FACTORS OF MORTALITY AND MORBIDITY IN NECROTIZING ENTEROCOLITIS

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Abstract

Necrotizing enterocolitis (NEC) is a devastating disease that is rapidly becoming the leading cause of neonatal mortality and morbidity. It is the most common gastro intestinal emergency among neonates and is characterized by severe inflammation and necrosis of the intestines mainly affecting the terminal ileum. The overall incidence of NEC can range from 0,72 to 1.8 per 1000 live births mainly preterm and low birth weight infants being affected(6). Mortality rates are high and ranged from 12% to 50% (5, 8, 10). A single institutional study was performed analyzing the patients admitted between 2003 and 2007 at the Children's Hospital "Louis Turcanu" with the confirmed diagnosis of NEC. A total of 17 patients were included in the study. Data regarding age, sex, gestational age, birth weight, maternal age, Bell stage, predisposing conditions, diet, method of treatment being collected. We compared the mortality rates between distinct subgroups of the patients with data from previous reports in the literature. NEC had occurred in 17 patients, 9 boys and 8 girls. 15 patients were preterm infants or were small for gestational age. Previous to NEC 13 patients were fed with formula and 4received human milk. There were 15 patients under 2500g at birth and 2 over 2500g. In 10 cases the debut of the disease was in the first 2 weeks of life. Overall mortality was 53%. Preterm infants had a higher mortality rate (57%) than term infants (33%). Morality rates increase with Bell stages from none in Stage I A to 100% for stage III A and 85% for stage III B. NEC develops mainly in preterm infants. Preterm infants also tend to develop more severe cases and necessitate surgical interventions more often. In term neonates NEC have usually an underlying condition. NEC occurs more often in formula fed infants. Factors like the age of the patient and maternal age have poor influence on mortality.

Key words: necrotizing enterocolitis, preterm infants, risk factors.

Introduction

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in premature newborn infants (1, 2). With aggressive management leading to the salvage of premature infants from the pulmonary standpoint, the incidence of NEC is increasing, and it is thought that NEC will soon replace pulmonary insufficiency as the leading cause of death in premature infants (3).

Although the exact etiology remains unknown, research suggests that it is multifactorial; ischemia and/or reperfusion injury, exacerbated by activation of proinflammatory intracellular cascades, may play a significant role.

Early signs of NEC are indistinguishable from sepsis neonatorum. The signs and symptoms are quite variable, ranging from feeding intolerance to evidence of sepsis, shock, peritonitis, and death. The usual presentation includes abdominal distension, gastric residuals, bilious vomiting, and bloody stools. Lethargy, apnea, and hypoperfusion also may be a prominent feature. Physical findings found on serial examination comprise progressive abdominal tenderness, muscular guarding, and abdominal wall erythema. The presence of an abdominal mass may indicate localized perforation or progressive peritoneal irritation. However, these physical findings may be minimal and misleading, even in infants with progressive disease leading to perforation (4).

The distal ileum and proximal colon are most commonly involved in necrotizing enterocolitis, although any region of the bowel may be involved. The aspect of the intestine is characterized by severe inflammation and patchy necrosis with/without perforation.

Until recent year's improvements in obstetrical and neonatal care that allowed survival of more and more low birth weight newborns, NEC was a poor defined entity. NEC becomes more frequent after the development of neonatal intensive care units in the 70's. For this reason NEC is considered to be an

„iatrogenic" disease caused by the medical progress (5).

Several epidemiologic studies have determinate the overall incidence of NEC range from 0.72 to 1.8 per 1000 live births (6). It occurs in 1-5% of all neonatal intensive care admissions and 5-10% of all very low birth weight (<1500 g) infants (7). Between 30 and 50% of the patients require surgical treatment (5, 8, 9). Mortality rates are high and ranged from 12% to 50% (5, 8, 10). The main risk factor for NEC is prematurity and/ or low birth weight. It is estimated that NEC occurs in 3% to 7% of preterm and low birth weight infants (8).

An important correlating factor of NEC development in these premature neonates is related to formula feeding versus human maternal milk. Studies had been carried out that compared incidence, morbidity and mortality for NEC in infants fed with formula and human milk. The results suggested that human milk reduce the incidence of NEC in preterm or low birth weight infants (11, 12, 13). Preterm infants fed exclusively with formula develop NEC 6-10 times more often than those fed breast milk alone and 3 times more common than those who received formula plus breast milk (14).

Mortality rates are tightly correlated with birth weight. Several reports showed a high incidence of NEC in the 401-750 gram infants – as high as 11.5% whereas the infants with a higher birth weight in the 1251-1500 grams have a decreased incidence of 4%. (8).

An important observation that confirms the relationship between prematurity and NEC is that full term infants rarely develop NEC. It is estimated that only one in 20 000 term babies develop NEC (15). NEC in full term neonates generally has an underlying congenital condition (15). Several reports mentioned that in full-term neonates NEC develop almost exclusively in patients fed with formula or mixture of human milk and formula (16, 17, 18). Other risk factors for NEC in term neonates are: peripartum asphyxia, polycytemia, umbilical catheterization, endotraheal intubation, sepsis. If it occurs in full term infants, NEC mortality and morbidity rates are similar as in preterm infants (5, 15).

Since prematurity is the single most important risk factor for NEC, it is possible that absent or reduced levels of specific factors that are normally expressed during later periods of gestation may contribute to the development of this condition. With this in mind, exogenous replacement of key factors may be clinically valuable as a means to reduce the incidence of NEC. Several potential preventive strategies have aimed at induction of gastrointestinal maturation with steroids, improvement in host defense with breast milk fêting or oral immunoglobulins, change in bacterial colonization with antibiotics, probiotics or fêting modifications, and reduction or antagonism of inflammatory mediators, none of which have led to consistently positive therapeutic results (19).

The main purpose of this study was to determine the presence of risk factors for the development of NEC that could improve the management strategy of this devastating disease in our institution. An extensive literature review was performed and the obtained data was compared similar studies.

Materials and methods

We reviewed the medical charts for all the patients that had the diagnostic of NEC and were admitted at"Louis Turcanu" Children Hospital in Timisoara during a 5 year period (2003-2007).

We recorded for each patient the presumed factors influencing morbidity and mortality: age of patient, sex, gestational age, birth weight, age of the mother, Bell stage, associated or underlying medical conditions. Patients were considered preterm if gestational age was under 36 weeks. Patients were divided by birth weight in 2 groups: <2500g and >2500g. The patient was considered small for gestational age if gestational age was over 36 weeks and birth weight was under 2500g. Maternal age was divided in 3 groups < 20, 20-30 and > 30 years. For staging the disease we used the criteria proposed described by Bell et al (20, 21).

For statistical analysis of the data we used EPSS (v 1.7) for Windows. Pearson bivariate correlation coefficient was calculated for each factor. P values < 0.05 are considered significant. Means between groups were tested using independent sample t-test.

Results

In the 5 years period 17 patients, 9 boys and 8 girls had the diagnostic of NEC. There were significant differences regarding mortality between boys and girls ($t= 3.337$, $p <0.05$). Age at admission ranged between newborn and 7 months, mean 28 days. In 10 of the cases the disease debut was before 14 days of life. The highest mortality was in the group where the debut of the disease was after the first 4 weeks of life, but with low correlation coefficient ($p> 0.05$).

Most of the patients (82%) were preterm infants. One infant was small for gestational age and only 2 were full term infants. Mortality rates were higher in preterm infants 57% vs. 33% ($t= 0.716$, $p> 0.05$).

The majority of the patients (13) were fed using formula and only 4 received a human milk regime. We

didn't found significant differences in mortality rates between the two regime group (t= 0.127, p> 0.05).

There were 15 patients under 2500g and 2 over 2500g. Mortality rates for the 2 groups are 60% and 50%. Pearson correlation coefficient for birth weight is 0.935.

Maternal age ranged between 20 and 41 years. 7 mothers were under 30 years old. No mothers under 20 years old were encountered. Mortality was higher for the group 20-30 years.

In table 1 are summarized the main factors analyzed by us.

Table 1 Correlation between risk factors and outcome.

Groups	Criteria	Patients	Mortality	P value
Gestational age	< 36 weeks	14	57%	0.485
	>36 weeks	3	33%	
Birth weight (g)	<2500	15	53%	0.935
	>2500	2	50%	
Regime	Human milk	4	50%	0.901
	Formula	13	53%	
Debut (days)	< 14	10	50%	0.525
	14-28	3	33%	
	>28	4	75%	
Sex	M	9	22%	0.005
	F	8	87%	
Maternal age (y)	<20	0	-	0.226
	20-30	7	71%	
	>30	10	40%	

Surgical treatment was necessary for 9 patients, 1 full term and 8 preterm infants. Surgical intervention for NEC included laparotomy, resection of the affected bowel and creation of a stoma. All patients that underwent surgery were included in bell stage III.

Morality rates vary with Bell stages from 0% in Stage I A, 16% in stage II A to 100% for stage III A and 85% for Bell stage III B. Pearson correlation coefficient for Bell stages was 0,01.

Table 2 Correlation between Bell stage and mortality rates.

Stage	Preterm	Full term	Total	Mortality
IA	1	0	1	0%
IB	0	0	0	0
IIA	4	2	6	16%
IIB	1	0	1	0%
IIIA	1	1	2	100%
IIIB	7	0	7	85%

There was a relatively large spectrum of predisposing conditions. Cardiac malformation and anemia were present in 6 patients. Perinatal asphyxia and cerebral hemorrhage were present in 7 patients. Other predisposing conditions were oligoamnios and intraamniotic infection. Associated disease included Down syndrome, lissencephaly, inguinal hernia, umbilical hernia, congenital muscular dystrophy, hypospadias, undescended testis. Only 2 preterm infants had no predisposing conditions. All term infants had at least one of the predisposing conditions, mean 2 conditions/ patient.

Table 3 Predisposing conditions.

	N	Cardiac malformations	Perinatal asphyxia	Cerebral hemorrhage	Anemia	Intraamniotic infection	Oligoamnios
Preterm	14	4	6	6	4	2	1
Term	3	2	1	1	2	1	0

Overall mortality was 53%. NEC was the direct cause of dead in 8 patients, 7 preterm and one term infant. One preterm patient had mild signs of NEC and recovered after treatment He had lissencephaly, patent ductus arteriosus and atrial septal defect and died from severe pulmonary disease after he had recovered from NEC.

Discussion

NEC is one of the most severe gastrointestinal emergencies in the neonatal period. Besides many animal and human studies, the morbidity and mortality rates have not improve significantly in the last decades. Several epidemiological studies have indicated that 90% of NEC develops in preterm infants (1, 2, 6, 10, 22). Prematurity is associated with higher morbidity and mortality rates for NEC (24, 25). In our study preterm and low birth weight infants represented approximately 88% of the cases and had a significant higher mortality rate than full term infants. In full term infants NEC have usually an underlying congenital condition (15). This was also the case of our 3 term infants, which had a higher rate of predisposing conditions, 2.1/ patient vs. 1.6/ patient. The most frequent predisposing condition was perinatal asphyxia and cerebral hemorrhage but neither one of the disease has statistic influence for mortality ($p > 0.05$). Other predisposing conditions were congenital cardiac malformations, anemia, oligoamnios and intraamniotic infection.

In our study no case of NEC did develop in a full term healthy infant. These findings are similar with that of Martinez-Tallo et al which found only 3 healthy full term newborns from 24 infants with NEC and Maayan-Metzger et al where 50% of infants had major known risk factors predisposing them for NEC (16, 23).

In Bell stage I group is only one preterm patient whom suffered fully recover after medical treatment. Bell stage II patients had a total of 16% mortality rate which is higher than that found by Bell et al (15%) for the same stage (20). 71% of Bell stage II and 88% of Bell stage III patients are preterm suggesting that premature patients developed more severe forms of NEC. This is probably due to poor intestinal defense mechanism. These patients had the highest number of surgical intervention and the highest mortality also.

In most of the cases the disease developed before 14 days of life (6). NEC developed in almost 60% of our cases before 14 days of life but the highest mortality was in the infants that developed NEC after 4 weeks of life. Because of the small dimension of the group we could not affirm that the age of the patient has statistical significant influence on mortality.

Previous reports suggested that human milk diet reduce the incidence of NEC (11, 12, 13). These was the case of our study were 76% of the patients were previously fed with formula. We didn't found significant differences between mortality rates in human milk and formula fed groups ($t = 0.205$, $p > 0.05$). This suggest that human milk despite it reduces the incidence of NEC, have poor or no influence in the mortality rates of NEC after it occurs.

Despite maternal age is a known risk factor for prematurity (26) it haves now influence on mortality from NEC (27). Rates of mortality are similar between maternal age groups.

Overall 53% mortality is similar to those in the previous reports (5, 8, 10). Statistic correlation between mortality and risk factors is low due to the small contingent analyzed. Larger cohorts are necessary in order to receive statistically significant results.

Conclusions

NEC develops mainly in preterm infants. Preterm infants also tend to develop more severe cases and necessitate surgical interventions more often. In term neonates NEC had usually an underlying condition.

NEC occurs more often in formula fed infants.

Factors like the age of the patient and maternal age have poor influence on mortality

Strategies to prevent perinatal predisposing factors for NEC in both preterm and full-term infants are the key to reduce NEC incidence.

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