DILEMMAS AROUND NECROTIZING ENTEROCOLITIS IN LATE PRETERM NEONATES

Maura Adelina Hincu[1], Gabriela-Ildiko Zonda[1,2*], Smaranda Diaconescu[1,3], Luminița Păduraru[1,2]
"Grigore T. Popa" University of Medicine and Pharmacy Iasi
1. Faculty of Medicine
"Cuza-Vodă" Clinical Hospital of Obstetrics and Gynecology, Iasi
2. Neonatal Intensive Care Unit
"Sf. Maria" Clinical Emergency Children's Hospital, Iasi
3. Department of Pediatric Gastroenterology
[*]Corresponding author. E-mail: ildikozonda@yahoo.com

DILEMMAS AROUND NECROTIZING ENTEROCOLITIS IN LATE PRETERM NEONATES (Abstract): Necrotizing enterocolitis is an acquired, multifactorial, and potentially severe gastrointestinal disease characterized by ischemia, necrosis, and inflammation of the bowel wall. It affects mostly very low birth weight preterm neonates, but approximately 10% of the cases are diagnosed in late preterm and term infants with risk factors for mesenteric ischemia like intrauterine growth restriction, polycythemia, birth asphyxia, chorioamnionitis, sepsis, or congenital gastro-intestinal or cardiac defects. In growth restricted newborns the incidence of necrotizing enterocolitis is approximately twice compared to those with adequate birth weight. In these fetuses blood flow to the brain is preserved at the expense of blood flow to other organs, including the gastrointestinal tract, which leads to mesenteric ischemia. An exclusive human milk diet might be protective due to growth factors, antibodies, cellular immune factors, probiotic bacteria, oligosaccharides, and stem cells, which are all present in fresh breastmilk. **Keywords**: NECROTIZING ENTEROCOLITIS, IUGR, CONGENITAL CARDIAC DEFECT, LATE PRETERM.

Necrotizing enterocolitis (NEC) is an acquired, multifactorial, and potentially severe gastrointestinal disease characterized by ischemia, necrosis and inflammation of the bowel wall. Being one of the most common neonatal gastrointestinal emergencies requiring surgery, this disease presents high mortality rate (10-30%), particularly among preterm infants (1,2). While some studies claim that the incidence of NEC remained stable in recent years (~10%) (3, 4), different studies revealed that due to the enhanced survival of extremely low birth weight (ELBW) newborns, the incidence has increased (11-15%) (5-7).

The risk of developing NEC depends on the gestational age (GA), the lower the GA, the higher the risk (8). For the survivors affected by NEC, there is high associated morbidity with neurodevelopmental sequelae and retinopathy of prematurity (2). Being one of the main causes of mortality and morbidity in neonatal intensive care unit (NICU), a better understanding of the pathogenesis of NEC is critical in order to

have an early diagnosis. Very low birth weight (VLBW) preterm infants represent the vast majority of patients affected by NEC, however about 10% of the cases are diagnosed in late preterm and term infants with risk factors for mesenteric ischemia like intrauterine growth restriction (IUGR), polycythemia, birth asphyxia, chorioamnionitis, sepsis, or congenital gastrointestinal or cardiac defects (9-12). The risk factors for different etiopathogenetic mechanisms of NEC, as well as most common laboratory and radiological findings are summarized in (tab. I).

TABLE I

Risk factors for different etiopathogenetic mechanisms of NEC and common laboratory and radiological findings.

	ISCHEMIC NEC	**INFECTIOUS NEC**
Medical history	Full-term/late preterm infant with IUGR Caesarean section 5-minute Apgar score < 7 Severe metabolic acidosis Hypoglycemia Severe anemia/ polycythemia 36ºC at 1 hr. of life Mother with preeclampsia or diabetes Placental abruption Gastroschisis/omphalocele Congenital heart disease (patent ductus arteriosus, hypoplastic left heart syndrome etc.) (13) Umbilical arterial catheterization (14)	Preterm infants (< 32 weeks GA) VLBW infants (< 1,500 g) Chorioamnionitis Premature rupture of membranes
Drugs	Indomethacin ± dexamethasone Ibuprofen Red blood cell transfusions (15)	H2 blocker (ranitidine/famotidine/nizatidine) (16,17) Empirical antimicrobials
Time of onset	Short term after birth (5.3 days) (11)	Later onset (15.3 days) (11)
Laboratory studies	• Blood culture negative • Negative gastric aspirate • Normal WBC • Low serum bicarbonate (due to poor tissue perfusion - isolated, without metabolic acidosis) • Inflammatory syndrome is absent - normal serial CRP values would favor aborted antibiotic therapy and early resumption of feedings (18).	• Blood culture may be positive in sepsis • Gastric aspirate may be positive (a negative gastric aspirate does not exclude a bacterial infection) • Inflammatory syndrome present -persistently elevated CRP after initiation of appropriate medical management suggests associated complications (18). Moderate to profound neutropenia - sepsis • Low hematocrit or hemoglobin may suggest infection or are low due to blood loses caused by consumptive coagulopathy • Low serum bicarbonate (associated with severe metabolic acidosis in sepsis) • Thrombocytopenia - reaction to gram-negative organisms and endotoxins or as part of consumptive coagulopathy (associated with high levels of PDF) • Fecal volatile organic compounds (VOCs) (19)

	ISCHEMIC NEC	INFECTIOUS NEC
Radiography	• Abnormal gas pattern • Dilated bowl loops • Thickened bowel walls	Radiological signs from ischemic NEC associated with: • Pneumatosis intestinalis • Portal venous gas • Abnormal free air • Intraperitoneal free fluid

CASE REPORT

Prenatal and birth history

Preterm female infant, GA 34 weeks, birth weight 1,800 g, first twin, of a dichorionic diamniotic pregnancy, born vaginally in a level II maternity to a 20 year old mother with inadequate prenatal care. In the last month of pregnancy, the mother had a urinary tract infection with *Escherichia coli* treated with antibiotic (Cefiximum). Apgar scores were of 8/9/9 at 1, 5 and 10 minutes, requiring early CPAP in the delivery room for 15 minutes.

The second twin was also female, with a BW = 2150 g, and Apgar scores of 9 at 1 minute and 10 at 5 minutes. Twin 2 had an uncomplicated course in the neonatal intensive care unit.

Hospitalization course prior to transport

The infant was admitted in the level II NICU at 20 minutes of life and the initial physical exam revealed intercostal and subcostal retractions, oxygen saturation (SpO_2) of 88%, a heart rate (HR) of 135 beats/minute (bpm), respiratory rate of 38 beats/minute and blood pressure (BP) 63/24/35 mmHg. The neonate required free-flow oxygen in order to maintain SpO_2 within normal range, parenteral nutrition, and prophylactic antibiotic (Ampicillin). Enteral feeding was initiated with formula on day of life (DOL) 2.

Initial laboratory studies revealed hemoglobin (Hb), hematocrit (Ht) white blood cell count (WBC) within normal range, negative C-reactive protein (CRP) and initial peripheral cultures (skin, external auditory canal, gastric liquid, and nasopharyngeal swabs).

On the fifth day of life the patient became unstable and clinical examination revealed recurrent desaturations (lowest value of SpO_2 = 50%) and coffee ground followed up by bilious emesis. Blood gas analysis showed mild respiratory acidosis (pH 7.26 and PCO_2 52.7 mmHg). Chest and abdomen X-Ray was normal. Blood and stool were sampled for bacterial cultures (and were negative after 72 hours). Feeds were stopped and ampicillin was replaced by intravenous gentamicin and colistin. At this point then transfer to level III center was requested. During transfer the neonate was stable with free flow oxygen.

Neonatal course at level III facility

The clinical examination at admission in the level III ICU revealed pale-greenish skin, hypotonia, shallow breathing, systolic murmur grade IV/VI, tachycardia (175-181 bpm) and bilious drainage with streaks of old blood. Immediately after admission, she presented severe recurring apneas requiring positive pressure ventilation (PPV) followed by intubation and mechanical ventilation (SIMV). Blood gas analysis showed respiratory acidosis with normal oxygenation (pH = 7.26, PCO_2 = 52.8

mmHg, PO_2 = 58 mmHg). Laboratory workup on admission revealed anemia, leucopenia (I/T = 0.47), elevated CRP and PCT (tab. II).

The X-Ray on admission revealed distended bowels with wall edema. Peripheral and blood cultures, as well as cerebrospinal fluid were collected.

TABLE II

Laboratory workup on admission and during hospitalization in the level III NICU up to DOL 17

Day of Life (DOL)	Hb (g/dl)	Ht (%)	WBC x10^3/mm^3	PLT x10^3/mm^3	CRP	PCT	Direct bilirubin	Urea
6	10.6	33.2	2.8	187	44.1	20.7	0	69.8
8	13	41.1	6.7	104	50.6	6.86	0.2	110.7
9	10.1*	31*						
10	12	37.9	9.8	120	125.2	1.06	0.4	66.3
14	10.6	33.1	17.9	249	87.5	1.11	1.4	79.5
17	14.3	43.7	16.3	174	37.6	0.79	0.9	71
*values from the arterial blood gas bulletin								

A nasogastric tube was placed for decompression of the dilated bowels and total parenteral nutrition (TPN) and intravenous antibiotics with broad-spectrum coverage (colistin, meropenem and gentamicin) were started. The cranial ultrasound revealed supernumerary ventricular cavity. Echocardiography showed Tetralogy of Fallot (TOF) with mild pulmonary stenosis, *patent foramen ovalae* and *ductus arteriosus*. Blood cultures and lumbar puncture were negative, and the peripheral cultures were positive for *Escherichia coli*. The newborn required mechanical ventilation for 21 days, three packed RBC's transfusions (15 ml/kg) for anemia and completed a 15-day course of antibiotic therapy for presumptive sepsis despite negative blood culture. Following treatment, clinical status improved slowly, and the laboratory tests normalized by DOL 17. Enteral feeds were restarted on DOL 15 with full feeding established on DOL 29.

Onward the clinical course of the infant was uneventful, however on DOL 55 the neonate presented marked abdominal distension and the X-ray revealed dilated intestinal loops. Following surgical consult, the newborn was transferred to the pediatric surgery department for further evaluation.

DISCUSSION

The etiology of NEC is not entirely understood as multiple factors appear to be involved, including hypoxia, acidosis, and hypotension, leading to ischemic damage of the mucosal barrier of the small intestine. Gram negative bacterial invasion of the mucosa may be another factor involved in the pathogenesis of NEC. Repeated radiographs are recommended, pneumatosis intestinalis and portal venous gas being pathognomonic signs, caused by anaerobic

bacteria, particularly by Clostridia.

Newborns with very low birth weight (< 1,500 g) and very preterm infants (< 32 weeks) are the most affected by this pathology (3, 20), as they have decreased ability to suppress the exaggerated inflammatory response or are unable to develop an inflammatory response to pathogenic bacteria (21). This case report presents a late preterm infant with a low birth weight and congenital heart disease. Hence, intestine mucosal injury and ischemia might have played a part in the development of NEC.

The signs and symptoms of necrotizing enterocolitis are highly variable, nonspecific and subtle (22). Physical examination findings may include abdominal distention, abdominal tenderness, visible intestinal loops, decreased bowel sounds, palpable abdominal mass, and erythema of the abdominal wall. Systemic findings may include respiratory failure, circulatory collapse, and decreased peripheral perfusion. The clinical course of this patient was marked by multiple days of parenteral nutrition and mechanical ventilation.

The role of inflammation in the pathogenesis of NEC is increasingly recognized. Antenatal inflammatory processes like chorioamnionitis may increase the susceptibility of preterm infants to develop NEC. Decreased intestinal mucosal thickness and increased mucosal permeability, as a result of inflammatory mediators, may explain this association (21). This twin derived from a mother with urinary tract infection in the third trimester, which seems to have complicated the course of the disease.

A recent meta-analysis investigating the outcomes of preterm infants affected by IUGR compared with those without growth restriction found that the incidence of NEC was at least 2.5 times higher in preterm infants with growth restriction (22). It is suggested that in such fetuses, blood flow to the brain is preserved at the expense of blood flow to other organs, including the gastrointestinal tract (23). Although the evidence suggests that newborns with IUGR and abnormal antenatal Doppler are at increased risk of developing NEC, early initiation of breast milk feeds does not appear to increase the incidence of NEC in this population (23).

Generally, this condition occurs after the first week post-partum when the intestine has been colonized (24). In this case, rapid initiation of enteral feeding with formula was a risk factor for NEC, due to changes in enteric blood flow and oxygen requirements during feeding. An exclusive human milk diet might be protective due to growth factors, antibodies, cellular immune factors, probiotic bacteria, oligosaccharides, and stem cells. Fresh maternal breast milk is superior to frozen or donor breast milk (25, 26). A prospective multicenter study concluded that the incidence of NEC was 6-10 times higher in exclusively formula-fed infants when compared with exclusively breast milk-fed newborns, and three times higher when compared with infants who received breast milk and formula (27). Early initiation of enteral feeds in preterm infants with very small non-nutritive volumes (known as trophic feeding or minimal enteral nutrition) is thought to have several advantages over complete fasting as a result of “priming” the gastrointestinal tract and aiding in its maturation processes (28-30). Initially, one of the differential diagnosis considered was feeding intolerance caused by lactose intoler-

ance. Neonatal lactose intolerance syndrome is based on a series of digestive system symptoms caused by the lack of lactase, leading to the inability of digesting the lactose in breast milk or cow milk. Symptoms of lactose intolerance include loose stools, abdominal bloating and pain, flatulence and vomiting (31). In this particular case, the neonate presented gastric residuals, abdominal tenderness, and recurrent apnea/bradycardia, which together with the systemic signs and abnormal blood work raised the suspicion of sepsis.

The reported frequency of NEC in infants with critical congenital heart disease (CCHD) ranges from 3% to 9% (32-35) with no relationship to feeding practices. However, in many centers infants with CCHD are managed with TPN and enteral feedings are deferred in the preoperative period (36, 37) as hypoxia, poor mesenteric perfusion, acidosis and hemodynamic instability are high risk factors for NEC. In our case the diagnosis of congenital heart defect was made on DOL 7, after the onset of symptoms and the deterioration of the infants' clinical status. TOF with mild pulmonary stenosis is unlikely to be a risk factor for NEC, but in this particular case it might have played a part in the intrauterine growth restriction, considering the fact that the other twin without cardiac pathology had an adequate birth weight and an uneventful clinical course. The growth restricted twin was at risk for both NEC and sepsis, making the differential diagnosis extremely challenging, as clinical signs are frequently non-specific and overlapped and laboratory test results may show similar abnormalities. However, the medical treatment in both cases follows the same general principles. The suggested antibiotic regimen includes ampicillin, gentamicin, and either clindamycin or metronidazole. While the patient is NPO, total parenteral nutrition must be provided. Antimicrobial therapy should always be adapted to the pathogen causing the disease. It is recommended to be justified by clinical, paraclinical and imagistic arguments in order to prevent bacterial antibiotic resistance.

If this conservative therapy is effective, infants may resume enteral feedings once signs of infection or abdominal pathology have disappeared. In some cases, this may take several days to a week. The presence of normal bowel movements suggests the return of bowel function. In infants with confirmed NEC who have worsening condition or bowel perforation or who do not respond to medical therapy, surgical intervention is indicated. Laparotomy is the standard approach, surgery being as conservative as possible, with removal only of portions of unquestionably necrotic or perforated intestine in an attempt to preserve as much intestine as possible (38).

For the neonatologist, the decision to refer the case to the pediatric surgeon and the timing of the referral are real challenges when faced with a neonatal patient with clinical deterioration despite maximal medical therapy, in the absence of free air in the abdominal cavity, as in the present case.

CONCLUSIONS

The peculiarity of this case consists in the association of multiple risk factors, as well as several etiological contexts - ischemic and infectious - which make inclusion into classical etiopathogenetic mechanistic patterns extremely difficult, if not impossible.

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