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ORIGINAL ARTICLE

The incidence and modifiable risk factors for necrotizing enterocolitis in preterm infants: a retrospective cohort study

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ABSTRACT

Objectives: To evaluate the incidence and modifiable risk factors for Necrotizing enterocolitis (NEC) in preterm infants born at ≤32 weeks of gestation weighing <1500 grams, at a private tertiary care hospital in Kenya.

Materials and methods: This retrospective cohort study was conducted at the Aga Khan University Hospital Neonatal Intensive Care Unit (NICU). Preterm infants born at ≤ 32 weeks' gestation and weighing <1500 grams admitted to NICU between 2009 and 2019, were recruited into the study. The primary outcome was NEC Bell Stage IIa-IIIb based on Modified Bell's criteria. Maternal and neonatal characteristics were evaluated. The association between variables of interest and NEC was determined using logistic regression analysis and the incidence of NEC for the study period was calculated.

Results: A total of 261 charts of infants born at ≤ 32 weeks' gestation, weighing <1500 were reviewed, and 200 charts met the inclusion criteria. Fifteen preterm infants developed the primary outcome of interest: NEC Stage ≥2a within the first 30 days of admission. The overall incidence of NEC for the study period was 7.5%. Three risk factors were identified as significantly associated with NEC on multivariate logistic regression analysis: antenatal exposure to steroids (OR = 0.056 CI = 0.003-0.964 $p = 0.047$), cumulative duration of exposure to invasive mechanical ventilation (OR = 2.172 CI = 1.242-3.799 $p = 0.007$) and cumulative duration of exposure to umbilical vein catheter (OR = 1.344 CI = 1.08-1.672 $p = 0.008$).

Conclusions: The overall incidence for the study period of NEC Stage ≥ II a was 7.5%. Exposure to antenatal steroids, duration of mechanical ventilation, and duration of umbilical vein catheterization were three independent modifiable risk factors for NEC Stage II a-Stage III b.

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Necrotizing enterocolitis; modifiable risk factors; preterm; very low birth weight; extremely low birth weight

Introduction

Necrotizing Enterocolitis (NEC) is a gastrointestinal emergency, most cases (90%) are reported in infants who are born before 37 weeks' gestation [1]. It affects 10% to 15% of very low birth weight infants (VLBW) globally and 5% to 22% of extremely low birth weight infants (VLBW) [2,3]. The incidence is inversely related to the gestational age (GA) and a five-fold increase is seen in ELBW infants compared to VLBW [4]. The overall global mortality from NEC is 30% and the mortality is more than 50% for surgical NEC [2]. Data from South Africa report a mortality rate of 48% to 50% amongst infants who underwent surgery [5,6]. This diagnosis results in high costs of care, prolonged hospitalization [7], long-term neurological (49%) and gastrointestinal complications (39%) complications [8,9].

Advances in the field of neonatology have resulted in the overall improvement in the survival rates of preterm infants in both developed and developing countries [10]. This population continues to grow and the highest preterm birthrate in the world occurs in Sub Saharan Africa and Southern Asia [11]. Locally Wagura et al. reported a high preterm birthrate of 18.3% at Kenya national referral hospital [12]. Whilst NEC causes significant morbidity and mortality, reliable data from our population is lacking.

NEC is characterized by inflammation and necrosis of the intestines of variable length and thickness with intestinal peroration in advanced disease, the diagnosis is made based on Modified Bell's criteria [13,14]. Given the acuity of NEC onset, noninvasive predictors would facilitate early diagnosis with an aim of

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reducing morbidity and mortality [15,16]. Agreeably, the pathophysiology of NEC which is multifactorial has not been fully understood. Studies have reported multiple risk factors with variable association, these include prematurity, low birth weight, use of bovine formula [16], low Apgar scores [17], patent ductus arteriosus [18], blood transfusion [19], sepsis [20], empiric antibiotics [21], umbilical catheterization [22] and chorioamnionitis [23] and mechanical ventilation [24,25] amongst others. Varying association occurs across different studies perhaps due to confounding, geographical location, differences in population and other environmental factors. NEC data is lacking from our Sub-Saharan population. We therefore sought to identify independent modifiable risk factors that are associated with NEC and to also determine the incidence of NEC in our population. Identifying these risk factors may inform the development of preventive measures and neonatal health policies in our Sub-Saharan context.

Methods and materials

Study population

This retrospective cohort study was conducted at Aga Khan university Hospital Nairobi (AKUHN), Kenya. Live preterm infants born and admitted at the AKUHN NICU between August 2009 and August 2019 were identified. The inclusion criteria were as follows: (1) Preterm infants born at $\leq$ 32 weeks' gestation, (2) Birthweight of $<$1500 grams, (3) Infants who had NEC Stage II a and greater based on Modified Bell's criteria [13,14] within 30 days of NICU admission. The exclusion criteria: (1) Infants who were missing charts or missing more than 10% of information on variables of interest, (2) Infants who died within 72 h of admission to NICU, (3) Infants with major congenital malformations like complex heart disease, (4) Out-born infants, (5) Infants diagnosed with focal intestinal perforation or spontaneous intestinal perforation.

Data collection procedures and definition of variables

Patients' medical charts were retrieved from the hospital Medical Records Department. Data were abstracted from the medical records using a structured data collection form. The following defined variables' were extracted from the patients charts: the dependent variable (primary outcome variable) NEC, defined as Stage II a and greater according to Modified Bell's criteria, mechanical ventilation, defined as duration of mechanical ventilation prior to the diagnosis of NEC, empiric antibiotics, defined as duration of empiric antibiotics prior to the diagnosis of NEC, duration Umbilical Vein catheterization (UVC), defined as duration UVC was insitu prior to the diagnosis of NEC, Duration of Umbilical Artery catheterization (UAC) defined as duration of UAC exposure prior to the diagnosis of NEC, first day of enteral feed initiation, volume of initial enteral feed (ml/kg/day), volume of enteral feeds advancement (ml/kg/day), gestation age and birth weight. Exposure to antenatal steroids, prolonged premature rupture of membranes, umbilical vein catheterization, umbilical artery catheterization, packed red blood cells transfusion (PRBC) Transfusion, NEC within 48 h of PRBC transfusion, proven sepsis defined as culture positive sepsis prior to diagnosis of NEC, type of enteral feed, and exposure to proton pump inhibitors like omeprazole.

Data analysis

The data were analyzed using SPSS version 23.0. Continuous variables were assessed for normality using the Shapiro-Wilk test. Means and standard deviation were determined for the normally distributed variables, whereas median and interquartile range were used for non-normally distributed variables. Analysis for categorical variables was done using percentages and frequencies. Comparisons between groups and computation of P-values was done using the student t-test and Mann-Whitney U test for the continuous variables while for categorical data the Chi-square test or Fischer's exact test was used. The association between variables of interest and NEC was determined using multivariate logistic regression analysis, factors that demonstrated an alpha level of $<$0.05 were considered significant.

Ethical considerations

We sought ethical approval and waiver of consent from the Aga Khan University research and ethics committee.

Results

In this study, 261 charts were reviewed, and only 200 charts met the inclusion criteria. Sixty-one ($n = 61$) clinical charts were excluded from the study due to: incomplete data or missing clinical chart volumes ($n = 17$), multiple congenital anomalies (complex cardiac anomalies, musculoskeletal anomalies, gastrointestinal anomalies $n = 14$), spontaneous/focal bowel

Table 1. Maternal and infants demographics and clinical characteristics.

Variables	$n = 200$(%)
NEC n (%)	
NEC Stage II a, II b, III a, III b	15 (7.5%)
No NEC	185 (92.5%)
Mean Birth Weight *g* SD	1102 +-265.5
Median Gestation *Age weeks + days* IQR	29 (23-32)
Gender n (%)	
Male	95 (47.5%)
Female	105 (52.5%)
Race n (%)	
Black	176 (88%)
Other	24 (12%)
Pregnancy n (%)	
Singleton	157 (78.5%)
Multiple	43 (21.5%)
Antenatal Steroids n (%)	
Yes	163 (81.5%)
No	37 (18.5%)
PPROM n (%)	
Yes	68 (34%)
No	132 (66%)
Mode of Delivery n (%)	
Cesarean Section	131 (65.5%)
Vaginal Delivery	69 (34.5%)
Median Apgar scores, *minute*, IQR	
1 min	7 (1-8)
5 min	8 (2-10)
Median duration of Mechanical Ventilation *days* IQR	3 (1-9)
Median duration of Empiric antibiotics exposure *days*, IQR	4 (1-17)
Umbilical vein catheterization exposure n (%)	
Yes	132 (66%)
No	68 (34%)
Median duration of UVC exposure *days*, IQR	7 (1-23)
Umbilical Artery Catheterization exposure n (%)	
Yes	74 (37%)
No	126 (63%)
Median duration of UAC exposure *days*, IQR	6 (1-23)
Type of enteral feeds exposure n (%)	
Breast Milk	151 (84%)
Formula	25 (15)
Mixed Feed	2 (1%)
Median day of enteral feed initiation *day*, IQR	3 (1-7)
Mean Volume of initial enteral feed, mls/kg/d ± SD	13.03 mls/kg/day (SD ±12.7)
Mean Rate of feed advancement, mls/kg/d ± SD	21.9 mls/kg/d (± SD 14.1)
PRBCs Transfusion n (%)	
Yes	112 (56%)
No	88 (44%)
NEC within 48 hrs of PRBCs Transfusion n (%)	
Yes	6 (5.4%)
No	106 (94.6%)
Proven Sepsis	
Yes	53 (26.5%)
No	147(73.5%)
Proton Pump Inhibitors(omeprazole)	
Yes	52 (26.5%)
No	148 (73.5%)

perforation ($n = 3$), out-born preterm infants ($n = 6$), and demise within 72 h of admission ($n = 21$). The demographic and clinical characteristics are shown in Table 1. The median gestational age of the study cohort was 29 weeks (IQR: 23-32), a large proportion (76%) of infants were born between 28-32 weeks' gestation and 24% were born at <28 weeks' gestation. The mean birthweight was 1102.6 grams (SD ±265.5). Fifteen preterm infants (7.5%) developed the primary outcome of interest: NEC Stage ≥2a. The median postnatal age at diagnosis was 11 days (IQR: 2-27). Mothers who had premature rupture of membranes were 34% ($n = 68$) and 81.5% ($n = 163$) had antenatal steroids.

Maternal and infant exposure variables in relation to the development of NEC are shown in Table 2. NEC diagnosis was highest in the group that did not receive antenatal steroids at 21.6% compared to the No NEC group 4.3% ($p = 0.001$). Preterm infants with NEC had a longer duration of exposure to mechanical ventilation [5 IQR (3-9). $p = 0.001$), and a longer duration of empiric antibiotics exposure [6 IQR (3-11), $p = 0.002$]. Breast milk (92.1%) was predominantly the

Table 2. Maternal and Infants characteristics in relation to NEC.

Variables	NEC $n = 15$	No NEC $n = 185$	P Value
Mean Birth Weight *g* SD	886.3 (±216.0 g)	1120.4 (±262.0) g	**0.001**
Gestation Age	27^{+2} (±2.3)	29.0 (±2.3)	**0.005**
Gender n (%)			
Male	8 (53.3%)	87 (47%)	0.638
Female	7 (46.7%)	98 (53%)	
Race n (%)			
Black	13 (86.7%)	163 (88.1%)	0.764
Other	2 (13.3%)	22 (11.9%)	
Pregnancy n (%)			
Singleton	11 (73.3%)	146 (78.9%)	0.613
Multiple	4 (26.7%)	39 (21.1%)	
Antenatal Steroids n (%)			
Yes	7 (46.6%)	156 (84.3%)	**0.001**
No	8 (53.4%)	28 (15.7%)	
PPROM n (%)			
Yes	7 (46.7%)	61 (33%)	0.282
No	8 (53.3%)	124 (67%)	
Mode of Delivery n (%)			
Cesarean Section	8 (53.3%)	123 (66.5%)	0.303
Vaginal Delivery	7 (46.7%)	62 (33.5%)	
Median Apgar scores, *minute*, IQR			
1 min	7 (3-8)	7 (3-9)	0.556
5 min	7 (4-9)	9 (3-10)	0.039
Median duration of Mechanical Ventilation *days* IQR	5 (3-9)	3 (1-6)	**0.001**
Median duration of Empiric antibiotics exposure *days*, IQR	6 (3-11)	5 (2-17)	**0.002**
Umbilical vein catheterization exposure n (%)			
Yes	15 (100%)	118 (63.6%)	0.404
No	0 (0%)	67 (36.2%)	
Median duration of UVC exposure *days*, IQR	9 (6-23)	6 (1-22)	**0.001**
Umbilical Artery Catheterization exposure n (%)			
Yes	12 (80%)	62 (33.5%)	0.12
No	3 (20%)	123 (66.5%)	
Median duration of UAC exposure *days*, IQR	8 (3-15)	5 (1-23)	**0.034**
Type of enteral feeds exposure n (%)			
Breast Milk	12 (7.9%)	139 (92.1%)	0.917
Formula	2 (8.3%)	23 (97.7%)	
Mixed Feed	0 (0.0%)	2 (100%)	
Median day of enteral feed initiation *day*, IQR	4 (2-13)	3 (2-7)	0.142
Mean Volume of initial enteral feed, mls/kg/d ± SD	10 (3.1-102)	10 (3.4-102.8)	0.536
Mean Rate of feed advancement, mls/kg/d ± SD	19.7 (4.2-78.5)	19.5 (5-80)	0.244
PRBCs Transfusion n (%)			
Yes	13 (86.7%)	99 (53.5%)	**0.013**
No	2 (13.3%)	86 (46.5%)	
NEC within 48 hrs of PRBCs Transfusion n (%)			
Yes	6 (100%)	0 (0%)	0.644
No	9 (8.5%)	97 (91.5%)	
Proven Sepsis			
Yes	10 (66.7%)	43 (23.2%)	**0.001**
No	5 (33.3%)	138 (76.8%)	
Proton Pump Inhibitors(omeprazole)			
Yes	4 (26.7%)	49 (26.5%)	0.988
No	11 (73.3%)	136 (73.5%)	

enteral feed of choice compared to preterm formula. Packed red blood cells transfusion exposure was high in the NEC group at 11.6% and 3.3% in the No NEC group ($p = 0.013$). Infants who had blood cultures taken prior to the diagnosis of NEC had a higher rate of proven bacterial or fungal infection in the NEC group (18.9%) in comparison to 3.4% in the No NEC group ($p = 0.001$).

Table 3 shows both univariate and multivariate logistic regression analysis. Three independent modifiable risk factors were identified; exposure to antenatal steroids with OR = 0.056 (0.003-0.964) $p = 0.047$, cumulative duration of mechanical ventilation OR = 2.172(1.242-3.799) $p = 0.007$ and duration of umbilical vein catheterization OR= 1.344(1.08-1.672). Diagnosis of sepsis prior to the development of NEC demonstrated reduced odds of developing NEC, OR = 0.327(CI: 0.038-2.805) however this was not statistically significant after controlling for all the other variables in the model ($p = 0.308$).

Discussion

In this retrospective cohort study, the incidence of NEC was 7.5%. Multivariable logistic regression analysis demonstrated three independent risk factors for NEC:

Table 3. Bivariate/simple and multivariate logistic regression analysis.

Variables	Unadjusted odds ratios OR CI 95%	P Value	Multivariate Analysis Adjusted OR 95%	P Value
Median birth Weight ± SD, g	0.996(0.994-0.999)	**0.002**	0.998(0.993-1.004)	0.555
Mean Gestation Age SD, week + days	0.750(0.607-0.928)	**0.008**	1.173(0.657-2.094)	0.589
Antenatal Steroids n (%)	0.302(0.100-0.910)	**0.033**	0.056(0.003-0.964)	**0.047**
Median Duration of mechanical Vent, IQR	2.066(1.527-2.795)	**0.001**	2.172(1.242-3.799)	**0.007**
Median duration of empiric antibiotics	1.392(1.137-1.704)	**0.001**	1.174(0.847-1.629)	0.335
Median duration of UVC exposure	1.292(1.119-1.447)	**0.001**	1.344(1.080-1.672)	**0.008**
Umbilical Artery Catheterization n (%)	0.188(0.57-0.614)	**0.006**	0.221(0.026-1.915)	0.71
Median duration of UAC exposure	1.089(0.940-1.261)	0.257		
Median first day of feeds initiation	1.52(1.004-2.299)	**0.048**	0.931(0.477-1.815)	0.833
Median rate of feed advancement	1.022(0.988-1.056	0.203		
Packed red blood cells transfusion n (%)	5.646(1.239-25.726)	**0.025**	1.949(0.0096-39.632)	0.644
Proven Sepsis n (%)	0.172(0.058-0.514)	**0.002**	0.327(0.038-2.805)	0.308

exposure to antenatal steroids, cumulative duration of mechanical ventilation and cumulative duration (line days) of umbilical vein catheterization. This association was maintained after adjusting for reported risk factors like gestation age, birth weight, proven sepsis, empiric antibiotics exposure and blood transfusion. The incidence of NEC was reduced in the group that had exposure to antenatal steroids. This finding was in line with Wong et al. multicenter Retrospective cohort study that demonstrated a reduction in the incidence of NEC in premature infants after maternal antenatal steroids use [26]. Travers et al. also demonstrated the benefit of steroids as he reported a reduction in the risk of developing NEC in preterm infants exposed to maternal steroids from 23 to 34 gestation weeks [27]. Roberts et al. reported a reduction in the incidence of NEC in preterm infants of 26-34 $^{+6}$weeks gestation [28]. Contrary to our results, Guthrie et al. reported an increase in the odds of developing NEC in preterm infants born at 23-34 weeks' gestation who were exposed to antenatal steroids [25]. Other studies have likewise reported no benefits of antenatal corticosteroid in decreasing the incidence of NEC in preterm infants [29,30]. Various experimental models have demonstrated that antenatal steroids reduce the incidence of NEC; partially due to increased maturation of the intestinal mucosal barrier as evidenced by decreased bacteria translocation, reduced uptake of macromolecules, lower intestinal permeability, and increased activity of digestive enzymes [31–33].

Our study also showed an increase in the incidence of NEC with increasing duration on mechanical ventilation. This finding is supported by prior studies by Gane et al. and Guthrie et al. [24,25]. In agreement with our observations, Zvizdic Z et al. also reported that infants who developed NEC had longer days on mechanical ventilation prior to NEC onset [34]. Another study also noted an increase in the incidence of NEC in mechanically VLBW infants [35]. It has been hypothesized that indwelling endotracheal tube may compromise the infants' mucosal barriers increasing the risk of infection [36,37]. Other studies note the inability to maintain normal gaseous exchange due to respiratory distress syndrome, this results in hypoxia which causes intestinal mucosa injury and hence increased risk of NEC [1]. Contrary to our findings Su et al. in a meta-analysis reported no significant association between NEC and mechanical ventilation for preterm born at 22 to 23, whilst our study showed protective effect, this study included extremely premature infants in whom the risk of surgical NEC is highest according to literature [38].

We also observed that an increase in the duration of exposure to UVC was associated with increased odds of NEC. Our finding was in line with Atef Alshafei et al. study which reported an increased risk of surgical NEC in UVC cohort compared to peripherally inserted central catheter (PICC) for preterm born between 23–30 weeks [39]. The increased risk of NEC with UVC exposure was also demonstrated by Sulemanji et al. in preterm infants $<$ 1500 [22]. He hypothesized that the malposition of the umbilical vein catheter into the hepatic portal vein or ductus venosus was associated with NEC due to increased portal venous pressure inducing mesenteric venous ischemia [22]. Contrary to our findings an RCT done by Butler O Hara M et al. reported no difference in the risk of NEC in a group of preterm infants who had early removal of umbilical catheter (within 10 days) versus the group that had late removal at 28 days [40].

The cumulative incidence of NEC for the study period of 10 years was 7.5%. Lee J.Y et al. reported a similar incidence of NEC stage $\geq$ IIa of 7.3% over a period of 11 years at a tertiary care hospital in South Korea for preterm infants born at $<$32 weeks' gestation weighing $\leq$1500 grams [41]. In a retrospective cohort study that included 70 tertiary care units in Japan, the incidence of NEC was 1.6% in infants $<$1500 grams. Globally Japan has the lowest incidence of NEC possibly due to the early and aggressive initiation of enteral feeds with unpasteurized human donor milk. Breast milk is known to be protective [42],

as it contains immunomodulatory factors like lactoferrin [43], maternal Soluble IgA [44] and epidermal growth factors [45]. Early enteral feeding is encouraged and does not increase the risk of NEC as reported in literature [46]. Other tertiary care units globally continue to experience a high incidence of NEC as reported by Battersby C et al.: incidence of NEC in Poland is 9%, this may be explained by the extension of intensive neonatal care services to extreme preterm infants who are at the limit of viability [3]. In our study, the incidence of NEC was 12.5% amongst ELBW preterm infants and 4.9% amongst VLBW preterm infants. This was slightly higher than the incidence of 10.9% and 4.7% reported by Moro et al. amongst ELBW preterm infants and VLBW preterm infants respectively [47]. However our findings are similar to the reported global incidence of NEC [3,4,47,48]

This was a single-center study, and therefore, the generalizability of these findings may be limited to private tertiary care units in our region. The reduced number of infants diagnosed with NEC could have influenced the statistical power to detect significant effects of exposure variables such as sepsis, empiric antibiotics, PRBCs transfusion, among others. These Variables have been previously reported in literature to have statistically significant association with NEC [3].

In conclusion, the incidence of NEC Stage IIa and greater was 7.5%. Antenatal steroids, duration of umbilical vein catheterization and duration of mechanical ventilation were the identified modifiable risk factors for NEC. Although this study does not prove causality, we recommend including these identified risk factors in the development of NEC predictor models to enable early diagnosis and management of NEC. Further studies could explore the validity and reliability of the NEC predictor models as primary prevention is a critical and fundamental intervention.

Disclosure statement

The authors declare no conflict of interest.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.

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