

# Thrombocytopenia Rates In Newborns Diagnosed With Gram-Negative Sepsis. Insights From NICU Experimental Based Study

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## Abstract

**Objective:** To evaluate the prevalence of thrombocytopenia observed in neonates admitted to the hospital with sepsis.

**Methods:** A total of 103 patients, including both males and females with ages below 28 days, who were admitted to the NICU (neonatal intensive care unit) with gram-negative sepsis were enrolled in this study. Blood samples were collected from each patient for sepsis and platelet analysis on the 1st and 3rd day of patients' admission and sent to the Ghurki Hospital laboratory for analysis. Thrombocytopenia was defined as platelet counts  $<150,000/\text{mm}^3$ . Thrombocytopenia was classified as mild, moderate, and severe. The type of organism and mortality rate related to thrombocytopenia were also recorded.

**Results:** Of 103 neonates, 64 (62.13%) were males while 39 (37.86%) were females. 88 (85.43%) had thrombocytopenia ( $p < 0.001$ ) whereas 15 (14.56%) had normal platelet count. *E. coli* was found to be the most common organism responsible for gram-negative sepsis. On day one, 61 (59.22%) patients had normal platelet count whereas 12 (11.65%), 14 (13.59%), & 16 (15.53%) neonates had mild, moderate & severe thrombocytopenia respectively. In contrast, on the third day, 18 (17.47%) neonates had normal platelet count, 6 (5.82%) had mild, 33 (32.03%) had moderate, and 46 (44.66%) had severe thrombocytopenia. 12/103 (11.65%) patients died, out of which 11 (10.68%) had thrombocytopenia.

**Conclusion:** Thrombocytopenia is a significant marker of gram-negative sepsis in neonates.

**Keywords:** Neonate, Neonatal Intensive Care Unit, Thrombocytopenia, Sepsis.

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## 1. Introduction

Thrombocytopenia is characterised by a platelet count of less than  $150 \times 10^9/\text{L}$ , which is often observed in newborns that are enrolled on the NICU (Neonatal Intensive Care Unit).<sup>1</sup> There are three classifications for thrombocytopenia: mild (platelet count  $100,000\text{--}150,000/\text{mm}^3$ ), moderate ( $50\text{--}99,000/\text{mm}^3$ ), and severe ( $<50,000/\text{mm}^3$ ).<sup>2</sup> Even after a great deal of research, thrombocytopenia in newborns remains a topic of interest because of the potential consequences of low platelet counts, including several types of bleeding, particularly intracranial and necrotizing enterocolitis, which can be fatal. Thrombocytopenia is thought to be a risk factor for haemorrhage, particularly when it occurs intraventricularly, as well as for death and poor neurodevelopmental outcomes.<sup>3</sup> One major cause of newborn thrombocytopenia is sepsis.<sup>4,5</sup> Neonatal sepsis occurs in 2824 live births per 100,000 worldwide, with a 17.61% death rate.<sup>6</sup> The incidence rate of thrombocytopenia was elevated in preterm and low-birth-weight newborns and in cases of late-onset neonatal sepsis, i.e., 59.30%, then in early-onset neonatal sepsis, i.e., 24%.

Thrombocytopenia was observed in 54% of meagre birth weight (VLBW) newborns in sepsis episodes that were confirmed by culture.<sup>5,7</sup> Neonatal sepsis is diagnosed by combining several procedures, including molecular techniques like PCR, blood cultures, nonspecific indicators like procalcitonin and C-reactive protein (when available), and clinical presentation.<sup>8</sup>

The causative microorganisms impact the duration of thrombocytopenia associated with sepsis. In contrast to Gram-positive infections, Fungal and Gram-negative infections lasted longer. They were frequent causes of thrombocytopenia.<sup>5</sup> It was discovered that thrombocytopenia connected to late-onset sepsis was severe and linked to increased morbidity and mortality.<sup>9</sup> A study conducted in India found that 59.51% of nosocomial sepsis cases had thrombocytopenia, with severe, moderate, and mild cases accounting for 12.50%, 20%, and 27% of cases, respectively.<sup>10</sup> Four out of ten neonates with sepsis in developed countries die or suffer from severe medical conditions, including considerable lifelong neurodevelopmental damage, despite significant advancements in neonatal care and increased

research.<sup>11</sup> The current study aimed to ascertain the prevalence of thrombocytopenia and associated gram-negative sepsis in newborns hospitalized in the intensive care unit.

## 2. Materials & Methods

This retrospective study was carried out at the NICU (neonatal intensive care unit) of the Department of Pediatrics and Neonatology, Ghurki Trust Teaching Hospital, following authorization from the Research and Ethics Board of Ghurki Trust and Teaching Hospital (Ref No.2023/01/R-02). Data was collected for twelve months. Non-probability consecutive sampling technique was used to select patients admitted to the hospital. The sample size was calculated using WHO sample size calculator 1.1 having a 95% confidence interval, anticipated population proportion of 0.57, and absolute precision of 0.09.<sup>12</sup>

A total of 103 patients, including both males and females with ages below 28 days, admitted to the NICU (Neonatal Intensive Care Unit) and had culture-positive gram-negative neonatal sepsis, were included in this study. The pathogen types that were grown in culture were noted. Following pathogens were tested for culturing; *E. coli*, *Serratia marcescens*, *Acinetobacter baumannii*, *Salmonella*, *Enterobacter*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.

Exclusions from the study included infants with extremely low birth weights (LBW) of less than 1000 g, babies older than 28 days, neonates with a family history of bleeding manifestations, newborns with a maternal history of placental insufficiency, and babies whose mothers had low platelet counts. Neonates with thrombocytopenia resulting from other conditions, such as SLE (systemic lupus erythematosus, idiopathic thrombocytopenic purpura (ITP) and neonatal alloimmune thrombocytopenia (NAIT), were omitted.

Upon admission, a blood sample was collected from each patient and sent to the Ghurki Hospital laboratory for platelet analysis to confirm thrombocytopenia and sepsis. On the third day of admission, another blood sample was collected for platelet analysis. Platelet counts were checked using the PC100 Platelet Counter. The blood samples were introduced into BACTEC Peds Plus/F culture vials at a volume of 1 to 2 ml and placed into a Bactec 9240 blood culture apparatus (BD Diagnostic Systems, Sparks, MD). The bottles under

study were subjected to a seven-day incubation period. Bottles exhibiting positive signal were directly transferred over agar of trypticase soy supplemented with blood of sheep (5%) on agar chocolate, as well as onto EMB (eosin-methylene blue) agar plates. Bacterial identification and assessment of susceptibility to antimicrobial agents were conducted using BD Diagnostic Systems, Sparks, MD [BD Phoenix AMS (Automated Microbiology System)] by the manufacturer's guidelines. Sepsis was confirmed after seven days. Platelet counts less than 150000/ $\mu$ L were used to characterize thrombocytopenia. There were three categories for thrombocytopenia severity: mild, moderate, and severe. Platelets counted 10000–150000/ $\mu$ L were considered mild, 50000–<100000/ $\mu$ L was considered moderate, and <50000/ $\mu$ L was considered severe.<sup>12</sup> Mortality associated with thrombocytopenia was recorded. The data was analysed using the Statistical Package for the Social Sciences, version 21 (SPSS). Qualitative variables are described as frequency and percentages. The quantitative data was reported as the mean  $\pm$  standard deviation. A T-test was performed to examine the association of all patients with and without thrombocytopenia on day one and day three respectively, with a p-value < 0.05 taken as significant using a 95% confidence interval.

## 3. Results

The study population was selected as per inclusion criteria. Out of 140 patients, 103 neonates with sepsis were included in the study and were evaluated accordingly.

**Table 1: Demographics of patients**

Gender	Number	Percentage (%)
Male	64	62.13%
Female	39	37.86%
Total	103	100%

On day one, 42 (40.78%) patients had thrombocytopenia. Whereas, on day 3, thrombocytopenic patients' number drastically increased to 85 (82.52%) as given in Table II. Overall, 88 (85.43%) patients had thrombocytopenia ( $p < 0.001$ ). Initially, the majority of the patients with sepsis had normal platelet counts. Moderate & severe thrombocytopenia was observed on the third day in most of the patients as depicted in Figure 1.

All 103 neonates were culture-positive for gram-negative sepsis. *E.coli* was found to be the most common organism in blood culture followed by *Serratia* &

Acinetobacter, Table 3. Thrombocytopenia was common in babies with E.coli & Serratia sepsis.

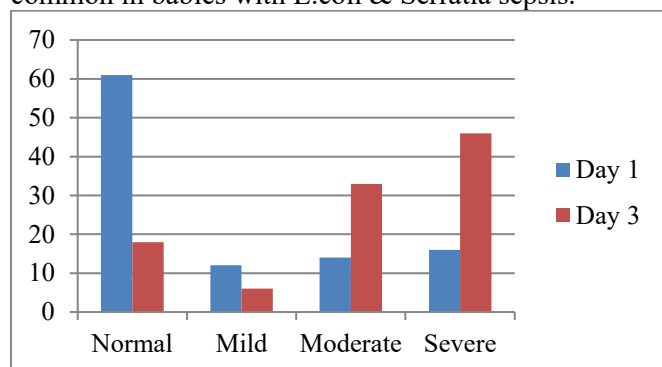


Figure 1: Severity of thrombocytopenia on days 1 & 3

12 neonates (11.65%) expired among all the newborns with sepsis, out of which 11 had thrombocytopenia, (Figure 2). Death rates among neonates with mild, moderate, and severe thrombocytopenia were 1 (8.33%), 1 (8.33%), and 9 (75%) respectively when last recorded.

Table 2: Severity of thrombocytopenia on days 1 and 3

Days	Normal	Mild TCP	Moderate TCP	Severe TCP	Total No. of TCP patients	Mean $\pm$ SD of TCPs	p-value	Statistically significant
Day 1	61 (59.22%)	12 (11.65%)	14 (13.59%)	16 (15.53%)	42 (40.78%)	71.50 $\pm$ 42.58	<0.001	Yes
Day 3	18 (17.47%)	6 (5.82%)	33 (32.03%)	46 (44.66%)	85 (82.52%)	53.07 $\pm$ 32.88	<0.001	Yes

Table 3: Distribution of organisms involved in gram-negative sepsis.

Organism	Number (%)	With thrombocytopenia
E. coli	43 (41.74%)	33 (36.25%)
Serratia marcescens	32 (31.06%)	31 (34.06%)
Acinetobacter baumannii	11 (10.67%)	9 (9.89%)
Salmonella	9 (8.73%)	7 (7.69%)
Enterobacter	5 (4.85%)	5 (5.49%)
Pseudomonas aeruginosa	3 (2.91%)	3 (3.29%)
Klebsiella pneumoniae	2 (1.94%)	2 (2.19%)
Proteus mirabilis	1 (0.97%)	1 (1.09%)

#### 4. Discussion

With a high incidence of morbidity and mortality, neonatal sepsis is one of the most prevalent and potentially fatal illnesses. It is also a significant reason for NICU admissions.<sup>13</sup> Thrombocytopenia is a prevailing clinical issue in newborns and a primary

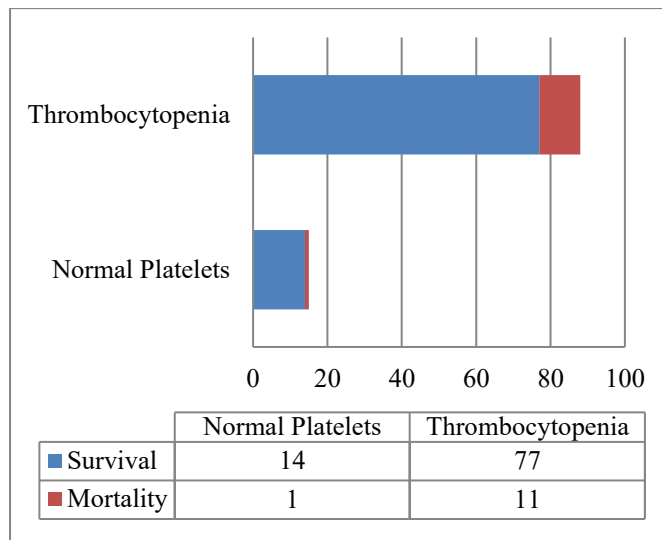


Figure 2: Relation between thrombocytopenia & mortality (n=103)

contributor to morbidity as well as mortality in those diagnosed with sepsis based on culture. This study aimed to evaluate thrombocytopenia rates in neonates diagnosed with culture-proven gram-negative sepsis. According to a Bangladeshi study, patients with gram-negative sepsis had a significant frequency of thrombocytopenia.<sup>14</sup> According to an Aligarh study, thrombocytopenia was more severe in gram-negative sepsis than in gram-positive sepsis.<sup>15</sup> In contrast to gram-positive sepsis in newborns, a Dutch study found that thrombocytopenia was independently related to gram-negative sepsis.<sup>10</sup>

The objective of our experimental study was to evaluate thrombocytopenia rates in neonates diagnosed with gram-negative sepsis admitted to the Neonatal Intensive Care Unit (NICU) at Ghurki Trust Teaching Hospital. We discovered that a substantial number of these newborns experienced thrombocytopenia, and the severity of this condition significantly worsened by the third day of hospitalization. The bacterium E. coli was

the primary culprit responsible, and infants with severe thrombocytopenia had a greater rate of death. According to a study by Khan et al. 32 males (46%) and 38 females (54%) had blood culture-positive sepsis.<sup>16</sup> Thrombocytopenia was found in 88 (85.43%) patients with gram-negative sepsis whereas 15 (14.56%) neonates had a platelet count of  $>150,000/\mu\text{L}$  when measured over six days. Ahmad et al. stated 67.8% of newborns with sepsis exhibited thrombocytopenia.<sup>15</sup>

A study conducted in Kashmir revealed that 119 (59.5%) of the 200 neonates with culture-positive sepsis had thrombocytopenia; of those, 54 (27%) had mild, 40 (20%) had moderate, and 25 (12.5%) had severe thrombocytopenia.<sup>16</sup> Among gram-negative organisms, *E. coli* was the most prevalent in 43 (41.74%) patients followed by *Serratia* 32 (31.06%) and *Acinetobacter* 11 (10.67%). Similarly, earlier research conducted in Bangladesh also exhibited *E. coli* to be the most common cause.<sup>17</sup> Other studies demonstrated *Klebsiella* as the most common pathogen responsible for culture-proven sepsis.<sup>11, 18.</sup>

We found that 12 (11.65%) out of 103 patients died, of which 11 had thrombocytopenia while one patient had a normal platelet count. These findings were consistent with earlier research investigations where patients with thrombocytopenia had a higher probability of dying than neonates without the condition.<sup>8, 19.</sup>

Thrombocytopenia in gram-negative sepsis is caused by multiple factors. Gram-negative bacteria secrete endotoxins that stimulate a strong inflammatory reaction, causing the activation of the coagulation cascade and depletion of platelets, potentially leading to disseminated intravascular coagulation (DIC). This mechanism greatly decreases platelet levels. In addition, sepsis-induced bone marrow suppression can hinder the synthesis of platelets. The literature extensively documents these pathways, providing strong support for our conclusions.<sup>20</sup>

The results of our study emphasize the significance of regularly monitoring platelet counts in newborns with gram-negative sepsis. Timely detection and intervention are vital to avert serious consequences such as cerebral hemorrhage and enhance survival rates. The significant occurrence of severe thrombocytopenia within three days of admission indicates that doctors should be attentive during the initial stages of treatment and contemplate assertive approaches to manage thrombocytopenia in these patients.

## 5. Conclusion

The study concludes that thrombocytopenia is a significant marker of gram-negative sepsis in neonates. There is a higher association between severe thrombocytopenia and mortality. Early detection of thrombocytopenia is pivotal to prevent high mortality in neonatal septicemia.

## Institutional Review Board Approval

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## CONFLICTS OF INTEREST- None

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## Contributions:

S.S, M.I, S.H, S.R, R.W, R.R - Conception of study

S.S, M.I, S.H, S.R, R.W, R.R - Experimentation/Study Conduction

S.S, M.I, S.H, S.R, R.W, R.R -

Analysis/Interpretation/Discussion

S.S, M.I, S.H, S.R, R.W, R.R - Manuscript Writing

S.S, M.I, S.H, S.R, R.W, R.R - Critical Review

S.S, M.I, S.H, S.R, R.W, R.R - Facilitation and Material analysis

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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