# Ticagrelor Aids Platelet-Mediated Clearance in a Refractory *Staphylococcus aureus* Endovascular Infection with Septic Emboli

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## BACKGROUND

The pore-forming alpha-toxin produced by *Staphylococcus aureus* (SA) decreases the viability and increases the clearance of platelets, a critical element of innate immune defense in endovascular infection. Our group recently identified that ticagrelor (TICA) blocks alpha-toxin-induced platelet clearance, protecting mice in a lethal systemic SA infection model. Here, we describe a case report in which TICA, added to antimicrobial therapy of a persistent methicillin-susceptible SA (MSSA) bacteremia associated with a septic aortic thrombus, resulted in immediate bacteremia clearance. We further explore TICA synergy with antibiotics and human platelets *in vitro.*

## METHODS

Antibiotic susceptibility of an MSSA strain from a patient treated with TICA for refractory bacteremia was tested by MIC and checkerboard assays in MHB or RPMI at standard ($10^5$ CFU/mL) or high ($10^7$ CFU/mL) inocula using TICA, ertapenem (ETP), cefazolin (CZ), or nafcillin (NAF) alone vs. ETP+CZ ± TICA. Killing assays with human platelets ± TICA against SA were also performed.

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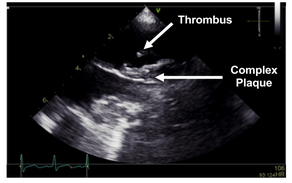
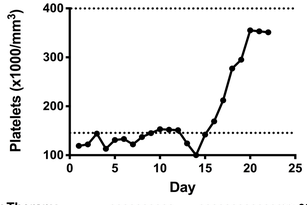
## RESULTS

SA bacteremia secondary to a septic aortic thrombus (>4 mm) with multiple secondary pyogenic foci refractory to standard CZ and subsequent salvage CZ+ETP for 5 days rapidly cleared within 24 h after the addition of TICA. Thrombocytopenia resolved concurrently. Discontinuation of TICA on day 12 led to rebound thrombocytopenia, and TICA was restarted, once again resulting in resolution of thrombocytopenia. TICA alone lacked *in vitro* activity against SA, nor was TICA synergistic with ETP+CZ. In contrast, addition of a physiological achievable concentration of TICA dramatically sensitized SA to human platelet killing ($p<0.001$) *in vitro*.




Minimum Inhibitory Concentration (mg/L)

| | NAF | | CZ | | ETP | | TICA | |
|---|---|---|---|---|---|---|---|---|
| | $10^5$ | $10^7$ | $10^5$ | $10^7$ | $10^5$ | $10^7$ | $10^5$ | $10^7$ |
| MHB | 0.50 | 1 | 1 | 4 | 0.50 | 1 | 64 μM | 64 μM |
| RPMI | 0.50 | 1 | 0.50 | 1 | 16 | 32 | 64 μM | 64 μM |

Minimum Inhibitory Concentration (mg/L) in CA-MHB

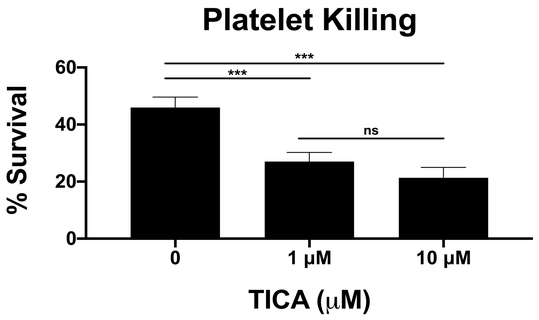
| | CZ | | ETP | |
|---|---|---|---|---|
| TICA | $10^5$ | $10^7$ | $10^5$ | $10^7$ |
| 0 | 1 | 4 | 0.50 | 1 |
| +16 μM | 0.50 | 1 | 0.50 | 0.50 |

Checkerboard (CA-MHB )

| TICA | $10^5$ | FICI | interpretation |
|---|---|---|---|
| 0 | CZ+ETP | 0.75 | additivity |
| +16 μM | CZ+ETP | 0.75 | additivity |

## CONCLUSIONS

In a complex case of aortic plaque rupture with septic thrombus, multiple septic emboli, and refractory MSSA bacteremia, addition of TICA to antimicrobial therapy yielded unanticipated immediate clinical and microbiological success. The profound therapeutic effect of TICA *in vivo* was corroborated by the enhanced staphylocidal activity of human platelets *in vitro* in the presence of physiological concentrations of the antiplatelet agent. TICA warrants further study as adjunctive treatment of refractory SA bacteremia due to a primary endovascular focus when thrombocytopenia is present.

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