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Daptomycin and combination daptomycin-ceftaroline as salvage therapy for persistent methicillin-resistant *Staphylococcus aureus* bacteremia

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To the Editor

We read with interest a recent report in the present journal describing synergistic bactericidal activity in vitro against a daptomycin nonsusceptible methicillin-resistant *Staphylococcus aureus* (MRSA) isolate [1]. A ceftaroline-daptomycin combination resulted in a reduction of 6.15 log₁₀ (CFU/mL) at 48 h. Beta-lactams with affinity for penicillin-binding protein (PBP) 1 enhance the antimicrobial activity of daptomycin; this effect appears to be mediated by improved daptomycin binding to the bacterial cell membrane [2]. Successful clearance of persistent MRSA infections using daptomycin and ceftaroline has been previously described in case reports and case series, but little published data directly compares regimens other than vancomycin for the treatment of persistent MRSA bacteremia.

We performed a retrospective chart review of patients with MRSA bacteremia persisting after treatment with vancomycin who were switched to daptomycin or daptomycin in combination with ceftaroline. We used pharmacy records to identify all patients who received these agents between January 2012 and June 2015. Patients included showed growth of MRSA in at least two blood cultures over a period of at least 72 hours while receiving parenteral vancomycin and were subsequently switched to therapy with

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DISCLOSURE OF INTEREST

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daptomycin or daptomycin plus ceftaroline for at least 72 hours. We excluded patients who did not have documented MRSA bacteremia on or after the date of switch from vancomycin to the second-line regimen (i.e. patients whose bacteremia had potentially already resolved). We included only the first episode of persistent MRSA bacteremia during the study period for each patient.

We collected demographic data, medical comorbidities, laboratory values on or nearest to the day of the first positive blood culture, the initial vancomycin trough, the source of the MRSA bacteremia (if identified) and any source control procedures performed, the first, second, and third-line antibiotic regimens used, the timing of regimen changes, and the dates of the first positive and persistently negative blood cultures. We defined “persistently negative” as the absence of recurrent bacteremia for at least two weeks. We recorded the minimal inhibitory concentration (MIC) values for vancomycin of the initial MRSA isolate in each case, as well as MIC values for ceftaroline and daptomycin when available; all vancomycin MIC determinations were obtained using an E-test.

The primary outcomes of interest were the duration of bacteremia after change in therapy (meaning both change from vancomycin and change to daptomycin plus ceftaroline), whether death occurred during admission or within 90 days of the first persistently negative blood culture, and whether recurrent MRSA bacteremia occurred within 90 days of the first persistently negative blood culture. We performed descriptive statistics and tests of significance with the Fisher’s Exact and Wilcoxon rank-sum tests in Microsoft Excel 2010. The institutional review board of Baylor College of Medicine and the Research and Development Committee of the Michael E. DeBakey VA Medical Center reviewed and approved the study; informed consent was not required and the study was performed within the institutions’ guidelines for the conduct of clinical research.

A total of 17 patients met the inclusion criteria for our study. Four patients received the combination of daptomycin and ceftaroline as 2nd-line therapy, eight patients received combination daptomycin and ceftaroline as 3rd-line therapy after having persistent bacteremia on daptomycin alone, and five patients received definitive therapy with daptomycin alone. Table 1 summarizes the demographics, comorbidities, and initial conditions of the patients in each group. The mean age was 68 years, 71% of patients were African-American, 29% were white, and all but one patient was male. Diabetes mellitus with end-organ disease (65%) and chronic kidney disease (53%) were the most common comorbidities; Charlson Comorbidity Indices ranged from 0 to 7.

The mean initial vancomycin trough was 17.4 µg/mL and did not vary between survivors and non-survivors; 6 of 17 patients had an initial trough less than 15µg/mL, 3 of whom had levels less than 10 µg/mL. The average daptomycin dose was 7.6 mg/kg (range: 5.7 to 13.8 mg/kg) and did not vary between survivors and non-survivors.

All patients received an Infectious Disease consultation and a focus of the MRSA bacteremia was identified in all but one case. The most commonly identified foci were osteomyelitis and native joint septic arthritis (n=8), endocarditis (n=5), epidural and lower extremity soft tissue abscesses (n=4), infected tunneled dialysis catheters (n=3), infected

prosthetic joints (n=2), and infected vascular grafts or pacemakers (n=2); some patients had multiple foci. Echocardiography was performed in every case and 65% of patients had transesophageal echocardiography. Eleven patients underwent one or more source control procedures for their persistent bacteremia; the remainder declined or were deemed not candidates for otherwise indicated source control interventions. Interventions included removal of prosthetic devices in seven cases, incision, drainage and debridement in five cases, and amputation of a great toe and foot in one case each.

We observed a trend toward shorter durations of bacteremia preceding the switch to combination daptomycin and ceftaroline therapy in patients who received this combination as 2nd rather than 3rd line therapy (6.8 versus 11.5 days; $p = 0.08$). The duration of bacteremia after the switch was similar between groups (5.8 days versus 4.3 days; $p=0.67$), resulting in a trend toward shorter overall duration in patients receiving early combination therapy (11.1 versus 17.3 days; $p= 0.11$).

Overall mortality in our case series was 53%. African-American patients had a nonsignificantly greater rate of mortality (67% versus 20%; $p=0.13$); other demographics were similar between groups. Table 2 presents the characteristics of patients who survived at 90 days after the first persistently negative culture versus those who did not. Both survivors and non-survivors had prolonged hospitalizations, with a mean duration of 36 days (range: 11–105 days). Among patients who received combination daptomycin and ceftaroline, survivors had a nonsignificantly shorter duration of bacteremia preceding the switch in therapy than non-survivors (8.5 versus 10.6 days; $p=0.799$), and the same duration of bacteremia after the switch (5.3 days for both groups). Receipt of combination daptomycin and ceftaroline as 2nd rather than 3rd-line therapy was not associated with 90-day mortality (75% versus 62.5%; $p=1.0$).

Evidence suggests that combination antibiotic therapy may benefit patients with MRSA bacteremia in certain clinical contexts [3]. In the present case series, patient receiving 2nd-line rather than 3rd-line therapy with combination daptomycin and ceftaroline had shorter total durations of bacteremia but similar rates of 90-day mortality. Among the combination therapy groups, patients who survived their infections received combination daptomycin-ceftaroline a mean 2.1 days earlier than patients who died. Overall mortality in the cohort was over 50%, consistent with prior studies of persistent MRSA bacteremia [4]. Mortality in the daptomycin alone group was lower (20%) than among the combination groups (62.5% and 75%), suggesting important clinical differences between the groups not captured in our data abstraction.

In addition to the favorable MRSA virulence-attenuating and innate immunity-enhancing effects associated with beta-lactams, ceftaroline has intrinsic bactericidal activity against MRSA and increases the bactericidal effect of daptomycin by enhancing daptomycin binding to bacterial cell membranes. This synergism appears to be retained in the treatment of bacteria in biofilms. An *in vitro* study of MRSA biofilm showed that the combination of ceftaroline and daptomycin was highly bactericidal and superior in this regard to ceftaroline plus rifampin, an important finding given the high incidence of prosthetic device infection in

patients with persistent MRSA bacteremia, including a quarter of the patients in our cohort [5].

Daptomycin and ceftaroline MIC values of MRSA exhibit a “seesaw” effect, wherein mutations associated with daptomycin nonsusceptibility confer enhanced susceptibility to ceftaroline and presumably other beta-lactams active against PBP1 [6]. This inverse correlation between daptomycin and ceftaroline MIC values maintains the synergism of the combination even in MRSA isolates with elevated MIC values to one or both agents. Reports of successful use of daptomycin and ceftaroline to treat serious infections due to multidrug resistant *Staphylococcus aureus* infections, including endocarditis with vancomycin-intermediate, daptomycin-nonsusceptible and vancomycin-intermediate, daptomycin-tolerant, and ceftaroline resistant *Staphylococcus aureus*, suggest that this synergistic activity is relevant *in vivo* [7–8].

One open question is whether a patient with persistent MRSA bacteremia benefits from a switch from vancomycin to another anti-MRSA agent. The majority of our patients who had persistent MRSA bacteremia provoking a change in therapy had MRSA isolates with a vancomycin MIC value of 1.5 or 2 ug/mL by E-test. Data suggesting that elevated vancomycin MIC in *Staphylococcus aureus* infection is associated with a poor treatment outcome regardless of whether vancomycin is used have not been consistently replicated [9]. The present findings reiterate that a low or borderline vancomycin MIC values, even when performed by E-test, does not guarantee the adequacy of vancomycin therapy for MRSA infections.

Limitations of our study include its retrospective nature and small sample size. The lack of association between combination daptomycin and ceftaroline therapy and mortality benefit may have been confounded by physician’s preference for more aggressive therapy in patients predicted to have a poor outcome.

Early combination therapy with daptomycin and ceftaroline shortens prolonged MRSA bacteremia and may be helpful in securing favorable clinical outcomes. Larger, adequately-powered studies should be performed to better evaluate the role of early combination daptomycin and ceftaroline in improving survival among patients with persistent MRSA bacteremia and high risk for mortality.

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REFERENCES

1. Shafiq I, Bulman ZP, Spitznogle SL, et al. A combination of ceftaroline and daptomycin has synergistic and bactericidal activity in vitro against daptomycin nonsusceptible methicillin-resistant *Staphylococcus aureus* (MRSA). *Infect Dis (Lond)*. 2017;49:410–416. [PubMed: 28116950]

2. Werth BJ, Sakoulas G, Rose WE, Pogliano J, Tewhey R, Rybak MJ. Ceftaroline increases membrane binding and enhances the activity of daptomycin against daptomycin-nonsusceptible vancomycin-intermediate *Staphylococcus aureus* in a pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother*. 2013;57:66–73. [PubMed: 23070161]
3. Davis JS, Sud A, O’Sullivan MVN, et al. Combination of Vancomycin and β -Lactam Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Pilot Multicenter Randomized Controlled Trial. *Clin Infect Dis*. 2016;62:173–180. [PubMed: 26349552]
4. Ok HS, Lee HS, Park MJ, et al. Predictors and clinical outcomes of persistent methicillin-resistant *Staphylococcus aureus* bacteremia: a prospective observational study. *Korean J Intern Med*. 2013;28:678–686. [PubMed: 24307843]
5. Barber KE, Smith JR, Ireland CE, Boles BR, Rose WE, Rybak MJ. Evaluation of Ceftaroline Alone and in Combination against Biofilm-Producing Methicillin-Resistant *Staphylococcus aureus* with Reduced Susceptibility to Daptomycin and Vancomycin in an In Vitro Pharmacokinetic/Pharmacodynamic Model. *Antimicrob Agents Chemother*. 2015;59:4497–4503. [PubMed: 25987623]
6. Barber KE, Ireland CE, Bukavyn N, Rybak MJ. Observation of “seesaw effect” with vancomycin, teicoplanin, daptomycin and ceftaroline in 150 unique MRSA strains. *Infect Dis Ther*. 2014;3:35–43. [PubMed: 25134810]
7. Baxi SM, Chan D, Jain V. Daptomycin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* endocarditis treated with ceftaroline and daptomycin: case report and brief review of the literature. *Infection*. 2015;43:751–754. [PubMed: 25805524]
8. Nigo M, Diaz L, Carvajal LP, et al. Ceftaroline-Resistant, Daptomycin-Tolerant, and Heterogeneous Vancomycin-Intermediate Methicillin-Resistant *Staphylococcus aureus* Causing Infective Endocarditis. *Antimicrob Agents Chemother*. 2017;61.
9. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA*. 2014;312:1552–1564. [PubMed: 25321910]

Table 1.

Characteristics of patients treated with combinations of daptomycin, ceftaroline, and vancomycin

	Daptomycin monotherapy (2nd line) N=5	Daptomycin + Ceftaroline (2nd line) N=4	Daptomycin + Ceftaroline (3rd line)* N=8
Age in years, mean (range)	65 (60–71)	62 (53–82)	72 (54–94)
Male gender (%)	100	100	88
Ethnicity			
Caucasian	40	0	38
African-American	60	100	62
Weight (kg)	87.5	66.8	81.3
Initial Cr (mg/dl)	3.43	2.4	5.5
Initial EGFR (ml/min)	50.7	81.6	41.3
Charlson Comorbidity Index Score:	3.2	4.8	5
Rate of ICU admission (%)	20	100	75
Alive at discharge (%)	100	100	75
Hemoglobin A1c	8.4	6.3	7.2
Initial leukocyte count (1000 cells/cmm)	17.6	12.7	15.8
Initial platelet count (1000 cells/cmm)	281.4	205.8	185.8
Echocardiography performed:	100	100	100
Transthoracic	20	75	25
Transesophageal	80	25	75
Infective Endocarditis diagnosed (%)	20	25	37.5
Infectious source identified (%)	100	75	100
Foreign body present (%)	20	50	75
Source control procedure performed if indicated (%)	60	75	75
Vancomycin MICs (µg/ml):			
1 or lower	1	1	0
1.5	3	2	5
2.0	2	1	3
Median daptomycin MIC (µg/ml)	0.4	0.25	0.4
Median ceftaroline MIC (µg/ml)	NA	0.5	0.63
Duration of bacteremia, mean (days)	12	11	17.3
Initial vancomycin trough, mean	17	10.4	21.3
Duration of vancomycin therapy, mean (days)	6.6	6.3	5
Duration of 2 nd -line therapy, mean (days)	31.2	30.5	6.8
Duration of 3 rd -line therapy if given, mean (days)	NA	NA	34.3
Duration of bacteremia before switch to daptomycin-ceftaroline if given, mean (days)	NA	6.8	11.5
Duration of bacteremia after switch to daptomycin-ceftaroline if given, mean (days)	NA	4.3	5.8

	Daptomycin monotherapy (2nd line) N=5	Daptomycin + Ceftaroline (2nd line) N=4	Daptomycin + Ceftaroline (3rd line)* N=8
Recurrent MRSA bacteremia within 90 days of initial bacteremia eradication (%)	20	25	0
Patients alive at 90 days after eradication of bacteremia (%)	80	25	37.5

* Daptomycin plus ceftaroline given as third-line therapy after 2nd line therapy with daptomycin (n=7) or vancomycin plus ceftaroline (n=1)

Table 2.

Characteristics of survivors versus non-survivors at 90 days after eradication of MRSA bacteremia

	Survivors (n=8)	Non-survivors (n=9)
Age in years, mean (range)	67 (54–82)	68 (53–94)
Male gender (%)	88	100
Ethnicity		
Caucasian	50	11
African-American	50	89
Weight (kg)	79.9	79.5
Initial Cr (mg/dl)	4.0	4.3
Initial EGFR (ml/min)	68.5	40.3
Charlson Comorbidity Index Score:	3.6	5.1
Rate of ICU admission (%)	38	56
Alive at discharge (%)	100	78
Hemoglobin A1c	8.7	6.2
Initial leukocyte count (1000 cells/cmm)	14.6	16.4
Initial platelet count (1000 cells/cmm)	263	179
Echocardiography performed:	100	100
Transthoracic	37	33
Transesophageal	63	67
Infective Endocarditis diagnosed (%)	25	33
Infectious source identified (%)	100	89
Foreign body present (%)	38	67
Source control procedure performed (%)	62	78
Vancomycin MICs		
1 µg/ml or lower	1	1
1.5 µg/ml	5	4
2.0 µg/ml	2	4
Median daptomycin MIC	0.38	0.5
Median ceftaroline MIC	0.75	0.5
Duration of bacteremia, mean (days)	13.2	15.1
Initial vancomycin trough, mean	16.5	18.3
Duration of vancomycin therapy, mean (days)	6	5.6
Duration of 2 nd -line therapy, mean (days)	19	20
Duration of 3 rd -line therapy if given, mean (days)	47	26
Duration of bacteremia before switch to daptomycin-ceftaroline if given, mean (days)	8.5	10.6
Duration of bacteremia after switch to daptomycin-ceftaroline if given, mean (days)	5.3	5.3
Recurrent MRSA bacteremia within 90 days of initial bacteremia eradication, mean (%)	13	11