Original Article

A Review of Necrotising Enterocolitis in Very Low Birth Weight Babies in a Tertiary Hospital in Johannesburg

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Abstract

Introduction: Necrotising enterocolitis (NEC) is the most common gastrointestinal complication in pre-mature infants. There are risk factors and modifying factors that have been identified and studied over the years, but not many studies have been conducted in middle-income countries. **Aims and Objectives:** This study aimed to describe the maternal, obstetric and neonatal characteristics in very low birth weight (VLBW) babies with NEC in a tertiary neonatal unit in South Africa. The survival to hospital discharge in VLBW babies with NEC was also determined. **Materials and Methods:** This study was a retrospective, cross-sectional, observational study of VLBW babies admitted to a tertiary neonatal unit between January 2013 and December 2017. The population comprised babies <1500 g and <37 weeks gestation. Maternal and neonatal risk factors of NEC were compared in infants with and without NEC. **Results:** In this study, 173 out of 2111 (8%) babies were diagnosed with NEC. HIV exposure, late-onset sepsis, respiratory support after initial resuscitation, administration of surfactant and blood transfusion were associated with NEC. Surgery was performed in 48/173 (27.7%) of babies with NEC. The mortality rate in babies with NEC was 49.1%. Death in babies with NEC was associated with surgery for NEC ($P = 0.01$), mechanical ventilation ($P < 0.001$) and late-onset sepsis ($P = 0.018$). **Conclusion:** Risk factors for NEC in our population are similar to other countries, with some variations such as HIV. Even though some prevention measures have been implemented, the mortality rate remains high.

Keywords: Necrotizing enterocolitis, very low birth weight infants, sub-Saharan Africa

Introduction

Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency in very low birth weight (VLBW) babies.[1] NEC is described as inflammation and necrosis of the gastrointestinal system and commonly occurs in pre-term babies.[2] The clinical presentation of NEC is broad and non-specific, and it is classified into three stages according to the modified Bell's classification.[3] NEC is one of the leading causes of neonatal death in intensive care units.[1] In a recent study, the rate of NEC was 5.5% in 2010 and accounted for 10% of the total neonatal deaths.[4]

Over the years, there has been a marked improvement in health care, better access to antenatal services for pregnant mothers and improved obstetric and neonatal care. There are also measures such as antenatal steroid administration which improve the outcome of pre-term labour.[5] These improvements have resulted in more pre-mature babies surviving the neonatal period; however, these babies are then at risk of developing complications such as NEC which are associated with pre-maturity.[6] The pathophysiology of NEC is unclear but is multifactorial. NEC is an inflammatory disorder of the gastrointestinal system, which occurs as a result of intrinsic and extrinsic factors.[7] Several risk factors for NEC have been identified; these include pre-maturity, VLBW, asphyxia, anaemia, blood transfusion, sepsis and patent ductus arteriosus (PDA).[7] Babies who are asphyxiated or require resuscitation are also at risk of developing NEC.[8]

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There is an association between anaemia and NEC, but it is not clear whether anaemia or blood transfusion causes NEC; usually, the babies who require transfusion are very ill. In a retrospective study, it was shown that 27% of patients were transfused within 48 h of being diagnosed with NEC.[9] There are other factors such as a family history of allergic disease, post-natal asphyxia secondary to meconium aspiration and intrahepatic cholestasis in pregnancy, leading to pre-maturity which has been linked to NEC, but they still require further study.[10] Human breast milk, as opposed to infant formula, has been shown to have a protective effect on the newborn gut.[11] There are variations in the introduction and daily increments of feeds in different centres. What is important is the early initiation of feeds to optimise nutrition and improve the babies' outcomes.[12] The gut microbiome is emerging as an important factor in human disease, and alteration of the gut microbiome is beneficial in some intestinal diseases. Concerning NEC, research has shown an association between gut dysbiosis and NEC; this would, therefore, be worth researching whether alteration of the gut microbiome would have an impact on NEC.[13] There are also factors, such as probiotics, that are beneficial in preventing NEC; however, further investigation is still required.[14] Even though a lot of research has been done on NEC and potentially modifiable factors have been identified, there has not been a significant decrease in morbidity and mortality. Even with early aggressive treatment, NEC still progresses and has significant morbidity with chronic gastrointestinal complications and poor neurodevelopment.

South Africa is a middle-income country with limited resources, and this affects the outcome of VLBW babies; efforts should, therefore, be made to identify conditions that add to the burden on the health system. In previous studies on causes of neonatal death, NEC is listed as one of the contributors and a modifiable cause of neonatal death.[15]

There is a paucity of studies in Sub-Saharan Africa to review the risk factors for NEC in VLBW. The current study aims to show the risk factors for NEC in a tertiary hospital in Johannesburg, South Africa. The results of the study may contribute to preventing or improving the outcome of NEC in South Africa.

Materials and Methods

Study design, sample and setting

This study was a retrospective, observational study. The population was VLBW babies (<1 500 g birth weight) admitted to the CMJAH neonatal unit from 1st January 2013 to 31st December 2017. VLBW babies who were admitted within 48 h of birth were included in the study. Those VLBW babies who were <500 g birth weight, those with missing data and those who died within 72 h of life were excluded.

CMJAH is a tertiary hospital in Johannesburg; the neonatal unit consists of four areas, admission, paediatric intensive care unit (shared with paediatrics) and high- and low-care ward. House staff (intern and registrar) and neonatal consultants managed the patients. Paediatric surgery was available at CMJAH during the study period.

Data

The database from CMJAH was used; this is an ongoing data collection system in the neonatal unit for the purpose of clinical audit and quality control. Data were captured onto a data collection sheet on the discharge of the patient. Details captured were maternal, obstetric and neonatal data, which were then entered into the data collection programme. There were various points of verifying the data once it had been entered. The data were managed using Research Electronic Data Capture (REDCap™), hosted by the University of the Witwatersrand.[16] Surgical management of the babies with NEC was determined by the attending staff at the time, and reasons for different interventions (pencil drain vs. laparotomy) were not recorded in the database.

Ethical considerations

Permission to conduct the study was obtained from the CEO of CMJAH, and a clearance certificate (M180704) was received from the Human Research Ethics Committee (Medical) of the University of Witwatersrand. The protocol was registered on the National Health Research Database.

Data analysis

The data were transferred to an Excel spreadsheet for data cleaning. Categorical variables were described using frequencies and percentages. Continuous variables were described using mean and standard deviation if normally distributed, skewed data was described using median and range. The study sample was divided into two groups, babies with NEC and those without and the two groups were compared. Categorical variables were compared using Chi-square analysis, and continuous variables were compared using unpaired *t*-tests or non-parametric methods, as appropriate. Only valid cases were included in the analysis of each variable (i.e., missing data were excluded). A *P* value of 0.05 or less was considered statistically significant. Those variables with a *P* value of 0.1 were entered into a binary logistic regression model with NEC as the outcome variable, to determine adjusted odds ratios for the variables associated with NEC.

Population

There were 2575 babies eligible for the study, of whom 468 were excluded according to the exclusion criteria. The final sample consisted of 2111 babies, 173 (8.2%) of whom were diagnosed with NEC [Figure 1 shows the flow of population selection].

Results

In this study, 916 (47.8%) mothers were between 20 and 29 years of age. Other maternal characteristics are listed in Table 1. Concerning gestational age, the majority of the babies were <30 weeks old, and the majority weighed more than 1 kg at birth. Of the 2111 babies, 1133 (53.8%) were female. Most babies 1769 (83.8%) were born at CMJAH.

Table 1: Maternal, obstetric and neonatal characteristics by necrotising enterocolitis (n=2111)

Characteristics	NEC		Total (n=2111)	P
	No (n=1938), n (%)	Yes (n=173), n (%)		
Maternal age (years)				
<20	171 (9.7)	12 (7.7)	183 (9.5)	0.217
20-29	851 (48.3)	65 (41.9)	916 (47.8)	
30-39	669 (37.9)	72 (46.5)	741 (38.6)	
40+	72 (4.1)	6 (3.9)	78 (4.1)	
Maternal race				
Black	1868 (96.8)	167 (96.5)	2035 (96.8)	0.826
Others	61 (3.2)	6 (3.5)	67 (3.2)	
Antenatal steroids				
No	890 (50.1)	78 (51.0)	968 (50.2)	0.837
Yes	886 (49.9)	75 (49.0)	961 (49.8)	
Maternal HIV				
Negative	1308 (69.0)	98 (59.4)	1406 (68.2)	0.011**
Positive	589 (31.0)	67 (40.6)	656 (31.8)	
Birth weight (kg)				
<1	491 (25.3)	49 (28.3)	540 (25.6)	0.388
At least 1	1447 (74.7)	124 (71.7)	1571 (74.4)	
Gestational age (weeks)				
<30	1366 (70.9)	137 (79.2)	1503 (71.6)	0.021**
At least 30	560 (29.1)	36 (20.8)	596 (28.4)	
Gender				
Male	892 (46.1)	80 (46.5)	972 (46.2)	0.927
Female	1041 (53.9)	92 (53.5)	1133 (53.8)	
HIV prophylaxis given				
No	24 (4.1)	1 (1.5)	25 (3.9)	0.302
Yes	555 (95.9)	64 (98.5)	619 (96.1)	
Mode of delivery				
NVD	803 (42.0)	81 (47.9)	884 (42.5)	0.133
Caesarean section	1110 (58.0)	88 (52.1)	1198 (57.5)	
Initial resuscitation on delivery				
No	486 (26.5)	43 (27.2)	529 (26.6)	0.845
Yes	1348 (73.5)	115 (72.8)	1463 (73.4)	
Face mask ventilation				
No	1078 (58.8)	86 (53.4)	1164 (58.3)	0.186
Yes	756 (41.2)	75 (46.6)	831 (41.7)	
Nasal CPAP				
No	522 (28.2)	35 (20.7)	557 (27.5)	0.038**
Yes	1331 (71.8)	134 (79.3)	1465 (72.5)	
Gastrointestinal perforation				
No	1923 (99.7)	155 (92.3)	2078 (99.1)	<0.001**
Yes	5 (0.3)	13 (7.7)	18 (0.9)	
Conventional ventilation				
No	1468 (80.3)	65 (38.2)	1533 (76.7)	<0.001**
Yes	360 (19.7)	105 (61.8)	465 (23.3)	
High-frequency ventilation				
No	1782 (98.9)	160 (96.4)	1942 (98.7)	0.007**
Yes	20 (1.1)	6 (3.6)	26 (1.3)	
Surfactant therapy at any time				
No	572 (29.7)	36 (21.6)	608 (29.0)	0.027**
Yes	1356 (70.3)	131 (78.4)	1487 (71.0)	

Contd...

Table 1: Contd.....

Characteristics	NEC		Total (n=2111)	P
	No (n=1938), n (%)	Yes (n=173), n (%)		
Bacterial sepsis on/before day 3				
No	1840 (95.6)	162 (96.4)	2002 (95.7)	0.626
Yes	84 (4.4)	6 (3.6)	90 (4.3)	
Sepsis after day 3				
No	1348 (69.7)	65 (38.2)	1413 (67.2)	<0.001**
Yes	586 (30.3)	105 (61.8)	691 (32.8)	
Fungal sepsis				
No	495 (86.5)	81 (77.1)	576 (85.1)	0.013**
Yes	77 (13.5)	24 (22.9)	101 (14.9)	
Indomethacin for any reason				
No	1919 (99.7)	172 (99.4)	2091 (99.7)	0.453
Yes	5 (0.3)	1 (0.6)	6 (0.3)	
Blood transfusion				
No	1140 (59.7)	59 (34.5)	1199 (57.6)	<0.001**
Yes	771 (40.3)	112 (65.5)	883 (42.4)	
Exchange transfusion				
No	1273 (99.1)	115 (100.0)	1388 (99.2)	0.319
Yes	11 (0.9)	0	11 (0.8)	
Feeds on discharge				
Formula milk	738 (48.6)	39 (48.1)	777 (48.5)	0.947
Breast milk	695 (45.7)	38 (46.9)	733 (45.8)	
Mixed	87 (5.7)	4 (4.9)	91 (5.7)	
Birth PCR result				
Negative	368 (95.3)	41 (93.2)	409 (95.1)	0.678
Positive	9 (2.3)	1 (2.3)	10 (2.3)	
Outstanding	9 (2.3)	2 (4.5)	11 (2.6)	

**Statistical significance @ $P \leq 0.05$. NEC: Necrotising enterocolitis, PCR: Polymerase chain reaction, NVD: Normal vaginal delivery, CPAP: Continuous positive airways pressure

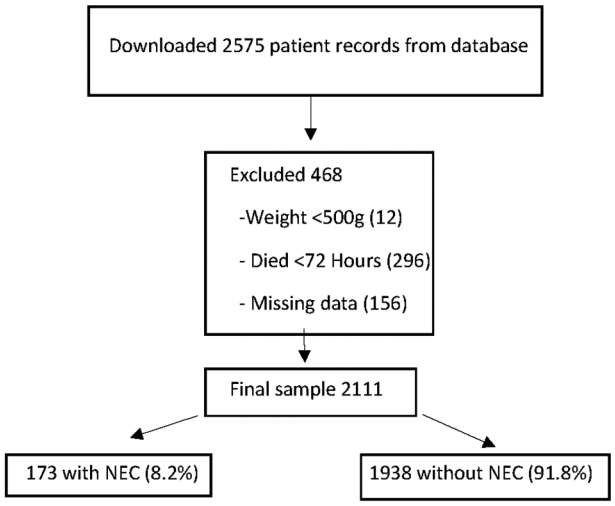


Figure 1: Derivation of sample for ewview of Necrotising enterocolitis (NEC) in very low birth weight infants

There was no significant relationship between maternal race, maternal age or antenatal steroid use and NEC. However, a significant association was found between maternal HIV and NEC (P = 0.011). Further, a significant relationship was found to exist between NEC and some baby-related factors, including gestational age (P = 0.021), nasal continuous positive airway pressure (NCPAP) (P = 0.038), previous NEC surgery (P < 0.001), gastrointestinal perforation (P < 0.001), conventional ventilation (P < 0.001), high-frequency ventilation (P = 0.007), surfactant therapy (P = 0.027), blood transfusion (P < 0.001) and sepsis after 3 days (P < 0.001).

Logistic regression was performed to explain the association between significant variables. Maternal HIV status was significantly associated with NEC (P = 0.012). Babies with HIV-positive mothers were 1.52 times more likely to have NEC than babies with HIV-negative mothers. Conventional ventilation, late-onset sepsis and blood transfusions had a strong association with NEC (P < 0.001). The odds of NEC were 6.59 times more in babies on conventional ventilation than in babies who are not on conventional ventilation. Furthermore, babies who developed sepsis 3 days or more after birth or had blood transfusions were 3.72 and 2.81 times more likely to have NEC than those who did not, respectively. Further, babies who had surfactant therapy or continuous positive airway pressure were 1.53 and 1.50 times more likely to have NEC than those who had not (P = 0.028 and 0.039, respectively). High-frequency oscillatory ventilator and fungal sepsis also had a significant association with NEC (P = 0.011 and 0.014, respectively). Table 2 summarises the findings of the logistic regression.

Table 2: Results of fitting logistic regression models for factors associated with necrotising enterocolitis

Variable	OR (95% CI)	*P*
Maternal age		
<20	Reference	
20-29	1.09 (0.58-2.06)	0.794
30 to 39	1.53 (0.81-2.89)	0.186
40+	1.19 (0.43-3.29)	0.741
Maternal HIV positive		
No	Reference	
Yes	1.52 (1.10-2.10)	0.012**
Birth weight (kg)		
<1	Reference	
At least 1	0.86 (0.61-1.21)	0.388
Resuscitation		
No	Reference	
Yes	0.96 (0.67-1.39)	0.845
Face mask ventilation		
No	Reference	
Yes	1.24 (0.90-1.72)	0.186
CPAP		
No	Reference	
Yes	1.50 (1.02-2.21)	0.039
Conventional ventilation		
No	Reference	
Yes	6.59 (4.74-9.16)	<0.001**
High-frequency ventilation		
No	Reference	
Yes	3.34 (1.32-8.44)	0.011**
Surfactant therapy at anytime		
No	Reference	
Yes	1.53 (1.05-2.25)	0.028**
Bacterial sepsis		
No	Reference	
Yes	0.81 (0.35-1.89)	0.627
Fungal sepsis		
No	Reference	
Yes	1.90 (1.14-3.19)	0.014**
Sepsis after day 3		
No	Reference	
Yes	3.72 (2.69-5.14)	<0.001**
Blood transfusion		
No	Reference	
Yes	2.81 (2.02-3.90)	<0.001**

**Statistical significance @. OR: Odds ratio, CI: Confidence interval, CPAP: Continuous positive airways pressure

Of the infants (173) who were diagnosed with NEC, the majority 125 (72.3%) did not need surgery, only 48 (27.7%) required surgery and, of those, more infants required laparotomy than those who received a pencil drain (38 vs. 10). The mortality rate of infants with NEC was 49.1% (85/173).

A significant relationship was found to exist between NEC mortality and NEC surgery ($P = 0.010$), conventional ventilation ($P < 0.001$) and late-onset sepsis ($P = 0.018$). Table 3 shows the relationship between maternal, obstetric and neonatal characteristics with mortality due to NEC in the group of neonates with NEC.

Discussion

The risks of NEC in CMJAH are similar to those in other studies. According to a study done by Bisquera *et al*., infants who developed NEC stayed in the hospital longer than infants who did not.[17] Maternal age and race were not significant; antenatal steroids were previously found to be protective in NEC,[5] but, in this study, the contrary was found. Maternal HIV was found not to increase the risk of NEC in a study done previously at CMJAH.[18] According to this study, the rate of NEC is higher in infants whose mothers were HIV positive ($P = 0.011$); this is surprising as the PMTCT programmes have been improved over the past years and more mothers are receiving prophylaxis during the antenatal period. Concerning gender studies, it has been shown previously that black males were at higher risk of NEC;[19] however, in this study, females (53.8%) were at higher risk, but gender was not a significant risk for NEC ($P = 0.93$).

Hypoxia and ischaemia have been implicated in the pathogenesis of NEC;[8] in this study, resuscitation at birth was not shown to be significant ($P = 0.084$), but respiratory support after resuscitation was significant ($P = 0.014$). All forms of ventilator support NCPAP, conventional ventilation and high-frequency ventilation during hospital admission appeared to increase the risk of NEC in this study. In addition, the administration of surfactants has also been shown to increase the risk of NEC. The immaturity of the gut mucosa in VLBW babies predisposes them to bacterial infections and sepsis[8] in the current study, and sepsis was shown to be significantly related to the development of NEC. However, the day of life when the diagnosis of NEC was confirmed was not recorded; therefore, it cannot be said whether sepsis was present before or at the time of NEC. The association between blood transfusions and NEC is unclear as the question is whether the blood transfusion or the anaemia increases the risk of NEC.[9] In the current study, blood transfusion was associated with NEC, but the time between transfusion and NEC was not recorded and, therefore, could not be analysed. Congenital cardiac lesions and the administration of ibuprofen and PDA ligation were not significant.

Feeding practices vary in different hospitals. The initiation of feeds and the volume of increments differ between hospitals in South Africa. Previous studies have shown that breast milk is protective to NEC,[11] but there are still questions about the comparison between fortified breast milk, formula and breast milk only.[11] In the current study, there were babies with missing feeding data as a result of deaths and being transferred out of the unit. Of those who remained, more babies were formula-fed, followed by breastfed, fortified breast milk and then those who were mixed-fed. The number of infants with NEC who were breastfed and given fortified

Table 3: Maternal, obstetric and neonatal characteristics, by necrotising enterocolitis mortality

Characteristics	Infants with NEC		Total (n=173), n (%)	P
	Survived (n=88), n (%)	Died (n=85), n (%)		
Maternal age (years)				
<20	9 (11.1)	3 (4.1)	12 (7.7)	0.141
20-29	29 (35.8)	36 (48.6)	65 (41.9)	
30-39	41 (50.6)	31 (41.9)	72 (46.5)	
40+	2 (2.5)	4 (5.4)	6 (3.9)	
Maternal race				
Black	85 (96.6)	82 (96.5)	167 (96.5)	1.000
Others	3 (3.4)	3 (3.5)	6 (3.5)	
Antenatal steroids				
No	39 (48.1)	39 (54.2)	78 (51.0)	0.518
Yes	42 (51.9)	33 (45.8)	75 (49.0)	
Maternal HIV				
Negative	55 (64.7)	43 (53.8)	98 (59.4)	0.158
Positive	30 (35.3)	37 (46.3)	67 (40.6)	
Birth weight (kg)				
<1	22 (25.0)	27 (31.8)	49 (28.3)	0.399
At least 1	66 (75.0)	58 (68.2)	124 (71.7)	
Gestational age (weeks)				
<30	72 (81.8)	65 (76.5)	137 (79.2)	0.455
At least 30	16 (18.2)	20 (23.5)	36 (20.8)	
Gender				
Male	40 (46.0)	40 (47.1)	80 (46.5)	1.000
Female	47 (54.0)	45 (52.9)	92 (53.5)	
HIV prophylaxis given				
No	0	1 (2.8)	1 (1.5)	1.000
Yes	29 (100.0)	35 (97.2)	64 (98.5)	
Mode of delivery				
NVD	37 (43.0)	44 (53.0)	81 (47.9)	0.220
Caesarean section	49 (57.0)	39 (47.0)	88 (52.1)	
Initial resuscitation on delivery				
No	19 (23.2)	24 (31.6)	43 (27.2)	0.284
Yes	63 (76.8)	52 (68.4)	115 (72.8)	
Face mask ventilation				
No	45 (55.6)	41 (51.2)	86 (53.4)	0.637
Yes	36 (44.4)	39 (48.8)	75 (46.6)	
Nasal CPAP				
No	19 (21.8)	16 (19.5)	35 (20.7)	0.850
Yes	68 (78.2)	66 (80.5)	134 (79.3)	
NEC surgery				
No	68 (80.0)	49 (61.3)	117 (70.9)	0.010**
Yes				
Type of NEC surgery				
Laparotomy	14 (82.4)	24 (77.4)	38 (79.2)	1.000
Pencil drain	3 (17.6)	2 (22.6)	10 (20.8)	
Gastrointestinal perforation				
No	80 (93.0)	75 (91.5)	155 (92.3)	0.778
Yes	6 (7.0)	7 (8.5)	13 (7.7)	
Conventional ventilation				
No	46 (52.9)	19 (22.9)	65 (38.2)	<0.001**
Yes	41 (47.1)	64 (77.1)	105 (61.8)	

Contd...

Table 3: Contd...

Characteristics	Infants with NEC		Total (n=173), n (%)	P
	Survived (n=88), n (%)	Died (n=85), n (%)		
High-frequency ventilation				
No	84 (98.8)	76 (93.8)	160 (96.4)	0.111
Yes	1 (1.2)	5 (6.2)	6 (3.6)	
Surfactant therapy at any time				
No	19 (22.9)	17 (20.2)	36 (21.6)	0.710
Yes	64 (77.1)	67 (79.8)	131 (78.4)	
Bacterial sepsis on/before day 3				
No	82 (97.6)	80 (95.2)	162 (96.4)	0.682
Yes	2 (2.4)	4 (4.8)	6 (3.6)	
Sepsis after day 3				
No	41 (47.1)	24 (28.9)	65 (38.2)	0.018**
Yes	46 (52.9)	59 (71.1)	105 (61.8)	
Fungal sepsis				
No	33 (71.7)	48 (81.4)	81 (77.1)	0.254
Yes	13 (28.3)	11 (18.6)	24 (22.9)	
Indomethacin for any reason				
No	88 (100.0)	84 (98.8)	172 (99.4)	0.491
Yes	0	1 (1.2)	1 (1.2)	
Blood transfusion				
No	26 (29.9)	33 (39.3)	59 (34.5)	0.203
Yes	61 (70.1)	51 (60.7)	112 (65.5)	
Birth PCR result				
Negative	22 (100.0)	19 (95.0)	41 (97.6)	0.476
Positive	0	1 (5.0)	1 (2.4)	

**Statistical significance @$P \leq 0.05$. NEC: Necrotising enterocolitis, PCR: Polymerase chain reaction, NVD: Normal vaginal delivery, CPAP: Continuous positive airways pressure

breast milk and formula-fed were similar, which raises the question of whether fortifying breast milk decreases its protective effect and increases the risk of NEC. With the implementation of PMTCT guidelines, it was expected that more mothers would be breastfeeding, but according to our results, that is not the case. Probiotics are not used in the unit; thus, their correlation with NEC could not be assessed. In a study comparing morbidity and mortality in CMJAH in VLBW infants, the survival rate was 73.4%, and NEC was one of the modifiable factors concerning improved outcomes.[15] In the current study, the survival rate was 82.3% overall. The survival rate of pre-mature babies has improved over the years and this increases the complications of pre-maturity such as NEC. Improved survival may therefore account for the reported increase in NEC from 5% to 8.2% in our neonatal unit.[4]

Similarly, in an international article reviewing the incidence of NEC in high-income countries, studies ranged from 1987 to 2014, it was also noted that there was an increase of NEC from 2% to 7% in babies <32 weeks gestation and an increase from 5% to 22% in babies <1000 g.[20]

In the current study, babies with NEC had a longer duration of hospital stay; some required surgery and had an increased risk of mortality.

Limitations

This was a retrospective analysis of an existing database, so some information was not available for analysis. In addition, we could only determine association, not causation.

Conclusion

The risk factors associated with NEC in the present study are similar to those reported elsewhere; unlike other reports, we found that maternal HIV was associated with NEC. The strong association between NEC and sepsis is confirmed in our results and highlights the need for adequate infection prevention and control. The findings of this retrospective study should be used to develop prospective interventional research to decrease the burden of NEC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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