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Case Report

Persistent Methicillin-Susceptible Bacteremia Rapidly Cleared with Cefazolin and Ertapenem Combination Therapy in a Patient with COVID-19

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1. Introduction

Staphylococcus aureus is a leading cause of bloodstream infections (BSIs), with an annual incidence in the United States of approximately 30 cases per 100,000 person-years [1]. S. aureus BSI is associated with high morbidity and mortality, with 30-day all-cause mortality rates ranging from 20 to 30% [2, 3]. In recent years, MSSA has once again emerged as the predominant cause of staphylococcal bacteremia [4]. Thus, optimizing treatment strategies for MSSA BSI is paramount.

The treatment of choice for MSSA BSI is source control along with an antistaphylococcal penicillin, such as oxacillin or nafcillin or cefazolin [5]. Persistent bacteremia, defined anywhere from 2 to 7 days of positive blood cultures despite appropriate antibiotic therapy, is associated with worse outcomes and higher mortality compared to bacteremias that clear rapidly [6, 7]. Unfortunately, modifications to antibacterial therapy, including the addition of rifampin [8] and daptomycin [9], have not proven beneficial in patients with MSSA BSI. The addition of gentamicin has been used historically but is no longer recommended due to an unacceptable risk of nephrotoxicity when combined with antistaphylococcal penicillins [5].

Recently, combination therapy with cefazolin and ertapenem has emerged as a possible rescue therapy in patients with persistent MSSA BSI. The combination demonstrated synergy both in vitro and in vivo in a murine skin infection model [10]. In a small case series, combination therapy was found to sterilize blood cultures within 24 hours of initiation in 8 of 9 patients with daily blood culture samples [11]. In another case report of a neonate with eight days of positive blood cultures, escalating to cefazolin and ertapenem preceded negative blood cultures 30 hours later [12]. More data, however, about clinical outcomes are needed. Here, we describe a case in which blood culture sterilization was observed within 24 hours of cefazolin and ertapenem combination therapy initiation following 11 days of positive blood cultures.

2. Case Description

A 45-year-old male with a past medical history significant for obstructive sleep apnea, congenital club foot status post corrective surgery years prior, and recently diagnosed...
COVID-19 (10 days prior to admission) presented to the emergency department with increasing weakness, fatigue, and loss of appetite. The patient got tested for COVID-19 after his partner developed respiratory symptoms. Respiratory symptoms at home included cough, shortness of breath, and fevers. The patient also reported using his continuous positive airway pressure machine during the day for increased dyspnea. Additionally, he reported progressive right ankle pain and redness over the last week. On physical exam, the right ankle was warm and erythematous without gross effusion and was tender to palpation and passive range of motion. Initial vital signs were remarkable for a respiratory rate of 28 breaths/minute, heart rate of 116 beats/minute, blood pressure of 184/96 mm-Hg, and a body mass index of 40 kg/m². Complete metabolic panel revealed an elevated glucose of 462 mg/dL, blood urea nitrogen of 80 mg/dL, and serum creatinine of 5.40 mg/dL. Follow-up cultures were sterilized within 24 hours of administration of the cefazolin and ertapenem combination therapy. As a case report, we cannot be certain of the causal link between the antibiotic change and the microbiological response to therapy. Further research is needed to determine the effectiveness and safety of this combination therapy. One final consideration is the timing of source control and appropriate antimicrobial therapy, blood cultures remained negative. This case report highlights the importance of considering alternative treatment options for recalcitrant MSSA BSI not responding to the standard of care therapy and source control.

3. Discussion

MSSA bacteremia is a common BSI associated with significant morbidity and mortality [2, 3]. Effective management includes source control and treatment with antistaphylococcal penicillin or cefazolin. Limited therapeutic options exist for recalcitrant MSSA BSIs not responding to standard therapy and source control. Here, we report on a patient with newly diagnosed diabetes mellitus, COVID-19 pneumonia, and concomitant MSSA BSI not responding to the standard of care therapy with oxacillin and initial source control procedures. Following more than 10 days of persistent bacteremia, blood cultures were sterilized within 24 hours of administration of cefazolin and ertapenem combination therapy.

Cefazolin and ertapenem bind to different penicillin-binding proteins (PBPs), with ertapenem selectively targeting PPB1 and cefazolin predominantly binding to PB2. Such complementary binding affinities provide the theoretical pharmacodynamic foundation for utilizing these two agents in combination. A recent case series highlights the potential utility of cefazolin and ertapenem in combination as salvage therapy for persistent MSSA BSIs [11]. In this series, 8 of 11 patients achieved negative blood cultures within 24 hours of initiation of salvage therapy. Most patients in this series had deep-seated infections, including 6 with endocarditis and 2 with spinal osteomyelitis and epidural abscesses. Additionally, the authors noted synergy when testing the combination in vitro and in a rat model of endocarditis [11]. While the duration of S. aureus bacteremia has not been associated with 90-day mortality, it has been associated with other significant complications. These include new metastatic foci of infection (often requiring surgical interventions), relapse of bacteremia, longer hospital stay, and complications due to longer hospital stay [7, 16]. Together, these serve as a rationale for salvage therapy with combination antimicrobials in recalcitrant bacteremia.

Regarding the management of the patient’s COVID-19 pneumonia, our patient initially received intravenous dexamethasone and remdesivir; however, the latter was held following the administration of a loading dose given the patient’s acute renal failure. Dexamethasone was continued for a complete 10-day course in accordance with clinical treatment guidelines [17]; however, new initiation of corticosteroids in patients with staphylococcal BSIs without concomitant shock has been associated with increased all-cause mortality at 28 and 90 days [18]. These data highlight the need to critically weigh the risks and benefits of continued dexamethasone therapy in the setting of secondary infections in patients with COVID-19.

One final consideration is the timing of source control relative to the initiation of cefazolin and ertapenem combination therapy. As a case report, we cannot be certain of the causal link between the antibiotic change and the subsequent microbiological response.
cessation of bacteremia, but the temporal proximity does raise this as a possibility. In addition, while an undrained epidural abscess could explain persistent fevers and symptoms, undrained collections are rarely the cause of continuous bacteremia (hence, our clinical use of continuous bacteremia as the sine qua non of endovascular infection). In total, this case suggests to us the possibility of an effect, and one worth reporting as a case study, in order to pique the interest of other clinicians or to contribute eventually to a case series, before undertaking a more rigorous study design.

### Table 1: Summary of hospital course.

| Day | $T_{\text{max}}$ | WBC | Scr | Cultures | Antimicrobials | Imaging | Comments |
|-----|----------------|-----|-----|----------|----------------|---------|----------|
| ED  | 40.5           | 8.0 | 5.10| Bcx: 2/2 MSSA; TTP 8.3 hours | Vancomycin 1750 mg IV $\times$ 1 | X-ray R foot/ankle, X-ray chest per HPI | Ortho attempted aspiration of R ankle—dry tap. Oxacillin 2g IV q4h started following detection of MSSA in ED blood cultures. |
| 1   | 37.9           | 8.1 | 4.44| Bcx: 2/2 MSSA | Cefepime 2g IV q24h, linezolid 600 mg IV q12h, remdesivir 200 mg IV $\times$ 1 | CT chest PE protocol: no PE, possible septic emboli and L IJ thrombophlebitis | Remdesivir stopped by MICU due to AKI. ID consulted. |
| 2   | 37.3           | 8.7 | 4.19| Bcx: 2/2 MSSA | Oxacillin 2g IV q4h | Ankle tissue culture: 5/5 MSSA; tracheal aspirate: MSSA | Panorex: periapical abscesses at #30. Duplex LEs: No DVTs. TTE: No vegetations MRI R ankle (Figure 1): diffuse skin thickening and edema of foot and ankle w/o evidence of OM; large complex tibiotalar joint effusion w/synovitis and abscess along the FHL muscle X-ray chest: mild interval improvement in b/l interstitial airspace opacities c/w COVID-19 pneumonia, septic pulmonary emboli CT CAP w/contrast: cavitating pulmonary septic emboli, fluid collection around L SC joint c/f early septic arthritis, phleghmon within R iliacus muscle. X-ray L knee/ankle: L knee medial osteoarthritus, L foot cellulitis, and acute on chronic achilles tendinopathy Tee: no vegetations noted MRI L knee/ankle: fluid collection extending dorsally from between the base of the L 3rd and 4th metatarsal, likely represents extension of adventitial bursitis. US lower back: loculated fluid collection deep and posterior in pelvis. MRI brain/spine (Figure 2): C2–C4 discitis/OM w/epidural abscess, no intracranial abnormality. CT spine: C3–C4 discitis/OM w/epidural abscess | OR with ortho s/p R ankle I&D and arthrotomy; R leg FHL abscess I&D. Dental consulted. |
| 3   | 37.3           | 7.6 | 2.53| Bcx: 2/2 MSSA | Oxacillin 2g IV q4h | | Weaned off BiPAP; CPAP at night only. Tooth #30 extracted. |
| 4   | 38.5           | 5.3 | 2.12| Bcx: 2/2 MSSA | | | Ceftriaxone added by ICU team for Gram-negative coverage given fever and tachycardia; X-rays looking for prior hardware; no surgical indication for SC joint per thoracic surgery. |
| 5   | 38.8           | 5.7 | 1.82| Bcx: 2/2 MSSA | | | MSK IR consulted for iliacus muscle phlegmon. Transferred to floor. |
| 6   | 38.9           | 6.2 | 1.57| Bcx: 2/2 MSSA; COVID-19 RNA nasopharyngeal swab: positive | Oxacillin 2g IV q4h, ceftriaxone 2g IV $\times$ 1 | | Ceftriaxone discontinued. ID recommend to change oxacillin to cefazolin plus ertapenem. Last dose dexamethasone given. Ortho spine consulted. |
| 7   | 38.7           | 4.2 | 1.47| Bcx: 2/2 MSSA | Oxacillin 2g IV q4h, ceftriaxone 1g IV q24h | | L 3rd/4th metatarsal aspiration; OR for cervical fusion/epidural abscess drainage with ortho spine. |
| 8   | 37.9           | 7.1 | 1.51| Bcx: 1/1 MSSA | | X-ray L shoulder/R knee: no evidence of OM or septic arthritis. MRI L knee/ankle/foot: severe L knee chondrosis, small L knee joint effusions, L ankle and foot cellulitis, small nonspecific collection extending dorsally from between the base of the L 3rd and 4th metatarsal, likely represents extension of adventitial bursitis. US lower back: loculated fluid collection deep and posterior in pelvis. MRI brain/spine (Figure 2): C3–C4 discitis/OM w/epidural abscess, no intracranial abnormality. CT spine: C3–C4 discitis/OM w/epidural abscess | |
| 9   | 37.7           | —   | —   | Bcx: 1/1 MSSA; TTP = 13.6 hours | | | |
| 10  | 37.2           | 7.1 | 1.39| Bcx: 2/2 MSSA; TTP = 22.5 hrs; L foot aspiration: MSSA; cervical spine wound: MSSA | Cefazolin 2g IV q8h, ertapenem 1g IV q24h | | |
| 11  | 36.9           | 6.0 | 1.23| Bcx: 2/2 no growth | | | |
| 12  | 37.2           | 4.1 | 1.10| Bcx: 2/2 no growth | | | |

Bcx, blood culture(s); TTP, time-to-positivity; FHL, flexor hallucis longus; SC, sternoclavicular; OM, osteomyelitis.
4. Conclusion

Cefazolin and ertapenem combination therapy resulted in successful sterilization of blood cultures within 24 hours of administration in a patient previously bacteremic for more than 10 days despite optimal pharmacotherapy. The patient’s MSSA BSI may have been aggravated by continued administration of dexamethasone for COVID-19. Clinicians should consider weighing the risks and benefits of dexamethasone administration in the setting of concomitant infections.

Consent

No written consent has been obtained from the patients as there are no patient identifiable data included in this case report/series.

Conflicts of Interest

The authors have no relevant conflicts of interest to disclose.

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