Clinical Outcomes with Definitive Treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA) Bacteremia with Retained Daptomycin and Ceftaroline Combination Therapy versus De-escalation to Monotherapy with Vancomycin, Daptomycin, or Ceftaroline

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AUTHOR CONTRIBUTIONS: Authors CN, LW, and MMS conceived and designed the analysis. CN collected the data. KC performed the statistical analysis. CN wrote the initial draft of the paper with revisions performed by all listed authors.
**ABSTRACT:** This retrospective single-center cohort study compared retained daptomycin and ceftaroline combination therapy versus de-escalation to vancomycin, daptomycin or ceftaroline monotherapy for MRSA bacteremia. No difference was found in the composite outcome of 60-day bacteremia recurrence, readmission or inpatient infection-related mortality for patients retained on combination therapy versus those de-escalated to monotherapy.

**Keywords:** MRSA bacteremia, daptomycin, ceftaroline
INTRODUCTION:

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 combination therapy, such as daptomycin and ceftaroline, is more effective at reducing duration of MRSA bacteremia and mortality, however there is lack of evidence to favor combination therapy over de-escalation to monotherapy for definitive treatment after blood culture clearance (7-14).

Daptomycin is FDA-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 rate of bacteremia clearance, there are limited clinical data surrounding the ideal duration of combination therapy for persistent MRSA bacteremia and whether 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 either daptomycin, ceftaroline, or vancomycin monotherapy.
METH
ODS:

Patient Population:

This was a single-center, retrospective cohort study comparing outcomes of hospitalized patients ages 18 to 89 years old 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 eight year study period. Prior to 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 anti-staphylococcal beta-lactam. Escalation to daptomycin with or without ceftaroline (“salvage therapy”) could be considered in patients with persistent bacteremia defined as seven 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 has not provided specific recommendations for MRSA bacteremia treatment based on 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 are routinely recommended for patients with MRSA bacteremia until documented clearance of bacteremia.

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

**Study Design:**

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

Patients were excluded due to the following: less than 72 hours of combination therapy, de-escalation prior to clearance of blood cultures, transferred from an outside hospital without records, duplicate patient records, those that were pregnant, incarcerated, left against medical advice prior to clearance of bacteremia, transitioned or discharged to hospice, no bacteremia clearance prior to death, less than ten days of total antibiotic therapy, polymicrobial bacteremia on admission, recurrent MRSA bacteremia defined as history of MRSA bacteremia within one year of the index admission, combination therapy within one year prior to admission, and transitioned to a non-monotherapy MRSA-active antibiotic.

Patients with MRSA bacteremia within one year prior to 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 or any origin, or an epidural abscess as a metastatic foci 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 definitions section below) 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 Wilcoxon-rank sum test, while categorical variables were compared using the Pearson chi-squared test or Fisher’s exact test, as appropriate. Demographic and clinical data were analyzed for the three groups in the monotherapy arm, with quantitative variables compared using Kruskal-wallis test and categorical variables compared using Pearson chi-squared test. A p-value less than or equal to 0.05 was considered statistically significant, and analysis was completed using SAS version 9.3 (Cary, NC).

Multivariable logistic regression models estimated adjusted odds ratios and the 95% confidence interval 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<0.2) and not on the causal pathway. A forward selection method was utilized for the potential confounders, and these
were included into the multivariable logistic regression model if they affected the exposure intercept by greater than fifteen percent. 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 one year where treatment with combination therapy of ceftaroline and daptomycin for at least 72 hours was given. Uncomplicated *Staphylococcus aureus* bacteremia as defined by IDSA guidelines as an individual with positive blood culture results without evidence of endocarditis, without prosthetic devices, follow up blood cultures negative at two to four days after initial blood cultures, defervescence within 72 hours of starting antibiotic therapy, and no metastatic sites of infection. 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 non-infectious cause, these patients were coded as mortality, not infection-related. Bacteremia recurrence was defined as at least one blood culture positive for MRSA within 60 days after documentation of negative blood cultures. Adverse drug events included the following: bone marrow suppression (as defined by chart documentation review), elevated creatine kinase (defined as greater than five times the upper limit of normal [greater than 1100 U/L]), hepatotoxicity (defined as transaminases increased to twice the upper limit of normal [ALT greater than 104 U/L and AST greater than 80 U/L]), and nephrotoxicity (defined as increase in serum creatinine of greater than 0.3 mg/dL within 48 hours or increase in serum creatinine to more than 1.5 times baseline within seven days). Rash 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 (see 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 were 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 versus the monotherapy group (58% vs 36%, p = 0.01). 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% versus 35%, p = 0.01) and pulmonary septic emboli (47% versus 27%, p = 0.01). 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 in the primary composite outcome when comparing rates of surgical intervention between combination therapy and monotherapy groups for endocarditis (p = 0.17), epidural abscess (p = 0.68), or osteomyelitis (p = 0.27), or in the primary composite outcome in the combination therapy and monotherapy groups for patients with endocarditis, osteomyelitis and/or epidural abscess (p = 0.31) or between the monotherapy groups (p = 0.18) shown in Table 4.

Median actual total antibiotic duration was 56 days for the combination therapy group (n = 35) versus 45 days for the monotherapy group (n = 35) with p = 0.5. 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) as shown in Table 1 (p = 0.55). Of the 66 patients in the combination therapy group, 27 were discharged on combination therapy, while 31 were
later de-escalated to monotherapy, five completed their course of combination during the index admission, two died during the index admission, and one was discharged on two anti-staphylococcal 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 group (21% vs 24%, p = 0.66). 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 versus monotherapy group (20% vs 18%, p = 0.75). Recurrence of bacteremia was seen in two patients in the combination therapy group and five patients in the monotherapy group (3% vs 7%, p = 0.45). Inpatient infection-related mortality was 2% in the combination group compared to 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 versus daptomycin or ceftaroline monotherapy (13-14).

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 the 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 to 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 versus 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 two studies. 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 ten days of combination therapy to account for delays in de-escalation secondary to institutional guidelines and differences in practice amongst 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 versus de-escalation to monotherapy would support de-escalation after bacteremia clearance, and may result in lower healthcare costs, decreased exposure to combination therapy, and decreased length of stay.

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. 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.

CONCLUSION:

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 versus 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.
POTENTIAL CONFLICT OF INTEREST: The authors of this manuscript have no conflicts of interest to declare.

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PATIENT CONSENT: Our study does not include factors necessitating patient consent.
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| Table 1: Baseline Demographics and Disease Characteristics |
|----------------------------------------------------------|
|                                                          |
| **Definitive Combination vs Monotherapy Comparisons**     |
|                                                          |
| **Combination** | **Monotherapy (N = 66)** | **Monotherapy (N = 74)** | **P-value (CT vs MT)** |
| Therapy        |                          |                          |                         |
| Gender         | Male                     | 31 (47)                  | 38 (51)                 | 0.61                     |
|                | Female                   | 35 (53)                  | 36 (49)                 |                          |
| Age            | 42 [32-55]               | 50.5 [37 – 63]           |                          | 0.03                     |
| Race           | White                    | 49 (74)                  | 60 (81)                 | 0.27                     |
|                | African American         | 12 (18)                  | 10 (14)                 |                          |
|                | More than One Race       | 0                       | 2 (3)                   |                          |
|                | Unknown or Not Reported  | 5 (8)                    | 2 (3)                   |                          |
| Charlson Comorbidity Score | 2 [1 – 4] | 3 [1 – 5] | 0.35 | 3 [2-5] | 1.5 [1-3] | 3 [2-4] | 0.04 |
| PITB Bacteremia Score | 2 [0 – 4] | 1 [0 – 3] | 0.27 | 2 [0-3] | 1 [1-3] | 1 [0-2] | 0.37 |
| Comorbidities  | History of Intravenous Drug Use | 38 (58) | 27 (36) | 0.01 | 8 (27) | 7 (39) | 12 (46) | 0.31 |
|                | Chronic Kidney Disease   | 12 (18)                  | 28 (38)                 | 0.01                     |
|                | Diabetes Mellitus        | 11 (17)                  | 28 (38)                 | 0.005                    |
|                | Hemodialysis             | 5 (8)                    | 10 (14)                 | 0.26                     |
|                | History of Liver Disease | 4 (6)                    | 7 (9)                   | 0.54                     |
|                | Solid Tumor Malignancy   | 4 (6)                    | 9 (12)                  | 0.25                     |
| **De-escalated Monotherapy vs Monotherapy Comparisons**  |
|                                                          |
| **DAP MT (N = 30)** | **CPT MT (N = 18)** | **VAN MT (N = 26)** | **P-value (All MT)** |
|                | 17 (57)                  | 8 (44)                   | 13 (50)                 | 0.7                      |
|                | 13 (43)                  | 10 (56)                  | 13 (50)                 |                          |
| Age            | 55.5 [37-66]             | 48.5 [38-57]             | 43.5 [37-67]            | 0.45                     |
| Type of Bacteremia          | Complicated | Uncomplicated | Duration (days) | P value |
|----------------------------|-------------|---------------|-----------------|---------|
| Hematologic Malignancy      | 4 (6)       | 1             | 8 [6 – 11]      | 0.34    |
| Solid Organ Transplant      | 3 (5)       | 1             | 7 [5 – 11]      | 0.20    |
| HIV/AIDS                    | 2 (3)       | 0.6           | 7 [5-12]        | 0.03    |
| Prosthetic Devices          | Cardiac Devices | 7 (11)       | 6 [4 – 9]       | 0.03    |
| Orthopedic Hardware         | 6 (9)       | 0.73          | 7 [5-12]        | 0.34    |
| Prosthetic Joint            | 3 (5)       | 0.67          | 7 [5-12]        | 0.21    |
| Vascular Grafts             | 1 (2)       | 0.21          | 7 [5-12]        | 0.21    |
| Other*                      | 3 (5)       | 0.34          | 7 [5-12]        | 0.34    |
| Type of Bacteremia          | 63 (95)     | 73 (99)       | 7 [5-12]        | 0.34    |
| Intensive Care Unit Stay    | 42 (64)     | 42 (57)       | 7 [5-12]        | 0.34    |
| Mechanical Ventilation      | 12 (18)     | 11 (15)       | 7 [5-12]        | 0.34    |
| Vasopressor Support         | 11 (17)     | 11 (15)       | 7 [5-12]        | 0.34    |
| Infectious Diseases Consult | 66 (100)    | 74 (100)      | 7 [5-12]        | 0.34    |
| Duration of Bacteremia (days) | 8 [6 – 11] | 7.5 [5 – 12] | 7 [5-12]        | 0.34    |
| Antibiotic Duration         | 47 [42-56]  | 44.5 [42-56]  | 4.5 [4 – 6]     | <0.0001 |
| Duration prior to escalation (days) | 6 [4 – 9] | 7 [5 – 11] | 5 [4-6]        | 0.04    |
| Duration of combination therapy (days) | 15 [13 – 21] | 4.5 [4 – 6] | 5 [4-6]        | 0.04    |
| Monotherapy duration after de-escalation (days) | 32 [27 – 45] | 40 [37-52] | 45 [42-56] | 40 [34-52] | 0.04 |
| Anticipated total antibiotic duration after bacteremia clearance (days) | 47 [42-56] | 44.5 [42-56] | 45 [42-56] | 42 [42-56] | 0.04 |
| Actual total antibiotic     | 56 [42 – 68]| 45 [42 – 61]| 45 [43 – 70]   | 0.5     |

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|                         | Bacteremia Duration after Antibiotic Escalation (days) | 0.06 | 1 [0-4] | 1 [0-4] | 1 [0-4] | 2 [0-4] | 0.74 |
|-------------------------|-------------------------------------------------------|------|---------|---------|---------|---------|------|
| **Vancomycin MIC**      |                                                       |      |         |         |         |         |      |
| 0.5 mcg/mL              | 4 (6)                                                 | 11 (15) | 0.15 | 3 (10) | 2 (11) | 6 (23) | 0.001 |
| 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) |      |
| **Metastatic Foci**     |                                                       |      |         |         |         |         |      |
| Endocarditis            | 37 (56)                                               | 26 (35) | 0.01 | 12 (40) | 4 (22) | 10 (38) | 0.43  |
| Pulmonary Emboli        | 31 (47)                                               | 20 (27) | 0.01 | 5 (17) | 7 (39) | 8 (31) | 0.21  |
| Osteomyelitis           | 16 (24)                                               | 15 (20) | 0.57 | 4 (13) | 3 (17) | 8 (31) | 0.3   |
| Septic Arthritis        | 15 (23)                                               | 16 (22) | 0.88 | 6 (20) | 3 (17) | 7 (27) | 0.77  |
| Epidural Abscess        | 13 (20)                                               | 10 (14) | 0.32 | 3 (10) | 5 (28) | 2 (8) | 0.16  |
| Splenic Abscess/Infarct | 3 (5)                                                 | 2 (3) | 0.67 | 1 (3) | 1 (6) | 0 (0) | 0.71  |
| Central Nervous System  | 2 (3)                                                 | 1 (1) | 0.6 | 0 (0) | 1 (6) | 0 (0) | 0.24  |
| No Metastatic Foci      | 6 (9)                                                 | 8 (11) | 0.74 | 3 (10) | 2 (11) | 3 (12) | -     |
| Other***                | 31 (47)                                               | 37 (50) | 0.72 | 15 (50) | 10 (56) | 12 (46) | 0.83 |
| **Surgical Intervention for Source Control** |                                                                 |      |         |         |         |         |      |
| Endocarditis            | 9 (14)                                                | 2 (3) | 0.17 | 1 (3) | 0 (0) | 1 (4) | 1     |
| Epidural Abscess        | 6 (9)                                                 | 6 (8) | 0.68 | 1 (3) | 3 (17) | 2 (8) | 0.71  |
| Osteomyelitis           | 5 (8)                                                 | 7 (9) | 0.27 | 2 (7) | 1 (6) | 4 (15) | 0.79 |
| **Other Positive Cultures for MRSA** |                                                   |      |         |         |         |         |      |
| Urine                   | 10 (15)                                               | 7 (9) | 0.3 | 1 (3) | 2 (11) | 4 (15) | 0.32  |
| Sputum                  | 24 (36)                                               | 14 (19) | 0.02 | 4 (13) | 5 (28) | 5 (119) | 0.49 |
| Pleural Fluid           | 3 (5)                                                 | 1 (1) | 0.34 | 0 (0) | 1 (6) | 0 (0) | 0.24  |
| Synovial Fluid          | 5 (8)                                                 | 9 (12) | 0.37 | 3 (10) | 3 (17) | 3 (12) | 0.82  |
| 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) | 0.45 | 2 (7) | 0 (0) | 9 (35) | 0.002 |
| Suspected or Confirmed Source | Bone | Other**** | Osteomyelitis | Septic Joint | Skin/Soft Tissue Infection | Central Venous Catheter-Associated | Intravenous Drug Use | Endocarditis | Epidural Abscess | Cardiac Device Infection | Prosthetic Joint Infection | Other | Unknown | Discharge Disposition | Other***** |
|-----------------------------|------|-----------|---------------|--------------|--------------------------|-----------------------------------|-----------------------|--------------|------------------|--------------------------|--------------------------|-------|---------|----------------------|-----------|
|                             | 0    | 1 (1)     | 1             | 0 (0)        | 1 (6)                   | 0 (0)                             | 0.24                  |              |                  |                          |                          |       |         | 0 (0)               | 0.24      |
| Pneumonia                   | 1 (2)| 4 (5)     | 0.37          | 1 (3)        | 3 (17)                  | 0 (0)                             | 0.06                  |              |                  |                          |                          |       |         | 3 (17)              | 0.06      |
| Osteomyelitis               | 1 (2)| 2 (3)     | 1             | 1 (3)        | 0 (0)                   | 1 (4)                             | 1                     |              |                  |                          |                          |       |         | 1 (4)               | 1.00      |
| Septic Joint                | 2 (3)| 0         | 0.22          | 0 (0)        | 0 (0)                   | 0 (0)                             | -                     |              |                  |                          |                          |       |         | -                   | -         |
| Skin/Soft Tissue Infection | 6 (9)| 6 (8)     | 0.84          | 4 (13)       | 1 (6)                   | 1 (4)                             | 0.56                  |              |                  |                          |                          |       |         | 0 (0)               | 0.28      |
| Central Venous Catheter-Associated | 7 (11) | 15 (20) | 0.12 | 6 (20) | 4 (22) | 5 (19) | 1 |              |                  |                          |                          |       |         | 0 (0)               | 0.34      |
| Intravenous Drug Use        | 36 (55) | 20 (27) | 0.0009 | 5 (17) | 6 (33) | 9 (35) | 0.25 |              |                  |                          |                          |       |         | 0 (0)               | 0.28      |
| Endocarditis                | 0    | 1 (1)     | 1             | 1 (3)        | 0 (0)                   | 0 (0)                             | 1                     |              |                  |                          |                          |       |         | 0 (0)               | 1.00      |
| Epidural Abscess            | 1 (2)| 1 (1)     | 1             | 0 (0)        | 1 (6)                   | 0 (0)                             | 0.24                  |              |                  |                          |                          |       |         | 0 (0)               | 0.24      |
| Cardiac Device Infection    | 0    | 4 (5)     | 0.12          | 3 (10)       | 1 (6)                   | 0 (0)                             | 0.28                  |              |                  |                          |                          |       |         | 0 (0)               | 0.28      |
| Prosthetic Joint Infection  | 0    | 2 (3)     | 0.5           | 2 (7)        | 0 (0)                   | 0 (0)                             | 0.34                  |              |                  |                          |                          |       |         | 0 (0)               | 0.34      |
| Other                       | 5 (8)| 4 (5)     | 0.73          | 3 (10)       | 1 (6)                   | 0 (0)                             | 0.28                  |              |                  |                          |                          |       |         | 0 (0)               | 0.28      |
| Unknown                     | 11 (17) | 11 (15) | 0.77 | 3 (10) | 2 (11) | 6 (23) | 0.38 |              |                  |                          |                          |       |         | 0 (0)               | 0.38      |
| Home                        | 9 (14) | 20 (27) | 0.05          | 14 (47)      | 3 (17)                  | 3 (12)                            | 0.008                 |              |                  |                          |                          |       |         | 0 (0)               | 0.008     |
| Other*****                  | 57 (86) | 54 (73) | 0.05 | 16 (53) | 15 (83) | 23 (88) | 1 |              |                  |                          |                          |       |         | 0 (0)               | 1.00      |

Data are presented as number (percent) or median [interquartile range] as appropriate. MIC = minimum inhibitory concentration. DAP = daptomycin, CPT = ceftaroline, and VAN = vancomycin. Definitive combination therapy including those included in the combination therapy group. De-escalated monotherapy group defined as the specific monotherapy that patients in the monotherapy group were de-escalated to when combination therapy was discontinued.

*Other prosthetic devices include: central intravenous access (10), prosthetic valves (4), inferior vena cava filter (1), and ureteral stent (1)
**Variable include missing data.
***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)
****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)
*****Other discharge locations include skilled nursing facilities, long term acute care hospitals, and mortality during index admission.
### Table 2: Treatment Outcomes

| Outcome                        | Combination Therapy N = 66 | Monotherapy N = 74 | P-value (CT vs MT) |
|--------------------------------|---------------------------|-------------------|-------------------|
| Composite Clinical Failure Outcome: 60-day Recurrence / Inpatient Infection-Related Mortality / 60-day Readmission | 14 (21) | 18 (24) | 0.66 |
| MRSA Bacteremia Recurrence Within 60 Days | 2 (3) | 5 (7) | 0.45 |
| Inpatient Infection-Related Mortality | 1 (2) | 4 (5) | 1 |
| Readmission Within 60 Days | 13 (20) | 13 (18) | 0.75 |
| Adverse Drug Event | Bone Marrow Suppression | 1 (2) | 0 | 0.47 |
| Elevated Creatine Kinase | 0 | 0 | |
| Hepatotoxicity | 0 | 0 | |
| Nephrotoxicity | 0 | 0 | |
| Rash | 0 | 0 | |
| Other* | 1 (2) | 1 (1) | 1 |
| Inpatient Length of Stay (Days) | 26 [20-41] | 24.5 [16-33] | 0.08 |

Data are presented as number (percent) or median [interquartile range] as appropriate.

*Other adverse drug events include: neutropenia (1) and pedal edema (1).
|                         | 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               |
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-day recurrence / Inpatient Infection-Related Mortality / 60-day Readmission | 13 (26)                                      | 7 (17)                                              | 0.31               | 3 (20)      | 3 (33)     | 1 (6)       | 0.18 |
| MRSA Bacteremia Recurrence Within 60 Days | 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 Days       | 12 (24)                                          | 5 (12)                                               | 0.15                | 2 (13)      | 2 (22)     | 1 (6)       | 0.42 |

Data are presented as number (percent) or median [interquartile range] as appropriate. DAP = daptomycin, CPT = ceftaroline, and VAN = vancomycin. Definitive combination therapy including those included in the combination therapy group. De-escalated monotherapy group defined as the specific monotherapy that patients in the monotherapy group were de-escalated to when combination therapy was discontinued.
Figure 1: Study Population

286 Patients with MRSA Bacteremia Identified

140 Patients Included

146 Excluded
- Less than 72 hours of combination therapy: 65
- Duplicate patient record: 1
- Less than 18 years old: 1
- Incarcerated: 16
- Polymicrobial bacteremia on admission: 9
- No clearance of bacteremia prior to death: 8
- Less than 10 days of total antibiotic therapy: 7
- Recurrence of MRSA bacteremia within previous 1 year: 18
- De-escalation to alternative monotherapy: 3
- Outside hospital records unavailable: 1
- Left against medical advice: 9
- Patient transitioned to hospice: 8

Combination Therapy
- 66

Monotherapy
- 74

Ceftaroline
- 18

Daptomycin
- 30

Vancomycin
- 26