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Study of correlation between thrombocytopenia and fungal sepsis in neosnates

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Abstract
Background: Thrombocytopenia is used as an early marker of sepsis in neonate. Fungal sepsis is associated with greater degree of thrombocytopenia than is seen with either gram positive or gram negative organisms.
Aims and Objectives: To study the correlation of thrombocytopenia in neonatal fungal sepsis.
Materials and Methods: This retrospective study was conducted from 1st January 2018 to 31st December 2018 in the NICU of D.Y. Patil medical college and hospital, Kolhapur, Maharashtra. Out of 131 blood cultures sent, 49 neonates with culture positive were included and grouped into fungal and bacterial sepsis as per the growth of organisms. Blood cultures were done on Automated BacT/Alert 3 D Rapid Bacterial Culture System, Biomerieux, France in Microbiology Laboratory. Platelet count was measured by automated cell counter and on peripheral smear by Pathologist. Thrombocytopenia was defined as platelet count less than 150000/mm^3. The data was analysed using Chi Square test.
Results: 33 (67%) and 16 (33%) cultures were positive for bacterial and fungal sepsis respectively. There were 20(60.6%) males and 13(39.4%) females in bacterial sepsis as compared to 9(56.25%) males and 7(43.75%) females in fungal sepsis group. Preterm babies outnumbered full term babies. The commonest organisms isolated from bacterial sepsis group was Klebsiella 13(39.39%) and Candida albicans 15(93.75%) from fungal sepsis. Thrombocytopenia was present in 14(87.5%) fungal as compared to 05(15.15%) bacterial sepsis group which was statistically significant. (P<0.05).
Conclusion: Thrombocytopenia was significantly associated with fungal sepsis in neonate and can be taken as marker of fungal sepsis.

Keywords: Fungal sepsis, neonate, thrombocytopenia

Introduction
Throughout the world, more than half million newborns are estimated to die from serious neonatal infections [1]. Sepsis is a systemic infectious disease which frequently affects newborns in Neonatal Intensive Care Unit (NICU) all around the world either bacterial or fungal sepsis [2, 3]. Fungal sepsis is less common than bacterial sepsis with incidence between 0.3% to 6.7% with mortality of 19% to 36% and morbidity of 57.2% [4, 5]. Common risk factors for fungal sepsis include prematurity and very low birth weight, central vascular catheterization, parenteral nutrition, use of broad spectrum antibiotics, H2 blockers and corticosteroids, endotracheal intubation and prolonged hospital stay.[5, 6] Most cases of fungal sepsis are health care related infections. Candida species are the most frequently isolated agents. [7] The diagnosis of fungal sepsis is difficult clinically still blood culture remains the 'Gold Standard' test to confirm the diagnosis of fungal sepsis.
Platelet count less than 150000/mm^3 in any neonate is defined as thrombocytopenia regardless of gestational age [8]. Thrombocytopenia is used as an early marker of sepsis in neonate either bacterial or fungal [9]. Fungal sepsis is associated with greater degree of thrombocytopenia than is seen with either gram positive or gram negative bacterial organisms [10]. There is paucity of literature regarding fungus specific platelet response in neonatal fungal sepsis. The present study was undertaken to study the correlation of thrombocytopenia with fungal sepsis in neonates.

Materials and Methods
This observational retrospective study was conducted for a period of one year from 1st January 2018 to 31st December 2018 in the NICU of D.Y. Patil medical college and hospital, Kolhapur, Maharashtra. The study was approved by Institutional Research Committee.

Out 131 blood cultures sent, 49 neonates with culture positive neonatal sepsis admitted in NICU during the study period were included in this study. The names of neonates with culture positive sepsis were collected from NICU register. Case records were obtained from hospital record section. Case records were analysed for gender, gestational age, birth weight, duration of hospital stay, use of broad spectrum antibiotics and indwelling central venous catheter along with clinical features like feed intolerance temperature instability, apnea, and increased need of ventilator support and laboratory markers like haemoglobin, total leukocyte count, differential count, platelet count and CRP. Thrombocytopenia which is defined as platelet count less than 150000/mm^3 [8]. In all neonates blood was collected from peripheral vein by taking all aseptic precautions in BacT/Alert 3D bottle and sent immediately to Microbiology laboratory for culture. Blood cultures were done on Automated BacT/Alert 3 D Rapid Bacterial Culture System, Biomerieux, France. Platelet count was measured by automated cell counter and confirmed on peripheral smear by Pathologist. Blood culture positive neonates were grouped into fungal sepsis and bacterial sepsis groups as per the growth of organisms either after 48 hours or 1 week of inoculation. All the data was recorded in a pre-structured validated proforma and the data was analysed using Chi Square test where p value < 0.05 was significant.

Results

Out of 131 blood cultures sent during the study period, 49 came positive for either bacterial sepsis or fungal sepsis. 33 (67%) and 16 (33%) blood cultures were positive for bacterial and fungal sepsis respectively. [Figure 1]

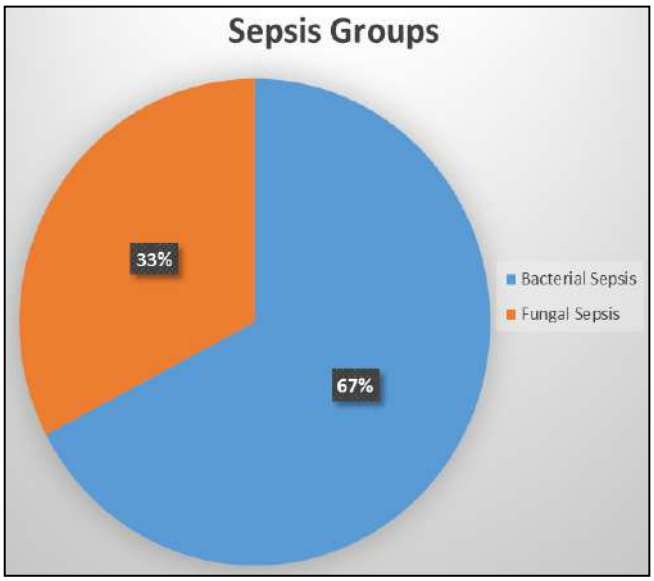

Fig 1: Incidence of bacterial and fungal Culture positivity in babies

Table 1: Gender distribution in bacterial and fungal sepsis groups

Sepsis Group	Males		Females		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Bacterial	20	60.60	13	39.40	33	100
Fungal	09	56.25	07	43.75	16	100
Total	29	59.18	20	40.12	49	100

In our study, there were 29 (59.18%) males and 20(40.12) females, out of that 20 (60.6%) males and 13(39.4%) females in bacterial sepsis group as compared to 9(56.25%)males and 7(43.75%) females in fungal sepsis group. [Table 1]

Table 2: Gestational age in bacterial and fungal sepsis group

Sepsis Group	Pre term		Full term		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Bacterial	11	42.3	15	57.69	26	100
Fungal	18	78.26	05	21.74	23	100
Total	29	59.18	20	40.12	49	100

Preterm babies outnumbered full term babies. There were 11(42.3%) preterm and 15(57.69%) full term babies in bacterial sepsis group while 18 (78.26%) preterm and 05 (21. 74%) full term babies in fungal sepsis group. [Table 2]

Table 3: Incidence of organisms isolated from bacterial and fungal sepsis group

Sepsis Group	Organisms Isolated	Number	Percentage	Total	
				Number	Percentage
Bacterial Sepsis	Klebsiella	13	39.39	33	67
	Pseudomonas Aeruginosa	04	12.12		
	Coagulase Negative Staph aureus	04	12.12		
	Escherichia Coli	03	09.09		
	Staphylococcus Aureus	03	09.09		
	Enterococcus	01	03.03		
	Acinetobacter	04	12.12		
	Burkholderia cepacia	01	03.03		
Fungal Sepsis	Candida albicans	15	93.75	16	33
	Candida Nonalbicans	01	06.25		
Total		49	100	49	100

The commonest organisms isolated from bacterial sepsis group was Klebsiella 13(39.39%) and Candida albicans 15(93.75%) from fungal sepsis group. [Table 3]

Table 4: Thrombocytopenia in bacterial and fungal sepsis group

Sepsis Group	Thrombocytopenia		P value
	Number	Percentage	
Bacterial	05	15.15	<0.05
Fungal	14	87.5	
Total	19	100	

The incidence of thrombocytopenia was present in 19 (38.77%) from both bacterial and fungal culture positive sepsis group. Out of which, thrombocytopenia was present in 14(87.5%) fungal as compared to 05 (15.15%) in bacterial sepsis group. Thrombocytopenia was significantly present in fungal sepsis group (P<0.05) [Table 4]

Discussion

The incidence of fungal sepsis in neonates has increased 11 fold over the past 15 years. Preterm neonates are predisposed to Candida infections because of underdeveloped immune system and increasing use of invasive interventions. Transmission of candida may be vertical from maternal vaginal infection or nosocomial. Colonisation of health workers is as high as 30%. Initial size of colonisation is usually the gastrointestinal tract [11]. Although not much studies on platelet count in sepsis, yet it has well described for more than 40 years that platelet with sepsis often have thrombocytopenia and the intravenous injection of lipopolysaccharides in mice induce rapid thrombocytopenia. Platelets are believed to be active participants in host defence. [12]

In our study, we demonstrated thrombocytopenia was statistically significantly present in fungal sepsis (87.5%) as compared to bacterial sepsis (12.5%). Study by James M *et al* [11]. observed that thrombocytopenia was present in 70% babies with fungal sepsis. Claveras TS *et al.* [13] concluded that thrombocytopenia is a highly specific marker of neonatal candida sepsis. Parvez A *et al.* [14] showed that mean platelet count at the time of onset of sepsis was more in gram negative sepsis and fungal sepsis. Guida JD *et al.* [15] found significantly low platelet count at the onset of sepsis in gram negative and fungal sepsis.

Platelets play an important role in linking innate and adaptive immune response. [16] Usually there can be multiple causes of thrombocytopenia in septic neonates but broadly it can be due to increased platelet destruction, decreased platelet production or mixed etiology. [17] Diffuse endothelial cell trauma, bacterial fungal toxins, increased platelet activation and increased platelet consumption due to DIC are among the factors that play a role in the mechanisms of thrombocytopenia Also platelets interact with invading microorganisms and are critically linked to proinflammatory innate immune response. Platelets express Toll like Receptors (TLR) especially TLR4 and this expression significantly modulates microbial lipopolysaccharide induced thrombocytopenia by stimulating adaptive immunity against invading microorganisms. [18] The major limitations of our study were its retrospective design and small number of cases studied.

Conclusion

Thrombocytopenia was significantly associated with fungal sepsis in neonate and can be taken as marker of fungal sepsis.

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