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Necrotizing Enterocolitis - The State of Art

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Necrotizing Enterocolitis – The State of Art

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ABBREVIATONS

NEC – necrotizing enterocolitis;
VLBW – very low birth weight;
LBW – low birth weight;
PAMP - pathogen-associated molecular pattern;
PAF – platelet activating factor;
TLR – toll like receptor;
MODS – multiple organ dysfunction syndrome;
NO – nitric oxide;
DIC – disseminated intravascular coagulopathy;
i-FABP – intestinal fatty acid binding protein;
l-FBAP – liver fatty acid binding protein;

INTRODUCTION

Necrotizing enterocolitis (NEC), first described as *enterocolitis ulcerosa necroticans* in 1953 by Schmid and Quaiser,[1,2] is the most common gastrointestinal emergency of the neonatal period, with intestinal inflammation as a common denominator for a wide range of clinical presentations and severity.

NEC mainly affects preterm infants (<37 weeks' gestation) with very low birth weight (VLBW) (< 1.500g) or low birth weight (LBW) (< 2.500g). This pathology is characterized by a variable degree of intestinal injury, ranging from inflammation and lesions on the gut wall barrier through ischemic necrosis and perforation of the intestine.[3,4]

In 1978 Bell´s classification for NEC was proposed to better characterize and understand this disease. This classification categorizes the severity of NEC in three stages: mild, moderate and severe, based on clinical and radiographic evidence. Newborns in stages II or III are at a higher risk for both morbidity and mortality.

The following have been identified as risks factors for the development of NEC: LBW, congenital diseases, formula feeding, and prematurity (in part due to a poorer microbiota and higher proportion of harmful species, as Proteobacteria). Also, the use of antibiotics at birth, contact with bacteria from the mother's skin or inability of breast-feeding can cause disruptions of the neonate's microbiota and enhance the risk of development of NEC.[3]

Despite several studies and intense research on the subject, some risks factors are yet controversial and a lot remains unknown about the multifactorial process and pathogenesis of NEC while no major therapeutic advances have been made and thus the high morbimortality remains unchanged.[5,6]

KEYWORDS: Necrotizing enterocolitis (NEC), preterm, very low birth weight (VLBW), intensive neonatal care.

EPIDEMIOLOGY

The incidence of NEC is inversely correlated with gestational age and birth weight while important variations in incidence have also been reported with geographic location and perinatal healthcare services and practices of the newborn, even in countries with the same resources in intensive neonatal care. These variations may be due to the criteria adopted by different countries to offer neonatal intensive care to babies at the limit of viability, to different clinical practices, such as, for example, with regard to enteral feeding.[7] The incidence varies globally, but usually sits around 10% in both VLBW and extreme preterm infants, with a high reported mortality of approximately 25%.[7–11] The lowest reported incidence of NEC is in Japan with only 2% of preterm neonates under 28 weeks' gestation developing NEC.[12]

NEC is the leading cause of death due to gastrointestinal diseases in preterm infants.[7–10]

It rarely occurs before the tenth day of life and is strongly associated with the use of antibiotics in the first week of life.[13] Despite all the developments and new research in neonatal care, morbidity and mortality related to NEC have not substantially changed in the last years.[7]

Approximately 50% of the cases require surgical intervention and typically involve the resection of necrotic sections.[6] The main consequences of this disease like short-gut syndrome, total parenteral nutrition dependency, cholestatic liver disease and neurodevelopmental delay, affect about half of infants with NEC.[5,6,9] Nearly 10% of those who survive will develop late gastrointestinal symptoms and a significant proportion of survivors with stage III NEC present a severe neurodevelopmental delay.[2,9]

Compared to unaffected neonates, preterm infants needing surgery have longer hospitalization (60 more days on average), and even those with NEC but not requiring surgery are estimated to be hospitalized in neonate intensive care units on average 20 more days than same gestational-age preterm infants.[5,10]

A retrospective review analysing mortality associated factors in infants referred to surgical treatment for advanced NEC concluded that the most common cause of mortality due to NEC is multiple organ dysfunction syndrome (MODS).[14] Even cases of NEC with minimal bowel involvement present a higher than usual mortality rate.[14]

PATHOPHYSIOLOGY

The exact pathophysiology of NEC remains unknow and it seems to be a multifactorial and complex disease.[4,11] Immature intestinal barrier, intestinal dysbiosis and genetic predisposition were recognized as predisposing factors to develop the disease.[10,11,15]

Available evidence suggests that NEC starts developing with an intraluminal bacteria disruption who invade the epithelium and intestinal villi.[4]

Toll-like receptor, especially TLR-4, an innate immune receptor found on the intestinal epithelial cells, binds to these bacteria, and activates the pathogen-associated molecular pattern (PAMP) receptors, that will increase the translocation of more bacteria to the intestinal epithelium.[4] The activation of TLR-4 results in barrier injury, that will culminate in vasoconstriction, ischemia and in the emergence of NEC.[4]

On the other hand, studies suggest that genetic variants can lead to upregulation of downstream signaling receptors of TLR-4 and some variants of human genes (*KFKB1, SIGIRR* and *NOD2*) have been systematically associated.[3,16,17] Furthermore, pro-inflammatory cytokines in TLR signaling, such as IL-6 and IL-8, are also elevated at the time of diagnosis of NEC.[3,10]

Some animal and human studies have concluded that the preterm intestine produces higher levels of TLR-4 compared with full-term ones.[18] Activation of TLR-4 through colonization of the intestine by bacteria, essentially by Gram negative bacteria, causes several harmful effects, such as an increase in proinflammatory cytokines and the apoptosis of enterocytes in the intestinal epithelium, while simultaneously reducing blood flow and predisposing to necrosis of segments of the intestine. [6]

Intestinal stem cells are responsible for the production of different types of mature cells, such as Paneth cells, enterocytes, goblet cells and entero-endocrine cells. These cells are activated in response to injury in the intestinal mucosa.[19] Leucine-rich repeat-containing, G-protein-coupled receptor 5 (LGR5), a stem cell marker, has been used to quantitatively measure these cells.[20] In the precise case of NEC, there is a decrease in this binding LGR5 – stem cells.[21]

Mediators like platelet activating factor (PAF), an endogenous phospholipid mediator, can initiate a potent inflammatory response in the intestinal tract.[22,23] Other mediators, like endotoxin lipopolysaccharide, tumor necrosis factor, nitric oxide (NO), cytokines, prostaglandins, and leukotrienes have also been proven to be involved in the development of NEC.[23] Experimental studies in animals submitted to the administration of these mediators were at higher risk for the development of NEC-like lesions.[4,22]

The activation of the of the immune system in newborns caused by the failure of the intestinal barrier, results in a cascade of responses, from which the release of NO will lead to the

production of peroxynitrite, another oxidant,[4,24] which in turn leads to the destruction of enterocytes, compromises their proliferation, and makes endothelial repair impossible.[4]

Preterm neonates with NEC have unusual intestinal microbiota with abnormal bacterial species and an overall reduction in microbiota diversity. This poor diversity is in the genesis of susceptibility to infections, especially when these neonates are submitted to invasive techniques, such as catheterization and enteric feeding.[10]

In addition, normal bacterial colonization in the intestines in preterm neonates occurs at a slower rate.[6]

Abnormal bacterial colonization is, as we know, a predisposing factor for the development of NEC, gram negative bacteria being the most associated with the emergence of NEC. However, there is not a single isolated organism strongly linked to the disease.[25]

Prophylactic antibiotic therapy in preterm newborns alters the normal intestinal flora and prevents anaerobic organisms to act as protective factors against disease.[26]

RISK FACTORS

The most important risk factors for NEC are prematurity, low birth weight, congenital diseases (mostly cardiac anomalies), formula feeding, gastrointestinal infection and compromised in-utero blood flow.[2,9,27]

I. Prematurity

Prematurity is characterized by vulnerability, circulatory insufficiency, underdevelopment of cardiac, respiratory, gastrointestinal systems and a higher risk for infections due to immunological deficiency and poor antibody response.[3,27] In preterm infants, the gut also has reduced peristalsis, a thin mucous layer, reduced tight junctions, increased enterocyte apoptosis and impaired enterocyte regeneration.[3] These combination of factors result in a weak gut barrier, which is an easy target for bacteria penetration. The lack of gut integrity leads to poor digestion, insufficient absorption of proteins, energy and nutrients, which are important for immunoprotection.[3]

Another factor contributing to the development of NEC in preterm infants is a decreased production of immune cells, like IgA, IgM, IgG and expression changes of TLRs, particularly TLR-4 and TLR-9, important agents in the innate immune response.[3] All these factors dramatically increase the vulnerability of these preterm newborns, with NEC rarely occurring in full-term infants. [2]

II. Low Birth Weight (LBW)

LBW currently is the most consensual and significant risk factor of NEC.[10,11] More than 90% of the NEC cases are preterm newborns with LBW.[27] The prevalence of NEC in newborns with VLBW is 4-7% and 30% of those will not survive.[9,28,29] The risk and absolute mortality of NEC is inversely proportional to higher birth weight.[2]

III. Formula Feeding

Formula feeding without supplemental breast milk has been proved to increase the risk of NEC 6.4 times.[10,30] Enteral feeding with artificial formula can cause mucosal injury by shifting fluid from the villi to the bowel lumen, which can result in an ischemic insult to the mucosa.[2]

Furthermore, malabsorbed carbohydrates can lead to the production of hydrogen and short chain fatty acids, with hydrogen being responsible for pneumatosis and abdominal distension, two major signs of the disease.

A recent practical guideline recommends that feedings should be advanced at a rate not higher than 15 to 35 mL/kg/day.[24]

IV. Infectious Agents

The bacteria most frequently involved with NEC are *Klebsiella pneumoniae, Escherichia Coli, Enterobacter, Pseudomonas aeruginosa, Clostridium perfringens, Staphylococcus epidermidis* and *Staphylococcus aureus*.[2,27] The most commonly associated viruses are Coronavirus, Rotavirus and Enterovirus. There have been some reports where *Candida albicans* was identified.[27]

V. Compromised Blood Flow in-utero

Maternal factors leading to low blood flow in-utero can predispose to the development of NEC, mostly in preterm neonates. Chorioamnionitis, increased body mass index, intrahepatic cholestasis, placental abruption, preeclampsia and addiction to smoke, drugs or alcohol are the most important factors.[4,21,24,31]

Two studies (odds ratio 0.60) have shown that cesarean section may be a protective factor rather than increasing the incidence of NEC.[11]

VI. Circulatory Failure

Respiratory complications in preterm infants are very common, particularly in less than 32 weeks' gestation. Respiratory failure can cause hypoxia, which limits nutrient and oxygen delivery to the gut and other organs and can, eventually, culminate in irreversible damage in ischemia-prone organs such as the gut.[2] Assisted ventilation is associated with an increase of the incidence of NEC,[11] while recurrent episodes of apnea, respiratory distress and umbilical vessel catheterization can also contribute to hypoxia in these newborns.[2]

Vasoconstrictive agents, like cyclooxygenase inhibitors (Indomethacin), which are commonly used in the treatment of patent ductus arteriosus, can have a deleterious effect on gut perfusion and lead to a deficient production of immune cells and energy.[3,4,10,24]

Ionotropic treatment for hypotension has also been associated with an increased risk of NEC.[11]

CLINICAL PRESENTATION

Initial symptoms of NEC may easily be confused with or mimic various neonatal pathologies, especially abdominal ones presenting with feeding intolerance, enterocolitis, spontaneous intestinal perforation, Hirschsprung disease, ileal atresia, meconium ileus and volvulus.

The first signs and symptoms of NEC are usually nonspecific, like temperature instability, apnea, desaturations, bradycardia, hypotension and lethargy. Other more specific signs that present are: wall erythema, vomiting, bloody stools, absent bowel sounds, abdominal tenderness, or distension and sometimes a mass in the right lower quadrant.[24,32]

However, the “classic” clinical presentation of NEC includes feeding intolerance, abdominal distention and bloody stools, in a preterm low birth weight neonate after 8-10 days of age.[33] Abdominal wall erythema is highly suggestive of NEC but not a common sign.[34]

This set of symptoms may progress rapidly over some hours or more slowly for up to a couple of days, eventually building up to a life-threatening condition, requiring urgent surgical intervention.[35]

The presence of colitis, characterized by the existence of bloody stools, is three times more frequent in late preterm infants than in extreme preterm infants. This may be due to the delayed gastric emptying and reduced intestinal motility. The extreme prematures more often have ileus, which can be suspected by the presence of bilious gastric aspirates.[36]

Without therapeutic intervention the typical progression leads to septic shock, peritonitis, disseminated intravascular coagulation and ultimately, death. Although, timely surgical intervention appears to effectively prevent fulminant disease progression.[2]

The distinction between newborns with NEC and those with bacterial sepsis without NEC is very important because the clinical management of these situations is very distinct. Antibiotherapy, parenteral nutrition, the length of fasting and most important the need of surgery are different.[37]

NEC is uncommon in full term babies, however when it occurs, these are very sick babies, with other pathologies, such as congenital heart disease, history of asphyxia during birth or other predisposing factors.[36]Despite this, premature newborns are still at greatest risk of developing NEC after a few days of life.

DIAGNOSIS

NEC classification is based in Bell's staging criteria from 1986, that considers three stages: mild or suspected, moderate and severe. The Bell´s staging criteria is based on systemic or gastrointestinal symptoms or signs and abdominal radiographic features.[38]

Bell's Stage I (mild): the newborns has systemic signs, such as temperature instability, lethargy, bradycardia and non-specific gastrointestinal signs: abdominal distension, food intolerance and occult blood in the stool.[39] This stage is characterized by nonspecific findings. Most of infants in this group do not have NEC and the more usual diagnosis is feeding intolerance common in newborns with VLBW.[38]

Bell´s stage II (moderate): These neonates present mild signs of instability, radiographic findings with confirmed pneumatosis with or without portal venous gas.[2,6,39] Medical treatment can be considered in this stage.

Bell's stage III (severe): the most important criteria of this stage is a perforated viscus.[33] In this stage we can find hemodynamic instability, severe thrombocytopenia, DIC peritonitis (IIIA) or pneumoperitoneum (IIIB).[2,15] The existence of extraluminal air outside the bowel is a sign of advanced NEC.[33]A full description of the stages criteria is shown on *Table 1*.

The modified Bell's staging criteria subdivides stages into IA and IB (whether bloody stool is present or not), IIA and IIB (whether the infant is mildly or moderately ill with metabolic acidosis) and IIIA and IIIB (the latter being defined by the presence of bowel perforation). These stages now also include neutropenia, thrombocytopenia, coagulation factors and metabolic acidosis as laboratory markers that are associated with advanced NEC, all this laboratory markers being considered nonspecific.[15]

Progression from stage I to stage II usually occurs within the first 24 to 48 hours. While progression from stage II or IIIA to stage IIIB is characterized by intestinal perforation and may take up to 5 to 7 days.[38]

If the disease is diagnosed in its early stages (Bell´s I or II), feedings can be discontinued early on, the stomach decompressed, and antibiotics initiated to treat a possible infection or sepsis.[24] However, newborns with stage III disease present high hemodynamic instability and have fast progression to fulminant conditions. [38]

The abdominal radiography is one of the keys for the diagnosis of NEC. Some important signs can suggest the diagnosis, such as pneumatosis intestinalis, portal venous gas and ascites.[2,6] On the abdominal radiograph, some initial, non-specific signs that suggest the development of NEC are dilated loops of bowel and gas-filled loops of bowel remaining unaltered on repeat examinations.[33] Other, more specific radiologic signs usually present, especially in later stages of NEC, are pneumatosis intestinalis and portal venous gas, both considered hallmarks and

almost pathognomonic findings, with pneumatosis intestinalis corresponding to the presence of gas in the bowel that originates from pathogenic bacteria. [2,33]

Pneumoperitoneum typically appears only with intestinal perforation and/or necrosis in patients with IIIB NEC.[2]

Currently, the use of doppler ultrasonography has been suggested as a means to identify newborns at risk of developing NEC, as well as to assess the bowel viability of those who already have the diagnosis, by measuring the velocity of blood flow in the celiac trunk and in the superior mesenteric artery.[2] A retrospective study concluded that the use of abdominal ultrasonography for the diagnosis of NEC has some advantages, offering the possibility of a timely diagnosis and allowing monitoring the evolution of the disease without the use of radiation.[40]However, abdominal radiography still remains the gold standard diagnostic imaging modality.[39]

In terms of analytic results, the most common findings are neutropenia, thrombocytopenia, metabolic acidosis and increased C-reactive protein.[2,15]

Some findings that have been proven as indicators of a higher clinical severity are the presence of free gas, focal fluid collection, increased echogenicity of the intestinal wall, absent intestinal perfusion, portal venous gas and pneumatosis intestinalis.[2]

A study by *Numanoglu* carried out with the objective of clarifying early signs of disease through simple laparoscopy or with fluorescein concludes that laparoscopy allows an earlier assessment of the existence of perforation and necrosis and, in the presence of ischemia, fluorescein seems to highlight the necrotic segments.[41]

Although other NEC classification systems and descriptions have emerged, such as the Vermont Oxford Network, Bell's classification remains the most widely used one.[42] Recently, Gordon proposed the "two out of three rule" for the diagnosis of NEC in preterm neonates,[42] which system is fully described in *Table 2.*

Despite several attempts to identify a specific disease biomarker, currently there is still no marker that can be accurately used as a disease predictor. Fecal calprotectin, a marker of inflammatory bowel disease, although useful, cannot yet be used as a marker of NEC, since there is no consensus on the cut-off point to be used.[43]

Similarly, intestinal fatty acid binding protein (i-FABP) and liver fatty acid binding protein (l-FABP), proteins released into the bloodstream when the intestinal mucosa is severely injured, have a medium-low specificity for NEC, which is why its dosage is not yet a considered reliable predictor NEC.[44,45]

The combination of urine i-FABP with fecal calprotectin and urine serum amyloid A, an acute phase reactant protein, improved diagnostic accuracy when compared to isolation of i-FABP.[46]

Table 1. – Bell's modified staging criteria for necrotizing enterocolitis

Bell´s Stage	Severity	Clinical Presentation	Radiology	Management
I	Suspected or Mild NEC	Temperature instability, hypotension, abdominal distension, bradycardia, apnea	Nonspecific	Discontinuation of enteral feeding
IIA	Mild to Moderate NEC	Mild systemic signs, marked abdominal distension, absent bowel sounds, bloody stools	Ileus, dilated bowel loops ± focal pneumatosis	Nasogastric decompression, intravenous fluids and antibiotics. Close clinical and radiological surveillance
IIB	Moderate NEC	Mild metabolic acidosis, thrombocytopenia, abdominal wall edema, tenderness	Extensive pneumatosis, ascites ± portal venous gas	
IIIA	Severe NEC	Respiratory and metabolic acidosis, hypotension, oliguria and DIC.	Prominent ascites, fixed bowel loop, pneumatosis and portal venous gas	Peritoneal drainage and/or exploratory laparotomy and resection of necrotic bowel
IIIB	Severe NEC	Signs of peritonitis, further deterioration, respiratory failure and shock	Pneumoperitoneum with evidence perforation	

Table build from references [2,6,38]

Table 2. - “Two out of three rule”

The diagnosis of NEC can be established if the preterm neonate has abdominal distension, ileus and/or bloody stools and has at least 2 of the following criteria:
⇒ Pneumatosis intestinalis and/or portal venous gas in the abdominal radiography or ultrasound; ⇒ Platelet consumption reduced by 150.000 within 3 days of diagnosis; ⇒ Post-menstrual age at disease onset more consistent with NEC than spontaneous intestinal perforation. *
Exclusion factors:
• Term newborns; • Newborns with known spontaneous intestinal perforation; • Presence of congenital anomalies; • Newborns with less than 80 mL/kg/day of enteral feeding.

Table build from references [42,47]

*NEC typically occurs after days of life and with total or predominant enteral feeding, while spontaneous intestinal perforation is a focal perforation of the intestine, usually in terminal ileum and is independent of enteral feeding and typically occurs within the first days of life.[28] Both diseases present with abdominal distension and hemodynamic instability. However, SIP is generally considered to present at an earlier pos-natal age than NEC and is not associated with pneumatosis intestinalis, the abdomen being characterized by a bluish discoloration and pneumoperitoneum is seen in the abdominal radiography.[45,48,49]

TREATMENT

I. Prevention Strategies

NEC is more frequent in preterm newborns with LBW, so the adoption of preventive strategies to reduce the incidence of NEC in this population is of particular importance.
It has been proved that the incidence of NEC can be reduced with some practices such as breast milk feeding, adhering to feeding guidelines, and probiotics and prenatal glucocorticoids prescription.[24]

Prenatal Glucocorticoids
The recent practical guidelines recommends that expecting mothers receive a single course of corticosteroids if preterm delivery is expected within 7 days, with a potential repeat dose 14 days later.[24]
The administration of antenatal corticosteroids accelerates lung maturation which intends to prevent respiratory complications and reduce the need of artificial ventilation after delivery. A study analyzing antenatal administration of glucocorticoids concluded that the incidence of NEC is significantly reduced in newborns whose mothers have been given glucocorticoids therapy.[50,51]

Breast Milk
Human breast milk has an osmolarity of around 300 mOsm/l while commercial enteral formulas have higher osmolarities of up to 450 mOsm/l.[15]
Multiple clinical trials have proved that breast milk significantly reduces the incidence of NEC,[4] the human milk components have protective effects, although its mechanisms or which components have more protective effects are not fully understood.[6] Breast milk contains the suitable proportions of macronutrients, bioactive agents and immune cells to provide adequate growth, immunologic defenses and the right conditions to favor colonization of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*.[3]
Some experimental studies have suggested that human milk inhibits TLR-4 signaling by preventing glycogen synthase kinase 3β acitivity.[6] In that way, through downregulation of TLR-4 signal, breast milk may reverse the inhibition of intestinal stem cell proliferation and contribute to mucosal healing.[6]
The use of donor breast milk can be a strong substitute the formula feeding and a potential good strategy to reduce NEC.[6,7,15,22] In this way, training and professional help for breastfeeding while encouraging mothers for this role is very important to prevent this disease.

In case of inability to breastfeed, the use of breast milk in small portions through enteral feeding has been shown to be a viable alternative for the prevention of NEC.[33]

Probiotics

Probiotics improve gut motility, the quality of intestinal mucus and control the production of inflammatory cytokines.[24]

A series of 24 clinical trials were analyzed in a systematic review evaluating the efficacy and safety of probiotics in preventing NEC and indicated that oral administration of probiotics decreases mortality and the incidence of severe NEC.[6,52]

There is a consensus that the use of probiotics is an important prevention strategy to help reduce the incidence of NEC without adverse reactions, particularly in newborns with VLBW.[4,6]

The European Society for Pediatric Gastroenterology Hepatology and Nutrition Working Group studied different types of probiotics, and currently recommends the use of *Lactobacilus rhamnosus GG ATCC53103* or the combination of *Bifidobacterium infantis Bb-02*, *Bifidobacterium lactis Bb-12* and *Strepococcus thermophilus TH-4*.[53]

Lactoferrin supplementation has also been studied as a means of preventing NEC and while there seems to be a positive association with a decrease of late-onset neonatal sepsis, there is no apparent correlation with stages II and III (Bell's classification) NEC.[54]

II. Management

Despite all current and previous investigation on the subject, the management of NEC remains a nonspecific one, especially for infants with mild (Bell´s stage I) or moderate (Bell´s stage II) necrotizing enterocolitis. Antibiotic administration, bowel rest with discontinuation of enteral feedings, fluid support, cardiorespiratory, metabolic acidosis and hyponatremia vigilance and sometimes inotropic support are indicated.[2,24]

In the past, guidelines supported delaying enteral feeding as it was thought to decrease the incidence of NEC. However, more recent reviews demonstrate that starting enteral feeds early seems to be safe for preterm and VLBW infants and even that beginning feeds at a higher volume may be beneficial.[15]

For "medical NEC", meaning Bell's stage I (suspected but not confirmed NEC) and Bell's stage II (pneumatosis intestinalis with or without portal venous gas), it is recommended to initiate parenteral nutrition and antibiotics for 72 hours pending culture reports and signs of clinical deterioration.[15,38] At the end of this time, if symptoms have not progressed and imagological findings are not found, feeding may be safely reinstituted.[38] In these stages, surgery is not indicated,[9] however if clinical deterioration occurs it needs to be considered.

Cases of NEC stage III require longer periods of therapy and hospitalization, with neonates with NEC spending on average, a period of two weeks under bowel rest and large spectrum intravenous antibiotics.[55] During this time of bowel rest, nutritional needs are met through peripheral intravenous alimentation.[38]

A randomized control trial that compared slow (18 ml/kg/day) and fast (30 ml/kg/day) feed advancement showed no significant difference in survival without moderate or severe neurologic deficits at 24 months in very preterm (<32 weeks) and VLBW infants. There was also no significative difference in the incidence in NEC between groups with fast and slow advancement of enteral feeding.[15,56]

Antibiotherapy is established aiming to prevent a possible onset of sepsis, with anti-fungal drugs, added if perforation is suspected or confirmed.[24]

The administration of broad-spectrum intravenous antibiotics should be started immediately after collection of blood for cultures.[57]

A study comparing various NEC management approaches amongst different pediatric surgeons, concluded that there is neither consensus nor strong evidence to establish a single antibiotic regimen. Antibiotics are prescribed empirically, according to institutional protocols and changed according to current strains resistances and microbiology results.[1]

In case of shock, use of ionotropic drugs and vasopressors agents is adequate, but they should not replace the administration of fluids. Dopamine can be given in low doses (5 to 15 μg/kg/min), as higher ones can compromise mesenteric blood flow. If necessary, Dobutamine (5 to 10 μg/kg/min) can also be administered, as can sodium bicarbonate, the latter one in case of severe metabolic acidosis.[38]

Fluid administration should consist of Ringer lactate, saline and albumin. In case of anemia, red blood cell concentrate should be preferred over blood transfusion. If severe thrombocytopenia (< 10.000/mm), massive bleeding or gastrointestinal bleeding is present, platelet transfusion may be indicated.[38]

III. Surgery

Surgical treatment is required in approximately 50% of the cases of NEC,[6,58] which consists in the surgical resection of the necrotic section of bowel, the control of intra-abdominal sepsis and aims to preserve of as much bowel as possible.

Surgery is normally necessary in Bell´s stage III, with the most frequent indications for surgical treatment including abdominal wall cellulitis, fixed dilated bowel, abdominal mass, hemodynamic instability, worsening laboratory values or clinical deterioration despite adequate medical treatment.[2,24]

However, deciding the ideal time for surgery is not always easy, as the diagnostic sensitivity of the disease is not very high and it remains unclear which is the best approach in some cases, which is especially true in the most severe stages.[40]

The most common surgical procedures for the treatment of NEC are drain placement, exploratory laparotomy with resection of the necrotic bowel, and in most cases, enterostomy with creation of a stoma.[33]

In case of advanced NEC presenting with intestinal perforation both the performance of a laparotomy or a primary peritoneal drainage may be legitimate options. However, a systematic review showed a larger than 50% increase in mortality with a peritoneal drainage approach instead of an exploratory laparotomy.[59]

Moreover, a study by Rees *et al.* concluded that in newborns with perforated NEC and weighting under 1000 g, performing just a peritoneal drainage is not a definitive treatment since 74% of the cases required laparotomy afterwards.[60]

The classical surgical approach consists in the resection of all intestinal necrotic sections, and simultaneous creation of a stoma, future anastomosis of the viable parts of the intestine being performed in a later operative time.[2] However, the creation of a stoma, especially jejunostomies, in a preterm neonate can lead to poor growth, and metabolic and nutritional disorders. Thus, despite the low weight, some surgeons choose to perform an anastomosis at the same operative time.[61,62]

When the entire intestine is damaged, the options are to close the abdomen and withdraw care or to create a diverting jejunostomy, that result in the infant depending upon enteral feeding for the rest of his life.[2]

FUTURE DIRECTIONS

Some risk factors are yet controversial, and a lot remains unknown about the multifactorial process and pathogenesis of NEC while no major therapeutic advances have been made and thus the high morbimortality remains unchanged.[5,6]

NEC remains one of the most common emergencies during the neonatal period and one of the leading causes of death in neonatal intensive care units. Despite several studies and intense research on the subject, there is still no consensus on the best diagnostic approach and the appropriate treatment for each stage. Some studies are underway to implement new and advanced therapeutic options.

One of the options for the future is the use of stem cells and breast milk derived exosomes, components of breast milk that seem to help in reducing intestinal epithelial injury and NEC incidence.[2,4]

Another promising possible prevention strategy is the use of amniotic fluid stem cell therapy where stem cells migrate and colonize possible intestinal injuries, increasing intestinal epithelium regeneration.[4,9]

A prospective study established the safety and feasibility of mild, hypothermia for 48 hours in preterm neonates with severe (Bell's stage III) NEC with MODS, but further randomized trails are warranted to evaluate its benefit and efficiency.[63]

While most of these studies are not yet validated, it is vital to establish and implement further preventive measures for the disease, as it has been done with probiotics, encouragement of breastfeeding and prenatal administration of glucocorticoids if prematurity is expected.

As for as diagnosis is considered, the use of Doppler ultrasonography seems to be beneficial in detecting at risk cases at an earlier stage.

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