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REVIEW ARTICLE

Necrotizing enterocolitis: a literature review

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Keywords:
Enterocolitis, Necrotizing, Risk Factors, Diagnosis, Neonatology, Etiolog.

Abstract

Objective: To update the topic through a literature review. Methods: A search was performed on the MEDLINE, PubMed, SciELO, LILACS and Cochrane platforms, using keywords on the topic and, after selecting the main articles, they were analyzed. **Conclusion:** Necrotizing enterocolitis (NEC) is an inflammation that affects the gastrointestinal tract (GIT) of newborns. The modified Bell stagind criteria classifies it, according to clinical and radiographic findings, into suspicion, confirmed or advanced. Pathogenesis is not completely understood. In term babies it occurs due to poor mesenteric perfusion. The classic form occurs in preterm infants, with multifactorial pathophysiology that includes: immaturity of the GIT, genetic predisposition, changes in the intestinal microbiota, pathogenic bacteria, characteristics of enteral nutrition and hypoxic-ischemic intestinal injury. All of these factors activate an intense inflammatory cascade, which can lead to intestinal necrosis. Risk factors are prematurity, low birth weight, sepsis, persistence of the ductus arteriosus, anemia and/or transfusion, among others. In addition to gastrointestinal symptoms (abdominal distention and pain, gastric residuals, vomiting and rectal bleeding), it has nonspecific symptoms such as temperature instability, apneas, hypoglycemia or even shock. On radiographic examination, bowel distention, pneumatosis, portal vein gas, pneumoperitoneum, intraperitoneal fluid or persistent dilated loops are found. The therapeutic approach includes fasting, broad-spectrum antibiotics, hemodynamic monitoring. Surgery is indicated when clinical worsening, perforation or suspicion of necrosis occurs. Among the preventive measures are: infection control, breastfeeding, protocols for the initiation and progression of enteral nutrition and administration of probiotics.

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INTRODUCTION

Definition and epidemiology

Necrotizing enterocolitis (NEC) is an inflammation that affects almost exclusively the gastrointestinal (GI) tract of newborns, predominantly preterm infants. Clinical findings can be nonspecific, making diagnosis difficult.

The first records of newborn deaths with pathological findings of intestinal perforation date back to the 19th century. In 1888, Paltauf described the cases of five patients who died of severe peritonitis. But it was not until the 20th century, in 1953, that Schmid and Quaiser first used the term necrotizing enterocolitis. In 1964, Berton reported clinical and imaging findings of 21 patients with NEC. In 1975, Santulli started the hypothesis that the development of NEC had three essential components: injury to the intestinal mucosa, presence of bacteria, and availability of a metabolic substrate (presence of enteral feeding)[1].

NEC is predominantly a disease of low birth weight (LBW) preterm infants, not necessarily small for gestational age (SGA), with subjects with extreme low birth weight (ELBW) and 28 weeks gestational age (GA) or less at higher risk[2,3]. Only 7-13% of the cases involve full-term infants[1].

Advances in the care of preterm infants have led to an increase in the population at risk for NEC, which has higher morbidity and mortality than any other gastrointestinal condition requiring surgery. It is the most common surgical emergency in newborns and the financial burden it imposes on healthcare systems is significant. In recent years, the management of the disease has changed from early aggressive surgery to support therapy in most cases[1].

The incidence among all newborns ranges from 5% to 12%, although it increases among individuals with lower GA and birth weight (BW). Lemon et al. (2001)[4] performed a large prospective multicenter study called the NICHD trial (Neonatal Research Network), which included 4438 patients with birth weight between 501g and 1500g. The authors found incidences of NEC of 14%, 9%, 5% and 3% in infants with BW in the 501-750g, 751-1000g, 1001-1250g and 1251-1500g ranges, respectively. This has been confirmed in other studies, which have also shown that incidence increases as GA decreases[2]. For this reason, it has been speculated that GI tract maturity plays an important role in the risk of NEC. There is also a variation in incidence according to disease staging. When NEC is suspected, incidence increases considerably, to 22% in infants with BW under 1000g[2].

Another problem related to the calculation of incidence is that it divides the number of cases by the total number of newborns, and some of them die within a few days of birth, even before they are fed, which makes it extremely unlikely that they have developed NEC; if early deaths (until the seven days after birth) are excluded and only patients that have been fed are included, incidence may reach 15%[1].

Categorization

NEC is categorized based on clinical and imaging findings. According to Bell's criteria, modified by Kliegman and Walsh in 1987, stage 1 is suspected NEC, stage 2 is definite NCE, in which there is almost always evidence of pneumatosis intestinalis, and stage 3 is advanced NEC, marked by pneumoperitoneum or other clinical findings suggestive of irreversible tissue damage with perforation, a condition treated primarily with surgery[5]. Choice of therapy is made based on disease staging (Table 1).

Diagnosing patients with stage 1 NEC is important since it may develop into definite enterocolitis and allow the early introduction of treatment. However, the increased survival of extreme preterm infants has led to an increase in the number of patients diagnosed with stage 1 disease who do not develop definite enterocolitis. There is no evidence that stage 1 NEC might progress to disease stage 2 or 3. These are often nonspecific cases of food intolerance that, when called NEC, are met with aggressive management[6].

Etiology and pathogenesis

The pathogenesis is not yet fully understood and is different according to gestational age. The classic and most common form of NEC occurs in preterm infants, with onset from the second week after birth. NEC occurs in full-term infants within the first days after birth and has poor mesenteric perfusion its main pathophysiology. The condition produces hypoxic-ischemic lesions in the gastrointestinal tract, which can occur in newborns with congenital heart disease, intestinal anomalies, fetal growth restriction, polycythemia, sepsis, perinatal asphyxia. More recently, it has been observed in children of mothers who use cocaine or opioid narcotics[7]. In these situations, in addition to low mesenteric flow, patients are often fed with formula with volumes larger than they might receive if they were breastfed[7].

Congenital heart diseases, especially the ones with left ventricular outflow tract obstruction (such as hypoplastic left heart syndrome) are a risk factor for developing NEC, especially in full-term newborns[6]. The authors of the study concluded that NEC related to heart disease should be considered as a different entity from traditional NEC, and suggested a change in nomenclature, since the treatment approach in these cases might include measures to improve cardiac output, which would be sufficient to restore mesenteric flow[6].

In children of cocaine-using mothers, mesenteric vasoconstriction might occur as a result of the

Table 1. Modified Bell's staging criteria for NEC.

STAGE	SYSTEMIC SIGNS	BOWEL SIGNS	IMAGING FINDINGS	TREATMENT
IA	Dysthermia, apnea, bradycardia, lethargy	Gastric residuals, abdominal distention, vomiting, fecal occult blood	Normal or distended loops	Fasting and antibiotics for three days
IB	Same as IA	Blood in stool	Same as IA	Same as IA
IIA	Same as IA	Lower or absent bowel sounds, possibly pain to abdominal palpation	Pneumatosis	Fasting and antibiotics for 7-10 days
IIB	Metabolic acidosis and thrombocytopenia	Absent bowel sounds, pain to palpation, possibly bowel wall cellulitis and mass in the RLQ	Possibly air in the portal system or ascites	Fasting and antibiotics for 14 days
IIIA	Mixed acidosis, hemodynamic and respiratory instability	Worsening of pain to palpation and distension, abdominal wall erythema	Ascites	Clinical support, paracentesis, surgery of patient does not improve within 24-48 hours
IIIB	Same as IIIA	Same as IIIA	Pneumoperitoneum	Surgery

Each stage of the disease includes the characteristics linked to the stages ranked lower in the scale. BS = bowel sounds, RLQ = right lower quadrant. Adapted from Kliegman RM, Walsh MC et al: Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr. 1987; 17:213-288.

alpha-adrenergic effects of the drug. In a study comparing preterm infants with NEC born from cocaine-using mothers against infants born from non-drug users, incidence of surgery, massive necrosis, and mortality was greater in the infants born from cocaine-using mothers[8].

NEC in preterm infants has a multifactorial pathophysiology and includes the interaction of important factors: GI tract immaturity, genetic predisposition, changes in intestinal microbiota, pathogenic bacteria, enteral nutrition characteristics, and hypoxic-ischemic bowel injury.

GI tract immaturity is due to dysmotility of the premature intestine, reduced mucin barrier, increased epithelial permeability, and reduced levels of immunoglobulins and immunity[3].

Several studies, including the ones performed with twin siblings, have shown that the risk of NEC is influenced by environmental and genetic factors. Studies have also found that African-Americans are at higher risk than Caucasians[1]. Genetic variations can lead to increased or dysregulated inflammatory response, thereby increasing the risk of NEC. This is observed in the following situations: lower expression or mutated form of the single-immunoglobulin and Toll-interleukin receptor; exacerbated action of the autophagy-related 16 like 1 (ATG16L1) gene; variants of mannose-binding lectin; increased expression of nuclear factor kappa-beta; polymorphisms in vascular endothelial growth factor[9].

Microbial dysbiosis reflects the inadequate initial colonization of the GI tract, which may occur due to practices commonly performed in neonatal intensive care units (NICU). Among these practices are: use of antibiotics in the first days after birth, little or no enteral feeding for prolonged periods, use of formula instead of breastmilk, and use of H2 receptor blockers (responsible for decreased gastric acid secretion), since gastric acidity is a natural protective factor that favors the preservation of the intestinal microbiota and protects the GI tract against NEC. Preterm infants have typically lower gastric acidity. Therefore, H2 blockers must be prescribed judiciously to these patients.

Bacteria play an important role in the pathogenesis of NEC. This can be demonstrated, for example, by the fact that the disease can occur in "epidemic waves", i.e., several cases within a short period of time, within the same unit and by the same infectious agent. It can affect patients without known risk factors. Pneumatosis, one of the main imaging findings, reflects the presence of gas in the submucosa produced by bacterial fermentation[1]. All this reinforces its relationship with infection.

About 90-95% of the cases of NEC occur after the initiation of enteral nutrition, reinforcing the role of diet as a metabolic substrate in the pathogenesis of the disease[3]. The fear that diet may contribute to NEC has led neonatologists to delay the initiation of enteral nutrition. However, studies have shown that this practice does not prevent NEC. In a systematic review, Morgan et al. (2013) analyzed nine randomized clinical trials that compared starting diet early versus starting it later (more than four days after birth) for VLBW infants and found that delaying the start of enteral nutrition did not decrease the incidence of NEC[10]. However, this study included few extreme preterm babies or extremely low birth weight infants, a group about which more studies are needed. Considering the rate at which enteral nutrition is introduced, there is no difference in the risk of NEC between introducing nutrition more slowly (10 to 20ml/kg/day) or more rapidly (30 to 40ml/kg/day)[11]. Another important factor is the type of nutrition used. There

is an increased risk of NEC when formula is used compared to breastmilk[12]. Probable explanations include the potential harm formula components cause to the intestinal barrier and the loss of protective elements from breastmilk (defense cells, immunoglobulins, probiotics, oligosaccharides, lactoferrin, alpha-lactalbumin, epidermal growth factor, complement C3, fatty acids, antiviral mucins, and others)[3].

Intestinal ischemia was once considered a very significant component. However, in recent years, the contribution of hypoxic-ischemic injury in NEC of preterm infants has been re-evaluated and it is no longer considered an important predisposing factor[3]. Still, it is likely that decreased intestinal blood flow contributes as an element in the inflammatory cascade, which might cause bowel injury. Involvement of the intestinal epithelial barrier with the possibility of bacterial translocation seems to be the first event that causes the release of inflammatory mediators[1].

All factors mentioned above contribute to the activation of an intense inflammatory cascade, which might lead to intestinal necrosis. The following inflammatory mediators have been linked to the pathogenesis of NEC: epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), and erythropoietin (EPO)[13]. EGF acts in the differentiation and proliferation of epithelial cells and, together with HB-EGF, acts in the repair of damaged intestinal mucosa[13]. Both are produced by newborns and are present in breastmilk. EPO has a role in the development of the GI tract[13].

Inflammatory cytokines seem to play an important role in the pathogenesis of NEC. Interleukins (IL-4, IL-10, and IL-11) have a protective role in the GI tract[13] and have been studied in potential therapeutic approaches.

Platelet-activating factor (PAF), lipopolysaccharides, nitric oxide (NO), and tumor necrosis factor (TNF-α) are mediators involved in the pathogenesis of NEC. PAF is an endogenous phospholipid with potent proinflammatory action, which is elevated in newborns with NEC[1].

Arginine is the substrate for forming NO, a potent vasodilator that regulates mucosal blood flow while helping to maintain its integrity. Therefore, it has a protective role in the GI tract[9,13]. A systematic review described a decrease in NEC in patients prescribed arginine supplementation[14].

The main and best-defined risk factors for developing NEC are, as previously mentioned, prematurity and low body weight. However, prenatal factors are also relevant, such as the presence of chorioamnionitis, confirmed in a meta-analysis published in 2013[15], and prolonged rupture of membranes[16].

Perinatal or delivery-related risk factors include altered blood flow, fetal growth restriction, and birth weight below the 10th percentile[16]. Impaired blood flow before or during delivery – caused by placental abruption, for example – can lead to fetal ischemia and increased risk of NEC[16]. SGA and fetal growth restriction increase the risk for NEC. Risk is higher when there are associated changes in Doppler scans[16]. Failure of transition mechanisms at birth, reflected in need for resuscitation, low APGAR scores, umbilical cord blood acidosis, and early need for mechanical ventilation have been associated with NEC[16].

Postnatal risk factors such as sepsis, keeping lower target saturation (between 85-89%) for newborns, patent ductus arteriosus (PDA) and its treatment, anemia and/or transfusion, increase the risk of NEC[16].

The relationship between packed red blood cell transfusion and risk of NEC has been discussed in some studies, which showed a temporal relationship between the two events. Authors have proposed that tissue hypoxia, inflammation, and dysregulation of mesenteric vascularization associated with transfusion might cause NEC. However, studies evaluating this relationship are conflicting. While a meta-analysis published in 2012[17] described increased risk of NEC up to 48 hours after transfusion, another meta-analysis published in 2017 did not evince such association[18]; and a third meta-analysis showed that transfusion may be a protective factor for NEC[19]. Thus, the relationship between NEC and blood transfusion remains an unresolved question. Damage to the bowel may occur both as a result of transfusion or anemia, either independently or in a combined manner[20]. This discussion has led authors to think that this might be a distinct entity, called transfusion-related NEC[6]. Given the uncertainties, it is recommended to suspend enteral diet before, during, and after transfusion. A systematic review comprising seven observational studies showed that keeping patient fasting during transfusion decreased the risk of NEC[21].

Patent ductus arteriosus may cause NEC by decreasing mesenteric blood flow. Treatment with indomethacin might further elevate risk by increasing mesenteric vascular resistance and decreasing blood flow to the GI tract. However, study findings have differed about this association. A meta-analysis comprising randomized, placebo-controlled clinical trials found no increase in the risk of NEC in individuals with a PDA with or without treatment[22].

Among several potential risk factors considered, the following did not increase the risk of NEC: route of delivery, time to cord clamping, presence or location of umbilical catheter, and postnatal administration of surfactant, caffeine, or corticosteroids[16].

Clinical symptoms and diagnosis

The clinical symptoms present in individuals with NEC vary substantially, and may be silent or fulminant. Clinical findings may be nonspecific and include lethargy, temperature instability, apnea, bradycardia, and hypoglycemia, or manifest in severe symptoms such as shock[1]. As

for more specific symptoms related to the involvement of the gastrointestinal tract, manifestations may start with abdominal distension and mild pain to palpation, progressing with worsening pain, reactive abdomen, palpable intestinal loops, gastric residuals, vomiting, and elimination of blood in feces (macroscopically or occult in blood)[5]. The presence of edema and erythema in the abdominal wall is suggestive of peritonitis, while bluish coloration in the abdomen or scrotum may indicate perforation of intestinal loops[1].

In laboratory tests, complete blood count may show leukocytosis and thrombocytopenia; arterial blood gas analysis shows metabolic acidosis with hyperlactatemia; and acute phase tests (such as C-reactive protein) are increased. In patients suspected with NEC, the collection of blood cultures is indicated to identify the etiologic agent.

Among the studied markers for NEC, PAF has been deemed good for diagnosis, while others, such as intestinal fatty acid-binding protein (I-FABP) and calprotectin, are useful as markers of severe disease, but not in screening diagnostics[1].

The main findings on imaging examination of the abdomen are: distension of intestinal loops, bowel wall thickening, pneumatosis (linear or cystic), air in the portal system, free air in the peritoneum (pneumoperitoneum), peritoneal fluid, fixed, and persistently dilated loops[5]. In the context of prematurity and clinical symptoms, presence of air in the portal system and pneumatosis are clear diagnostic signs of NEC. However, although classically described and used in diagnosis, staging, and treatment of the disease, the analysis of abdominal radiographs in patients suspected with NEC is complex and challenging, with experts (neonatologists, surgeons, and radiologists) often disagreeing about the interpretation of findings. Radiographs are performed sequentially every 6-8h within the first 24 hours of symptom onset, depending on severity of involvement[1].

Abdominal ultrasound (US) examination has been recently described as a highly sensitive method for the diagnosis of NEC, since it shows pneumatosis, fluid in the abdominal cavity, and decreased intestinal blood flow. A comparative study between US scans and plain abdominal radiographs found that US was superior for showing air in the portal system and fluid in the cavity, which are of great use in the diagnosis of NEC[23].

Intraoperative findings include: distention of the bowel loops, gas collection in the submucosa, change in coloration according to the degree of ischemia and/or necrosis, intestinal perforation, fluid in the abdominal cavity[1]. The most affected site is the terminal ileum, followed by the colon. Macroscopic findings in surgical specimens vary from focal disease, in single or multiple occurrences (discontinuous), to pan-necrosis (total NEC), when there is necrosis of at least 75% of the bowel. Histology alterations vary, the most common being coagulation necrosis of the superficial mucosa[1].

Considering the difficulties in identifying and treating NEC, studies have looked into more accurate methods for diagnosis and prescription of surgery. In 2017, Battersby C. et al. developed a score based on gestational age and clinical and imaging findings to determine the likelihood that a given patient has NEC. To use the score, one must first add up the points according to clinical and imaging findings (Table 2). To analyze the risk of NEC, patients are divided into three groups according to gestational age: < 30 weeks, 30 weeks to 36 weeks and 6 days, and ≥ 37 weeks. After calculating the total points and defining the gestational age group to which the patient belongs, the patient's probability of definite disease is assessed in a chart (Graph 1). Each of the gestational age groups has different cutoff points, below which the chance of NEC is considered very low[24].

Differential diagnosis

The main conditions considered in the differential diagnosis for NEC are food protein-induced enterocolitis syndrome (FPIES) and spontaneous intestinal perforation.

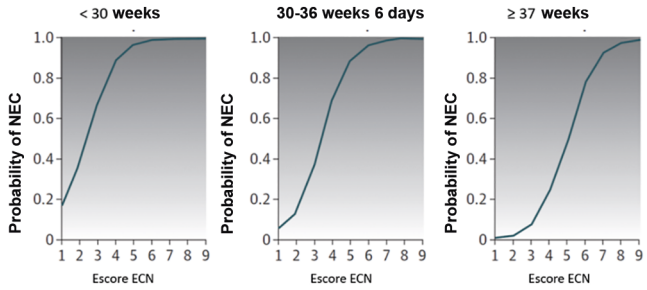
FPIES is a non-IgE mediated food antigen hypersensitivity reaction that has been described outside the neonatal period. Symptoms and signs include blood in the stool, vomiting, diarrhea, lethargy, abdominal distension, and pneumatosis intestinalis. Symptoms appear one to four weeks after exposure to the food antigen and improve after it has been eliminated, which is the gold standard for diagnosis. As in NEC, it is more common in infants fed formula. The question is whether FPIES might occur in the neonatal period, since it might be an important differential diagnosis of NEC, with a different treatment approach[6].

Spontaneous intestinal perforation affects mainly extremely low birth weight infants in the first two weeks

Table 2. Score based on clinical and imaging findings.

FINDINGS	SCORE
Abdominal pallor	1
Pain to abdominal palpation	1
Increased and/or bilious gastric residuals associated with distended abdomen	1
Pneumoperitoneum and/or fixed loop and/or air in the portal system	1
Blood in stool	2
Pneumatosis	3
TOTAL	1-9

A score is first calculated (Table 2) and then, depending on gestational age, the probability of developing NEC is found in the corresponding chart (Graph 1). Adapted from Battersby C, Longford N, Costeloe K, Modi N, for the UK Neonatal Collaborative Necrotising Enterocolitis Study Group: Development of a Gestational Age-Specific Case Definition for Neonatal Necrotizing Enterocolitis. JAMA Pediatr. 2017; 171(3):256-263.



Graphic 1. Probability (%) of NEC according to score and gestational age.

after birth. It differs from NEC in that it is an isolated perforation without an area of necrosis or neutrophilic infiltrate. The perforation is usually accompanied by thinning or absence of the muscularis propria. The pathophysiology is poorly understood. It has not yet been defined whether postnatal use of corticoids or non-steroid anti-inflammatory drugs is related to onset of disease[6].

Therapeutic approach

In the absence of evidence of necrosis or intestinal perforation, the initial approach to NEC includes fasting; keeping an orogastric tube open for gastric decompression and to monitor output; performing tests; prescribing broad-spectrum antibiotics; monitoring blood volume and hemodynamic status to assess the need for inotropic support; and considering parenteral nutritional support. Detailed physical examination must be performed and serial abdominal imaging (every 6-8 hours) obtained to detect early cases that require surgery[1].

In general, the treatment of NEC can be planned depending on the stage of disease (Table 1). In cases of suspected NCE, the treatment suggested by some authors is shorter (around three days), extending to seven to 10 days when NEC is confirmed; in stage 3A disease, surgery may be required if the patient does not improve within 24 hours; grade 3B NEC requires surgery[5].

Despite the above indications, the ideal moment for surgery (when there is loop necrosis, but before perforation) remains a great challenge in clinical practice. The main goal of surgery is to remove the portion of the loop that is necrotic, preserving as much of the bowel as possible. Surgery is usually indicated clinical condition deteriorates, in cases of perforation (presence of pneumoperitoneum or ascites), or when necrosis is suspected[3].

The best surgical approach in advanced disease with perforation is still controversial. Several studies and clinical trials have looked into the matter. Surgical options include exploratory laparotomy, which may involve resection of necrotic areas of the intestinal loop with anastomosis or, in some cases, placement of a percutaneous peritoneal drain; when drainage is chosen, most patients are referred to exploratory laparotomy[1].

Prognosis

The most common complication of NEC is bowel stenosis, especially in patients not submitted to surgery due to fibrosis of the ischemic sites[1]. Malabsorption syndrome and shortened bowel syndrome may also occur, the most serious long-term complication of patients treated with surgery; prolonged parenteral nutrition may cause liver failure and cholestasis; and, more rarely, recurrent NEC and late ulceration of the anastomosis may occur[1]. Mortality related to ECN is high, ranging from 15% to 30% of cases[1].

In the long term, NEC may also increase the risk for neurological disorders. A follow-up study of preterm extremely low birth weight infants found a relationship between NEC and global developmental delay, with alterations in neurological physical examination and low scores in the Bayley scale, possibly due to vasoconstriction and hypoxic-ischemic events caused by intense inflammatory reaction[25].

Prevention

The importance of prevention and early identification of NEC is becoming increasingly evident in view of the severity of the disease and its impact on morbidity and mortality of preterm infants.

Antenatal corticosteroid therapy (ACS) apparently aids in GI tract maturation. A meta-analysis comprising 10 randomized clinical trials showed that ACS decreased the relative risk for NEC by 50%[26]. Progesterone prescribed to mothers at risk of preterm labor also decreases the risk of NEC[16].

A preventive measure that can be adopted is infection control, since NEC can occur in epidemic outbreaks. In this regard, the oral use of immunoglobulins to increase patient immunity has been studied, but satisfactory results have not yet been obtained[1].

Breast milk confers several protective factors to newborns, including IgA, which inhibits Escherichia coli growth and provides active and passive immunity to infants[3]. Breastfeeding decreases the risk of NEC. A clinical trial published in 2017 with newborns with birth weight between 500 and 1250 g compared a group fed exclusively with breastmilk with another group fed a mixed diet (breastmilk and formula). The study revealed a 50% decrease in cases of NEC and a nearly 90% decrease in cases of NEC requiring surgery in the group fed exclusively breastmilk. In individuals given breastmilk alone, the number needed to treat (NNT) to prevent one case of NEC was eight and to prevent one case of surgery for NEC was 10[12].

In regards to nutrition, the use of protocols for the initiation and gradual increase of enteral nutrition has been effective in preventing NEC[27]. The explanation for this is that early initiation of trophic enteral nutrition and adequate diet progression allow the gastrointestinal transit to eliminate possible toxic agents and assist in the maturation of GI tract immune defenses[3].

A meta-analysis on methods to reduce colonization and bacterial overgrowth in the gastrointestinal tract showed that the use of probiotics reduced the incidence of NEC by 30%[28]. These findings are promising, but more studies are still needed to prove the efficacy and safety of supplementation with probiotics. Lactoferrin is a glycoprotein with antimicrobial and immunomodulatory properties. A meta-analysis including four randomized clinical trials showed that lactoferrin has a protective effect against NEC[29]. The use of erythropoietin to decrease exposure to blood transfusion led to a lower risk of NEC, as demonstrated in a meta-analysis featuring randomized clinical trials[30].

Some alternatives have been considered to deter the inflammatory cascade and decrease the incidence of NEC. A meta-analysis published in 2017 showed that the use of arginine decreases the risk of NEC[14]. Administration of EGF and PAF antagonists or PAF-degrading enzymes, also appears to be protective for the GI tract. However, more studies are needed in order to evaluate the use of these mediators[1,3].

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