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Research Article

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Necrotizing Enterocolitis: Incidence, Risk Factors, and Associated Morbidities in a Large Cohort of Infants with Very Low Birth Weight

Renata Bastos Lopes[1,15*], José Maria de Andrade Lopes[1*], Maria Elisabeth Lopes Moreira[1], Saint Clair Gomes Jr[1], João Henrique Carvalho Leme de Almeida[1], José Luiz Muniz Bandeira Duarte[2], Daniela Marques de Lima Mota Ferreira[3], José Mariano Junior[4], Maria Rafaela Conde Gonzales[5], Regina Silva[6], Jucille do Amaral Meneses[7], Walusa Assad Gonçalves Ferri[8], Marynea Silva do Vale[9] , Ligia Maria Suppo Rugolo[10], Ruth Guinsburg[11], Renata de Araújo Monteiro Yoshida[12], Jorge Hecker Luz[13], Jamil Pedro Siqueira Caldas[14], Fernando de Freitas Martins[15], Filomena B. Mello[16], Edneia V Lima[17], Rede Brasileira de Pesquisas Neonatais[18]

[1]Instituto Nacional de Saúde da Criança, Mulher e Adolescente Fernandes Figueira, Fundação Oswaldo Cruz, RJ, Brazil

[2]Hospital Pedro Ernesto, Universidade do Estado do Rio de Janeiro-RJ, Brazil

[3]Universidade Federal de Uberlandia MG, Brazil

[4]Maternidade Escola Hilda Brandão, Santa Casa de Belo Horizonte- MG, Brazil

[5]Universidade Estadual de Londrina Londrina, PR, Brazil

[6]Universidade Federal do Paraná-Paraná, PR, Brazil

[7]Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil

[8]Hospital das Clínicas da Universidade de São Paulo- Ribeirão Preto, SP, Brazil

[9]University Federal do Maranhão-São Luiz, MA, Brazil

[10]Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botacatu, SP, Brazil

[11]Universidade Federal de São Paulo-São Paulo, SP, Brazil

[12]Universidade Estadual de São Paulo, São Paulo, SP, Brazil

[13]Pontifícia Universidade Catolica of Rio Grande do Sul, RS, Brazil

[14]Universidade Federal de Campinas, Campinas, SP, Brazil

[15]Maternidade Perinatal, Rio de Janeiro, RJ, Brazil

[16]Hospital e Maternidade Santa Joana, São Paulo, SP, Brazil

[17]Hospital Promatre Paulista, São Paulo, SP, Brazil

[18]Brazilian Neonatal Research Network-RBPN, Brazil

[*]**Corresponding authors:** Renata Bastos Lopes and José Maria de Andrade Lopes, Instituto Nacional de Saúde da Criança, Mulher e Adolescente Fernandes Figueira, Fundação Oswaldo Cruz, RJ, Brazil

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Abstract

Objective: Necrotizing Enterocolitis (NEC) causes morbidity and mortality in infancy. This study investigated the incidence, risk factors, morbidity, and mortality rates in a cohort of infants with very low birth weight in Brazil. **Study Design:** Data were collected from 17 Neonatal Intensive Care Units (NICUs) for infants with very low birth weight of gestational ages 24-36 weeks and delivered during 2015-2019. Data were analyzed using a multivariate logistic regression analysis. **Results:** Of 7793 newborns, 561 (7.2%) met the criteria for NEC, of whom 295 (52%) underwent clinical treatment and 266 (48%) underwent surgical intervention. NEC incidence varied across neonatal units (from 4.5% to 12.9%) and was stable during the study period for the whole population. However, the incidence over the study period increased from 9.7% in 2015 to 13.9% in 2019 for infants weighing<1000 g. Patients with NEC had lower birth weight, gestational age, and Apgar scores and significantly higher mortality rates than those without ($p<0.001$). Late-onset sepsis, birth weight, and mechanical ventilation were independent risk factors for NEC. **Conclusion:** NEC is strongly associated with NICU mortality and largely varies between infants in the NICU. Moreover, the incidence of NEC among extremely low birth infants is constantly increasing.

Keywords: NEC; Risk factors; VLBW; Mortality

Introduction

Necrotizing Enterocolitis (NEC) is the most commonly acquired gastrointestinal disease in the neonatal period and occurs predominantly in preterm infants. Its consequences, including intestinal necrosis, sepsis, and death, often cannot be avoided, even with early detection and aggressive treatment [1,2]. The incidence of NEC varies among Neonatal Intensive Care Units (NICUs), ranging between 3% and 11% in preterm infants of very low birth weight [3,4]. There is a well-defined inverse relationship between the incidence of NEC and gestational age at birth among preterm infants, with those with very low birth weight (<1500 g) being at risk the most [5]. NEC-induced mortality can vary at 20%-50%, but the impact of NEC on mortality with different levels of care remains unknown [6-8].

NEC is believed to be a disease with multifactorial pathophysiology. Factors such as intestinal immaturity, imbalance of vascular tone, abnormal intestinal colonization, and local immunological factors in the intestinal wall contribute to the development of the disease [9]. Molecular studies suggest that individual inflammatory response plays an important role in NEC pathogenesis [10,11]. In addition to prematurity, other factors involved in the pathophysiology of NEC include asphyxia, bacterial infection, mesenteric ischemia, and infant feeding practices [1].

This study aimed to describe the incidence of and risk factors for NEC and its association with general mortality in a multicentric cohort of infants with very low birth weight.

Materials and Methods

This cohort study comprised 17 Brazilian NICUs. The candidate population comprised infants with very low birth weight admitted to these NICUs between January 2015 and December 2019. Eligibility criteria were birth weight of 500-1500 g and gestational age between 24 weeks 0 days and 36 weeks and 6 days. Exclusion criteria were presence of congenital malformations and death within the first 12 hours of life. Infants diagnosed with spontaneous intestinal perforation were excluded.

Antenatal variables were corticosteroid use (any dose), antenatal magnesium sulfate supplementation, maternal

hypertension, chorioamnionitis, and multiple births. Perinatal variables included type of delivery and need for resuscitation at birth. Neonatal variables were sex, gestational age, birth weight, Apgar score, respiratory distress syndrome, surfactant use, need of mechanical ventilation, use of continuous positive airway pressure, PDA, patent ductus arteriosus ligation, and sepsis. Early onset sepsis was defined as a positive blood culture up to day 3 of life and late-onset sepsis was defined as a positive blood culture any time after that.

NEC was considered present if the infant had NEC diagnosed at surgery, on a postmortem examination, or on clinical and diagnostic imaging based on the presence of one of the following criteria:

- Bilious gastric aspirate or emesis
- Abdominal distension or discoloration
- Occult or gross blood in stool (no fissure)

And at least one of the following diagnostic imaging findings:

- Pneumatosis intestinalis
- Hepato-biliary gas
- Pneumoperitoneum

The incidence of NEC was calculated for each NICU and by year for all infants and for those with a birth weight <1000 g separately. Univariate analyses were performed to explore associations between NEC and morbidity conditions and antenatal and neonatal risk factors.

Statistical analysis

A descriptive assessment was conducted to examine the variables of interest. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as absolute frequencies or percentages. McNemar's test and Fisher's exact test were used for categorical variables. For continuous variables, groups were evaluated using Student's t-test and analysis of variance.

Logistic regression analyses were performed to examine the independent effect of risk factors. Variables with statistical significance in the univariate analysis ($p<0.05$) were included in addition to variables traditionally associated with NEC. We also analyzed risk factors for mortality to assess the impact of NEC on this outcome. Odds Ratios (ORs) were estimated with Confidence Intervals (CIs) at 95%. A p value <0.05 indicated significance. Statistical Package for the Social Sciences version 19.0 was used for statistical analysis (IBM, Armonk, NY, USA).

The study was approved by the Research Ethics Committee of the Fernandes Figueira Institute (CAAE: 51107315.1.0000.5269) as well as the ethics committees of all participating hospitals.

Results

A total of 7793 newborns were included in the analysis, of whom 561 (7.2%) developed NEC, with wide variation in incidence between NICUs. Baseline characteristics of the population are described in Table 1. The mean birth weight was 1084 (± 272) g [2925 newborns (37.5%) weighed <1000 g], and the mean gestational age was 29.6 (± 2.7) weeks (Table 1). Of the 561 patients with NEC, 295 (52%) underwent clinical treatment and 266 (48%) underwent surgery.

Characteristics	
BW, g	1084 (±272)
GA, weeks	29.6 (±2.7)
BW <1000 g, n (%)	2925 (37.5)
Male sex, n (%)	4016 (52)
Maternal hypertension, n (%)	3319 (43)
Magnesium sulfate use, n (%)	3628 (47)
Chorioamnionitis, n (%)	816 (10.5)
Antenatal corticosteroids, n (%)	6410 (83)
Cesarean delivery, n (%)	5946 (76.3)
Apgar score, 1 min	4 (±3)
Apgar score, 5 min	6 (±4)
Delivery room intubation, n (%)	2507 (32.2)
Chest compression, n (%)	238 (3.1)

BW: Birth Weight; GA: Gestational Age

Table 1: Baseline characteristics of newborns with very low birth weight from 17 Brazilian NICUs between 2015 and 2019.

A total of 2639 patients (33.9%) had PDA, and 149 (3.2%) required surgical ligation. There were 5380 (69%) cases of RDS, with 3962 (50.9%) receiving surfactant at some point. A total of 4550 newborns (58.4%) received mechanical ventilation, and 2442 (31.3%) had some degree of intracranial hemorrhage, with 542 cases (6.9%) being severe. Postnatal corticosteroids were administered to 682 (8.8%) newborns. The mean hospitalization time was 55 (± 39) days, and the 5-year mortality rate was 16.6% (Figure 1).

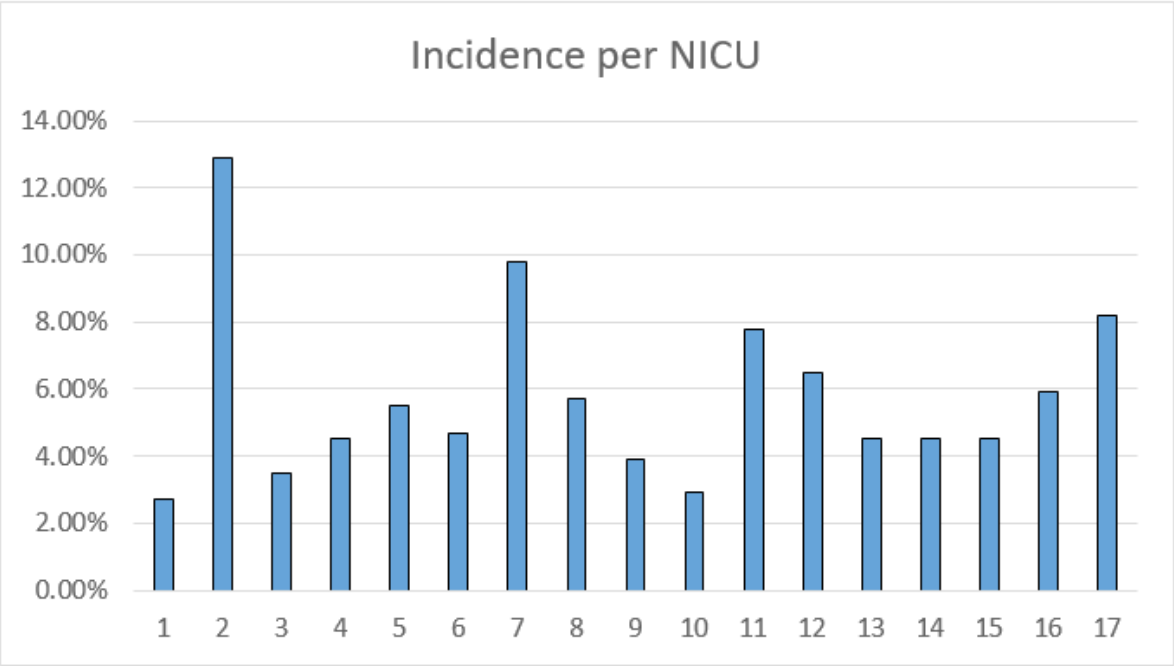

Figure 1: Incidence of necrotizing enterocolitis in 17 Brazilian neonatal intensive care units.

There was no significant change in the annual incidence of NEC aggregated across NICUs for all babies. However, in infants weighing <1000 g, incidence increased between 2015 and 2019 (9.7%, 11.9%, 10.6%, 12.5%, and 13.9%, respectively).

Univariate analyses showed that newborns with NEC had lower birth weight (950 ± 257 vs. 1 095 ± 270 g), lower gestational age (28.3 ± 2.5 vs. 29.6 ± 2.7 weeks), were more often intubated in the delivery room, and had lower 1- and 5-minute Apgar scores than those without NEC. NEC was also more frequent in newborns with PDA (10.3% vs. 5.6%, $p < 0.001$) who had surgical ligation of their ductus arteriosus (16.8% vs. 6.7%, $p < 0.010$) and received mechanical ventilation at some point after admission (10.8% vs. 2.1%, $p < 0.01$) (Table 2). Newborns with NEC had significantly longer NICU stays than those without (75 vs. 55 days, $p < 0.001$).

Factors	With NEC	Without NEC	P value
Total	561	7232	
BW, g	950	1095	<0.0001
GA, weeks	28,3	29,6	<0.0001
BW < 1 000 g, n (%)	11.6%	4.5%	<0.001
ANS, n (%)	7.2%	7.3%	0.54
Cesarean delivery, (%)	8.8%	6.7%	<0.01
Multiple birth, (%)	6.5%	7.5%	0.13
Maternal hypertension, (%)	7.0%	7.3%	0.68
Chorioamnionitis, (%)	9.8%	6.8%	<0.05
Male sex, n (%)	8.5%	6.5%	<0.01
Intubation, n (%)	9.5%	6.1%	<0.001

Magnesium sulfate use, (%)	8.1%	6.4%	<0.002
PDA, n (%)	10.3%	5.6%	<0.001
PDA surgery, n (%)	16.8%	6.7%	<0.001
MV, n (%)	10.8%	2.1%	<0.001
IVH (%)	10.7%	5.6%	<0.001

ANS: Antenatal Steroids; BW: Birth Weight; C-section: Cesarean section; GA: Gestational Age; MV: Mechanical Ventilation; NEC: Necrotizing Enterocolitis; PDA: Patent Ductus Arteriosus; IVH: Intraventricular Hemorrhage

Table 2: Incidence of study factors for infants with and without NEC.

NEC occurred more frequently in the lower birth weight groups (<1000 g, 11.6% vs. >1000 g, 4.5%) and was inversely related to birth weight (Figure 2). The incidence of NEC was higher in infants with very low birth weight than in those with normal weight in both early (10% vs. 7%) and late- (19% vs 5.7%) onset sepsis groups. There were no significant differences between groups related to maternal hypertension, antenatal corticosteroids, multiple births, or hypothermia at admission (Table 2).

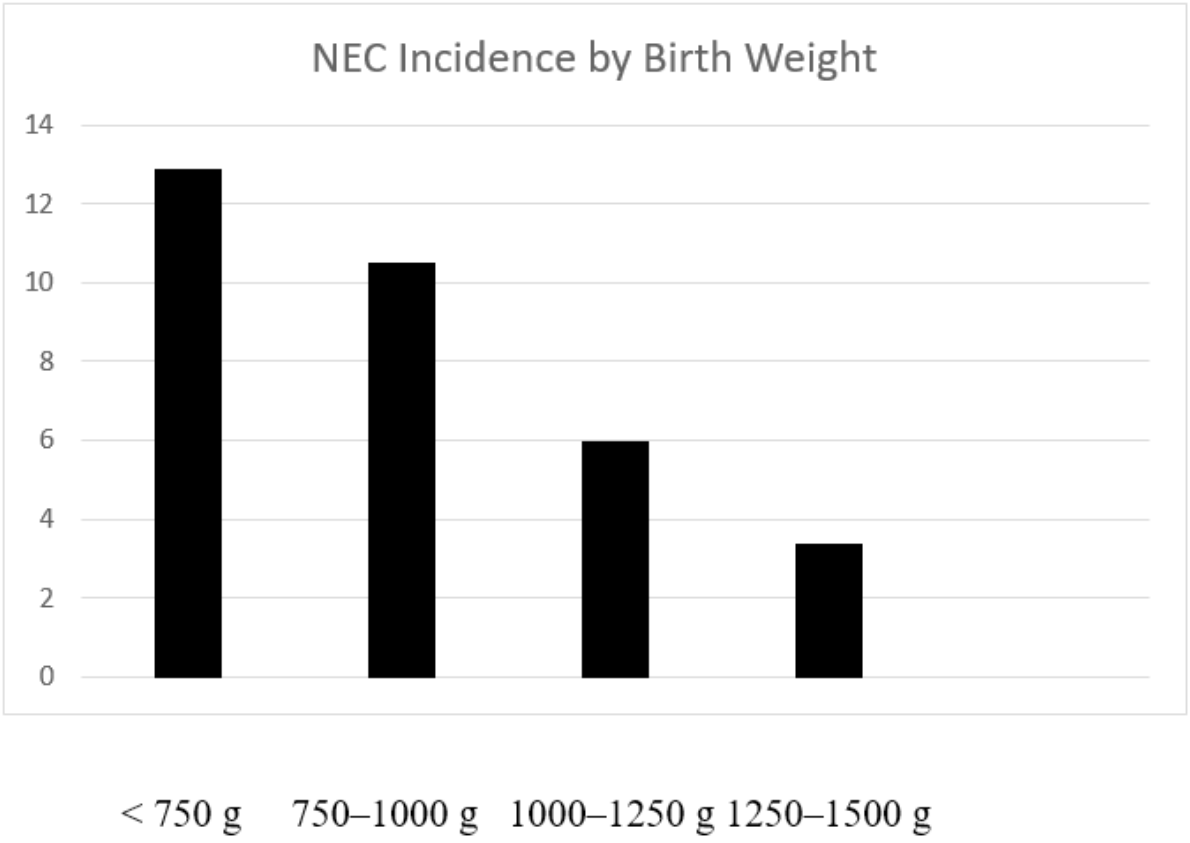

Figure 2: Necrotizing enterocolitis incidence by birth weight.

NEC was significantly associated with neonatal death. Newborns with NEC had a mortality rate of 41.2%, which was significantly higher than that of newborns without (14.7%) (OR: 4.1 (3.4–4.9) (p< 0.001).

Multivariate analysis

The logistic regression models found three of the study risk factors to have a significant independent association with NEC: late-onset sepsis (adjusted odds ratio [aOR], 5.4; 95% confidence level [CI], 4.1-7.1), birth weight (aOR, 0.9; 95% CI, 0.9-0.99), and mechanical ventilation (aOR, 2.8; 95% CI, 1.8-4.3). NEC remained an independent risk factor for mortality, along with antenatal steroid use, maternal hypertension, low 1- and 5-minute Apgar scores, cesarean delivery, male sex, patent ductus arteriosus, early or late-onset sepsis, lower birth weight, and surfactant administration.

Discussion

The overall incidence of NEC was 7.2% in this cohort, which was consistent with that in studies reported from other countries [3,4]. There is a global concern regarding the increasing incidence of perinatal diseases such as NEC and bronchopulmonary dysplasia owing to advances in perinatal medicine and a reduction in mortality [12]. The literature shows conflicting results regarding changes in the incidence of NEC over time. Although a recent study has shown an increasing incidence of the disease over the years [5], it remained stable over the 5 years of the study in our population, except for in infants weighing < 1000 g. Our results were similar to those found by Fanaroff, et al., Stoll, et al. and Kusuda et al. [13-15].

As reported in the literature, lower birth weight and gestational age were risk factors for NEC in this study. Intubation in the delivery room and low Apgar scores in the first and fifth minutes were also associated with the occurrence of NEC, suggesting an association with perinatal asphyxia.

Positive relationships between patent ductus arteriosus, its surgical ligation, and NEC have also been described. Some authors suggest that hemodynamic changes caused by clamping of the ductus arteriosus, including sudden reduction in cardiac output and a sudden increase in peripheral vascular resistance, have an impact on intestinal perfusion, thus predisposing newborns to NEC [16,17].

NEC appears to be associated with infection; however, a definitive pathogen has not been determined [18]. NEC can occur in institutional epidemics, and general measures of infection control are usually effective in controlling it, supporting an infectious basis for outbreaks [2,19]. Reperfusion is involved in the induction of an inflammatory cascade, vascular endothelial injury, and increased susceptibility to bacterial translocation. In our study population, patients with late-onset sepsis had a 4-fold higher risk of developing NEC [22].

In multivariate analyses, risk factors that remained in the model included low birth weight, mechanical ventilation, and late-onset sepsis. As described in the literature, sepsis, low gestational age, and birth weight are well-established risk factors for NEC [4,16,22]. In this study, lower birth weight and sepsis were also independent risk factors following adjustment in the multivariate model.

This relationship needs to be further explored, as sepsis rates and some other variables had great variability and could explain the difference in the incidence of NEC among centers. NEC was an important risk factor for neonatal death, with a corresponding mortality rate twice as high as that observed among newborns without NEC. Similar findings were observed in a German study, in which the mortality rate of patients with NEC was 19%, while the mortality rate for those without was 6.2% [20].

The strength of this study is the large size of the cohort drawn from 17 NICUs distributed throughout Brazil. Additionally, the variables were well defined, and data were collected prospectively. However, the analysis was restricted to pre-existing variables in the database. Consequently, some important factors including dietary practices, use of human milk or formula for infant feeding, and timing of onset of solid feeding were not analyzed.

The incidence of NEC in this population was comparable to that in developed countries [21]. Although the large-scale use of human milk is provided by milk banks across the country, we were unable to explore this relationship and any influence in our results.

In this large cohort, there was wide variability in the incidence of NEC in different units. Birth weight, mechanical ventilation, and late-onset sepsis remained significant risk factors for NEC in the adjusted models. Further exploration of the relationship between NEC and mortality at different levels of care is warranted.

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Ethical approval and consent to participate: Consent for publication. Availability of Data and Materials

Author Contributions

Authors in individual units were responsible for data collection and processing. Renata Bastos Lopes, José Maria de Andrade Lopes, Maria Elisabeth Lopes Moreira, and Saint Clair Gomes Jr were responsible for data processing, statistical analysis, and writing of the manuscript.

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