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Successful use of nafcillin and ceftaroline combination therapy for persistent MSSA bacteraemia and endocarditis: a case series

Erin F. Warren[1], R. Jake Crocker[1], Benjamin Tabor[1], Morgan Pizzuti[1], Y. Vivian Tsai[1], Kayla Antosz[1,2], Sarah Battle[3,4], Divya Ahuja[3,4] and P. Brandon Bookstaver[1,2]*

[1]Department of Pharmacy, Prisma Health Richland, 5 Richland Medical Park Drive, Columbia 29203, SC, USA; [2]Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, 715 Sumter Street, Columbia 29208, SC, USA; [3]Department of Internal Medicine, University of South Carolina School of Medicine, 6311 Garners Ferry Road, Columbia 29209, SC, USA; [4]Department of Medicine, Division of Infectious Diseases, Prisma Health-University of South Carolina Medical Group, 1 Richland Medical Park Drive, Suite # 420, Columbia 29203, SC, USA

*Corresponding author. E-mail: bookstaver@cop.sc.edu

@Bbookstaver_USC, @vivianytsai, @MorganPizzuti, @bt_pharmd, @ErinFWarren, @JakeCrocker3, @KaylaAntosz

MSSA bacteraemia is an increasingly common cause of morbidity and mortality.[1] While anti-staphylococcal penicillins or cefazolin are recognized as preferred therapies, data are limited for optimal management strategies in persistent MSSA bacteraemia.[2] The use of combination β-lactam therapy has been examined as a potential strategy.[3] This report highlights successful use of the novel combination, nafcillin plus ceftaroline, for persistent MSSA bacteraemia in the setting of endocarditis.

Patient case 1

A 26-year-old man with a history of asthma and IV drug use was transferred from an outside facility 10 days following initial diagnosis of MSSA bacteraemia and tricuspid native valve endocarditis. Upon transfer, the patient was febrile (100.2°F), tachycardic (130 beats per min), with a WBC count of 21 000 cells/mm^3 and elevated serum creatinine (SCr). Due to positive blood cultures on admission, cefazolin 2 g IV every 8 h was continued. Repeat blood cultures initially cleared on hospital day (HD) 3, although he remained febrile. On HD 18, repeat blood cultures were obtained, given intermittent fevers, and were positive for MSSA. Blood cultures on HD 24 remained positive, thus cefazolin was discontinued and nafcillin 2 g IV every 4 h was initiated. On HD 25, ceftaroline 600 mg IV every 8 h was initiated in combination with nafcillin. Repeat blood cultures on HD 28 were negative with concurrent resolution of fever and tachycardia, and normalization of SCr. Blood cultures remained negative on three subsequent instances during the hospitalization. The patient underwent valve repair on HD 31 and ceftaroline was discontinued on HD 36. Nafcillin was discontinued on HD 39 due to lower-extremity oedema and cefazolin was initiated. The patient was discharged on HD 60 after a one-time dose of dalbavancin 1500 mg IV to complete the intended duration.

Patient case 2

A 59-year-old woman with a history of type 2 diabetes mellitus, hypertension, congestive heart failure with cardiac pacemaker, and MSSA endocarditis (4 months prior) presented to the emergency department febrile (103.9°F), hypotensive (90/50 mmHg), encephalopathic, with a WBC count of 14 000 cells/mm^3 and acute kidney injury (SCr 1.69 mg/dL, CL_{CR} 36.9 mL/min). Upon admission, the patient was empirically treated with vancomycin and cefepime. Blood cultures on HD 2 were positive for MSSA and antibiotic therapy was optimized to cefazolin 2 g IV every 12 h. On HD 2, transthoracic echocardiogram revealed vegetations along the right atrial wall and pacemaker lead, diagnostic of endocarditis. On HD 4, blood cultures remained positive for MSSA, and oral rifampicin 300 mg twice daily was added. Blood cultures were persistently positive on HD 7, with no change in time to positivity. Cefazolin and rifampicin were discontinued and renally dose-adjusted ceftaroline 600 mg IV every 12 h was initiated in combination with continuous infusion nafcillin 12 g IV over 24 h. On HD 10, blood cultures obtained prior to pacemaker removal on the same day had cleared. The patient exhibited clinical improvement and was transitioned to cefazolin 2 g IV every 8 h on HD 15, to complete 6 weeks of therapy.

One rationale for dual β-lactam therapy is complementary PBP binding, leading to PBP saturation, and thus enhanced activity.[3,4] PBPs 1, 2 and 3 are vital for growth and survival of MSSA; therefore, binding of β-lactams to these PBPs is lethal.[4] Nafcillin's potent activity against MSSA is facilitated by its binding to PBPs 1–3. In an *in vitro* study, IC_{50}s of oxacillin for PBP 1, 2 and 3 were 0.045, 0.125 and 0.110 mg/L, respectively, corresponding to higher affinity for PBP1.[4] Ceftaroline offers novel, potent activity against MRSA due to PBP2a binding; however, when used for MSSA, it has been shown to have IC_{50}s of 0.100, 0.034 and 0.049 mg/L to PBPs 1, 2 and 3, respectively.[4]

This *in vitro* activity corresponds to a high affinity for PBPs 2 and 3 and correlates to lower MICs.[4] This complementary PBP binding profile of ceftaroline and nafcillin make for a synergistic combination for the treatment of MSSA infections while both agents maintain strong activity against PBPs 1–3. Sader *et al*.[5] reported 100% susceptibility among MSSA bloodstream isolates ($n=2413$) to ceftaroline, and slightly higher potency of ceftaroline when compared with ceftriaxone, linezolid and vancomycin. Furthermore, similar to nafcillin, ceftaroline's activity appears unaltered against MSSA isolates that exhibit cefazolin inoculum effect.[6] Unfortunately, ceftaroline susceptibility testing was not available at our institution at the time.

Current literature on combination β-lactam therapy for persistent MSSA infections consists of case series of ertapenem plus cefazolin or anti-staphylococcal penicillins.[3,7,8] Ulloa *et al*.[7] evaluated cefazolin plus ertapenem for persistent MSSA bacteraemia ($n=11$), including six endocarditis cases, several exhibiting increased cefazolin MICs. In the presence of ertapenem, the bacterial inoculum was reduced below the limit of detection. Eight of nine (88%) patients with daily blood cultures had clearance within 24 h of initiating combination therapy. The median duration of bacteraemia prior to combination therapy was 6 days.

El-Dalati *et al*.[8] evaluated the use of combination therapy, primarily ertapenem plus oxacillin, in 10 patients with persistent MSSA bacteraemia, including 7 endocarditis cases. Patients received a median of 3 days of targeted monotherapy prior to switching to their respective combination regimens. In each case, blood cultures cleared in a median of 1 day, with the majority clearing prior to the obtainment of source control. Other potential mechanisms to explain the *in vivo* effects of ertapenem combination, including stimulation of IL-1β, have been suggested.[9] While an ertapenem-based combination was considered in the cases presented, ceftaroline's known potency combined with local experience for MRSA infections and ability to avoid introducing a carbapenem were the deciding factors.

Dual β-lactam therapy, including nafcillin plus ceftaroline, provides a promising option for persistent MSSA bacteraemia, especially in high-inoculum infections. Further investigation of this combination using a controlled study design is warranted.

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Transparency declarations

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