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Ceftaroline Plus Daptomycin for Refractory Methicillin-Resistant *Staphylococcus aureus* Bacteremia in a Child

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Persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia can be difficult to treat, with growing adult literature supporting the combination of ceftaroline and daptomycin for these patients. Here, we report a pediatric patient with persistent MRSA bacteremia with associated cellulitis, fasciitis, myositis, and a deep venous thrombosis causing septic pulmonary emboli. After being unable to clear the bacteremia on vancomycin and then daptomycin monotherapy, the bacteremia cleared quickly with rapid clinical improvement after the addition of ceftaroline to daptomycin. In support of this case, we also review the adult literature supporting treatment with this combination of antibiotics.

ABBREVIATIONS CRP, C-reactive protein; FDA, US Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*

KEYWORDS antibacterial agents; bacteremia; ceftaroline; child; daptomycin; methicillin-resistant *Staphylococcus aureus*; staphylococcal infections

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Introduction

Refractory or persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia can be a very challenging clinical situation. A growing number of case reports in addition to *in vitro* data have suggested a role for the addition of ceftaroline to daptomycin for refractory cases of staphylococcal bacteremia (particularly MRSA) in the treatment of adult patients.[1–4] There is limited evidence on the use of ceftaroline in pediatrics for the treatment of bacteremia, and there are no known pediatric cases published on the use of coadministered daptomycin and ceftaroline. Here, we present the case of a pediatric patient with refractory MRSA bacteremia that benefitted from this combination therapy, as well as a review of the available adult literature.

Case

A 12-year-old female presented with bilateral hip pain progressing during 1 week that worsened with movement. She was febrile to 38.0°C while seeing her pediatrician and was sent to the emergency department. Her past medical history included attention deficit hyperactivity and reactive attachment disorders, with no history of being immunocompromised or of recent antibiotic exposure. She had no previous surgeries. Her medications included fluoxetine, lisdexamfetamine, and guanfacine. She had no medication allergies. Her family history was largely unknown because she was adopted. On exam, she was afebrile on presentation, with tachycardia to 131 beats per minute and with vital signs otherwise within normal limits. Her weight was 31.3 kg. She had tenderness upon palpation of her bilateral thighs and hips, with associated pain with all passive and active movements of both hips. She had no warmth or erythema of any joints and no tenderness elsewhere. She had no skin lesions. She did have mild right lower quadrant abdominal tenderness.

Initial laboratory studies were significant for a white blood cell count of 14.4 × 10^3/μL (×10^9/L; with 75% neutrophils, 13% lymphocytes, 10% monocytes, 1% eosinophils, and 1% immature granulocytes), serum creatinine of 0.46 mg/dL, albumin of 2.2 g/dL, erythrocyte sedimentation rate of 57 mm/hr, and C-reactive protein (CRP) 22.9 mg/dL. X-rays of the pelvis, bilateral hips, and femurs demonstrated soft tissue edema around the right femur, with no effusions on bilateral hip ultrasound. An abdominal ultrasound revealed a proximal right common femoral vein thrombosis, confirmed on lower extremity duplex imaging. She received fluid resuscitation and was admitted. Therapeutic subcutaneous enoxaparin (Lovenox, Sanofi-Aventis US LLC, Bridgewater, NJ) at 1 mg/kg per dose every 12 hours was started for the deep vein thrombosis. The dose was adjusted based on anti-Xa concentrations, with the patient ultimately requiring 1.5 mg/kg per dose every 12 hours.

She developed a fever to 39.4°C on hospital day 2, with initial blood culture growing MRSA (see Table 1 for sensitivities). Intravenous vancomycin (Vancocin, Hospira, A Pfizer Company, Lake Forest, IL) was initiated via a syringe pump at 20.8 mg/kg per dose every 8 hours. With an initial and appropriately timed vancomycin trough of 12.4 mg/L prior to the fourth dose, the

Table 1. *Staphylococcus aureus* Blood Culture Susceptibilities

Antibiotic	MIC, mg/L*
Ceftaroline	0.75
Clindamycin	0.19
Daptomycin	1.0
Oxacillin	96
Trimethoprim/sulfamethoxazole	0.094
Vancomycin	2

MIC, minimal inhibitory concentration
* The MICs remained consistent on all blood cultures.

dosage was changed to 22.4 mg/kg per dose every 8 hours. Magnetic resonance imaging of the pelvis and proximal lower extremities showed diffuse and symmetric cellulitis, fasciitis, and myositis without a drainable abscess or osteomyelitis. A computed tomography pulmonary angiogram revealed a filling defect in a right lower lobe pulmonary artery with necrotizing pneumonitis and an associated moderate pleural effusion. Septic emboli were also present in the upper lobes. Three serial transthoracic echocardiograms showed no vegetations.

Daily blood cultures remained positive for 9 consecutive days (Table 2), and the patient continued with daily fevers until day 12. For treatment of the MRSA sepsis, she was continued on vancomycin for 3 days and then switched to intravenous daptomycin (10 mg/kg/day via syringe pump; Cubicin, Merck Sharp & Dohme Corp, Whitehouse Station, NJ) monotherapy on day 5, given the vancomycin minimal inhibitory concentration of 2 mg/L and delay in achieving a therapeutic concentration of 15 to 20 mg/L. With continued fevers and persistent bacteremia, intravenous ceftaroline (12 mg/kg per dose every 8 hours via syringe pump; Teflaro, Forest Pharmaceuticals Inc, St Louis, MO) was added to daptomycin on day 9. The blood culture drawn on day 11 was the first negative culture during admission. Although the blood culture on day 12 was positive, all subsequent cultures from day 13 onward remained sterile. With the clearance of bacteremia, the patient defervesced and CRP trended towards normalization.

The initial nidus of her infection was likely from the skin, leading to the cellulitis, fasciitis, myositis, and bacteremia. This proinflammatory state likely led to the development of a deep venous thrombosis that became a septic thrombus in the setting of the bacteremia, leading to septic pulmonary emboli. She did not show clinical improvement until ceftaroline was added to daptomycin. She was discharged on day 18 to complete a 6-week total course of daptomycin (starting from the negative blood culture on day 13) given the endovascular foci of infection. The ceftaroline was continued for 4 weeks from the same start date for synergy. The enoxaparin was transitioned to warfarin prior to discharge when her internal normalized ratio reached the target range of 2 to 3. At subsequent follow-up appointments her CRP gradually normalized and her symptoms abated as she was able to return to all previous activities. After being on anticoagulation for 3 months, follow-up venous duplex imaging revealed resolution of her thrombus, and warfarin was discontinued.

Discussion

The patient described above was deemed to have failed vancomycin treatment, which we speculate was related to the elevated minimal inhibitory concentration of 2 mg/L and delay in achieving target serum concentrations. Clinical practice guidelines for the treatment of refractory MRSA bacteremia and vancomycin treatment failure recommend large-dose daptomycin (10 mg/kg/day) if the organism is susceptible, plus a second agent with a β-lactam being an option.[5] β-Lactams have been shown to act synergistically with daptomycin in the treatment of MRSA *in vitro* by reducing the cell net positive charge that may increase the binding of daptomycin to the cell surface. In addition, the combination may prevent the selection of daptomycin-resistant strains.[6] A case series of 7 adult patients with MRSA bacteremia refractory to vancomycin- and daptomycin-based regimens showed that the addition of antistaphylococcal β-lactams (nafcillin or oxacillin) to daptomycin resulted in rapid bacteremia clearance.[3]

Limited evidence is available comparing different β-lactams paired with daptomycin, but ceftaroline is an attractive option given its bactericidal activity against MRSA.[7] MRSA strains have been shown to be nearly 100% susceptible to ceftaroline in 2 large pediatric studies (99.4% by Pfaller et al[8] and 99.8% by Sader et al[9]). Ceftaroline has been approved by the US Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections as well as community-acquired bacterial pneumonia in children.[10] It has not been approved for the treatment of MRSA bacteremia in children or adults, but several published adult cases have shown favorable outcomes with the use of ceftaroline monotherapy for this indication.[11,12] Daptomycin is newly FDA approved for use in pediatrics in complicated skin and soft tissue infections and *S aureus* bacteremia.[13] Previous reports have shown evidence for its use in invasive Gram-positive infections in children, and a randomized controlled trial demonstrated daptomycin to be comparable to the standard of care (primarily with vancomycin or cefazolin used) in the treatment of *S aureus* bacteremia.[14,15]

In vitro studies have shown that the combination of daptomycin plus ceftaroline improves antibacterial activity.[1–3] The addition of ceftaroline increases daptomycin cell membrane binding and increases killing by cathelicidin LL-37 and neutrophils.[2–4] This combination has even restored daptomycin susceptibility in nonsus-

Table 2. Trend of Pertinent Laboratory Studies and Antibiotics

Hospital Day	WBC, ×10⁹/L (% neutrophils)	Platelets, ×10⁹/L	CRP, mg/dL	ESR, mm/hr	Blood Culture + MRSA	Antibiotic
1	14.4 (75)	260	22.9	57	—	—
2	—	—	—	—	1/1	VAN
3	19.3 (80)	218	—	—	1/1	VAN
4	18.4 (79)	225	23.2	—	1/1	VAN
5	—	—	—	78	1/1	VAN→DAP
6	20.2 (81)	357	—	—	1/1	DAP
7	17.3 (79)	433	20.2	—	1/1	DAP
8	15.5 (75)	518	—	—	1/1	DAP
9	17.0 (79)	775	—	—	1/1	DAP + CPT
10	18.3 (73)	999	—	—	1/1	DAP + CPT
11	17.5 (77)	1168	—	—	0/1	DAP + CPT
12	—	—	12.1	57	1/1	DAP + CPT
13*	11.2 (70)	1422	—	—	0/1	DAP + CPT
14	10.3 (67)	1188	—	—	0/1	DAP + CPT
15	9.4 (70)	1036	—	—	0/1	DAP + CPT
16	—	—	—	—	0/1	DAP + CPT
17	—	—	4.9	102	—	DAP + CPT
18	8.5 (61)	674	—	—	—	DAP + CPT

CPT, ceftaroline; CRP, C-reactive protein; DAP, daptomycin; ESR, erythrocyte sedimentation rate; MRSA, methicillin-resistant Staphylococcus aureus; VAN, vancomycin; WBC, white blood cell count

* Resolution of fevers.

ceptible strains.[1,3] An *in vitro* study evaluating 2 strains of MRSA (one daptomycin susceptible and heterogeneous vancomycin intermediate, and the other daptomycin nonsusceptible and vancomycin intermediate) compared ceftaroline plus daptomycin to ceftaroline plus vancomycin and each as monotherapy in the treatment of MRSA bacteremia, and favored the combination of daptomycin plus ceftaroline.[4] Another model showed that the combination of ceftaroline and daptomycin had more rapid and sustained activity compared with ceftaroline, daptomycin, or vancomycin monotherapy.[16]

Rose et al[1] reported a case of an adult patient with endocarditis and 11 consecutive positive blood cultures for MRSA while on treatment with daptomycin, with eventual development of reduced daptomycin susceptibility. Ceftaroline was subsequently added to daptomycin, with clearance of the bacteremia within 4 days along with reduction in size of the cardiac vegetation. Sakoulas et al[2] reviewed a case series of 26 adult patients with refractory staphylococcal bacteremia that had a median duration of bacteremia of 10 days, with a median clearance time of 2 days after the addition of ceftaroline to daptomycin. In the case described, ceftaroline was chosen as the second agent instead of other β-lactams to add to daptomycin, given its independent bactericidal activity against MRSA (felt to be important in the setting of pulmonary involvement) and support from these *in vitro* studies and adult reports.

Summary

This literature review provides support that coadministered ceftaroline plus daptomycin may be a viable option for the treatment of refractory MRSA bacteremia in adult patients, with this case report showing promise in a pediatric patient as well. All of the *in vivo* data are retrospective, and prospective studies looking at this combination versus monotherapy in addition to other combinations are much needed. It is possible that β-lactams in general provide synergy to daptomycin as a class without special benefit for ceftaroline. Given ceftaroline's bactericidal nature against MRSA, however, and the growing evidence of use in adult patients with MRSA bacteremia, ceftaroline may be a worthwhile addition to daptomycin in these difficult-to-treat pediatric patients.

ARTICLE INFORMATION

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