Methicillin-resistant Staphylococcus aureus bacteraemia and endocarditis treated with ceftaroline salvage therapy

Tony T. Ho1, Jose Cadena1,2, Lindsey M. Childs2,3, Miguel Gonzalez-Velez1 and James S. Lewis II1,3,4*

1Department of Medicine—Division of Infectious Diseases, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA; 2South Texas Veterans Health Care System—Audie L. Murphy Hospital, 7400 Merton Minter Drive, San Antonio, TX 78229, USA; 3University of Texas at Austin College of Pharmacy—Pharmacotherapy Education and Research Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA; 4University Health System—Department of Pharmacy, 4502 Medical Drive, San Antonio, TX 78229, USA

*Corresponding author. University Health System, 4502 Medical Drive, Inpatient Pharmacy, MS-102, San Antonio, TX 78229, USA. Tel: +1-210-358-0421; Fax: +1-210-358-4168; E-mail: james.lewis@uhs-sa.com

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Background: One of the newest methicillin-resistant Staphylococcus aureus (MRSA) antibiotics to receive FDA approval is ceftaroline fosamil, a member of a new subclass of cephalosporins with unique activity against MRSA. However, ceftaroline is currently only FDA approved for complicated skin/soft tissue infections and community-acquired pneumonia; there are currently no clinical data regarding its use in MRSA bacteraemia and endocarditis. We report a series of six patients in which ceftaroline was utilized as salvage monotherapy in persistent MRSA bacteraemia or endocarditis.

Methods: Using pharmacy records, 11 ceftaroline-treated patients were identified between January 2011 and November 2011 at University Health System and the South Texas Veterans Health Care System in San Antonio, TX, USA. All cases were reviewed and six patients received ceftaroline therapy for MRSA bacteraemia or endocarditis due to persistent or recurrent bacteraemia while on standard antibiotics (vancomycin or daptomycin).

Results: All six patients experienced rapid clearance of their bacteraemia after starting ceftaroline. In the case of endocarditis for which the patient subsequently developed heart failure and required valve replacement, there was no evidence of growth from cultures taken from the excised valve, suggesting sterilization within 13 days of starting ceftaroline.

Conclusions: Ceftaroline exhibits potent anti-MRSA activity in both in vitro and animal studies, including rabbit endocarditis models; however, the lack of clinical data has limited its use in bacteraemia and endovascular infections in humans. We hope that this series serves as an initial stepping stone for further evaluation of this compound for more invasive infections due to MRSA.

Keywords: vancomycin-intermediate Staphylococcus aureus, VISA, pharmacodynamics, pharmacokinetics

Introduction

Optimal therapy for persistent methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia (lasting >7 days, with ≥5 days of appropriate therapy) is not clearly established.1 Daptomycin is FDA approved for the treatment of MRSA bacteraemia. However, there are concerns about its use in patients failing vancomycin therapy due to the observation that daptomycin MICs may increase with the vancomycin MIC.2 Ceftaroline fosamil is a new cephalosporin that is active against MRSA.3 The ceftaroline MIC₉₀ for MRSA as well as the FDA susceptible breakpoint for S. aureus is 1 mg/L.4 We report six patients that received ceftaroline therapy for MRSA bacteraemia between January and September 2011 (Table 1).

Case 1

A middle-aged male with a history of intravenous drug use (IVDU) and coagulase-negative staphylococcal spinal osteomyelitis was admitted with worsening back pain and fever. Blood cultures were positive for MRSA. He was started on vancomycin, dosed for a trough of 15–20 mg/L (attained by day 2), and cleared his bacteraemia on day 7. A transthoracic
Table 1. Summary of cases and outcomes

<table>
<thead>
<tr>
<th>Case</th>
<th>Source of MRSA bacteraemia</th>
<th>Duration of bacteraemia (days)</th>
<th>Prior therapy (days)</th>
<th>VAN MIC (mg/L)(^a)</th>
<th>DAP MIC (mg/L)(^a)</th>
<th>Linezolid MIC (mg/L)(^a)</th>
<th>Ceftaroline MIC (mg/L)(^b), dose/duration(^b)</th>
<th>Complications</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>endocarditis</td>
<td>13 days, cleared and relapsed day 17, cleared on day 18 (start of ceftaroline therapy)</td>
<td>13 (VAN), then 4 (DAP) day 17: 4</td>
<td>2</td>
<td>NA</td>
<td>0.5—VISA isolate, 600 mg iv q8h for 42 days</td>
<td>mitral valve replacement, ESBL Klebsiella pneumonia bacteraemia; responded to 10 days of meropenem</td>
<td>resolution</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>endocarditis</td>
<td>15</td>
<td>15 (VAN)</td>
<td>1.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5, 600 mg iv q8h ×3 weeks, then linezolid 600 mg bid ×3 weeks</td>
<td>none</td>
<td>resolution</td>
</tr>
<tr>
<td>3</td>
<td>skin and soft tissue, uveitis, endocarditis</td>
<td>2(^c)</td>
<td>22 (VAN)</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>0.5, 600 mg q8h ×3 weeks, then linezolid 600 mg orally bid ×3 weeks</td>
<td>none</td>
<td>resolution</td>
</tr>
<tr>
<td>4</td>
<td>urinary tract infection, uveitis, ethmoid osteomyelitis</td>
<td>11</td>
<td>11 (VAN)</td>
<td>2</td>
<td>2</td>
<td>0.5</td>
<td>0.5, 600 mg q12h for 10 days</td>
<td>GI bleeding</td>
<td>death</td>
</tr>
<tr>
<td>5</td>
<td>prostatitis, septic thrombophlebitis</td>
<td>13</td>
<td>12 (VAN)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0.5, 600 mg q8h for 2 weeks, then VAN for 4 weeks</td>
<td>none</td>
<td>resolution</td>
</tr>
</tbody>
</table>

bid, twice daily; DAP, daptomycin; ESBL, extended-spectrum β-lactamase; GI, gastrointestinal; iv, intravenously; NA, not available; q8h, every 8 h; q12h, every 12 h; VAN, vancomycin; VISA, vancomycin-intermediate S. aureus.

\(^a\)All MICs determined using Etest.

\(^b\)All ceftaroline infusions administered over 1 h. No ceftaroline therapeutic drug monitoring was performed.

\(^c\)Progression of ocular lesions while on therapy with vancomycin and appearance of new pulmonary nodules/lesions consistent with embolization.
Ceftaroline for MRSA bacteraemia

echocardiogram (TTE) revealed a 1.7 cm mitral valve vegetation with severe regurgitation. On hospital day 9, he was again bacteraemic, which persisted for 4 days. A transoesophageal echocardiogram (TEE) revealed a vegetation with valve perforation. His therapy was changed to 6 mg/kg daptomycin daily. The MRSA bacteraemia cleared in <48 h. On hospital day 17, the patient became bacteraemic once more; the MRSA isolate was now vancomycin intermediate and daptomycin non-susceptible (Table 1). Daptomycin was discontinued and 600 mg of ceftaroline every 8 h was initiated. The bacteraemia cleared within 48 h. The patient underwent mitral valve replacement on hospital day 32 (day 13 of ceftaroline). Culture and histopathology of the valve was negative for MRSA. The patient completed 6 weeks of ceftaroline.

**Case 2**

A male in his mid to late 30s with a past medical history of diabetes mellitus (DM) and IVDU presented to the emergency department with a temperature of 38.9°C, tachycardia, tachypnoea and delirium. He also had bilateral knee and ankle swelling, scattered petechiae and splinter haemorrhages. Blood tests revealed leucocytosis (26900/μL) with 28% bands. Vancomycin (1 g every 8 h) and piperacillin/tazobactam (4.5 g every 8 h) were initiated. Blood, urine and knee fluid cultures were positive for MRSA.

A TEE revealed a 1.0×1.0 cm vegetation attached to the mitral papillary muscle. Piperacillin/tazobactam was discontinued and vancomycin was changed to a 3.5 g continuous infusion targeting serum concentrations of 20–30 mg/L. The patient continued to fever with leucocytosis, and his course was complicated by multiple septic emboli to his skin, kidneys, spleen and brain.

After 15 days of persistent MRSA bacteraemia, therapy was changed to 600 mg of ceftaroline every 8 h. Blood cultures obtained 2 days later were negative. The patient completed 3 weeks of ceftaroline therapy and was discharged with 3 weeks of linezolid.

**Case 3**

A middle-aged female was transferred to our institution due to persistent MRSA bacteraemia and uveitis/endophthalmitis. Her past medical history included DM and recurrent staphylococcal skin infections. Four blood cultures grew MRSA.

Therapy was initiated with 1 g of vancomycin every 12 h and changed to continuous infusion, with serum concentrations maintained between 20 and 30 mg/L. The patient tolerated the vancomycin therapy well, with cessation of fevers and malaise, and clearance of blood cultures within 48 h. TTE was negative for vegetation. An abscess on her back also grew MRSA upon incision and drainage.

On hospital day 22, her ophthalmologic examination revealed an enlargement in the retinal lesion. A CT scan of the chest and abdomen revealed multifocal airspace opacities with cavitation and renal abscess. A TEE was performed, which detected a new small anterior mitral leaflet vegetation. Blood cultures remained negative, but the patient was considered a vancomycin treatment failure. The patient was converted to 600 mg of ceftaroline every 8 h for 3 weeks and completed an additional 3 weeks of therapy with linezolid.

**Case 4**

An elderly male was admitted for altered mental status with leucocytosis and elevated troponins. He had a history of DM and chronic kidney disease. He was started on 1 g of vancomycin every 12 h and 1 g of ceftriaxone daily. Initial urine and blood cultures grew MRSA. Blood cultures remained persistently positive for MRSA through hospital day 11.

The patient was converted to 6 mg/kg daptomycin every 48 h with continually positive blood cultures; a chest CT scan revealed a new large right pleural effusion with right upper lobe consolidation. The patient was changed to 600 mg of ceftaroline every 12 h on day 11 of therapy. Blood cultures performed after 2 days of ceftaroline therapy were negative.

Unfortunately, the patient developed acute respiratory failure requiring intubation and evidence of upper gastrointestinal bleeding on day 21 of hospitalization, and the patient expired.

**Case 5**

A female in her early to mid 40s with a history of uncontrolled DM (HbA1c of >16.0%) presented to an outside hospital with altered mental status. Her family reported a 3 week history of a left eye infection treated with gentamicin drops. Laboratory test results were significant for an elevated white blood cell count of 18000/μL and glucose of 556 mg/dL. An anterior chamber paracentesis revealed purulent material, which was culture positive for MRSA. A CT scan of the sinuses revealed left maxillary/ethmoid/frontal opacification with bony changes; she was started empirically on linezolid, cefepime, metronidazole, micafungin and liposomal amphotericin B. The patient underwent a left maxillary and mandibular advancement as well as an anterior ethmoidectomy, with cultures significant for MRSA. Blood and urine cultures from admission were significant for MRSA; TEE revealed a 1.5–2 cm aortic vegetation. The patient’s antibiotics were de-escalated to 1 g of vancomycin twice daily and her dose was adjusted to maintain trough serum concentrations of 15–20 mg/L. The patient remained bacteraemic for 12 days. The patient was changed to 600 mg of ceftaroline every 8 h, with sterilization of blood cultures the following day. The patient received 2 weeks of ceftaroline therapy and was transitioned back to vancomycin to finish a 6 week course of therapy.

**Case 6**

A male in his mid to late 40s with a history of diabetes, cirrhosis and MRSA skin infections requiring incision and drainage presented with a 2 week history of dysuria with suprapubic and bilateral flank pain. The patient was somnolent, hypotensive and febrile to 38.9°C. Blood and urine cultures from admission were positive for MRSA, and blood cultures remained positive despite therapeutic serum concentrations of vancomycin.

A TEE was negative for vegetations; CT of the chest and abdomen revealed septic emboli and prostatitis. Evaluation of the eye revealed an endophthalmitis and cultures returned
positive for MRSA. Ultrasound revealed a non-occlusive right internal jugular vein thrombosis, associated with his central line. The line was removed, but the patient developed bleeding complications and was a poor candidate for thrombectomy. Due to the pulmonary infection, daptomycin was considered an inappropriate option. The patient was transitioned to 600 mg of ceftaroline every 8 h on hospital day 8; blood cultures cleared by day 13. The patient completed 22 days of ceftaroline therapy before being transitioned to daptomycin for home intravenous therapy.

**Discussion**

Ceftaroline has in vitro and in vivo bactericidal activity against S. aureus and maintains activity despite a loss of susceptibility to daptomycin as well as vancomycin. An in vitro study compared ceftaroline activity with that of ceftobiprole, cefepime and ceftriaxone against 4546 clinical isolates. Ceftaroline was the most potent agent against methicillin-susceptible S. aureus, with an MIC90 of 0.25 mg/L, and was more potent than ceftobiprole against MRSA in both community- and healthcare-associated isolates (MIC90s of 0.5 and 1 mg/L, respectively).

Vidaillac et al. performed an in vitro pharmacodynamic study utilizing a hollow fibre model examining simulated regimens of 600 mg of ceftaroline every 12 h and 600 mg of ceftaroline every 8 h. For the studied strains with an MIC of 0.5 mg/L, the every 12 h regimen produced a free T>MIC of 83%, whereas the every 8 h regimen produced a free T>MIC of 100%. Even at an MIC of 1 mg/L, the every 8 h regimen produced a free T>MIC of 92%. Given the severity of the infections in the above patients as well as the above data, we elected to utilize the more aggressive dose of 600 mg every 8 h to ensure an optimal percentage T>MIC.

Human data utilizing ceftaroline for MRSA endocarditis are lacking. However, in an in vivo study using a rabbit endocarditis model, the activity of ceftaroline was compared with that of linezolid and vancomycin against MRSA. Ceftaroline displayed superior bactericidal activity and was the most effective drug against a heterogeneous glycopeptide-intermediate S. aureus. The duration of bacteraemia once patients were converted to ceftaroline was extremely short in our series and is consistent with the aforementioned data, though it is important to note that all of our patients received multiple doses of MRSA-active therapy prior to the initiation of ceftaroline therapy. The limited patient follow-up information suggests clinical and microbiological cure, with no relapses or emergence of resistance. The one death in a patient receiving ceftaroline therapy resulted from factors not associated with his infection.

The use of ceftaroline in MRSA bacteraemia is currently devoid of clinical data. We hope that these cases will prompt further evaluation of this antibiotic for invasive MRSA infections.

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**Transparency declarations**

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**References**