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Infection. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Infection. 2015 December ; 43(6): 751–754. doi:10.1007/s15010-015-0763-0.

Daptomycin Non-Susceptible, Vancomycin-Intermediate *Staphylococcus aureus* Endocarditis Treated with Ceftaroline and Daptomycin: Case Report and Brief Review of the Literature

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Abstract

We report a case of clearance of persistent bacteremia due to daptomycin-non-susceptible, vancomycin-intermediate *Staphylococcus aureus* native mitral valve endocarditis with a combination of ceftaroline and daptomycin, in an 81 year-old medically complex patient who was not an operative candidate.

Keywords

ceftaroline; *Staphylococcus aureus*; bacteremia; endocarditis; antimicrobial resistance

Introduction

Drug-resistant *Staphylococcus aureus* infections remain a major clinical problem in healthcare settings [1]. Data on the efficacy of therapies for vancomycin-intermediate or vancomycin-resistant *Staphylococcus aureus* (VISA or VRSA, respectively) are currently limited. Extensive literature has demonstrated efficacy of daptomycin in treating methicillin-resistant *Staphylococcus aureus* (MRSA). In vitro data additionally indicate activity of daptomycin against VISA and VRSA [2]; however, its use can be limited by cross resistance to vancomycin [3, 4]. Similarly, data on therapies for daptomycin-non-susceptible (DNS) *Staphylococcus aureus* are limited. While vancomycin can be effective, its use can also be limited by cross-resistance [3, 4].

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Conflicts of Interest: None.

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Ceftaroline fosamil is a broad spectrum beta-lactam antibiotic with anti-staphylococcal activity, currently approved for bacterial pneumonia and skin/soft tissue infections, including those caused by MRSA. Beyond these indications, there is accumulating literature supporting its use as salvage therapy for VISA endocarditis as well as DNS *Staphylococcus aureus* infections [5-9].

We report an unusual case of dually-resistant (daptomycin non-susceptible/vancomycin intermediate) *Staphylococcus aureus* (DNS VISA) endocarditis in which a combination of ceftaroline and daptomycin achieved clearance of bacteremia. This report adds to the growing literature on the potential role of ceftaroline and daptomycin in treating highly drug-resistant *Staphylococcus aureus* infections.

Case Report

An 81-year old woman with diabetes and end-stage renal disease on hemodialysis presented to the hospital with chest pain and pleurisy. Vital signs and electrocardiogram (EKG) were unremarkable, troponin tests were negative, and the patient was discharged. Blood cultures were negative. One week later, the patient re-presented with recurrent chest pain, pleurisy, and new left-sided shoulder pain. Temperature was 38.7 C, pulse was 99 beats/minute; blood pressure and oxygen saturation were normal. White blood cell (WBC) count was $12{,}600 \times 10^6$/L. Blood cultures were drawn, empiric vancomycin and cefepime were initiated, and the patient was admitted to the hospital.

Blood cultures drawn at admission both revealed *Staphylococcus aureus*. Cefepime was discontinued and vancomycin monotherapy was continued. On hospital day 2, the patient's dialysis catheter was removed due to concern for a central line associated bloodstream infection. Blood cultures identified MRSA with a vancomycin minimum inhibitory concentration (MIC) of 2 mcg/mL, indicating susceptibility by broth microdilution testing (Trek Diagnostic Systems, Cleveland, OH). The vancomycin MIC was confirmed by Epsilometer test (Etest; B Biodisk North America, Piscataway, NJ). Daptomycin MIC was 4 mcg/mL, indicating DNS MRSA. Blood cultures drawn on day 2 were also positive for DNS MRSA.

Given persistent bacteremia, on day 4, a transthoracic echocardiogram (TTE) was done. The study was of average quality, visualized all valves, and did not show valvular vegetations. On day 5 a full-spine MRI was negative for vertebral osteomyelitis or spinal epidural infection. Blood cultures on day 5 were no growth. On day 6, due to persistent left shoulder pain, an MRI was done and showed a glenohumoral effusion, erosion of the glenoid surface and mild irregularity of the medial humeral head cortical surface, raising concern for septic arthritis. Shoulder joint aspiration showed WBC $40{,}500 \times 10^6$ cells/L, and synovial fluid bacterial culture grew MRSA (vancomycin MIC = 2 mcg/mL, daptomycin MIC = 4 mcg/mL). On day 7, operative debridement of the left shoulder was performed, and joint fluid cultures again grew MRSA. A trans-esophageal echocardiogram at that time revealed a 1.8 × 0.8 cm independently mobile mitral valve mass with trace mitral regurgitation. No paravalvular abscess or leaflet perforation was present.

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Blood cultures on day 9 were again positive, growing recurrent DNS MRSA. Vancomycin trough levels had been adequate: 15 mcg/mL on hospital day 5. Vancomycin susceptibility was re-tested by Etest; MIC was 4 mcg/mL, indicating vancomycin-intermediate *Staphylococcus aureus* (VISA). Daptomycin MIC was repeated and again was 4 mcg/mL, indicating DNS VISA.

On day 11, blood cultures showed persistent DNS VISA. Ceftaroline sensitivity testing was ordered, and vancomycin was switched to empiric ceftaroline (500 mg load, then 400 mg twice daily, intravenous) plus daptomycin (10 mg/kg following first and second dialysis session of the week, and 12 mg/kg following third dialysis session of the week). Although mitral valve replacement was indicated, the patient was deemed not to be an operative candidate due to end-stage renal disease, diabetes, advanced age and limited mobility. The patient also expressed a preference for medical therapy.

The ceftaroline MIC from the culture taken on day 9 was 0.5 mcg/mL, consistent with antibiotic susceptibility. Blood cultures on days 13, 15, 18 and 19 remained positive for DNS VISA, but on day 21 (day 11 of ceftaroline), blood cultures were negative. Subsequent blood cultures on days 23, 25, 27 and 28 also remained negative, consistent with a durable clearance of bacteremia. The patient completed six weeks of ceftaroline/daptomycin therapy, and blood cultures one week and four weeks after discontinuation of therapy remained negative.

The patient was readmitted to the hospital four weeks after completion of therapy due to palpitations and acute dyspnea, and atrial fibrillation and heart failure were diagnosed. TTE showed a dilated left atrium, progressive mitral regurgitation, and a diminished mitral vegetation size. After reconsideration for mitral valve replacement, the patient was transitioned to palliative-focused care, where she passed away in the subsequent days. Blood cultures during this final hospitalization showed no growth.

Discussion

We report a case of a patient with prolonged dually resistant (vancomycin intermediate and daptomycin non-susceptible) *Staphylococcus aureus* bacteremia due to mitral native valve endocarditis that was ultimately cleared on a combination salvage regimen of ceftaroline and daptomycin. Despite clearance of bacteremia, the patient succumbed from presumed valvulopathy-associated heart failure. This is one of only two cases to our knowledge of DNS VISA endocarditis infection in which bacteremia was cleared with a ceftaroline based regimen.

Although valve replacement was indicated under standard endocarditis management guidelines, our patient was not a candidate for surgical therapy. Our report adds to a growing literature demonstrating that the combination of ceftaroline and daptomycin can achieve clearance of bacteremia, including in situations where surgery is the preferred management and only presumed route to durable cure.

In this case, although the isolate was not susceptible to daptomycin, we combined daptomycin with ceftaroline empirically due to accumulating evidence that concomitant

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beta-lactam treatment (here, with ceftaroline) might improve susceptibility to daptomycin through attenuation of net positive surface charge thereby increasing daptomycin binding [5, 7, 10, 11, 9]. Ceftaroline activity may have been mutually enhanced due to the phenomenon known as the “seesaw” effect, by which anti-staphylococcal beta-lactam susceptibility increases as lipopeptide (and glycopeptide) susceptibility decreases.

Prior reports on the combined use of daptomycin with anti-staphylococcal beta-lactams show variability in whether or not daptomycin MIC decreases with the addition of beta-lactam. We did not observe this phenomenon of a reduced daptomycin MIC in our patient: both her initial and subsequent blood cultures all showed daptomycin non-susceptibility; however, we did not perform synergy testing to assess the daptomycin MIC in the presence of ceftaroline.

Literature describing ceftaroline use for patients with endocarditis due to MRSA [6, 9-13], VISA [6, 9], and DNS *Staphylococcus aureus* [7, 8, 10, 14-16] is limited (summarized in Table 1), but suggests a role for ceftaroline as salvage therapy, either alone or in combination with daptomycin. Daptomycin non-susceptible MRSA is still rare. Prolonged exposure to vancomycin has been shown to be an important risk factor [17]. In varying clinical contexts, DNS MRSA infections have been treated with ceftaroline, linezolid and vancomycin [7, 8], as well as with daptomycin with adjunctive rifampin [18] or beta-lactams [5].

Literature on dually-resistant DNS VISA endocarditis infections is even sparser. Limited case reports on DNS VISA endocarditis document treatment with regimens including linezolid, telavancin, gentamicin and rifampin, as well as high-dose daptomycin [14, 16]. However, to our knowledge, only one prior patient with DNS VISA endocarditis has been successfully treated with ceftaroline; this patient survived [10]. In that case, the daptomycin resistance was transient whereas in our patient, the daptomycin resistance was persistent.

In addition to treatment considerations, this case emphasizes the importance of performing MIC testing on vancomycin or daptomycin isolates by multiple methods. The initial broth microdilution MIC result was one dilution lower than the E-test result for vancomycin, consistent with prior literature [19] and particularly true at the MIC cutoff for VISA, where at least two MIC methods are recommended [20]. Also, this patient was prescribed a higher dose of ceftaroline than is normally recommended in hemodialysis (400 mg intravenous every 12 hours instead of 200 mg every 12 hours). This strategy was used based on limited data suggesting that higher dosing has been effective in MRSA endocarditis [13, 21, 22].

In summary, we report a patient with dually resistant vancomycin intermediate/DNS *Staphylococcus aureus* bacteremia due to mitral valve endocarditis who cleared bacteremia with a combination of daptomycin and ceftaroline. Although the patient ultimately succumbed to heart failure, and was not a candidate for operative valve replacement, this report adds to a growing body of literature supporting a potential role for ceftaroline/daptomycin in managing difficult highly drug-resistant *Staphylococcus aureus* infections. Prospectively enrolled clinical studies are needed to better define the benefits of this therapy, as treatment options are often limited in this highly morbid condition.

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Acknowledgments

None.

Funding: This work was supported by UCSF Traineeship in AIDS Prevention Studies, National Institutes of Health [T32 MH-19105] to S.M.B and National Institutes of Health [UCSF-CTSI KL2TR000143] to V.J.

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Table 1

Ceftaroline use in patients with infective endocarditis (IE)/complicated bacteremia due to *Staphylococcus aureus* resistant to methicillin, vancomycin or daptomycin.

	Daptomycin-susceptible				Daptomycin-non-susceptible (DNS)			
	Author	**N (total)**	**N (IE)**	**Comment**	**Author**	**N (total)**	**N (IE)**	**Comment**
MRSA[a]	Ho [6]	5	1		Jongsma [7]	1	1	
	Polenakovik [10]	30	8	1 case with transient DNS VISA				
	Tattevin [11]	5	5	Ceftaroline used with daptomycin in 1/5 case				
	Lin [13]	10	6					
	Fabre [12]	29	15	Ceftaroline used with TMP/SMX in 23/29 cases; used with daptomycin in 2/29 cases				
	Sakoulas [9]	20	10	Ceftaroline used with daptomycin in all 20 cases				
	Author	**N (total)**	**N (IE)**	**Comment**	**Author**	**N (total)**	**N (IE)**	**Comment**
VISA	Ho [6]	1	1		Polenakovik [10]	1	1	Case with transient DNS VISA
	Sakoulas [9]	2	1	Ceftaroline used with daptomycin in both cases				

Abbreviations: MRSA: methicillin resistant Stop/iy/ococcus aureus; VISA: vancomycin *intermediate Staphylococcus aureus;* MSSA: methicillin *susceptible Staphylococcus aureus;* MRSE: = methicillin resistant *Staphylococcus epidermidis;* IE: infective endocarditis [includes definite, probable and possible cases]; TMP/SMX: trimethoprim/sulfamethoxazole.

[a] VISA cases not included In the MRSA category.