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THROMBOCYTOPENIA AMONG NEONATES HAVING CULTURE-PROVEN SEPSIS AT A TERTIARY CARE HOSPITAL IN PAKISTAN

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Date Received:
Mar 5th, 2022
Date Revised:
July 27th, 2022
Date Accepted:
Aug 6th, 2022

This article may be cited as
Zehravi SS, Khan M,
Sheikh M, Hanif M, Wa-
jid S. Thrombocytopenia
among neonates having
culture-proven sepsis at
a tertiary care hospital in
Pakistan. *J Postgrad Med
Inst* 2022;36(3):181-5.
[http://doi.org/10.54079/
jpmi.36.3.3067](http://doi.org/10.54079/jpmi.36.3.3067)

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ABSTRACT

Objectives: To determine the frequency of thrombocytopenia in culture-positive neonatal sepsis.

Methodology: This hospital-based cross-sectional study was conducted at a tertiary care hospital of Pakistan between July to December 2021 at the Department of Pediatrics, National Institute of Child Health Karachi - Pakistan. All the neonates admitted to NICU with signs and symptoms of sepsis and positive blood culture were enrolled for this study. Complete blood count, C - reactive protein (CRP) and blood culture were sent. All the data regarding age, gender, birth weight, platelet count, and the organism isolated on blood culture was recorded in a proforma. Data was analyzed statistically and $p \leq 0.05$ was considered to be statistically significant.

Results: Two hundred forty-six babies were included in the study. The mean gestational age was 37 ± 0.56 weeks and birth weight was 3.4 ± 0.67 kg. Male to female ratio was 1.2:1 and the mean age of admission was 6.37 ± 5.99 days. Thrombocytopenia was found in 192 (78.4%) of neonates. There was a significant association of *Burkholderia cepacia* ($p=0.002$), *Klebsiella pneumonia* ($p=0.032$), and *Serratia marcescens* ($p=0.027$) with thrombocytopenia.

Conclusions: Thrombocytopenia is strongly associated with gram-negative bacteria and the most prevalent organism found in thrombocytopenic neonates was *Burkholderia cepacia*.

Keywords: Thrombocytopenia; Sepsis; Gram-Negative Organisms; *Burkholderia cepacia*; *Klebsiella pneumonia*, *Serratia marcescens*.

INTRODUCTION

Neonatal sepsis is defined as a clinical syndrome comprising the signs and symptoms of systemic infection with a positive blood culture under one month of life.^{1,2} The prevalence of sepsis in developing countries is between 49 to 170 cases for 1000 live births, while in the case of more economically developed countries the ratio is 1 to 10 cases per 1000 live births.³ Neonatal sepsis is a major cause of morbidity and the world's third leading cause of neonatal death.⁴⁻⁶ It is responsible for approximately 30-50% of developing countries' neonatal deaths.⁷ Each year south Asia accounts for 3.5 million cases of neonatal sepsis.⁸ Incidence of neonatal sepsis in Pakistan is approximately 29.5%.⁹ Thrombocytopenia is defined as a platelet count below $150,000/\text{mm}^3$ It is a serious problem for up to 50% of those receiving NICU care.¹⁰⁻¹² In Indian, Pakistani, and international studies, the reported frequency of thrombocytopenia in neonatal sepsis was 82.6%, 68.24%, and 49% respectively.^{11,13,14}

Thrombocytopenia is one of the common hemato-

logical specific markers for early detection of neonatal sepsis and the determination of its outcome.¹³ The pathogenesis of thrombocytopenia in sepsis involves endothelial damage by bacteria leading to platelet aggregation and their clearance from the body by the reticuloendothelial system. Therefore, thrombocytopenia occurs due to an imbalance in the production and consumption of platelets and it is decreased within 24-48 hours after the onset of infection and is considered a major cause of thrombocytopenia in neonatal sepsis.^{10,15-17} Patients with a high index of suspicion should be managed early to prevent complications such as septic shock.^{11,18} The platelet count serves as an early and inexpensive marker of neonatal sepsis which can be used to diagnose sepsis until the culture reports are available. The more severe the thrombocytopenia, the worst the prognosis.¹

The majority of investigations on this subject were conducted internationally and found that newborn sepsis had a greater frequency of thrombocytopenia. This study aimed to determine the frequency of thrombocytopenia in newborn sepsis and its association with

specific micro-organisms isolated from a culture which has rarely been studied previously. This aspect of the study would further enable for the early diagnosis and the immediate implementation of a specific treatment directed against the specific pathogenic organism.

METHODOLOGY

This cross sectional study was conducted in July to December 2021, at a tertiary care hospital of Pakistan. The study was performed in NICU after the permission of ethical committee of hospital (IERB No: 07/2021, Dated 19.06.2021) and the patient's parents or guardians provided their written informed consent for the study. The study comprised of 246 neonates who were admitted to the NICU with sepsis-related signs and symptoms and whose blood cultures were positive.

The study excluded neonates with other thrombocytopenia-causing conditions such as neonatal alloimmune thrombocytopenia (NAIT) or primary immune thrombocytopenic purpura (ITP), drug-induced thrombocytopenia, malaria, maternal history suggesting placental insufficiency, neonates with family history of bleeding disorders, and neonates receiving exchange transfusions.

Under all aseptic measures 5ml blood sample of each child was collected and sent to the NICH laboratory for CBC, CRP and blood culture before the administration of antibiotics. Blood culture was sent only once at the time of admission and only culture positive patients were included in the study. Concomitant sampling was necessary in order to establish the association between positive blood culture and platelet count. The sample for platelet count was collected in EDTA bottle and run on the automated hematology cell counter (Sysmex KX-21). The sample for blood culture was collected in bottle containing 15ml of culture media

and incubated at 37°C for up to 7 days. If any gas production, cloudiness or hemolysis is observed subcultures are performed for the identification of bacteria. The sample is termed as sterile if no growth is appreciated after 7 days of inoculation.

All the data regarding age, gender, birth weight, platelet count, and the organism isolated on blood culture was recorded in a proforma. After collection of data the analysis was conducted by using Statistical Package for Social Science (SPSS) software, Version 22. Chi-square test was used for the association of thrombocytopenia in gram-positive bacteria and gram-negative bacteria and fungal species that are suspected to cause sepsis. p value ≤ 0.05 was taken as significant.

RESULTS

A total of 255 cases of sepsis were initially included and due to unavailability of data, 9 cases of sepsis were excluded from the study. A total of 246 patients were enrolled for this study and their data was subjected to further analysis. The study group has 1.2 times more males as compared to females (54.5% vs. 45.5%). Mean age at admission was 6.37± 5.99 days, mean birth weight was 3.4± 0.67 kg and mean gestational age was 37± 0.56 weeks. Demographic features of enrolled patients are summed up in Table 1.

The babies who had Early onset sepsis

(EOS) were 184 (74.8%) and the babies with late onset sepsis (LOS) were 62 (25.2%) respectively. Thrombocytopenia was found in 78.04% 192 babies of 246 neonates enrolled to this study. In babies who had sepsis via Gram negative organisms were found in 76.4 % (n=188, p=0.025) and the results of Gram positive organisms were found in 2.03% (n=5, p=0.025) and there were no cases of thrombocytopenia in fungal sepsis shown in Figure 1.

Considering individual microorganisms, the results showed neonatal sepsis caused by Burkholderia cepacia showed a significance with thrombocytopenia (p=0.002), Klebsiella pneumonia (p=0.032) and Serratia marcescens (p=0.027). Other microorganisms discovered throughout the research did not show a significant relationship with thrombocytopenia as shown in Figure 2. The present study showed another significant finding about the increased CRP levels (>10mg/L) in 208 (84.5%) of the neonates.

DISCUSSION

In neonates, thrombocytopenia is seen as a major complication with culture proven sepsis and a reliable marker of neonatal mortality.¹⁹ Most studies conducted globally determined the frequency of thrombocytopenia in neonatal sepsis, however, very limited literature is available to establish the association of thrombocytopenia with specific micro-organisms.

Table 1: Characterization of patients based on demography

Gender	Male	134
	Female	112
Age	EOS	184
	LOS	62
Birth Weight (Kg)	1 - < 1.5	25
	1.5 - <2.5	97
	>2.5	124
Mode of Delivery	Spontaneous Vaginal Delivery	107
	Cesarean Section	139

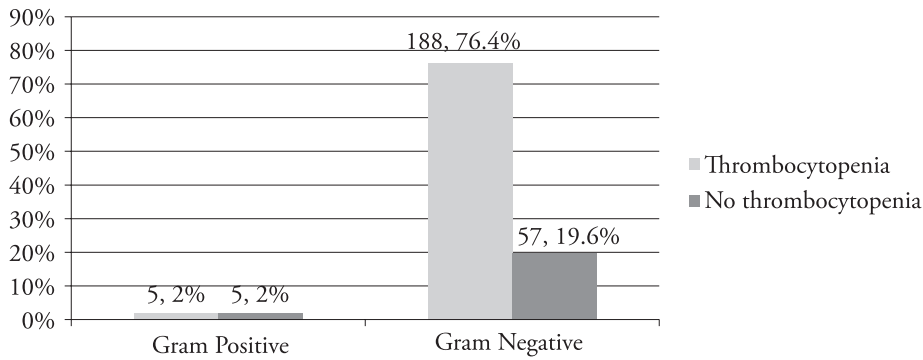


Figure 1: Association of thrombocytopenia in gram-positive and gram-negative organisms.

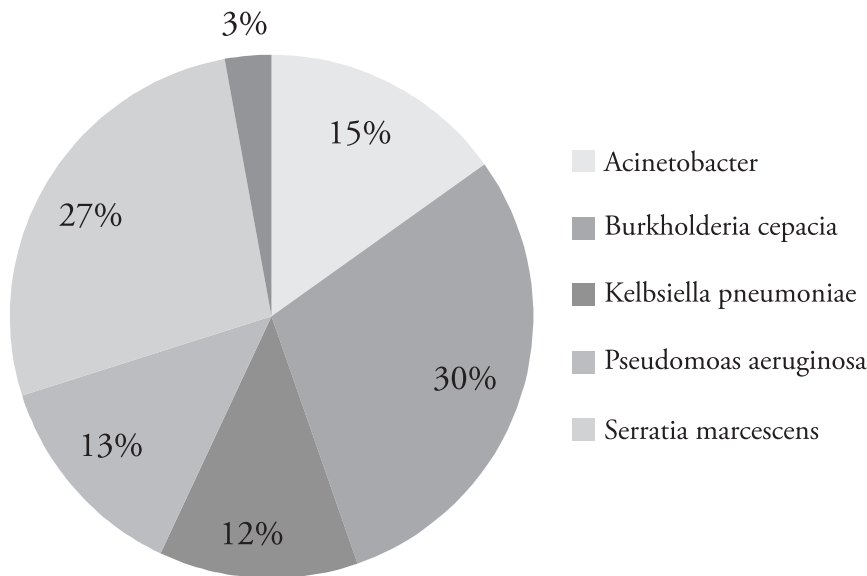


Figure 2: Association between thrombocytopenia in microorganisms responsible for neonatal sepsis

In our study thrombocytopenia was found in 78.4% (192/246) of the neonates. This finding was in contrast to the study conducted at Netherlands in 2017 that concluded thrombocytopenia to be found in half (226/460) of septic neonates.¹⁰ Another study conducted at India in 2021 revealed findings consistent with our study.¹⁶

This study reported a higher incidence of sepsis in males as compared to female neonates, approximately 1.2 times higher than females, which is similar to that demonstrated in a study conducted at Multan, Pakistan and Nigeria.^{4,20} The reason behind male predilection in sepsis is thought to be caused by male sex hormones that are found to suppress cell mediated immunity, while female

sex hormones confer a protective effect.²⁰

In this study, Early onset sepsis (EOS) was found in 184 (74.8%) and late onset sepsis (LOS) in 62 (25.2%) babies. These findings are identical to those found in a study conducted at Nigeria and Multan, Pakistan.^{4,20} The results of the study conducted at Lahore were contrary to our study demonstrating a higher incidence of LOS.²¹

C-reactive protein is an acute phase protein secreted by the hepatocytes in response to inflammation. In multiple studies statistically significant association has been established between high CRP levels and neonatal sepsis indicating it to be a marker of septicemia. The present study revealed

elevated CRP levels in 208 (84.5%) of the neonates, which coincides with the findings of the studies conducted at Saudi Arabia and Africa.^{22,23}

According to our study blood cultures yielded Gram negative organism in 96% of the neonates, out of which 76% developed thrombocytopenia. 4% of the cultures revealed Gram positive organisms with half of the patients having a low platelet count. The afore mentioned findings are consistent with the previous studies.^{12,14} Moreover, these finding can possibly be explained by the strong association of thrombocytopenia with the causative organism. The study of Bhatt et al. demonstrated highest incidence of thrombocytopenia in Klebsiella sepsis, followed by Burkholderia cepacia, Acinetobacter, Enterobacter and Candida sepsis.¹²

Previous literature also reported that the gram negative bacteria produce thrombocytopenia either by antibody mediated destruction of platelets or directly by their endotoxins.^{10,12} This study also explored some of the notable causes of thrombocytopenia i.e; Burkholderia cepacia, Klebsiella pneumonia and Serratia marcescens amongst the gram negative. These findings favored the previous studies that reported Klebsiella as the most common etiology behind thrombocytopenic neonates.¹⁶

CONCLUSION

Thrombocytopenia is a major complication of neonatal sepsis and leads to morbidity and mortality if prompt treatment is not administered. It can serve as an initial and cheap marker of neonatal sepsis until blood culture report is available. Our study showed that gram negative organisms have a strong association with thrombocytopenia. Amongst the gram negative organisms, Burkholderia cepacia, Klebsiella pneumonia and Serratia marcescens were found to cause significant thrombocytopenia. Hence, any neonate suf-

fering from thrombocytopenia should receive antibiotics directed against these pathogens until the culture reports are available.

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Author's Contribution

SSZ helped in data collection and wrote the manuscript. MK and MH contributed to the manuscript writing. MS helped in the analysis of the data. SW contributed to the collection of data and write up of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.