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STATE OF THE ART ISTH 2020

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# The role of platelets in sepsis

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## Abstract

A State of the Art lecture titled "The role of platelets in sepsis" was presented at the ISTH congress in 2020. Sepsis is a life-threatening organ dysfunction caused by a dysregulated and multifaceted host response to infection. Platelets play a significant role in the coordinated immune response to infection and therefore in the inflammation and coagulation dysfunction that contributes to organ damage in sepsis. Thrombocytopenia has a high incidence in sepsis, and it is a marker of poor prognosis. The genesis of thrombocytopenia is likely multifactorial, and unraveling the involved molecular mechanisms will allow development of biomarkers of platelet function in sepsis. Such platelet biomarkers can facilitate study of antiplatelet interventions as immunomodulatory treatment in sepsis. Finally, relevant new data on this topic presented during the 2020 ISTH virtual congress are reviewed.

KEYWORDS

infection, inflammation, platelets, sepsis

**Essentials**

- Platelets play an important role in coagulation and the immune response.
- Thrombocytopenia has a high incidence in sepsis and is a marker of poor prognosis.
- Platelet activation and modulation of neutrophil and monocyte function occurs in sepsis.
- Relevant new data on this topic presented during the 2020 ISTH virtual congress are reviewed.

## 1 | SEPSIS

Sepsis is a life-threatening condition that can occur as a result of an infection. The most common causative agents are gram-positive bacteria such as *Staphyloccoccus aureus* and *Streptococcus pneumoniae*, followed by gram-negative bacteria such as *Escherichia coli*.[1] Sepsis is a significant global health problem. The World Health Organization issued a resolution on sepsis in 2017 that urged all member states to take action to increase awareness of sepsis and invest in the development of new diagnostic and treatment strategies. It has long been established that both the pathogenicity of the infecting microorganism and the underlying inflammatory response of the infected host contribute to morbidity in infection.[2] Sepsis occurs when immune response networks fail to control the pathogen and do not maintain the inflammatory response at the local site of infection. The pathogenesis of sepsis is a highly complex syndrome that involves multiple components of the immune, coagulation, and tissue homeostasis systems over time.[3] The most recent clinical guidelines (Sepsis 3) define sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection,"[4] assessed using the Sequential Organ Failure Assessment (SOFA) score. The dysregulated host response in sepsis manifests first as

a systemic inflammatory response (SIRS), followed by a compensatory anti-inflammatory response (CARS) and immune suppression.[5] The overall result is life-threatening collateral damage to host tissue and organs, the etiology of which is poorly understood (Figure 1). Furthermore, the SIRs and CARS phases can overlap, which complicates both diagnosis and therapeutic intervention. On the one hand, SIRS can potentially be treated by dampening the immune response, while on the other hand, CARS requires immune boosting to prevent secondary infections. Eradication of infecting pathogens by antibiotics has a positive effect on the outcome of sepsis; however, therapeutic interventions aimed at modifying the systemic inflammatory response have so far failed. The increasing prevalence of antibiotic resistance among pathogens may have a disastrous impact if alternative treatment strategies do not become available.

Sepsis encompasses a vastly heterogeneous patient group, which differs depending on the site of infection, type of pathogen, underlying host factors, and individual host responses. Unfortunately, our enhanced understanding of the pathogenesis of sepsis has not yet led to improved patient stratification for treatment of sepsis. Intensive research is ongoing to characterize sepsis at the molecular level over time.[6,7] An important aim is to identify distinct phenotypes and stages of sepsis, based on clinical and biomarker profiles[8] or genomic profiling,[9] and to target specific immunomodulatory therapies to these patient groups.

## 2 | EXPERIMENTAL MODELS OF SEPSIS

Experimental mouse models remain essential to enhance our understanding of sepsis. The strengths and weaknesses of individual sepsis models have been reviewed elsewhere.[10,11] Translation of therapeutic success from mouse models to human clinical trials has failed in the majority of cases, and to address this challenge, recommendations for standardization of sepsis models have been proposed.[12] Nonetheless, experimental models in rodents remain a fundamental step in enhancing our knowledge of the pathobiology of sepsis. An overview of three broad categories of experimental sepsis models is given in Figure 2, together with factors that will influence study design and reproducibility between models. The pathogenesis and outcome of sepsis in an experimental model should be monitored at multiple levels using biomarkers of pathogen load, inflammation, coagulation dysfunction, and organ damage. Administration of the bacterial endotoxin lipopolysaccharide (LPS) is the most commonly used model for sepsis. An overwhelming systemic inflammatory response is generated to a single pathogen-associated molecular pattern (PAMP) from gram-negative bacteria. This model recapitulates some of the key features of sepsis, but it does not take into account the multifactorial nature of infection or the influence of bacteria, in particular gram-positive pathogens. To investigate multiple aspects of the dynamic

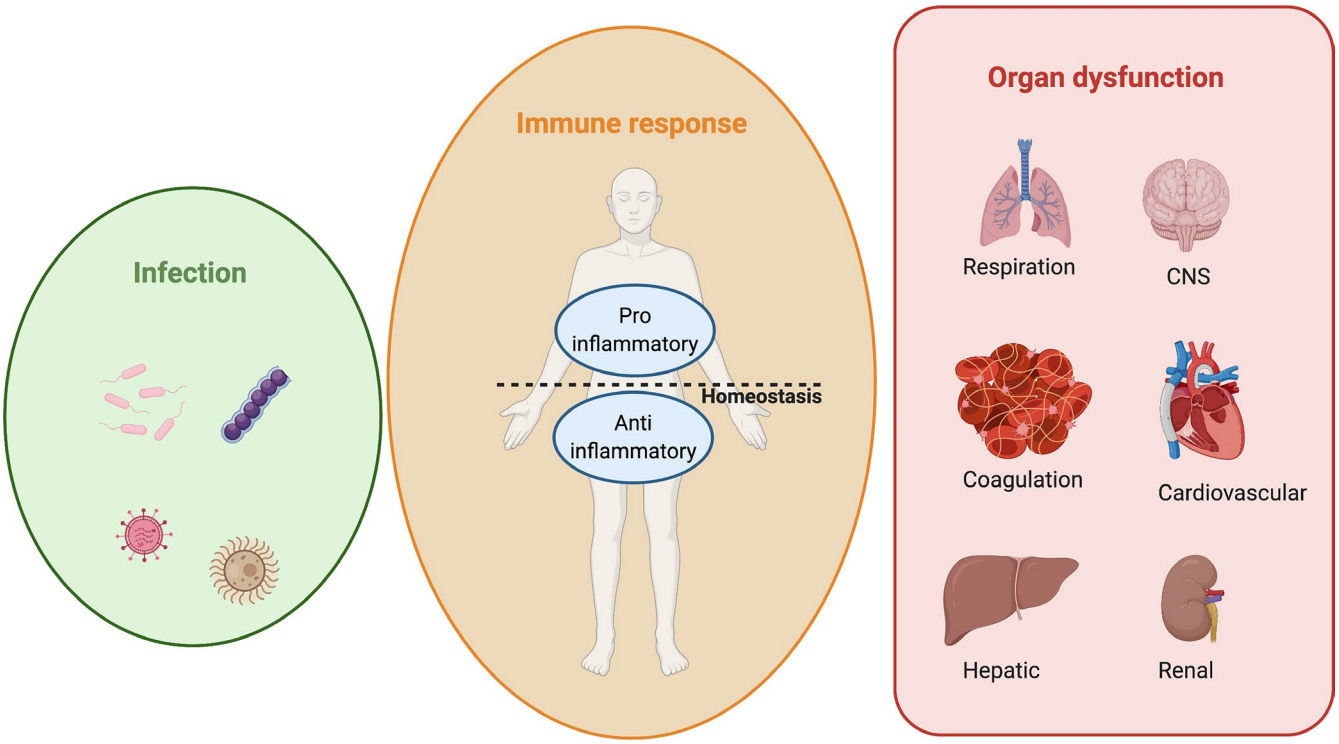


**FIGURE 1** Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Gram-positive bacteria, gram-negative bacteria, viruses, or fungi can cause infection at a local site resulting in activation of the immune response. Sepsis occurs when an overwhelming systemic pro-inflammatory response is generated and compensatory anti-inflammatory responses fail to rebalance the systems to homeostasis. Significant damage is mediated to host tissue, resulting in organ dysfunction that can affect in six major systems. CNS, central nervous system

host-pathogen interaction during sepsis, exogenous pathogenic bacteria are administered at a local site in a susceptible mouse strain. Alternatively, endogenous infection can be achieved by surgical disruption of the gastrointestinal tract, such as cecal ligation and puncture (CLP). A polymicrobial infection is initiated, and multiple components of the interaction between the host and the host-adapted pathogens can be assessed during sepsis progression. All three experimental models have generated important insights on the role of platelets in infection, inflammation, and sepsis. Observations made in a particular model will reflect distinct aspects of sepsis, and complementary models can be applied to determine the role of platelets in diverse infections and at distinct stages of sepsis.

## 3 | COAGULATION DYSFUNCTION IN SEPSIS

The coagulation system encompasses a network of plasma proteins, endothelial cells, and platelets that collaborate to maintain vascular integrity. In response to endothelial disruption, platelet receptors are exposed to their ligands, von Willebrand factor (VWF), and collagens, resulting in adhesion and aggregation at the endothelium. Vessel damage also exposes tissue factor (TF) and a cascade of plasma serine proteases are activated to generate thrombin that cleaves fibrinogen to a fibrin clot. Thrombin is also a potent activator of endothelial cells and platelets, an example of the extensive crosstalk that exists between components of the coagulation system in health and disease. It has long been established that the coagulation system becomes activated by inflammation and is subsequently dysregulated in sepsis.[13] At the most advanced stage, disseminated intravascular coagulation (DIC) may occur. DIC results in fibrin deposition in the microvasculature and diminished fibrinolysis, which likely contributes to organ dysfunction in affected organs by impairing oxygen delivery to the tissue.[14]

Coagulation dysfunction is clearly detrimental in sepsis, and anticoagulation therapy with heparins, antithrombin, or thrombomodulin may be beneficial for the treatment of DIC.[15] To achieve a successful outcome it would be important to administer anticoagulation therapy to an adequately stratified group of patients with confirmed DIC that may benefit from the intervention. During the initial immune response to an infection activation of the coagulation system may even contribute to immune defense and containment of pathogenic bacteria. Fibrin clot formation initiated in response to infection and inflammation has been reported to entrap bacteria and limit dissemination to the bloodstream and

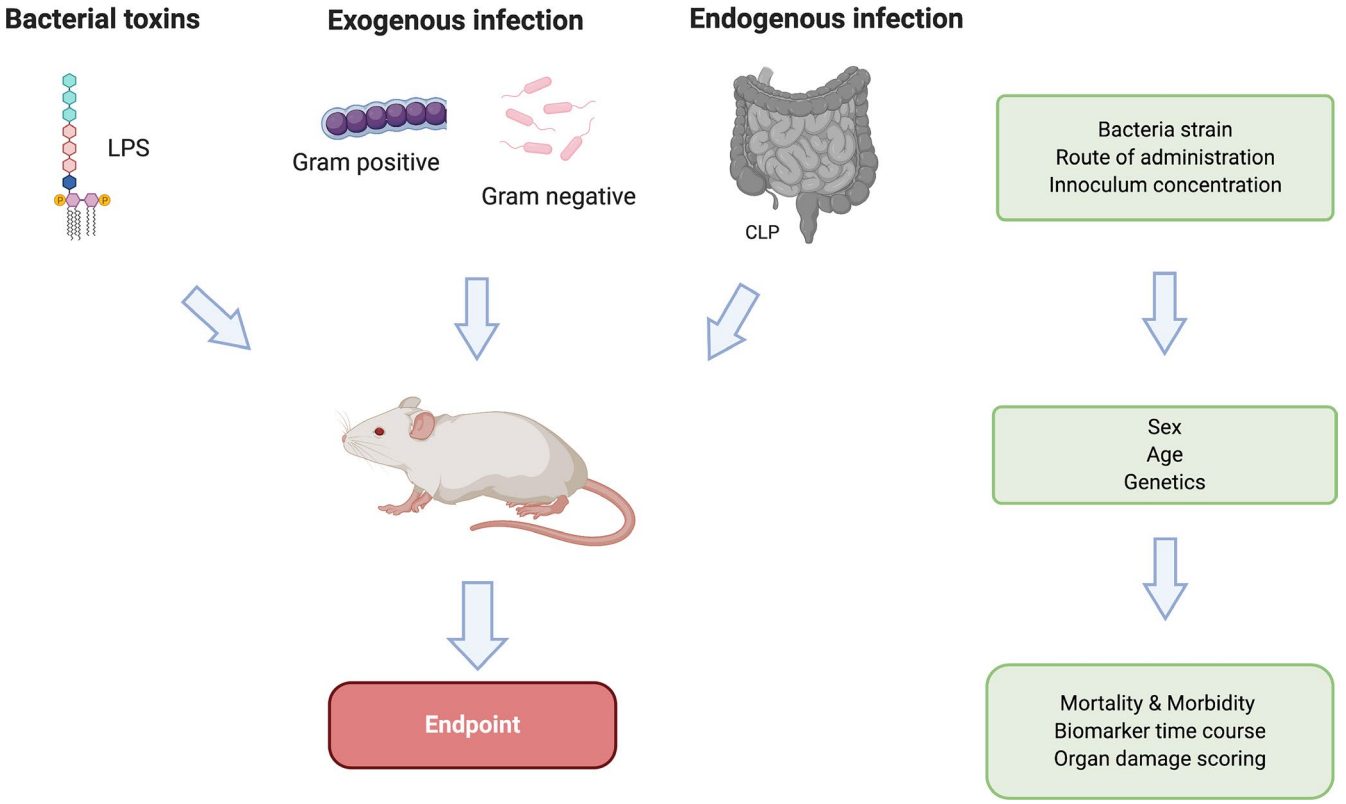


**FIGURE 2** The pathogenesis of sepsis is investigated in experimental models in mice. Sepsis can be modeled by systemic or local administration of a bacterial toxin, most commonly lipopolysaccharide (LPS), systemic or local administration of defined strains of pathogenic bacteria, or surgical manipulation to expose normally sterile sites to endogenous bacteria in the normal flora. The green boxes summarize key factors associated with the pathogen, the host and the experimental endpoint that should be considered in study design. CLP, cecal ligation and puncture model

organs in a process designated "immunothrombosis."[16] The importance of fibrin formation for immune defense is implied by the fact that many successful pathogens produce virulence factors that can mediate plasmin activation and fibrinolysis at the bacterial surface, perhaps as a means to escape entrapment in a fibrin clot.[17] Further insight on the molecular mechanisms involved in dysregulation of the coagulation system in sepsis may yield biomarkers for improved stratification of patients for anticoagulation therapy or potentially identify novel therapeutic targets for organ supportive therapy.

## 4 | THROMBOCYTOPENIA IN SEPSIS

Coagulation dysfunction contributes to the SOFA score of organ dysfunction in sepsis and the circulating platelet count is used for assessment.[15] Thrombocytopenia is a relatively common finding in critically ill patients within the intensive care unit (ICU).[18] The relative change in the platelet count over time after admission to the ICU can distinguish survivors from nonsurvivors.[19] The incidence of thrombocytopenia is particularly high in patients with sepsis, and the level of thrombocytopenia is a marker of poor prognosis associated with increased risk of bleeding, increased organ dysfunction and in some cases with an increased 28-day mortality.[20,21,22] Multiple mechanisms likely contribute to severe thrombocytopenia, which occurs late in the clinical progression of sepsis. Decreased platelet production, increased platelet activation and consumption in thrombi, or increased destruction may remove platelets from the circulation. It is therefore important to understand the multifaceted molecular mechanisms underlying thrombocytopenia to clarify the role of platelets and identify biomarkers of platelet function that occur earlier in the clinical progression of sepsis.

### 4.1 | Platelet production

The immature platelet fraction and the mean platelet volume (MPV) are additional platelet biomarkers that can be monitored to assess platelet production. A recent systematic review concludes that an increase in circulating immature platelets is associated with severe sepsis and increased mortality.[23] This indicates that platelet production is not only maintained but also increased in sepsis.

### 4.2 | Platelets in DIC

Significant endothelial activation and dysfunction is a driving force for sepsis pathogenesis. The vascular integrity is compromised resulting in increased permeability, increased TF exposure and VWF release, downregulation of anticoagulant effectors, and an overall procoagulant status.[24] Platelets adhere and aggregate at the activated endothelium and provide a procoagulant membrane surface for additional fibrin clot formation in DIC.[25] Platelet consumption in these thrombi likely contributes to the thrombocytopenia observed in sepsis. A viscous cycle is generated since CD40L released by activated platelets stimulates further activation of the endothelium.[26] Platelet aggregates are observed in the organ microvasculature in a model of LPS-induced sepsis[27] and polymicrobial sepsis.[28] Platelet thrombi are present in the microvasculature in the liver, and this is associated with increased organ dysfunction in a model of polymicrobial sepsis[29] and a model of streptococcal sepsis.[30]

### 4.3 | Platelet activation in human sepsis

Increased platelet activation has been reported for patients with sepsis, although the sample size in these studies is often relatively small. The ex-vivo platelet population exhibits increased surface-bound thrombospondin and increased platelet-leukocyte complex formation, which correlates with organ dysfunction.[31,32] Platelet aggregation in response to ex vivo stimulation is decreased,[33,34] indicating that platelet activation has occurred in vivo. Upregulation of P-selectin to the activated platelet surface and platelet-monocyte complex formation is higher in patients with gram-positive sepsis than those with gram-negative sepsis,[35] suggesting that distinct platelet phenotypes may be associated with distinct pathogens. Intriguingly, TF protein synthesis and platelet procoagulant activity is increased in a subpopulation of patients with sepsis.[36] In an elegant recent study, the platelet transcriptome and translatome were investigated in sepsis.[37] The gene encoding the αIIb subunit of the integrin complex, glycoprotein (GP) IIb/IIIa, was upregulated in human platelets and this was also confirmed for mouse platelets after CLP. It is apparent that platelet activation occurs in human sepsis and further elucidation of the distinct triggers and consequences of this activation may facilitate development of alternative and potentially more sensitive biomarkers of platelet function in inflammation and sepsis.

## 5 | PLATELETS IN THE IMMUNE RESPONSE

The role of platelets in sepsis was first investigated in terms of their significant role in hemostasis and thrombosis. Sepsis is caused by a dysregulated host response to infection; therefore, the role of platelets in sepsis should also reflect the now established role of platelets in the immune response. Platelets are innate immune cells that elaborate an impressive immune receptor repertoire for recognition of inflammatory mediators, damage-associated molecular patterns, PAMPs, and leukocytes.[38] Upon activation, platelets release potent immunomodulatory cargo, reviewed in Manne et al.[39] Platelets modulate endothelial and leukocyte function via direct receptor-mediated contact, release of extracellular vesicles, and release of cytokines and chemokines. The contribution of platelets to the immune response to bacterial, malaria, and viral infection has

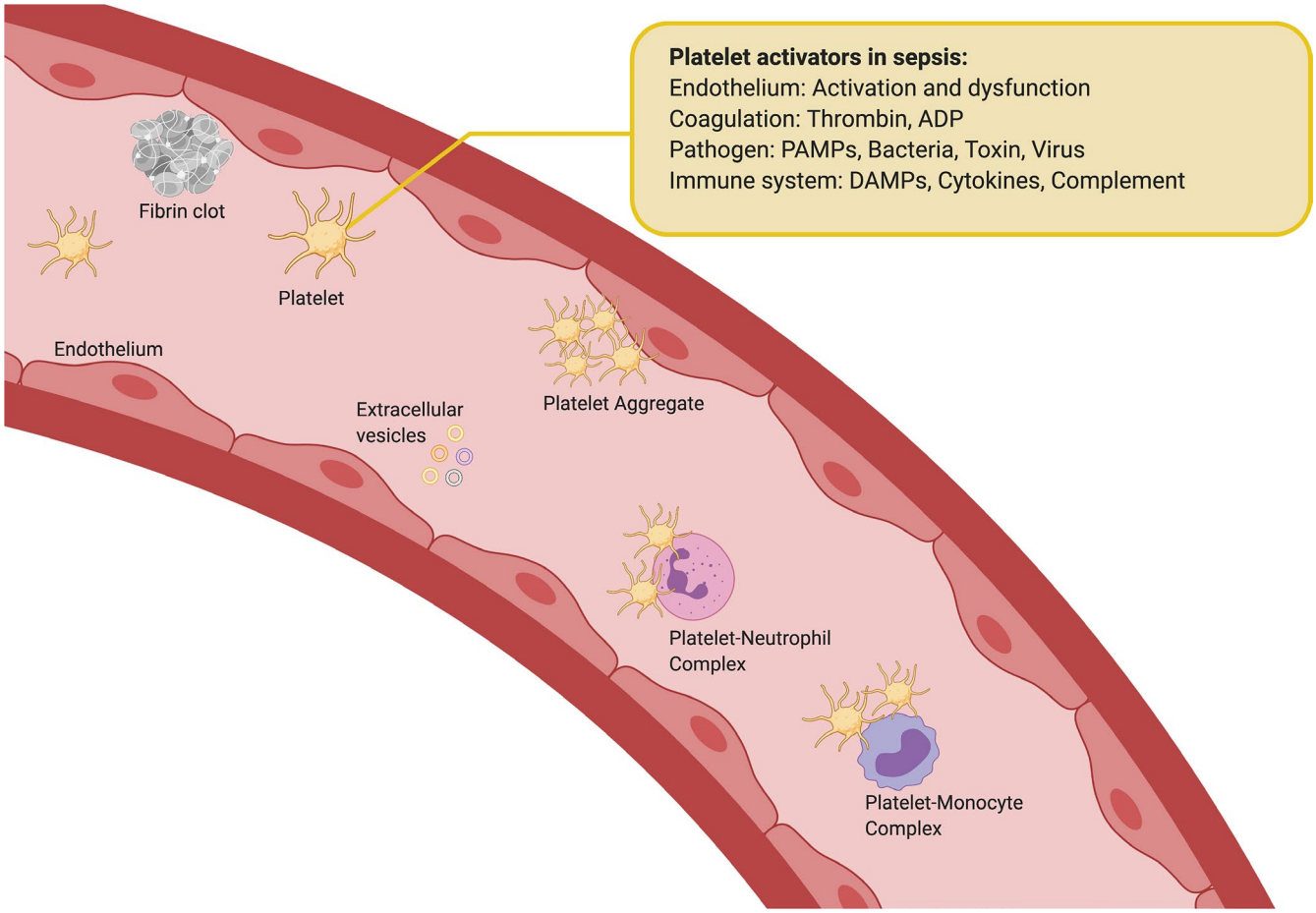


**FIGURE 3** Platelets in sepsis. Platelets are sentinel cells that patrol the bloodstream. Platelets can rapidly become activated in sepsis by either the pathogen, components of the activated coagulation system, or immune mediators. Activated platelets release granule proteins and extracellular vesicles (EVs), which exert immunomodulatory effects on endothelial cells and leukocytes. Activated platelets form homotypic platelet aggregates that can be stabilized by fibrin clots and build thrombi in the vasculature. Upon activation, platelets form heterotypic complexes with neutrophils or monocytes that directly influence immune cell function. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns

been extensively reviewed elsewhere.[40,41,42] Platelets also have an emerging role in the immune response during coronavirus disease 2019 (COVID-19), reviewed in Koupenova.[43] An overview of potential platelet interactions in inflammation and sepsis is shown in Figure 3 and discussed below.

## 5.1 | Platelet activation by bacteria

Clawsson and coworkers first reported that platelets can directly bind to and entrap bacteria in platelet-bacteria aggregates.[44] Platelet activation and aggregation is now known to occur in response to many gram-positive bacteria, reviewed in Cox et al.45 Importantly, multiple platelet receptors can be engaged directly by distinct bacterial proteins or indirectly using a plasma protein bridge. Recently, a common mechanism of platelet activation has been described for the significant human pathogens *Staphylococcus aureus* and *Streptococcus pneumoniae*.[46] The platelet IgG receptor FcγRIIA is critical for recognition of the IgG opsonized bacteria in collaboration with the platelet GPIIb/IIIa receptor, and release of platelet factor 4 (PF4) enhances this platelet activation. In subsequent work, it has been demonstrated that the gram-negative bacteria *Escherichia coli* is also recognized by platelet FcγRIIA in collaboration with GPIIb/IIIa.[47] The evidence is clear that platelet activation occurs in response to bacteria; however, the consequences of these interactions for the platelet phenotype has not been investigated as extensively.

M protein released from *Streptococcus pyogenes* forms a complex with plasma fibrinogen and IgG engages the platelet GPIIb/IIIa and FcγRIIA receptors to mediate platelet activation.[48] This results in C1q acquisition and complement activation at the platelet surface and increased immune-mediated destruction of these platelets in vitro.[49] Mouse platelets lack the FcγRIIA receptor, which is a significant challenge to investigating these platelet-bacteria interactions in experimental models of sepsis. Importantly, FcγRIIA transgenic mice have been generated, and it is extremely beneficial to study bacterial sepsis and organ dysfunction in this background.[50] A recent study used FcγRIIA transgenic mice to demonstrate a dominant role for this receptor in immune complex–mediated thrombocytopenia and

platelet sequestration in mouse models of systemic inflammation, including stimulation with immune complexes of IgG and LPS that are highly relevant to sepsis with gram-negative bacteria.[51] Collectively, these studies demonstrate that platelet activation and degranulation may follow thrombocytopenia, and further work should investigate this phenomenon for other bacteria and bacterial factors in in vivo experimental models.

## 5.2 | Antibacterial effects of platelets

The consequences of platelet activation for the bacteria are likely to be strain and species dependent. Activated platelets release bactericidal antimicrobial peptides, but not all bacteria are susceptible.[52] Platelet FcγRIIA is important for uptake and killing of IgG opsonized *E coli*.[53] Platelets can also exert PF4 and IgG-dependent bactericidal effects on *E coli*[54] and *S aureus*; however, *S pneumoniae* is not susceptible to this bactericidal mechanism.[55] *S pyogenes* is not killed by activated platelets in platelet-bacteria aggregates formed in vitro [56] and depletion of platelets before infection with *S pyogenes* is associated with decreased bacterial survival and dissemination, implying that platelets enhance streptococcal survival in this model.[57]

In experimental mouse models of bacterial infection, the formation of platelet-bacteria aggregates is important for removing some bacterial species from the circulation in a sophisticated collaboration with complement C3, and tissue resident immune cells of the spleen and liver.[58,59,60] In experimental models of sepsis following lung infection, depletion of platelets before initiation of infection leads to increased bacterial growth at the local site of infection and an overall increased mortality.[61] Collectively, these studies demonstrate that platelets employ multiple bactericidal effects that contribute to immune defense.

## 5.3 | Immunomodulatory effects of platelets

Human and mouse platelets express functional toll-like receptor 4 on the surface.[62,63] Traditional features of platelet activation, including P-selectin expression and platelet aggregation, are not observed in response to LPS.[64] Significantly, potent platelet-dependent tumor necrosis factor production is induced on LPS administration to mice.[63] Human platelets release immunomodulatory granule proteins, most notably CD40L, on stimulation with LPS after acquisition of CD14 from plasma.[65,66]

GPVI and C-type lectin receptor (CLEC-2) are important immunoreceptor tyrosine-based activation motif–bearing receptors expressed on both human and mouse platelets.[67] Recent work has described a role for these receptors in inflammation and sepsis. In a murine model of pneumosepsis, GPVI but not CLEC-2, is essential for maintenance of the local immune defense in the lung.[68] Mice lacking functional GPVI show increased bacterial load and decreased platelet-leukocyte complex formation at the local site of infection. CLEC-2 contributes to thrombosis and organ damage in a mouse model of systemic infection with *Salmonella typhimurium*.[69] In recent work, CLEC-2 has been ascribed a significant immunomodulatory role in two murine models of either LPS- or CLP-induced sepsis.[70] CLEC-2 engagement by podoplanin regulates immune cell recruitment and cytokine-driven inflammation and protects against organ damage in both models.

Neutrophils and monocytes are key cellular orchestrators of the innate immune response and, as such, become pathologically dysregulated in sepsis.[7] Activated platelets form complexes with neutrophils (PNCs) and monocytes (PMCs) and the subsequent crosstalk results in modulation of leukocyte function.[71] Immunomodulatory effects of platelets on neutrophil and monocyte function related to sepsis are summarized in Figure 4.

PNC formation occurs in blood stimulated with LPS, and these complexes are sequestered in the lung and liver vasculature of mice treated with LPS.[62] Upon robust activation, neutrophils exhibit neutrophil extracellular trap (NET) formation. NETs are composed of a network of externalized chromatin with antimicrobial peptides and associated enzymes that mediate bacterial killing.[72] PNC formation mediated by LPS induces NET formation.[73,74] This platelet-dependent NET formation can immobilize bacteria in the vasculature of the lungs and liver and may prevent bacterial dissemination. This is likely to be a double-edged sword since histones associated with NETs initiate further platelet adhesion, activation, and pathological thrombosis.[75] In experimental models of sepsis initiated by LPS, *S aureus*, or *E coli*, excessive NET formation contributes to intravascular thrombosis in the liver and mediates organ damage.[76,77] Importantly, treatment of mice with intravenous DNase breaks down the NETs and restores local vascular blood flow. Eradication of NET formation is therefore under investigation as a treatment strategy to counteract organ damage in sepsis; however, this strategy needs to be carefully evaluated to avoid potential detrimental effects on bacterial entrapment. Recent work has demonstrated that NETs do not participate in bacterial containment in the cerebrospinal fluid in a rat model of meningitis [78] or in the liver in a mouse model of sepsis.[79] Crucially, the relative contribution of platelets, fibrin, and fibrinolysis to distinct phases in the progression of different infections from bacterial entrapment to organ dysfunction and sepsis should be established. Molecular mechanisms identified in such studies may represent biomarkers of sepsis progression.

The anucleate platelet is not expected to migrate; however, a recent study applied state-of-the-art imaging techniques to demonstrate active platelet migration to sites of infection and subsequent aggregation with the infiltrating bacteria.[80] This results in immunomodulation, whereby neutrophil recruitment, phagocytosis, and NET formation are enhanced. PNC formation is not always beneficial for neutrophil function and pathogen-dependent phenotypes should be investigated. The M protein released from *S pyogenes* stimulates PNC formation in the absence of NET formation.[81] Fibrinogen is enriched in these PNCs, and neutrophils are functionally impaired, exhibiting decreased chemotactic ability as compared with thrombin-stimulated PNCs.

Platelets can avidly form PMCs; however, the impact on monocyte function has not been fully elucidated. Engagement of platelets can enhance monocyte adhesion to the activated endothelium,[71]

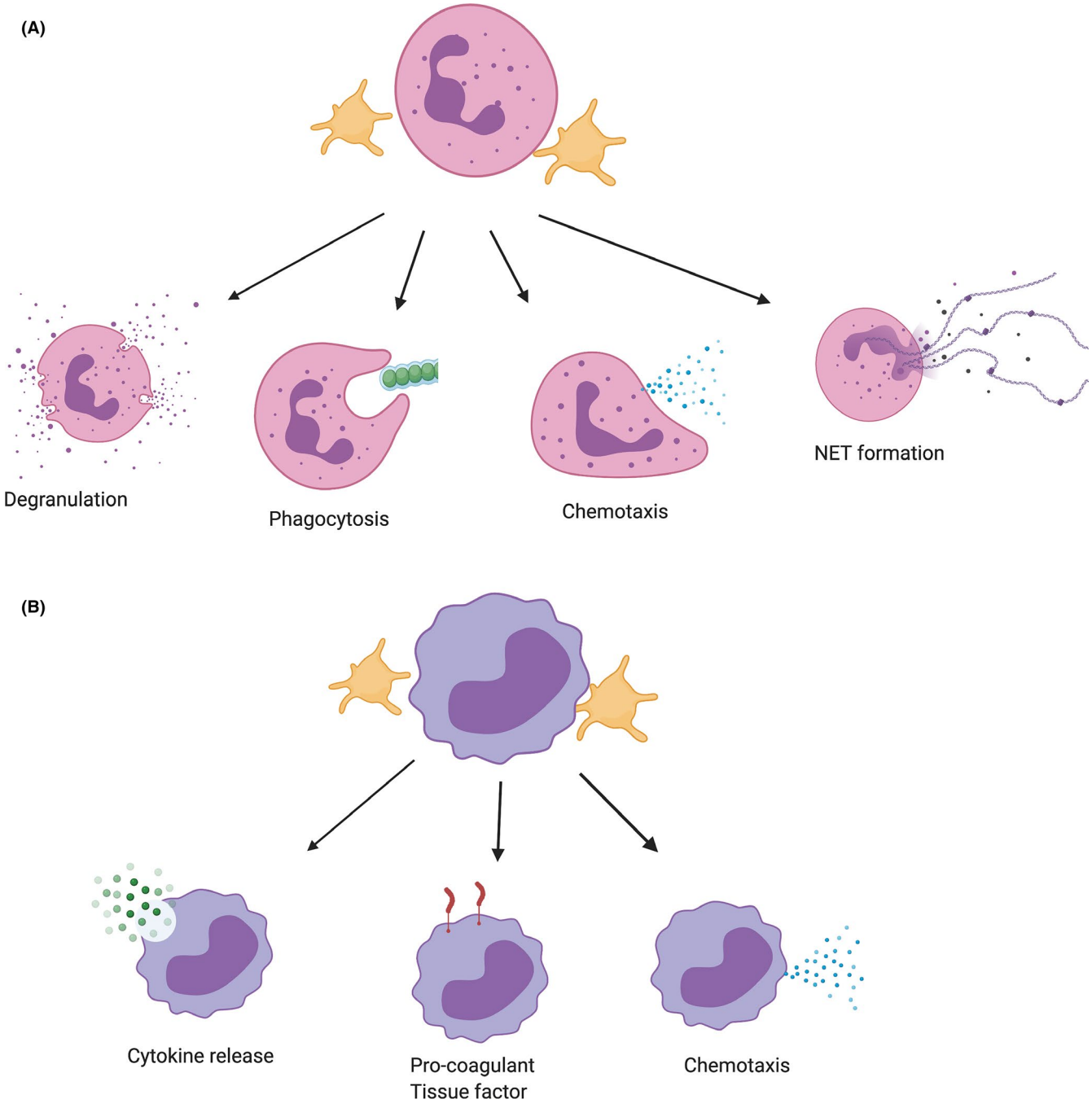


**FIGURE 4** The immunomodulatory effects of platelets on neutrophils and monocytes. Activated platelets upregulate surface receptors that mediate direct binding to neutrophils (A) and monocytes (B). Platelet activation is an important modulator of neutrophil and monocyte function during the immune response to infection and the pathogenesis of inflammatory disease. Activated platelets at the endothelium produce chemokines and provide an adhesive surface for both neutrophils and monocytes. Neutrophils in complex with platelets release their granule contents, exhibit increased phagocytosis, and increased neutrophil extracellular trap (NET) formation. Monocytes in complex with platelets upregulate procoagulant tissue factor (TF) to the surface and increase synthesis of key inflammatory mediators and cytokines

stimulate cytokine release,[82] and procoagulant activity.[83,84] As previously described, ICU patients with sepsis exhibit thrombocytopenia. Intriguingly, it has been demonstrated that these patients with thrombocytopenia exhibit increased systemic cytokine levels, in particular interleukin (IL)-8 and IL-10 and increased plasma markers of endothelial dysfunction.[85] This provides important evidence of an immunomodulatory role for platelets in the pathogenesis of sepsis in human patients.

## 6 | PLATELETS AS A THERAPEUTIC TARGET IN SEPSIS

Antiplatelet therapy in sepsis has been proposed to combat the contribution of platelets to organ dysfunction based on results from experimental models in mice and retrospective studies of human patients with sepsis. For example, administration of clopidogrel

before induction of sepsis decreases plasma markers of liver damage in a mouse model.[86] Pharmacological blockade of platelet production in response to thrombopoeitin decreases organ damage in the lungs and liver in mouse models of sepsis.[87] A retrospective study of critically ill patients indicates that antiplatelet therapy at the time of sepsis is associated with reduced mortality,[88] while in another study antiplatelet therapy was not associated with reduced mortality.[89] Since platelets exhibit a plethora of functions in inflammation and thrombosis at distinct stages of infection and sepsis, the correct timing of antiplatelet therapy needs to be carefully considered. Enhanced understanding of the platelet phenotype in sepsis should facilitate identification of biomarkers for identification of patients with sepsis that will benefit from antiplatelet therapy and potentially reveal novel antiplatelet and anti-inflammatory targets.

## 7 | ISTH CONGRESS 2020 REPORT

Abstracts presented at the 2020 ISTH congress reported important insights on the pathogenesis of endothelial dysfunction and DIC in sepsis and the potential role of platelets in COVID-19. However, these valuable contributions are not the focus of this review and will not be discussed herein. A number of abstracts presented significant advances on the role of platelets in sepsis both in patient material and in experimental models.

The incidence of thrombocytopenia in patients with sepsis in the ICU was investigated by Russell and coworkers in a large multicenter patient cohort.[90] Platelet counts were monitored on admission to the ICU and followed for 5 days. On admission, 37% of patients were thrombocytopenic, and this had risen to 52% by day 3. Significantly, patients with thrombocytopenia had an increased 28-day mortality. In a single-center cohort of ICU patients with sepsis, the platelet count and MPV, on addition of platelet agonists ex vivo, was investigated on inclusion in the study.[91] The MPV post–arachidonic acid stimulation was found to be significantly different between survivors and nonsurvivors.

In a single-center cohort of ICU patients, Hoppensteadt and coworkers[92] investigated platelet function in patients with sepsis and suspected DIC. The plasma levels of CD40L, PF4, VWF, and microparticles were determined. Importantly, PF-4 levels were significantly decreased in nonsurvivors as compared to survivors. This study confirms the association of platelets with DIC and provides potential novel biomarkers to assess platelet function. Weiss and coworkers[93] assessed platelet activation in a cohort of ICU patients at three time points over the course of disease. Traditional assays of platelet function, aggregometry, and upregulation of CD62P and GPIIb/IIIa, were combined with comprehensive analyses of signaling cascades downstream of GPVI receptor engagement. The majority of patients exhibited reduced platelet activation and aggregation upon ex vivo stimulation with agonists. In particular, GPVI-dependent signaling failed to occur, and the ability to recover this response over time was associated with increased survival. Collectively, these two studies confirm the relevance of mapping distinct platelet phenotypes in patients with sepsis.

Although platelet function was not under investigation in the work from Abrams and coworkers,[94] the work is an excellent example of how we can move forward to determine distinct biomarkers that can be used to identify patients with sepsis for tailored treatments. The ability of plasma from ICU patients to induce NET formation on addition to isolated healthy neutrophils ex vivo was used to stratify patients into absent, mild, moderate, and strong NET formation. Strong NET formation was associated with sepsis and predicted DIC and mortality. In a complementary mouse model of sepsis, similar results were obtained and anti–IL-8 therapy reduced NET formation and organ damage in this model.[94]

Megakaryocytes are the precursor cells to platelets. Krauel and coworkers[95] report that LPS circulates in the blood and penetrates to the bone marrow of mice in a CLP model of sepsis. IL-6 mRNA was upregulated in megakaryocytes from these mice. This reveals an intriguing immunomodulatory role for megakaryocytes. Furthermore, the immunomodulatory role of platelets is highlighted in the abstract from Parra-Izquierdo and coworkers,[96] which describes the pathways involved in toll-like receptor 2/6 engagement on platelets and subsequently profiles the platelet activation responses that occur.

## 8 | CONCLUSIONS

Platelets have emerged as important immune cells in the host defense to infection and consequently in the dysregulated response in sepsis. Activated platelets drive central events that contribute to organ dysfunction in experimental models of sepsis; however, additional insight is required both from experimental models and from patient cohorts. Future work should focus on clarifying molecular mechanisms underlying platelet phenotypes in distinct infections, distinct stages in the progression to sepsis, and organ-specific pathogenesis. Multiple parallel immune defense networks collaborate in the dysregulated responses in sepsis. It is increasingly clear that multicomponent biomarker profiles can characterize sepsis response in individual patients. Further, it is likely that in the future, platelet-derived biomarkers will be used to identify patients that might benefit from antiplatelet therapies.

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