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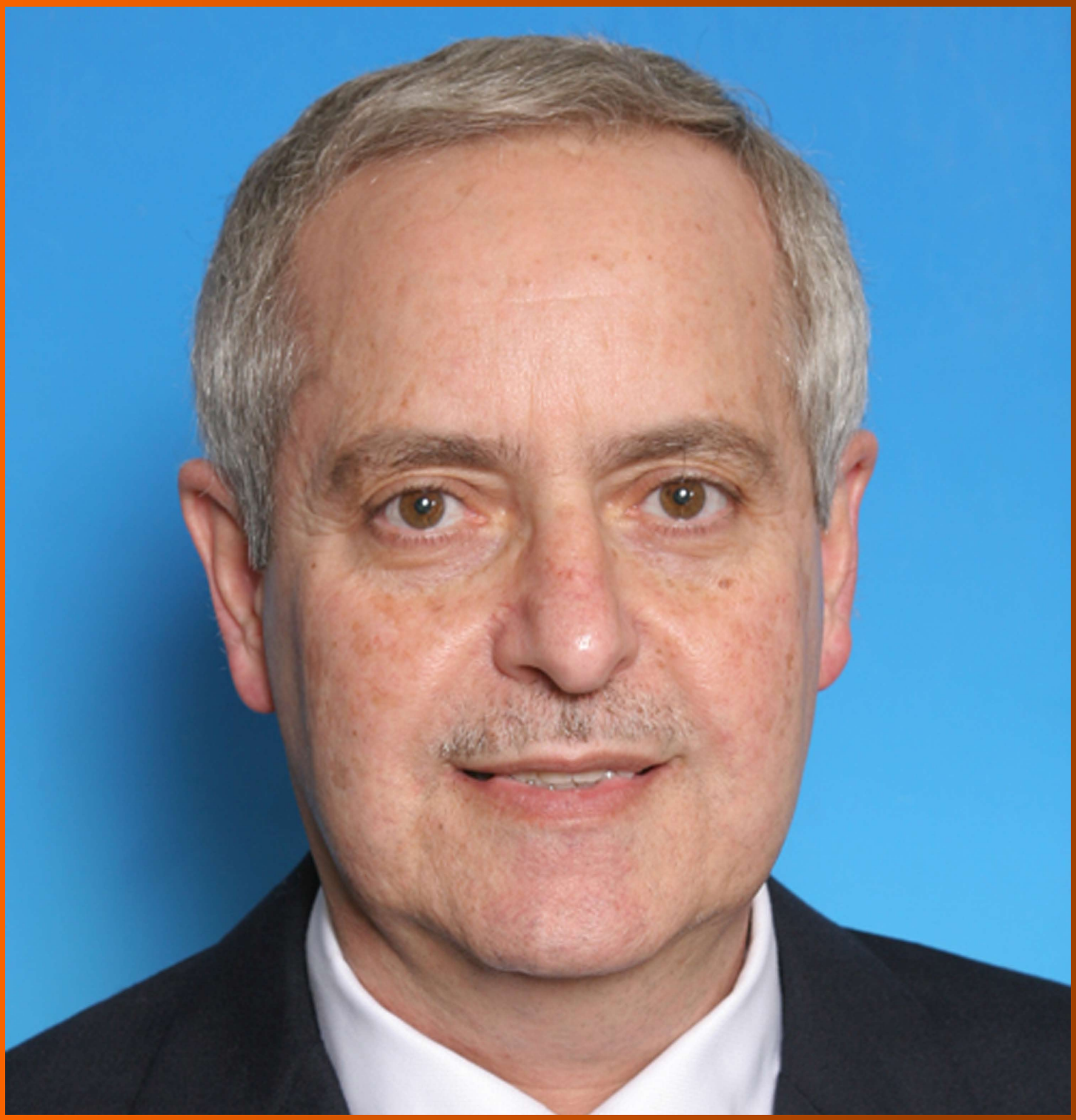

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WJCID will focus on a broad spectrum of topics on infectious diseases that will cover epidemiology, immune-pathogenesis, genetic factors, host susceptibility to infection, vector control, novel approaches of treatment, molecular diagnostic and vaccines. It will provide a common stage to share the visions, new approaches, most advanced techniques, and to discuss research problems that will help everyone working in the field of various infections to exchange their views and to improve public health. *WJCID* will also focus on broad range of infections like opportunistic infections, zoonotic infections, tropical and neglected tropical diseases, emerging infections, *etc.* and following topics related to these issues: (1) Causative agents discussing various pathogens; (2) Vectors and Mode of transmission; (3) Host-pathogen interaction and immune-pathogenesis of the disease; (4) Epidemiology of the infection and vector control strategies; (5) Genetic factors covering both host and pathogen; (6) Molecular diagnostic techniques vaccines; and (7) Recent advances in cell tissue culture, lab techniques, *etc.* Various other related fields like medical microbiology, pharmacology of herbs, bioinformatics, *etc.* will be included.

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EDITORIAL

Is it enough to eliminate hepatitis C virus to reverse the damage caused by the infection?

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Abstract

Hepatitis C virus (HCV) infection represents one of the major causes of chronic liver disease, hepatocellular carcinoma and morbidity/mortality worldwide. It is also a major burden to the healthcare systems. A complete elimination of the HCV from the body through treatment is now possible. However, HCV not only alters the hepatic function. Several extra-hepatic manifestations are present in HCV-infected patients, which increase the mortality rate. Liver and gut are closely associated in what is called the "gut-liver axis". A disrupted gut barrier leads to an increase in bacterial translocation and an activation of the mucosal immune system and secretion of inflammatory mediators that plays a key role in the progression of liver disease towards decompensated cirrhosis in HCV-infected patients. In addition, both qualitative and quantitative changes in the composition of the gut microbiota (GM) and states of chronic inflammation have been observed in patients with cirrhosis. Thus, a successful treatment of HCV infection should be also accompanied by a complete restoration of GM composition in order to avoid activation of the mucosal immune system, persistent inflammation and the development of long-term complications. Evaluation of GM composition after treatment could be of interest as a reliable indicator of the total or partial cure of these patients. However, studies focused on microbiota composition after HCV eradication from the body are lacking, which opens unique opportunities to deeply explore and investigate this exciting field.

Key words: Hepatitis C infection; Inflammation; Virus eradication; Direct-acting antivirals; Gut microbiota

Core tip: Hepatitis C infection represents one of the major causes of chronic liver disease, hepatocellular carcinoma and morbidity/mortality worldwide. A complete elimination of the hepatitis C virus (HCV) from the body through treatment is now possible. However, HCV not only alters the hepatic function. In fact, changes in gut microbiota composition (GM) and gut barrier that leads to an increased bacterial translocation and inflammation have also been observed. Thus, a successful treatment

of HCV infection should be accompanied by a complete restoration of GM and inflammation. Studies focused on GM after HCV eradication are lacking, which opens unique opportunities to deeply explore this exciting field.

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Infection with hepatitis C virus (HCV) is one of the major causes of liver damage and morbidity/mortality worldwide[1]. The spectrum of this disease is quite variable, ranging from acute hepatitis to cirrhosis and hepatocellular carcinoma (HCC). In fact, HCV is considered the most important risk factor for the development of this type of cancer[2], one of the more common cancers in the general population that has substantially increased in recent years.

HCV infection is a major burden to the healthcare systems, as it is the most frequent indication for virus-related liver transplantation in the western world[3]. In addition, patients diagnosed with HCV showed increased morbidity, with higher hospital admission rates[4] and with mortality rates three times higher than that of the general population[5]. In a recent meta-analysis, the number of people with anti-HCV antibodies has been estimated at 185 million in 2005 (2.8% of the human population), with an estimation of 130-170 million people chronically infected[6]. Overall, between 300000-700000 people die every year due to liver diseases associated with HCV-infection[7,8].

Liver is, by far, the most affected organ, but HCV infection is definitely not a liver-limited disease. Actually, HCV infection has been associated with other extra-hepatic manifestations that include thyroid diseases, renal and cardiovascular diseases, eye and skin diseases, lymphomas, mixed cryoglobulinemia, dyslipidemia, diabetes and central nervous system diseases (brilliantly reviewed by several authors)[9-13]. In fact, up to 74% of HCV-infected patients experienced some form of these extra-hepatic manifestations[14]. Therefore, HCV infection showed a higher mortality rate due to the presence of these extra-hepatic complications[15-17]. Several studies have also suggested that HCV may infect other tissues apart from liver. Thus, HCV has been found in peripheral blood mononuclear cell[18,19], kidney, heart, pancreas, and in intestine[20,21]. The infected extra-hepatic tissues might act as potential reservoirs for HCV, and could play a role in both HCV persistence and reactivation of infection but could also contribute to the aforementioned extra-hepatic manifestations associated with HCV infection. Despite the fact that a growing interest has recently emerged concerning the extra-hepatic manifestations of chronic HCV infection, as demonstrated by the increasing number of reviews recently published, there is no scientific evidence that could demonstrate an association between the presence of the virus in other tissues different from liver and the extra-hepatic complications. Therefore, this issue deserves further investigation.

One area of investigation that has been the focus of much recent interest in the last years is the role of intestinal microbiota in health and disease[22]. Microbiota is defined as the collective microbial community inhabiting a specific environment, including bacteria, archaea, viruses, and some unicellular eukaryotes. Microbiota, its evolutive dynamics and influence on host through its protective, trophic and metabolic actions, has a key role in health and opens unique opportunities for the identification of new markers of the physiopathological state of each individual. Recent studies have demonstrated that changes in gut microbiota (GM) contribute to an increased intestinal permeability and, consequently, increased bacterial translocation and endotoxemia, which triggers inflammation and several deleterious actions[23]. In this sense, changes in GM composition is associated with plenty disorders, including liver disorders[22,24-27].

The effects of GM are not limited to the intestine (gut). Indeed, the gut and the liver are closely associated and there is continuous bidirectional communication between these two organs through the bile, hormones and other products of digestion and absorption. This association is known as the "gut-liver axis" and includes transfer of molecules associated with the gut microbiome to the liver and on the other way round[24,28]. Therefore, it is plausible that the composition of the intestinal microbiota could have direct and indirect effects on the function and physiology of the liver and possibly liver disease progression[29-31]. In addition, it has also been suggested that several liver products, such as bile acids, could directly influence the GM composition[30].

A disrupted gut barrier leads to an increase in bacterial translocation and to an activation of the mucosal immune system and secretion of inflammatory mediators that has a key role in the development of several liver disorders associated with HCV-infection, especially in the progression of liver disease towards decompensated cirrhosis in both HCV-mono infected and HCV/HIV co-infected patients[32-36]. In this context, the study carried out by Sandler *et al*[37] (2011) in HCV-infected patients showed that LPS-induced activation of both circulating monocytes and resident Kupffer cells was associated with severe hepatic fibrosis and failure to respond to therapy (based on interferon or pegylated interferon with or without ribavirin) and predicts progression to end-stage liver disease independent of the degree of fibrosis. In addition, several studies have demonstrated both qualitative and quantitative changes in the composition of the GM in patients with cirrhosis (summarized by Betrapally *et al*[38]). More specifically, the alteration in GM of cirrhotic patients (with and without HCV infection) is characterized by an overgrowth of potentially pathogenic bacteria (*i.e.,* gram negative species) and a decrease in autochthonous familiae[24]. Significant differences in the microbiota community and metabolic potential have

also been detected in the fecal microbiota of patients with hepatitis B liver cirrhosis[39]. Therefore, preservation of GM composition - through the usage of different approaches such as probiotics, prebiotics, *etc.,* arises as a promising tool to prevent and/or to treat the development of these liver disorders[40-44]. However, studies focused on microbiota composition of a large population of HCV patients (over the entire disease spectrum) are lacking and only studies concerning cirrhosis and HCC independently of their etiology can be found.

On the other hand, it is important to mention that one of the main objectives of health professionals when treating infectious diseases is to eliminate the pathogenic microorganism responsible for such disorder. To achieve this, physicians are provided with a large arsenal of antibiotics, antivirals, antiretroviral, *etc*., that have appeared in the last decades thanks to the spectacular progress of scientific research. In the context of HCV-infection, the last five years have been crucial in the fight against this infection. A few years ago, physicians only had therapies based on the combination of weekly pegylated interferon-α and daily doses of ribavirin to treat this infection. The efficacy of these therapies was not higher than 50%, and their mechanism of action was not direct against the virus, but was based on enhancing the immune system. In 2011, the arrival of first-generation direct-acting antivirals has shown successful rates of virus elimination from the body in more than 75% of the cases. Unlike the previous therapies, these new regimens cause fewer side effects, they do not require monitoring and most of them are pangenotypic. These therapies are also simpler and require a shorter duration. Thus, and despite the fact that there is not an effective vaccine yet, this could be the beginning of the end of hepatitis C disease[1,45]. However, a complete cure of HCV-infection requires not only the elimination of the virus from the body, but also would imply an improvement in liver and in the extra-hepatic manifestations. In this sense, the study from Innes *et al*[46] (2015), demonstrated a clear association between achievement of HCV cure [as evidenced by sustained viral response (SVR)] and a decrease in both liver-related and all-cause mortality. A large study of HCV-infected patients in the Veteran's Administration database also demonstrated that non-liver-related mortality was significantly reduced among patients who achieved SVR who had comorbidities that included coronary artery disease, diabetes, and hypertension. It was suggested that decreased chronic inflammation associated with HCV was a key factor in mortality decline[47,48]. It is important to highlight that changes in microbiota composition are present in states of chronic inflammation. Thus, a successful treatment of HCV infection should be also accompanied by a complete restoration of GM composition in order to avoid activation of the mucosal immune system, persistent inflammation and the development of different long-term complications. Thus, evaluation of GM composition after treatment could be of interest as a reliable indicator of the total or partial cure of these patients. Only a very preliminary study has been recently published in this regard[49]. It demonstrated that the pro-inflammatory state and the changes observed in GM composition of HCV-infected patients with cirrhosis were not improved regardless of at least one year of SVR. This persistent dysbiosis could contribute towards varying rates of improvement after HCV eradication in cirrhosis. However, what happen in HCV-infected patients with a lower degree of fibrosis/liver damage? Could HCV have a direct effect on GM composition since the presence of this virus has been demonstrated in intestine? or the changes observed in GM are only secondary to liver damage induced by the virus? These are only a few questions that arise in this exciting field and that deserve further investigation. A deep evaluation of the short, medium and long-term consequences of the new HCV treatments is needed, specially focused on the effects on GM composition, bacterial translocation and inflammation.

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MINIREVIEWS

Platelet indices in neonatal sepsis: A review

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Abstract

Thrombocytopenia is a common hematological abnormality in neonates with sepsis. The autoanalyzers now-a-days readily provide platelet indices along with platelet counts without any additional cost. However these indices are not given proper weightage often. The important platelet indices available for clinical utility include mean platelet volume (MPV), platelet distribution width and plateletcrit that are related to morphology and proliferation kinetics of platelets. Studies in adult patients reported their role in the diagnosis of severe sepsis and prognosis of adverse clinical outcomes including mortality. Abnormal MPV can aid diagnosing the cause of thrombocytopenia. Low MPV associated with thrombocytopenia has been found to result in clinical bleeding. Other indices, however, are less studied. The studies addressing the importance of these platelet indices in neonatal sepsis are limited. The current review gives an overview of potential utility of important platelet indices in neonatal sepsis.

Key words: Sepsis; Platelet indices; Thrombocytopenia; Bleeding; Neonate

Core tip: Sepsis in neonates often results in thrombocytopenia and changes in platelet indices. The important platelet indices such as mean platelet volume (MPV), platelet distribution width and plateletcrit are related to morphology and proliferation kinetics of platelets. All these indices are readily available with no additional cost while performing routine blood counts using autoanalyzers. Studies in adult patients reported the potential role of platelet indices in the diagnosis of severe sepsis and prognosis of adverse clinical outcomes including mortality. Abnormal MPV can aid diagnosing the cause of thrombocytopenia. Low MPV associated with thrombocytopenia has been found to result in clinical bleeding. The current review gives an overview of potential utility of important platelet indices in neonatal sepsis.

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INTRODUCTION

Neonatal sepsis is often accompanied by thrombocytopenia and late onset sepsis remains an important cause of thrombocytopenia in neonates[1-5]. Although important platelet indices are readily available while obtaining routine complete blood counts (CBC), they are less studied. The platelet indices have gained more importance in the recent studies. Among many platelet indices, the indices related to morphology and platelet kinetics such as mean platelet volume (MPV), platelet volume distribution width (PDW) and plateletcrit (PCT) are studied in sepsis. The role of platelet indices in sepsis has been reported in adult studies. Such studies reported their role in the diagnosis of sepsis and severe sepsis[6,7]. In addition, these indices have been found to be useful in the prognosis of adverse clinical outcomes including mortality[6-8]. Guclu *et al*[6] reported that MPV and PDW were significantly different between sepsis patients and control group. They concluded that patients having PDW greater than 18% have higher risk for death. Gao *et al*[7] reported usefulness of MPV in predicting adverse outcome in septic shock patients. Usefulness of continuous monitoring of MPV and thereby identifying the change in MPV 72 h after admission in stratifying mortality risk in patients with severe sepsis and/or septic shock was reported by Kim *et al*[8]. Furthermore, Becchi *et al*[9] reported the usefulness of MPV trend in sepsis patients along with platelet count.

A combination of increased destruction and inadequate production of platelets during sepsis-induced thrombocytopenia of the neonate may result in release of young platelets into the circulation. An increased proportion of young platelets may result in increased MPV. A significant increase in MPV from baseline values in neonatal sepsis has been reported by Guida *et al*[2]. O'Connor *et al*[3] described changes of MPV in neonates with Coagulase negative *Staphylococcus* sepsis. In the subsequent sections, the changes of platelet indices during neonatal sepsis and clinical utility of three important indices have been discussed.

PLATELET INDICES

CBC tests with automated hematology analyzers are one of the most commonly ordered tests during neonatal sepsis work up. These analyzers rapidly measure the platelet count and also the platelet indices. Platelet indices are biomarkers of platelet activation. These indices are of diagnostic and prognostic value without any added costs in a variety of settings including sepsis. In automatic CBC profiles, MPV, PDW and PCT are a group of platelet indices determined together. These indices are related to morphology and proliferation kinetics of platelets and hence have a definite clinical utility in patients with sepsis. The other indices include mean platelet component, mean platelet mass, platelet component distribution width, platelet large cell ratio (P-LCR) and immature platelet fraction (IPF). The latter indices are studied very rarely. P-LCR often correlates to MPV but is more sensitive to changes in platelet size[7]. The IPF rises in patients with peripheral consumption or destruction of platelets. It is normal or low in patients with marrow failure.

The MPV is the arithmetic mean volume of the platelets derived from the platelet histogram on automated Coulter counters. It is expressed in femtoliters (fL). The platelet volume is regulated by cytokine dependent megakaryocyte ploidy and platelet number[10,11]. In the settings of decreased platelet production such as sepsis, young platelets that are bigger and more active enter the circulation and hence MPV levels increase. Increased MPV indicates increased platelet diameter. Therefore, increased MPV is useful clinically as a marker of production rate and platelet activation. The average MPV is 7.2–11.7 fL in healthy human subjects. The paucity of gestational age-based normative data has limited the clinical utility of MPVs in neonatal medicine. Wiedmeier *et al*[12] reported that MPVs are rather constant from 22 to 42 wk of gestation with a slight but statistically significant decrease between the earlier vs later gestations. They also provided 5th and 95th centile for MPV for different gestations.

PDW is an indicator of volume variability in platelets size and reflects the heterogeneity in platelet morphology[10,11]. It increases when there is platelet anisocytosis. The PDW reference intervals range from 8.3% to 56.6%. Under physiological conditions, there is a direct relationship between MPV and PDW; both usually change in the same direction.

PCT is the volume occupied by platelets in the blood as a percentage and calculated according to the formula, PCT = platelet count × MPV/10000. Under physiological conditions, the amount of platelets in the blood is maintained in an equilibrium state by regeneration and elimination. The normal range for PCT is 0.22%-0.24%.

MECHANISMS OF THROMBOCYTOPENIA AND ALTERATIONS IN PLATELET INDICES DURING SEPSIS

Because thrombocytopenia is a commonly encountered hematologic complication in neonates with sepsis, the mechanisms for thrombocytopenia have been explored. The measurement of circulating megakaryocyte precursors provides a good indicator of megakaryocytopoiesis, and hence platelet production in neonatal sepsis[13]. Thrombopoietin (Tpo) is the principal physiologic regulator of megakariocytopoiesis and platelet production. The circulating Tpo levels were found to be high in the face of low platelet counts in neonates with sepsis[14]. Immune cells recognize pathogens through Toll-like Receptors (TLRs). The TLRs allow platelets to recognize bacterial proteins during sepsis and regulate platelet immunity and function[15]. Two TLRs, TLR2 and TLR4, have been shown to augment platelet activation and alter its function from hemostatic regulator to immune sentinel. Furthermore,

septic neonates up-regulate Tpo production, leading to increased megakaryocytopoiesis and platelet release[16]. As platelet indices are biomarkers of platelet activation, in the settings of sepsis, these indices also change accordingly.

MPV

Among platelet indices MPV is the most commonly studied platelet index in neonatal sepsis. During conditions of rapid platelet turnover, increased MPV signifies the release of larger, younger platelets into the circulation. Although MPV varies with gestational age and chronologic age, construction of rigorous normal curves for values of the MPV is difficult in premature infants. Wiedmeier *et al*[12] found MPVs being rather constant from 22 to 42 wk of gestation. However, it is wiser to obtain the baseline values of MPV for comparison with subsequent values during neonatal sepsis.

A statistically significant increase in MPV with neonatal sepsis from baseline values (mean change in MPV 0.30 femtoliters; 95%CI: 0.12–0.47) was reported by Guida *et al*[2]. They reported this abnormality while studying platelet counts in 154 blood culture proven neonatal sepsis. The study involved Gram negative, Gram positive and fungal infections in neonates. They did not observe any organism-specific changes in MPV. O'Connor *et al*[3] reported increased MPV during coagulase-negative Staphylococcal sepsis in neonates even though platelet counts were normal.

The relationship between platelet count (PC) and MPV was studied by Becchi *et al*[9]. The results were expressed as means and frequency distributions. They reported a negative correlation (95%CI; r = -0.34; P < 0.0001) between PC and MPV with an inverse trend during sepsis course.

Catal *et al*[17] found a positive correlation between MPV and other inflammatory markers, IL-6 and CRP in neonatal sepsis. A MPV value of 10.35 fL was identified as the cut off value in patients probably resulting in sepsis with a sensitivity of 97.8% and specificity of 78.7% (AUC = 0.949; P < 0.001), and a MPV value of 10.75 fL was determined as the cut off value at diagnosis in patients possibly resulting in death with a sensitivity of 95.2% and a specificity of 84.9% (AUC = 0.944; P < 0.001).

Mitsiakos *et al*[18] reported that platelet mass levels could play an important role in predicting the occurrence of intracranial hemorrhage in neonates with sepsis.

The effects of different infectious agents on platelet count and indices in neonatal sepsis were studied by Akarsu *et al*[19]. They studied these values at baseline and at least 10 d after the onset sepsis. A MPV of > 9.5 fL and PDW of > 16.8 were considered high. Of 86 sepsis episodes involving Gram negative and Gram positive bacteria, 39.5% were found to be associated with thrombocytopenia, 13.9% with an elevation in baseline MPV and PDW, 11.6% with an elevation in baseline MPV and 72.1% with an elevation in baseline PDW. Neonates with MPV over 10.8 fL and/or PDW over 19.1 were found to have significantly increased bacteremia. Although there was an increase in MPV and PDW from baseline, there were no differences between different organism groups.

An understanding of the pathophysiology of alterations in platelet volume and the inverse relationship between platelet volume and count hence is a prerequisite for the successful clinical application of platelet volume measurements[20].

PLATELET DISTRIBUTION WIDTH

Farias *et al*[21] reported the PDW median of 13.3% with a reference range of 10.0%-17.9% for the 5th-95th percentiles with a confidence interval of 95% for normal individuals. Akarsu *et al*[19] addressed PDW changes in neonatal sepsis. By considering PDW of > 16.8 as high, they found an elevated baseline PDW in 72.1% of neonates with sepsis. However they did not find any organism specific response in PDW. Catal *et al*[17] reported higher levels of PDW along with higher MPV during sepsis episodes on consecutive days among non-survivors.

PLATELETCRIT

Of the several platelet indices PCT is studied less often in neonatal sepsis. The variation in MPV affects PCT. There is a significant overlap of PCT between thrombocytopenic patients and patients with normal platelet counts. Role of platelet mass in predicting the occurrence of intracranial hemorrhage in neonates with sepsis has been reported by Mitsiakos *et al*[18].

LIMITATIONS IN CLINICAL UTILITY OF PLATELET INDICES

Platelet volumes are frequently measured in blood samples collected in ethylenediaminetetraacetic acid (EDTA). Factors affecting platelet counting such as interference from cells or cell fragments, inadequate detection of large platelets or platelet clumps also influence platelet indices that are calculated from the platelet distribution curve[22]. An overestimation of MPV, a higher PDW and an increase in fraction of large cells may occur if red blood cells are misclassified as platelets. In severe thrombocytopenia, difficulties in obtaining a sufficient platelet distribution curve may limit the calculation of other platelet indices. Concerns have been raised about the recommended anticoagulant for platelet counting, K2 or K3 EDTA, because it affects MPV. Transmission electron microscopy findings suggested more activation of platelets in EDTA samples[23]. ACD/Na2EDTA has been suggested as an ideal anticoagulant for the study of MPV because it inhibits platelet activation while maintaining the platelets in their normal discoid shape[24]. The methods of measurement of MPV are also important. EDTA causes an increase in MPV from 7.9% within 30 min to 13.4% over 24 h when measured by impedance and decreases by 10% when determined by an optical method. Because

time delay is likely to affect PDW and other indices sample needs to be processed within 120 min. Pseudo-thrombocytopenia due to agglutination of platelets caused by EDTA should also to be kept in mind[25].

MPV, PDW and PCT are not only altered in sepsis but also in other neonatal pathological conditions[26-29]. This fact further complicates the clinical utility of platelet indices during neonatal sepsis. Gestational age, prematurity and birth asphyxia having some influence on these indices has been reported by Kannar *et al*[26]. Premature neonates with sepsis may have other comorbidities such as bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). Higher MPV level was noted in BPD and IVH groups in a study by Bolouki Moghaddam *et al*[27].

A decreased platelet count and PCT, an increased PDW and no difference in MPV among preterm neonates have been reported by Wasiluk *et al*[28] while studying samples from umbilical arterial blood. The large platelet count (LPLT) was found to be diminished in preterm neonates (5.23%) in comparison with term neonates (6.12%). They also reported higher MPV, lower LPLT and lower PCT among small for gestation neonates. Higher PDW, lower PCT and higher but not statistically significant MPV in preterm neonates compared to term neonates were reported by Sandeep *et al*[29].

CONCLUSION

Sepsis in neonates often results in thrombocytopenia and changes in platelet indices. The important platelet indices available for clinical utility include MPV, PDW and PCT. All these indices are readily available with no additional cost while performing routine blood counts using autoanalyzers. Platelet indices are helpful in the diagnosis as well as follow-up of sepsis including assessing the response of antimicrobial treatment if interpreted cautiously. High MPV and PDW have a high specificity for the identification of bacteremia and have a good predictive value. Neonatal studies support their clinical application but limitations should be kept in mind while interpreting results.

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