

# Role of C-Reactive Protein and Platelet Count in Gram Positive Versus Gram Negative Sepsis in Newborn

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## ABSTRACT

**Introduction:** Early diagnosis of neonatal sepsis remains difficult task in clinical practice. To delay treatment until signs and symptoms of sepsis are risk of preventable mortality. Study aimed to identify the role of CRP and Platelet in distinguishing Gram Positive Versus Gram Negative Sepsis in Newborn

**Material and Methods:** Prospective diagnostic study was performed in NICU of Kilpauk Medical College Hospital. Three blood samples are collected from a peripheral vein under strict aseptic precautions in the respective containers for blood culture, C-reactive protein estimation and platelet count before administration of empirical antibiotic.

**Results:** 207 newborns were included in the study, Blood culture was positive in 88 out of the 207 cases, C-reactive protein was positive in 92 cases and thrombocytopenia was observed in 74 cases. CRP was found to be positive in more number of culture positive cases than culture negative cases. Low platelet count points towards a predominant gram negative sepsis

**Conclusion:** CRP can be used as early marker for sepsis in limited resource setting. More evidence required to support thrombocytopenia in gram negative sepsis.

**Keywords:** sepsis, CRP, platelet count, thrombocytopenia

## INTRODUCTION

The newborn infant is susceptible to infection due to immaturity of both natural and acquired immune systems.<sup>1</sup> Compared to developed nations, the incidence of neonatal sepsis in India is quite high accounting for 40% of all neonatal deaths.<sup>2</sup> The presentation of sepsis is usually by a variety of subtle non specific clinical signs and symptoms which may at times evade even the most skilled Pediatrician. The newborn responds to the stress of sepsis in a stereotyped manner. So Sepsis must be considered as a strong possibility for any clinical deterioration in a neonate unless the event is explained by other causes.<sup>2</sup> Neonatal septicemia causes considerable morbidity and mortality. So diagnosis of the infection gains paramount importance as earlier diagnosis reduces morbidity.<sup>3</sup> Blood culture remains the gold standard in not only identifying the infecting organism but also provides vital information regarding the antibiotic sensitivity pattern so that proper usage of drugs can be made. But the problem with blood culture is that it takes at least 48 to 72 hours to detect bacterial growth which causes a considerable time lag in initiating appropriate treatment. To circumvent this problem the strategy commonly used is to use empirical antibiotic therapy covering both gram negative and gram positive organisms. It has its own disadvantages in the form of side effects of unnecessary drug usage and the propensity for emergence of resistant strains. Also, in a developing country like India the economic burden of the extra antibiotic therapy may be far reaching. So the need of the hour is to identify a test to confirm the presence of sepsis earlier as well as to find out a parameter which reliably

distinguishes between gram positive and gram negative sepsis which may help in choosing the appropriate antibiotic without having to rely on the empirical coverage.

Aim of the study was to identify the role of platelet count and C-reactive protein in Gram positive and Gram negative sepsis in neonates and to ascertain whether platelet count can be used as a criterion to distinguish between Gram positive and Gram Negative neonatal sepsis.

## MATERIAL AND METHODS

A Prospective diagnostic study was performed in Neonatal Intensive Care Unit, Department of Pediatrics, Kilpauk Medical College Hospital, Chennai from 2010 October and 2012 October. Institutional Ethics committee approval and informed consent from the parents were obtained. The newborns (207) were included in the study group if they satisfy any one of the following criteria. The neonates should fulfill the inclusion criteria. The newborns with prior antibiotic administration were excluded from the study. Only intramural deliveries are included in the study. Both Term and Preterm babies irrespective of the gestational age and birth weight were included in the study. Newborns belonging to both sexes were admitted to this study. Only newborns within seven days of life were included in the study population.

**Neonatal criteria** - Newborns within 7 days of life showing the under-mentioned signs and symptoms, Respiratory distress or apnea or gasping respiration, Temperature instability – Hypothermia or Fever, Lethargy, poor cry, refusal of feeds, vomiting, ileus, abdominal distension, Poor peripheral perfusion, Bradycardia or Tachycardia, More than 10 pustules in the body or purulent umbilical discharge along with periumbilical erythema, Neonatal convulsions, irritability, hypotonia, altered sensorium.

**Maternal Criteria:** Maternal fever with evidence of bacterial infection within 2 weeks prior to delivery, Rupture of membranes more than 18 hours, Foul smelling liquor, Evidence of chorioamnionitis, More than 3 vaginal examinations or one unclean vaginal examination during labor, Prolonged labor (sum of first and second stage of labor more than 24 hours).

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Three blood samples are collected from a peripheral vein under strict aseptic precautions in the respective containers for blood culture, C-reactive protein estimation and platelet count before administration of empirical antibiotic. If at any point of time, if a newborn was found to have parameters in the exclusion criteria it was excluded from the study.

**STATISTICAL ANALYSIS**

Statistical analysis was done with the help of SPSS version 21. Descriptive statistics and chi square test were used to infer results.

**RESULTS**

207 newborns that fulfilled the inclusion criteria, were included in the study. Out of the 207 cases, 112 were male babies and the rest 95 were female. Male newborns contributed to 54.1% of the study population and females accounted for 45.9%. On categorizing the newborns based on birth weight, 11 babies were of very low birth weight, 107 newborns were of low birth weight, 88 babies were in normal birth weight and one baby weighed more than 4,000 grams. Blood culture was positive in 88 out of the 207 cases, C-reactive protein was positive in 92 cases and thrombocytopenia was observed in 74 cases. *Klebsiella* is the commonest organism causing sepsis in our Neonatal Intensive Care Unit. The other gram positive organisms encountered are *Escherichia Coli*, *Pseudomonas*, *Enterobacter* and *Acinetobacter* (Figure-1). The Gram positive organisms grown are Coagulase Positive and Coagulase negative *Staphylococci*, Group B Beta Hemolytic *Streptococcus* and *Enterococcus*.

CRP was found to be positive in more number of culture positive cases than culture negative cases. The Negative predictive value of C-reactive protein estimation in our study population is 97.39% and the overall diagnostic accuracy is 95.17% (Table-1). The sensitivity of using platelet count as a distinguishing parameter of Gram positive and Gram negative sepsis as per our study is 14.29% and specificity is 4.054%. The overall diagnostic accuracy is 5.62% (Table-2).

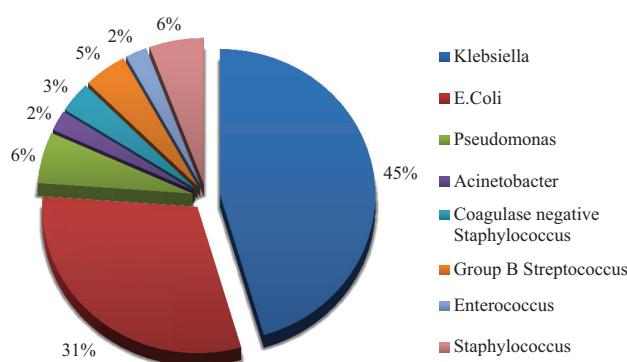
In our study, thrombocytopenia was observed in 73 cases of culture positive sepsis and in 1 case of culture negative sepsis. On statistical analysis, thrombocytopenia has a sensitivity of 82.95% in culture positive sepsis and specificity of 99.16. The overall diagnostic accuracy is 92.27% (Table-3).

Mode of delivery does not affect the positivity or negativity of CRP in a statistically significant manner (Table-4).

On analysis no significant statistical difference between mode of delivery and platelet count was found.

60 very low birth weight babies out of 107 and 50 term babies out of 88 normal birth weight babies had positive CRP. As per data CRP was positive in more number of Low Birth weight babies but the statistical analysis did not show a significant association (Table-5).

Thrombocytopenia was more frequently observed than normal platelet count in very low birth weight babies with clinical suspicion of sepsis compared to other groups. But the statistical analysis did not show a significant difference regarding the incidence of thrombocytopenia and sepsis (Table-5). No statistically significant difference exists between EOS/LOS and CRP. Thrombocytopenia was more prevalent in late onset sepsis than early onset sepsis. But there was no statistically significant difference.



**Figure-1:** Organism growth in Blood culture

	Culture Positive	Culture Negative	Total
CRP Positive	85	7	92
CRP Negative	3	112	115
Total	88	119	207

**Table-1:** Evaluation of CRP as a distinguishing parameter for Gram positive and Gram Negative sepsis

	Gram Positive	Gram Negative	Total
Thrombocytopenia	2	71	73
Normal Platelet count	12	3	15
Total	14	74	88

**Table-2:** Evaluation of Platelet Count as a distinguishing parameter for Gram positive and Gram Negative sepsis

	Culture Positive	Culture Negative	Total
Thrombocytopenia	73	1	74
Normal Platelet count	15	118	133
Total	88	119	207

**Table-3:** Thrombocytopenia cases

Mode of Delivery	CRP Positive	Thrombocytopenia
LSCS	49	41
Labour Naturale	42	32
Outlet Forceps	1	1
Total	92	74

**Table-4:** Mode of Delivery and CRP positive, Thrombocytopenia

Birth weight in Grams	CRP Positive	Thrombocytopenia
< 1,500 Grams	7	7
1,500 to <2,500 Grams	47	43
2,500 to < 4,000 Grams	38	24
> 4,000 Grams	0	0
Total	92	74

**Table-5:** Crosstabs Birth weight in grams-group and Platelet Count

**DISCUSSION**

Out of the 207 babies under evaluation, 112 were male babies and the rest 95 were female. Male babies contributed to 54.1% of the study population and female babies accounted for 45.9%. This is in accordance with the study of Fanaroff AA, et al who found that the incidence of sepsis is considerably higher in male newborns than the female ones.<sup>4</sup> Of the 207 babies with clinical suspicion of sepsis, the blood culture was positive in

88 newborns. The rate of culture positivity of our study was 42.51% which is in correlation with Zuhair M. Al-Musawi<sup>5</sup> et al whose study revealed a 45% growth in culture. This is also in accordance with the study by K.V.Shyamala, et al which showed a culture positive rate of 51.3%.<sup>6</sup> Similarly Rekha Sriram et al reported a 50.4% on culture positivity in a study group of 115 neonates.<sup>7</sup> This correlates with the study of K.V.Shyamala, et al<sup>6</sup> but is in contrast with the study by Guida JD et al<sup>8</sup> which showed a predominant incidence of gram positive organisms. In this context, many of the studies conducted in the Indian subcontinent showed a high prevalence of gram negative sepsis while the western studies show a predominant gram positive growth.<sup>9</sup> The role of CRP in predicting culture positive sepsis is analyzed. The sensitivity of CRP as per our study was 96.59% with the lower and upper confidence intervals at 90.45 and 98.83. The sensitivity of our study is in agreement with the study done by Rekha Sriram et al which showed a value of 91.4% but is little bit higher in comparison to the study by Grzywna W, et al which showed the sensitivity of qualitative analysis of CRP at 66%.<sup>7,10</sup> The specificity of CRP as per our study is 94.12% with 88.35 and 97.12 being the respective lower and upper confidence intervals. The specificity correlates with the study conducted by Zuhair M. Al-Musawi et al<sup>5</sup> who showed a specificity of 96%. The sensitivity as per our study was a bit higher compared to his study which showed a sensitivity of 73% only. The positive predictive value of our study was 92.39% which is almost equal to his study which showed a value of 94.8%. Again, our negative predictive value was 97.39% which is on the higher side compared to that study which has a value of 78%. This might be because of the qualitative nature of our CRP assay while the other studies have been performed with quantitative analysis of CRP. The overall prevalence of thrombocytopenia in our study group is 64.25% which is in accordance with the study done by Torkaman M, et al.<sup>11</sup> It also correlates with the study done by K.V Shyamala, N.K. Subbalakshmi, K. Raghuvra<sup>6</sup> which showed a 69.9% prevalence of thrombocytopenia. This is in accordance with the study done by Guida J D, et al who also similarly found no statistical significance between thrombocytopenia and gram negative sepsis.<sup>8</sup> Like our study, they also noted a partial thrombocytopenia in gram positive sepsis. In a recent study done in 2009 in Italy, Manzoni P, et al had reciprocated our analysis concluding that thrombocytopenia is not an organism specific marker of sepsis.<sup>12</sup> On the other hand, the analysis by Scheifele DW, et al is in contrast with our study and states that the endotoxemia in necrotizing enterocolitis with gram negative organisms leads to thrombocytopenia.<sup>13</sup> Our study is also not in accordance with Rowe MI, et al<sup>14</sup> who had documented thrombocytopenia in gram negative sepsis.

## CONCLUSION

As per our study results, qualitative analysis of C-reactive protein can be used as an early marker of sepsis especially in resource limited settings. Although thrombocytopenia occurs predominantly in gram negative sepsis, there is insufficient evidence to support the use of platelet count to differentiate between gram positive and gram negative sepsis.

## REFERENCES

1. Current Pediatrics diagnosis and treatment 19<sup>th</sup> edition- pages 33-126.

2. Management of Neonatal Sepsis – NNF guidelines 2011
3. Mathur NB. Neonatal Sepsis. *Indian Pediatr* 1996 Aug; 33: 663-74.
4. Fanaroff AA, Korones SB, Wright LL, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. The National Institute of Child Health and Human Development Neonatal Research Network. *Pediatr Infect Dis J*. 1998;17:593–598.
5. Zuhair M. Al-Musawi. The role of CRP in the diagnosis and duration of antibiotic therapy in neonatal sepsis. *Kufa Med J* 2008;11:33-40.
6. K.V Shyamala, N.K. Subbalakshmi, K. Raghuvra. Role of CRP and platelet count in newborn sepsis. *J Chi Clin Med*. 2010;5:474.
7. Rekha Sriram. Correlation of Blood culture results with the Sepsis score and the Sepsis screen in the diagnosis of Neonatal Septicemia. *Int J Biol Med Res*. 2011;2:360–368.
8. Guida J D, Anette MK, Leef KH, McKenzie SE, and Paul DA. Platelet Count and Sepsis in Very Low Birth Weight Neonates: Is There an Organism-Specific Response? *Pediatrics*. 2003;111:1411-1415.
9. Reese Clark, Richard Powers, Robert White, Barry Bloom, Pablo Sanchez and Daniel K Benjamin, *J Peri*. 2004;24: 382–388.
10. Grzywna W, Stempniewicz K, Bodzek P, Stempniewicz E, Dyrek B. Evaluating the usefulness of qualitative analysis of latex c-reactive protein for diagnosing neonatal sepsis. *Ginekol Pol*. 1992;63:447-50.
11. Torkaman M, Afsharpaiman S H, Hoseini M J, Moradi M et al Platelet count and neonatal sepsis: a high prevalence of Enterobacter spp. *Sing Med J*. 2009;50:482-485.
12. Manzoni P, Mostert M, Galletto P, Gastaldo L, Gallo E, Agriesti G, Farina D. Is thrombocytopenia suggestive of organism-specific response in neonatal sepsis? *Pediatr Int*. 2009;51:206-10.
13. Scheifele DW, Olsen EM, Pendray MR. Endotoxemia and thrombocytopenia during neonatal necrotizing enterocolitis. *Am J Clin Pathol*. 1985;83:227-229.
14. Rowe MI, Buckner DM, Newmark S. The early diagnosis of Gram negative septicemia in the pediatric surgical patient. *Ann Surg*. 1975;182:280-286.

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