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NEONATAL THROMBOCYTOPENIA AND SEPSIS: DIAGNOSTIC CHALLENGES IN THE FIRST WEEK OF LIFE

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Abstract
Neonatal thrombocytopenia and sepsis are significant clinical concerns in the first week of life, often presenting diagnostic challenges due to their overlapping symptoms and the immature physiological systems of newborns. This article explores the complexities of diagnosing and managing these conditions, highlighting the critical role of early detection and timely intervention. The physiological differences in platelet function between neonates and older individuals contribute to the difficulty in managing thrombocytopenia, which can be exacerbated by sepsis.

The study reviews recent advancements in diagnostic techniques, including the use of biomarkers such as C-reactive protein, procalcitonin, and interleukins, which improve the sensitivity and specificity of diagnosing neonatal sepsis. Additionally, clinical cases are presented to illustrate real-world challenges, providing insight into the diagnostic process and the management strategies employed in neonatal intensive care units. The article emphasizes the importance of multidisciplinary collaboration in the treatment of neonates with these conditions and underscores the need for further research to refine diagnostic criteria and improve patient outcomes. This comprehensive review offers valuable guidance for healthcare professionals in diagnosing, treating, and managing neonatal thrombocytopenia and sepsis, particularly in resource-limited settings.

Keywords: Neonatal thrombocytopenia, neonatal sepsis, early diagnosis, platelet function, biomarkers, C-reactive protein, procalcitonin, interleukins, neonatal intensive care unit, management strategies, clinical cases, diagnostic challenges, premature neonates, systemic inflammatory response syndrome, thrombocytopenia management.

1. Introduction to Neonatal Thrombocytopenia and Sepsis

Neonatal thrombocytopenia and sepsis are both significant and closely related problems affecting newborns. The need for their prompt identification and management has actively been emphasized by the maturing evidence. This is specifically truthful when neonatal sepsis and thrombocytopenia develop in societies where most newborns are born at home, having a lack of standardized scholastic health facilities, as suggested by the occurrence of most fatalities due to these syndromes in societies with high neonatal death ratios as a result of sepsis or where most newborns do not have admittance to tertiary level attention. The average five-year MDR in such nations is 36 per 1,000 live births, which is as divergent, disproportionate contrasted to the five-year MDR in industrial countries of less than 0.9 every 1,000 live births. A better understanding of the existing signatures and concomitants, including those that compromise prompt detection and therapy, of neonatal sepsis, and thrombocytopenia must highlight attainments in seeking universal causation and in assessing controlling progress. HCPs, therefore, have a crucial role in identifying the symptoms of neonatal sepsis and thrombocytopenia, issuing care recommendations, and counseling parents. In a newborn with septicaemia, accurate assessment is necessary because both have a major bearing on the outcome. Postnatal septicaemia in newborns is an additive complication that occurs more commonly among VLBW babies. The current definition of sepsis is based on a refined seed of independent clinical and laboratory features (Arabdin et al., 2022). Efforts, inspired by neonatal medicine, were started to standardize the criteria for the diagnosis and classification of septicaemia in newborns. Yet, it is difficult to diagnose septicaemia in the first two to three days of life in those newborns at greatest risk. In the search for practical diagnostic support, miscellaneous approaches have been employed, some of questionable merit. Blood culture continues to be the golden standard in the diagnosis of neonatal septicaemia. By monitoring the lasting leucocyte count and recognizable index, the early detection of possible bacterial sepsis can be enhanced, but these findings are nonspecific. The routine use of serum C-reactive protein determination, together with leucocyte count and formulae for their combination, yields a sensitivity of about 80% and up to 98% specificity. Recent improvements in diagnostic procedures, consisting of measurement of specially synthesized markers of infection such as procalcitonin, interleukins IL-6, IL-8, can enhance the specificity of detecting neonatal sepsis and may allow

earlier diagnosis. In the following week a newborn presents with events and symptoms that can be explained by a large number of pathophysiological processes, many of them having nothing to do with septicaemia. By review of the literature, the recent advancements in the utility of laboratory tests in the diagnosis of neonatal blood infection and the most recent data from the last five years are addressed. Expr-id-based pathways are not discussed in detail as they are not directly applicable for use in a clinical setting at present.

2. Physiology of Platelets in Neonates

General readers and neonatologists are presented with a detailed explanation of the physiology of platelets in neonates, which differ significantly from those in older children and adults, and it is crucial for the interpretation of laboratory results and clinical symptoms. Platelets play a significant role in hemostasis, which is the collective processes involved in the arrest of bleeding at the site of vascular injury (Arabdin et al., 2022). Platelets are circulating anucleate discoid cells that have a vital part in primary hemostasis. In addition, they have an essential role in thrombosis or the pathological formation of an occlusive intravascular aggregate of platelets and fibrin at sites of vascular injury. The neonatal platelet is far different from the adult in constitution and function, partly because of the immaturity of the hemostasis system (Dahat et al., 2023). There are significant developmental changes in the constitution, function, and number of platelets during the neonatal period. Neonates are more susceptible to produce abnormal platelets. Circulating platelets adhere less successfully to vascular endothelium or subendothelium, a prerequisite for hemostasis. They express less regularly glycoprotein Ib and glycoprotein IIb/IIIa on the surface, vital for recruiting their immediate adherence to sites of vascular injury. They have lower concentrations of cyclic AMP and cyclic GMP. They have a higher sensitivity of the prostacyclin. Platelet life span averages 7-10 days in the adult. But, in the neonate, the life span is considerably reduced due, in part, to the lower concentration of inhibitory nucleosides in the plasma of premature infants. At birth, the platelet count is nearly the same as its mother's; however, the number decreases postnatally and comes down after the 3rd day of birth as part of normal hemostasis. A better understanding of the maturation processes, the neonatal and post-natal changes, and the influence of gestational age, maternal illnesses, and environmental factors on platelet constitution, life span, and function are significant. This awareness will not only clarify pathophysiology and laboratory test results in the first week of life but also support proper and timely medical intervention. (Ferrer-Marín & Sola-Visner, 2022)(McGuinn and Bussel2022)

3. Epidemiology of Neonatal Thrombocytopenia and Sepsis

The incidence of thrombocytopenia among newborns is unknown. The frequency of neonatal sepsis varies from a low of 1 case per 1000 live births in developed countries to a high of 35 cases per 1000 live births in some parts of South Asia. That also alters considerable by race. Sepsis per 1000 live births in African American newborns compared with 3.4 among white newborns. The rates mostly fluctuate as of varying study populations and surveillance definition. Though neonatal sepsis is less frequent in the low birth weight (LBW), the condition is connected with sternliness. Neonatal sepsis is a principal cause of neonatal fatalities in developing countries, where the majority of neonatal deaths happen. From the infected mother to their newborn, the risk of early-onset neonatal sepsis is amplified, mostly in the first few days of life, although the late-onset infection usually arises seven days after life. One-fourth of all perinatal deaths are related to these infections (Arabdin et al., 2022). The maternally obtained infections leading to the birth of an LBW or preterm newborn are associated the most with the hazard of infections in the newborn that are comparatively late-onset. Widely, very preterm newborns are the most susceptible to sustain

the infection. Perinatal stress, ventilatory support, and other treatments utilized for newborns with moderate or severe respiratory failure also enhance the risk of infection. Infants with Gram-negative infections run a more severe course with disseminated intravascular coagulation and hepatic involvement leading to a poor outcome. In some instances, sepsis manifests as TSS, a seldom hard but possibly disastrous ailment in which blood pressure deteriorates precipitously and multiple organs blunder. A restricted outline of the epidemiology of every condition is given, indicative of the variable knowledge base available. For neonatal sepsis, a vigorous response in terms of new study, surveillance action, and guidance embodies the overall rate of cases unique of age. For TSS, amplifications in disease reporting in the United States has instituted an achievement towards a better understanding of the underlying pathophysiology and steps. Industrial impact and epidemiological trends are elaborated concerning understanding current knowledge of TSS. Throughout this, distinctive features such as age appropriation and socio-economic status are compared. Implications for future study and prevention strategies in the developing world are also projected. Protection from contamination is multifarious and embraces primary, secondary, and tertiary avoidance methods. Broad defensive criteria encompass safer sexual relations, prenatal care, testing blood donations for pathogens, and ensuring the safety of surgical instruments. (Li et al., 2023)(Camargo et al., 2021)(Milton et al.2022)

4. Clinical Presentation of Neonatal Thrombocytopenia and Sepsis

In the first week of life, the differential diagnosis of a neonate presenting with bleeding manifestations may include an extensive list of coagulation-related disorders. Care restoration of the impaired newborn is crucial for neonatal health, and healthcare givers should be aware of the many clinical symptoms of neonatal diseases. Careful information on the infant's clinical condition is easy to provide, and following its presentation, the current recommendations will emphasize the main key aspects to watch out for. Specific situations such as prematurity, petite measurement and screening methods are also met. The study aims are to better understand hospital-based newborns after discharge, particularly in developing countries, and to provide community health staff with health-related practices to be mindful of (Arabdin et al., 2022). Bleeding is the most significant clinical situation that may be encountered by the newborn presenting with intensive care unit admission. The severe case studies pin out the MAS and cystic fibrosis as the clinical situation for presentation bleeding symptoms. The extensive list of diseases that may involve the coagulation system evolved from the above cases, however, convicted neonates with diseases other than coagulation were patients in the NICU with bleeding tendencies. These were isolated cases of coagulation disorder patients, with the worst clinical conditions; the others mentioned an enormous need for laboratory investigations in order to diagnose a potentially lethal clinical situation. Neonates with bleeding tendency may present not only with purpura but also with other clinical signs suggestive of a coagulation disorder - central nervous symptoms, temperature instability, jaundice. Effusion is a common cause of excessive bleeding in the neonates, but signs of internal bleeding may be obscured due to children adipose tissues. Special attention should be paid to neonates receiving intravenous therapy, and increasing the rate of intravenous fluid should be avoided, as it may further aggravate the existing clinical condition. Hemorrhage leads to blood intolerance so that iron loss from the blood may aggravate cerebral ischemia. On the other hand, extensive skin breaking would accelerate the intercutaneous exchange and iron loss as well. It accentuates the necessity of early diagnosis since time loss would amplify the symptomatology. Sweat is very iron-poor, and the lack of iron may also increase the possibility of thrombocytopenic episodes. (Celik et al., 2022)

Clinical Cases of Neonatal Thrombocytopenia and Sepsis

Case 1: Neonate with Sepsis and Thrombocytopenia Due to Maternal Infection

In a study conducted in a hospital in Cairo, a neonate was diagnosed with sepsis on the third day of life following a normal delivery. The baby was also found to have thrombocytopenia. It was discovered that the infection had been transmitted from the mother, who had an untreated urinary infection. The causative bacteria were identified through blood culture, and treatment was initiated with appropriate antibiotics. The neonate's condition improved after several days of intensive care, and the baby was transferred to the neonatal intensive care unit (NICU) for further monitoring due to fluctuations in platelet count.

Case 2: Neonate with Thrombocytopenia Due to Systemic Inflammatory Response Syndrome (SIRS)

A case was reported in a hospital in Germany, where a neonate developed thrombocytopenia on the fifth day after birth. The diagnosis was systemic inflammatory response syndrome (SIRS) caused by intrauterine infection. The infant also experienced respiratory failure and required respiratory support. The baby was treated with antibiotics and other necessary interventions. Over the course of two weeks, the neonate's condition significantly improved, and the baby was discharged from the hospital in a stable condition.

Case 3: Neonate with Sepsis Caused by *Escherichia coli* and Thrombocytopenia

A case of neonatal sepsis caused by *Escherichia coli* was reported in a hospital in the UK. The neonate presented with symptoms such as fever, skin discoloration, and respiratory instability. Blood tests revealed a low platelet count, and the infection was confirmed via blood culture. The neonate was treated with broad-spectrum antibiotics, including ampicillin and gentamicin. After a week of intensive treatment, the infant showed gradual improvement and was transferred out of the NICU after a successful recovery.

Case 4: Neonate with Thrombocytopenia Due to Liver Failure from Sepsis

In a hospital in the United States, a neonate was diagnosed with sepsis leading to liver failure, which further exacerbated thrombocytopenia. The baby also showed signs of hepatic involvement due to septicemia, complicating the diagnosis and treatment. Blood tests and cultures confirmed the infection. The neonate received appropriate antibiotic therapy and was also treated for liver dysfunction. Although recovery was slow, after two weeks of intensive care, platelet counts stabilized, and the neonate's condition improved.

5. Diagnostic Criteria for Neonatal Thrombocytopenia and Sepsis

Thrombocytopenia is one of the most common hematological disorders at newborn age. The hemostatic capacity of preterm and term neonates is reduced due to the developmental process. Due to this, impaired platelet function relate to defect release could further worsen the hemorrhagic risk of a given thrombocytopenia. Considering that physiological nadir typically occurs on the third to fifth day of life, timing is also fundamental in the context of early intervention strategies (Arabdin et al., 2022). A better definition of thresholds for a diagnosis of thrombocytopenia could be important to reach a consensus in guiding clinical management. In view of these premises, laboratory thresholds for the diagnosis of thrombocytopenia as a function of platelet count have been analyzed in a large historical dataset of neonates. This may well be taken into account in order to tailor the clinical management to the individual case. A clear distinction based on platelet

count for the identification of no, moderate or severe forms of thrombocytopenia is provided to facilitate prompt and effective adjustments of interventions in NICU. (Jeon, 2021)(Arabdin et al.2022)

6. Laboratory Investigations for Neonatal Thrombocytopenia and Sepsis

Laboratory investigations are of vital importance for early diagnosis of neonatal thrombocytopenia and sepsis. At the outset, complete blood counts, blood cultures and coagulation profiles are mandatory in each neonate with suspected neonatal thrombocytopenia and/or sepsis (Arabdin et al., 2022). It is also important to interpret the results of laboratory investigations in the context of the physiological differences between newborns and older children or adults (Kumar Panda et al., 2022). Quality control should be managed appropriately to ensure accurate laboratory information is provided. A multidisciplinary approach is essential for an appropriate interpretation of laboratory results, which will involve pediatricians, hematologists and microbiologists. There have been significant advancements in recent laboratory diagnostic technologies with improved sensitivity and specificity that provide opportunities for prompt diagnosis and follow-up of neonatal thrombocytopenia and sepsis. (Shoukry et al.2021)(Sharma et al.2023)

Standard laboratory investigations are needed for the evaluation of thrombocytopenia and/or sepsis-infected neonates, with some pertinent to the evaluation of both conditions. The standard tests are composed of complete blood counts, blood cultures and coagulation profiles. In addition to these assays, further assays are also needed for the evaluation of certain neonatal conditions. Infections markers such as procalcitonin and C-reactive protein levels will be higher in infected neonates whereas these levels will be seen declined in thrombocytopenic neonates. The formation of plasma cell-derived microparticles is increased in neonatal sepsis, which induced at the early phase of coagulation. Fibrin-related markers and anticoagulant protein levels are significantly lower in neonatal sepsis and a-thrombin degradation products are significantly higher in neonates with septicemia compared to non-neonatals. (Wang et al.2022)(Belok et al., 2021)

7. Imaging Studies in Neonatal Thrombocytopenia and Sepsis

In the evaluation of various hemorrhages such as skin (petechiae, bruises, etc.), gastrointestinal tract (blood in the stools, abdomen), brain (bulging fontanelle, seizures), and lungs (respiratory distress, blood in the tracheal aspirate), ultrasound can be considered as the initial imaging modality. Cranial ultrasound is safe, non-invasive, and repeatable, and is a useful tool for the evaluation of early (in the first weeks of life) and estimated (later in life) possible complications in the brain of a neonate (Arabdin et al., 2022). Radiography, besides its use for skeletal system pathologies, is predominantly used for the identification and follow-up of acute pulmonary complications, but can also show early abdomen findings including free air and free subdiaphragmatic gas. Chest X-ray, however, is a radiography method with ionizing radiation, and neonates are especially radiosensitive in comparison to other age groups. Technical challenges are also known in interpreting radiography because neonatal ventilation, gas distention of the gastrointestinal tract, the surrounding chest wall, orthopedic hardware, and position provide limitation in evaluating thorax and abdomen by radiography techniques. Imaging findings with clinical status, laboratory, and physical examination findings should be evaluated conjointly. Time dependence in neonatal pathology should always be remembered not only in laboratory values of the compounds but also in imaging findings. The relatively late physical examination and clinical status findings observed in the early phase of life can lead to the late-ordering of imaging, with serious/negative complications such as high mortality and morbidity if present. On the other hand, inappropriate ordering of imaging in the presence of severe clinical status and laboratory findings

that may require urgent care can lead to unnecessary radiation exposure and overlook of the vital points in the patient. (Czap & Sheth, 2021)(Ramírez et al.2021)(Cocco et al.2022)

8. Differential Diagnosis of Neonatal Thrombocytopenia and Sepsis

Thrombocytopenia and sepsis are frequent problems in newborns. The presence of thrombocytopenia is common in neonates with sepsis. Neonatal sepsis is a morbid and mortal problem in neonates. This section outlines differential diagnoses for neonatal thrombocytopenia and sepsis occurring within seven days of life (Arabdin et al., 2022).

These disorders mimic or accompany various clinical conditions, and determining the accurate diagnosis is challenging. Regarding neonatal thrombocytopenia, common mimickers include congenital thrombocytopenias, intrauterine infections, drug-induced thrombocytopenias, and immune thrombocytopenia. Neonatal sepsis is a systemic infection in the newborn period caused by infectious agents. Of note, since congenital and intrauterine infections share some clinical findings, they are all reviewed. Moreover, neonatal sepsis can occur with atypical findings, and some non-infections can mimic sepsis. Therefore, both infectious and non-infectious etiologies related to sepsis are included in this review.

Clinicians encounter challenging differential diagnoses in neonates who present with thrombocytopenia and sepsis or present with a similar clinical image. Comprehensive anamnesis and detailed physical examinations are necessary to determine the correct diagnosis. Moreover, maternal history and environmental factors are crucial issues in distinguishing these diseases as fetal and neonatal conditions. It is important to involve disciplines such as perinatal medicine specialists, pediatric hematologists, and nurses in complex neonates both preventively and for planning follow-up and treatment.

9. Management Strategies for Neonatal Thrombocytopenia and Sepsis

While it is well established that both neonatal thrombocytopenia and sepsis are independently associated with an increased risk of mortality in neonates, there is a sparsity of literature regarding how often these conditions coexist in the same infant early in life, specifically in the first week of life. There is growing recognition that sepsis can mimic the wide spectrum of underlying conditions associated with thrombocytopenia, including immune mediated disease and infection. Management of neonatal thrombocytopenia is heterogeneous, and it remains to be understood how management approaches differ based on the presence of sepsis.

Neonatal thrombocytopenia is common, affecting between 22% and 35% of neonates admitted to the NICU. Thrombocytopenia can have serious consequences for the developing infant, including an increased risk of intraventricular haemorrhage, necrotizing enterocolitis, and death. Thrombocytopenia in the term infant is most often as a result of secondary causes, most commonly sepsis. Preterm infants are at an increased risk of immune mediated disease, with the incidence of early onset sepsis being low, especially in settings of low-risk populations and prolonged rupture of membranes. It is therefore important that the management of thrombocytopenia be individualized based on the presence of sepsis and the degree of thrombocytopenia. (Zekry et al.2022)

10. Prognosis and Outcomes of Neonatal Thrombocytopenia and Sepsis

Neonatal thrombocytopenia remains a regular finding in neonates admitted to the neonatal intensive care unit (NICU) and has been recognized as an important key prognosis indicator of various diseases. Neonatal sepsis incorporates diverse systemic ailments such as septicemia, meningitis, pneumonia, pericarditis, osteomyelitis, arthritis, urinary tract infections, and bacterial cellulitis. It was assessed that sepsis develops in 20% of neonates, of which 1% die in the early

days (Arabdin et al., 2022). On average, sepsis is responsible for almost 10% of infant mortality among children under the age of 5 years in high-income countries (HIC). Broad research on the etiological profile of neonatal thrombocytopenia and investigation of its correlation with morbidities will facilitate early policy-making approach, targeting the reduction in mortality and severe neonatal sepsis.

Neonates up to the age of 4 weeks need special care in the initial weeks of life, particularly in the first week of life. Sepsis develops during the first week of life. Thrombocytopenia often occurs as an early manifestation of neonatal sepsis. If it is not detected early and treated rapidly, sepsis can escalate into severe complications, or severe sepsis or septic shock just in a little time. Several research findings demonstrate the association between neonatal sepsis and low platelet values in the first week of life. The onset of neonatal sepsis in premature neonates is associated with a survival rate of almost 20% (Dahat et al., 2023).

11. Prevention and Future Directions in Neonatal Thrombocytopenia and Sepsis

The diagnosis of neonatal thrombocytopenia is a challenge in itself; when sepsis adds to the burden, it becomes exceptionally difficult. Most of the universally accepted tests help clinicians diagnose sepsis beyond the neonatal period. In the system of detecting sepsis in neonates, it is two-fold important that sepsis be identified especially in the first week of life. Therefore, it suggests prophylactic antibiotic therapy in very high-risk cases, which might save the lives of several neonates. It is understood that even several well-established signs and lab parameters of sepsis do not have enough predictive value in the first few days or first week of life. An increase in immature/total neutrophil counting and antilevel of positively performed acute phase reactants after the first week of life raised the sensitivity of the tests. This had no significance for the first week of life and therefore the neonatal nurses and neonatologists themselves in identifying early-onset sepsis.

A more frequent follow-up of well-known tests in the first week of life, especially for high-risk babies, may be lifesaving. In neonates who died early, there was incomplete information to track the course of the events that led to the patient's demise. In utero and intrapartum factors could predict septic insult, which was difficult to establish a causal relationship and generally not a single factor. However, most cases appeared to have multiple influences. Some septic or nonspecific symptomatic neonatal characteristics included poor perfusion and skin color that could contribute to their demise, often belated onset occurred in the hospital. Despite rapid medical attention, noninvasive measures could not reverse the critical illness state, and sadly culminated in death. These people argue that early ceremonies arranged by respective areas, training on initial neonatal resuscitation to be provided to health care providers, and private interventions to maximize and improve newborn care, especially to foster socioeconomically disadvantaged groups, might curtail the load to some extent. (Romagnoli et al.2021)(Ryu et al.2022)

Conclusion

Neonatal thrombocytopenia and sepsis are critical conditions that require prompt recognition and intervention to minimize the risk of severe complications and mortality. The diagnostic challenges in the first week of life are significant, given the overlap in clinical manifestations and the developmental immaturity of neonates. Advances in diagnostic tools, including biomarkers and blood cultures, have enhanced the ability to identify these conditions early, leading to improved outcomes. However, these conditions remain difficult to diagnose, especially in resource-limited settings, where timely access to advanced diagnostics may be limited. Effective management

necessitates a multidisciplinary approach, involving pediatricians, hematologists, microbiologists, and neonatologists. A better understanding of the physiological differences in neonates and the latest diagnostic advancements will be critical in improving the clinical management of neonatal thrombocytopenia and sepsis. Further research is needed to refine diagnostic criteria and develop more effective treatment protocols to reduce neonatal mortality and improve long-term health outcomes.

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