Clinical Outcomes with Continuation of Combination Antibiotic Therapy versus De-escalation to Monotherapy for Patients with MRSA Bacteremia.

Courtney Nichols, MD[1]; Lynn Wardlow, PharmD, MBA, BCIDP[2]; Kelci Coe, MPH[1]; Mohammed Mahdee Sobhanie, MD[1]

[1]Division of Infectious Diseases; [2]Department of Pharmacy, The Ohio State University Wexner Medical Center, Columbus, Ohio

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Background

- Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is a serious infection commonly complicated by metastatic sites of infection resulting in increased morbidity and mortality.
- Previous studies have demonstrated shortened durations of bacteremia and lower mortality rates with combination therapy (CT) compared to monotherapy (MT)[1,2].
- Overall, there is a lack of evidence to favor continued combination therapy over de-escalation to monotherapy for completion of treatment after clearance of bacteremia.
- Multiple *in vitro* studies have illustrated similar efficacy between treatment with prolonged CT versus those treated with CT followed by de-escalation to MT, with no difference in outcomes between treatment groups[3,4].

Objectives

- This study aimed to compare the inpatient all-cause mortality, readmission rate, and recurrence of MRSA bacteremia in patients treated with daptomycin and ceftaroline CT who were either retained on prolonged CT versus those de-escalated to either daptomycin, ceftaroline, or vancomycin monotherapy.

Primary Outcomes

Composite End Point of Clinical Outcomes, including:
1. Inpatient all-cause mortality
2. 60-day bacteremia recurrence
3. 60-day readmission

Secondary Outcomes

- Incidence of medication-related adverse events
- Difference in total inpatient length of stay (LOS)

Methods

- Single-center, retrospective study at The Ohio State University Wexner Medical Center.
- Statistical analysis: categorical and continuous variables analyzed using descriptive statistics, Wilcoxon-rank sum, Chi-squared and Fisher's exact test with p ≤ 0.05 for significance. Multivariate logistic regression also performed in order to examine the relationship between which therapy patients received and the composite outcome while controlling for confounding.

Inclusion Criteria

- Adult patients 18-89 years old
- Diagnosed with MRSA bacteremia between November 1, 2011 and July 31, 2019
- ≥ 72 hours of CT with daptomycin and ceftaroline
- Patients included only once during index case of MRSA bacteremia

Exclusion Criteria

- Prisoners
- Patients <18 years old or greater than >89 years old
- Receipt of less than 72 hours of CT
- Receipt of less than 10 total days of antibiotic therapy
- Blood cultures positive during index admission for other non-MRSA pathogens (i.e. polymicrobial bacteremia)
- Patients with previous admission within 1 year for MRSA bacteremia
- Patient transitioned to hospice care
- Patients who left against medical advice
- Patients transferred from outside hospital and records unobtainable
- Death prior to bacteremia clearance
- Transitioned to hospice care
- De-escalated to monotherapy with other agent

- Patients who were continued on combination therapy for more than 10 days or more were included in the combination therapy group.
- Patients who were de-escalated to monotherapy prior to 10 days of antibiotic therapy were included in the monotherapy group.
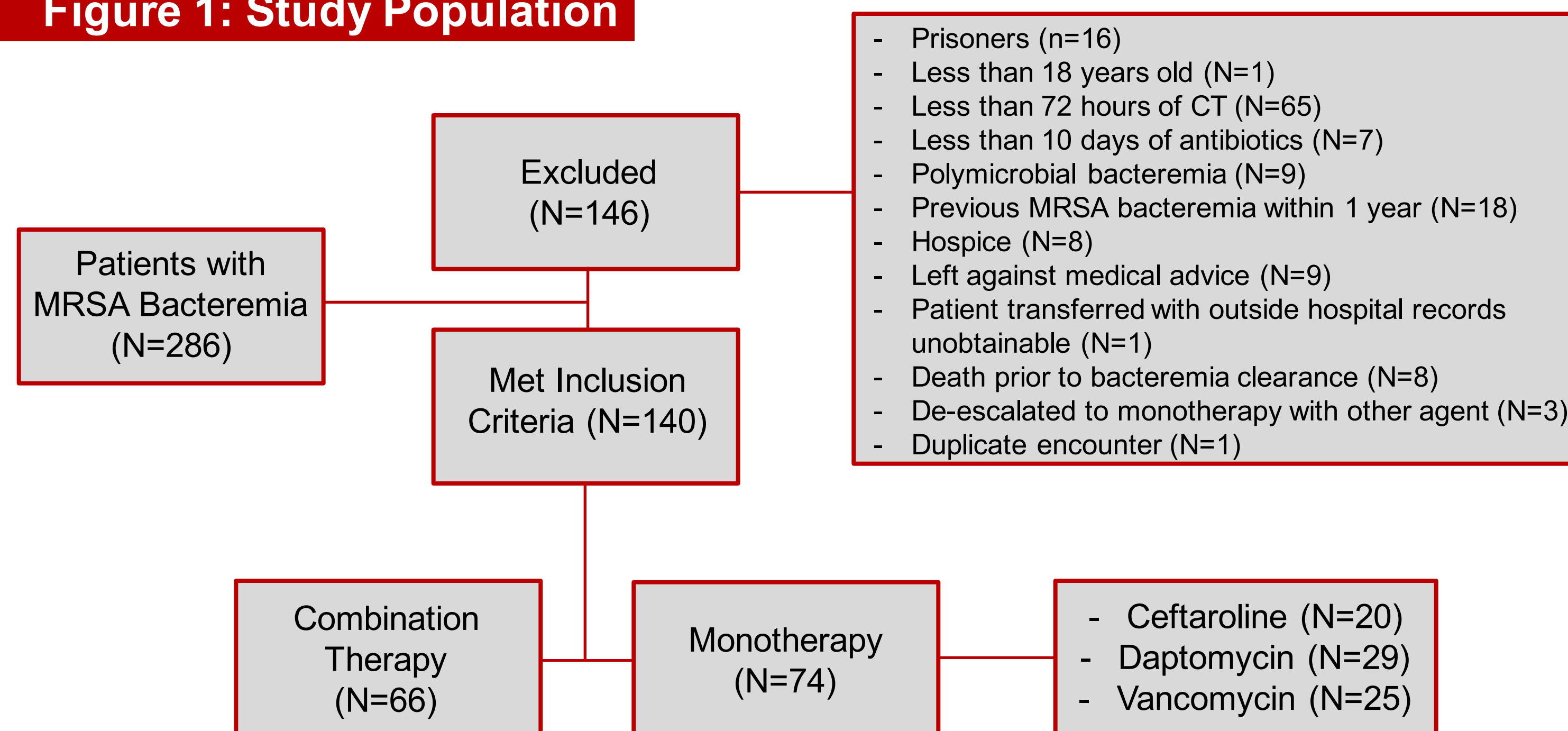
Results

Figure 1: Study Population

Table 1: Patient Demographics

	Combination Therapy N = 66	Monotherapy N = 74	p-value
Gender:			
Male	31 (47)	38 (51)	0.61
Female	35 (53)	36 (49)	
Age, years – median (IQR):	42 (32-55)	50.5 (37-63)	0.03
Race:			0.27
White	49 (74)	60 (81)	
African American	12 (18)	10 (14)	
More than 1 race	0 (0)	2 (3)	
Unknown or Not Reported	5 (8)	2 (3)	
Charlson Comorbidity Score – median (IQR)	2 (1-4)	3 (1-5.0)	0.35
PITT Bacteremia Score – median (IQR)	2 (0-4)	1 (0-3.0)	0.27
Co-morbidities:			
History of Intravenous Drug Use (IVDU)	38 (58)	27 (36)	0.01
Diabetes Mellitus	11 (17)	28 (38)	0.005
Chronic Kidney Disease (CKD)	12 (18)	28 (38)	0.01
End stage renal disease on Hemodialysis	5 (85)	10 (14)	0.26
Liver Disease	4 (6)	7 (9)	0.54
Solid Organ Malignancy	4 (6)	9 (12)	0.25
Hematologic Malignancy	4 (6)	5 (7)	1
Neutropenia	0 (0)	0 (0)	-
HIV/AIDS	2 (3)	1 (1)	0.6
Solid Organ Transplant	3 (5)	3 (4)	1
Identified Metastatic Foci of Infection:			
Central Nervous System	2 (3)	1 (1)	0.60
Osteomyelitis	16 (24)	15 (20)	0.57
Septic Arthritis	15 (23)	16 (22)	0.88
Pulmonary Emboli	31 (47)	20 (27)	0.01
Endocarditis	37 (56)	26 (35)	0.01
Splenic abscess/infarct	3 (5)	2 (3)	0.67
Epidural abscess	13 (20)	10 (14)	0.32
Other site of infection	31 (47)	37 (50)	0.72
Prosthetic Devices Present:			
Prosthetic Joint	3 (5)	2 (3)	0.67
Cardiac Device	7 (11)	15 (20)	0.12
Orthopedic Hardware	6 (9)	8 (11)	0.73
Vascular Graft	1 (2)	5 (7)	0.21
Other Prosthetic Device	3 (5)	12 (16)	0.03
Duration of Bacteremia, days – median (IQR)	8 (6-11.0)	7.5 (5-12.0)	0.33
Antibiotic Duration Prior to Escalation, days – median (IQR)	6 (4-9.0)	7 (5-11.0)	0.20
Bacteremia Duration after Antibiotic Escalation, days – median (IQR)	2 (0-4.0)	1 (0-3.0)	0.06

*Values presented as n(%) unless otherwise defined.

Results

Table 2: Primary and Secondary Outcomes of Continued Combination Therapy vs Monotherapy

	Combination Therapy (N = 66)	Monotherapy (N = 74)	p-value
Composite Clinical Outcome:	14 (21)	18 (24)	0.66
Inpatient mortality	3 (5)	8 (11)	0.22
60-day bacteremia recurrence	2 (3)	5 (7)	0.45
60-day readmission	13 (20)	13 (18)	0.75
Adverse medication-related events:			
Nephrotoxicity	0 (0)	0 (0)	-
Hepatotoxicity	0 (0)	0 (0)	-
Elevated creatinine kinase	0 (0)	0 (0)	-
Bone marrow suppression	1 (2)	0 (0)	0.47
Rash	0 (0)	0 (0)	-
Other specified mediation-related event	1 (2)	1 (1)	1.00
Total inpatient LOS, days – median (IQR)	26 (20-41)	24.5 (16-33)	0.08

*Values presented as n(%) unless otherwise defined.

Table 3: Multivariate Analysis of Primary Outcomes for CT and MT

	Estimate	Odds Ratio	Confidence Interval
Monotherapy	0.195	1.22	0.52-2.82
Chronic Kidney Disease	0.789	2.20	0.87-5.57
Intravenous Drug Use	0.808	2.24	0.93-5.43

Conclusions

- Our study showed no significant difference in the composite clinical outcome of inpatient mortality, 60-day bacteremia recurrence, and 60-day readmission rate between patients treated with prolonged daptomycin and ceftaroline CT compared to patients de-escalated to either daptomycin, ceftaroline, or vancomycin monotherapy.
- Multivariable logistic regression comparing primary outcomes for CT and MT showed unadjusted odds ratio of 1.19 (confidence interval 0.54-2.64). When adjusted for proven confounders of CKD and IV drug use, adjusted odds ratio was 1.22.
- Secondary outcomes showed no statistically significant difference in length of stay or adverse drug reactions between patients treated with CT versus those treated with MT.
- Limitations of this study include a selection bias due to retrospective nature of study, small sample size, and a small number of the compared outcomes in this patient population.
- Larger randomized controlled trials are necessary to evaluate if these results are reproducible on a larger scale when a higher number of composite outcomes are observed.

Funding

References

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