THE IMPACT OF RISK FACTORS ON THE EVOLUTION OF VLBW PRETERM INFANTS WITH NECROTIZING ENTEROCOLITIS

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Abstract

Necrotizing enterocolitis is the most common gastrointestinal complication of preterm infant. The incidence of NEC increase when two or more risk factors are associated to the preterm birth. Objective: A retrospective longitudinal study was conducted in a 3rd level neonatal intensive care unit in Romania. We evaluated the role of risk factors on NEC's severity and outcome. Material and methods: In the study group were enrolled preterm neonates with birth weight below 1500 g and gestational age less than 32 week with NEC. Were analyzed the influence of risk factors like maternal preeclampsia, enteral feeding type, pH gas values and blood transfusion on NEC' s severity and outcome. Quantitative and qualitative data were analyzed by using SPSS v. 25. Results: From the 596 VLBW neonates admitted in the study period 37 developed NEC, incidence of 6, 2% of NEC in the unit. We found a significant association of basal excess with NEC severity. This could have a predictive value on NEC's severity. 50% of preterm fed with formula had a severe outcome and were transferred to pediatric surgery. There was no statistically significant difference of transfusion counts between the patients who died and those who had good outcome (Mann-Whitney U test: p=0.61>0.05). Conclusion: Exposure of preterm infants to formula determined a higher rate of unfavorable evolution compared to ones fed with own mother milk. A significant link between NEC's severity and basal excess was found .No association between NEC and blood transfusion could be demonstrated.

Keywords: necrotizing enterocolitis, preterm, enteral feeding, metabolic acidosis

Introduction

Necrotizing enterocolitis (NEC) is the most often digestive tube pathology of preterm infants. The incidence of the disease among premature babies is 7-10%. The disease is more frequent as gestational age decreases. Onset typically occurs in infants aged between 2 weeks and 2 months [8, 13]. Growth restriction associated with prematurity is an important risk factor of morbidity. The incidence and the severity of the disease are higher if two risk factors are associated.

Mortality is high, reaching 30%. Mortality is higher among infants who develop severe forms of the disease that require surgical treatment. In the case of survivors, the risk of digestive sequelae – short gut syndrome, as well as neurological sequelae, is increased [2]. The etiology of the disease is not yet completely understood. What is certainly known at this point is its multifactorial etiology. NEC is accompanied by inflammation, ischemia and infection. In advanced stages, intestinal wall necrosis, perforation and peritonitis occur. Altered intestinal flora, pathogen colonization are an important link in NEC pathogenesis. Bacterial colonization has certain particularities in premature infants. Studies have demonstrated that before 33 weeks of gestation, bifid bacteria colonization is limited [3]. Elevated concentrations of gram-negative germs are an important risk factor in the pathogenesis of the disease. Enteral feeding of preterm infants with breast milk facilitates their colonization with bifid bacteria and significantly reduces the incidence of NEC among them. Breast milk exerts its protective effect through the presence of secretory IgA, fatty acids and antimicrobial proteins in its structure.

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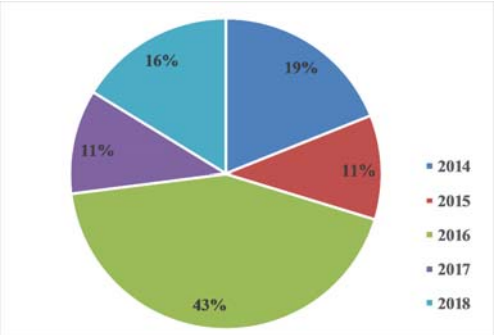

Fig. 1. Description of the patients' year of birth.

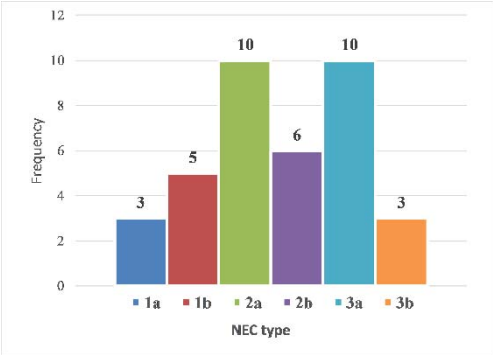

Fig. 2. Description of the patients' NEC type.

Stage	Form	Clinical findings	Abdomen examination	Radiological findings
I	Suspected	Temperature instability, apnea, bradycardia	Elevated gastric residuals, mild abdominal distention, occult blood in stool	Normal or mild ileus
IIA	Mild	Similar to stage I	Prominent abdominal distention ±tenderness, absent bowel sounds, grossly bloody stools	Ileus, dilated bowel loops, focal pneumatosis
IIB	Moderate	Mild acidosis, thrombocytopenia	Abdominal wall edema and tenderness, ±palpable mass	Extensive pneumatosis, early ascites, ±portal venous gas
IIIA	Advanced	Respiratory and metabolic acidosis, mechanical ventilation, hypotension, oliguria, disseminated coagulopathy	Worsening wall edema and erythema with induration	Prominent ascites, persistent bowel loop, no free air
IIIB	Advanced	Vital signs and laboratory evidence of deterioration, shock	Evidence of perforation	Pneumoperitoneum

Table 1. Bell classification of NEC[4]

Characteristic	All	F	M	Stat (p-value)
Gender [a]	37	19 (51.4%)	18 (48.6%)	0.232 (0.816)
Gestational age, weeks [b]	28 (26 to 30.5)	28.5 (26 to 31)	28 (25 to 30)	143.5 (0.399)
Weight, g [b]	920 (695 to 1255)	995 (697.5 to 1312.5)	800 (650 to 1200)	144.5 (0.420)
Apgar score [b]	7 (4.5 to 7.5)	6 (4 to 7.25)	7 (5 to 8)	151.5 (0.547)
pH [b]	7.28 (7.15 to 7.31)	7.29 (7.15 to 7.33)	7.24 (7.15 to 7.30)	133.5 (0.254)
NEC debut day [b]	14 (7 to 20)	13.5 (6 to 25.25)	15 (8 to 16)	163 (0.808)
[a] n (%), Z-test for proportion; [b] median (Q1 to Q3), Q=quartile, Mann-Whitney Test				

Table 2. Description of preterm infants with NEC

	Growth restriction N (%)	Antenatal corticoids n (%)	Preeclampsia n (%)	Surfactant n (%)	Transfer to pediatric surgery n (%)	Transfusion n (%)
Present	9 (24.33%)	20 (54.05%)	13 (35.14%)	21 (56.76%)	13 (35.14%)	28 (75.68%)
Absent	28 (75.67%)	17 (45.95%)	24 (64.86%)	16 (43.24%)	24 (64.86%)	9 (24.32%)
Total	37 (100%)	37 (100%)	37 (100%)	37 (100%)	37 (100%)	37 (100%)

Table 3. Frequency for the presence /absence of evaluated factors

Antenatal corticoids	Outcome		Total
	Death	Good state	
Yes	8	12	20
No	6	11	17
Total	**14**	**23**	**37**

Table 4. The relationship between corticoid treatment and the outcome

Preeclampsia	NEC type					Total
	1	2a	2b	3a	3b	
Preeclampsia -yes	2	4	2	4	1	13
Preeclampsia-no	6	6	4	6	2	24
Total	**8**	**10**	**6**	**10**	**3**	**37**

Table 5. The relationship between the Preeclampsia and NEC type

Enteral feeding start day	Enteral feeding type		Total n (%)
	OMM n (%)	Formula n (%)	
0	1 (4.76%)	0 (0%)	1 (2.7%)
1	0 (0%)	1 (6.25%)	1 (2.7%)
2	12 (57.14%)	6 (37.5%)	18 (48.65%)
3	3 (14.29%)	2 (12.5%)	5 (13.51%)
4	2 (9.52%)	4 (25%)	6 (16.22%)
6	1 (4.76%)	0 (0%)	1 (2.7%)
7	1 (4.76%)	1 (6.25%)	2 (5.41%)
10	0 (0%)	1 (100%)	1 (100%)
13	0 (0%)	1 (6.25%)	1 (2.7%)
14	1 (4.76%)	0 (0%)	1 (2.7%)
Total	**21 (100%)**	**16 (100%)**	**37 (100%)**

Table 6. The relationship between the start day and the type of enteral feeding

Exposure to formula (days)	Frequency	Percent
0	1	6.3
2	2	12.5
3	1	6.3
5	2	12.5
9	1	6.3
11	1	6.3
12	1	6.3
13	2	12.5
14	2	12.5
15	1	6.3
25	1	6.3
33	1	6.3
Total	16	100.0

Table 7. Frequency of exposure to formula milk

Enteral feeding	Initial outcome				Total
	death	good	poor	transfer to pediatric surgery	
Without formula	4	10	2	5	**21**
With formula	1	7	0	8	**16**
Total	**5**	**17**	**2**	**13**	**37**

Table 8. The relationship between the evolution of NEC and the type of feeding

BE < - 10	NEC type					Total
	1	2a	2b	3a	3b	
Severe acidosis	5	0	2	6	0	**13**
Mild/no acidosis	3	10	4	4	3	**24**
Total	**8**	**10**	**6**	**10**	**3**	**37**

Table 9. The relationship between NEC type and BE(<- 10)

Regarding the study of the NEC etiology, there are no specific animal models that reproduce the form of disease found among preterm infants. The inflammatory ischemic mechanism is complex, intricate with bacterial colonization. Under the action of TLR4-mediated bacterial stimulation, the intestinal mucosa is damaged, which will facilitate the entry of bacteria into circulation. In mesenteric circulation, bacteria through interaction with TLR4 will induce a decrease in the level of nitric oxide that will have a vasoconstrictor effect. [11, 18, 20]

The use of feeding protocols in clinical practice has led to a decrease in the incidence of the disease over the past years. Antenatal corticosteroids also contributes to the reduction of the disease incidence. [12, 17]

Aim

The aim of the study was to evaluate the role of risk factors on the incidence, severity and evolution of NEC, as well as to determine the factors causing an unfavorable evolution of NEC in the studied population. The study is relevant for the geographical region and the population in

which it was conducted, given the presence of particularities regarding pregnancy follow-up and the prophylaxis of pregnant women with imminent premature delivery.

Material and method

A longitudinal retrospective study was conducted at the Neonatology Department of the Gynecology Clinic I Cluj-Napoca, between 2014 and 2018. The clinic where the study was carried out is a third-level facility which serves an important part of the population in North-Western Romania (4 counties), preterm infants less than 32 weeks of gestation being admitted to this center. The current study included all preterm infants who were diagnosed with NEC in the mentioned period. Data were systematically extracted from the records of Neonatology department.

Modified Bell criteria were used for diagnosis. Diagnosis was based on clinical and laboratory criteria, according to the existing protocol (Table 1). Staging was performed for suspected disease, mild, moderate and advanced forms. (Table 1)

Abdominal X-ray was carried out at the time when clinical signs suggestive of NEC appeared: increased abdominal circumference, changes in abdominal skin color, bilious, bloody gastric residuals over 1 ml, enteral nutrition intolerance to more than 3 consecutive meals, positive Gregersen's reaction on stool examination. Radiological investigations were performed with the portable device available in the department.

pH gas value parameters

In parallel to the clinical and radiological elements, pH gas value were monitored in all infants with NEC. The blood gas values were determined from venous blood with the device available in the department. The aim was to find out if there was a significant link between the pH gas value, basal excess, lactate and NEC onset in order to detect the disease at an early stage. Thus, early initiation of conservative treatment allows limiting the unfavorable evolution and the need for surgical treatment.

Data processing

Qualitative data were described with the help of frequencies, percentages, frequency tables and Graphs (pie charts and column charts). Evaluating the existence of a link between two independent groups was done with Fisher exact test or Chi2 test. Proportions were compared with a test Z-proportions.

For quantitative data, the normality was tested using the Shapiro test. For data not following a normal distribution, frequencies, percentages, the median, the 25 %(Q1) and the 75 %(Q3) (IQR=interquartile range) were used for the statistical description. The Mann-Whitney Test was used to compare 2 independent groups.

The significance level was set at 0.05. Data analysis was made using SPSS v. 25.

Results

Characteristics of the group

Between 2014 and 2018, in the clinic were admitted to the intensive care unit 596 (460 inborn and 166 out born) preterm newborns having a gestational age of 32 weeks or less and birth weight below 1500 g, but only 37 (6.20%) of them were diagnosed with NEC and were included in this study. Most of the NEC cases were diagnosed in babies born in the maternity unit (inborn), just 35.14% (13/37) being NEC cases transferred from other lower-level units (outborn). (Table 2)

Most of the preterm with NEC from the study group were born in 2016 (43%) (Fig. 1).

The majority of the patients in the study group had a gestational age of less than 30.5 weeks and a weight less than 1200 g (table 2). Close to half of the preterm newborns, 45.95% (17/37), were delivered by cesarean section. (Table 2)

Diagnosis of NEC was made based on clinical and radiological findings, according to Bell criteria, the most frequently observed NEC types being 2a and 3a (Fig. 2).

The outcome of the preterm newborns was good in 62.16% (23/37) of the cases.

Analysis of risk factors

Several factor were considered for analysis and their presence was noted in Table 3.

Antenatal corticoids were applied to 20 of the preterm newborns (Table 4). There was no statistically significant link between the presence of corticoids and the patients' outcome (Chi2 test: $p=0.76>0.05$). (Table 4)

Next, we checked if there was a link between the presence of preeclampsia and patients' NEC type, but no statistically significance was found (Fisher exact test: $p=0.96>0.05$). (Table 5)

From the multiple factors have a role in NEC pathogenesis, in this study we have firstly considered those related to feeding: the time when enteral nutrition started (since day of birth, Table 6), the type of milk used for feeding own mother milk (OMM) or preterm formula (Table 6) and the length of exposure to formula (Table 7). The median for enteral feeding start day was 2, with an IQR between 2 and 4 days. Thus, for the majority of the infants with NEC enteral feeding started during the first 3 days of life. In one case, enteral feeding was not initiated before NEC onset. This case had an early NEC onset and developed the severe form of the disease, which required transfer to the service of pediatric surgery. (Table 6)

The exposure to formula had different length as presented in table 7.

Regarding the type of milk used at the onset of enteral nutrition, cases fed with OMM were predominant (21/37). Exposure to formula until NEC onset was present in 43.24% (16/37) of cases. The median for exposure to formula was 11.5 days, with an IQR between 3.5 and 14 days.

The initial evaluation of outcome was presented in table 8 with regard to the type of feeding. (Table 8)

Besides the feeding type, the transfusion was evaluated: for the patients who died the median number of transfusions was 2 (IQR 1-3.25), while the median for those who had a good outcome was 1 (IQR 0-5). There was no

statistically significant difference of transfusion counts between the patients who died and those who had a good outcome (Mann-Whitney U test: p=0.61>0.05).

Next, the study aimed to check if there was a link between acidotic status and the development of NEC. We checked the link between the NEC type and pH value, basal excess (BE) and lactate. For BE we considered the value lower than -10 relevant for metabolic acidosis and results are presented below. (Table 9).

There was a statistically significant link between BE under -10 and patients' NEC type (Fisher exact test: P=0.007<0.05).

It was observed that the more severe the NEC type, the less favorable was the immediate prognosis (Table 10).

The NEC forms in the study group based on Bell criteria are shown in Table 10. Cases with stage 1-2 were predominant. There was a statistically significant link between the NEC type and outcome - final (Fisher exact test: p=0.0005<0.05). Death was observed more frequently in patients with more severe NEC (10 cases with 3a and 3b forms).

Discussion

Necrotizing enterocolitis is a gastrointestinal emergency with a complex pathogenic mechanism, more frequent in preterm infants. The incidence of the disease varies depending on gestational age. However, there are several risk factors that contribute to the increase in the disease incidence. [1, 2, 13]

In the study performed, we aimed to identify the risk factors that influence the incidence of NEC in the preterm population in our center. We analyzed the role of each factor on the severity of NEC, as well as on the evolution of the disease towards cure or death. Since the patients' data were collected from medical records, there were sources of errors. The analyzed risk factors are those described by other studies as being relevant for the incidence of NEC [1, 2].

During the study period we had an incidence of 6.20% of NEC. This finding is similar of our studies.[2,8] The incidence of NEC decreased in the past years due to the progresses on care of very low birth weight premature.[4]

Antenatal corticoids, an important prophylaxis for respiratory distress in preterm infants, periventricular hemorrhage, with a known influence on intestinal maturation as well.

In our study, this prophylactic measure was applied in a proportion of 54.1% of the studied sample. This percentage is lower than the ones of other studies. [15, 22] This situation is caused by the incomplete follow-up of pregnancies. There is a large number of preterm pregnancies in our area that are not followed up or are incompletely followed up and arrive late to our unit, administration of maternal corticoids being delayed. In the study group, 13 infants (35.13%) were outborn, of which 7 had a gestational age of less than 28 weeks. For these cases, in utero transfer was not possible, since they arrived to the units where they were born during the expulsion or advanced labor, which did not allow in utero transfer.

Preeclampsia has an impact on the fetus and newborn. Maternal hypertension, especially its severe form, is a factor that may influence mesenteric circulation, with an increase in the incidence of neonatal NEC. The incidence of preterm births and IUGR is higher in hypertensive compared to normotensive mothers. IUGR is an important risk factor for the development of NEC. In the studied group, preeclampsia had no effect on the severity of NEC (p>0.05) [6].

Growth restriction had 9 patient (24.33%) of the study group. We found no correlation of growth restriction with NEC's outcome. But it has to be considered that we had a small number of cases.

Enteral nutrition plays an important role in the pathogenesis of NEC. This can be an important risk factor in the genesis of the disease. Aggressive enteral nutrition will contribute to a significant increase in the incidence of NEC. Breast milk is the ideal solution for preventing NEC. [3, 5, 7]

In the studied group, most of the infants were enteral fed with own mothers milk starting from the second day of life, in progressively increasing doses. In the unit, an enteral nutrition protocol was adopted in 2016, based on which the enteral feeding volume is increased every 5 days in newborns with a weight of less than 1000 g, and every 3 days in those weighing less than 1250 g. The number of NEC cases has decreased after this protocol was adopted. Many studies have evidenced the fact that a slow increase in the volume of enteral feeding is an important method for preventing NEC [7, 12].In our country for preterm enteral feeding can be used only OMM and formula since there are no milk banks in Romania

Regarding the type of milk used and the time of initiation of enteral feeding, there were no differences in approach during the study period.

Exposure to preterm formula was present in 16 cases (43.2%) of the premature infants included in the study. Formula was used in 11 cases as initial enteral feeding, and in 5 cases it was used as a complement to breast milk. Formula is used in preterm newborns whose mothers have delivered by cesarean section, have no milk secretion on the third day of life, as well as in those who receive therapies contraindicating breast feeding, and also in the case of outborn babies admitted without their mothers. Preterm formula is used in these cases as the only alternative for enteral nutrition.

Although formula was used in 40% of the cases, no significant link was found between formula administration and NEC severity and evolution. However, the relatively small number of cases and the presence of multiple associated risk factors contributing to the development of the disease should be taken into consideration.

The benefits of feeding with breast milk cannot be replaced by formula. Although at this point the only enteral nutrition alternative for preterm infants in Romania is own mother's milk, in our center we attempt to limit as much as possible the use of formula in premature infants. Feeding with formula induces an alteration of intestinal microbiota,

with bacterial multiplication and changes in the intestinal mucosa [1, 8, 9, 14, 21].

If there is a probability for feeding with breast milk, initiation of enteral feeding is delayed up to 36-48 hours, especially if prematurity is associated with intrauterine growth restriction. It should be considered that excessive delay of enteral nutrition is not beneficial because it induces intestinal mucosal atrophy, altered absorption, changes in the exocrine secretory function and deviation of the inflammatory status towards a pro-inflammatory state mediated by cytokines and chemokine, which is not a desirable effect in the case of preterm infants. [21, 22, 23] Breast milk has a protective effect against NEC in the digestive tract of premature babies. Some studies show that this protective effect is dose dependent [1, 9, 13, 17].

Knowing the fact that anemia is associated with a pro-inflammatory state and transfusion for their treatment has an impact on NEC incidence, we analyzed the influence of blood transfusion on NEC in the study group. In 9 cases, blood transfusion was not needed, while 28 cases (75.7%) required at least one transfusion. However, transfusion administration did not prove to be significantly correlated with NEC severity and evolution (Table 6). Some studies report the occurrence of post-transfusion NEC within 36-48 hours. [10] In our case, we could not demonstrate a higher incidence of NEC after erythrocyte mass transfusion or a link between transfusion and NEC severity. However, these studies describe a higher incidence of NEC in preterm infants who, in addition to receiving blood transfusion prior to NEC, also had severe RDS that required long-term invasive respiratory support and treatment for PDA, respectively. [10, 19]

The analysis of risk factors for NEC in the study group showed that a factor with a significant predictive value for NEC was the modification of pH gas values. The value of excess bases was significantly correlated with NEC severity (Table 7). Metabolic acidosis, elevated lactate levels are predictive factors for the development of NEC in preterm infants. [19, 20]

Regarding the evolution of NEC cases in the study, 62, 2% of the cases showed a favorable evolution. The cases transferred to the service of pediatric surgery had an unfavorable evolution. The mortality rate among infants with NEC was over 37, 8% in the study period. Surgical cases have an increased mortality rate (69, 2%). Other studies report a mortality rate between 20% and 40% of NEC cases [15, 25, 26].

The limitations of the study were represented by the relatively small number of cases and also, by the retrospective nature of data collection for the study group. Multicenter studies in larger groups are required. Considering the implication of multiple risk factors in the pathogenesis of the disease, its prediction, early identification of risk and initiation of treatment are elements that allow reducing the disease incidence.

Conclusions

The analysis of risk factors in the study performed revealed a significant association of NEC with the acid-base status of the preterm infant, the study group showing a significant association of NEC with the value of excess bases.

Exposure of preterm infants to formula determined a higher rate of unfavorable evolution through NEC compared to preterm infants who were exclusively fed with breast milk. No link between the development of NEC and blood transfusion could be demonstrated in our study.

Despite the progress made in the care of very low birth weight infants, NEC remains a complication that has no specific etiological treatment. Due to the multiple pathogenic mechanisms involved, the possibility of specific therapy is limited.

It is important to identify specific diagnostic means and possibly, to detect specific biomarkers with a predictive value for NEC. Early NEC diagnosis and initiation of therapy limit the number of surgical cases that generally have an unfavorable evolution, resulting in long-term complications or death.

The protective role of feeding with breast milk is known, which is why this enteral nutrition modality should be promoted.

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