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Risk factors and survival for late onset sepsis in very-low-birth-weight infants in a public hospital, Johannesburg, South Africa

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Abstract: *Background:* Despite advances in neonatal care that have improved survival of very-low-birth-weight (VLBW) infants, neonatal sepsis (NNS) remains a common cause of morbidity and mortality.
Objectives: To review risk factors and short-term outcomes of late onset sepsis (LOS) in VLBW infants at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa.
Methods: This was a secondary analysis of an existing database of VLBW infants admitted at CMJAH from 1st January 2014 to 31st December 2018. Characteristics of infants with LOS were compared with those infants without LOS to elicit factors associated with LOS.
Results: A total of 1974 VLBW infants were enrolled for the study and 698/1974 (35.4%) had LOS. Factors associated with LOS after multivariate logistic regression were patent ductus arteriosus (PDA) (p <0.038), blood transfusion (p <0.001), necrotizing enterocolitis (NEC) (p <0.025), surgery for NEC (p <0.013) and surgery for any other reason (p <0.043). The mortality rate was increased in infants with LOS compared to those without LOS, 31.23% versus 16.38% (p < 0.001). There were 901 episodes of sepsis in 698 infants with LOS. The majority of the sepsis episodes were caused by Gram-positive organisms 450/901 (49.9%). Gram-negative and fungal organisms were responsible for 353/901 (39.2%) and 98/901 (10.9%) of the LOS respectively.
Conclusion: A third of VLBW infants in the study developed LOS. Sepsis caused by Gram negative organisms is associated with increased mortality. Active surveillance of LOS and adopting available alternatives to invasive procedures that are medically proven could greatly help to reduce the incidence of LOS in VLBW infants.

Keywords: Very Low Birth weight, Late Onset Sepsis, Infants, Risk factors, Survival.

Introduction

Neonatal sepsis (NNS) is a common cause of morbidity and mortality worldwide, especially in low-and-middle-income countries (LMICs)[1]. In South Africa, (SA), NNS accounts for 11.6% of all neonatal deaths making it the third leading cause of neonatal deaths[2]. In studies done in Ethiopia, Cameroon and Central Vietnam, NNS accounted for 31.0%, 32.0% and 37.8% of neonatal deaths respectively[3,4,5] .

NNS is classified as early-onset sepsis (EOS) or late onset sepsis (LOS)[6,7,8]. LOS – which is more common than early onset sepsis (EOS) – presents after 72 hours of life[6,7]. In a South African study done at a tertiary hospital in 2012, the incidence of NNS was 10.3 per 100 admissions, of which LOS accounted for 83.7% of cases of NNS[9]. LOS is from organisms acquired in the hospital or the community (for infants delivered at home or discharged home) [1, 8]. LOS often occurs while the infants are in the neonatal unit and the infection may be transmitted by direct contact with hospital personnel, parents, visitors – most commonly through hand contamination or contaminated equipment[1].

The group mostly affected by LOS are VLBW infants[1,8]. A number of factors predispose VLBW infants to infection, such as: immunological immaturity, multiple invasive procedures, prolonged intravenous (IV) access, mechanical ventilation and hospital stay, use of total parenteral nutrition or other invasive procedures[1,8]. Organisms implicated in LOS are fungi and bacteria – the latter being more common. In a study done at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

retrospectively for 2012, bacterial infection was the cause of LOS in 89.8% of cases and fungi were responsible for 10.1% of cases of LOS[9]. Organisms causing NNS change over time, dependent on the environmental [9,10] pathogens[9]. This is evident in two studies done at CMJAH at different periods of time, ten years apart Motara et al. reported Gram-positive organisms being the predominant cause of LOS and years later Lebea at al. reported Gram negative organisms as the commonest cause [9,10] . These studies used the same definition.

LOS and its outcomes increase hospital costs which becomes a serious burden in LMICS. Risk factors for NNS are clearly documented in the literature but there are few studies done, especially in Africa, that look into risk factors of LOS in VLBW infants. It is important to know which factors play a major role in causing LOS so that infection prevention and control measures can be implemented or revised to reduce the incidence of these factors. Therefore, the aim of this research is to describe the risk factors associated with LOS in VLBW infants in Johannesburg, SA.

Materials and methods

This was a secondary analysis of an existing database performed at CMJAH neonatal unit. CMJAH is a central referral hospital in Johannesburg, SA. The study population included all VLBW infants admitted within 48 hours of life from the 1st January 2014 to 31st December 2018. Infants with birth weight less than 500g, those who died within the first 72 hours of life and neonates with relevant missing variables were excluded.
LOS was defined as positive blood culture of organisms deemed to be significant after 72 hours of life (6,7) Organisms cultured but considered to be contaminants were *Bacillus Spp*, *Corynebacterium Spp* and *Streptococcus viridans*. Patients with the above-mentioned organisms cultured were included in the group without LOS. Although there is lack of consensus on the role of *Coagulase Negative Staphylococci* (CoNS) in NNS, these were considered significant pathogens in this study [11,12].

The following definitions were used in the study:

- Necrotising enterocolitis was defined as NEC II or III according to the Bell's staging criteria [13]
- Resuscitation at birth was defined as the need for ventilation with bag-valve-mask or T-piece resuscitator or chest compressions.
- Chronic lung disease (CLD) was defined as persistent oxygen requirements up to or beyond 28 days of chronological age[1].
- Retinopathy of prematurity (ROP) was defined as ROP stage 3 or 4 according to the International Committee for the Classification of ROP[14].
- Invasive respiratory support included conventional mechanical ventilation and high frequency oscillator ventilation.
- Non-invasive respiratory support included modes of ventilation that do not require the patient to be intubated, such as nasal continuous positive airway pressure (NCPAP) and high flow nasal cannula oxygen.
- A workup to exclude sepsis was done in infants who had clinical symptoms and signs of infection and post-surgery. Empiric antibiotics were initiated when sepsis was suspected, and antibiotics were targeted when culture results were available.
- Other surgery included all surgery excluding NEC surgery.

Database

The neonatal records were retrieved from the REDCap (Research Electronic Data Capture) database, hosted by the University of Witwatersrand[15].The information was captured at discharge for all infants admitted to the neonatal unit and for the purpose of quality control was verified at several stages of collection. Permission was granted by the host of the REDCap database at the neonatal unit of CMJAH to access the data.

Data Analysis

Data was entered into an MS Excel (version 2013) spreadsheet for data cleaning and imported to IBM SPSS (version 25) for analysis. Continuous variables were described using mean and standard deviation for the variables with a normal distribution. Median and interquartile ranges were used for variables with non-normally distributed data. Categorical variables were described using frequencies and percentages. The study population was divided into two groups, one with LOS and the other with no LOS; associated factors and outcomes were compared between the two groups. Continuous variables were compared using the Student's t-test or Mann-Whitney U analysis. Categorical variables were compared using the Chi-squared analysis. Only valid cases were analysed for each variable (i.e., missing values were excluded). A p-value of less than 0.05 was considered significant. A binary logistic regression was done considering LOS as the outcome variable, to determine adjusted odd ratios for factors associated with LOS. Those factors with a p value <0.05 on univariate analysis were included in the binary logistic regression.

Ethics statement

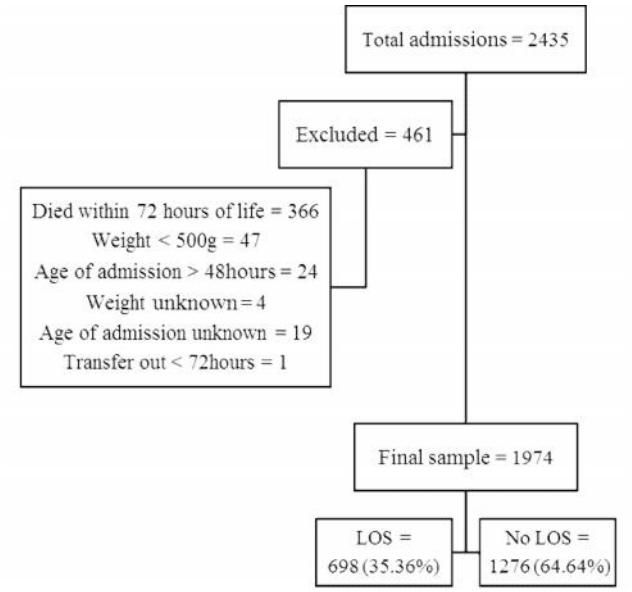
The research protocol was approved by the Human Research Ethics Committee of the University of Witwatersrand. Ethics clearance certificate number M190862.

Results

A total of 2435 VLBW (<1500g) infants were admitted during the study period, 1 974 infants fulfilled the inclusion criteria (see Figure 1); 35.36% (698/1974) devel-

oped late onset sepsis.

Fig 1: Study participants included in the review of risk factors and survival for late onset sepsis in very low birth weight infants admitted to Charlotte Maxeke Johannesburg Academic Hospital, 1st January 2014 – 31st December 2018



Patients' characteristics are summarized in Table 1. Most patients were inborn (n = 1664/1973, 84.33%) and delivered via caesarean section (n = 1129/1955, 57.75%). Most patients were female (n = 1067/1967, 54.25%). The median maternal age was 28.0 years (IQR 24.0 – 33.0 years). The median gravidity was 2 (IQR 2 – 3). There was an antenatal care attendance rate of 78.72% (n = 1554/1974). Antenatal steroids were received in 53.24 % of cases (n = 1051/1974). There were 30.50 % (602/1974) of mothers who tested positive for HIV.

Table 1: Characteristics of very-low-birth-weight infants studied

Clinical characteristics	VLBWI (1 974) (Median, IQR)
Gestational age, weeks	29 (28-31)
Birth weight, grams	1150 (960-1320)
Duration of non-invasive ventilation, days	2 (1-5)
Duration of invasive ventilation, days	4 (2-8)
Length of hospital stay, days	31 (19 -49)

VLBWI = very-low-birth-weight infants, IQR = inter-quartile range

Resuscitation in the delivery room was required in 863/1974 (43.72%) of the patients. Respiratory distress syndrome (RDS) was diagnosed in 1748/1974 (88.55%) of the patients, 1392/1974 (70.52%) required NCPAP at some time during their admission. There were 619/1974 (31.36%) infants with CLD, of which 394/619 (63.65%) of the patients received postnatal steroids. NEC occurred in 175/1974 (8.87%) and PDA was diagnosed in 213/1974 (10.79%) of the infants. Of the infants screened for ROP, 108/670 (16.12%) developed ROP. The overall survival of the VLBW infants was 78.42 % (1548/1974).

The total sample was divided into two groups, those with LOS and those who had no LOS. The variables were compared between the groups. The significant variables relating to the development of LOS are summarized in Table 2.

There were no significant differences between the groups with regards to maternal age, parity or gravidity, place of birth, use and duration of high flow oxygen, undergoing exchange transfusion and major birth defect. No significant association was observed between LOS and ROP.

There were 901 episodes of sepsis in 698 infants who had LOS. The majority of the sepsis episodes were caused by Gram-positive organisms including CoNS 450/901(49.9%). Gram-negative and fungal organisms were responsible for 353/901 (39.2%) and 98/901 (10.9%) of LOS respectively. Some patients 203/698 (29.08%) had more than one organism (from different classes) as cause of LOS.

There was an increased mortality in the group with LOS as compared to the group without LOS (31.23% vs. 16.38%, $p < 0.001$). An increased mortality was observed in patients who had LOS caused by Gram-negative organisms as compared to Gram-positive organisms (49.20% vs. 19.40%, $p < 0.001$). There were no significant differences in survival between those with LOS caused by bacterial or fungal organisms.

Multivariable logistic regression analysis of factors significantly associated with outcome (LOS vs. No LOS) in very low birth weight infants

After an adjustment by multivariate logistic regression, the variables that remained significantly associated with LOS are NEC (P <0.025), NEC surgery (P <0.013), other surgery (P <0.043), PDA (P <0.038), blood transfusion (P <0.001) which are displayed in table 3, while the rest of the variables as previously indicated in Table 2 were found not to be associated with increased risk of LOS.

Table 2(a): Demographic Factors

Variable	LOS	No LOS	P-value	OR	95% CI
Patient characteristics					
Birth weight, grams, (median, IQR)	1060 (900- 1220)	1207 (1020 – 1360)	<0.001	0.99	0.99-1.00
Gestational age, weeks, (median, IQR)	27 (27- 30)	28 (28-31)	<0.001	0.86	0.82-0.89
Mode of delivery, n/N (%): NVD C/S	319/692 (46.10) 373/692 (53.90)	510/1263 (40.38) 753/1263 (59.62)	0.014	0.78	0.65-0.95
5-minute Apgar score, (median, IQR)	8 (7- 9)	9 (7 -9)	<0.001	0.91	0.87-0.96
Resuscitation at birth, n/N (%)	345/698 (49.43)	518/1276 (40.60)	<0.001	1.43	1.18-1.72
Table 2 (b): Respiratory conditions, interventions, and complications					
RDS, n/N (%)	653/698 (93.55)	1095/1276 (85.82)	<0.001	2.39	1.7-3.37
Surfactant administered, n/N (%)	569/698 (81.52)	830/1276 (65.05)	<0.001	2.37	1.89-2.96
Nasal septal necrosis, n/N (%)	28 /698(4.01)	11 /1276(0.86)	<0.001	4.80	2.38-9.71
Pneumothorax, n/N (%)	12/698 (1.72)	9/1276 (0.71)	0.036	2.46	1.03-5.87
NCPAP, n/N (%)	593/698 (84.96)	799 /1276(62.62)	<0.001	3.37	2.66-4.27
CMV, n/N (%)	278/698 (39.83)	173/1276(13.56)	<0.001	3.37	2.66-4.27
Duration of non-invasive respiratory support, days (median, IQR)	4 (1- 8)	2 (1 -3)	<0.001	1.07	1.05 -1.10
Duration of invasive respiratory support, days (median, IQR)	6 (3- 12)	4 (2- 7)	<0.001	1.06	1.03 -1.09
Oxygen on Day 28, n/N (%)	358/ 698(51.30)	261/1276 (20.45)	<0.001	4.00	3.34-5.0
Steroids for CLD, n/N (%)	213/698 (30.52)	181/1276(14.18)	<0.001	2.65	2.1-3.32
Table 2 (c): Hospital Course					
Spontaneous intestinal Perforation, n/N (%)	10/698 (1,43)	6/1276 (0,47)	0.023	3.07	1.11-8.5
NEC 2 – 3, n/N (%)	118 /698(16.91)	57/1276 (4.47)	<0.001	4.35	3.1-6.0
NEC surgery, n/N (%)	30/698(4.30)	14/1276 (1.10)	<0.001	4.35	3.1-6.0
Other surgery, n/N (%)	32/698 (4.58)	7/1276 (0.59)	<0.01	8.71	3.82-19.8
NNJ requiring PTT, n/N (%)	490/698 (70.20)	785/1276(61.52)	<0.001	1.47	1.20-1.79
PDA, n/N (%)	145/698 (20.77)	68/1276 (5.33)	<0.001	4.6	3.43-6.32
Blood transfusion, n/N (%)	526/698 (75.36)	370 /1276(28.99)	<0.001	7.48	6.06-9.24
KMC, n/N (%)	219/698(31.38)	603/1276(47.26)	<0.001	0.51	0.42-0.62
Length of stay, days, (median, IQR)	46 (26 -65)	27 (17- 40)	<0.001	1.03	1.02-1.04

Foot note: NVD Normal vaginal delivery; IQR interquartile range; C/S – Caesarean Section
RDS – respiratory distress syndrome; NCPAP – nasal continuous airways pressure
CMV – conventional mechanical ventilation; CLD chronic lung disease
NEC – necrotizing enterocolitis
NNJ – neonatal jaundice
PTT- phototherapy
PDA – patent ductus arteriosus
CLD – Chronic Lung disease
KMC – Kangaroo Mother Care

Table 3: Factors significantly associated with outcome (LOS vs. No LOS) in very low birth weight infants after multivariate logistic regression

Variable	OR	95% CI	P-value
NEC 2 – 3	3.20	2.20- 4.66	<0.001
Nasal CPAP	2.02	1.55- 2.65	<0.001
Other surgery	5.73	2.32- 14.15	<0.001
PDA	2.13	1.53- 2.99	<0.001
Blood transfusion	5.31	4.24-6.64	<0.001

Discussion

This study showed that there are multiple risk factors other than immunological immaturity that predispose VLBW infants to LOS, the majority being the complications of prematurity and its interventions. The rate of mortality was higher in the LOS group compared to the group without LOS, similar to other studies in VLBW infants [8,16]. LOS caused by Gram-negative organisms caused higher mortality. A study done by Ballot *et al.* in the same unit 4-years prior to our study found the same

result, however that study included term infants and EOS (17).

In our study, the incidence of LOS in VLBW was 35.4%, which is higher than the 25.0% reported in the multicenter study by Stoll *et al* [16]. Even with the center-to-center variability reported by Stoll *et al*. of 11.5 – 32.4%, our study showed a higher incidence. The reason for these results might be because the current study was conducted 11 years later when there have been advances in the care for VLBW infants, where more survive to later develop LOS. Both studies included CoNS as a significant cause of LOS: the study by Stoll *et al.* had higher numbers of CoNS sepsis (55%) compared to our study (44%). Other studies have found a lower incidence of LOS than our study: Hornik *et al*. found an incidence of 12.2%, Escalante *et al*. found an incidence of 22.2% [8, 18]. Hornik *et al.* performed their study eight years prior to our study and only looked at patients admitted in NICU where space and care is optimal. Escalante *et al.* performed theirs in 2001 to 2013 and included centers in the private sector in South America.

The majority of LOS was caused by Gram-positive organisms, followed by Gram-negative organisms. Some patients had more than one episode of LOS, caused by organisms from different classes. In studies done at the same institution eight years apart but in all infants including VLBW infants there was a shift in predominance from Gram-positive organisms in 2002-2003 to Gram-negative organisms in 2012 [9, 10]. Our study's findings concur with studies done by Stoll *et al.* and Hornik *et al.* which stated that Gram-positive organisms were responsible for the majority of LOS in VLBW infants [8, 16].

There appears to be an increasing trend of fungal septicemia. In the studies done in the same institution, the incidence of fungal LOS was 7.8% in 2002-2003 and 10.1% in 2012 [9, 10]. In our study the incidence is yet higher at 10.9%. This could be because this study was only focusing on LOS in VLBW infants (unlike the other studies which looked at all infants) or it could represent an increased prevalence of fungal infection. Our study still revealed an increased incidence of fungal LOS as compared to studies done in VLBW infants in other countries which again supports an increase in the prevalence of fungal sepsis over the years [8, 16]. The overuse of broad-spectrum antibiotics has increased antimicrobial resistance and rate of fungal sepsis [1, 19].

After adjustment with multivariable logistic regression, our study showed that LOS was not directly proportional to smaller birth weight or gestational age at birth. The complications of prematurity which are directly proportional to lower birth weight and GA could have been the cause of the association prior the adjustment as the median for birth weight and gestational age was lower in the LOS group. Previous studies have found an association between lower GA and LOS [16,18]. One would have expected lower gestational age and birth weight to be directly proportional to LOS as these patients tend to stay longer in hospital and may be predisposed to sepsis while awaiting weight gain and resolution of complications of prematurity.

Our study revealed that there was no association between place of birth, antenatal care (ANC), antenatal steroids (ANS), sex and multiple gestation, which agrees with the study by Stoll *et al* [16]. However, Escalante *et al.* reported antenatal care and steroids to be protective against LOS (18). This supports the finding that perinatal steroids decrease the incidence of neonatal complications (RDS, NEC, etc.) which would predispose patients to sepsis. Perhaps, our study showed no protection against LOS by ANC and ANS because the ANC attendance rate is poor (78.7%) as well as ANS coverage rate (46.8%).

Mode of delivery did not show significant association with sepsis in our study, a finding in contrast with that found by Escalante *et al* [18]. while Stoll *et al.* found no association between NVD and LOS [16]. Antenatal antibiotics were associated with LOS in other studies [8, 18]. Although we did not look at maternal antibiotic use, maternal chorioamnionitis (in which most of the mothers received antenatal antibiotics) was found to have no association, which concurs with study by Stoll *et al.* which reported that there was no association between LOS and antenatal antibiotics.

Some complications of prematurity are associated with LOS and further prolonged hospital stay in preterm babies. There was a significant association of LOS with NEC and PDA, findings were also supported by studies done in VLBW infants [8,16,18]. PDA results in increased pulmonary blood flow and interstitial oedema which predispose to LOS. Meanwhile, sepsis is implicated in the pathogenesis of NEC.

Alterations in the skin and/or mucous membrane barriers predispose to sepsis, which is evident in our study, where increased number of patients who had undergone surgery had LOS. Improvements can be made to wound care in these patients. With regards to the type of NEC surgery, laparotomy with ileo/colostomy was associated with increased risk of LOS as compared to laparotomy with primary closure in our study.

An interesting observation in this study which was not found in the literature was the association of blood transfusion with LOS. This association could be as a result of LOS causing anemia in addition to other causes of anemia which include prematurity that requires transfusion. This observation also puts into question the sterility followed during blood transfusion. There was no significant association in patients that had exchange transfusion for severe NNJ.

Surprisingly, kangaroo mother care (KMC) does not seem to be protective against LOS in our study. This is in contrast with a meta-analysis review by Boundy *et al.* that reported KMC to have decreased the risk of neonatal sepsis [20]. The type of KMC done most commonly at CMJAH is continuous KMC where the mother stays with the baby in the KMC cubicle. Typically, this separates them from other sick infants and the staff caring for them. KMC also favors rapid weight gain and consequently babies get discharged early before developing

episodes of sepsis. One would have expected KMC, particularly the type done at CMJAH, to decrease the risk of LOS.

After adjusting for complications of prematurity, LOS was not associated with prolonged hospital stay in our study. LOS is commonly associated with prolonged hospital stay in other studies[8, 16, 18, 21]. This is a challenge that hospitals are faced with as complications of prematurity contribute to long hospital stay. Preventing complications of prematurity will reduce the duration of hospital stay and costs. Patients should be discharged as soon as they are well and discharge weights need to be revised.

Study Limitations

This was a retrospective review of an existing database. As such, some important factors stated to be risk factors of LOS in the literature such as central lines, total parenteral nutrition and their duration could not be analyzed. Furthermore, we did not follow up the infants post discharge to assess the long-term complications of LOS such as neurological impairment.

Conclusion

A third of VLBW infants in the study developed LOS during their stay in neonatal unit while awaiting weight gain or resolution and treatment of complications of prematurity. Certain factors have been noted to be associated with LOS, such as PDA, NEC, blood transfusion and surgery. The majority of LOS were caused by Gram -positive organisms, however Gram-negative organisms were associated with increased mortality. The prevalence of fungal sepsis is increasing. LOS increases neonatal morbidity and mortality. Interventions required to manage the sepsis and other conditions associated with prematurity, pose a financial constraint to the health sector.

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Author Contributions

KO, DE, and RS were involved in the conception and design of the study, the acquisition, analysis, and interpretation of data and approved the final version to be published and are accountable for all aspects of the work. OA drafted the manuscript. KO, OA, DE, RS was involved in the interpretation of data, critically revised the manuscript for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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