Associated Factors and Common Pathogens of Positive Cultures in Infants With Definitive Septicemia Admitted to NICU

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Abstract- Immune system immaturity in newborns exposes them to infections, among which bloodstream infection is of great importance due to high mortality and morbidity and treatment costs. The aim of the present study was to evaluate common pathogens in blood culture positive cases and its determinants. This study was conducted in two phases, including a cross-sectional phase to collect the cases of definitive septicemia and a case-control phase on neonates admitted to the Neonatal Intensive Care Unit of Vali-e-Asr Hospital with clinical suspicion of sepsis during 2015-2019. The eligible cases were selected based on the study criteria. After extracting descriptive statistics, to evaluate causal relationships, culture-positive and culture negative cases were compared in terms of neonatal disease in the second phase. SPSS-22 was used for data analysis. The most common bacterial families were Staphylococcus (34.30%), Acinetobacter (10.46%), and Klebsiella (7.55%), among which coagulase negative Staphylococcus was the most common organism (13.08%). The most common antibiotics prescribed were ampicillin (75.1%), amikacin (58%), and gentamycin (44.8%). Factors that had a significant association were the occurrence of septicemia were gestational hypertension, premature rupture of membranes, conjunctivitis, TORCH infections, and low gestational age. The results of this study will be helpful in anticipation and management of neonatal septicemia through shedding light on some determinants of common blood culture pathogens like infections and obstetric complications in NICU admitted neonates.

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Introduction

The neonatal period is a critical time in the life of a newborn, and immune system immaturity exposes them to several infections. It is estimated that more than 1.1 million neonatal deaths occur due to invasive infections across the world annually, among which bloodstream infection (BSI) is of great significance due to high mortality and morbidity (especially in developing countries) and increased cost of care (1,2). The epidemiology of BSI and its determinants vary by region, NICU, and time depending on conditions so that it will even change over time in the same NICU (2). The risk factors associated with BSI are different across the world (3). Neonatal sepsis is defined as systemic bacterial, viral, or fungal infection associated with hemodynamic changes and other clinical manifestations. The term sepsis is used when a pathogen is found in sterile body fluids like the blood and cerebrospinal fluid (CSF); however, the term systemic inflammatory response syndrome (SIRS) can also be used in neonatal sepsis.

Neonatal sepsis is divided to early-onset and late-onset forms. In early-onset sepsis, clinical

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manifestations often appear within the first 72 hours and the infection is acquired before or during delivery indicating vertical transmission of the infection from the mother to the infant (4). Late-onset sepsis, which is caused by nosocomial and community-acquired pathogens, develops 3-7 days after birth. The overall rate of early sepsis, defined as positive culture results for CSF or blood samples obtained within the first three days of life, was 0.98 cases per 1000 live births in one study (5). The most common organisms in early neonatal sepsis are Streptococcus agalactiae (Group B Streptococcus, GBS) and Escherichia coli. GBS is the most common pathogen; however, E. coli is more prevalent in preterm or VLBW infants (6,7).

Late-onset neonatal sepsis may be caused by other anaerobic gram-negative bacteria or Listeria monocytogenes. The incidence of neonatal listeriosis has reduced dramatically in recent years (8). However, coagulase-negative staphylococci are still the most common causative agents of infections in the NICU setting (6,9-11).

Prematurity and low birth weight are the most important neonatal risk factors. Immune system dysfunction and not receiving maternal IgG antibodies increase the risk of infection in preterm infants. In addition, placement of venous catheters, intubation, and other invasive procedures can also facilitate pathogen entry into the body and increase the risk of nosocomial infection (12).

Classically, to diagnose sepsis, it is necessary to isolate the causative organism from the blood, CSF, urine, pleural fluid, synovial fluid, or peritoneum and identify it. It has recently been possible to identify common bacteria and fungi as well as resistant genes in positive culture mediums using multiplex CPR (13). In addition, the signs and symptoms of BSI are vague in both groups making an accurate diagnosis challenging indicating the importance of empirical management with antibiotics to reduce mortality and morbidity.

In developing countries, antibiotic therapy is often initiated according to international guidelines without adaptation to local susceptibility patterns. Increased incidence of drug resistance across the world and the variability of antibiotic susceptibility patterns by region indicate the importance of local antibiotic susceptibility profiles in effective empiric antibiotic therapy (1).

Considering the above and the significance of the regional epidemiology of BSI in to determine common pathogens as well as any change in the pattern of these infections, the preset study was conducted to identify common pathogens in blood cultures and its determinants. The results of the present study can provide useful information for better clinical management including effective empirical antimicrobial therapy, reducing the morbidity and managing modifiable factors, and reducing mortality in the NICU setting.

Materials and Methods

The present study was conducted in two phases. The first phase was a cross-sectional descriptive study, and the second phase was a nested case control study. The study population comprised all infants suspected of septicemia admitted to the NICU of Vali-e-Asr Hospital during 2015-2019. In the first phase, using the Vali-e-Asr Hospital's Neonatal Registry System and Lab Data Registry System, the eligible cases were selected according to the study criteria. The infants that were admitted for sepsis workup and their data were registered completely and accurately in the system were included in the first phase of the study. In the second phase, infants with early-onset septicemia were assigned to the case group and infants without a disseminated infection (negative blood, urine, and CSF culture results) were assigned to the control group. The infant was excluded from the study in case of admission for any reason other than septicemia or incomplete data registration.

Due to the cross-sectional and descriptive design of the first phase, all eligible cases in the study period were evaluated. In the second phase, according to the methodology of nested case-control studies, the case group and control groups were compared. The size of the case group was about 2.5 times the control group including non-septic infants.

Finally, the data was analyzed using the SPSS software version 22. Qualitative variables are described as relative and absolute frequency and quantitative variables are presented as mean and standard deviation (SD). For between-group comparison, chi square was used for qualitative variables; for quantitative variables, due to a non-normal data distribution (as confirmed by the Kolmogorov-Smirnov test), Mann-Whitney U test was used for comparison between two groups and Kruskal-Wallis test was applied for comparison between three groups. Finally, logistic regression analysis was done to address the confounding effect and possible interaction of some variables. The level of significance was set at 0.05 for all tests.

Results

After retrospective assessment of the data available in Neonatal Registry System, of the data of 4196 newborns that were admitted between 2015 and 2019, the data of 1284 mothers and infants with clinical suspicion of neonatal sepsis was included in the study. In other words, 1284 neonates (30%) were suspected of septicemia, among those 344 had definitive sepsis as confirmed by a positive culture (8% of all infants and 27% of cases with a clinical suspicion). The most common bacterial families were Staphylococcus (34.30%), Acinetobacter (10.46%), and Klebsiella (7.55%).

The most common and effective antibiotics are presented in Table 5. The most common antibiotics prescribed were ampicillin (75.1%), amikacin (58%), and gentamycin (44.8%).

Of 1200 newborns, the sex data of 1199 infants were available (42.6% female and 57.3% male). Moreover, of 1200 expecting mothers, the obstetric data of1195 mothers were available of whom 178 (14.8%) had a vaginal delivery and 1017 (84.8%) had a C-section. According to the chi square test, sex (P=0.46) and type of delivery (P=0.70) had no significant correlation with septicemia.

The length of hospital stay was significantly longer in cases with confirmed septicemia compared to patients with unconfirmed septicemia. Moreover, the mean birth weight and gestational age of the septicemic cases were lower than those with unconfirmed septicemia (Table 1).

According to the chi square test, gestational hypertension, administration of corticosteroids during pregnancy, administration of magnesium sulfate during pregnancy, premature rupture of membranes (PROM), conjunctivitis, congenital infections, and meningitis during pregnancy had a significant relationship with neonatal sepsis (Table 2).

In another analysis, cases with confirmed septicemia were divided into three groups, including Gram-positive, Gram-negative, and fungal infection according to the pathogen. The mean length of stay was significantly longer in the fungal infection group compared to the other two groups; moreover, the mean Birth weight was higher in the Gram-positive group (Table 3).

Due to the large number of variables and the possibility of their confounding effects on one another, multivariable regression analysis was used. This test showed the possible effect of some variables on the occurrence of septicemia (Table 4). According to the results, gestational hypertension, administration of magnesium sulfate, conjunctivitis, and TORCH infections increased the odds of neonatal sepsis (OR=1.8, 1.66, 7.2, and 3.6, respectively). Moreover, each one-week reduction in the gestational age increased the odds of neonatal sepsis by 0.03 times.

Table 1. Comparison of baseline factors between cases and controls

Variable	Case group			Control group			*P*
	Mean	Median	Standard deviation	Mean	Median	Standard deviation	
Wight	1886.29	1720	922.97	2535.93	2600	816.88	0.0001
Length of stay (days)	32.96	27	25.36	11.14	7	12.65	0.0001
Gestational age	33.44	34	4	34.11	34.42	3.91	0.012

Table 2. Association of pregnancy outcomes with neonatal sepsis

Outcome	Case group	Control group	*P*
Chorioamnionitis	13(%43.3)	17(%56.7)	0.07
Chronic hypertension	17(%27.9)	44(%72.1)	0.88
Gestational hypertension	82(%39.8)	124(%60.2)	0.0001>
Chronic diabetes	9(%25.7)	26(%74.3)	0.69
Gestational diabetes	57(%30.6)	129(%69.4)	0.51
Steroid use in pregnancy	114(%35.6)	206(%64.4)	0.001>
Magnesium sulfate use in pregnancy	54(%43.2)	71(%56.8)	0.0001>
PROM	71(%36.2)	125(%63.8)	0.01

Table 3. Factors affecting type of pathogen

Variable	Gram-positive		Gram-negative		Fungal		*P*
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	
Wight	1975.80	905.91	1607.15	829.90	1676.94	883.93	0.01
Length of stay (days)	29.50	22.86	38.91	27.24	60.33	20.15	0.0001
Gestational age	230.78	27.90	224	28.16	222.28	31.68	0.129

Table 4. Factors affecting septicemia occurrence according to logistic regression analysis

Variable	Beta coefficient	*P*	OR	95% confidence interval	
				Lower limit	Upper limit
Chorioamnionitis	0.488	0.221	1.62	0.74	3.56
Gestational hypertension	0.614	0.0001	1.84	1.32	2.58
Steroid use in pregnancy	0.250	0.120	1.28	0.93	1.76
Magnesium sulfate use in pregnancy	0.410	0.070	1.50	0.96	2.34
PROM	0.509	0.004	1.66	1.17	2.35
Meningitis	22.13	0.998	4119045318.26	0.001>	-
Conjunctivitis	1.98	0.0001	7.25	2.75	19.11
Omphalitis	21.99	0.999	3563942176.46	0.001>	-
Congenital infections	1.28	0.015	3.62	1.27	10.25
Gestational age	-0.36	0.034	0.96	0.93	0.99

Table 5. The most common antibiotics used for treatment

Antibiotic	Frequency (n.)	Percent (%)
Ampicillin	965	75.1
Amikacin	746	58
Gentamicin	576	44.8
Vancomycin	277	21.5
Meropenem	190	14.8
Tazocin	140	10.9
Fluconazole	86	6.6

Discussion

A study was conducted to evaluate common pathogens in positive cultures and their determinants in neonates admitted to the NICU. A total of 1200 neonates were included in the study of which 344 had a definitive diagnosis of neonatal sepsis. The most common bacterial families were Staphylococcus (34.30%), Acinetobacter (10.46%), and Klebsiella (7.55%). Coagulase-negative staphylococcus (13.08%) was the most common family among staphylococci, which was consistent with studies conducted by Worth *et al.*, Mitt *et el*., and Ohlin *et al.,* (14-16). However, coagulase-negative staphylococcus was not among common pathogens isolated from neonates admitted to the NICU in a study by Caviaro *et al.*, (16). Several studies have investigated the prevalence of different pathogens in neonatal sepsis. In the present study, the mean birth weight and gestational weight were significantly lower in infants with confirmed sepsis compared to neonates with unconfirmed septicemia, which was consistent with the results of a study by Escalante *et al*., that reported a lower weight and gestational age in neonates with LOS and a study by Caviaro in which although infection developed in all newborns, low birth weight neonates (below 1000 g) were at a major risk for it (16,17). Ozkan *et al.,* found that the main factors associated with EOS were PROM, history of antibiotic therapy during pregnancy, and chorioamnionitis. The history of antibiotic use was the main factor associated with LOS, while low birth weight was the main factor in infants with VLOS (18). In a study in 2018 by Cailes *et al*., most infections were LOS, and infection was more common in premature (<37 weeks gestation) and LBW (<2500 g) neonates, which is consistent with the results of the present study (19). Gandra *et al*., conducted a study in India and found that 13.8% of the admitted newborns had early-onset septicemia. The most common organisms isolated from the patients were Klebsiella (39.4%) and Acinetobacter (33.3%). This study found no association between intrapartum risk factors and the occurrence of septicemia, which is not consistent with our findings. Another finding of this study was a significant association between premature birth (<35 weeks gestation) and the occurrence of early-onset septicemia, which was in line with or findings (20). A

case-control study by Rafi *et al*., showed that maternal factors that had a significant association with development of sepsis in newborns included UTI in the third trimester, premature birth (<37 weeks gestation), and birth weight less than 2500 g, which is consistent with our findings. However, the most common organisms in this study were Escherichia coli (40.7%) and Staphylococcus aureus (27.5%) (21).

The most common bacterial families were Staphylococcus (34.30%), Acinetobacter (10.46%), and Klebsiella (7.55%), and the most common antibiotics prescribed were ampicillin (75.1%), amikacin (58%), and gentamycin (44.8%).

The results showed a significant correlation between early-onset neonatal sepsis and some intrapartum factors and pregnancy complications. More attention should be paid to timely prenatal maternal care to reduce the cases of neonatal sepsis. Moreover, it is recommended that antimicrobial susceptibility testing should be performed before antimicrobial therapy to reduce the length of hospital stay and costs.

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