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Clinical assessment of hemodynamic variation in the platelet count and indices in neonatal sepsis in Bihar

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Abstract
Septicemia is a common cause of high neonatal mortality. It is caused by organisms invading the blood stream, which may be caused by bacterial, viral, fungal and protozoal infections. Septicemia is characterized by positive blood culture, neutrophilia, thrombocytopenia, elevated C-reactive protein and increased erythrocyte sedimentation rate. Septic shock is the most dangerous complication of septicemia. Thrombocytopenia is considered when platelet count falls below 150×109/ L. Endotoxins or platelet activating factor may cause abnormal bleeding. After 72 hrs of birth, thrombocytopenia may be severe and prolonged. Thrombocytopenia is caused by disseminated intravascular coagulation. Platelet indices studied are mean platelet volume, platelet distribution width and plateletcrit. Hence the present study is being undertaken to evaluate thrombocytopenia and variations in platelet indices in neonatal sepsis.
The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. The 100 cases of the neonatal sepsis were enrolled in the present study. The cases were divided in two study groups. The Group A consist of 50 patients of sepsis cases. The remaining 50 cases were enrolled in Group B as control without sepsis. Smears are made from peripheral blood and stained by Leishmans stain and examined to confirm thrombocytopenia. Platelet indices collected from automated machine Sysmex XT-2000i and Sysmex XE -2100.Bacterial and fungal organism type is detected by Blood culture and Gram staining. (From microbiology department).
The data generated from the present study concludes that Thrombocytopenia was the most sensitive marker for culture-positive sepsis. The platelet count decreased with development of sepsis and PDW and MPV increased in septic babies. Platelet indices did not differ significantly with gestational age or with Gram-positive or Gram-negative blood culture. This study is useful for evaluating platelets indices as a marker of neonatal sepsis alone or with combination to pre-existing sepsis screen.

Keywords: hemodynamic variation, platelet count, indices, neonatal sepsis, DMCH, etc

Introduction
Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis). Neonatal sepsis is the single most important cause of neonatal deaths in the community, accounting for over half of them. If diagnosed early and treated aggressively with antibiotics and good supportive care, it is possible to save most cases of neonatal sepsis.
Neonatal sepsis encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, pyogenic arthritis, osteomyelitis, and urinary tract infections. Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes. Sepsis related mortality is largely preventable with rational antimicrobial therapy and aggressive supportive care.
Neonatal sepsis is a type of neonatal infection and specifically refers to the presence in a newborn baby of a bacterial blood stream infection (BSI) (such as meningitis, pneumonia, pyelonephritis, or gastroenteritis) in the setting of fever. Older textbooks may refer to neonatal sepsis as "sepsis neonatorum". Criteria with regards to hemodynamic compromise or respiratory failure are not useful clinically because these symptoms often do not arise in neonates until death is imminent and unpreventable. Neonatal sepsis is divided into two categories: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS refers to sepsis presenting in the first 7 days of life (although some refer to EOS as within the first 72 hours of life), with LOS referring to presentation of sepsis after 7 days (or 72 hours, depending on the system used). Neonatal sepsis is the single most common cause of neonatal death in hospital as well as community in developing country.
It is difficult to clinically exclude sepsis in newborns less than 90 days old that have fever (defined as a temperature > 38 °C (100.4 °F). Except in the case of obvious acute viral bronchiolitis, the current practice in newborns less than 30 days old is to perform a complete workup including complete blood count with differential, blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) studies and CSF culture, admit the newborn to the hospital, and treat empirically for serious bacterial infection for at

least 48 hours until cultures are demonstrated to show no growth. Attempts have been made to see whether it is possible to risk stratify newborns in order to decide if a newborn can be safely monitored at home without treatment despite having a fever. One such attempt is the Rochester criteria.

Neonatal sepsis may be categorized as early onset (day of life 0-3) or late onset (day of life 4 or later). Of newborns with early-onset sepsis, 85% present within 24 hours (median age of onset 6 hours), 5% present at 24-48 hours, and a smaller percentage present within 48-72 hours. Onset is most rapid in premature neonates.

Early-onset sepsis is associated with acquisition of microorganisms from the mother. Infection can occur via hematogenous, transplacental spread from an infected mother or, more commonly, via ascending infection from the cervix. Organisms that colonize the mother's genitourinary (GU) tract may be acquired by the neonate as it passes through the colonized birth canal at delivery. The microorganisms most commonly associated with early-onset infection include the following [1]: Group B Streptococcus (GBS); Escherichia coli; Coagulase-negative Staphylococcus; Haemophilus influenza; Listeria monocytogenes.

Trends in the epidemiology of early-onset sepsis show a decreasing incidence of GBS disease following the widespread adoption of prenatal screening and treatment protocols [2, 3, 4].

In a study involving 4696 women, prenatal cultures showed a GBS colonization rate of 24.5%, with a positive culture rate of 18.8% at the time of labor [5]. As many as 10% of prenatally culture-negative women were found to have positive cultures at the time of labor. In the study, intrapartum antibiotic prophylaxis occurred appropriately in 93.3% of cases, with 0.36 of 1000 infants developing early-onset GBS disease [5].

Trends in late-onset sepsis show an increase in coagulase-negative streptococcal sepsis, with most isolates showing susceptibility to first-generation cephalosporins [2]. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus may become colonized via contact with the environment or caregivers.

Pneumonia is more common in early-onset sepsis, whereas meningitis and bacteremia are more common in late-onset sepsis. Early-onset sepsis is 10 to 20 times more likely to occur in premature, very low birthweight infants [6]. Premature infants often have nonspecific, subtle symptoms; considerable vigilance is therefore required in these patients so that sepsis can be identified and treated in a timely manner.

The infectious agents associated with neonatal sepsis have changed since the mid-20th century. During the 1950s, S aureus and E coli were the most common bacterial pathogens among neonates in the United States. Over the ensuing decades, Group B Streptococcus (GBS) replaced S aureus as the most common gram-positive organism causing early-onset sepsis.

Currently, GBS and E coli continue to be the most commonly identified microorganisms associated with neonatal infection. Additional organisms, such as coagulase-negative Staphylococcus epidermidis, L monocytogenes, Chlamydia pneumoniae, H influenzae, Enterobacter aerogenes, and species of Bacteroides and Clostridium have also been identified in neonatal sepsis.

Meningoencephalitis and neonatal sepsis can also be caused by infection with adenovirus, enterovirus, or coxsackievirus. Additionally, sexually transmitted diseases (eg, gonorrhea, syphilis, herpes simplex virus [HSV] infection, cytomegalovirus [CMV] infection, hepatitis, human immunodeficiency virus [HIV] infection, rubella, toxoplasmosis, trichomoniasis, and candidiasis) have all been implicated in neonatal infection.

Bacterial organisms with increased antibiotic resistance have emerged and have further complicated the management of neonatal sepsis [7]. The colonization patterns in nurseries and personnel are reflected in the organisms currently associated with nosocomial infection. In neonatal intensive care units (NICUs), infants with lower birth weight and younger gestational ages have an increased susceptibility to these organisms.

S epidermidis, a coagulase-negative Staphylococcus, is increasingly seen as a cause of nosocomial or late-onset sepsis, especially in the premature infant, in whom it is considered the leading cause of late-onset infections. Its prevalence is likely related to several intrinsic properties of the organism that allow it to readily adhere to the plastic mediums found in intravascular catheters commonly required for the care of these infants.

The bacterial capsule polysaccharide adheres well to the plastic polymers of the catheters. Also, proteins found in the organism (AtlE and SSP-1) enhance attachment to the surface of the catheter. The adherence creates a capsule between microbe and catheter, preventing C3 deposition and phagocytosis [8, 9].

Biofilms are formed on indwelling catheters by the aggregation of organisms that have multiplied under the protection provided by the adherence to the catheter. Slimes are produced at the site from the extracellular material formed by the organism, which provides a barrier to host defense as well as to antibiotic action, making coagulase-negative staphylococcal bloodstream infection (BSI) more difficult to treat. The toxins formed by S epidermidis have also been associated with necrotizing enterocolitis.

In addition to being a cause of neonatal sepsis, coagulase-negative Staphylococcus is ubiquitous as part of the normal skin flora. Consequently, it is a frequent contaminant of blood and cerebrospinal fluid (CSF) cultures. When a culture grows this organism, the clinical presentation, colony counts, and the presence of polymorphonuclear neutrophils (PMNs) on Gram staining of the submitted specimen often help differentiate true infection from contaminated culture specimens.

In addition to the specific microbial factors mentioned above, numerous host factors predispose the newborn to sepsis [10]. These factors are especially prominent in the premature infant and involve all levels of host defense, including cellular immunity, humoral immunity, and barrier function. Immature immune defenses and environmental and maternal factors contribute to the risk for neonatal sepsis, morbidity, and mortality, particularly in preterm and/or very low birthweight (VLBW) infants [10, 11]. There may also be a genetic association [10].

PMNs are vital for effective killing of bacteria. However, neonatal PMNs are deficient in chemotaxis and killing capacity. Decreased adherence to the endothelial lining of blood vessels reduces their ability to marginate and leave the intravascular space to migrate into the tissues. Once in the tissues, they may fail to degranulate in response to

chemotactic factors.

Furthermore, neonatal PMNs are less deformable and thus are less able to move through the extracellular matrix of tissues to reach the site of inflammation and infection. The limited capacity of neonatal PMNs for phagocytosis and killing of bacteria is further impaired when the infant is clinically ill. Finally, neutrophil reserves are easily depleted because of the diminished response of the bone marrow, especially in the premature infant [12].

Neonatal monocyte concentrations are at adult levels; however, macrophage chemotaxis is impaired and continues to exhibit decreased function into early childhood. The absolute numbers of macrophages are decreased in the lungs and are likely decreased in the liver and spleen as well. The chemotactic and bactericidal activity and the antigen presentation by these cells are also not fully competent at birth. Cytokine production by macrophages is decreased, which may be associated with a corresponding decrease in T-cell production [13].

Although T cells are found in early gestation in fetal circulation and increase in number from birth to about age 6 months, these cells represent an immature population. These naive cells do not proliferate as readily as adult T cells do when activated, and they do not effectively produce the cytokines that assist with B-cell stimulation and differentiation and granulocyte/monocyte proliferation.

Formation of antigen-specific memory function after primary infection is delayed, and the cytotoxic function of neonatal T cells is 50%-100% as effective as that of adult T cells. At birth, neonates are deficient in memory T cells. As the neonate is exposed to antigenic stimuli, the number of these memory T cells increases.

Natural killer (NK) cells are found in small numbers in the peripheral blood of neonates. These cells are also functionally immature in that they produce far lower levels of interferon gamma (IFN-γ) upon primary stimulation than adult NK cells do. This combination of findings may contribute to the severity of HSV infections in the neonatal period.

The fetus has some preformed immunoglobulin (Ig), which is primarily acquired through nonspecific placental transfer from the mother. Most of this transfer occurs in late gestation, such that lower levels are found with increasing prematurity. The neonate's ability to generate immunoglobulin in response to antigenic stimulation is intact; however, the magnitude of the response is initially decreased, rapidly rising with increasing postnatal age [14].

The neonate is also capable of synthesizing IgM in utero at 10 weeks' gestation; however, IgM levels are generally low at birth, unless the infant was exposed to an infectious agent during the pregnancy, which would have stimulated increased IgM production [15].

IgG and IgE also may be synthesized in utero. Most IgG is acquired from the mother during late gestation. The neonate may receive IgA from breastfeeding but does not secrete IgA until 2-5 weeks after birth. Response to bacterial polysaccharide antigen is diminished and remains so during the first 2 years of life.

Complement protein production can be detected as early as 6 weeks' gestation; however, the concentration of the various components of the complement system varies widely from one neonate to another. Although some infants have had complement levels comparable to those in adults, deficiencies appear to be greater in the alternative pathway than in the classic pathway [16].

The terminal cytotoxic components of the complement cascade that lead to the killing of organisms, especially gram-negative bacteria, are deficient. This deficiency is more marked in preterm infants. Mature complement activity is not attained until infants reach 6-10 months of life. Neonatal sera have reduced opsonic efficiency against GBS, E coli, and Streptococcus pneumoniae because of decreased levels of fibronectin, a serum protein that assists with neutrophil adherence and has opsonic properties.

The physical and chemical barriers to infection in the human body are present in the newborn but are functionally deficient. Skin and mucous membranes are broken down easily in the premature infant. Neonates who are ill, premature, or both are at additional risk because of the invasive procedures that breach their physical barriers to infection. Because of the interdependence of the immune response, the individual deficiencies of the various components of immune activity in the neonate conspire to create a hazardous situation when the neonate is exposed to infectious threats.

The intestines are colonized by organisms in utero or at delivery through swallowing of, and exposure to, amniotic fluid and genitourinary tract secretions. The immunologic defenses of the gastrointestinal tract are not mature, especially in the preterm infant. Lymphocytes proliferate in the intestines in response to mitogen stimulation; however, this proliferation is not fully effective in responding to a microorganism, as antibody response and cytokine formation are immature until approximately 46 weeks' gestation.

Necrotizing enterocolitis has been associated with the presence of a number of species of bacteria in the immature intestine. Overgrowth of these organisms in the neonatal lumen can be a component of the multifactorial pathophysiology of necrotizing enterocolitis.

Septicemia is a common cause of high neonatal mortality. It is caused by organisms invading the blood stream, which may be caused by bacterial, viral, fungal and protozoal infections. Septicemia is characterized by positive blood culture, neutrophilia, thrombocytopenia, elevated C-reactive protein and increased erythrocyte sedimentation rate. Septic shock is the most dangerous complication of septicemia. [17].

Thrombocytopenia is considered when platelet count falls below 150×109/ L [18]. Endotoxins or platelet activating factor may cause abnormal bleeding. After 72 hrs of birth, thrombocytopenia may be severe and prolonged. Thrombocytopenia is caused by disseminated intravascular coagulation. Platelet indices studied are mean platelet volume, platelet distribution width and plateletcrit. Hence the present study is being undertaken to evaluate thrombocytopenia and variations in platelet indices in neonatal sepsis.

Methodology

The Present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Bihar. The 100 cases of the neonatal sepsis were enrolled in the present study. The cases were divided in two study groups. The Group A consist of 50 patients of sepsis cases. The remaining 50 cases were enrolled in Group B as control without sepsis. Smears are made from peripheral blood and stained by Leishmans stain and examined to confirm thrombocytopenia. Platelet indices collected from

automated machine Sysmex XT-2000i and Sysmex XE - 2100. Bacterial and fungal organism type is detected by Blood culture and Gram staining. (From microbiology department).

Neonates were evaluated by thorough history from mother and detail clinical examinations. Peripheral venous blood was collected from all the newborns and sent for investigations for blood culture, sepsis screen and platelets indices. On the results obtained they were classified to in to three groups; proven sepsis-culture positive; suspected-screen positive but culture negative; and clinical sepsis-both screen and culture negative.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Neonates who had signs and symptoms suggestive of neonatal sepsis. Newborns with any of features were kept under clinical sepsis category. Risk factors for perinatal sepsis.

Exclusion criteria: Mother with History s/o ITP, SLE / other autoimmune disorders, on medication during pregnancy (sulfonamides, quinine / quinidine) (thiazides, tolbutamide, vancomycin, hydralazine, and heparin), Neonate with h.s/o bleeding disorder in family, trisomies, Turner /Noonans syndrome

Results & Discussion

The exact mechanisms of increases of MPV and PDW in neonatal sepsis are not entirely clear. It has been reported that coagulation and platelet activation can occur during early stages of sepsis. During activation process, platelets change in shape of the platelets from a discoid form to a spherical form with pseudopodia in order to acquire a larger surface, formation of pseudopodia can increase PDW value. Also, some researches reports that MPV is associated with function and activation of platelet. Generally, increase rate of platelet consumption leads to the release of young platelets from the bone marrow. Young platelets are more active than older platelets and also have a larger size, so MPV is frequently elevated.

The criteria for diagnosis of neonatal sepsis are positive blood culture, elevated CRP, increased ESR, neutrophilia and thrombocytopenia. Platelet count below 150×109 /L indicates thrombocytopenia. Variation in platelet indices are high MPV (>10.8fL), high PDW (>19.1%) and decreased plateletcrit (P<0.001) [20]. Mean platelet volume is a measurement of average size of platelets found in blood. Normal value of MPV is 7.5 - 11.5 fL. MPV is inversely proportional to platelet count in normal subjects. Platelet distribution width is an indicator of variation in platelet size. Normal value of PDW is 9-13 fL. Plateletcrit is the product of the MPV and platelet count, which indicates the volume of circulating platelets in a unit volume of blood. Principle used by analyser method for platelet detection is Hydro dynamic method (DC detection) [19]. Fungal and gram negative pathogens are associated with low platelet count and more prolonged thrombocytopenia compared with gram positive pathogen [21].

Table 1: Basic Details

Group	Group A	Group B
Cases of	**Neonatal Sepsis**	**Without Sepsis**
No. of Cases	50	50
Age		
Less than 72 hrs	22	24
More than 72 hrs	28	26
Sex		
Male	30	34
Females	20	16
Weight		
Less than 2.5 kg	33	39
More than 2.5 kg	17	11
Gestational Age		
Preterm	34	32
Term	16	18

Table 2: Platelet Count Indices

Group	Group A	Group B
Cases of	**Neonatal Sepsis**	**Without Sepsis**
No. of Cases	50	50
Platelet Count		
Less than 1.5 lakhs/mm3	41	10
More than 1.5 lakhs/mm3	9	40
Mean platelet volume (MPV)		
Less than 10.8 fl	36	13
More than 10.8 fl	14	37
Platelet distribution width (PDW)		
Less than 19.1 fl	38	18
More than 19.1 fl	12	32

E Guclu *et al*., 14 found PDW as a significant parameter in neonates with sepsis. Ferhatcatal *et al*., found that there is significant differences between control and sepsis group in terms of platelet count, PDW/MPV [23]. Thrombocytopenia is also known to be of prognostic value. Thrombocytopenia was found to be consistently associated with poor prognosis, confirming the finding of other studies [22].

The relationship between platelet indices and various diseases has been the subject of increasing study because of their rapid and widespread availability. Haematology analysers with coulter principle, measure platelet volume by changes of electrical properties, which depends on platelet vertical diameter; other analysers based on laser optical technology determine platelet volume by cross diameter of platelet. Regardless of the method of measurement, activated platelets seem larger. MPV is inversely commensurate to the rate of maturation of platelet. (5) MPV value decreased in conditions, which are associated with reduction of platelet production in the bone marrow, such as aplastic anaemia and myelodysplastic syndrome and chemotherapy induced bone marrow suppression [24]. Increases of MPV value suggests that proportion of younger platelets in the blood circulation are increased, and is indicate increased platelet destruction or production, such as hypersplenism and immune thrombocytopenia [26]. PDW is an indicator of the heterogeneity in platelet size. Increases of PDW suggest a large range of platelet because of swelling, immaturity and destruction [25]. Thrombocytopenia is a common hematologic finding in critically ill patients,

and is associated with increased mortality. It is also a known fact in preterm infants with sepsis. A close relationship between sepsis and thrombocytopenia has been suggested in some studies. Mannan *et al*. in their study showed that 50% cases of neonatal sepsis had thrombocytopenia [27]. Another study by Guida *et al*. showed that 54% of very low birth weight neonates with culture proven neonatal sepsis, developed thrombocytopenia [28]. Abdulla *et al*. showed that 42.8% babies with sepsis had thrombocytopenia [29]. Thrombocytopenia was found in 25% of our neonatal population, which is lower than previous studies. Neonatal sepsis refers to generalized bacterial infection and is a serious condition requires rapid and accurate diagnosis. There have been a few reports which have evaluated the relationship between platelet indices and sepsis disorder.

Clinical studies that have examined the association between platelet count and indices and sepsis demonstrate contradictory results. In a study conducted in newborns, Patrick *et al*. reported that levels of MPV and PDW were higher in patients with bacteraemia than controls [30]. Guclu *et al*. reported significant change in MPV in patients with sepsis compared to healthy controls, but platelet count was not significantly different. Van der Lelie *et al*. showed that MPV was increased in 13 of the 25 sepsis patients, and returned to normal values after the disease was controlled [31]. In a cohort study performed on newborn with sepsis, thrombocytopenia and elevated MPV were prominent features [32]. Conversely, Acikgoz *et al*. reported that MPV and PDW not significantly different between sepsis patients with DIC and without DIC [33]. In addition to sepsis, MPV and PDW also have a positive correlation with many different diseases such as diabetes, myocardial infarction and various infections [34]. Elevated white blood cell and neutrophil counts are the main laboratory findings in the diagnosis of sepsis. These findings suggested that platelet count and platelet indices may serve as useful indicators of neonatal sepsis. However, no significant differences were found in either platelet count or MPV and PDW of neonates between those with early and late on-set sepsis.

Neonates are fragile and can deteriorate rapidly, so one should be prompt in management. However, the diagnosis of sepsis in neonates presents as a challenge because the clinical signs of sepsis are non-specific. Since clinical signs alone cannot make a specific diagnosis of sepsis, we have to rely on investigations to guide us. Among these blood culture is the gold standard for the diagnosis for neonatal sepsis. Even this gold standard is not without its limitations. To overcome this limitation and to guide early diagnosis, sepsis screens (CRP, micro ESR, haematological parameters) are used. It has been seen that platelet count decreases and mean platelet volume (MPV) and platelet distribution width (PDW) increase in neonates with sepsis, but these indices have not been extensively studied in neonatal sepsis.

Conclusion

The data generated from the present study concludes that Thrombocytopenia was the most sensitive marker for culture-positive sepsis. The platelet count decreased with development of sepsis and PDW and MPV increased in septic babies. Platelet indices did not differ significantly with gestational age or with Gram-positive or Gram-negative blood culture. This study is useful for evaluating platelets indices as a marker of neonatal sepsis alone or with combination to pre-existing sepsis screen.

References

1. Klinger G, Levy I, Sirota L, *et al*, for the Israel Neonatal Network. Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants. Am J Obstet Gynecol. 2009; 201(1):38.e1-6. [Medline].
2. Van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology. 2010; 97(1):22-8. [Medline].
3. [Guideline] Verani JR, McGee L, Schrag SJ, for the Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010; 59(RR-10):1-36. [Medline]. [Full Text].
4. Berardi A, Rossi C, Spada C, *et al*, for the GBS Prevention Working Group of Emilia-Romagna. Strategies for preventing early-onset sepsis and for managing neonates at-risk: wide variability across six Western countries. J Matern Fetal Neonatal Med. 2019; 32(18):3102-8. [Medline].
5. Lin FY, Weisman LE, Azimi P, *et al*. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. Pediatr Infect Dis J. 2011; 30(9):759-63. [Medline]. [Full Text].
6. Weston EJ, Pondo T, Lewis MM, *et al*. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J. 2011; 30(11):937-41. [Medline].
7. Morales WJ, Dickey SS, Bornick P, Lim DV. Change in antibiotic resistance of group B streptococcus: impact on intrapartum management. Am J Obstet Gynecol. 1999; 181(2):310-4. [Medline].
8. Strunk T, Richmond P, Simmer K, Currie A, Levy O, Burgner D, *et al*. Neonatal immune responses to coagulase-negative staphylococci. Curr Opin Infect Dis. 2007; 20(4):370-5. [Medline].
9. Power Coombs MR, Kronforst K, Levy O. Neonatal host defense against Staphylococcal infections. Clin Dev Immunol, 2013; 2013:826303. [Medline].
10. Srinivasan L, Kirpalani H, Cotten CM. Elucidating the role of genomics in neonatal sepsis. Semin Perinatol. 2015; 39 (8):611-6. [Medline].
11. Groer MW, Gregory KE, Louis-Jacques A, Thibeau S, Walker WA. The very low birth weight infant microbiome and childhood health. Birth Defects Res C Embryo Today. 2015; 105(4):252-64. [Medline].
12. Koenig JM, Yoder MC. Neonatal neutrophils: the good, the bad, and the ugly. Clin Perinatol. 2004; 31(1):39-51. [Medline].
13. Weinberg AG, Rosenfeld CR, Manroe BL, Browne R. Neonatal blood cell count in health and disease. II. Values for lymphocytes, monocytes, and eosinophils. J Pediatr. 1985; 106(3):462-6. [Medline].
14. Landor M. Maternal-fetal transfer of immunoglobulins. Ann Allergy Asthma Immunol. 1995; 74(4):279-83. quiz 284. [Medline].
15. Griffiths PD, Stagno S, Pass RF, Smith RJ, Alford CA Jr. Congenital cytomegalovirus infection: diagnostic

and prognostic significance of the detection of specific immunoglobulin M antibodies in cord serum. Pediatrics. 1982; 69(5):544-9. [Medline].
16. Kohler PF. Maturation of the human complement system. I. Onset time and sites of fetal C1q, C4, C3, and C5 synthesis. J Clin Invest. 1973; 52(3):671-7.
17. Behrman RE, Jeusan HB, Kliegman RM, ‘‘Pathogenesis And Epidemiology”,Chapter 98, Nelson Textbook Of Pediatrics, ED 17, Stoll B.J,Elsevier Publication, New Delhi, 2004, 630-639
18. Larson L, Alexander JL. ‘‘Disorder of primary hemostasis”, chapter 36, clinical laboratory haematology, Mc.kencie. SB, Pearson Education publishers, New Jersy, 2004, 710-712.
19. Bain JB, Lewis SM, Bates I. ‘‘Basic Hematological Techniques”, Chapter 3, Practical Hematology, Dacie and lewis, Bain J.B, Elsevier Publication, New Delhi, 2008, 51
20. Patrick CH, Lazarchick J. ‘‘The effect of bactermia an automated platelet measurements in neonates”,Am J Clini Pathol. 1990; 93(3):39
21. Guida JD, Kunig AM, ‘‘Platelet Count and sepsis in very low birth weight neonates: Is there an organism specific response”, Official Journal of American academy of Pediatrics, 2003, 1411-1415.
22. Torkman M, Afsharpaiman SH, Hoseini MJ, *et al*. Platelet count and neonatal sepsis: A high prevalence of Enterobacter spp. Singapur Med J. 2009; 50(5):482-5.
23. Catal F, Tayman C, Tonbul A, Bilici M. Mean platelet volume may simply predict the severity of sepsis in preterm infants. Clinical Laboratory. 2014; 60(7):1193-200.
24. Gao Y, Li Y, Yu X, *et al*. The impact of various platelet indices as prognostic markers of septic shock. PLoS One. 2014; 9(8):e103761.
25. Borkataky S, Jain R, Gupta R, *et al*. Role of platelet volume indices in the differential diagnosis of thrombocytopenia: a simple and inexpensive method. Hematology. 2009; 14(3):182-6.
26. Ahmad MS, Waheed A. Platelet counts, MPV and PDW in culture proven and probable neonatal sepsis and association of platelet counts with mortality rate. J Coll Physicians Surg Pak. 2014; 24(5):340-4.
27. Mannan M, Shahidullah M, Noor MK, *et al*. Utility of Creactive protein and hematological parameters in the detection of neonatal sepsis. Mymensingh Medical Journal. 2010; 19(2):259-63.
28. Guida JD, Kunig AM, Leef KH, *et al*. Platelet count and sepsis in very low birth weight neonates: is there an organism-specific response? Pediatrics. 2003; 111(6 Pt 1):1411-5.
29. Alshorman A, Maghayreh M, Khriesat W, *et al*. The effect of neonatal sepsis on platelet count and their indices. Jordan Medical Journal. 2008; 42(2):82-6.
30. Patrick CH, Lazarchick J. The effect of bacteremia on automated platelet measurements in neonates. American Journal of Clinical Pathology. 1990; 93(3):391-4.
31. Van der Lelie J, Von dem Borne AK. Increased mean platelet volume in septicaemia. Journal of Clinical Pathology. 1983; 36(6):693-6.
32. El-Mashad GM, El-Sayed HM, Rizk MS, *et al*. Mean platelet volume and serum uric acid in neonatal sepsis. Menoufia Medical Journal. 2017; 30(2):581-7.
33. Acikgoz S, Akduman D, Eskici Z, *et al*. Thrombocyte and erythrocyte indices in sepsis and disseminated intravascular coagulation. Journal of Medical Biochemistry. 2012; 31(1):60-4.
34. Lee IR, Shin JI, Park SJ, *et al*. Mean platelet volume in young children with urinary tract infection. Scientific Reports, 2015; 5:18072.