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Neonatal necrotizing enterocolitis: a focus on

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Abstract. – **Necrotizing enterocolitis (NEC) is a multifactorial worldwide problem, representing the most frequent gastrointestinal emergency in neonates. Extremely common in preterm infants, it is also registered in fullterm low birth weight neonates.**

Despite extensive research, its etiopathogenesis is not completely understood and this neonatal disease remains associated with high morbidity and mortality rates.

This review proposes an interdisciplinary focus on recent developments in NEC etiopathogenesis, diagnosis and management.

Key Words:

Neonatal necrotizing enterocolitis, Preterm infant, Fullterm low birth weight baby, Risk factors, Diagnosis, Management.

Introduction

Described for the first time by Genersich in the past century[1], nowadays NEC represents the most common cause of non obstructive acute abdomen occurring in neonates, characterised by necrotic damage of intestinal mucosa. It usually affects premature infants, but it has also been reported in term babies, mostly with a background of congenital heart and endocrine diseases and too rarely in older, immunologic compromised, infants[2].

Despite several decades of research, its etiopathogenesis remains elusive and it appears the interaction of multiple factors that determine the final common inflammatory-ischaemic pathway, the background of necrotizing enterocolitis.

Gastrointestinal, like abdominal distension and bloody diarrhea, and systemic symptoms lead to diagnosis, confirmed by radiological findings of pneumatosis intestinalis.

Despite numerous studies on its medical and/or surgical approach, prevention represents the NEC starting-point.

This review focuses on status of the art and recent developments on NEC knowledge.

Epidemiology

This acute gastrointestinal disease presents an annual world rate ranging from 0.3 to 2.4 cases per 1000 live births in premature babies and an esteemed incidence in full-term neonates of 0.05 per 1000 live births[3]. Therefore, neonatal necrotizing enterocolitis records an overall incidence of 2-5% in all prematures and up to 13% in babies weighting at birth less than 1500 gr[4].

Male and black babies seem to be affected with higher frequency than female and white, but there is not a consensus on this regard[5].

Ninety per cent of NEC cases occur in premature infants, with an incidence inversely related to birth weight and maturity degree: babies born earlier develop NEC at a later chronological age.

In term infants this neonatal emergency is a rare event, that develops much earlier than in preterms, occurring within the first days/week of life[6].

Mortality rates range from 10% to 40%, depending on gestational age, birth weight and coexisting diseases[7].

Survivors can also develop significant short and long-term medical (protracted parenteral nutrition) and/or surgical (strictures) morbidities.

Etiopathogenesis

Not yet clearly understood, NEC aetiology seems to be related to multiple factors. The predominant hypothesis is that necrotizing enterocolitis represents the final finding of multiple synergistic events that induce mucosal damage. In fact, it is likely that risk factors, such as prematurity, ischaemia, infective agents and enteral feedings, may play a role in NEC determinism.

Prematurity

Epidemiological studies have reported a strong association between prematurity and NEC because of structural and functional gastrointestinal incompetence[8]. In fact, in premature babies there are a deficient gastric acid and pepsine production and low amilolytic, lipolytic and proteolytic secretion rates; trypsinogen secretion is very low and does not respond to feeding.

In preterms, lactose absorption results incomplete and the glucose-galactose carrier on the apical villous enterocytes membrane is not completely developed[9]. In addiction, only low bile salts rates are available and its active ileal reabsorption is immature[10].

Intestinal wall seems more permeable because of the greater fluidity of the microvillous membrane, with higher lipid/protein ratio that determines the uptake of intact molecules[11]. So, feedings are not completely digested and various toxins not hydrolysed.

Preterm babies present an impaired immune response with a lower antibodies response and IgA secretion and a smaller T-lymphocytic intestinal population.

Current evidences have focused the attention on the lack of endogenous host defence; in fact, in preterm, it has been underlined the absence of lysozyme-conteining intestinal Paneth cells and the lower enteric defensin expression, resulting on bacterial survival, adherence and wall translocation[12].

Ischaemia

Much attention has been focused on the causative role of ischaemia in the pathogenesis of NEC.

Immature neonatal enteric barrier is particularly susceptible to reduced mesenteric blood flow. In animal model and human studies, mucosal hypoxic-ischaemic injury is attributed to a diminished perfusion to the intestinal mucosa, particularly on the ileo-cecal region. This is due to a compensatory mechanism that shunts blood flow to vital organs[13]. The redistribution of mesenteric output, called " the diving reflex", occurs in response to neonatal hypoxic episodes, such as in asphyxia, respiratory distress syndrome, hypotension, shock, persistent ductus arteriosus, hypothermia[14].

Intestinal vascular suffering may be due to thromboembolic phenomena, partially caused by neonatal polycytemia and hyperviscosity. The correlation between umbelical arterial catheterism and thromboembolic injury seems not confirmed[15], to the contrary than happens for mesenteric blood flow reduction due to umbelical catheterization[16].

Ischaemic changes can also be increased by riperfusion[17]: preterm baby is particularly susceptible to mucosal free radicals injuries, followed by platelet activation with release of vasoconstrictor eicosanoids and enterocyte apoptosis induction[18].

Infection

In addiction to prematurity and ischaemic insults, it seems that infectious agents may play a role in NEC development, as underlined in epidemic cases without ulterior evident predisposing factors. In the majority of cases is too difficult identify the causative pathogen, in fact numerous different microorganisms (bacteria, viruses and mycetes) have been isolated in NEC cases, but many of them are part of the normal neonatal intestinal flora[19] (Table I). Therefore, it is possible that normal bowel microflora, in preterms and low birth-weight fullterm babies, could become enteropathic[20].

Factors like structural and functional bowel wall immaturity, incomplete substrates digestion and absorption, incompetence of defensive mechanisms and inappropriate use of antibiotics could increase the virulence of mi-

Table I. Infectious agents implicated in necrotizing enterocolitis.

Bacteria	Viruses	Mycetes
Clostridia *C. butyricum* *C. difficile* *C. perfringens* Escherichia coli Klebsiella pneumoniae Pseudomonas aeruginosa Salmonella Staphilococci *S. aureus* *S. epidermidis*	Coronavirus Coxsackie B Rotavirus	Candida species

croorganisms, like Escherichia coli and Clostridia, frequently implicated in NEC pathogenesis[21].

Finally, the efficacy of pre- and probiotic prophylactic therapy, due almost in part to intestinal bifidobacterium colonization and intraluminal pH reduction, seems to confirm the role, not well defined yet, of infectious agents in NEC determinism[22].

Enteral feedings

There is the evidence that enteral feedings may promote NEC development. In fact diet can influence the intestinal ecosystem; large volume and hyperosmolar enteral formula feedings may alter the bowel environment[23]. An excess of undigested nutrients may induce bacterial colonisation and overgrowth, hydrogen gas production, intestinal distension and mucosal injury, evolving to wall necrosis and pneumatosis intestinalis.

Conversely, breast feeding seems to protect infants against necrotizing enterocolitis[24]. Breast milk, in fact, contains large quantities of anti-inflammatory components (like cytokins, growth factors, leukocytes, macrophages), lysozyme and IgG, pre- and probiotics that stimulate lactobacillar and bifidobacterial growth, modulating the intestinal microflora composition to the host benefit[25].

Considered as the result of all the underdescribed risk factors, NEC represents the final common response of the neonatal gastrointestinal system to this variety of pathologic events.

Diagnosis

First of all, NEC diagnosis is based on clinical manifestations (Table II). Initial symptoms may be subtle and aspecific and can include apnoea, temperature instability and lethargy.

A symptomatological triad, characterised by abdominal distension, gastric contents retention and bloody stools, lead to clinical diagnosis. Severe and fulminant NEC presents with respiratory failure, rapid cardiovascular and haemodinamic collapse and shock.

Diagnostic necrotizing enterocolitis confirmation is based on radiological hallmark of pneumatosis intestinalis, present in 90% of cases, small bowel dilatation and portal vein air[26]. In advanced stadia, radiological and echographical signs of ascitis and pneumoperitoneum may be available.

Recent studies have emphasised the role of Magnetic Resonance Imaging (MRI) in the non invasive diagnosis of intestinal necrosis in premature infants with NEC suspicion[27].

Laboratory studies, like haemochromocytometric exam, blood culture, serum electrolytes, arterial blood gas analysis, and blood pressure monitor are very important for infant management, following the Bell staging criteria[28].

Recent studies have shown the importance of platelet-activating factor (PAF), a potent pro-inflammatory phospholipid, in inflammatory mediated bowel damage; blood determination of PAF and its related lipids (PAF-LL) has been proposed as an effective complement to clinical and radiological studies for NEC diagnosis[29]. In addiction, human intesti-

Table II. NEC associated signs.

Gastrointestinal	Systemic
Increased abdominal girth	Lethargy
Abdominal tenderness	Temperature instability
Feeding intolerance	Apnoea/respiratory distress
Delayed gastric emptying	Acidosis
Vomiting	Glucose instability
Occult/gross blood in stools	Decreased peripheral perfusion
Change in stool pattern/ diarrhea	Disseminated intravascular coagulopathy
Abdominal mass	Circulatory collapse
Erythema of the abdominal wall	

nal fatty acid binding protein (hIFABP) serum determination may be used as a possible diagnostic marker for intestinal mucosal injury[30].

The NEC differential diagnosis includes ileus secondary to neonatal sepsis, spontaneous intestinal perforation, congenital cause of intestinal obstruction, such as ileal atresia, intestinal malrotation and/or volvulus, Hirschsprung disease, neonatal appendicitis and neonatal pseudomembranous colitis[31].

Prevention

Prevention represents the starting point of NEC management. It could be reached increasing the intestinal host defence mechanisms and with gut decontamination, protecting the intestine from inflammatory mediated bowel injury.

Induction of bowel maturation could be reached with pre- and postnatal employment of corticosteroid therapy[32]. Bacterial colonisation and NEC are drastically reduced if feeds are acidified and the gastric pH is less than 4.

Expressed breast milk fed preterm is 20 times less likely to develop necrotizing enterocolitis than formula fed baby. In fact, there is the evidence that breast milk contains multiple immunoprotective factors, which could enhance intestinal host defences and reduce bacterial colonisation[33].

If maternal milk is not available, oral administration of IgA preparation may be able to reduce NEC incidence. In addiction, arginine supplementation (1.5 mmol/kg/day), per os or via parenteral nutrition given, seems to reduce the incidence of all stages of NEC[34].

Antimicrobial preventive use is still debated; vancocin per os, poorly absorbed, seems the first antibiotic choice against the most frequently NEC isolated germs[35].

Platelet-activating factor (PAF) inhibitors have been used in research and could be useful in NEC prevention[36].

Treatment

NEC treatment must be initiated timely, at the first clinical suspect and it must be modulated according to bowel involvement degree and severity of its presentation, as indicated in Table III[37].

In suspected disease enteral feedings must be withheld and total parenteral nutrition (TNP) must be started to prevent nutritional deterioration.

In non surgical definite NEC, enteral feeding can be restarted about 10-14 days after radiographic normalisation.

Gastrointestinal decompression is needed at the first abdominal sign. Low continuous suction may be achieved using large bore nasogastric tube; the output must be monitored and intravenous (IV) replacement of solutions must be considered if copious secretions amounts are removed.

Broad-spectrum antimicrobial therapy is initiated at the first symptoms, after blood and urine culture collections. Antibacterial coverage for gram-positive and gram-negative organisms is essential and anaerobic coverage is needed in advanced cases. Antibiotic treatment is usually based on a combination of 2-3 drugs, in the majority of cases ampicillin, an aminoglycoside and metronidazole, IV administered for a chronological range, varying between three to 14 days, depending on clinical stage[38].

Antifungal treatment, based on fluconazole, should be considered in prematures with prolonged antibacterial therapy who continue to clinically deteriorate.

Babies with severe illness may experience intravascular depletion due to fluid shift to the extracellular space and may progress to shock. In these cases, repeated use of volume expanders, such as normal saline solutions and albumin, and low dopamin doses (2-3 mg/kg/die) are necessary[39].

Thrombocitopenia and consumption coagulopathy may occur and they should be treated with platelet and fresh frozen plasma transfusions[40].

Except in milder cases, intubation and ventilatory support are required to improve respiratory status.

If NEC medical treatment fails to reach the goal, in cases of progressive clinical deterioration and when bowel perforation is suspected, surgical management is indicated[41]. The main surgical approach is laparotomic with bowel inspection to identify any necrotic area. Bowel lavage may be performed and peritoneal fluid collected for culture. After necrotic areas resection an enterostomy is usually performed with subsequent reanasto-

Table III. NEC management based on staging criteria.

Stage	Systemic signs	Intestinal signs	Radiological signs	Treatment
IA Suspected NEC	Temperature instability, apnoea, bradycardia, lethargy	Increased gastric residuals, mild abdominal distension, emesis, heme-positive stools	Normal or intestinal dilatation, mild ileus	Nothing per os (NPO), antibiotics for 3 days pending culture
IB Suspected NEC	Same as stage IA	Grossy bloody stools	Same as stage IA	Same as stage IA
IIA Definite NEC (mildly ill)	Same as stage IA	Same as stage IA plus absent bowel sounds, ± abdominal tenderness	Intestinal dilatation, ileus, pneumatosis intestinalis	NPO, antibiotics for 7-10 days
IIB Definite NEC (moderate ill)	Same as stage IIA plus mild metabolic acidosis, mild thrombocytopenia	Same as stage IIA plus absent bowel sounds, definite abdominal tenderness, ± abdominal cellulitis or right lower quadrant mass	Same as stage IIA plus portal vein gas, ± ascitis	NPO, antibiotics for 14 days, bicarbonate for acidosis
IIIA Advanced NEC (severely ill, intact bowel)	Same as stage IIB plus hypotension, bradycardia, severe apnoea, combined respiratory and metabolic acidosis, DIC, neutropenia	Same as stage IIB plus signs of generalised peritonitis, marked tenderness and distension of the abdomen	Same as stage IIB plus definite ascitis	Same as stage IIB plus fluid resuscitation, inotropic support, ventilation therapy, paracentesis
IIIB Advanced NEC (severely ill, perforated bowel)	Same as stage IIIA	Same as stage IIIA	Same as stage IIB plus pneumoperitoneum	Same as stage IIIA plus surgical intervention

Modified from Walsh[37].

mosis. Only on a limited number of patients parcellary necrotic gut resection is followed by primary anastomosis.

Peritoneal drenage under local anaesthesia has been suggested in infants extremely small, less than 1000 gr, with severe NEC to allow systemic stabilisation and recovery[42].

Prognosis

Necrotizing enterocolitis represents the most common cause of death in neonates undergoing surgery.

The average mortality ranges between 10% to 40%, even higher in severe cases. Only early diagnosis and management remain critical to improve the outcome of these patients.

Infants who have survived acute NEC remain at high risk to develop short-term and/or long-term morbidities.

Small patients with medical NEC could require protracted periods of nothing per os and central venous access for prolonged parenteral nutrition, with the significant risk of sepsis. In addiction protracted hyperalimentation and absence of enteral nutrition may cause cholestasis and hyperbilirubinemia.

Babies surviving NEC with resected bowel are too vulnerable to bacterial overgrowth, impaired absorption and life-threatening sepsis.

About 10-35% of all survivors will develop stricture, the most common long-term gastrointestinal complication of necrotizing ente-

rocolitis. Crampy pain, abdominal distension, vomiting, constipation and persistent melena must suggest the presence of bowel stricture and require barium enema studies and surgical approach[43].

Short-bowel syndrome represents the most serious long-term NEC complication, occurring after extensive bowel resections; nutritional regimes are necessaries to guarantee adequate calories, minerals and vitamins intake for gut nutrition and remodelling. Clinical signs, such as poor weight gain, weight loss, diarrhea, abdominal distension, and laboratory evidence of steatorrhea, anemia and hypoprotidemia lead to diagnosis[44].

Infants surviving severe NEC may also suffer neurodevelopmental impairment, due almost in part to prematurity and undernutrition related to nutrients malabsorption[45].

Meticulous follow-up must be started at discharge, based on periodic clinical visits, growth measurements and laboratory studies and it must be strictly follow the baby until the age of two years[46].

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