes severely affected and the infant may require ventilatory support.

Hypotension may require volume expansion with either albumin or normal saline or vasopressor agent namely dopamine or dobutamine. Anaemia may require correction and thrombocytopenia would require platelet transfusion. Coagulation disorders if present should be treated appropriately.

Severe metabolic acidosis can be expected and treatment with sodium bicarbonate should be offered as necessary. Electrolyte disturbance should be watched for and appropriate changes to fluid management should be made.

Antibiotic therapy already commenced may require reviewing in the light of culture reports and treatment with Metronidazole should be maintained.

Serial radiological examinations (abdominal X-ray 6 hourly or when prompted by clinical changes) are necessary in the acute stage of the illness. It is recommended to do supine and lateral decubitus films in order to detect intestinal perforation early.

Although NEC usually responds to intensive medical

treatment, between 30 to 50% of infants progress to the advanced stage III and develop complications requiring surgery.

Surgical Management

There is no consensus on either the indication of or the timing and type of surgery for infants with NEC.¹⁹ Development of gangrenous bowel and perforation is considered to be the absolute indication for surgery. Pneumoperitoneum when present is a useful guide. Other clues to the development of intestinal gangrene are used as relative operative indications. They are :

- (1) Presence of a fixed dilated intestinal loop on serial X-rays.
- (2) Abdominal mass or an abscess secondary to localised perforation.
- (3) Clinical deterioration over 12-24 hours despite intensive medical support, as evidenced by persistent or worsening metabolic acidosis, persistent thrombocytopenia, increasing ventilatory status and deteriorating haematological parameters.

The goals of surgical intervention are to remove non viable bowel and preserve all viable bowel. Surgical procedures adopted for treatment of NEC fall into four categories :

- (1) Resection of necrotic bowel and primary anastomosis.
In stable infants with localised disease, it is the procedure of choice.
- (2) Resection of necrotic bowel and exteriorising the ends as proximal stoma and distal mucous fistula. Restoration of intestinal continuity requires a second operation which is usually performed when the infant is thriving.
Radiological exclusion of stricture in the distal bowel is necessary before the second operation.
- (3) Proximal jejunostomy is undertaken usually when there is extensive small bowel disease.

TABLE 3. Complications of NEC

Immediate	Delayed
1. Abdominal Intestinal perforation Intra abdominal abscess and peritonites	1. Abdominal Short gut syndrome Malabsorption syndrome Recurrence
2. Systemic Shock Sepsis Acute tubular necrosis And renal failure	Bowel Stricture Bowel Atresia Enterocolic fistula Anastamotic leak Anastamotic stenosis Cholestasis
3. Hematological Thrombocytopenia, Neutropenia and disseminated Intravascular coagulation	2. Systemic Chronic salt and water depletion Failure to thrive, weight loss Subnormal head circumference Subnormal body weight Neurodevelopmental impairment

- (4) Peritoneal drainage under local anaesthetic for decompression and release of contaminated material. It is a useful palliative procedure in the very tiny infants with perforation.

Complications : Complications may be due to the disease or the management. These are listed in Table 3

OVERALL OUTCOME

Table 4 depicts the outcome in medically and surgically treated cases as reported by different authors. With rapid advances in neonatal intensive care facilities and proper selection of cases the mortality and morbidity in medically managed cases has reduced drastically over the years.²⁰ Babies who require surgery are generally very high risk cases and survivors among them are likely to have neurodevelopmental delay.²¹

Prevention

Based on the expanding knowledge of the pathogenesis of NEC several prophylactic strategies have been developed. These strategies cover two major aspects of pathogenesis namely microbial infection and immature intestines.²²

Microbial Infection

Enteral antibiotics have been tested for the prevention of NEC the results are conflicting and routine use is not recommended.²³ Although theoretically gastrointestinal acidification may inhibit bacterial colonisation of the gut its value in preventing NEC is far from proven.

On immunological grounds exclusive expressed breast milk feeding should be expected to have protective effect on the gut of the preterm newborn infants. Although the results of a multicentre trial showed favourable results, the inappropriate study design casts uncertainty. Oral immunoglobulin administration showed a decrease in incidence of NEC and this particular strategy appears to be promising. Further confirmation is considered necessary before recommending for routine practice.

Immature Intestines

Meta-analysis of 12 controlled trials of antenatal corticosteroid therapy showed that the risk of developing NEC was greatly reduced. The use of antenatal corticosteroids should therefore be encouraged.²⁴

TABLE 4. Outcome in Medically Vs Surgically Managed Cases

	Medical	Surgical
1. Mortality rate		
Kleigman RM (1981) 27	46%	54%
Kabeer A (1995) 28	10%	44%
Chacko J (1999) 33	8.3%	62.5%
2. Neurodevelopmental delay		
Chacko J (1999) 33	9%	66%

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The beneficial effects of early enteral feedings and slow increments while carefully monitoring tolerance have been recognised in strategies to prevent NEC.

NEC is largely a disease of the immature infant and immaturity of the local host defenses of the gut is a factor. Also, immaturity of gut immunity causes susceptibility to specific infections and/or poorly regulated inflammatory responses, both of which can cause localised injury to the gut. The breast milk is believed to provide an array of specific and non specific immune factors that may protect from NEC.

Experimentally systemic administration of pro-inflammatory cytokines have been shown to induce hemorrhagic intestinal necrosis that characterises NEC. Based on this phenomenon PAF acetylhydrolase has been used to alleviate bowel necrosis and many of the other features of NEC.

Several gastrointestinal trophic factors that influence the pre and post natal growth and development of the gastrointestinal tract have been identified and are considered to be potentially effective when used therapeutically to enhance gastrointestinal maturation and repair following injury.²⁵ The value of enteral glutamine supplementation-for decreased gastrointestinal morbidity in new infants has been demonstrated.²⁶

Although no single strategy has been shown to be highly successful in preventing NEC, all the methods do have scientific merits and deserve consideration by clinicians in their efforts to decrease the incidence and/or severity of this disease.

FUTURE DIRECTIONS

Scope for intervention in the future lies in the success of identification of a single pathogen or virulence factor, the viability of therapeutic use of gastrointestinal trophic factors for their protective value and on the value of inhibitors of inflammatory mediators in preventing and modifying the process of NEC.

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