

## Severe IUGR and Long Duration of Antibiotic Treatment may Overcome the Benefits of Appropriate Feeding Strategies to Prevent Necrotizing Enterocolitis

Ağır İntrauterin Gelişme Geriliği ve Uzun Süreli Antibiyotik Kullanımı Prematürelere Nekrotizan Enterokolit Gelişimini Önlediği Bilinen Beslenme Stratejilerinin Koruyuculuğunu Azaltabilir

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### ABSTRACT

**Aim:** To compare the characteristic features of premature neonates who developed necrotizing enterocolitis (NEC) or not and review the risks for NEC in our neonatal intensive care unit.

**Materials and Method:** Ninety four premature neonates with gestational age  $\leq$  35 weeks and/or birth weight  $\leq$ 1500 g were included into the study. Characteristic features of the study neonates were compared.

**Results:** NEC occurred in 15.9% of the study population. Seventy nine neonates who did not develop NEC and 15 neonates who developed stage II and III NEC were compared. The rate of intrauterine growth restriction (IUGR), late onset sepsis and therefore broad-spectrum antibiotic usage were significantly higher in the group who developed NEC. At the time of diagnosis 93 % of NEC positive patients were on full feeds either with breast milk only or breast milk + fortifier, none of them were formula fed, 7 % of the cases were never fed. Surgery was performed in all stage III NEC patients and overall mortality rate was 33%.

**Conclusion:** Our findings suggest that together with exclusive breast feeding regimen, other strategies to prevent NEC should be implemented in this high risk preterm neonates.

**Key Words:** Necrotizing enterocolitis, prematurity, risk factors

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### ÖZET

**Amaç:** Bu çalışmanın amacı nekrotizan enterokolit (NEK) olan ve olmayan premature yenidoğanları karşılaştırarak, NEK gelişimi açısından ünitemizdeki risk faktörlerini gözden geçirmekti.

**Yöntem ve Gereç:** Gestasyon yaşı  $\leq$  35 hafta ve doğum tartısı  $\leq$  1500 gram olan 94 premature yenidoğan çalışmaya dahil edildi. Çalışmaya katılan yenidoğanların karakteristik özellikleri karşılaştırıldı.

**Bulgular:** NEK, çalışmaya katılan hastaların %15.9'da görüldü. NEK olmayan 79 ve Evre 2 ve 3 NEK olan 15 hasta karşılaştırıldı. İntrauterin gelişme geriliği (IUGR) ile geç sepsis ve dolayısıyla geniş spektrumlu antibiyotik kullanımı NEK grubunda anlamlı olarak yüksek bulundu. Tanı sırasında NEK olan hastaların %93'ü anne sütü veya güçlendirilmiş anne sütü ile beslenirken formül süt ile beslenen yoktu ve %7'si hiç beslenmemişti. Evre 3 NEK olan hastaların tümüne cerrahi tedavi uygulandı ve mortalite %33 idi.

**Sonuç:**NEK sıklığının yüksek olduğu üniterelerde anne sütüyle beslenmeye ek stratejilerin geliştirilmesi gereklidir.

**Anahtar Sözcükler:** Nekrotizan enterokolit, prematürite, risk faktörleri

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## INTRODUCTION

Necrotizing enterocolitis (NEC) is the disease of gastrointestinal tract that predominantly affects premature neonates. Associated with advances in neonatal intensive care, survival of premature neonates has increased resulting in more NEC cases reported. On the basis of large, multicenter, neonatal network databases from the United States and Canada, the mean prevalence of the disorder is about 7% among infants with birth weight between 500 and 1500 g (1). The mortality rate is between 20 to 30 % and is higher in infants with lower birth weight, earlier gestation and surgical interventions. There is an inverse relationship between gestational age and prevalence of NEC (2). The etiology and pathophysiology is not well-known but studies strongly suggest a multifactorial etiology. Risk factors associated with NEC are prematurity, low birth weight, formula feeding and alterations in bacterial colonization of the gastrointestinal tract (1,3). It usually presents with feeding intolerance, abdominal distension, bloody stools and/or abdominal discoloration. Early imaging signs of NEC are dilated bowel loops, paucity of gas, 'fixed bowel loops' on repeated abdominal radiography (1). The pathognomonic findings on abdominal radiography are pneumatosis intestinalis, portal venous gas and 'free air' outside the bowel.

In this study our aim was to evaluate characteristic features of premature neonates who developed NEC and who did not during NICU stay and to determine the strategies that could be contributing to high incidence of NEC in our unit.

## MATERIALS and METHODS

Ninety four premature neonates with gestational age  $\leq 35$  weeks and/or birth weight  $\leq 1500$ g who were followed in NICU of Gazi University Hospital beyond 1st week of life between January 2011 and January 2015 were included in the study. Major congenital anomalies and gastrointestinal malformations and neonates who died in the first week of life were excluded.

Fifteen neonates were diagnosed as stage II and III NEC. NEC was diagnosed by clinical and radiological findings, classified according to the modified Bell's staging criteria (1). All patients suspected as NEC were followed radiographically every 6 hours. Abdominal distension, gastric residues, bloody stool, vomiting and feeding intolerance were accepted as clinical findings of NEC.

Features including gestational age, gender, birth weight, 1st and 5th minute APGAR scores, resuscitation in the delivery room, the mode of delivery, presence of early and late onset sepsis, antibiotic therapy, antenatal steroid administration, maternal chorioamnionitis, intrauterine growth restriction (IUGR), type of feeding, presence of hemodynamically significant patent ductus arteriosus (PDA) and treatment with ibuprofen and long-term consequences of prematurity including retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) and periventricular leukomalacia (PVL) were all recorded for both NEC negative and NEC positive infants. Onset and duration of NEC, the way of feeding (human milk, fortified human milk, formula) at the time of diagnosis, the period to reach full feeds after an episode of NEC were evaluated for NEC positive infants. Sepsis was diagnosed by clinical and/or laboratory findings. Study was approved by Gazi University ethics commission.

### Statistical Analysis

Descriptive statistical analyses were done by using SPSS 15.0 version (SPSS, Chicago IL, USA). Inter group comparisons for numeric data were performed by Mann Whitney U test, and event ratios were compared by Chi Square test,  $p < 0.05$  was considered significant.

## RESULTS

Between January 2011 and January 2015, 94 premature infants followed in the NICU of Gazi University Hospital were included in the study. The frequency of NEC in our unit was 15.9%. Demographic data of neonates who developed NEC and who did not are shown in Table 1. There was no statistically significant difference between two groups regarding gender but female gender was higher among neonates who developed NEC (60% versus 47%). Fifty three % of neonates who developed NEC and 19% of neonates who did not had IUGR defined as below 10th percentile for gestational age according to Fenton curves.

None of the cases had developed NEC within 48 hours of erythrocyte transfusion making transfusion associated NEC an unlikely diagnosis in this group. Eighty % of neonates with NEC and 48% of neonates without NEC were diagnosed to have late onset sepsis and treated with broad spectrum antibiotics. There was no significant difference regarding early onset sepsis between two groups.

NEC developed at mean  $28 \pm 15.4$  days of the life. Sixty percent of them were fed with breastmilk, 33% were fed with fortified human milk and 7% of them were never fed enterally. Neonates who were on full feeds had been there for  $13 \pm 10$  days at the time of diagnosis. After the diagnosis of NEC neonates were not fed for mean  $13 \pm 6$  days and reached full feeds in  $30 \pm 13.7$  days after treatment. Stage II NEC was diagnosed in 73% of cases and 26,7 % of patients were stage III NEC who were all treated surgically. Four patients (33%) died; 1 from stage II NEC and 3 from stage III NEC group.

There was statistically significant difference between birth weight of groups ( $p:002$ ). The gestational age of the neonates in groups were similar. Rates of maternal chorioamnionitis, need for resuscitation in delivery room, antenatal steroid administration, PDA and type of feeding were similar between two groups as well as 1st and 5th minute APGAR scores.

The patients were also evaluated with regards to long term complications of prematurity. BPD developed more frequently in NEC positive infants (50% versus 7.9%). PVL and ROP rates were similar between groups.

**Table 1:** Characteristic features of Neonates with and without NEC

	NEC + (n=15)	NEC - (n=79)	P value
Birth Weight (g) (median-range)	825 (465-1415)	1100 (505-1600)	<b>0.002</b>
Gestational Age (w) (median-range)	28 (26-35)	29 (24-35)	0.2
Female (%)	60	47	0.9
IUGR (%)	53	19	<b>0.02</b>
Maternal Chorioamnionitis (%)	27	14	0.09
Need for resuscitation in DR (%)	33	57	0.09
1st Minute APGAR (median-range)	6 (1-8)	6 (0-9)	0.8
5th Minute APGAR (median-range)	9 (5-10)	8 (3-10)	0.4
Antenatal steroid (%)	93	77	0.1
Patent Ductus Arteriosus (%)	33	39	0.6
MV (%)	60	22	<b>0.03</b>
Late Onset Sepsis (%)	80	48	<b>0.003</b>
Breast Milk (%)	93	80	0.09
Early onset sepsis (%)	6.7	6.3	0.9
ROP (%)	10	4	0.4
PVL (%)	20	9	0.3
BPD (%)	50	7.9	0.0001
Exitus (%)	33	5	<b>0.01</b>

IUGR: Intra uterine growth restriction, ROP: Retinopathy of premature, PVL: Periventricular leukomalacia, BPD: Bronchopulmonary dysplasia MV: Mechanical ventilation, DR: delivery room

## DISCUSSION

NEC is a severe disease of gastrointestinal tract that often develops in the ileum but can involve any segment of the gastrointestinal tract. NEC is primarily disease of premature neonates but it can be seen in late preterm and term neonates with predisposing risk factors such as low Apgar scores, chorioamnionitis, exchange transfusions, prolonged rupture of membranes, maternal illicit drug use, intestinal anomalies, perinatal stress that affects mesenteric blood flow and congenital heart disease (4,5). On the basis of large, multicenter, neonatal network databases from the United States and Canada, the mean prevalence of the disorder is about 7% among infants with birth weight between 500 and 1500 g (1). In our unit the mean prevalence was 15.9 % for the reported period, higher than the literature which led us to search associated risk factors and design this retrospective study. NEC develops at about 29-32 weeks of postmenstrual age after the start of enteral feeds (3). The more premature the neonate, the later this condition occurs (6). In term and late preterm neonates the disease usually occurs in the first week of life (5). All of our cases were preterm neonates and NEC occurred mean  $28 \pm 15$  days after birth. Mean gestational age of the cases were  $28.7 \pm 2.5$  weeks. Patients were on full feeds for  $13 \pm 10$  days at the time of the diagnosis which is consistent with literature.

It is known that exclusive breastfeeding is protective against NEC and formula facilitates development of NEC due to lack of immunoprotective factors in formula and abnormal bacterial colonization(7); however our cases developed NEC although 60% of them were exclusively breast-fed neonates and 33% were on fortified human milk prior to NEC development. This finding led us to think that the high prevalence of NEC in our unit was associated with other accompanying risk factors. Surprisingly 7% of NEC cases were never fed for which we think intrauterine intestinal ischemia was the primary cause.

One potential risk factor for the development of NEC is the rate of advancement of enteral feeds. Results regarding the rate of advancement of enteral feeds and development of NEC are conflicting. Rapid advancement of enteral feeding has been found to increase the incidence of NEC in some trials (9), however some recent studies have shown no difference in NEC rates between groups fed with rapid versus slow advancement strategy (10).

A recent Cochrane Review evaluated the effects of advancing enteral feeds in very small birth weight neonates. It was shown that there was not a statistically significant difference between slow (15-20 mL/kg/day) and fast (30-35 mL/kg/day) advancement on the development of NEC (11). The feeding strategy of our unit has been more on the slow side with 20ml/kg/day advancement and the incidence of NEC was high, when we compared the NEC cases and neonates who did not develop NEC, the feeding strategy was same but other risk factors for NEC like IUGR, late onset sepsis and thereby long duration of broad spectrum antibiotics were significantly higher in the NEC group.

Most of the studies about epidemiologic features of NEC did not find a statistically significant relationship between gender and NEC. Some of them demonstrated that the incidence of NEC was higher in males (3) but in our small group although not statistically significant 60 % of cases were female.

The preterm neonate's bowel is rapidly colonized within 7-10 days of life (12). Treatments such as antibiotic therapy, mechanical ventilation and total parenteral nutrition impair the intestinal colonization, prevent or delay the acquisition of commensal bacteria and facilitate colonization with pathogen bacteria. Exposure to long periods of antibiotics may trigger NEC (13). It was remarkable that when we compared the 2 groups late onset sepsis and thereby broad-spectrum antibiotic treatment for long periods was significantly higher in neonates with NEC.

Antibiotic duration seems to affect intestinal colonization of neonate (14). Antibiotics may suppress or eradicate protective anaerobic bacteria and potentiate overgrowth of pathogenic enteric aerobic Gram-negative rods. Overgrowth of pathogenic enteric bacteria is greatly increased after 3 days of antibiotic exposure (15), as is the risk of NEC (16). Colonization is important for physiological and immunological development of intestine and absorbance of nutrients (17). So alterations in colonization could increase the risk of NEC (18). Cotten and colleagues demonstrated association between longer duration of initial empirical antibiotic therapy started in the first postnatal day and death and NEC for ELBW infants whose initial blood and cerebrospinal fluid culture results were sterile (16). Another study supporting the findings of Cotten et al has demonstrated that exposure to antibiotics for more than 10 days caused nearly threefold increase in the risk of development of NEC (2). In growth restricted fetuses, placental insufficiency and abnormal Doppler flow in the umbilical artery have been associated with NEC (19). In a review it was demonstrated that NEC was increased in cases with absent/reverse umbilical arterial Doppler flow compared with controls (20) most likely due to decreased splanchnic perfusion and intestinal injury. In our group IUGR ratio was significantly higher in the NEC group compared to neonates who did not develop, however we were not able to obtain doppler flow measurements.

Several studies have shown relation between clinical chorioamnionitis (CC) and histological chorioamnionitis (HC) and NEC (21). A current systematic review and meta-analysis has demonstrated that HC is associated with a threefold increase risk of NEC and CC is associated with a modest increase in NEC risk. In our study the ratio of maternal HC was similar between NEC groups although there was a tendency for higher incidence in NEC group.

Another common therapeutic intervention for preterm neonates is administration of packed red blood cells (PRBC) for acute or chronic anemia. Some studies have reported association between PRBC and development of NEC (22) and in a meta-analysis it was demonstrated that the risk of NEC increased within 48 h period after PRBC transfusion (23). In our study none of the cases occurred within 48 hours of transfusion.

The mortality rate in neonates with confirmed NEC is more than 20%. For neonates who requires surgical intervention, mortality rate is 30-40% (3). In our study the mortality rate of neonates with NEC was 33.3%. We lost 5 of 15 patients. 4 of 5 patients were stage III NEC and required surgery intervention. The mortality rate of neonates who did not develop NEC was 5%.

In conclusion our self assessment for NEC cases has revealed that despite being breast fed exclusively 15 preterm out of 94 preterm newborns had developed NEC with a 33 % mortality. Our findings should be warning for clinicians taking care of this vulnerable population. Late onset sepsis, thereby broad-spectrum antibiotic treatment for long duration if associated with IUGR may overcome the protective effects of breast feeding. Units with high rates of NEC may need to reconsider their overall preterm care in addition to feeding practices; probiotics or lactoferrin administration may also be included in preventive strategies.

#### Conflict of interest

No conflict of interest was declared by the authors.

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