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Risk factors for sepsis in very low birth weight neonates

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Abstract: Neonatal sepsis is a leading cause of neonatal morbidity and mortality, particularly in the developing countries. Delay in identification and treatment of neonatal sepsis are among the main contributors to the high mortality. The present study was conducted to find out the risk factors, in-hospital outcomes of sepsis and treatment plan, to help neonatologists facing challenges in managing neonatal infection. The study was conducted from January 2017 to December 2018 in a level III neonatal intensive care unit (NICU) of Northern India. The retrospective study was done to evaluate the risk factors for sepsis in VLBW neonates and to compare the outcomes of VLBW infants who developed culture positive sepsis versus those with suspected sepsis. Past medical records of VLBW infants were retrieved from hospital information system. Data was analysed by SPSS version 18 (SPSS Inc., Chicago, IL, USA). Quantitative variable with normal distribution were presented as mean ± standard deviation (SD) while qualitative variables were expressed as percentages. p-value ≤0.05 was considered statistically significant. A total of 265 VLBW neonates were admitted during the study period out of which 59 (22.3%) developed culture positive sepsis. Among these 13(22.0%) were early onset sepsis (EOS) and rest was late onset sepsis (LOS). On univariate analysis, birth weight <1000 g, extramural birth, need for surfactant administration, mechanical ventilation, presence of central venous catheter, parenteral nutrition, delay in initiation and time to reach 100 mL/kg and 180 mL/kg enetral feeds, thrombocytopenia, severe thrombocytopenia and positive CRP were significantly associated with culture positive sepsis. Independent factors associated with VLBW sepsis included extramural birth, mechanical ventilation and presence of central venous catheter were associated with culture positive sepsis. The risk factors for LOS in VLBW infants identified in our study were extramural birth, mechanical ventilation and presence of

central venous catheter. Although prematurity and low-birth weight are the most established factors for sepsis in VLBW neonates, no significant co-relation was found in the present study.

Keywords: Sepsis, Septic Shock, Neonates, VLBW, EOS, LOS

Introduction:

Infections contribute to one-fifth of neonatal deaths in India [1] and burden of neonatal sepsis in our country is as high as 16 per 1000 live births.[2] Nearly two-third of the neonates developing sepsis are low birth weight and half of them are preterm in our country.[3] Infections are the major cause of morbidity and mortality in preterm very low birth weight (VLBW) neonates. Rate of blood culture positive in early and late onset sepsis among VLBW neonates is less than 2% and 25% respectively, as reported by National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and is associated with substantial morbidity and mortality.[4] Despite high burden of sepsis, only a few prospective studies discuss the epidemiology of neonatal sepsis in India.

Various maternal and neonatal risk factors for sepsis among VLBW neonates include poor prenatal care, shorter gestation, prolonged rupture of membranes, chorioamnionitis, urinary tract infections, resuscitation at birth, including emergent endotracheal intubation or insertion of an umbilical vascular catheter, prolonged intravenous access and parenteral nutrition.[4,5] Predictors of sepsis related mortality in VLBW neonates include gestational age ≤28 weeks, birth weight ≤1000 g, five-minute Apgar ≤7, gram-negative sepsis, mechanical ventilation, and intravascular catheter insertion.[6] A recent meta-analysis describes male gender, extramural birth, need for artificial ventilation, prematurity and premature rupture of membranes (PROM) as risk factors for neonatal sepsis in India.[7] In order to reduce the disease burden and contribute towards better understanding of sepsis in VLBW neonates, the present study was conducted to find out the risk factors, in-hospital outcomes of sepsis and treatment plan, to help neonatologists facing challenges in managing neonatal infections.

Subjects and Methods:

The present retrospective study was conducted from January 2017 to December 2018 in a level III neonatal intensive care unit (NICU) of Northern India after obtaining approval from the Institute Ethics Committee. The objectives of our study were evaluation of risk factors for sepsis in VLBW neonates and to compare the outcomes of VLBW infants who developed culture positive sepsis versus those with suspected sepsis. The study

population consisted of all the VLBW neonates managed during the study period. Although a VLBW neonate developed more than one episode of sepsis, we included details of only first episode in a single neonate due to limitations of retrospective data retrieval. Neonates with major congenital malformations and those requiring extensive resuscitation (chest compression or medications) at birth were excluded. Past medical records of VLBW infants were retrieved from hospital information system. Potential risk factors for neonatal sepsis were compared between those with and without culture positive sepsis.

All the VLBW neonates were shifted to the NICU for management of prematurity and its related problems. Neonates delivered to mothers with intrapartum fever, chorioamnionitis, and PROM were evaluated for sepsis and started on empirical antibiotics as per unit protocol. If the neonate remained asymptomatic and sepsis screen and blood culture were negative, antibiotics were stopped after 48 hours. If the neonate remained symptomatic and/ or sepsis screen was positive and blood culture was negative, antibiotics were continued for 5-7 days. Blood culture positive sepsis was treated for a total duration of 14 days with sensitive antibiotics.

Admitted VLBW neonates were evaluated for sepsis if two or more signs and symptoms were present: fever (>38°C) or temperature instability (frequent incubator adjustment) or hypothermia (<36.5°C), unexplained metabolic acidosis (base excess≤ 10Eq/l), tachycardia (>200/min) or new/more frequent bradycardia (<80/min), new hyperglycemia (>140mg/dl), capillary refill time > 2sec, new or more frequent apnea (>20sec), skin appearing off color, increased oxygen requirement by 10% or need for intubation, unstable condition or apathy. Blood culture and sepsis screen negative episodes of deterioration were treated with antibiotics for 5-7 days, blood culture positive - gram positive and negative sepsis and meningitis were treated with antibiotics for 10 days, 14 days and 21 days respectively. Sepsis episode was classified as early onset and late onset depending on blood culture performed at ≤ 72 hours of age and >72 hours of age, respectively.

Clinical, demographic and laboratory data were collected from the medical records. Maternal details noted were history of fever, antibiotic exposure, history suggestive of urinary tract infection, leaking per vaginum and other medical and obstetric disorders. Neonatal demographic data, clinical and laboratory details were also recorded.

Statistical Analysis: Data were analysed by SPSS version 18 (SPSS Inc., Chicago, IL, USA). Quantitative variable with normal distribution were presented as mean ± standard deviation (SD) while qualitative variables were expressed as percentages. The difference between the normally distributed means and percentages were

compared by student t test and Chi square test respectively. Non-parametric means were compared by Mann-Whitney U test. A p value ≤0.05 was considered statistically significant.

Results:

A total of 265 VLBW neonates were admitted during the study period of which 59 (22.3%) developed culture positive sepsis of which 13(22.0%) were early onset sepsis (EOS) and rest was late onset sepsis (LOS). One hundred fifty-seven (59.2%) neonates developed clinical deteriorations warranting evaluation for sepsis and initiation of antibiotics but blood and/or CSF culture remained sterile compatible with suspected sepsis. Forty percent of these deteriorations were early onset. Only 49 (18.4%) neonates did not develop any episode of sepsis.

Table 1 demonstrates the baseline characteristics of the study population. Mean gestation and birth weight of the neonates developing culture positive sepsis were significantly lower compared to suspect and no sepsis groups. Significantly higher proportions of neonates were extremely low birth weight and extramural in the culture positive sepsis groups. Table 2 describes the risk factors for culture positive sepsis. PROM was present in 7.6% and 31.7% of the cases of culture positive EOS and early onset suspected sepsis group respectively, however, the difference was not statistically significant. Other risk factors significantly associated with culture positive sepsis were surfactant administrations, need for invasive mechanical ventilation, presence of central venous catheters and need for parenteral nutrition. Time of initiation of enteral feeds and days to reach 100 mL/kg and full feeds of 180 mL/kg were significantly longer in culture positive sepsis group compared to suspect and no sepsis groups.

Clinical deteriorations suggestive of sepsis has been delineated in table 3. Clinical features significantly more common in culture positive neonates included oxygen desaturations (SpO2<80%), intraventricular hemorrhage, meningitis (biochemical and culture positive both), encephalopathy, abdominal distension, bleeding from gastrointestinal tract, necrotising enterocolitis, cholestasis, tachycardia, hypotension, shock, higher lactate levels, hyperglycemia and acute kidney injury. Investigations revealed significantly lower median platelet counts in the culture positive sepsis group while total counts and absolute neutrophil counts remained comparable between the groups. Significantly higher proportion of neonates in culture positive group had positive CRP, thrombocytopenia and severe thrombocytopenia. They were also significantly higher requirement

for treatment of shock in the form of saline bolus, inotropes and steroids and blood product transfusion (red blood cells and platelets) in the culture positive group.

Profile of organisms grown in culture positive sepsis group is shown in table 4. A total of 59 cultures obtained from 59 neonates grew 66 organisms. Seven cultures were positive for two organisms. Gram negative bacterial (GNB) infections contributed to two-third of the culture positive sepsis in our VLBW neonates with most common GNB being Acinetobacter. Shock and mortality were most common in GNB sepsis followed by fungal sepsis.

Discussion:

The present observational study evaluated the clinical features, risk factors, causative organisms and outcomes of VLBW neonates developing culture positive sepsis. A total of 59 (22.3%) neonates developed culture positive sepsis. Proportion of EOS and LOS included 13 (22.0%) and 46 (78.0%), respectively. Culture positive meningitis complicated 8.4% of the cases of culture positive sepsis. Common manifestations of sepsis included desaturations, abdominal distension, hyperglycemia, hypotension and shock. Independent risk factors of culture positive sepsis were found to be extramural birth, mechanical ventilation and presence of central venous catheter. Most common pathogen isolated from culture positive sepsis was Acinetobacter associated with case fatality rate of 84.6%. Culture positive sepsis carried a high mortality rate of 47.5% compared to 5.7% in suspected sepsis group. The mortality rate of infants with sepsis was 47.4% (27/57).

The present observational study evaluated the clinical features, risk factors, causative organisms and outcomes of VLBW neonates developing culture positive sepsis. A total of 59 (22.3%) neonates developed culture positive sepsis. Proportion of EOS and LOS included 13 (22.0%) and 46 (78.0%), respectively. These results are contradictory to what found in the previous studies in Africa, wherein they reported higher incidence of EOS than late onset of neonatal sepsis. [8,9,10]

Culture positive meningitis complicated 8.4% of the cases of culture positive sepsis. Common manifestations of sepsis included desaturations, abdominal distension, hyperglycaemia, hypotension and shock. Although PROM was present in 7.6% of culture positive EOS cases and 31.7% of cases in early onset suspected sepsis group, however, the difference was non-significant. Independent risk factors of culture positive sepsis were found to be extramural birth, mechanical ventilation and presence of central venous catheter. Similar results were reported

by Murthy et al, wherein they reported that need for artificial Ventilation, out-born admissions, gestational age <37 weeks and PROM significantly increase the chances of neonatal sepsis.

Prematurity and low birth weight are the well-known neonatal risk factors in developing countries [8-14]. Unfortunately, this study did not observe an association between preterm or low birth weight and risk of neonatal sepsis. Smaller sample size might influence the result along with health service-related factors and study design.

In present study, GNB infections contributed to two-third of the culture positive sepsis with Acinetobacter being the most common GNB in our VLBW neonates. GPB contributed 35.5% followed by infection due to fungal species in 15.3%. The results of this study are congruent with study by Hornik et al, in VLBW infants, wherein they found that, that GNB caused 58.2% of EOS, followed by 34.3% episodes by gram-positive and only 2.7% by Candida sp. [15]

This study did not observe significant co-relation between Apgar scores at 1st and 5th minute to be associated with incidence of neonatal sepsis. While the importance of Apgar score in minimizing the risk of neonatal sepsis in VLBW infants is not doubted, this study did not observe a statistically significant co-relation, which could be because of small number of neonates with culture positive sepsis in our study.

Conclusion:

The risk factors for LOS in VLBW infants identified in our study were extramural birth, mechanical ventilation and presence of central venous catheter. Although prematurity and low-birth weight are the most established factors for sepsis in VLBW neonates, no significant co-relation was found in the present study. This might be due to the fact that this retrospective study included patients from a single tertiary care centre and thus lack generalizability to the total population of neonatal sepsis in India. Therefore, improved research and robust system for reporting of risk factors in VLBW neonates admitted to hospitals is required to reduce the burden of neonatal sepsis in India.

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Conflicts of Interest

Authors declare that there is no conflict of interest regarding the publication of this paper.

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Tables:

Table 1. Baseline characteristics of the study population

Parameters	**Culture positive sepsis (n=59)**	**Suspected sepsis (n=157)**	**No sepsis (n=49)**	**P value**
Gestation, wk, Mean ± SD	29.3 ± 2.8	30.0 ± 2.7	30.7 ± 3.2	**0.03***
Gestation, wk, Median (IQR)	29 (28-32)	30 (28-32)	31 (29-33)	**0.02**[#]
Birth weight, g, Mean ± SD	1069.9 ± 242.8	1141.3 ± 233.3	1189.4 ± 243.8	**0.02***
ELBW <1000g, n (%)	22 (37.2)	35 (22.2)	9 (18.4)	**0.04**[$]
Males, n (%)	39 (66.1)	91 (58.0)	30 (61.2)	0.54[$]
Extramural, n (%)	27 (45.8)	38 (24.2)	4 (8.2)	**<0.001**[$]
Small for gestational age, n (%)	15 (25.4)	50 (31.8)	20 (40.8)	0.23[$]
Antenatal steroid exposure, n (%)	31 (52.5)	75 (47.7)	22 (44.8)	0.71[$]
Caesarean delivery, n (%)	44 (74.5)	118 (75.2)	40 (81.6)	0.61[$]
Need for PPV in the delivery room, n (%)	12 (20.3)	30 (19.1)	7 (14.3)	0.68[$]
Apgar score at 1 min, median (IQR)	7 (6-8)^	7 (6-8)[@]	8 (7-8)[£]	0.24[#]
Apgar score at 5 min, median (IQR)	8 (7-9) ^	8 (8-9) [α]	8 (7-9) [£]	0.73[#]
Day of life of deterioration in case of LOS, Median (IQR)	8.5 (5-14) ^^	5.5(4-14) [α α]	Not applicable	**0.002**[#]
EOS (≤72 hr), n (%)	13 (22.0)	63 (40.1)	Not applicable	**0.01**[$]
PROM, n (%)[ß]	1 (7.6)	20 (31.7)	5 (10.2) [ß]	0.05[$]

ELBW – Extremely low birth weight; EOS - Early onset sepsis; IQR – Interquartile range; LOS – Late onset sepsis; PPV – Positive pressure ventilation; PROM – Prolonged rupture of membrane; SD – Standard deviation ; ^ *- Data available for n= 37;* ^^ *- Data available for n= 46;* [@] *- Data available for n= 123;* [α] *- Data available for n= 122;* [α α] *- Data available for n=94;* [£] *- Data available for n= 45; ß – Percentage of PROM has been calculated for neonates developing EOS; Data available for n= 45;* - Student t test;* [#] *- Mann Whitney U test;* [$] *- Fisher exact test*

Table 2. Risk factors for sepsis in very low birth weight neonates

Risk factor for sepsis	**Culture positive sepsis (n=59)**	**Suspected sepsis (n=157)**	**No sepsis (n=49)**	**P value**
PROM, n (%)ß	1/13 (7.6)	20/63 (31.7)	5 (10.2)	0.05$
Exchange transfusion, n (%)	0	3 (1.9)	2 (4.0)	0.39$
Surfactant administration, n (%)	31 (52.5)	47 (29.9)	8 (16.3)	**<0.001$**
Presence of CVC, n (%)	34 (57.6)	37 (23.6)	5 (10.2)	**<0.001$**
Day of initiation of feeds, median (IQR)	2 (2-4) ^	2 (2-3) @	1 (1-2) α	**<0.001#**
Days to reach 100 mL/kg feeds, median (IQR)	9 (5-14) ^^	7 (5-11) @ @	5 (2-6) α	**<0.001#**
Days to reach 180 mL/kg feeds, median (IQR)	16 (11-22.5) ^ ^ ^	11 (8-16) @ @	9 (6-10) α	**<0.001#**
Parenteral nutrition, n (%)	54 (91.5)	133 (84.7)	29 (59.1)	**<0.001$**
Invasive ventilation, n (%)	43 (72.9)	63 (40.1)	9 (18.4)	**<0.001$**

CVC – Central venous catheter; IQR – Interquartile range; PROM – Prolonged rupture of membrane; ^ - Data available for n= 52; ^^ - Data available for n= 37;^^^ - Data available for n= 37; @ - Data available for n= 151; @@ - Data available for n= 131; α - Data available for n= 4; ß – Percentage of PROM has been calculated for neonates developing EOS;# - Mann Whitney U test; $ - Fisher exact test

Table 3. Clinical features, investigations, treatment and outcomes of VLBW neonates with culture proven and suspect sepsis.

Variables	Culture positive sepsis (n=59)	Suspect sepsis (n=157)	P value
Clinical features			
Respiratory features			
PPHN, n (%)	1 (1.6)	1 (0.6)	0.47$
Pulmonary haemorrhage, n (%)	3 (5.3)	2 (1.2)	0.12$
Desaturations, n (%)	52 (88.1)	108 (68.8)	**0.004**$
Pneumonia, n (%)	1 (1.6)	2 (1.2)	1.00$
CNS manifestations			
IVH, n (%)	6 (10.2)	2 (1.2)	**0.005**$
Meningitis (overall) , n (%)	8 (13.6)	8 (5.0)	**0.034**$
Culture positive meningitis, n (%)ß	5/8 (62.5)	0/8 (0)	**0.03**$
Encephalopathy, n (%)	18 (30.5)	21 (13.3)	**0.003**$
Seizures, n (%)	1(1.6)	3 (1.9)	1.00$
GI manifestations			
Abdominal distension, n (%)	30 (50.8)	37 (23.6)	**<0.001**$
GI bleed, n (%)	10 (16.9)	1 (0.6)	**0.00**$
NEC, n (%)	10 (16.9)	1 (0.6)	**0.00**$
Cholestasis, n (%)	8 (13.6)	0	**0.00**$
Hemodynamic features			
Tachycardia, n (%)	18 (30.5)	9 (5.7)	**<0.001**$
Hypotension, n (%)	27 (45.8)	7 (4.5)	**<0.001**$
Shock, n (%)	32 (54.2)	12 (7.6)	**<0.001**$
Lactate, median (IQR)	4.1 (2.3-6.5)@	1.8 (1.4-2.5)£	**<0.001**$
Miscellaneous			
UTI, n (%)	1 (1.6)	1 (0.6)	0.47$
Bone infection, n (%)	0	2 (1.2)	1.00$
Hyperglycemia, n (%)	27 (45.8)	13 (8.3)	**<0.001**$
AKI, n (%)	10 (16.9)	1 (0.6)	**0.00**$
Sclerema, n (%)	0	2 (1.2)	1.00$
Investigations			
WBC, median (IQR)	6650(2800- 12300) ^	6800 (4800-10500)α	0.58#
ANC, median (IQR)	3400(492-5600)^^	2480 (1260-5080) α α	0.75#
APC, median (IQR)	49000 (15000- 144000)^	170000(84000-268000) α α α	**<0.001**#
Thrombocytopenia, n (%)	45(77.6) ^	49(33.6) α α α	**<0.001**$
Severe thrombocytopenia (<50000/ µL) , n (%)	29 (50.0) ^	7 (47.9) α α α	**<0.001**$
CRP, positive, n (%)	34 (58.6) ^	11 (7.0)€	**<0.001**$
Treatment			
NS bolus, n (%)	26 (44.1)	12 (7.6)	**<0.001**$
Inotropes, n (%)	40 (67.7)	16 (10.1)	**<0.001**$
Hydrocortisone, n (%)	14 (23.7)	11 (7.0)	**<0.001**$
FFP transfusion, n (%)	10 (16.9)	13 (8.3) €	0.06$

Platelet transfusion, n (%)	21 (35.5)	7 (4.5) [€]	**<0.001** [$]
PRBC transfusion, n (%)	26 (44.1)	16 (10.1) [€]	**<0.001** [$]
Outcome			
Mortality, n (%)	28 (47.5)	9 (5.7) [€]	**<0.001** [$]

AKI – Acute kidney injury; ANC – Absolute neutrophil count; APC – Absolute platelet count; CNS – Central nervous system; CRP – C-reactive protein; FFP – Fresh frozen plasma; GI – Gastro-intestinal; IQR – Interquartile range; IVH – Intraventricuar hemorrhage; NEC – Necrotising enterocolitis; NS – Normal saline; PPHN – Persistent primary arterial hypertension; PRBC – Packed red blood cell transfusion; WBC – White blood cell count; UTI – Urinary tract infection; ß – Percentage of culture positive meningitis has been calculated for neonates developing meningitis; [@] *- Data available for n= 54;* [£] *- Data available for n= 141;* ^ *- Data available for n= 58;* ^^ *- Data available for n= 53;* [α] *- Data available for n= 147;* [α α] *- Data available for n=115;* [α α α] *- Data available for n=146;* [€] *- Data available for n=157;* [#] *- Mann Whitney U test;* [$] *- Fisher exact test*

Table 4. Organisms isolated from the blood of neonates with culture positive sepsis[@]

Organism	n=59	Mortality in different infection group[α]	Shock in different infection group[ß]
Total GNB, n (%)	**36 (61.0)**	**23 (63.9)**	**24/36 (69.2)**
Acinetobacter baumanni, n (%)	13 (22.0)	11 (84.6)	-
Burkholderia cepacia, n (%)	1 (1.6)	1 (100.0)	-
Klebsiella pneumoniae, n (%)	11 (18.6)	7 (63.6)	-
Escherichia coli, n (%)	2 (3.4)	1 (50.0)	-
Elizabethkingia meningoseptica, n (%)	1 (1.6)	0	-
Enterobacter cloacae, n (%)	2 (3.4)	0	-
Pseudomonas, n (%)	3 (5.1)	2 (66.7)	-
GNB, unidentified, n (%)	3 (5.1)	3 (100.0)	-
GPC, n (%)	**21 (35.5)**	**3 (14.3)**	**5/21 (23.8)**
Enterococcus, n (%)	8 (13.6)	0	-
Staphylococcus aureus, n (%)	6 (10.2)	2 (33.3)	-
Coagulase negative Staphylococcus, n (%)	3 (5.2)	1 (33.3)	-
GPC, unidentified, n (%)	4 (8.4)	0	-
Fungal, n (%)	**9 (15.3)**	**3 (33.3)**	**5/9 (55.6)**
Candida albicans, n (%)	3 (5.1)	1 (33.3)	-
Candida pelliculosa, n (%)	1 (1.6)	1 (33.3)	-
Candida parasilosis, n (%)	1 (1.6)	0	-
Candida tropicalis, n (%)	1 (1.6)	1(33.3)	-
Candida, species not identified	3 (5.1)	0	-

GNB – Gram negative bacilli; GPC – Gram positive cocci; [@] - A total of 59 cultures obtained from 59 neonates grew 66 organisms so cumulative percentages exceed 100; 7 cultures were positive for two organisms; Percentage of mortality in different infection group is calculated by number of deaths in neonates infected with a particular bacteria/ Total number of cultures growing that bacteria (row percentage), so total number of deaths exceed 28 which the actual number of deaths in neonates developing culture positive sepsis; [ß]- Row percentages have been calculated; due to the growth of two organisms in 7 cultures, total number of neonates developing shock exceed 32 which is the actual number of neonates developing shock in culture positive sepsis group.