Ceftriaxone for the Treatment of Methicillin-susceptible Staphylococcus aureus Bacteremia: A Case Series

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Abstract

Methicillin-susceptible Staphylococcus aureus (MSSA) causes 45% of S. aureus bloodstream infections (BSI) and is the most important cause of BSI-associated death. The standard of care therapy is an anti-staphylococcal penicillin or cefazolin, but dosing frequencies for these agents are often infeasible; multiple daily doses tie up infusion lines and are impractical for outpatient antibiotic infusion. Ceftriaxone represents a promising alternative, with once daily dosing and a short infusion time. Currently, treatment with ceftriaxone for invasive MSSA infections is infrequent, with minimal data supporting the clinical utility of ceftriaxone for MSSA BSI. In this case series, we identified 15 patients receiving ceftriaxone for treatment of MSSA BSI, either following standard of care therapy or as initial therapy. Patients were evaluated for clinical cure (CC)(clearance of BSI and normalization of white blood cell count) and microbiological cure (MC)(clearance of blood cultures and no recurrence of organism within 60 days). CC was observed in seven patients, with MC observed in all patients. Only one patient was readmitted to the hospital. This case series provides vital data to support ceftriaxone for treatment of MSSA BSI. With few readmissions and recurrences of infection, ceftriaxone was an effective option for maintenance therapy after resolution of the BSI. Ceftriaxone appears to be a viable alternative for the treatment of MSSA BSI.

Keywords: Bacteremia, beta-lactam, ceftriaxone, infectious diseases, methicillin-susceptible Staphylococcus aureus

INTRODUCTION

Staphylococcus aureus is a leading cause of bloodstream infections (BSI) and BSI-associated death.[1] The incidence of methicillin-susceptible S. aureus (MSSA) was 24.2/100,000 persons in 2013; the case fatality ratio was 20.2%. [2,3] Standard of care, first-line therapy options for MSSA BSIs are anti-staphylococcal penicillins or cefazolin.[4-7] Ceftriaxone which has in vitro MSSA susceptibility (95%–100% susceptible),[8-10] is relatively inexpensive, has a long half-life enabling once-daily dosing, and does not require dosage adjustments in renal dysfunction, making it a viable alternative option.[10] Despite this, ceftriaxone treatment for invasive MSSA is infrequent. Since minimal data support ceftriaxone for these infections, our objective was to report clinical outcomes for MSSA BSIs treated with either standard of care therapy (SOCT) followed by ceftriaxone or ceftriaxone initially. Clinical cure (CC) was defined as clearance of BSI and normalization of white blood cell count (WBC) and temperature within 7 days of the first positive blood culture. Microbiological cure (MC) was defined as clearance of blood cultures and no repeated organism isolation within 60 days.

Case Reports

Case 1
A 74-year-old male admitted for altered mental status from an outside hospital (OSH) had a past medical history (PMH) of diabetes mellitus (DM), diabetic retinopathy, and atrial fibrillation. Blood and urine cultures revealed MSSA, and treatment was de-escalated from vancomycin to ceftriaxone 2 g every 24 h on day 3. Transesophageal echocardiogram (TEE) revealed no vegetations, but an epidural abscess was identified on day 4. Magnetic resonance imaging (MRI) revealed septic
A 49-year-old male was admitted for symptoms of an upper respiratory tract infection with a nonhealing diabetic foot wound secondary to longstanding DM with diabetic neuropathy and HTN. Blood cultures revealed MSSA on day 1, and ceftriaxone 2 g every 24 h was initiated on day 2 with clearance observed on day 3. X-rays suggested osteomyelitis, and a below the knee amputation was performed on day 5. Postamputation, ceftriaxone 2 g every 24 h was continued for 4 weeks. The patient was readmitted twice the following month, once for a fall that caused bleeding at the site of the amputation and once for debridement, but cultures did not reveal any MSSA, and no MSSA BSI-related recurrence was noted on either admission.

A 57-year-old male was admitted for MSSA bacteremia due to a TEE displayed a large vegetation on the right atrial junction. He received vancomycin until day 3, when blood cultures revealed MSSA. Oxacillin 2 g every 4 h was administered from hospital days 4 through 7, then oxacillin was changed to ceftriaxone 2 g every 24 h for 4 weeks of therapy.

Case 5
A 54-year-old female admitted for shortness of breath, weakness, and fatigue with a PMH of HTN, DM, heart failure, atrial fibrillation, and end-stage renal disease (ESRD) had positive MSSA blood cultures from admission. A definitive source for the MSSA BSI was not determined but assumed to be foreign body material (tunneled dialysis catheter, Foley catheter, and implantable cardiac device). She was initiated on ceftriaxone 2 g every 24 h on day 3 and cultures cleared on day 8. She received 4 weeks of ceftriaxone (25 days inpatient and 3 days outpatient).

Case 6
A 56-year-old male with PMH including DM and hypertension (HTN) was admitted for septicemia secondary to cellulitis of the left great toe. He received vancomycin until day 3, when blood cultures revealed MSSA. Oxacillin 2 g every 4 h was administered from hospital days 4 through 7, then oxacillin was changed to ceftriaxone 2 g every 24 h for 4 weeks of therapy.

Case 7
A 58-year-old female admitted for shortness of breath, weakness, and fatigue with a PMH of HTN, DM, heart failure, atrial fibrillation, and end-stage renal disease (ESRD) had positive MSSA blood cultures from admission. A definitive source for the MSSA BSI was not determined but assumed to be foreign body material (tunneled dialysis catheter, Foley catheter, and implantable cardiac device). She was initiated on ceftriaxone 2 g every 24 h on day 3 and cultures cleared on day 8. She received 4 weeks of ceftriaxone (25 days inpatient and 3 days outpatient).

Case 8
A 60-year-old male was admitted for cellulitis of the left lower leg. He continued to worsen despite 5 days of outpatient therapy with clindamycin. Foot ulcer and blood cultures from hospital day 1 grew MSSA; MRI was not indicative of osteomyelitis or septic arthritis. Clindamycin was discontinued, and oxacillin 2 g every 4 h was initiated on day 5. On day 7, oxacillin was changed to ceftriaxone 2 g every 24 h for 4 weeks of outpatient therapy.

Case 9
A 61-year-old male with PMH of uncontrolled DM was admitted for cellulitis of the left lower leg. He continued to worsen despite 5 days of outpatient therapy with clindamycin. Foot ulcer and blood cultures from hospital day 1 grew MSSA; MRI was not indicative of osteomyelitis or septic arthritis. Clindamycin was discontinued, and oxacillin 2 g every 4 h was initiated on day 5. On day 7, oxacillin was changed to ceftriaxone 2 g every 24 h for 4 weeks of outpatient therapy.

Case 10
A 62-year-old male with PMH of uncontrolled DM was admitted for cellulitis of the left lower leg. He continued to worsen despite 5 days of outpatient therapy with clindamycin. Foot ulcer and blood cultures from hospital day 1 grew MSSA; MRI was not indicative of osteomyelitis or septic arthritis. Clindamycin was discontinued, and oxacillin 2 g every 4 h was initiated on day 5. On day 7, oxacillin was changed to ceftriaxone 2 g every 24 h for 4 weeks of outpatient therapy.

Case 11
A 63-year-old female admitted for diabetic ketoacidosis (DKA), sepsis, right hand cellulitis, and a right patellar fracture. Her PMH included ESRD, DM, and diabetic nephropathy. She was treated for DKA in the intensive care unit, and her dialysis port was removed as a source of infection. Dialysis port cultures and blood cultures revealed MSSA. She was initially treated with vancomycin, which was de-escalated to oxacillin for days 5 through 9. Oxacillin was switched to cefazolin 2 g every 48 h for days 10 through 13, then changed to ceftriaxone 2 g every 24 h on day 14. She was discharged home on day 21 with 4 weeks of outpatient ceftriaxone.

Case 12
A 64-year-old female with PMH of invasive breast carcinoma with reported tenderness around her chemotherapy port for
1 week was admitted for Gram-positive BSI. The chemotherapy port was removed on day 2 and cultured MSSA. Vancomycin was discontinued in favor of oxacillin 2 g every 4 h until day 5, when oxacillin was discontinued, and she was discharged on 2 weeks of ceftriaxone 2 g every 24 h.

**Case 13**
A 35-year-old female was admitted for fever with swelling and pain at the site of the peripherally inserted central catheter (PICC) in her left arm. She had a PMH of gastroparesis with multiple abdominal surgeries and was reliant on total parenteral nutrition. Blood cultures revealed MSSA, and her PICC was removed for 48 h before a new one was placed. She received ceftriaxone 1 g every 24 h on days 1–3. Ceftriaxone was switched to oxacillin 2 g every 6 h on day 4. She was changed back to ceftriaxone 2 g every 24 h on day 12, then discharged to a long-term acute care (LTAC) facility on day 23. She continued ceftriaxone at LTAC for 8 additional days.

**Case 14**
A 24-year-old male with PMH of testicular cancer and recent chemotherapy was admitted from an OSH with fever and given cefepime. On day 2, blood and sputum cultures became positive for MSSA, and cefepime was de-escalated to oxacillin 2 g every 4 h. A chest CT displayed cavitary lesions determined to be caused by MSSA. It was suspected that the MSSA BSI was due to septic emboli from a central line infection, and his chemotherapy port was removed. On day 8, oxacillin was discontinued, and he was initiated on ceftriaxone 2 g every 24 h. He was discharged on day 10 to complete 4 weeks of therapy. Nine days after discharge, he was readmitted with progressive shortness of breath, fever, chills, and night sweats. A pleural fluid culture yielded MSSA, so he received ceftriaxone on days 1–4 and oxacillin on days 4–7. He was discharged on ceftriaxone therapy to complete the 4 weeks.

**DISCUSSION**
We described the successful use of ceftriaxone for MSSA BSI [Table 1]. Of the 15 cases presented, four received ceftriaxone therapy on MSSA identification, whereas 11 received SOCT first. All ceftriaxone-treated patients empirically received vancomycin for 2.5 ± 1.7 days and achieved MC with a duration of bacteremia of 6.8 ± 5.2 days. However, only 75% achieved CC. A CC was not observed in case #1 due to prolonged bacteremia (14 days) though this is likely attributed to inadequate source control. Of the 11 patients treated with SOCT first, 10 received vancomycin therapy for 2.6 ± 1.0 days before initiation of SOCT, and all 11 received SOCT for 6.1 ± 3.0 days before ceftriaxone. All achieved MC, but only 5/11 (45.5%) demonstrated CC. Of CC failures, 5 (86%) had prolonged elevation of WBC. Ceftriaxone was started on the majority (81.8%) of these patients post bloodstream clearance. These data demonstrate ceftriaxone may be an appropriate agent once bacteremia is resolved, particularly in an outpatient setting [Table 2]. This is supported by only a single case of MSSA readmittance.

These cases demonstrated similar ceftriaxone cure rates as previously published literature.[7] While only four

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**Table 1: Summary of patient cases**

| Patient case | Infection source | Treatment | Clinical cure? | Microbiological cure? | LOS (days) | MSSA BSI-related readmission? |
|--------------|------------------|-----------|----------------|-----------------------|-----------|-------------------------------|
| 1            | UTI              | CRO       | No             | Yes                   | 44        | No                            |
| 2            | IE               | SOCT→CRO  | No             | Yes                   | 13        | No                            |
| 3            | SSTI             | SOCT→CRO  | Yes            | Yes                   | 7         | No                            |
| 4            | Prosthetic device| CRO       | Yes            | Yes                   | 28        | No                            |
| 5            | Septic arthritis | CRO       | Yes            | Yes                   | 13        | No                            |
| 6            | Unspecified      | SOCT→CRO  | No             | Yes                   | 23        | No                            |
| 7            | Osteomyelititis  | CRO       | No             | Yes                   | 13        | No                            |
| 8            | Surgical site    | SOCT→CRO  | No             | Yes                   | 12        | No                            |
| 9            | SSTI             | SOCT→CRO  | No             | Yes                   | 9         | No                            |
| 10           | Central line     | SOCT→CRO  | Yes            | Yes                   | 5         | No                            |
| 11           | Dialysis port    | SOCT→CRO  | No             | Yes                   | 21        | No                            |
| 12           | Chemo port       | SOCT→CRO  | Yes            | Yes                   | 5         | No                            |
| 13           | Central line     | SOCT→CRO  | Yes            | Yes                   | 23        | No                            |
| 14           | Pneumonia        | SOCT→CRO  | Yes            | Yes                   | 10        | Yes                           |
| 15           | CNS              | SOCT→CRO  | Yes            | Yes                   | 14        | No                            |

LOS=Length of stay, MSSA=Methicillin-susceptible *Staphylococcus aureus*, BSI=Bloodstream infection, UTI=Urinary tract infection, IE=Infective endocarditis, CRO=Ceftriaxone, SOCT=Standard of care therapy, SSTI=Skin and soft tissue infections, CNS=Central nervous system.
patients received ceftriaxone initially, clinical success was 75% compared to 83% in the Patel et al. study. However, our series represented a more diverse and younger population (60% males, average age 47 years) compared to a VA Institution (100% males, average age 68 [SOCT] and 63 [ceftriaxone] years)\(^\text{[11]}\). Another evaluation comparing ceftriaxone versus cefazolin demonstrated similar duration of SOCT therapy before initiation of ceftriaxone\(^\text{[12]}\). However, neither the source of BSI nor specific outcomes of each antimicrobial were reported. Unlike a study comparing ceftriaxone versus nafcillin for outpatient parenteral therapy against MSSA,\(^\text{[13]}\) no adverse events were observed in any of our patients.

However, higher rates of treatment failure with ceftriaxone versus cefazolin for MSSA bacteremia, including a possible increased mortality, have been observed\(^\text{[11,14]}\). Of note, one study included high-acuity patients and failed to state whether patients received adequate duration of treatment with ceftriaxone before treatment failure was declared\(^\text{[11]}\). The second study declared ceftriaxone to have higher mortality rates but was not considered statistically significant, and no other outcomes were measured\(^\text{[14]}\).

This case series provides vital data to support ceftriaxone for treatment of MSSA BSI. The majority of patients received SOCT before ceftriaxone therapy, so while the CC and MC may be attributed to SOCT, it is important to note that these infections require prolonged courses of therapy. Therefore, the few recurrences of infection demonstrate that ceftriaxone was an effective option for maintenance therapy after resolution of the BSI.

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**Table 2: Comparison of treatment durations in days**

| Patient case | Total duration of antibiotic therapy | Duration of initial SOCT therapy | Corrected total duration of CRO therapy | Duration of CRO therapy inpatient | Duration of CRO therapy outpatient |
|--------------|-------------------------------------|---------------------------------|---------------------------------------|----------------------------------|-----------------------------------|
| 1            | 100                                 | 0                               | 100                                   | 41                              | 56                                |
| 2            | 50                                   | 8                               | 42                                    | 0                               | 42                                |
| 3            | 32                                   | 4                               | 28                                    | 0                               | 28                                |
| 4            | 28                                   | 0                               | 28                                    | 25                              | 3                                 |
| 5            | 42                                   | 0                               | 42                                    | 6                               | 36                                |
| 6            | 17                                   | 10                              | 7                                     | 0                               | 7                                 |
| 7            | 28                                   | 0                               | 28                                    | 12                              | 16                                |
| 8            | 50                                   | 8                               | 42                                    | 1                               | 41                                |
| 9            | 31                                   | 3                               | 28                                    | 0                               | 28                                |
| 10           | 32                                   | 4                               | 28                                    | 0                               | 28                                |
| 11           | 45                                   | 9                               | 36                                    | 8                               | 28                                |
| 12           | 15                                   | 3                               | 12                                    | 0                               | 12                                |
| 13           | 32                                   | 9                               | 23                                    | 15                              | 8                                 |
| 14           | 28                                   | 7                               | 21                                    | 3                               | 18                                |
| 15           | 67                                   | 11                              | 56                                    | 0                               | 56                                |

SOCT=Standard of care therapy, CRO=Ceftriaxone

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**Conflicts of interest**

There are no conflicts of interest.

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