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Necrotizing Enterocolits

Jayasree C

a. Department of Paediatrics, Amrita Institute of Medical Sciences, Kochi, Kerala*

ABSTRACT

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Necrotizing Enterocolits is the most common acquired gastrointestinal disease that occurs in the neonates especially the premature infants. As the advances in neonatal intensive care have progressed and as premature newborns are surviving long enough for the disease to develop, the incidence of NEC has increased. There is an inverse relationship between NEC and the gestational age, the extreme preterm babies being at highest risk. Although it is mainly a disease of preterms, it can occur in terms and late preterms.

Coagulation necrosis is the hallmark of the pathologic findings of NEC. Fetal intestine is a relatively dormant organ and the low level of blood flow and oxygen delivery is adequate to meet its limited tissue oxygen demand. Postnatally, the gut is a site of intense metabolic activity with a dramatic increase in growth during the first weeks of life. The basal vascular resistance within the newborn intestinal circulation significantly decreases in the first several days after birth.

Keywords: Necrotizing Enterocolits, Neonate, Preterm baby

*See End Note for complete author details

Necrotizing Enterocolits is the most common acquired gastrointestinal disease that occurs in the neonates especially the premature infants. As the advances in neonatal intensive care have progressed and as premature newborns are surviving long enough for the disease to develop, the incidence of NEC has increased. There is an inverse relationship between NEC and the gestational age, the extreme preterm babies being at highest risk. Although it is mainly a disease of preterms, it can occur in terms and late preterms. The incidence is approximately 2-4% of all NICU admissions and in 5-10% of VLBW babies. The mortality of NEC ranges from 25% to 30%. In addition these infants require prolonged hospitalization than infants of similar maturity with no NEC and have higher incidence of neurodevelopment sequelae. In the National Institute of Child Health and Human Development studies, NEC was a significant and independent predictor of neurodevelopmental morbidity.[1]

EPIDEMIOLOGY

As the incidence of NEC is inversely related to birth weight and gestational age, the infants who weigh less than 1000g at birth have the highest attack rates. The average age at onset of NEC in premature infants seems to be related to the post menstrual age, with babies born earlier developing the disease at a later chronological age. The average age of onset has been reported to be 20.2days for babies born at less than 30 weeks gestational age, 13.8 days for babies at 31-33 weeks GA and 5.4 days for babies born after 34 weeks gestation. Term infants develop NEC much earlier, with an average age of onset within the first week of life or, sometimes, within the first 1-2 days of life. Studies have suggested that the pathophysiology of the disease may be different in the term and near term infants and may include entities such as cow's milk protein induced enterocolitis and glucose 6 phosphate dehydrogenase deficiency besides asphyxia and maternal cocaine use.[2]

Genetic factors: infant's genetic background may contribute to the susceptibility for NEC. Cytokines play a major role in tissue injury and cytokine genetics with exploration of cytokine polymorphism has been studied extensively. A carrier state of genetic polymorphisms may be associated with higher perinatal morbidity including NEC. Vascular endothelial growth factor VEGF G+405C polymorphism is associated with higher incidence of preterm birth and VEGF C-2578A polymorphism may participate in the development of perinatal complications such as NEC and acute renal failure. The mutant variant of the IL-4 receptor gene was associated with a lower incidence of NEC than in those who did not, suggesting that this mutation might protect against the development of NEC in infants.[3] G6PD deficiency also was found to be a marker for severe NEC and should be considered a risk factor for NEC.[14]

Corresponding Author:
Dr. Jayasree C, Clinical Professor, Department of Paediatrics, Amrita Institute of Medical Sciences, Kochi, Kerala.
Email: imaksb@yahoo.co.in

Risk Factors for NEC

The single most important risk factor for NEC is prematurity .Others are Prematurity, Perinatal asphyxia, PROM, RDS, Polycythemia, Shock, PDA, Hypertonic formula, Aminophylline and Vitamin E Aminophylline increases risk by slowing gut motility and by production of oxygen free radicals during their metabolism to uric acid Vitamin E increases risk by its hyper tonicity and impairment of leukocyte function.

Etiopathogenesis

Although the exact cause and pathogenesis remain uncertain, NEC likely results from initial mucosal injury secondary to a variety of factors leading to a loss of mucosal integrity in an immature gut. Using the luminal substrate provided by the enteral feedings, bacterial proliferation ensues, followed by invasion of the damaged mucosa, leading to inflammation and coagulative necrosis.

Prematurity

The exact mechanism by which prematurity predispose to NEC is not clearly known, but factors like immaturity of gastrointestinal motility, digestive ability, circulatory regulation, intestinal barrier function, abnormal colonization by pathogenic bacteria "and underdeveloped intestinal defense mechanisms play a role.

(a) Immature intestinal motility and digestion probably predispose premature infants to NEC. The development of intestinal motility begins in the second trimester and matures in the third trimester. An intrinsic immaturity of the enteric nervous-system which delays transit and less organized motility patterns leads to poor clearance of bacteria and subsequent bacterial overgrowth. Fetal hypoxia or perinatal asphyxia in both term and preterm infants is known to reduce the intestinal motility. In addition preterms have poor digestive and absorptive ability. The major intestinal host defenses include enhanced salt and water secretion, expression of antimicrobial proteins and peptides and intestinal mucins.[3] Preterm infants have immature intestinal secretive and absorptive mechanisms. The mucus lining the enterocytes has the function of lubrication, mechanical protection and protection against the acidic environment provided by the gastric and duodenal secretions. The degree of protection conferred by the mucus depends in part to the maturity of the mucus, which is immature in the premature babies. The two main antimicrobial peptides produced by the intestinal cells are defensins and cathelicidins. These have activity against a wide range of microbes including bacteria, virus, fungi and protozoa. Reduced activity of these biochemical defenses may be caused by the reduced defensin expression.

(b) Intestinal Circulatory Regulation: Intestinal ischemia leading to mucosal damage is a critical factor in the development of NEC. Coagulation necrosis is the hallmark of the pathologic findings of NEC. Fetal intestine is a relatively dormant organ and the low level of blood flow and oxygen delivery is adequate to meet its limited tissue oxygen demand. Postnatally, the gut is a site of intense metabolic activity with a dramatic increase in growth during the first weeks of life. The basal vascular resistance within the newborn intestinal circulation significantly decreases in the first several days after birth. The decrease is mediated by 3 vascular control mechanisms –NO which causes vasodilatation, the myogenic response – a process in which an increase in intravascular pressure induces vasoconstriction in some blood vessels, endothelin- which provides the vasoconstrictor tone. As a consequence of this reduction there is a dramatic increase in the rate of intestinal flow and oxygen delivery, which is the normal transition in intestinal circulatory adaptation. Any interruption of this normal transition, may lead to intestinal ischemia. Reber and colleagues[6] proposed that disruption or loss of endothelial cell function within the newborn intestine is the key antecedent of the intestinal ischemia in NEC. Ischemia –reperfusion sequence, platelet activating factor, bacterial translocation and intestinal stasis with subsequent short chain fatty acids related mucosal disruption are some of the potential factors that could lead to endothelial dysfunction. Pathologically, ischemia induces a local inflammatory response that results in activation of a proinflammatory cascade with mediators such as PAF, TNF –a complement, prostaglandins and leukotrienes.

*Normal intestinal flora: T*he normal intestinal flora is a panel of micro-organisms that reside in the gastrointestinal tract, which helps to preserve its mucosal integrity and facilitates optimal nutrient absorption. The normal intestinal flora varies widely from person to person. In the adult gut the intestinal flora contains around 400 species of bacteria, compared to around 20 species in a preterm gut. Infants are born with a sterile gut that soon becomes colonized. During the first 12-24 hours of extra- uterine life, the first colonizing bacteria – E.coli and enterococci appear, followed shortly by the obligate anaerobes. The principal sources of this colonization are the maternal flora followed by the environmental flora. In healthy breast fed infants bifidobacteria and lactobacillus predominate. In formula

fed infants, coliforms, enterococci and bacteroids predominate with occasional bifidobacterium. The fermentation of the carbohydrate is a major function of the intestinal flora. The short chain fatty acids produced during fermentation act as inhibitory agent against pathogens. Bifidobacteria and lactobacilli commonly found in breast fed infants produce lactic acid from break down of sugars. This decreases the intra- luminal PH and facilitates the growth of lactic acid bacteria. Along with this, the growth of most of the pathogenic bacteria is inhibited under these acidic conditions. The coliform bacteria found in formula fed infants break down sugars to carbon dioxide and water, yielding a near neutral PH and creates a microenvironment that favors growth of pathogenic organisms. The intestinal flora of breast fed infants is not only richer in in bifidobacteria but also includes fewer species liable to be pathogenic.

(c) Abnormal Intestinal Flora: The role of microbes in the causation of NEC comes from the findings of bacteremia and endotoxinemia in affected neonates and the pathognomonic imaging finding of pneumatosis intesinalis, which likely represents submucosal gas production by bacterial fermentation. The efficacy of broad spectrum antibiotics and the efficacy of probiotic administration in some trials also have provided indirect evidence of the role of microbes in NEC. Because NEC does not occur in utero intestinal bacteria might have a role in pathogenesis, especially if abnormal colonization occurs.

Feeding and NEC: The human milk is highly advantageous for the baby and the incidence of NEC is significantly lower among breast fed infants than those fed with commercial formulas. The protective effects include better tolerability, early maturation of the mucosal barrier, presence of constituent like glutamate, nucleotides and the presence of inhibitors of proinflammatory cytokines such as platelet activating factor acetylhydrolase. Although human milk reduces the risk of NEC, it does not eliminate the risks completely.

DIAGNOSIS

NEC should be suspected in any infant with symptoms of sepsis and where the abdominal symptoms and signs predominate. The classical triad of abdominal distension, increased pre-feed gastric aspirates and bleeding PR, along with the evidence of gas in the intestinal wall or portal system is considered diagnostic of NEC.

INVESTIGATIONS

CBC with manual differential count, Complete work up for sepsis, Coagulation profile, Serum electrolytes and blood sugar, Blood gas, Stool for occult blood.

The most common triad of laboratory abnormalities found – metabolic acidosis, hyponatremia and thrombocytopenia.

Abdominal X ray AP and cross table – look for bowel wall edema (bowel wall thickness>the thickness of the intervertebral disc at that level.), dilated bowel loops (width of the loop > the transverse diameter of the vertebral body at that level), pneumatosis intestinalis, portal or hepatic venous air, pneumoperitoneum.

Staging of NEC (Bell's Staging)

Stage I	-	suspicious signs and symptoms.
Stage II	-	suspicious signs and symptoms + pneumatosis intestinalis on radiograph.
I A	-	mildly ill.
IB		moderately ill with systemic toxicity.
Stage III	-	signs and symptoms + pneumatosis and critically ill.

A- Impending perforation.

B- Proven perforation

MONITORING

Clinical

Abdominal girth 2-4 hourly

Gastric aspirate –quantity and nature.

Continuous monitoring of SPO2 and HR.

BP and RR hourly till stable.

Laboratory

Hematocrit and blood glucose 6-8 hourly.

S.electrolytes 12th hourly for the first 48-72 hours and then once daily.

Platelet count daily till stable and then after48 hours.

ABG 8th hourly till stable.

MANAGEMENT

Assess ventilatory status and provide oxygen/ mechanical ventilation as needed.

Medical management

Stop all enteral feeds and medications.

NPO - Stage I - 5 days
II - 7-10 days
III - 14 days.

Total parenteral nutrition should be instituted for all stages.

GIT decompression -using 8-10 Fr nasogastric tube. Replace the aspirate with N/2 saline with KCl (1ml per 100ml), every 8 hours.

IV fluids - give the normal maintenance for stage I and II. In stage III more than 200ml/kg /day may be required because of third space losses. Maintain adequate tissue perfusion using sympathomimetic agents like dopamine if required. FFP if there is abnormal coagulation profile. Injection Vitamin K if there is bleeding. Correct metabolic acidosis. Start antibiotics as per unit policy. Clindamycin is added if there is perforation

Duration of antibiotics – stage I 5 days, II A7-10days, IIB & III 14 days.

Surgical management : Indications – GI perforation /full thickness necrosis.

Relative indications include abdominal mass, evidence of clinical deterioration like persistent metabolic acidosis, oliguria, ventilatory failure, hypovolemia, leucopenia thrombocytopenia, fixed loop on serial X rays.

Surgical treatment consists of resecting the affected portion of the bowel. Initially an ileostomy with a mucus fistula is typically performed with reanastamosis later. Patients who are extremely small and ill may not tolerate laparotomy. If such a patient develops pneumoperitoneum, placing a peritoneal drain under local anesthesia is another option. To define the procedure of choice for perforated NEC, Moss and colleagues performed a meta-analysis comparing primary peritoneal drainage versus laparotomy.[8] Ten uncontrolled observational studies treating a total of 475 patients were analyzed. There was no statistically significant survival advantage between primary peritoneal drainage and laparotomy. Definite evidence based guidelines for the best surgical treatment in terms of survival outcome remains to be determined.

Preventive Measures

The exact cause and pathogenesis of NEC remain enigmatic. The preventive measures have been developed over the years based on experimental data and clinical observations.

Feeding Practices

As there is an association between the onset of enteral feeding and the onset of NEC and delay in the initiation of feeds was thought to postpone the onset of the disease. But this practice can lead to mucosal atrophy and increased mucosal permeability. Brown and Sweet proposed that aggressive enteral feeding protocols contributed to the incidence of NEC.[9] By adopting a cautious feeding regimen they were able to significantly reduce the incidence of NEC. Later trials showed that there was no difference in the incidence of NEC between unfed infants and those fed early small enteral feeds for the first 7-10 days. Many neonatologists advocate the use of small enteral feedings known as gut stimulation. These trophic feeds stimulate the maturation of GI function, although they have not been shown to decrease the incidence of NEC. As breast milk decreases the incidence of NEC, it is better to start breast milk rather than formula when available over the first 7-10 days of life followed by judicious advancement of feeds. The currently available data do not provide evidence that slow advancement of feeds reduces the risk of NEC.[13] Further studies are required to evaluate the effects of the rate of increment of enteral feeds on the clinical outcome in ELBW babies.

Antenatal Steroids

As one of the risk factors for NEC is GI immaturity, several studies have evaluated the effects of antenatal steroids on the incidence of NEC. The majority of studies concluded that antenatal steroids decrease the incidence of NEC. Single course of antenatal steroids was associated with a decrease of NEC.

Immunoglobulins

Preterms possess decreased levels of immunoglobulin particularly secretory IgA. Trials have evaluated the prophylactic immunoglobulin administration on the incidence of NEC. Though there are few studies which show that the incidence of NEC can be decreased by the administration of oral immunoglobulin preparations in which breast milk is not available, other studies failed to a show a decreased incidence. For the Cochrane Neonatal Collaborative Review Group, Foster and Cole recently concluded that the available evidence does not support the administration of oral immunoglobulin for the prevention of NEC.[9]

Amino acid Supplementation

Ischemia plays an important role in the pathogenesis of NEC because coagulative necrosis, the hall mark of ischemia is noted in pathologic specimens obtained from infants afflicted with NEC. The vasodilator nitric oxide has a role in regulation of intestinal blood flow, maintenance of mucosal integrity and intestinal barrier function. NO is generated during the enzymatic conversion of L- arginine to L –citrulline by the constitutive isoform of NO synthase. A relative deficiency of arginine leading to inadequate NO production might predispose to vasoconstriction, ischemia – reperfusion injury and ultimately the development of NEC. Zamora et al[10] reported lower levels of plasma arginine at the time of diagnosis of NEC, compared with control subjects. Amin et al[11] reported that L arginine supplementation reduces the incidence of NEC in premature infants. They found that NEC developed in 5 infants out of 75 in the treatment group compared with 21 out of 77 in the control group. But further studies are needed to clarify the role of aminoacids like L arginine in the pathogenesis of NEC.

Human Milk

Human milk decreases the incidence of NEC. Artificially fed infants have a 6-10 fold increase in the incidence of NEC.[9] There are several factors in the breast milk like immunoglobulins, erythropoietin, IL-10, epidermal growth factor and platelet-activating factor acetyl hydrolase. Platelet activating factor (PAF), a potent phospholipid inflammatory mediator produced by inflammatory cells, endothelial cells, platelets and bacteria of the intestinal flora has been implicated in the pathogenesis of NEC. Elevated PAF levels and decreased levels of PAF –acetyl hydrolase are demonstrated in human infants with NEC. PAF – AH activity is seen in human milk and not in cow's milk. Recombinant human plasma PAF-AH has been shown to block PAF mediated inflammatory reactions in vitro if administered before exposure to PAF in animal models of NEC. Chaplin et al evaluated the supplementation of poly unsaturated fatty acids in a neonatal rat NEC model. With PUFA supplementation there was a decreased incidence of NEC and decreased intestinal expression of PAF synthesizing enzyme PLA2 and the PAF receptor. These studies suggest the possibility of using recombinant PAF- AH or PUFA supplementation in newborn formula as a mechanism for the prevention of NEC.

Probiotics

The human body lives in a heavily contaminated bacterial environment. There are 20 times more bacteria than cells in our body. The body maintains a complex equilibrium between this bacterial environment and its own immune system. The normal intestinal flora of the humans helps to preserve the mucosal integrity and optimal nutrient absorption. In healthy breast fed infants bifidobacteria and lactobacilli predominate. Merely by colonization of the gut, these organisms offer resistance against exogenous potentially pathogenic bacteria. The bifidobacteria and lactobacilli, commonly found in breast fed infants break down ingested sugar to lacticacid, which in turn decreases the intraluminal PH and inhibits the growth of pathogenic bacteria. The preterm infants have an abnormal pattern of bowel colonization when compared to healthy term infants. The predominant species of bacteria in stools of ELBW were E.coli, Enterococcus, Staphylococcus, Klebsiella, Enterobacter. The abnormal colonization can create a reservoir of antibiotic resistant bacteria, with the potential of subsequently contributing to the pathogenesis of NEC.

There are several mechanisms by which probitics decrease the incidence of infection and NEC in preterm infants. They include an increased mucosal barrier to bacterial translocation and bacterial products, reduction in the incidence of suspected or proven neonatal NEC, improved enteral nutrition leading to reduction in the use of intravenous feeding, changes in the pattern of gastrointestinal tract colonization leading to decreased in number of the pathogenic bacteria, competitive exclusion of potential pathogens, modification of host responses to microbial products and up regulation of the immune responses. Use of probiotics could lead to reduction in the incidence of sepsis use of antibiotics and prevention of NEC.[12]

There have been few clinical trials that have reported the outcomes for preterms given probiotics. Early studies concentrated on the safety and colonization potential of probiotics while more recent studies studied outcomes including NEC, enteral feed tolerance and weight gain. In a well established neonatal rat model of intestinal ischemia and reperfusion, Caplan et al showed that bifidobacteria supplementation resulted in intestinal colonization and subsequent reduction in the incidence of NEC like lesions.[16] Based on the preliminary animal data and observations of a decreased incidence of NEC in human milk fed preterm infants, it was postulated that probiotics may offer similar protection against NEC in premature neonates. Placebo preparations were not used in most studies, instead outcomes in infants given supplemented with probiotics and unsupplemented feeds were compared.

SAFEstart: (Simulated Amniotic Fluid for Enteral administration) – swallowing amniotic fluid in utero is necessary for proper intestinal maturation.

SAFEstart contains erythropoietin and granulocyte–colony stimulating factor. Receptors for these growth factors are present on the luminal villus surfaces in the neonatal intestine. The binding of granulocyte –colony stimulating factor and erythropoietin to their receptors induces an antiapoptotic effect. Studies comparing babies given this SAFEstart and sham solution showed a better tolerance of milk in the babies given the test solution. [3]

Pentoxifylline: inhibits tumor necrosis factor – alpha, reduces mucosal injury and improves healing in ischemia –reperfusion experiments. Studies using Pentoxifylline to prevent NEC have found mixed results.

Prognosis

The overall survival after NEC is around 70%. Mortality is higher in babies less than 28 weeks of gestation and birth weight of less than 1000g. Extensive disease, bacteremia, DIC or persistent ascites are bad prognostic indicators. The outcome of uncomplicated NEC is comparable with that of other low birth babies. Neurodevelopmental problems are more common among infants who need surgery compared with gestation and birth weight matched infants without NEC or those with NEC requiring only medical treatment. There is a link between NEC and PVL, which may be due to common antenatal risk factors or result from shock, cytokine release, hypotension or acidosis.[15] NEC is an independent and significant predictor of neurodevelopmental morbidity. Infants with perforated NEC requiring massive bowel resection for disease control and survival subsequently may develop short bowel syndrome, characterized by malabsorption and diarrhea. There is increased incidence of cholelithiasis and vitamin B12 deficiency in babies who had ileal resection for NEC. For babies surviving NEC, long term neurodevelopmental follow up is essential.

END NOTE

Author Information

Dr. Jayasree C,
Clinical Professor, Department of Paediatrics,
Amrita Institute of Medical Sciences, Kochi, Kerala

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