ORIGINAL ARTICLE

# Risk Factors for Necrotizing Enterocolitis in Very Low Birth Weight Infants in a Tertiary Care Hospital

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**Background:** Necrotizing enterocolitis (NEC) is a severe gastrointestinal condition correlated with increased morbidity and mortality in very low birth weight (VLBW) infants. The pathophysiology of NEC remains elusive due to its multifactorial nature. However, the identification and prevention of significant factors that cause NEC can improve the outcome of these neonates.

**Objective:** To identify factors associated with the development of definite NEC, based on the modified Bell staging criteria stage II and III, in VLBW infants in a setting of tertiary care hospital.

**Materials and Methods:** A single-center, case-control study was conducted in VLBW infants who were admitted to the neonatal intensive care unit (NICU) of Bhumibol Adulyadej Hospital, Bangkok, Thailand, between January 2008 and December 2022. Clinical data were collected from the electronic medical records. For each case of NEC, two controls without NEC, as non-NEC, were matched based on gestational age and period of hospitalization in the department. Data of mothers, infants, feeding patterns, and comorbidities prior to the diagnosis of NEC were analyzed.

**Results:** There were 65 and 130 infants in the NEC and the non-NEC group, respectively. Infants in both groups had similar baseline characteristics. Multiple logistic regression showed the amount of human milk at the age of 14 days (adjusted OR 0.08, p<0.001) was a protective factor against NEC. Conversely, prolonged parenteral nutrition (PN) use (adjusted OR 4.81, p<0.001) and septic shock (adjusted OR 4.36, p=0.02) were risk factors for NEC.

**Conclusion:** Early initiation of human milk may reduce the incidence of NEC. On the other hand, infants requiring extended PN and suffering septic shock were at an increased risk of developing NEC.

**Keywords:** Necrotizing enterocolitis; Very low birth weight infants

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Necrotizing enterocolitis (NEC) is a severe gastrointestinal condition that causes significant morbidity and mortality in very low birth weight (VLBW) infants, which is defined as those with birth weight of less than 1,500 g[1-6]. An infant with NEC has a mortality rate of as high as 20% to 30%[7]. Complications arising from NEC include intestinal obstruction, developmental delays, and short bowel syndrome (SBS), which is defined as intestinal failure with a residual small bowel length below 50% of the total small bowel length of age[3,8]. Moreover, infants with NEC may have prolonged hospitalization, leading to increased resource utilization and financial burden for the family, as well as an elevated risk of stress and depression[9].

The global prevalence of NEC is 7% among VLBW infants[10]. However, research conducted in Thailand indicates a significantly higher incidence of NEC, which reports around 10% to 15%[11-13]. Recognition of its risk factors to prevent the development of NEC is one of the keys to improving clinical outcome of VLBW infants. Gitau et al. found that cumulative duration of exposure to umbilical vein catheter and cumulative duration of exposure to invasive mechanical ventilation were risk factors for NEC[14], while Lamireau et al. found that early-onset neonatal sepsis (EONS) was the only risk factor for NEC[15]. However, Supabanpot's study conducted in Thailand between 2010 and 2018 found that the amount of human milk was a significant protective factor against NEC[16]. Risk factors for NEC from each study vary according to practice guidelines, available resources, and local organism epidemiology.

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The present research aimed to identify specific risk and protective factors for NEC in VLBW infants in the neonatal intensive care unit (NICU) Bhumibol Adulyadej Hospital (BAH). The secondary objective was to identify risk factors for surgical NEC and the cases with mortality.

## Material and Methods

A single-center, matched case-control study was conducted in VLBW infants admitted to the NICU, BAH, Bangkok, Thailand between January 2008, and December 2022. The present study was approved by the Hospital's Institutional Review Committee (IRB No. 48/65).

Inclusion criteria for cases were VLBW infant diagnosed with definite NEC, based on the modified Bell staging criteria stage II and III, by a neonatologist. Those who did not have NEC were categorized as a control group. Infants who had gastrointestinal malformations, congenital anomalies, early neonatal death of less than seven days, had been transferred to another hospital, or had insufficient information were excluded.

For each case of NEC, two controls without NEC were matched by two criteria, gestational age (GA) and period of hospitalization in the NICU, which had to be as close as possible by using random matching method.

Data obtained from electronic medical records was reviewed. The baseline demographic data collected consisted of GA, birth weight, gender, multiple gestations, death, and length of hospital stay. Data on maternal conditions, infant conditions, feeding patterns, and comorbidities prior to the development of NEC were also gathered. Maternal factors included maternal age, prolonged premature rupture of membrane (PPROM) defined as rupture of membranes more than 18 hours, antenatal use of steroid, and mode of delivery. Infant factors included APGAR at 5 minutes, duration of umbilical artery and umbilical vein catheter used, and lowest hematocrit (Hct) before transfusion. The feeding pattern consisted of the onset of enteral feeding, the onset of breast milk (BM) feeding, proportion of BM within 14 days after birth, which was defined as the percentage ratio between BM and formula feeding, the quantity of human milk on the fourteenth day of life expressed as mL/kg/day, formula feeding defined as proportion of formula feeding at or greater than 50% within fourteen days, time to full enteral feeding at least 150 mL/kg/day, and duration of parenteral nutrition (PN). Data of comorbidities included respiratory distress syndrome, EONS, late-onset neonatal sepsis, patent ductus arteriosus (PDA), intraventricular hemorrhage of grade III or IV, septic shock, and hypovolemic shock.

Secondary objective included risk factors for surgical NEC defined as NEC that require surgical intervention such as NEC stage IIIB and NEC stage IIIA with clinical deterioration despite maximal medical treatment, with fixed bowel loops, and fluid collection, and the cases with mortality.

### Sample size estimation

The sample size was calculated based on the rate of birth asphyxia in VLBW infants with NEC and non-NEC from Lu et al. study[17], which was 46% versus 26%. A type I error of 0.05, and a beta of 0.1 were used, resulting in an actual sample size of 65 subjects for the case group and 130 subjects for the control group.

### Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Mac, version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to define the baseline characteristics of both groups. Continuous variables were presented as means and standard deviation or medians and interquartile range (IQR) using an independent t-tests and the Mann-Whitney U test, depending on their distribution. Categorical variables were presented as frequencies and percentages using chi-Square tests and Fisher's exact tests. Multiple logistic regression was used to determine variables that were independently associated with NEC by using the backward likelihood ratio method. A p-value of less than 0.05 was considered statistically significant.

## Results

Of the 585 VLBW infants admitted to the NICU of BAH during the study period, 65 cases developed NEC, giving an incidence of 11.1%. One hundred ninety-five cases were analyzed, which included 65 in the NEC group and 130 in the non-NEC group. Cases and controls selection method are shown in Figure 1. The incidence trend of the condition was stable through the study period.

Demographic data in both groups are shown in Table 1. There were no statistically significant differences in GA with 29.6 versus 30.1 weeks, and birth weight at 1,240 versus 1,146.5 g, between the NEC and the non-NEC groups. The mortality rate was significantly higher in the NEC group at 35.4%

**Table 1.** Demographic data of VLBW infants in NEC (n=65) and non-NEC groups (n=130)

| | NEC | Non-NEC | p-value |
|---|---|---|---|
| GA (week); mean±SD | 29.6±2.4 | 30.1±2.5 | 0.22 |
| BW (g); median [IQR] | 1,240 [916 to 1,499] | 1,146.5 [915.5 to 1,367] | 0.05 |
| ELBW; n (%) | 20 (30.8) | 44 (33.9) | 0.67 |
| SGA; n (%) | 6 (9.2) | 25 (19.2) | 0.07 |
| Male; n (%) | 39 (60.0) | 64 (49.2) | 0.16 |
| Twin; n (%) | 5 (7.7) | 17 (13.1) | 0.26 |
| Death; n (%) | 23 (35.4) | 4 (3.1) | <0.001 |
| LOS (day); median [IQR] | 62 [29 to 98] | 54 [38.3 to 82.5] | 0.93 |

NEC=necrotizing enterocolitis; GA=gestational age; BW=birth weight; ELBW=extremely low birth weight; LOS=length of stay; SD=standard deviation; IQR=interquartile range

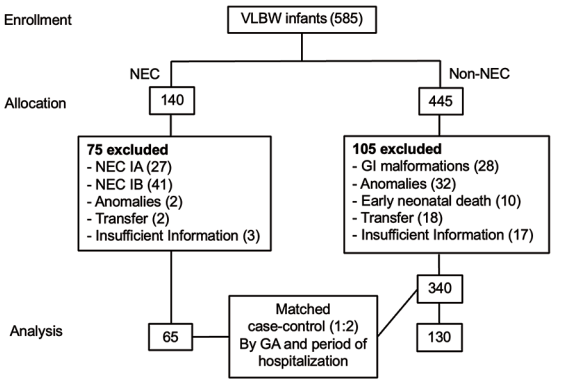


**Figure 1.** Study flow.

VLBW=very low birth weight; NEC=necrotizing enterocolitis; GI=gastrointestinal; GA=gestational age

versus 3.08%.

Among 65 infants in the NEC group, 29 and 36 infants were compatible with NEC stages II and III, respectively. The median onset of NEC was nine days (IQR 4 to 13.5). Half of them (34 out of 65) required surgical management and about one third died (23 out of 65). SBS was found in eleven infants, or 16.92%, while intestinal stricture was observed in five infants (7.69%).

The authors found significant differences between cases and controls. The infants in the NEC group had a higher rate of maternal PPROM at 9.2% versus 4.6% (p=0.04), a lower rate of antenatal steroids of 44.6% vs. 63.9% (p=0.01), lower Hct at 28.6% versus 35.2% (p<0.001) and higher rate of septic shock at 52.3% versus 8.5% (p<0.001) compared to non-NEC group. Regarding feeding pattern, infants in the NEC group had more delayed initiation of enteral feeding with 17 versus 7 hours (p=0.02), lower BM proportion within fourteen days at 0% versus 45.8% (p<0.001), lower BM on the fourteenth day of life of 3 versus 75 mL/kg/day (p<0.001), higher rate of formula feeding of 50% or greater within fourteen days for 64.6% versus 21.5% (p<0.001), compared to the non-NEC group. However, there were no significant differences in the incidences of birth asphyxia and EONS between the two groups. All of the data is shown in Table 2.

Multiple logistic regression showed the amount of human milk of 20 mL/kg/day or more on the fourteenth day of life was a protective factor against NEC in BAH (adjusted OR 0.08, 95% CI 0.02 to 0.30, p<0.001). Conversely, prolonged PN use for more than fourteen days (adjusted OR 4.81, 95% CI 1.91 to 12.16, p<0.001) and septic shock (adjusted OR 4.36, 95% CI 1.43 to 13.27, p=0.02) were independent risk factors for NEC as shown in Table 3.

In subgroup analysis, parameters were compared between infants with surgical NEC, which was 34 cases, and infants with medical NEC, which was 31 cases. At fourteen days of life, less frequency of infants in the surgical group had BM proportion of more than 20%, with 5.9% versus 32.3% (p=0.01), compared to medical NEC group. Moreover, multiple logistic regression revealed that receiving BM at a proportion of more than 20% was a significant protective factor against surgical NEC (adjusted OR 0.15, 95% CI 0.03 to 0.73, p=0.02). However, the study identified no factors significantly associated with mortality.

## Discussion

The present research was a case-control study of factors associated with NEC in VLBW infants. The study demonstrated that the incidence rate of NEC in NICU BAH was 11.1%, similar to the study in Ramathibodi Hospital at 10.6%, China at 12.8%, and Indonesia at 10.1%, although the figure was higher than in those reported in developed countries at 2.68% to 7.81%[10,15,16,18-20]. The varying incidence

**Table 2.** Univariate analysis of factors affecting NEC (n=65) and non-NEC (n=130)

| | NEC | Non-NEC | p-value |
|---|---|---|---|
| Maternal | | | |
| Age (year); mean±SD | 28.1±6.6 | 29.2±6.8 | 0.30 |
| PPROM; n (%) | 6 (9.2) | 6 (4.6) | 0.04 |
| Dexamethasone[a]; n (%) | 29 (44.6) | 83 (63.9) | 0.01 |
| Vaginal birth; n (%) | 43 (66.2) | 59 (45.4) | 0.01 |
| Infant; median [IQR] | | | |
| 5-minute APGAR | 9 [7 to 10] | 9 [7 to 10] | 0.26 |
| UAC (day) | 7 [4 to 10] | 6 [0 to 7] | 0.03 |
| UVC (day) | 10 [7 to 14] | 9 [5 to 12] | 0.12 |
| Pre Tx hct | 28.6 [26 to 32.4] | 35.2 [30 to 44.4] | <0.001 |
| Nutrition | | | |
| Start feeding (hour); median [IQR] | 17 [4 to 48] | 7 [3 to 24] | 0.02 |
| Start BM (day); median [IQR] | 4 [2.5 to 7] | 5 [3 to 7] | 0.79 |
| BM prop (%); median [IQR] | 0 [0 to 13.7] | 45.8 [1.8 to 73.4] | <0.001 |
| BM D14; n (%) | 3 (4.6) | 75 (57.7) | <0.001 |
| PN D14; n (%) | 45 (69.2) | 39 (30.0) | <0.001 |
| Formula prop[b]; n (%) | 42 (64.6) | 28 (21.5) | <0.001 |
| Enteral feeding[c] (day); median [IQR] | 28 [14 to 42] | 13 [9 to 18] | <0.001 |
| Comorbidities; n (%) | | | |
| RDS | 35 (53.9) | 84 (64.6) | 0.15 |
| EONS | 19 (29.2) | 24 (18.5) | 0.09 |
| LONS | 22 (33.9) | 54 (41.5) | 0.30 |
| PDA | 32 (49.2) | 63 (48.5) | 0.13 |
| IVH grade III-IV | 5 (7.7) | 5 (3.9) | 0.07 |
| Septic shock | 34 (52.3) | 11 (8.5) | <0.001 |

NEC=necrotizing enterocolitis; PPROM=prolonged premature rupture of membrane; UAC=umbilical artery catheter; UVC=umbilical vein catheter; Pre Tx hct=hematocrit before transfusion; BM prop=proportion of breast milk within 14 days; BM D14=breast milk at day of life 14 ≥20 mL/kg/day; PN D14=parenteral nutrition >14 days; RDS=respiratory distress syndrome; EONS=early onset neonatal sepsis; LONS=late onset neonatal sepsis; PDA=patent ductus arteriosus; IVH=intraventricular hemorrhage; SD=standard deviation; IQR=interquartile range

(a) Dexamethasone at least 1 dose; (b) Proportion of enteral feeding ≥50% within 14 days; (c) Time to full enteral feeding at least 150 mL/kg/day

**Table 3.** Multiple logistic regression of selected factors affecting NEC

| | Crude OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
|---|---|---|---|---|
| BM D14 | 0.04 (0.01 to 0.13) | <0.001 | 0.08 (0.02 to 0.30) | <0.001 |
| PN D14 | 5.83 (3.01 to 11.32) | <0.001 | 4.81 (1.91 to 12.16) | <0.001 |
| Septic shock | 11.87 (5.40 to 26.05) | <0.001 | 4.36 (1.43 to 13.27) | 0.02 |

NEC=necrotizing enterocolitis; OR=odds ratio; CI=confidence interval; BM D14=breast milk at day of life 14 ≥20 mL/kg/day; PN D14=parenteral nutrition >14 days

of NEC may be attributed to the clinical comorbidities experienced by each infant. Additionally, factors such as socioeconomic status and the availability of equipment facilities for NICU care were found to be correlated with a survival rate[3,15].

The present research found that prolonged PN used and septic shock were the risk factors for NEC in VLBW infants. The finding about PN was similar to a recent multicenter case-control study in Netherland[21]. In that study, Berkhout, et al. concluded that the cumulative number of parenteral feeding days was a risk factor associated with NEC (adjusted OR 1.19, 95% CI 1.07 to 1.31, p=0.001). There was no previous study that showed an association between septic shock and NEC, except for a study of Lu et al. His study in 238 infants found that sepsis was a risk factor for NEC (adjusted OR 3.95, 95% CI 1.92 to 6.38, p=0.003)[17]. It is already well-established in pediatric surgery literature that neonatal sepsis is a known risk factor for NEC. In septic shock, combined effects of pathogenic bacteria, intestinal flora imbalance, intestinal wall barrier dysfunction,

toxic intestinal paralysis, and direct destruction of intestinal epithelial cells can also cause NEC[22].

There was only one protective factor found against NEC from the present research. It was BM consumption, which showed that consuming 20 mL/kg/day or more at the age of fourteen days provides protection. This finding corresponded to another study in Thailand[16]. Supabanpot investigated 50 VLBW infants with NEC and found that the amount of human milk received at fourteen days of age was the only protective factor (adjusted OR 0.98, p<0.001, 95% CI 0.98 to 0.99), similar to a systematic review and meta-analysis study by Altobelli that found a dose-response relationship between NEC and proportion of human milk[23]. Mother's own milk (MOM) has bioactive components such as immunoglobulin A and probiotics that act synergistically to provide protection from NEC[3]. The American Academy of Pediatrics recommends that all preterm infants should receive human milk[24]. Therefore, to improve preterm outcomes and decrease NEC rate in VLBW infants in NICU BAH, the establishment and maintenance of milk supply and BM management should be promoted to the mothers of these preterm infants. Furthermore, if the MOM was not available, donor human milk should be provided instead of formula feeding.

The recent study by Youn, et al. comparing between infants with medical and surgical NEC, which included 57 versus 77 infants, revealed that PDA was found more frequently in the surgical group (crude OR 3.40, p<0.001). This differed from the present study that there was no significant difference in PDA between both groups (p=0.71). However, the authors found the proportion of BM within fourteen days of 20% or greater was a protective factor for NEC with surgical management, which the number needed to treat was 2.42[25].

The strength of the present study was that it had a suitable sample population with corrected matched case and controls that had been collectively investigated over 15 years, thereby providing high statistical power for the detection of new potential factors. However, the present study had limitations as it was conducted in a single tertiary hospital. Besides, clinical practices might have changed over time since the study was retrospective. Further investigation in future studies, feeding protocols, pathogens, and factors related to neonatal sepsis should be added.

## Conclusion

The present study indicates that early initiation of human milk within the first fourteen days is not only a protective factor against NEC, but also protective factor for advanced NEC that requires surgical management. On the other hand, septic shock and prolonged use of PN increase the risk of developing NEC and should be avoided.

## What is already known on this topic?

The incidence of NEC in Thailand was reported to be 10% to 15%. The factors associated with NEC already known include the cumulative duration of exposure to umbilical vein catheters, cumulative duration of exposure to invasive mechanical ventilation, EONS, and the amount of human milk.

## What does this study add?

The incidence of NEC among VLBW infants in NICU BAH was 11.1%. Early initiation of human milk feeding has been shown to be protective against NEC, while factors such as septic shock and prolonged use of PN increase the risk. Notably, infants requiring surgical intervention for NEC tend to receive less human milk in the early days compared to those managed medically. These findings underscore the importance of promoting early and adequate human milk feeding as part of NEC prevention strategies, while closely monitoring high-risk infants who may need surgical care.

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## Conflicts of interest

The authors declare no conflict of interest.

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