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MAJOR ARTICLE

Clinical Outcomes With Definitive Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia With Retained Daptomycin and Ceftaroline Combination Therapy vs De-escalation to Monotherapy With Vancomycin, Daptomycin, or Ceftaroline

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Background. Lower mortality has been observed with combination therapy compared to monotherapy for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia; however, there is a lack of evidence for continued combination therapy over de-escalation to monotherapy following bacteremia clearance.

Methods. This was a single-center, retrospective study evaluating patients with MRSA bacteremia hospitalized from November 1, 2011, through July 31, 2019. Patients who received three to ten days of combination therapy followed by de-escalation to monotherapy were directly compared to patients retained on combination therapy. The primary composite outcome included inpatient infection-related mortality, 60-day readmission, and 60-day bacteremia recurrence.

Results. A total of 286 patients with MRSA bacteremia were identified, with 146 patients omitted based on exclusion criteria. The study population included 66 in the combination therapy group and 74 in the monotherapy group. Study population was 51% female (n = 71) and 78% white (n = 109) with median age of 46 years (IQR 34.5–61). No significant difference was observed in the primary composite outcome (21% combination therapy group vs 24% monotherapy group; P =.66), with retained observations after controlling for confounders. Within this outcome, there was no significant difference in 60-day readmission (20% combination therapy group vs 18% monotherapy group; P =.75), bacteremia recurrence (3% combination therapy group vs 7% monotherapy group; P =.45), or inpatient infection-related mortality (2% combination therapy group vs 5% monotherapy group; P = 1.00).

Conclusions. No difference was found in the composite outcome of 60-day bacteremia recurrence, readmission, or inpatient infection-related mortality for patients with MRSA bacteremia retained on combination therapy versus those de-escalated to monotherapy.

Keywords. ceftaroline; daptomycin; MRSA bacteremia.

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is a serious illness that can be associated with multiple foci of infection, leading to increased morbidity and mortality [1–5]. Current Infectious Diseases Society of America (IDSA) treatment guidelines for persistent MRSA bacteremia advise source control with consideration of combination antibiotic therapy without recommendation for a specific combination regimen or duration of therapy [6]. Studies have shown that combination therapy, such as daptomycin and ceftaroline, is more effective at reducing the duration of MRSA bacteremia and mortality; however, there is a lack of evidence to favor combination therapy over de-escalation to monotherapy for definitive treatment after blood culture clearance [7–14].

Daptomycin is Food and Drug Administration approved as monotherapy for MRSA bacteremia, but has improved efficacy when combined with a beta-lactam antibiotic due to changes in cell surface charge and increased daptomycin binding [13, 15–17]. Ceftaroline is a unique beta-lactam due to its innate activity against MRSA [13, 18, 19]. Thus, combination therapy with ceftaroline and daptomycin is an appealing option due to both agents having efficacy individually as well as synergistic activity against MRSA [13, 19, 20]. While initial treatment with daptomycin and ceftaroline combination therapy has been shown to improve the rate of bacteremia clearance, there are limited clinical data surrounding the ideal duration of combination therapy for persistent MRSA bacteremia and whether

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de-escalation is appropriate after bacteremia clearance. Multiple in vitro studies have illustrated similar efficacy between samples treated initially with daptomycin and ceftaroline followed by continued combination therapy or de-escalation to monotherapy [13]. There are few in vivo studies to evaluate outcomes between these treatment options.

The purpose of our study was to compare a composite clinical failure outcome of inpatient infection-related mortality, 60-day readmission, and 60-day recurrence of MRSA bacteremia in patients treated with daptomycin and ceftaroline combination therapy who were either retained on combination therapy or de-escalated to daptomycin, ceftaroline, or vancomycin monotherapy.

METHODS

Patient Population

This was a single-center, retrospective cohort study comparing outcomes of hospitalized patients aged 18 to 89 years admitted with an index episode of MRSA bacteremia from November 1, 2011, through July 31, 2019, who received at least 72 hours of combination therapy with ceftaroline and daptomycin and were either retained on combination therapy or de-escalated to monotherapy with either vancomycin, daptomycin, or ceftaroline. Study data were collected and managed using REDCap electronic data capture tools hosted by The Ohio State University [21, 22].

Institutional Practices

Prescribing practices for MRSA bacteremia were variable throughout the 8-year study period. Before the creation of an institutional guideline in 2014, decisions surrounding initial and salvage therapy selection for MRSA bacteremia were determined based on the treating physician's clinical judgment. The first iteration of this guideline recommended vancomycin for treatment of MRSA bacteremia, with consideration of daptomycin or ceftaroline as an alternative if patients had previously received treatment with vancomycin, with no guidance pertaining to timing of antibiotic de-escalation. In May 2017, the guideline was revised to recommend initial treatment of MRSA bacteremia with vancomycin with or without the addition of an antistaphylococcal beta-lactam. Escalation to daptomycin with or without ceftaroline ("salvage therapy") could be considered in patients with persistent bacteremia, defined as 7 days of positive blood cultures after initiation of appropriate antibiotic therapy. While guidelines were in place for the majority of the study period, the decision to escalate antibiotic therapy to daptomycin and ceftaroline combination therapy was at the discretion of the treating provider. Following escalation to daptomycin and ceftaroline combination therapy, guidance supported de-escalation back to monotherapy after 72 hours of negative blood cultures. This document did not provide specific recommendations for MRSA bacteremia treatment based on the vancomycin minimum inhibitory concentration (MIC) of the organism. During the study period, Infectious Diseases consult was not mandated for MRSA bacteremia, but strongly encouraged. Initiation of daptomycin or ceftaroline at this institution required approval either by the Infectious Diseases consult service or antimicrobial stewardship team. Daily blood cultures were routinely recommended for patients with MRSA bacteremia until documented clearance of bacteremia.

Patients who were discharged from the study institution did not always follow up in the affiliated outpatient Infectious Diseases clinic, and before 2017 there was no formal outpatient parenteral antimicrobial therapy (OPAT) program to provide advanced monitoring and standardize the documentation of adverse events and outpatient discontinuation of antibiotics.

Study Design

Patients maintained on combination therapy for at least 10 days were assigned to the combination group, while those receiving <10 days of total combination therapy were assigned to the monotherapy group. Due to institutional guidelines and to account for differences in practice among providers, a cutoff point of 10 days of combination therapy was chosen by the research team as a prolonged duration of combination therapy to distinguish the 2 treatment groups.

Patients were excluded due to the following: <72 hours of combination therapy, de-escalation before clearance of blood cultures, transferred from an outside hospital without records, duplicate patient records, those who were pregnant, incarcerated, left against medical advice before clearance of bacteremia, transitioned or discharged to hospice, no bacteremia clearance before death, <10 days of total antibiotic therapy, polymicrobial bacteremia on admission, recurrent MRSA bacteremia (defined as history of MRSA bacteremia within 1 year of the index admission), combination therapy within 1 year before admission, and transitioned to a nonmonotherapy MRSA-active antibiotic.

Patients with MRSA bacteremia within 1 year before the index admission were excluded, as history and previous treatment of MRSA bacteremia may have influenced decisions surrounding escalation to combination therapy. For patients with endocarditis, osteomyelitis of any origin, or an epidural abscess as a metastatic focus of infection, study investigators assessed source control, defined as surgical intervention.

The vancomycin MIC for each MRSA isolate was recorded as well and determined using MicroScan WalkAway or WalkAway*plus* (Beckman Coulter) for patients admitted from November 2011 through March 2018, and then Vitek (Biomerieux) starting in April 2018 through the end of the study period.

Total antibiotic duration after bacteremia clearance was collected based on both actual and anticipated end of antibiotic therapy date, to account for anticipated actual end of therapy

missing data. Actual end of therapy dates were censored for patients who died during the index admission. No patients included in this study were discharged on oral antibiotic therapy.

Outcomes

The primary outcome was a clinical failure composite of inpatient infection-related mortality, 60-day readmission, and bacteremia recurrence within 60 days of documented clearance. Secondary outcomes included comparison of adverse drug events (defined in the "Definitions" section) and hospital length of stay for patients treated with retained combination therapy and those de-escalated to monotherapy.

Statistics

Demographic and clinical data were analyzed using descriptive statistics. Quantitative variables were compared using the Wilcoxon rank-sum test, while categorical variables were compared using the Pearson chi-square test or Fisher exact test, as appropriate. Demographic and clinical data were analyzed for the 3 groups in the monotherapy arm, with quantitative variables compared using the Kruskal-wallis test and categorical variables compared using the Pearson chi-square test. A P value of ≤.05 was considered statistically significant, and analysis was completed using SAS, version 9.3 (Cary, NC, USA).

Multivariable logistic regression models estimated adjusted odds ratios and 95% confidence intervals and were utilized to control for confounding between the relationship of the exposure and the primary composite outcome. Variables were considered for inclusion into the model if they were statistically significant at the univariate level with the exposure and the outcome ($P < .2$) and not on the causal pathway. A forward selection method was utilized for the potential confounders, and these were included in the multivariable logistic regression model if they affected the exposure intercept by >15%. A post hoc subgroup analysis was performed to evaluate the primary composite outcome in patients with metastatic foci of infection with presumed high bacterial burden including epidural abscess, osteomyelitis, and/or endocarditis.

Definitions

The index admission was defined as the first admission for MRSA bacteremia within 1 year where treatment with combination therapy of ceftaroline and daptomycin for at least 72 hours was given. Uncomplicated *Staphylococcus aureus* bacteremia was defined by IDSA guidelines as an individual with positive blood cultures and the following: no evidence of endocarditis, no prosthetic devices, follow-up blood cultures negative 2-4 days after initial blood cultures, defervescence within 72 hours of starting antibiotic therapy, and no metastatic sites of infection [6]. Date of bacteremia clearance was defined as the collection date of the first blood culture finalized as negative following positive culture. Inpatient infection-related mortality was defined as death secondary to MRSA bacteremia based on death summary. In cases where etiology for mortality was documented as unclear or secondary to noninfectious cause, these patients were coded as mortality, not infection-related. Bacteremia recurrence was defined as at least 1 blood culture positive for MRSA within 60 days after documentation of negative blood cultures. Adverse drug events included the following: elevated creatine kinase (defined as >5 times the upper limit of normal [>1100 U/L]), hepatotoxicity (defined as transaminases increased to twice the upper limit of normal [ALT >104 U/L and AST >80 U/L]), and nephrotoxicity (defined as increase in serum creatinine of >0.3 mg/dL within 48 hours or increase in serum creatinine to >1.5 times baseline within 7 days). Rash, bone marrow suppression, and other adverse events were collected based on documentation in the medical record of a possible medication-associated event.

RESULTS

A total of 286 patients were initially identified with MRSA bacteremia during the study period. Of these 286 patients, 146 were excluded (Figure 1). All patients were initially treated with monotherapy, predominantly vancomycin (137), followed by daptomycin (1), linezolid (1), and clindamycin (1). Of 140 patients included in this study, 66 were contained within the combination therapy arm and 74 in the monotherapy arm. In the monotherapy group, 18 received ceftaroline, 30 received daptomycin, and 26 received vancomycin. All patients included in this study received an Infectious Diseases consult during their admission.

Demographics for both groups are compared and summarized in Table 1. A higher percentage of patients with a history of intravenous (IV) drug use was observed in the combination therapy group vs the monotherapy group (58% vs 36%; $P = .01$). Uncomplicated MRSA bacteremia was observed in 5% of patients in the combination therapy group and 1% in the monotherapy group. The combination therapy group had a higher rate of endocarditis (56% vs 35%; $P = .01$) and pulmonary septic emboli (47% vs 27%; $P = .01$). There was no statistically significant difference between the monotherapy de-escalation regimens in patients with endocarditis, osteomyelitis, and/or epidural abscess (Table 1). No statistically significant difference was observed when comparing rates of surgical intervention between the combination therapy and monotherapy groups for endocarditis ($P = .17$), epidural abscess ($P = .68$), or osteomyelitis ($P = .27$), in the primary composite outcome in the combination therapy and monotherapy groups for patients with endocarditis, osteomyelitis, and/or epidural abscess ($P = .31$) or between the monotherapy groups ($P = .18$) (Table 4).

The median actual total antibiotic duration was 56 days for the combination therapy group (n = 35) vs 45 days for the monotherapy group (n = 35), with $P = .5$. No statistically significant difference was seen in the median anticipated total antibiotic therapy

duration between the combination therapy group (47 days) and the monotherapy group (44.5 days; $P = .55$) (Table 1). Of the 66 patients in the combination therapy group, 27 were discharged on combination therapy, while 31 were later de-escalated to monotherapy, 5 completed their course of combination therapy during the index admission, 2 died during the index admission, and 1 was discharged on 2 antistaphylococcal agents other than daptomycin and ceftaroline combination therapy.

Outcomes assessments are further summarized in Table 2. No statistically significant difference was observed in the primary composite clinical failure outcome between the combination and monotherapy groups (21% vs 24%; $P = .66$). The finding of no observed difference persisted within the multivariable logistic regression model when controlling for confounders of IV drug use and chronic kidney disease (as shown in Table 3). Readmission rates were similar in the combination group vs monotherapy group (20% vs 18%; $P = .75$). Recurrence of bacteremia was seen in 2 patients in the combination therapy group and 5 patients in the monotherapy group (3% vs 7%; $P = .45$). Inpatient infection-related mortality was 2% in the combination group compared with 5% in the monotherapy group, which was not statistically significant ($P = 1$).

No statistically significant differences in adverse drug events or inpatient length of stay were observed between groups (as shown in Table 2).

DISCUSSION

MRSA bacteremia is frequently encountered in the clinical setting, with increasing prevalence over the last few years and significant attributable mortality [1–5]. While several studies have previously demonstrated improved outcomes such as lower mortality and readmission rates when patients with MRSA bacteremia are treated with combination therapy, evidence for de-escalation to monotherapy after initiation of a combination therapy regimen remains limited [12, 14, 23]. The results of our study are supported by previous in vitro studies demonstrating equivalence in bacteremia clearance and maintained bacterial suppression when comparing definitive treatment with daptomycin and ceftaroline combination therapy vs daptomycin or ceftaroline monotherapy [13, 14].

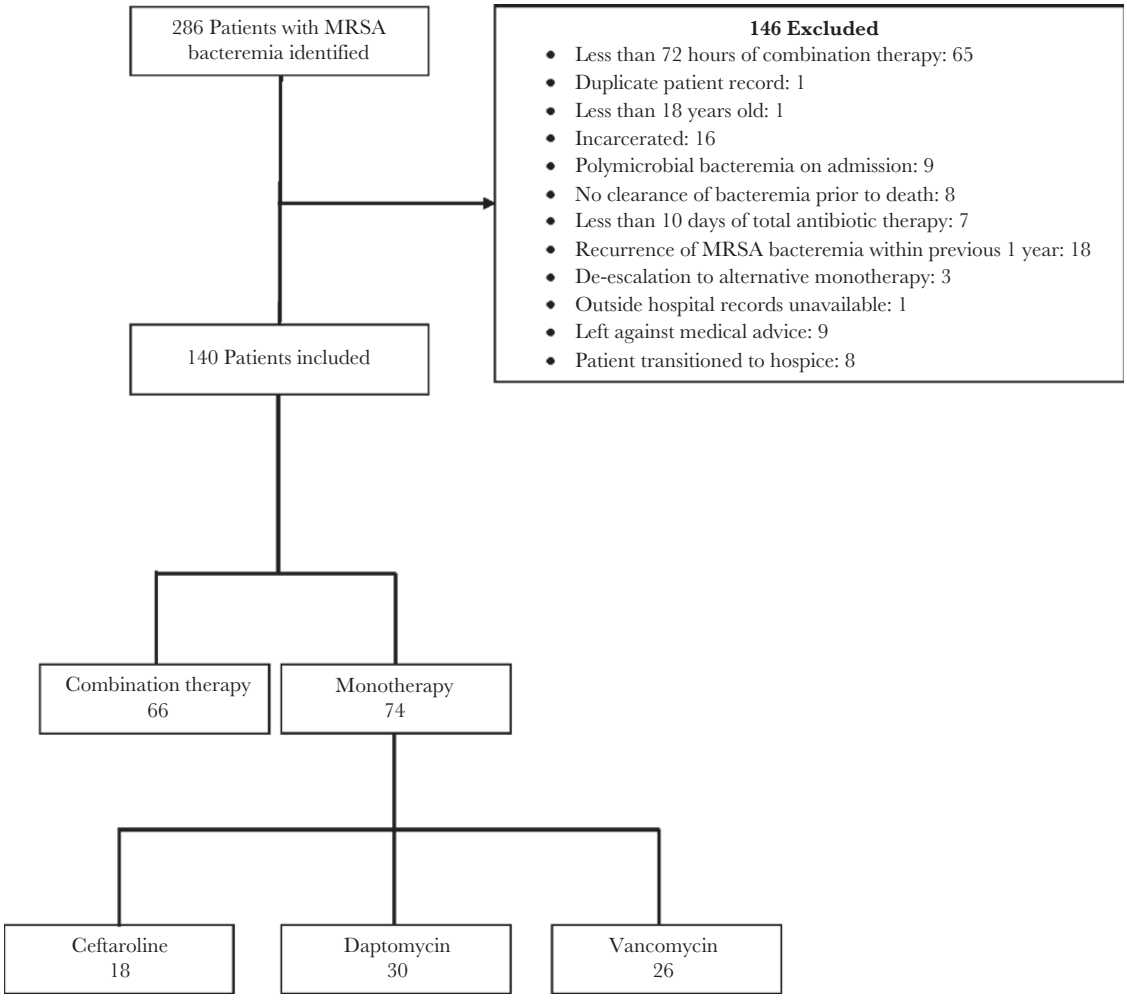

Figure 1. Study population. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 1. Baseline Demographics and Disease Characteristics

		Definitive Combination vs Monotherapy Comparisons			De-escalated Monotherapy vs Monotherapy Comparisons			
		Combination Therapy (n = 66)	Monotherapy (n = 74)	*P* Value (CT vs MT)	DAP MT (n = 30)	CPT MT (n = 18)	VAN MT (n = 26)	*P* Value (All MT)
Gender	Male	31 (47)	38 (51)	.61	17 (57)	8 (44)	13 (50)	.7
	Female	35 (53)	36 (49)		13 (43)	10 (56)	13 (50)	
Age		42 [32–55]	50.5 [37–63]	.03	55.5 [37–66]	48.5 [38–57]	43.5 [37–67]	.45
Race	White	49 (74)	60 (81)	.27	24 (80)	14 (78)	22 (85)	.81
	African American	12 (18)	10 (14)		5 (17)	3 (17)	2 (8)	
	>1 race	0	2 (3)		1 (3)	0 (0)	1 (4)	
	Unknown or not reported	5 (8)	2 (3)		0 (0)	1 (6)	1 (4)	
Charlson Comorbidity Score		2 [1–4]	3 [1–5]	.35	3 [2–5]	1.5 [1–3]	3 [2–4]	.04
PITT Bacteremia Score		2 [0–4]	1 [0–3]	.27	2 [0–3]	1 [1–3]	1 [0–2]	.37
Comorbidities	History of intravenous drug use	38 (58)	27 (36)	.01	8 (27)	7 (39)	12 (46)	.31
	Chronic kidney disease	12 (18)	28 (38)	.01	16 (53)	3 (17)	9 (35)	.04
	Diabetes mellitus	11 (17)	28 (38)	.005	13 (43)	6 (33)	9 (35)	.72
	Hemodialysis	5 (8)	10 (14)	.26	6 (20)	1 (6)	3 (12)	.39
	History of liver disease	4 (6)	7 (9)	.54	2 (7)	2 (11)	3 (12)	.79
	Solid tumor malignancy	4 (6)	9 (12)	.25	3 (10)	1 (6)	5 (19)	.43
	Hematologic malignancy	4 (6)	5 (7)	1	2 (7)	0 (0)	3 (12)	.36
	Solid organ transplant	3 (5)	3 (4)	1	2 (7)	0 (0)	1 (4)	.78
	HIV/AIDS	2 (3)	1 (1)	.6	1 (3)	0 (0)	0 (0)	1
Prosthetic devices	Cardiac devices	7 (11)	15 (20)	.12	10 (33)	2 (11)	3 (12)	.08
	Orthopedic hardware	6 (9)	8 (11)	.73	2 (7)	2 (11)	4 (15)	.58
	Prosthetic joint	3 (5)	2 (3)	.67	2 (7)	0 (0)	0 (0)	.33
	Vascular grafts	1 (2)	5 (7)	.21	2 (7)	0 (0)	3 (12)	.36
	Other[a]	3 (5)	12 (16)	.03	8 (27)	2 (11)	2 (8)	.16
Type of bacteremia	Complicated	63 (95)	73 (99)	.34	30 (100)	17 (94)	26 (100)	.24
	Uncomplicated	3 (5)	1(1)		0 (0)	1 (6)	0 (0)	
Intensive care unit stay during admission		42 (64)	42 (57)	.41	18 (60)	9 (50)	15 (58)	.79
Mechanical ventilation during admission		12 (18)	8 (11)	.21	3 (10)	3 (17)	2 (8)	.8
Vasopressor support during admission		11 (17)	11 (15)	.77	6 (20)	2 (11)	3 (12)	.7
Infectious Diseases consult		66 (100)	74 (100)	-	30 (100)	18 (100)	26 (100)	1
Duration of bacteremia, d		8 [6–11]	7.5 [5–12]	.33	7 [5–12]	7 [4–9]	9 [6–12]	.43
Antibiotic duration, d	Duration before escalation, d	6 [4–9]	7 [5–11]	.20	7 [5–12]	7 [5–11]	7 [4–9]	.35
	Duration of combination therapy, d	15 [13–21]	4.5 [4–6]	<.0001	5 [4–6]	5 [4–7]	4 [3–5]	.16
	Monotherapy duration after de-escalation, d	32 [27–45]	40 [37–52]	.04	41 [37–51]	40 [34–52]	39 [37–52]	.93
	Anticipated total antibiotic duration after bacteremia clearance, d	47 [42–56]	44.5 [42–56]	.55	45 [42–56]	44.5 [42–56]	42 [42–56]	.69
	Actual total antibiotic duration after bacteremia clearance, d[b]	56 [42–68]	45 [42–61]	.5	45 [43–70]	47 [44–136]	42 [42–52]	.13
Bacteremia duration after antibiotic escalation, d		2 [0–4]	1 [0–3]	.06	1 [–1 to 4]	1 [0–2]	2 [0–3]	.74
Vancomycin MIC	0.5 mcg/mL	4 (6)	11 (15)	.15	3 (10)	2 (11)	6 (23)	.001
	1.0 mcg/mL	38 (58)	33 (45)		16 (53)	2 (11)	15 (58)	
	2.0 mcg/mL	24 (36)	30 (41)		11 (37)	14 (78)	5 (19)	

Table 1. Continued

		Definitive Combination vs Monotherapy Comparisons			De-escalated Monotherapy vs Monotherapy Comparisons			
		Combination Therapy (n = 66)	Monotherapy (n = 74)	*P* Value (CT vs MT)	DAP MT (n = 30)	CPT MT (n = 18)	VAN MT (n = 26)	*P* Value (All MT)
Metastatic foci	Endocarditis	37 (56)	26 (35)	.01	12 (40)	4 (22)	10 (38)	.43
	Pulmonary emboli	31 (47)	20 (27)	.01	5 (17)	7 (39)	8 (31)	.21
	Osteomyelitis	16 (24)	15 (20)	.57	4 (13)	3 (17)	8 (31)	.3
	Septic arthritis	15 (23)	16 (22)	.88	6 (20)	3 (17)	7 (27)	.77
	Epidural abscess	13 (20)	10 (14)	.32	3 (10)	5 (28)	2 (8)	.16
	Splenic abscess/infarct	3 (5)	2 (3)	.67	1 (3)	1 (6)	0 (0)	.71
	Central nervous system	2 (3)	1 (1)	.6	0 (0)	1 (6)	0 (0)	.24
	No metastatic foci	6 (9)	8 (11)	.74	3 (10)	2 (11)	3 (12)	-
	Other[c]	31 (47)	37 (50)	.72	15 (50)	10 (56)	12 (46)	.83
Surgical intervention for source control	Endocarditis	9 (14)	2 (3)	.17	1 (3)	0 (0)	1 (4)	1
	Epidural abscess	6 (9)	6 (8)	.68	1 (3)	3 (17)	2 (8)	.71
	Osteomyelitis	5 (8)	7 (9)	.27	2 (7)	1 (6)	4 (15)	.79
Other positive cultures for MRSA	Urine	10 (15)	7 (9)	.3	1 (3)	2 (11)	4 (15)	.32
	Sputum	24 (36)	14 (19)	.02	4 (13)	5 (28)	5 (119)	.49
	Pleural fluid	3 (5)	1 (1)	.34	0 (0)	1 (6)	0 (0)	.24
	Synovial fluid	5 (8)	9 (12)	.37	3 (10)	3 (17)	3 (12)	.82
	Cerebrospinal fluid	0	0	–	0 (0)	0 (0)	0 (0)	-
	Catheter tip	2 (3)	2 (3)	1	1 (3)	0 (0)	1 (4)	1
	Abscess	7 (11)	11 (15)	.45	2 (7)	0 (0)	9 (35)	.002
	Bone	0	1 (1)	1	0 (0)	1 (6)	0 (0)	.24
	Other[d]	16 (24)	11 (15)	.16	5 (17)	3 (17)	3 (12)	.84
Suspected or confirmed source	Pneumonia	1 (2)	4 (5)	.37	1 (3)	3 (17)	0 (0)	.06
	Osteomyelitis	1 (2)	2 (3)	1	1 (3)	0 (0)	1 (4)	1
	Septic joint	2 (3)	0	.22	0 (0)	0 (0)	0 (0)	-
	Skin/soft tissue infection	6 (9)	6 (8)	.84	4 (13)	1 (6)	1 (4)	.56
	Central venous catheter–associated	7 (11)	15 (20)	.12	6 (20)	4 (22)	5 (19)	1
	Intravenous drug use	36 (55)	20 (27)	.0009	5 (17)	6 (33)	9 (35)	.25
	Endocarditis	0	1 (1)	1	1 (3)	0 (0)	0 (0)	1
	Epidural abscess	1 (2)	1 (1)	1	0 (0)	1 (6)	0 (0)	.24
	Cardiac device infection	0	4 (5)	.12	3 (10)	1 (6)	0 (0)	.28
	Prosthetic joint infection	0	2 (3)	.5	2 (7)	0 (0)	0 (0)	.34
	Other	5 (8)	4 (5)	.73	3 (10)	1 (6)	0 (0)	.28
	Unknown	11 (17)	11 (15)	.77	3 (10)	2 (11)	6 (23)	.38
Discharge disposition	Home	9 (14)	20 (27)	.05	14 (47)	3 (17)	3 (12)	.008
	Other[e]	57 (86)	54 (73)		16 (53)	15 (83)	23 (88)	

Data are presented as number (%) or median [IQR], as appropriate. Definitive combination therapy including those included in the combination therapy group. De-escalated monotherapy was defined as the specific monotherapy that patients in the monotherapy group were de-escalated to when combination therapy was discontinued.

Abbreviations: CPT, ceftaroline; CT, combination therapy; DAP, daptomycin; IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MT, monotherapy; VAN, vancomycin.

[a]Other prosthetic devices include central intravenous access (10), prosthetic valves (4), inferior vena cava filter (1), and ureteral stent (1).

[b]Variable include missing data.

[c]Other metastatic sites includes skin/soft tissue infections not specified above (22), device infections (15), pneumonia/empyema (12), septic emboli not specified above (8), intracardiac thrombus (6), endocarditis not excluded (4), epidural phlegmon (3), infected hematoma (1), and right endophthalmitis (1).

[d]Other positive cultures include device culture (14), skin/soft tissue infections not included above (7), valve culture (3), intra-abdominal infections (3), and vitreous culture (1).

[e]Other discharge locations includes skilled nursing facilities, long-term acute care hospitals, and mortality during index admission.

Table 2. Treatment Outcomes

		Combination Therapy (n = 66)	Monotherapy (n = 74)	*P* Value (CT vs MT)
Composite clinical failure outcome: 60-d recurrence/inpatient infection-related mortality/60-d readmission		14 (21)	18 (24)	.66
MRSA bacteremia recurrence within 60 d		2 (3)	5 (7)	.45
Inpatient infection-related mortality		1 (2)	4 (5)	1
Readmission within 60 d		13 (20)	13 (18)	.75
Adverse drug event	Bone marrow suppression	1 (2)	0	.47
	Elevated creatine kinase	0	0	
	Hepatotoxicity	0	0	
	Nephrotoxicity	0	0	
	Rash	0	0	
	Other[a]	1 (2)	1 (1)	1
Inpatient length of stay, d		26 [20–41]	24.5 [16–33]	.08

Data are presented as number (%) or median [IQR], as appropriate.

Abbreviations: CT, combination therapy; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MT, monotherapy.

[a]Other adverse drug events include: neutropenia (1) and pedal edema (1).

Table 3. Multivariable Logistic Regression—Clinical Failure Outcome

	Adjusted Odds Ratio	95% Confidence Interval
Chronic kidney disease	2.20	0.87–5.57
Intravenous drug use	2.24	0.93–5.43
Monotherapy	1.22	0.52–2.82

However, it is important to note these in vitro studies do not evaluate the optimal timing of antibiotic de-escalation after combination therapy initiation. Our study focused on evaluating differences in outcomes based on definitive therapy selection rather than initial treatment for MRSA bacteremia. The results of this investigation demonstrated that patients de-escalated to monotherapy with daptomycin, ceftaroline, or vancomycin after clearance of bacteremia did not have increased rates of readmission, bacteremia recurrence, or inpatient infection-related mortality when compared with patients retained on daptomycin and ceftaroline combination therapy. Additionally, these results are consistent with findings by Ahmad et al. and their comparison of outcomes with vancomycin or daptomycin monotherapy vs treatment with supplemental ceftaroline following bacteremia resolution. The authors found no differences in mortality, bacteremia recurrence, readmission, acute kidney injury, or leukopenia between groups [24]. Patient characteristics and total duration of bacteremia were similar across the 2 studies. The authors of the former study separated patients into cohorts of monotherapy or combination therapy based on the continuation or discontinuation of ceftaroline within 24 hours of negative finalized cultures. In comparison, this study used a cut-point of 10 days of combination therapy to account for delays in de-escalation secondary to institutional guidelines and differences in practice among Infectious Diseases providers. The present analysis enhances current knowledge by providing further evidence in a larger patient population that treatment with monotherapy after bacteremia clearance is comparable to retained combination therapy with daptomycin and ceftaroline and may support definitive therapy with monotherapy regimens in clinical practice. Additional studies illustrating similar patient outcomes with prolonged combination therapy vs de-escalation to monotherapy would support de-escalation

Table 4. Treatment Outcomes for Patients With Endocarditis, Epidural Abscess, and Osteomyelitis

	Definitive Combination vs Monotherapy Comparisons			De-escalated Monotherapy vs Monotherapy Comparisons			
	Combination Therapy (n = 50)	Monotherapy (n = 41)	*P* Value (CT vs MT)	DAP MT (n = 15)	CPT MT (n = 9)	VAN MT (n = 17)	*P* Value (All MT)
Composite clinical failure outcome: 60-d recurrence/inpatient infection-related mortality/60-d readmission	13 (26)	7 (17)	.31	3 (20)	3 (33)	1 (6)	.18
MRSA bacteremia recurrence within 60 d	2 (4)	2 (5)	1	1 (7)	0 (0)	1 (6)	1
Inpatient infection-related mortality	1 (2)	2 (5)	1	1 (7)	1 (11)	0 (0)	1
Readmission within 60 d	12 (24)	5 (12)	.15	2 (13)	2 (22)	1 (6)	.42

Data are presented as number (%) or median [IQR] as appropriate. Definitive combination therapy included those in the combination therapy group. De-escalated monotherapy was defined as the specific monotherapy that patients in the monotherapy group were de-escalated to when combination therapy was discontinued.

Abbreviations: CPT, ceftaroline; CT, combination therapy; DAP, daptomycin; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MT, monotherapy; VAN, vancomycin.

after bacteremia clearance and may result in lower health care costs, decreased exposure to combination therapy, and decreased length of stay.

The strengths of this study include that patients were comparable in terms of severity of illness, race, and gender between the combination therapy and monotherapy groups. Also, no significant difference in outcomes between the groups persisted after controlling for multiple confounders. The limitations of this study include selection bias given the retrospective nature, small sample size allowing potential for type II error, and differences in demographics of the population that were not fully elucidated in this study due to limited sample size. Another limitation of this study was the heterogeneity of monotherapy regimens selected for de-escalation and a lack of complete data recorded for outpatient adverse events and actual end of therapy dates, potentially confounding the comparison.

CONCLUSIONS

In this study, no significant difference in infection-related inpatient mortality, 60-day MRSA bacteremia recurrence, or 60-day hospital readmission between patients treated with prolonged daptomycin and ceftaroline combination therapy vs those de-escalated to monotherapy with daptomycin, ceftaroline, or vancomycin was demonstrated. Larger randomized controlled trials are necessary to see if these results are reproducible on a larger scale when a higher number of composite outcomes are observed.

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