Platelets

ISSN: 0953-7104 (Print) 1369-1635 (Online) Journal homepage: www.tandfonline.com/journals/iplt20

Bridging specialties: repurposing platelet drugs prescribed by cardiologists to help infectious disease doctors treat *Staphylococcus aureus* bacteremia

Matthew Geriak, Dani Geriak, Victor Nizet & George Sakoulas

To cite this article: Matthew Geriak, Dani Geriak, Victor Nizet & George Sakoulas (2026) Bridging specialties: repurposing platelet drugs prescribed by cardiologists to help infectious disease doctors treat *Staphylococcus aureus* bacteremia, Platelets, 37:1, 2612045, DOI: 10.1080/09537104.2025.2612045

To link to this article: https://doi.org/10.1080/09537104.2025.2612045

PLATELETS
2026, VOL. 37, NO. 1, 2612045
https://doi.org/10.1080/09537104.2025.2612045

Taylor & Francis
Taylor & Francis Group

COMMENT

Bridging specialties: repurposing platelet drugs prescribed by cardiologists to help infectious disease doctors treat *Staphylococcus aureus* bacteremia

Matthew Geriak[a], Dani Geriak[b], Victor Nizet[c,d], and George Sakoulas[c,e]

[a]Sharp Healthcare Central Research Pharmacy, San Diego, CA, USA; [b]Workday, Healthcare Industry, Los Angeles, CA, USA; [c]Division of Host-Microbe Systems and Therapeutics, Department of Pediatrics, University of California San Diego School of Medicine, La Jolla, CA, USA; [d]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Caifornia, San Diego, La Jolla, CA, USA And; [e]Sharp Rees-Stealy Medical Group, San Diego, CA, USA

ABSTRACT

The platelet is the most important cell in the bloodstream in providing endovascular immunity against *Staphylococcus aureus* bacteremia. Both quantitative and qualitative thrombocytopenia have been associated with increased mortality in patients with *S. aureus* bacteremia. Patients with end-stage renal disease are particularly vulnerable to both an increased risk of getting *S. aureus* bacteremia and endocarditis, but also in treatment failure resulting in prolonged infection and relapse. In this commentary, we highlight the important host–pathogen relationship between *S. aureus* and the human platelet. In particular, we describe virulence factor-mediated platelet clearance from the circulation and improvement in platelet counts as a marker of treatment success. P2Y12 inhibitors deployed in the treatment of cardiovascular disease have been shown to attenuate the effect of *S. aureus* on platelet clearance. Therefore, we believe that partnerships between investigators in cardiology, hematology, and infectious disease with particular focus on platelet pathophysiology are poised to improve outcomes in select patients with *S. aureus* endovascular infection.

PLAIN LANGUAGE SUMMARY

What is the context?

- The platelet is the most important cell in the bloodstream in providing endovascular immunity against *Staphylococcus aureus* bacteremia.
- Both quantitative and qualitative (e.g. caused by kidney disease) thrombocytopenia have been associated with increased mortality in patients with *S. aureus* bacteremia.
- Some *S. aureus* strains enhance platelet clearance through expression of alpha-toxin.

What is new?

- Anti-platelet drugs that inhibit P2Y12 that are normally used in patients with coronary artery disease have been shown to protect platelets from being cleared by alpha-toxin producing S. aureus.
- In one case, the P2Y12 inhibitor ticagrelor was used to increase platelet counts resulting in clearance of an *S. aureus* bloodstream infection that was not responding to antibiotics

What is the impact?

- This review highlights considerable overlap that exists between how platelets and endothelial cells interact in the bloodstream during S. aureus bloodstream infections and during heart attacks.
- Collaboration between cardiology and infectious disease researchers may be critical in better understanding and treatment of serious S. aureus bloodstream infections.

ARTICLE HISTORY
Received 30 April 2025
Revised 2 July 2025
Accepted 11 December 2025

KEYWORDS
Bacteremia; *Staphylococcus aureus*; thrombocytopenia

S. aureus has become the leading cause of bacterial endocarditis worldwide, particularly in developed nations, due to its extensive arsenal of virulence factors that modulate the host–pathogen interaction, including an ability to attenuate platelet activity—a crucial component of endovascular immunity. The roles of platelets in endovascular immunity remain underappreciated. Through their antimicrobial properties

CONTACT : George Sakoulas gsakoulas@health.ucsd.edu Division of Host-Microbe Systems and Therapeutics, Department of Pediatrics, University of California San Diego School of Medicine, La Jolla, CA, USA

and their ability to recruit macrophages and other leukocytes to sites of infection, platelets play a key role in preventing endovascular infections from arising due to normal transient bacteremia. Notably, bacterial resistance to platelet microbicidal proteins (PMP) has been identified as a phenotypic marker associated with an increased propensity for establishing endocarditis.[1] Patients on hemodialysis with uremic thrombocytopathy (commonly referred to as 'uremic platelet syndrome') face a significantly higher risk of developing endocarditis compared to the general population. Indeed, up to 1 in 20 chronic hemodialysis patients will eventually develop bacterial endocarditis.[2]

In the initial phase of endovascular infection, *S. aureus* interacts with platelets and counteracts the host's antimicrobial defenses by inducing platelet apoptosis, thereby evading the immune system and enhancing its own survival. Thrombocytopenia may arise either through direct platelet destruction or via platelet surface modifications that lead to their clearance by the reticuloendothelial system, which mistakenly recognizes the modified platelets to be senescent (Figure 1).[3] Specifically, *S. aureus* α-toxin reduces platelet viability and induces platelet sialidase activity, resulting in desialylation of platelet glycoproteins. Consequently, these desialylated platelets are recognized and bound by the hepatic Ashwell–Morell receptor (AMR), leading to their accelerated clearance.[3] Under normal physiologic conditions, desialylation is a natural process that accompanies platelet aging and senescence, allowing the AMR to clear older platelets and make room for younger, more functional ones. In essence, *S. aureus* exploits this mechanism by inducing premature platelet desialylation, tricking the host into clearing young platelets as if they were senescent.[3]

Platelet dynamics in the early stages of *S. aureus* bacteremia carry prognostic significance. Notably, thrombocytopenia—rather than leukopenia or neutropenia—is associated with increased mortality in *S. aureus* bacteremia.[3] Therefore, therapies aimed at preserving platelet survival could be instrumental in improving outcomes for patients with *S. aureus* endovascular infections. Potential mechanisms by which antiplatelet drugs may attenuate *S. aureus* virulence include (1) inhibiting *S. aureus* adhesion to host cells by targeting microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), (2) preventing *S. aureus* α-toxin-mediated thrombocytopenia, and (3) enhancing the innate platelet-mediated bactericidal response against *S. aureus*.

Ticagrelor is a reversible platelet P2Y12 inhibitor and an adenosine reuptake inhibitor. In the Platelet Inhibition and Patient Outcome (PLATO) study, ticagrelor was associated with lower rates of death from vascular causes, myocardial infarction, and stroke.[4] A post-hoc analysis of PLATO further revealed that ticagrelor recipients had significantly reduced mortality from pneumonia and

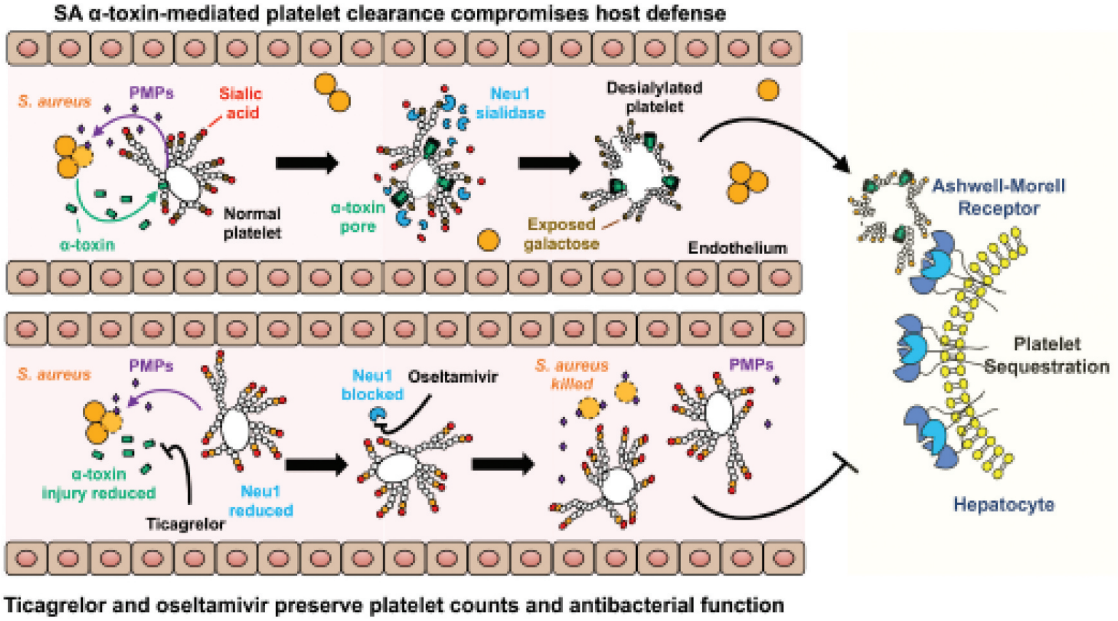

Figure 1. Ticagrelor and oseltamivir inhibit platelet desialylation by *S. aureus*, preventing platelet sequestration from the circulation by hepatocytes in bacteremia (Adopted from reference 3).

sepsis. Subsequently, ticagrelor was found to exhibit antibacterial activity against Gram-positive bacteria, although at concentrations exceeding those achieved with standard dosing.[4] Nevertheless, the influence of ticagrelor on the integrity and composition of the bacterial cytoplasmic membrane can enhance the efficacy of vancomycin and daptomycin against resistant *S. aureus* strains (MRSA and VRSA).[5] Further studies demonstrated that ticagrelor exhibits anti-staphylococcal activity at clinically relevant concentrations in the presence of platelets and other innate immune system components.[4] Ticagrelor, along with the neuraminidase inhibitor oseltamivir, protects platelets from *S. aureus*-mediated clearance by inhibiting α-toxin-induced platelet desialylation, thereby preventing hepatic AMR-mediated clearance.[4]

A thorough evaluation of ticagrelor in a murine model showed that it protected mice from development of endocarditis despite no appreciable effects on bacterial growth.[6] The authors found considerable attenuation of *S. aureus* virulence in the host–pathogen interaction, including endothelial cell adhesion and platelet aggregation. *S. aureus* inhibition to key host proteins such as von Willebrand factor and cell-surface fibrinogen.[6] Interestingly, clopidrogel did not demonstrate these properties and did not prevent *S. aureus* endocarditis in this model.[6]

In a clinical case demonstrating a direct benefit of ticagrelor in active infection, ticagrelor was added to antimicrobial therapy for a patient with persistent *S. aureus* bacteremia and septic shock requiring intensive care. The infection was associated with a septic thrombus at the site of a ruptured atherosclerotic plaque in the aortic arch. The addition of ticagrelor led to the resolution of thrombocytopenia and rapid clearance of the bacteremia.[7] The patient was treated for 3 months and made a full recovery, aside from residual osteoarticular morbidity.[7] Clopidogrel, another P2Y12 inhibitor, has also been linked to reduced mortality in patients hospitalized with *S. aureus* bacteremia in retrospective analysis.[8] However, as mentioned above, the benefit of clopidrogel in preventing endocarditis was not noted in the murine model.[6]

The platelet is increasingly recognized as a critical component of endovascular innate immunity. Impaired platelet function, whether due to quantitative or qualitative deficiencies (e.g., uremic thrombocytopathy), negatively impacts the host's ability to combat serious endovascular infections such as endocarditis. Among human pathogens, *S. aureus* represents the pinnacle of endovascular virulence, as evidenced by its status as the leading cause of bacterial endocarditis.

Protecting platelet function appears to be an important yet underutilized therapeutic strategy in the treatment of *S. aureus* endocarditis. The surprisingly low rate of coronary artery stent infections following percutaneous coronary intervention (PCI) may indirectly reflect the unrecognized antimicrobial prophylactic effects of ticagrelor and other P2Y12 inhibitors, which are routinely administered for 6–12 months after PCI. The profound attenuation of *S. aureus* virulence observed by reducing endothelial adhesion and platelet aggregation translating into prevention of endocarditis in murine models essentially may offer a direct explanation for this potential prophylactic benefit of ticagreolor against infections in PCI. It would be valuable to investigate if patients receiving dual anti-platelet therapy (DAPT) following PCI exhibit lower infection rates compared to those on single therapy. However, because baseline rates of direct cardiac stent infections are extremely low, a very large patient cohort would be required to evaluate the impact of DAPT in that setting.

While laboratory data and retrospective clinical data suggest compelling potential benefits of P2Y12 inhibitors in *S. aureus* bloodstream infections, prospective clinical data remain limited to a single case report. Intriguingly, a recent retrospective cohort study using the TriNetX global health research network found that patients with ACS treated with aspirin and ticagrelor had significantly lower rates of *S. aureus* bacteremia, endocarditis, and sepsis compared to those receiving aspirin with clopidogrel or prasugrel.[9] However, randomized, controlled prospective trials are needed in select patients with *S. aureus* endovascular infections, where the potential benefits may outweigh the risks of hemorrhagic complication. Additional caution should be employed in utilizing antiplatelet therapy in cases where bacteremia progresses to sepsis whereby increased vascular permeability and the inflammatory response adds to the bleeding risk level. With growing recognition of the pathophysiologic overlap between acute coronary syndromes and *S. aureus* endovascular infections, collaborative research between cardiologists and infectious disease specialists will be essential for optimal trial design. Such interdisciplinary efforts could help bridge the

gap in treatment strategies and improve patient outcomes beyond what antibiotic therapy alone can achieve.

Conflicts of Interest

GS has received speaking honoraria from Allergan/AbbVie, Paratek, and Nestle and has consulting fees from Allergan/AbbVie and Paratek. Other authors have no disclosures.

References

1. Yeaman MR. Platelets: at the nexus of antimicrobial defence. Nat Rev Microbiol. 2014;12(6):426–437. doi: 10.1038/nrmicro3269. PMID: 24830471.
2. Bhatia N, Agrawal S, Garg A, Mohananey D, Sharma A, Agarwal M, Garg L, Agrawal N, Singh A, Nanda S, et al. Trends and outcomes of infective endocarditis in patients on dialysis. Clin Cardiol. 2017;40(7):423–429. doi: 10.1002/clc.22688. Epub 2017 Mar 16. PMID: 28300288; PMCID: PMC6490541.
3. Sun J, Uchiyama S, Olson J, Morodomi Y, Cornax I, Ando N, Kohno Y, Kyaw MMT, Aguilar B, Haste NM, et al. Repurposed drugs block toxin-driven platelet clearance by the hepatic Ashwell-Morell receptor to clear Staphylococcus aureus bacteremia. Sci Transl Med. 2021;13(586):eabd6737. doi: 10.1126/scitranslmed.abd6737. PMID: 33762439; PMCID: PMC9121309.
4. Lancellotti P, Musumeci L, Jacques N, Servais L, Goffin E, Pirotte B, Oury C. Antibacterial activity of ticagrelor in conventional antiplatelet dosages against antibiotic-resistant Gram-positive bacteria. JAMA Cardiol. 2019;4(6):596–599. doi: 10.1001/jamacardio.2019.1189. PMID: 31066863; PMCID: PMC6506905.
5. Leeten K, Jacques N, Esquembre LA, Schneider DC, Straetener J, Henriksen C, Musumeci L, Putters F, Melo S, Sánchez-López E, et al. Ticagrelor alters the membrane of *Staphylococcus aureus* and enhances the activity of vancomycin and daptomycin without eliciting cross-resistance. mBio. 2024;15(10):e0132224. doi: 10.1128/mbio.01322-24. Epub 2024 Sep 23. PMID: 39311589; PMCID: PMC11481878.
6. Oury C, Meyers S, Jacques N, Leeten K, Jiang Z, Musumeci L, Lox M, Debuisson M, Goffin E, Pirotte B, et al. Protective effect of ticagrelor against infective endocarditis induced by virulent *Staphylococcus aureus* in mice. JACC Basic Transl Sci. 2023;8(11):1439–1453. doi: 10.1016/j.jacbts.2023.02.003. PMID: 38093743; PMCID: PMC10714181.
7. Ulloa ER, Uchiyama S, Gillespie R, Nizet V, Sakoulas G. Ticagrelor increases platelet-mediated *Staphylococcus aureus* killing, resulting in clearance of bacteremia. J Infect Dis. 2021;224(9):1566–1569. doi: 10.1093/infdis/jiab146.
8. Caffrey AR, Appaneal HJ, Kl L, Lopes VV, Ulloa ER, Nizet V, Sakoulas G. Impact of clopidogrel on clinical outcomes in patients with *Staphylococcus aureus* bacteremia: a national retrospective cohort study. Antimicrob Agents Chemother. 2022;66(6):e0211721. doi: 10.1128/aac.02117-21. Epub 2022 Apr 13. PMID: 35416712; PMCID: PMC9211425.
9. Essa H, Ding WY, Rana F, Zhao SS, Anson M, Austin P, Hernández G, Lal P, Lip GYH, Alam U. Aspirin and ticagrelor versus aspirin and clopidogrel or prasugrel and the effect on staphylococcal-associated infections: a real-world study. Clin Ther. 2024;46(9):689–695. doi: 10.1016/j.clinthera.2024.07.001. Epub 2024 Aug 16. PMID: 39153912.