

Review

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Review

# Thrombocytopenia in Sepsis

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**Abstract:** Platelets, traditionally known for their role in hemostasis, have emerged as key players in immune response and inflammation. Sepsis, a life-threatening condition characterized by systemic inflammation, often presents with thrombocytopenia, which at times can be significant. Platelets contribute to the inflammatory response by interacting with leukocytes, endothelial cells, and the innate immune system. However, excessive platelet activation and consumption can lead to thrombocytopenia and exacerbate the severity of sepsis. Understanding the multifaceted roles of platelets in sepsis is crucial for developing effective therapeutic strategies. Targeting platelet-mediated inflammatory responses and promoting platelet production may offer potential avenues for improving outcomes in septic patients with thrombocytopenia. Future research should focus on elucidating the mechanisms underlying platelet dysfunction in sepsis and exploring novel therapeutic approaches to optimize platelet function and mitigate inflammation. This review explores the intricate relationship between platelets, inflammation, and thrombosis in the context of sepsis.

**Keywords:** platelets; sepsis; thrombocytopenia; infection; activation; phagocytosis; leukocyte; immune

## 1. Introduction

Platelets are small (2-5  $\mu\text{m}$ ) anucleated cellular elements essential to maintenance of coagulation homeostasis that survive in circulation for up to 10 days following release from the bone marrow in their immature forms, which then derive into smaller functional mature platelets in the vasculature [1,2]. Notably, platelets are also derived from megakaryocytes found in the lungs which may account for about half of all platelets found in peripheral circulation with the capacity to further reconstitute platelet counts when significant thrombocytopenia develops [3,4]. Platelet functions can be impaired under innate or acquired conditions that affect the ability of platelets to properly maintain homeostasis or to assist physiologic non-hemostatic processes [5].

In the setting of tissue injury, platelets through a number of its receptors adhere to the exposed subendothelial extracellular matrix at the site of injury, specifically to collagen, von Willebrand factor, laminin, fibronectin and thrombospondin triggering multiple signaling cascades that strengthen platelet adherence [1,6]. Further enhancement of platelet aggregation and recruitment to the injury site occurs through platelet-platelet interactions mediated by the integrin receptor  $\alpha\text{IIb}\beta 3$  which initiates the formation of a fibrin-rich hemostatic plug [1,6], as well as  $\text{Fc}\gamma\text{RIIIa}$  among other receptors which incidentally is also important during active bacterial clearance [7]. As a result, the focus of this review will be to understand basic concepts of how platelets exert their non-hemostatic functions in the setting of infection such as in sepsis.

## 2. Additional Platelet Physiological Roles

Use of platelet transfusions to relieve thrombocytopenia or to address platelet dysfunction is one of the most common interventions occurring in clinical practice across medical disciplines. However,

the effect of platelet transfusions go far beyond coagulation exemplifying their importance to immunity, inflammatory processes, promoting neoplastic angiogenesis and metastasis [8]. Platelets are capable of modulating immune responses either through their interaction with endothelial cells and leukocytes [9,10], or through release of antimicrobial mediators stored within platelets in response to infection [11,12]. Indeed, it has been reported that platelets in their granules contain more than 300 bioactive proteins that span functions in immunity, inflammation, cell growth and proliferation to name a few [3,13]. Furthermore, it has become increasingly evident that there is an interplay between the immune system, inflammation and cancer, and that platelets play a major role in the convergence between these [14]. Along these lines, platelets'  $\alpha$ -granules contain fibrinogen, von Willebrand factor, platelet factor (PF)-4, coagulation factors, immunoglobulins, growth factors, protease inhibitors, while dense-granules are rich in adenosine diphosphate, serotonin, nucleotides, histamine, dopamine among others [3,13]. These are some examples of mediators found in platelets that carry out functions in different physiologic responses through the body.

Platelets can be seen as the "swiss-army knife" in circulation. Through its conserved role in immune defense, pathological conditions such as heparin-induced thrombocytopenia (HIT), serves to illustrate how the intricate interplay between their activation, immune mechanisms/dysfunction, and clinical complications can disrupt normal homeostasis. HIT is a known complication of using heparin as anticoagulation caused by development of anti-PF4-heparin antibodies. Formation of such antibodies to PF4-heparin complexes as seen in HIT may be indicative of an evolutionarily conserved immune defense mechanism. PF4 found in platelets'  $\alpha$ -granules is actively released during platelet activation, binding directly to polyanions on bacteria leading to antibody formation with specificity for PF4-polyanion complexes that targets bacteria, opsonizing them and enhancing their phagocytosis; however, these antibodies can also cross-react with epitopes of PF4-heparin antigenic complexes leading to their detection with commercially available anti-PF4 assays even in the absence of prior heparin exposure [15]. Thus, PF4 may represent an opsonin to defend against bacteria and antibodies detected during HIT testing can be seen as a bacteria-targeted humoral immune response [15]. Evidence for this can be found in the rapid formation of IgG antibodies to PF4-heparin occurring soon after first heparin exposure, suggesting that IgM was pre-formed at the time heparin was given and that bacterial surface polyanions are the original offending antigen [16,17]. Furthermore, the ability of PF4 to bind with increasing avidity progressively truncated forms of lipopolysaccharide (LPS) found on the surface of Gram-negative bacteria, as shown by the improved binding to phosphates on lipid A molecules devoid of the O antigen and the LPS core, typifies epitopes that mimic PF4-heparin complexes [18]. This provides evidence of a conserved anti-bacterial immune mechanism mediated by platelets' PF4 [18].

Platelets presence is essential at the crossroads between inflammation and thrombosis. This relationship is indicated by results obtained from annexin knockout mice. In this model, reperfusion injuries show greater platelet adherence, and administration of annexin A1 directly upregulated thromboxane B and modulated phosphatidylserine expression on platelets resulting in cerebral protection through both reduction of platelet activation and enhanced phagocytosis by neutrophils [19]. Likewise, platelets through their toll-like receptors (TLR) and adhesion molecules sense their immediate microenvironment, and function to recruit neutrophils and monocytes to infection sites while stimulating inflammatory cascades [20–22]. Platelets also modulate macrophage responses so that pro-inflammatory mediators release is reduced, thus rescuing mice from septic shock via a cyclooxygenase 1-dependent signaling pathway [23]. These effects, however, can be affected by the age of the donor since platelets from older subjects have shown to both aggregate monocytes and worsen pro-inflammatory responses [24]. Collectively, these findings stress that the interplay between inflammation and thrombosis is highly complex and will require extensive investigation.

### 3. Immune-Associated Platelet Functions in Sepsis

Platelets are quantitatively the most abundant cellular blood element and represent a native surveillance system hunting for foreign molecules [25]. As a result, thrombocytopenia seen in sepsis

may represent a process during which platelets that came into contact with foreign mediators/organisms are actively removed from circulation, or are consumed due to tissue damage caused by the infection. For example, in viral infections such as dengue, decreases in platelet counts are observed soon after exposure to the virus with thrombocytopenia becoming apparent as early as day 4 [26]. Specifically, the number of dengue viral copies inside platelets correlate with C3 and IgG binding, increased surface P-selectin expression indicative of platelet activation, and enhanced clot formation [26]. These infected platelets are in turn phagocytosed by monocytes leading to their clearance from circulation [26].

During sepsis, epidermal growth factor receptor on platelets is central to their activation so that platelets can attract and augment macrophages' immune function through production of reactive oxygen species (ROS), while concurrently upregulating their pro-inflammatory macrophage M1 phenotype through increased expression of inducible nitric oxide synthase and CD64 resulting in bacteria clearance [24]. Similarly, platelet collagen receptor glycoprotein VI (GPVI) has been shown to be essential to host defense as indicated by data from GPVI-/- knockout mice which have impaired platelet activation and platelet-leukocyte complex formation leading to increased *Klebsiella pneumoniae* growth and infection [27]. This is of importance since GPVI is a member of the immunoglobulin receptor superfamily and the major receptor for collagen, a prime trigger for platelet activation [28]. Platelets also efficiently directly kill Gram positive bacteria in an Fc $\gamma$ RIIa-independent manner as indicated by results using *Staphylococcus aureus*, and this process does not require PF4 opsonization but release of bactericidal mediators [29]. This contrasts to results obtained with Gram negative shiga-toxin -producing *Escherichia coli* O157:H7 infection which reduced CD47 expression on platelets in a TLR-dependent manner resulting in enhanced platelet phagocytosis by activated macrophages [30].

Platelets express Fc receptors for antigen recognition [31,32], as well as pro-inflammatory mediators IL1- $\beta$  and CD40 ligand (L) [33,34]. The latter is important since the adaptive immune response requires CD40 and soluble CD40L, both of which are actively secreted by activated platelets in response to microbial infection [14,35,36]. Furthermore, platelets readily activate proteins of the complement pathway which further activate and recruit additional platelets to the site of infection [37]. Concomitant interaction of platelets with hepatic Kupffer cells represent an additional mechanism by which microbial-platelet clearance occurs [38]. Therefore, the phagocytic capabilities of platelets constitute an evolutionary preserved immune mechanism since thrombocytes of non-mammalian lower vertebrates readily internalize bacteria which are then quickly killed through phagolysosomal fusion [39,40].

Platelet-leukocyte contact also depends on expression of cell adhesion molecules such as P-selectin, and receptors that bridge endothelial cells communication with leukocytes [41]. In regard to how activated platelets stimulate monocytes via cytokines such as TGF- $\beta$ , it has been shown that CD16 expression on monocytes is induced by platelets causing them to develop into intermediate CD14+CD16+ cells that subsequently differentiate into M2 macrophages capable of antibody-dependent cellular phagocytosis [42]. Platelets are also necessary for formation of neutrophil extracellular traps (NET) which are partly triggered by platelet-leukocyte interactions and the release of proinflammatory mediators from platelets, thus indirectly trapping bacteria, viruses and fungi diminishing their propagation [43]. This occurs through binding of platelet TLR4 to bacterial LPS leading to platelet-neutrophil binding which induces NET formation [44]. This has been confirmed in human infections with either Gram-negative or Gram-positive bacterial infections [45]. Platelets' phosphatidylinositol 3-kinase catalytic subunit p110 $\beta$  has also been shown to be important for platelet-neutrophil/monocyte binding that when deficient or inhibited results in bacterial dissemination [46]. These results are significant since p110 $\beta$  has also been shown to be involved in tumorigenesis and inflammation [47,48], providing evidence that these processes are closely associated under physiological conditions.

Platelet interactions with bacteria that either induces phagocytosis or activates platelets to initiate an immune response can be subdivided into three major categories which are: direct

interaction, indirect, and interactions mediated by secreted mediators. These subsequently lead to three distinct mechanisms: adhesion, phagocytosis, and activation [49,50]. An example of direct platelet activation by bacteria is the binding of the Hs antigen expressed by strains of *Streptococci* to platelet's GP1b [51]. An example of indirect interaction is binding of bacterial protein A to plasma's von Willebrand factor followed by binding of the complex to Gp1b [52]. Alternatively, an example of the third category is when bacteria secrete immunogens that initiate a thrombin-like cascade through activation of protease-activated receptor-1 [53]. This activation leads to subsequent release of bactericidal mediators present in platelet granules, in addition to formation of platelet-bacteria thrombi as seen in sepsis and disseminated intravascular coagulation [49].

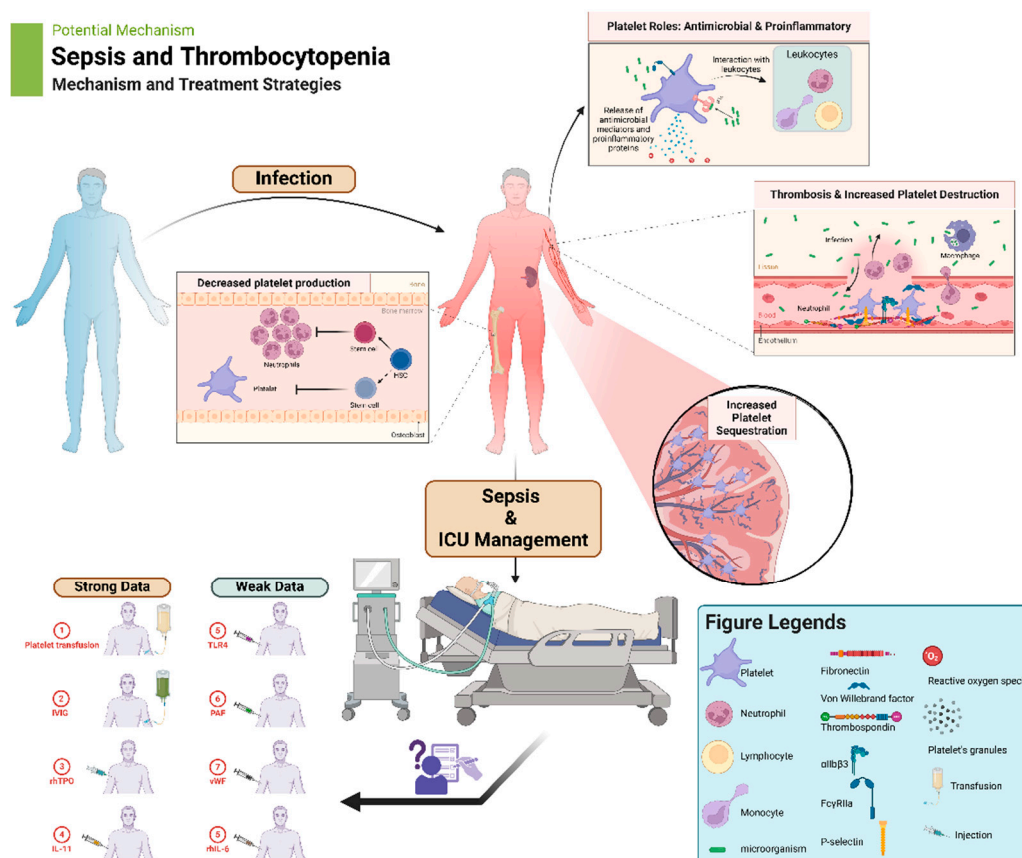
By now it should not come as a surprise that the role of platelets as bonafide immune cells is coming into focus since the cellular ancestor of platelets and leukocytes, the thrombocyte, is pivotal to the immune systems of fish and birds [14,48]. It is with this knowledge that platelets' role during infection should be seen as multifaceted and not driven by their hemostatic function. Their central place as part of an evolutionarily-preserved immune response to defend the body from infectious threats should expand our understanding of additional effects when they are used during transfusions, and especially when patients are treated for their thrombocytopenia.

#### 4. Clinical Implications

Thrombocytopenia in sepsis holds significant clinical importance, serving not just as a laboratory finding but as a vital prognostic indicator that can profoundly impact patient management and outcomes [54–57]. Studies have shown that septic patients with thrombocytopenia face a higher risk of adverse outcomes, including bleeding complications, prolonged intensive care unit (ICU) stays, and overall increased mortality, compared to subjects with normal platelet counts [58]. For instance, a retrospective study involving 7,981 patients revealed that a  $\leq 10\%$  reduction in platelet counts was associated with significantly lower 30-day mortality and shorter ICU stays compared to those with  $>10\%$  reduction [59]. This study highlighted that thrombocytopenia in septic shock is associated with higher mortality, with case-fatality rates proportionally increasing with greater severity of thrombocytopenia.

The degree of thrombocytopenia in sepsis also directly correlates with the presence and worsening of multi-organ dysfunction [55]. This correlation implies that correction of the thrombocytopenia as well as targeted antimicrobial coverage has the potential to be the therapeutic intervention that can more significantly improve prognosis and influence outcomes during sepsis (Figure 1). Additional factors contributing to development of thrombocytopenia in sepsis include higher sequential organ failure assessment scores, low PaO<sub>2</sub>/FiO<sub>2</sub> ratios, and requirement for high vasopressor doses [57]. The poor response to platelet transfusions in sepsis, as indicated by low corrected count increments [60], is influenced by increased platelet consumption or destruction, fever, and conditions like splenomegaly and disseminated intravascular coagulation (DIC) that may develop [60,61]. As a result, a clear understanding of these factors is crucial for optimizing transfusion strategies and improving patient outcomes. However, despite the diminished platelet transfusion response, some studies have suggested that outcomes such as mortality and red blood cell (RBC) transfusion needs do not differ between patients with good and poor platelet increments [62].

Even though the management of thrombocytopenia in sepsis remains controversial due to conflicting evidence for and against platelet transfusions, there is an understanding among clinicians and researchers that this needs to be addressed to improve outcomes [63,64]. Further research is fundamental to establish a unified approach to manage sepsis-associated thrombocytopenia (SAT), that takes under consideration its multifactorial nature. Thus, emerging approaches in treating sepsis, such as the use of intravenous immunoglobulins (IVIG) and even administration of recombinant human thrombopoietin (rhTPO), show promise in enhancing platelet production and possibly reducing their destruction, offering potential new strategies for managing thrombocytopenia in such setting [65,66].



**Figure 1.** This figure illustrates the mechanisms of sepsis-related thrombocytopenia, including decreased platelet production, increased destruction, and sequestration. It also outlines treatment strategies such as platelet transfusion, IVIG, rhTPO, IL-11, and targeting TLR4, PAF, and vWF pathways. **Abbreviations:** HSC (Hematopoietic Stem Cell), IVIG (Intravenous Immunoglobulin), rhTPO (recombinant human Thrombopoietin), IL-11 (Interleukin-11), TLR4 (Toll-Like Receptor 4), PAF (Platelet-Activating Factor), vWF (Von Willebrand Factor), FcγRIIa (Fc Gamma Receptor IIa), αIIbβ3 (Integrin Alpha-IIb Beta-3), rhIL-6 (recombinant human Interleukin-6). Figures were generated with BioRender.com.

## 5. Management of Thrombocytopenia

### 5.1. Platelet Transfusions

The Association for the advancement of Blood and Biotherapies has provided recommendations for platelet transfusion thresholds for hospitalized patients, specifically, transfusion for platelet counts  $\leq 10 \times 10^9/L$  to prevent spontaneous bleeding, prophylactic transfusion for counts  $< 20 \times 10^9/L$  for central venous catheter placement, and platelet transfusions when patient is  $< 50 \times 10^9/L$  neurological surgery among others. [67]. However, guidance that is specific for SAT is lacking.

The majority of clinical trials looking at platelet transfusions in setting of infection have focused on hematology patients, creating a significant data gap for septic populations [68]. In this setting, prophylactic platelet transfusion in patients with severe thrombocytopenia ( $10\text{--}50 \times 10^9/L$ ) showed reduced bleeding incidents in transfused patients even among those in intensive care units [68]. Retrospective studies, however, have found conflicting results in which higher platelet transfusion thresholds ( $20\text{--}50 \times 10^9/L$ ) compared to lower thresholds ( $< 20 \times 10^9/L$ ) were associated with reduced mortality [63], while others saw increased mortality, fewer ICU-free days, and similar RBC transfusion rates [64]. Likewise, looking at the impact of platelet transfusions on mortality in sepsis patients with severe thrombocytopenia ( $\leq 50 \times 10^9/L$ ), it has been reported that platelet transfusions in this group were associated with higher in-hospital mortality rates but that these had no effect in either 90-day mortality or ICU length of stay [69]. Thus, platelet transfusions in sepsis patients present a complex picture in regard to overall therapeutic benefit. When adverse outcomes to transfusions

occur, they are made worse by the frailty of recipients, severity of underlying clinical condition, possible complications such as volume overload compounded by excessive transfusions and infusion of fluids, transfusion reactions, increased risk of thrombosis, and immune dysfunction [64,70–72]. Moreover, platelet transfusions can also contribute to microvascular dysfunction by exacerbating the activation of the coagulation cascade while simultaneously inhibit anticoagulation and fibrinolysis [64,71,73].

Despite these stated risks, platelet transfusions may offer benefits to still to be defined groups of patients with sepsis by improving endothelial barrier function, reducing inflammation through their immunomodulatory effects, and promoting tissue repair [74,75]. As a result, having a clear understanding of the etiology of thrombocytopenia—whether due to hypersplenism, bone marrow suppression, medication-induced (HIT), or secondary to dilutional effects—is essential for optimizing clinical management. Under specific circumstances, strategies such as leukoreduction, platelet additive solutions, or human leucocyte antigens (HLA)- and human platelet alloantigens (HPA)-matched transfusions could improve count increments but their benefit in sepsis patients still require formal investigation [73,76].

### 5.2. Intravenous Immunoglobulins (IVIG)

The administration of IVIG as a potential therapeutic approach for thrombocytopenia, particularly when immune-mediated platelet destruction is suspected may not be without merit [77]. IVIG modulates the immune response by disrupting autoantibody-mediated platelet clearance [78], making it a plausible treatment option in SAT [79,80], especially when mechanisms mirror those encountered in immune thrombocytopenia [81,82]. It is believed that IVIG is able to do this through its anti-idiotypic effect over circulating antibodies. In this case, elevated levels of platelet-associated IgG observed in septic thrombocytopenia further support its use and future research should establish its role as a therapeutic approach [83].

Results from a randomized blinded clinical trial found that IVIG significantly increased platelet counts in patients with septic thrombocytopenia, increasing counts by 411% in the IVIG group versus 261% in the placebo group by day 9 [81]. Additionally, a report of a septic COVID-19 patient with severe immune thrombocytopenia showed a rapid platelet count recovery and improved oxygenation after combined IVIG with corticosteroid therapy without occurrence of adverse events [84]. Along these lines, reports of pregnant women with thrombocytopenia and signs of infection showing a >60% improvement in counts after receiving IVIG with low-dose rhTPO highlights its therapeutic potential in specific patient populations [80].

In contrast, IVIG therapy in severe fever with thrombocytopenia syndrome (SFTS) has been associated with higher fatality rates and significant adverse events, such as worsening viral loads and suppressed immune cell counts [85]. These findings, derived from a retrospective study, warrant cautious interpretation due to its methodological limitations, including single-center design, SFTS patient selection, and lack of randomization. Interestingly, IgM-enriched IVIG significantly reduced mortality, hospital stays, and APACHE II scores in sepsis patients, showing greater efficacy compared to standard IVIG [86]. Even when higher doses of IVIG were used, therapeutic benefit has been reported through the rapid inhibition of platelet activation, lending support to a broader role in managing thrombocytopenia occurring secondary to immune dysregulation [87,88].

Altogether, IVIG shows promise in rapidly increasing platelet counts and improving outcomes in selected patients with SAT [81,84,86]. Its use may be particularly beneficial for those at high risk of bleeding or undergoing invasive procedures. However, careful patient selection and further studies are needed to establish its true efficacy and safety either as a standalone therapy or in combination with other treatments.

### 5.3. Recombinant Human Thrombopoietin (rhTPO)

This recombinant grown factor effectively increases platelet counts with minimal side effects by promoting differentiation and maturation of bone marrow stem cells into megakaryocytes, thereby

enhancing platelet production without altering their morphology or function [89–92]. These benefits have been well demonstrated during chemotherapy-induced, immune-mediated, and sepsis-associated thrombocytopenia, resulting in overall lower transfusion dependency [89,93–95]. A meta-analysis of ten randomized controlled trials involving 681 patients with SAT showed that rhTPO significantly increased platelet counts, decreased 28-day mortality, reduced number of platelet units transfused, reduced transfusion volumes, and shortened ICU stays compared to conventional antibiotic therapy alone or in combination with IVIG [65]. Furthermore, retrospective data of 213 patients lend support to rhTPO use, showing greater platelet count increases specially in patients with initial counts  $\leq 30 \times 10^9/L$  and APACHE II scores  $>15$  [92]. Even though this growth factor is costly, the reduction in ICU stays may provide a strong incentive to its use even when 28-day mortality may remained unchanged [92].

#### 5.4. Recombinant Human IL-11

Interleukin-11 (IL-11), a cytokine interacting with hematopoietic and non-hematopoietic cells, has demonstrated therapeutic potential in systemic inflammatory conditions including sepsis [96,97]. Specifically, its strong thrombopoietic effect favors its use as potential therapy for SAT [97,98]. A study of 105 patients found that treatment with IL-11 significantly improved platelet counts and reduced IL-6 levels between days 3 and 14 [99]. The therapy also downregulated the sepsis marker procalcitonin and lowered the APACHE II score of patients, in a background of lower 28-day mortality rate compared to conventional therapy [99]. However, IL-11's role in treating SAT remains mostly underexplored. Although preliminary studies suggest its efficacy in light of improved clinical outcomes, the data is still limited and randomized clinical trials are needed to validate its therapeutic potential in septic patients [100].

#### 5.5. Recombinant Human IL-6

Elevated IL-6 levels, a hallmark of sepsis, correlate with disease severity and act as diagnostic and prognostic markers [101]. Notably, there is an inverse relationship between thrombocytopenia and cytokine activation in sepsis [102], prompting exploration of anti-IL-6 therapies to mitigate inflammation and restore platelet counts since this cytokine is likely a key driver of the cytokine storm in sepsis. Tocilizumab (TCZ), a recombinant humanized monoclonal antibody targeting the IL-6 receptor, has shown potential in managing sepsis, particularly in COVID-19 patients [103,104]. By inhibiting both membranous and soluble IL-6 receptors, TCZ suppresses the IL-6-mediated inflammatory cascade [105]. However, TCZ's role is complex; while it may dampen cytokine-driven platelet consumption, reports of TCZ-induced thrombocytopenia raise concerns [103]. This physiologic duality underscores the need for further research into its safety and efficacy in septic patients, especially those with existing thrombocytopenia. With this in mind, the RESCUE trial aiming to further evaluate IL-6 inhibition on patients with inflammation and atherosclerotic disease via another monoclonal antibody zilvivekimab will provide needed evidence to establish if inhibition of this cytokine proves beneficial to patients [106].

#### 5.6. TLR4 Inhibition

TLR4 is a key membrane-spanning protein in the innate immune system, recognizing pathogen-associated molecular patterns such as LPS from Gram-negative bacteria [107,108]. Expressed on various cell types, including platelets, TLR4 activation triggers intracellular signaling cascades, leading to NF- $\kappa$ B pathway activation that results in release of pro-inflammatory cytokines. This process contributes to systemic inflammation and sepsis progression, positioning TLR4 as a potential therapeutic target for modulating sepsis-associated inflammation [21]. TAK-242, a TLR4 antagonist, has shown promise as adjunct therapy for thrombocytopenia in sepsis by mitigating LPS-induced systemic inflammation, thus reducing end-organ damage and slowing sepsis progression [109–111].

Its ability to specifically target inflammatory pathways underscores its potential to improve outcomes in septic patients with thrombocytopenia.

Activation of TLR4 on platelets by LPS also triggers pro-thrombotic and pro-coagulant responses including platelet aggregation, ATP release, P-selectin expression, and platelet-neutrophil aggregate formation [112]. These mechanisms contribute to both inflammation, coagulopathy, and DIC seen in sepsis. TLR4 also interacts with CD14, damage-associated molecular patterns (e.g., HMGB1), and NETs, amplifying inflammatory and coagulation pathways that link thrombocytopenia and sepsis progression [110–112]. Despite mechanistic evidence supporting TLR4's role in thrombocytopenia in sepsis, clinical trials investigating its therapeutic potential remain lacking. Future studies will be needed to translate these findings into effective clinical interventions.

### 5.7. Platelet-Activating Factor (PAF) Inhibition

PAF's role in LPS-induced thrombocytopenia and neutropenia was shown by a study looking at 42 dogs treated with LPS, PAF, or saline, with some animals being pre-treated with TCV-309, a potent PAF antagonist. Thrombocytopenia and neutropenia occurred in all but the saline group, with TCV-309 significantly reducing LPS-induced thrombocytopenia, suggesting PAF as a mediator and potential therapeutic target for SAT [113]. PAF appears central to severe sepsis, where bacterial endotoxins trigger its production, leading to hypotension, organ damage, and thrombocytopenia [113]. Use of recombinant PAF-acetylhydrolase demonstrated reduced mortality in severe sepsis patients, underscoring its therapeutic potential [114]. Moreover, PAF receptor (PAF-R) activation exacerbates inflammatory responses in infectious diseases, such as dengue fever, where it worsens thrombocytopenia and increases mortality [115]. Also, its role in inflammation related to HIV and SARS-CoV-2 further emphasizes its relevance across infectious conditions [115]. Thus, targeting PAF-R represents a promising approach for treating SAT. Clinical trials to study the safety and efficacy of PAF inhibitors in the setting of sepsis are justified.

### 5.8. Von Willebrand Factor (vWF)-Binding Function

Sepsis disrupts the delicate balance between vWF and the enzyme known as a disintegrin and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13), leading to lower ADAMTS13 activity in a background of elevated vWF levels [116,117]. This imbalance results from increased vWF and removal of ADAMTS13 from the circulation rather than intrinsic changes in ADAMTS13 itself which when persisting even post-ICU augments thrombotic risks [116]. Studies in *Staphylococcus aureus*-associated sepsis further emphasize this imbalance's impact. In this research, high vWF and low ADAMTS13 activity correlate with severe illness in humans, while in mice, vWF deficiency improves survival and ADAMTS13 deficiency worsens it [118]. Similarly, GPIb-IX, appears to be important for vWF-mediated platelet adhesion, emerges as a therapeutic target. In LPS-induced sepsis models, a dysfunctional GPIb $\alpha$  mutant or the synthetic vWF-binding inhibitor MP $\alpha$ C significantly reduced mortality, thrombosis, and platelet loss [119]. These findings position vWF-mediated adhesion as a target for development of therapies in SAT.

## 6. Discussion

Thrombocytopenia in sepsis is a complex clinical complication with significant implications for patient outcomes. It presents frequently in sepsis, affecting nearly half of septic patients and serving as a critical and negative prognostic marker [120,121]. While traditionally viewed as primarily one of the most important hemostatic mediators [122], platelets play a crucial role in the immune response to infection [123]. Thus, thrombocytopenia has profound immune repercussions in patients battling infections. By directly interacting with pathogens, modulating inflammatory responses, and promoting immune cell function, platelets role in both innate and adaptive immunity cannot be denied [124].

The pathogenetic mechanisms seen in sepsis can involve decreased platelet production due to bone marrow suppression, increased destruction through DIC, and platelet sequestration in the spleen and other organs [120,121,125]. The totality of findings presented here makes it evidently clear of the complex interplay of pathophysiological mechanisms and clinical impact have over the possible management strategies needed for thrombocytopenia in sepsis [125]. Clinical implications are profound; thrombocytopenia correlates with higher risks of bleeding, prolonged ICU stays, and increased mortality [121]. Specially, since studies consistently show that even a modest reduction in platelet count is associated with worse outcomes, emphasizing the importance of frequent monitoring and timely intervention [59]. Therefore, the cumulative data underscore the complexity of thrombocytopenia in sepsis and the necessity for targeted management strategies.

A critical aspect of managing septic patients is the consideration of platelet transfusions. While platelet transfusions are often employed to treat thrombocytopenia, their efficacy in sepsis has remained controversial [126,127]. The timing of transfusion, number of platelet units given, and underlying disease severity could influence outcomes. While some studies have suggested benefits in reducing bleeding and improving survival, particularly with higher transfusion thresholds [63,127], others report no improvements in outcomes instead suggesting increased mortality among recipients, possibly due to the severity of illness and complications such as transfusion-related infections, immune dysfunction and the immunomodulatory effects mediated by platelets themselves [64,128].

Emerging therapies such as rhTPO and immunomodulatory agents offer potential for enhancing platelet production and reducing destruction [127]. As pointed out earlier in the text, IVIG have shown promise in this regard, particularly in cases where immune-mediated platelet destruction is suspected. Randomized controlled trials and case studies highlight IVIG's ability to significantly increase platelet counts and improve clinical outcomes in SAT are encouraging [80,81]. However, the effectiveness of IVIG is not universal. For instance, in SFTS, IVIG treatment was associated with increased mortality and adverse immunological effects, highlighting the need for careful patient selection and monitoring after its use [85]. In addition to transfusions and IVIG, adjunctive therapies targeting specific pathways involved in platelet production and destruction are potential therapies that can help patients. These include agents that are immunomodulatory in nature, inhibit platelet receptor interactions, and address underlying conditions such as hypersplenism and bone marrow suppression (Figure 1) [113,114,116]. The use of high-dose IVIG in conditions like HIT illustrates the potential for targeted therapies to mitigate platelet activation and limit platelet consumption [87].

The management of thrombocytopenia in sepsis likely requires a tailored approach that considers individual patient factors and the underlying pathophysiology of a patient's presentation. Any research looking at this patient population, should account for as many of these variables as possible and recruit patients accordingly so that results can be extrapolated to address the diverse nature of thrombocytopenia in sepsis. Future research ought to include robust randomized clinical trials that establish the benefits of those approaches mentioned in this review. Addition of platelet function tests and advanced diagnostic tools could further refine treatment strategies, ensuring that interventions are timely, effective and safe. Nevertheless, the data is clear that the armamentarium needed to treat thrombocytopenia in setting of infection is likely to grow in the coming years.

## 7. Conclusions

In conclusion, thrombocytopenia in sepsis is a critical and complex condition with significant implications for patient management and outcomes. A comprehensive understanding of its pathophysiology and clinical impact, coupled with evidence-based management strategies, is essential for improving patient care. Future studies should aim to clarify the role of various treatment modalities, including platelet transfusions and adjunctive therapies as those presented here, in optimizing outcomes for septic patients with thrombocytopenia.

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