# Umbilical arterial catheter duration as risk factor for Bell's Stage III necrotizing enterocolitis in preterm neonates

Renjini Lalitha[1] ⓘ | Matthew Hicks[2] | Mosarrat Qureshi[2] | Kumar Kumaran[2]

[1]Department of Pediatrics, Division of Neonatal-Perinatal Medicine, University of Western Ontario, London, Ontario, Canada

[2]Department of Pediatrics, Division of Neonatal-Perinatal Medicine, Edmonton, Alberta, Canada

**Correspondence**
Renjini Lalitha, The Division of Neonatal-Perinatal Medicine, London Health Sciences Centre, 800 Commissioners Rd. East, London, ON N6A 5W9, Canada.
Email: Renjini.Lalitha@lhsc.on.ca

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## Abstract

**Objectives:** To explore risk factors for Stage-III necrotizing enterocolitis (NEC-III) in preterm neonates.

**Methods:** This was a retrospective case-control study of neonates born <33 weeks gestational age (GA) who were admitted to a tertiary neonatal intensive care unit, between 2015 and 2018. NEC-III cases were compared with Stage-II NEC (NEC-II) and non-NEC controls. Two to four non-NEC controls were matched by GA ± 1 week and date of birth ± 3 months, to one NEC-III case. Univariate and multivariate analyses were used to examine risk factors for NEC-III.

**Results:** Of 1360 neonates born <33 weeks, 71 (5.2%) had NEC-II and above, with 46% being NEC-III. Mean age of onset of NEC-III was 13.7 days versus 23.9 days for NEC-II ($p = 0.01$). Neonates with NEC-III were of lower GA (NEC-III 25.4 weeks, NEC-II 27.3 weeks, and non-NEC 26 weeks; $p = 0.0008$) and had higher Score for Neonatal Acute Physiology Perinatal Extension-II scores (NEC-III 47.5, NEC-II 28.4 and non-NEC 37, $p = 0.003$). Multivariate analysis showed duration of umbilical arterial catheter (UAC) >5 days was significantly associated with the development of NEC-III with adjusted odds ratio (AOR) 3.8; 95% confidence interval (CI) (1.05–13.66) for NEC-III versus non-NEC and AOR 5.57; 95% CI (1.65–18.73), $p = 0.006$ for NEC-III versus NEC-II. Rupture of membranes (ROM) >1 week was associated with NEC-III (AOR 6.93; 95% CI [1.56–30.69] vs. non-NEC and AOR 11.74; 95% CI [1.14–120.34] vs. NEC-II).

**Conclusion:** The increased association of NEC-III with duration of UAC and ROM could be further examined in prospective studies, and an upper limit for UAC duration could be considered in NEC prevention bundles.

**KEYWORDS**
necrotizing enterocolitis, neonates, preterm, risk factors, umbilical arterial catheter

## 1 | INTRODUCTION

Necrotizing enterocolitis (NEC) is a serious intestinal inflammatory disease in neonates first described in 1965 by Mizrahi et al.[1] The disease is characterized by inflammation and injury of the gut wall barrier that may advance to necrosis and potentially, perforation of the gut.[2,3] NEC occurs in 5%–10% of very low birth weight neonates (VLBW).[4,5]

NEC is categorized into three stages based on modified Bell's staging criteria, namely, Stage I—suspected NEC, Stage II proven NEC, and Stage III

Advanced NEC based on severity of clinical signs and symptoms, radiological findings and laboratory abnormalities as described in Appendix 1.[6,7] The clinical presentation of NEC can be highly variable mimicking sepsis but the presence of pneumatosis intestinalis and/or portal venous gas on X-rays or necrotic bowel at the time of surgery helps to differentiate NEC stage II or above from sepsis. While stage I NEC includes patients with mildest symptoms, radiological signs of pneumatosis intestinalis confirm Stage II NEC. Stage III NEC (NEC-III) is the severe form and reported to comprise 20%–40% of all cases. There is a high mortality rate with significant morbidity in survivors.[8,9] NEC-III not only shows all the clinical and radiological signs of stage I and II NEC but also deterioration of vital signs, presence of shock, coagulopathies, bowel necrosis, and pneumoperitoneum. Several risk factors are associated with the development of NEC.[4,10–12] The most consistent epidemiologic risk factors for NEC have been identified as prematurity and enteral feeding practices.[13,14]

More recently, Sulemanji and group, through their observational study found the presence of an umbilical venous catheter (UVC) into the portal vein or ductus venosus was associated with an increased incidence of NEC in VLBW neonates.[15] While there is some evidence showing impaired splanchnic circulation with umbilical artery catheterization (UAC),[16,17] there are conflicting results on its presence or tip position and associated development of NEC.[18,19] Although Thompson et al. looked at risk factors for NEC-totalis (defined as greater than 80% intestinal necrosis),[20] there have been no studies looking at risk factors for NEC-III in general.

## 1.1 | Study rationale

NEC-III has a high case fatality rate and is associated with prolonged hospital stay, total parenteral nutrition dependence, liver dysfunction, neurodevelopmental disabilities, growth failure, short bowel syndrome, intestinal scarring, and need for surgical intervention.[8,9] To date there have been no study comparisons assessing risk factors for the development of NEC-III, and specifically, its association with duration of umbilical line placement. The aim of this exploratory study is to develop a specific hypothesis for the prediction of NEC-III development in preterm neonates, which could be tested in future research.

## 1.2 | Objectives

1. To assess the risk factors associated with the development of NEC-III in preterm neonates born less than 33 weeks gestational age (GA).

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### What is Known

- Stage-III necrotizing enterocolitis (NEC-III) has high mortality and morbidity among all types of NEC. Risk factors for the development of NEC in general have been documented in many studies but those for NEC-III in particular remain unexplored.

### What is New

- NEC-III occurs earlier compared to NEC-II suggesting a unique predisposing factor to its development.
- Duration of umbilical artery catheterization (UAC) greater than 5 days was associated with the development of NEC-III.
- An upper limit for the duration of UAC might be warranted for the prevention of NEC.

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2. To investigate the association of the presence and duration of umbilical catheterization with the development of NEC-III in preterm neonates born less than 33 weeks GA.

## 1.3 | Definitions

1. NEC was scored according to the following criteria: (a) definite pneumatosis (air within the bowel wall) or portal/hepatic gas as diagnosed by x-ray or ultrasonography or (b) surgical or autopsy diagnosis of NEC. Diagnosis of "suspected NEC" or x-rays showing pneumoperitoneum without pneumatosis will not be classified as NEC. NEC cases were staged as per Modified Bell's staging criteria (Supporting Information S1: Appendix S1).
2. Vasoactive agents are agents that increase myocardial contractility (inotropes) and/or increase vascular tone like vasopressors. The Vasoactive Inotrope score quantifies the amount of cardiovascular therapy using a weighted sum of all the inotropic and vasopressor agents (Supporting Information S1: Appendix S2).

## 2 | METHODS

This was a single-center retrospective case-control study conducted at a level three neonatal intensive care unit (NICU) in West Canada between January 2015 and December 2018 using a combination of neonatal database and chart review This center is one of the largest tertiary perinatal centers in Canada with a 69 bed NICU that receives approximately 1300

admissions annually. Neonates born less than 33 weeks who were managed as NEC-III during the study period formed the case group and those with NEC-II and without NEC formed the two control groups. The NEC-III cases were compared with NEC-II (1NEC-III: 1NEC-II) and with non-NEC controls (1 NEC-III case: 2–4 non-NEC) that were matched for GA ± 1 week, and date of birth within 3 months. Neonates with lethal congenital malformations, chromosomal/genetic abnormalities, congenital heart defects (except for patent ductus arteriosus, ventricular septal defects, and atrial septal defects), and intestinal anomalies were excluded. All cases of NEC that were managed in the NICU were reviewed in detail by the local NEC working group committee consisting of neonatologists, neonatal fellows, radiologists, nurse practitioners, nurses, nutritionists, and clinical educators. The diagnosis of NEC and its stages were confirmed by this committee, using Modified Bell's staging criteria (Supporting Information S1: Appendix S1).

## 2.1 | Data collection

We conducted extensive chart and database review for maternal and neonatal demographics, and perinatal data such as GA, birth weight, sex, antenatal steroid/magnesium sulfate, pregnancy-related morbidities, mode of delivery, Apgar score, surfactant use, and cord gases. Data on feeding, vasoactive agents, respiratory support, sepsis, presence of patent ductus arteriosus (PDA), need for nonsteroidal anti-inflammatory drugs (NSAIDS) for PDA treatment, presence and duration of umbilical lines, and presence of malpositioned umbilical lines before diagnosis of NEC in both NEC-III and NEC-II groups or within 60 days of life for non-NEC group were also collected.

## 2.2 | Statistical analysis

Given the retrospective and exploratory nature of the study, an a priori sample size calculation was not performed and a sample of convenience was used. All statistical analyses were performed with Intercooled Stata Version 15.0 (StataCorp). All data were anonymized for analysis. Groups within the study were compared using descriptive statistical methods. Maternal and neonatal characteristics were compared between groups using Pearson's $\chi^2$ and Fisher's exact tests for categorical variables and one-way analysis of variance (for comparing three groups—NEC-III, NEC-II, and non-NEC) or Student's $t$ test for comparing continuous variables. Histograms and boxplots were used to assess underlying assumptions of normal distribution and normality of variances. Multivariate logistic regression models were built to identify risk factors associated with the development of NEC-III compared to NEC-II and controls using a forward and backward stepwise selection approach and variables were included if they had a $p$ value less than 0.2 in bivariate analysis. Associations between variables and outcomes were expressed as adjusted odds ratios (AORs) and 95% confidence intervals (CIs). A $p$ value < 0.05 was considered significant. Adjustments for multiple comparisons were not made given the exploratory nature of this work. Unmatched analyses are presented. This study was approved by the Northern Alberta Clinical Trials and Research Center and the Human Research Ethics Office at the University of Alberta.
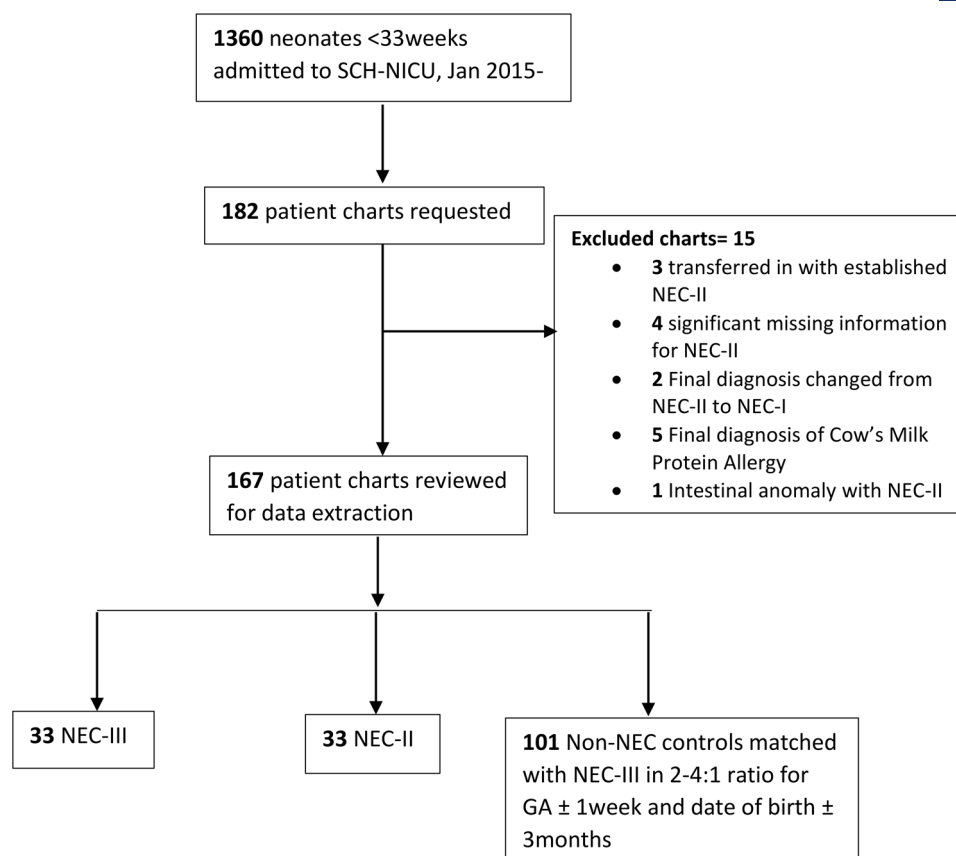
## 3 | RESULTS

A total of 1360 preterm neonates born less than 33 weeks were admitted to our center during the 4-year study period. The incidence of NEC-II and NEC-III was 5.2% in VLBW, with 46% of cases meeting the criteria for NEC-III (Figure 1). Neonates with NEC-III were of lower GA (25.4 ± 2.3 weeks) compared to NEC-II (27.3 ± 2.7 weeks) ($p = 0.0003$, data not shown). Average age of onset of NEC-III was 13.7 (12.2 standard deviation [SD]) days versus 23.9 (18.8 SD) days for NEC-II ($p = 0.01$).

Table 1 compares the demographic, clinical, and biochemical characteristics of the NEC-III, NEC-II, and non-NEC groups. Severity of illness was defined using the Score for Neonatal Acute Physiology Perinatal Extension-II (SNAPPE-II score). Neonates with NEC-III had a higher severity of illness (SNAPPE-II 47.5; SD 25.1) than NEC-II infants (SNAPPE-II 28.4; SD 19.5) and non-NEC infants (SNAPPE-II 37; SD 22.1), ($p = 0.003$). Infants who developed NEC-III were on vasoactive agents longer (7.5 days vs. 3.2 days and 4.2 days for NEC-III, NEC-II, and non-NEC, respectively; $p = 0.09$), although this was not statistically significant. There were no significant differences in the baseline lactate/maximum metabolic deficits after birth, need for normal saline bolus, and peak vasoactive inotrope scores within the first 3 days of life between groups. Rates of antenatal steroids exposure and Apgar scores <7 at 10 min were not statistically significant among study groups.

Table 1 also compares feeding characteristics between the groups. The timing of first enteral feeds was not statistically different between the groups. The majority of neonates with NEC-III never achieved full enteral feeds before the development of NEC (60.6% in NEC-III vs. 36.3% in NEC-II, $p \leq 0.0001$). Among those who achieved full enteral feeds, the mean days to full feeds did not differ between the groups.

The presence, position, and duration of both umbilical lines were analyzed between NEC-III, NEC-II, and non-NEC groups as shown in Table 2. The rate

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┌──────────────────────────────────┐
│ 1360 neonates <33weeks           │
│ admitted to SCH-NICU, Jan 2015-  │
└──────────────────────────────────┘
                 │
                 ▼
┌──────────────────────────────────┐
│ 182 patient charts requested     │
└──────────────────────────────────┘
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**Excluded charts= 15**
- **3** transferred in with established NEC-II
- **4** significant missing information for NEC-II
- **2** Final diagnosis changed from NEC-II to NEC-I
- **5** Final diagnosis of Cow's Milk Protein Allergy
- **1** Intestinal anomaly with NEC-II

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┌──────────────────────────────────┐
│ 167 patient charts reviewed      │
│ for data extraction              │
└──────────────────────────────────┘
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┌───────────────┐  ┌───────────────┐  ┌──────────────────────────────────┐
│ 33 NEC-III    │  │ 33 NEC-II     │  │ 101 Non-NEC controls matched     │
└───────────────┘  └───────────────┘  │ with NEC-III in 2-4:1 ratio for  │
                                       │ GA ± 1week and date of birth ±   │
                                       │ 3months                          │
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**FIGURE 1**  Study flow diagram. GA, gestational age; NEC-I, stage-I necrotizing enterocolitis; NEC-II, stage-II necrotizing enterocolitis; NEC-III, stage-III necrotizing enterocolitis; NICU, neonatal intensive care unit; SCH, Stollery Philip C. Etches Hospital.

of UAC insertion after birth was significantly higher in NEC-III (87.1%) than NEC-II (55.9%) and non-NEC (72.3%, $p = 0.02$). In addition, UAC remained in place longer than 5 days in NEC-III compared to NEC-II and non-NEC neonates (NEC-III 75%, NEC-II 36.4%, and non-NEC 47%, $p = 0.007$). X-ray confirmed optimal UAC and UVC positions were not statistically different between the groups. We further examined the collinearity between UAC days and SNAPPE-II score in all the study neonates. SNAPPE-II scores were significantly higher at 48.1 (SD 18.6) in neonates who had UAC in place for >5 days compared with infants with UAC in place for ≤5 days at 25.8 (SD 21.3), $p ≤ 0.0001$. Specifically, among neonates who developed NEC, SNAPPE-II scores were also significantly higher in those who had UAC in place for >5 days as opposed to those with UAC in place for ≤5 days (51 [SD 18.6] vs. 20.1 [SD 18.9]).

Multivariate logistic regression analyses were performed to assess factors that were independently associated with NEC-III development. For this analysis, we created models that included all variables that were $p < 0.2$ in bivariate analysis and performed logistic regression analysis. Most variables including SNAPPE-II scores did not remain in the final parsimonious

regression model. After adjustment for known confounders, length of UAC greater than 5 days had 5.57 (1.65–18.73) and 3.8 (1.05–13.66) odds of developing NEC-III compared to NEC-II cases ($p = 0.006$) and non-NEC controls (0.041), respectively (Table 3).

# 4  |  DISCUSSION

In this retrospective case-control study, we investigated the risk factors for NEC-III using Bell's criteria in preterm neonates born less than 33 weeks. We found duration of UAC over 5 days and rupture of membranes more than 7 days were significantly associated with increased risk for NEC-III. NEC-III can have devastating outcomes in preterm neonates making it important for us to understand risk factors and possible preventive interventions. To the best of our knowledge, this is the first study to date that has looked at risk factors in particular the duration of umbilical lines in association with NEC-III development.

The incidence of NEC-III was higher in our study than what is reported in the literature.[8] This could be explained in part by the fact that our unit is one of the largest units in Canada that cares for a large proportion

**TABLE 1** Baseline characteristics comparing NEC-III, NEC-II, and non-NEC groups.

| Variable | NEC III (*n* = 33) | NEC II (*n* = 33) | Non-NEC (*n* = 101) | *p* Value |
|---|---|---|---|---|
| Gestational age in weeks, mean (SD) | 25.4 (2.3) | 27.3 (2.7) | 26.0 (1.9) | 0.0008 |
| Birth weight in grams, mean (SD) | 838.3 (291.5) | 1003.6 (350.5) | 909.1 (289.7) | 0.0847 |
| Male sex, *n* (%) | 18 (54.5) | 22 (66.7) | 64 (63.4) | 0.560 |
| Outborn births, *n* (%) | 4 (12.9) | 17.1 (6) | 10.9 (1) | 0.629 |
| C-section, *n* (%) | 18 (54.5) | 18 (54.5) | 61 (60.4) | 0.651 |
| Antenatal steroids—yes, *n* (%) | 27 (81.8) | 31 (93.9) | 96 (95.0) | 0.062 |
| ROM >24 h, *n* (%) | 17 (51.5) | 29 (87.9) | 65 (64) | 0.066 |
| ROM >1 week, *n* (%) | 7 (21.9) | 1 (3.1) | 12 (12.1) | 0.124 |
| Chorioamnionitis—yes, *n* (%) | 7 (21.2) | 5 (15.2) | 34 (33.8) | 0.079 |
| PIH—yes, *n* (%) | 1 (3.0) | 11 (33.3) | 11 (10.9) | 0.003 |
| IUGR—yes, *n* (%) | 1 (3) | 5 (15.1) | 2 (2) | 0.012 |
| Normal UA dopplers, *n* (%) | 27 (81.8) | 28 (84.8) | 88 (87.1) | 0.185 |
| AEDF UA dopplers, *n* (%) | 0 | 5 (15.2) | 5 (5) | |
| REDF UA dopplers, *n* (%) | 1 (3) | 1 (3) | 5 (5) | |
| Apgar score <7 at 10 min, *n* (%) | 11 (33.3) | 4 (12.1) | 17 (16.8) | 0.069 |
| DCC, *n* (%) | 16 (49.5) | 17 (51.5) | 51 (50.5) | 0.9721 |
| SNAPPE II, mean (SD) | 47.5 (25.1) | 28.4 (19.5) | 37.0 (22.1) | 0.0031 |
| First blood lactate level within 12 h after birth, mean (SD) | 3.8 (3.3) | 3.9 (2.4) | 3.8 (2.7) | 0.9888 |
| Max BE in first 12 h after birth, mean (SD) | −7.0 (3.6) | −5.3 (2.2) | −5.6 (3.0) | 0.1190 |
| NS bolus within first 72 h of life—no, *n* (%) | 15 (45.5) | 21 (63.6) | 54 (53.5) | 0.701 |
| Vasoactive agents within first 72 h of life—yes, *n* (%) | 15 (45.5) | 12 (36.4) | 44 (43.6) | 0.428 |
| Days on vasoactive agent, mean (SD) | 7.5 (8.0) | 3.2 (2.0) | 4.2 (5.0) | 0.0886 |
| Peak VIS, mean (SD) | 6.3 (8.4) | 3.8 (7.6) | 4.2 (6.3) | 0.2848 |
| Postnatal steroids—yes, *n* (%) | 0.0 (0) | 3 (9.1) | 14 (13.9) | 0.093 |
| Indomethacin prophylaxis—yes, *n* (%) | 6 (18.2) | 4 (12.1) | 9 (8.9) | 0.261 |
| PDA—yes, *n* (%) | 20 (60.6) | 20 (60.6) | 59 (58.4) | 0.958 |
| Abdominal aorta Doppler normal, *n* (%) | 11 (64.7) | 14 (73.7) | 40 (63.5) | 0.491 |
| Number of courses for PDA treatment, mean (SD) | 0.74 (0.86) | 0.54 (0.89) | 0.73 (1.04) | 0.5902 |
| EONS, *n* (%) | 0.0 (0) | 2 (6.1) | 1.0 (1) | <0.001 |
| LONS, *n* (%) | 9 (27.3) | 7 (21.2) | 14 (13.9) | 0.138 |
| Days of antibiotics, mean (SD)[c] | 5.2 (3.7) | 5.4 (4.4) | 14.8 (14.1) | <0.0001 |
| PRBC—yes, *n* (%) | 19 (57.6) | 15 (45.5) | 61 (60.4) | 0.202 |
| Number of PRBCs, mean (SD) | 1.4 (1.6) | 0.9 (1.4) | 1.8 (2.0) | 0.0829 |
| First enteral feed in hours, mean (SD)[a] | 10.1 (4.4) | 9.6 (5.4) | 11.3 (6.0) | 0.4187 |
| First enteral feed in days, mean (SD)[b] | 2.1 (1.9) | 2.8 (4.2) | 2.0 (1.9) | 0.6242 |

**TABLE 1** (Continued)

| Variable | NEC III (n = 33) | NEC II (n = 33) | Non-NEC (n = 101) | p Value |
|---|---|---|---|---|
| Never achieved full feeds, n (%) | 20 (60.6) | 12 (36.4) | 0 (0) | <0.001 |
| Days on TPN, mean (SD)[c] | 10.4 (6.5) | 12.9 (9.3) | 18.0 (10.4) | 0.0004 |

*Note*: One-way analysis of variance reported for continuous variables and Fisher's exact test for categorical variables.

Abbreviations: AEDF, absent end diastolic flow; BE, base excess; DCC, delayed cord clamping; EONS, early onset neonatal sepsis; $HCO_2$, bicarbonate; IUGR, intrauterine growth retardation; LONS, late-onset neonatal sepsis; $MgSO_4$, magnesium sulfate; NEC-II, necrotizing enterocolitis stage II; NEC-III, necrotizing enterocolitis stage III; non-NEC, non-necrotizing enterocolitis; NS, normal saline; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; PRBC, packed red blood cell; REDF, reverse end diastolic flow; ROM, rupture of membrane; SD, standard deviation; SNAPPE II, Score for Neonatal Acute Physiology Perinatal Extension-II; TPN, total parenteral nutrition; UA, umbilical artery; VIS, vasoactive inotrope score.

[a]First feed received within first 24 h of life.

[b]First feed received after 24 h of age.

[c]Before NEC onset in NEC-III and NEC-II groups and within the first 60 days in non-NEC group.

**TABLE 2** Comparison of umbilical catheters between NEC-III, NEC-II, and non-NEC groups.

| Variable | NEC-III (n = 33) | NEC-II (n = 33) | Non-NEC (n = 101) | p Value |
|---|---|---|---|---|
| Presence of UAC—yes, n (%) | 27 (87.1) | 19 (55.9) | 73 (72.3) | 0.020 |
| High UAC, n (%) | 23 (92) | 17 (89.5) | 68 (95.8) | 0.467 |
| Days of UAC,[a] mean (SD) | 8.4 (3.0) | 7.1 (3.5) | 7.3 (3.6) | 0.3599 |
| UAC longer than 5 days,[b] n (%) | 21 (75) | 12 (36.4) | 47 (47) | 0.007 |
| Central UVC, n (%) | 14 (50) | 19 (61.3) | 49 (50) | 0.552 |
| Days of UVC, mean (SD) | 7.2 (3.4) | 8.8 (4.2) | 7.4 (4.1) | 0.1749 |

Abbreviations: NEC-III, necrotizing enterocolitis stage III; NEC-II, necrotizing enterocolitis stage II; non-NEC, non-necrotizing enterocolitis; UAC, umbilical arterial catheter; UVC, umbilical venous catheter.

[a]If a UAC was successfully placed.

[b]If a UAC was present for 5 days or longer.

**TABLE 3** Multivariate analysis comparing NEC-III to NEC-II and non-NEC.

| Variable | NEC-III versus NEC-II | | NEC-III versus non-NEC | |
|---|---|---|---|---|
| | Adjusted OR (95% CI) | p Value | Adjusted OR (95% CI) | p Value |
| UAC in place for >5 days | 5.57 (1.65–18.73) | 0.006 | 3.8 (1.05–13.66) | 0.041 |
| Rupture of membranes >1 week | 11.74 (1.14–120.34) | 0.038 | 6.93 (1.56–30.69) | 0.041 |

Abbreviations: CI, confidence interval; NEC-III, necrotizing enterocolitis stage III; NEC-II, necrotizing enterocolitis stage II; non-NEC, non-necrotizing enterocolitis; OR, odds ratio; UAC, umbilical arterial catheter.

of VLBW neonates. Our unit also functions as a referral center for a wide catchment area. Unlike NEC-II, NEC-III presented earlier in our study, by the second week of life, suggesting a unique predisposing development factor other than feeding practices for preterm neonates.

Numerous factors can influence intestinal blood flow in preterm neonates such as type and advancement of enteral feeding, use of vasoactive agents or NSAIDs, presence of PDA, red blood cell transfusion, sepsis, and umbilical catheterization and its position.[16,17,21–23] Our study showed that neonates with NEC-III were generally sicker than the control group at birth with higher SNAPPE-II scores and longer duration of vasoactive agents. This can influence regional gut flow through the diving reflex and local vasoconstrictive effects of the agents, respectively.

While vasoactive agent use may be associated with NEC development,[24–27] currently there is lack of robust evidence to incriminate one agent over the other.[28] Longer duration of vasoactive therapy may suggest extensive circulatory impairment requiring vasoactive therapy. This may lead to derangement in intestinal

microcirculation resulting in hypoperfusion and intestinal assault, thus increasing the risk for NEC-III. Neither duration of vasoactive use nor the use of vasoactive agents significantly increased the risk of NEC-III in our study. Although there was a trend in longer duration of vasoactive agents use in NEC-III, a larger sample size may be required to demonstrate significance. Additionally, our study did not look into the granularity of agents used. Two common vasoactive agents used in the preterm population in our center were dopamine and epinephrine.

Antibiotic exposure and its increased association with NEC development have been demonstrated through several studies.[29–33] More recently, meta-analysis by Esaiassen et al.[34] revealed prolonged antibiotic exposure in noninfected preterm neonates increased the incidence of NEC. Our study did not find such an association. On the contrary, we showed that decreased use of antibiotics increased the incidence of NEC in our cohort. This finding is congruent with findings of others[35–37] demonstrating early antibiotic exposure to be protective against NEC development. The postulated mechanism for this protective effect could be due to targeted manipulation of intestinal microbiomes from early antibiotic exposure that are pathogenic for NEC development. This hypothesis suggests that early colonization may serve an important role in maintaining gut health in these preterm neonates.

Umbilical catheterization is a common procedure performed in VLBW neonates. While a UVC helps with delivery of fluids, parenteral nutrition, intravenous medications, and central venous pressure monitoring, a UAC is used for blood sampling and invasive blood pressure monitoring. Rarely, UACs are used for the administration of fluids and nonvasoactive medications when alternative access is not available. A few retrospective and observational studies have shown intestinal disturbances such as bowel distension, ischemia, and NEC associated with umbilical arterial and venous cannulation and its tip position.[22,38–40] Postulated mechanism of UAC causing intestinal disturbances include microthrombi released by UACs, the vasospasm of splanchnic blood vessels, and reduction in the lumen diameter due to the presence of the catheter in the abdominal aorta, which may lead to decreased blood flow.[38–40] Literature on the effects of UACs on the regional intestinal circulation remains controversial.[16,17,41,42] It has been postulated that malpositioned UVCs lead to portal venous congestion which may cause intestinal injury.[43] Disturbances in intestinal blood flow due to UAC and UVC may predispose VLBW neonates to the development of NEC when enterally fed.[44,45]

Our study demonstrated for the first time that the presence of an UAC greater than 5 days is associated with the development of NEC II and NEC-III. We did not observe an association between location of UAC tip and NEC, which is congruent with the existing scientific evidence.[19] On the other hand, both the presence and the location of UVC tip were not associated with NEC in our study population.

Risk of NEC-III increased by over 10-fold and that for NEC-II by sevenfold when there was prolonged rupture of membranes (over 1 week) in our cohort. This might be due to increased placental inflammatory markers that the fetus is exposed to that may potentially cause disturbances in intestinal blood flow and intestinal injury. Even though clinical chorioamnionitis was not associated with the development of NEC in our cohort, the antenatal inflammatory process is often clinically silent and evident only in histopathology.[46,47]

Our study has several strengths and limitations. Data collection was limited to one individual, which reduces the introduction of bias as the definition of the clinical parameters assessed were consistent for all the study participants. The short study period limits the potential differences in the way information is recorded in the charts as well as potential changes in the standard of care. The short study period limits any significant change in the standard of practice in preterm neonatal care. Although the data collection process in our study was comprehensive, it is limited to a single institution's experience, and therefore affecting the generalizability of the results. The retrospective nature of the data also makes the availability of information limited to those recorded in electronic and paper charts, which may have been confounded by related variables that were not measured in this study.

# 5 | CONCLUSION

The presence of an UAC for greater than 5 days and prolonged rupture of membranes greater than 1 week were associated with severe forms of NEC in VLBW neonates in our study. These data support the need for additional prospective studies to examine the effect of UAC catheter duration on NEC development and consideration for institutional guideline development regarding the use and duration of UAC with respect to NEC prevention until further data is available.

## CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

## ORCID
*Renjini Lalitha* 🔟 https://orcid.org/0000-0001-7745-1529

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