



Case report

Intravenous (IV) cefazolin with oral probenecid: A novel daily regimen for the management of Methicillin Sensitive *Staphylococcus aureus* (MSSA) bacteremia in a patient with renal dysfunction



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ABSTRACT

A 78 year old man developed a methicillin sensitive *Staphylococcus aureus* (MSSA) post-operative wound infection following an elective L2-L4 laminectomy. He was treated with surgical debridement which was to be followed by a planned 6 weeks course of cefazolin. However, two weeks post debridement, a follow-up MRI revealed an L3-L5 epidural abscess, septic arthritis and vertebral osteomyelitis prompting repeat surgical debridement. No purulence was noted, and operative cultures were negative for growth. His hospital course was complicated by acute kidney injury and a renal biopsy revealed crescentic glomerulonephritis consistent with post infectious glomerulonephritis. He was treated with daptomycin, followed by oral linezolid. Five months after his original laminectomy, he developed purulent drainage from his back wound. Blood cultures grew MSSA and a repeat aspirate done by interventional radiology also grew MSSA. He improved with nafcillin and was transitioned to telavancin on discharge to facilitate once daily treatment. While on telavancin he developed increasing back pain and fever. Therefore, the regimen was changed to IV cefazolin and oral probenecid for five weeks followed by oral cephalexin to complete a total of 12 weeks of therapy. There is no evidence of disease recurrence one year after completion of therapy. IV cefazolin with oral probenecid may represent a once daily IV treatment option for patients with MSSA bacteremia and kidney disease.

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Introduction

Although *Staphylococcus aureus* represents a commensal organism in 30 % of humans, it is one of the most common causes of invasive blood stream infections [1]. Furthermore, *Staphylococcus aureus* is associated with a mortality rate of up to 60 % in cases of bacteremia [2]. Additionally concerning, is that the incidence of *Staphylococcus aureus* bacteremia and infective endocarditis has been increasing [3]. The optimal treatment of methicillin sensitive *Staphylococcus aureus* (MSSA) bacteremia involves using an anti-staphylococcal beta-lactam such as oxacillin, nafcillin or cefazolin. Alternative agents such as vancomycin, ampicillin/sulbactam, piperacillin/tazobactam, and ceftriaxone have all been associated with increased mortality when compared to an anti-staphylococcal beta-lactam for the management of MSSA bacteremia [4–6]. Unfortunately, administration of anti-staphylococcal beta-lactams is challenging for patients with severe MSSA infections as frequent

IV administration is necessary and therapy is often prolonged for several weeks. Therefore, alternative dosing strategies for patients who require daily dosing for this disease are needed. In this report, we discuss a case of MSSA bacteremia that was successfully managed with the unique use of daily IV cefazolin and oral probenecid.

Case report

A 78 year old man with type II diabetes mellitus and lumbar stenosis underwent elective L2 to L4 posterior laminectomy. Approximately 3 weeks after his surgery the surgical wound began to drain and he was taken to the OR for incision and drainage. Operative cultures grew MSSA and he was started on cefazolin. Initially, he was thought to have only a superficial surgical site infection, but MRI was obtained due to ongoing wound drainage which revealed a fluid collection in the dorsal epidural space which was suspicious for abscess. He underwent repeat surgical debridement and a 6-week course of cefazolin was planned. However, he was readmitted 2 weeks later with recurrent wound drainage and drenching sweats. A repeat MRI revealed an increase

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in the epidural fluid collection and probable new septic arthritis at L3/4 and L4/5. He underwent another operative debridement, but no purulence was found. Blood and intraoperative cultures were sterile. His post-operative course was complicated by cardiac arrest, recurrent fever, pseudomeningocele with recurrent wound drainage, and recurrent MSSA bacteremia. Additionally, he developed acute kidney injury which initially was attributed to acute interstitial nephritis from beta-lactam therapy; consequently, cefazolin was changed to daptomycin. Due to lack of improvement in renal function, a renal biopsy was obtained and revealed evidence of crescentic glomerulonephritis, consistent with post-infectious glomerulonephritis. Despite high dose steroid therapy, his renal function failed to improve. A second renal biopsy was then performed which revealed focal proliferative glomerulonephritis and diffuse acute tubular injury. He completed the 6 week course of therapy with daptomycin, followed by oral linezolid. Five months after his original laminectomy the patient developed purulent drainage from his back wound which prompted readmission. A MRI of the lumbar spine was obtained which revealed a multilobulated fluid collection in the posterior paraspinal soft tissues from L3 to L5 measuring approximately 4.7 × 4.4 × 6.6 cm. Blood cultures again grew MSSA and a repeat aspirate performed by interventional radiology (IR) grew MSSA on culture. He was started on IV nafcillin with rapid clearance of the bacteremia after 2 days of therapy. On day 3 of hospitalization, successful percutaneous ultrasound-guided drainage by of a paraspinal collection at the L2-L4 laminectomy bed was performed. Under IR guidance, approximately 40 mL of purulent fluid were aspirated from the laminectomy bed. Gram stain of the fluid revealed 4+ WBCs with 2+ Gram positive cocci in pairs and culture ultimately grew 3 + MSSA. Upon discharge, he was transitioned from IV nafcillin to IV telavancin to allow for once daily administration in an outpatient infusion center.

Six days following hospital discharge, while on IV telavancin, the patient reported a fever (100.6 °F). His renal function was noted to be stable with an estimated creatinine clearance of 30 mL/min using the Cockcroft-Gault equation. Due to concern for treatment failure and the patient's strong desire not to be admitted to a hospital or skilled nursing facility, he was changed to 2 g cefazolin daily along with 1 g oral probenecid to be given at an outpatient infusion center. The lumbar drain was removed 18 days after discharge as the output was less than 10 mL/day. The regimen of IV cefazolin with probenecid was continued for 5 weeks and given the clinical improvement, the patient was transitioned to oral cephalexin for an additional 2 months before the antimicrobial therapy was discontinued. Three weeks following discontinuation of antimicrobial therapy, a repeat MRI of the lumbar spine revealed decreased edema in the paraspinal soft tissue. After 12 months of follow-up, the patient had not experienced a relapse in MSSA bacteremia nor a recurrent abscess of the lumbar spine.

Discussion

To our knowledge, this is the first case of MSSA bacteremia that was successfully treated with daily IV cefazolin in combination with oral probenecid. Due to the limitations of the patient's medical insurance, a once daily infusion in the outpatient setting was desired. Given the patient's renal insufficiency, we postulated that once daily IV therapy with cefazolin and oral probenecid would provide a therapeutic alternative. Clearance of beta-lactams by the kidneys involves tubular secretion. Probenecid increases plasma levels of beta-lactam antimicrobials by competitively inhibiting renal tubular secretion. This advantageous drug interaction was validated clinically over 50 years ago in patients with gonorrhea given the main therapeutic challenge in patients at that time was maintaining a high concentration of penicillin in the

serum [7]. The duration of the serum concentration above 2 µg/mL ranged from 1.6 to 4 h when injectable penicillin was given alone compared to 3.8–10 hours when oral probenecid had been given with injectable penicillin. The prolonged half-life of penicillin when given with probenecid represents important pharmacokinetic implications given beta-lactams exhibit time dependent killing [8].

The pharmacokinetics and pharmacodynamics of other beta-lactams, including cefazolin, have been studied when given in combination with probenecid [9–13]. Healthy male volunteers were observed to have higher serum concentrations of cefazolin when 2 g of cefazolin with 1 g of probenecid by mouth were administered compared to 2 g of cefazolin alone [13]. In another pharmacokinetic study of 6 healthy adult male volunteers, serum cefazolin concentrations over 24 h after a single dose of 2 g of IV cefazolin with 1 g of oral probenecid were greater than 2 µg/mL, which should be adequate for the treatment of *Staphylococcus aureus* when considering current Clinical and Laboratory Standards Institute breakpoints [12]. More importantly, the elimination half-life was 1.6 h for cefazolin alone compared to 2.7 h when cefazolin was combined with probenecid. In a study of 12 subjects, oral probenecid when administered with IV cefazolin was again demonstrated to prolong the cefazolin serum half-life by up to 40 % when compared to the same subjects who received cefazolin alone [10]. Clinicians should take note of these results given the efficacy of cefazolin is only achieved by the maintenance of the time above the pathogen's minimum inhibitory concentration. The use of probenecid to augment and prolong cefazolin serum concentrations has also been studied in the treatment of cellulitis. A randomized, double-blind study identified no significant difference in clinical outcomes in patients receiving 2 g of daily ceftriaxone with 1 g of oral probenecid compared to 2 g of daily cefazolin with 1 g of oral probenecid for the treatment of cellulitis [14]. In another randomized, prospective study, a once-daily regimen of 2 g of cefazolin with 1 g of probenecid by mouth was compared with a once-daily regimen of 1 g of ceftriaxone plus oral placebo for the treatment of cellulitis. Clinical cure occurred at the end of treatment in 86 % and 96 % of patients, respectively (P = 0.11) [15]. The once-daily regimen of 2 g of cefazolin with 1 g of probenecid by mouth yielded a cefazolin serum trough concentration of 2.35 µg/mL [15]. Unfortunately, cefazolin would have needed to be administered every 12 h based on our patient's renal function using standard dosing [10]. Based on the pharmacokinetic data of cefazolin when administered with probenecid and the patient's renal function, we anticipated this novel regimen for MSSA bacteremia would result in clinical cure and allow for once-daily IV administration. While cefazolin trough levels could not be obtained as they are not commercially available, our patient's clinical cure was likely attributed to the unique use of cefazolin with probenecid. In conclusion, we report a case in which cefazolin 2 g daily and probenecid 1 g by mouth daily was used in the treatment of MSSA bacteremia. This regimen may represent a daily intravenous treatment option for MSSA bacteremia in patients with CKD. However, further studies are warranted to further evaluate the use of this regimen.

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None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Sunish Shah: Contributed to literature review and scientific writing.

Marjorie Golden: Contributed to supportive care of the patient and review of the report.

Jeffrey E. Topal: Contributed to supportive care of the patient and review of the report.

Dayna McManus: Contributed to original thought for therapy and review of the report.

CRediT authorship contribution statement

Sunish Shah: Writing - original draft. **Marjorie Golden:** Writing - review & editing. **Jeffrey E. Topal:** Writing - review & editing. **Dayna McManus:** Writing - review & editing, Conceptualization.

Declaration of Competing Interest

None.

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