A single-center case series of methicillin-resistant *S. aureus* bacteremia with elevated minimum inhibitory concentrations to vancomycin

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INTRODUCTION:

- Methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious nosocomial pathogen.[1]
- Vancomycin remains the gold-standard therapy, however, increasing rates of treatment failure are seen in setting of increased minimum inhibitory concentration (MIC) to vancomycin.[2]
- Alternative agents remain limited, with daptomycin as the most significant secondary agent, though it has been observed to have rising MIC with increasing vancomycin MIC.[3]
- Recently, increased attention has been paid to use of combination therapy for the treatment of MRSA bacteremia, especially in the setting of vancomycin failure. Notable regimens have included the use of combination with vancomycin[4]/daptomycin and B-lactams[5], or daptomycin-ceftaroline combination,[6] though studies have been inconclusive on their benefit.[7]
- Our aim for was to review clinical characteristics, antibiotic regimens, and outcomes for patients who developed MRSA bacteremia with MIC ≥ 2 from 8/2014-3/2019.

METHODS:

Identify the first positive single- patient MRSA blood isolate from pathogen database

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Clinical data review into REDCap (n=332)

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Identify patients who developed a MRSA isolate with MIC ≥ 2 to vancomycin (n=25)

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Detailed data extraction and description of clinical course

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Univariate analyses of patients who developed MIC ≥ 2 to vancomycin (n=24) in comparison to larger cohort (n=48).

RESULTS

- In total, 25 patients developed MRSA bacteremia with a vancomycin MIC ≥ 2. Four patients developed recurrence of bacteremia (>30 days after last positive blood culture).
- Combination therapy with vancomycin or daptomycin and a beta-lactam was used in 8 cases (32% of cases).
- 18 patients developed persistent bacteremia (bacteremia >7 days)
- Average number of days to clearance was 17 (range 1-69 days).

RESULTS:

Factor, n (%)	↑ MIC Levels (*n* = 24)	Factor, n (%)	↑ MIC Levels (*n* = 24)
Clonal Complex		*Comorbidities*	
CC8	12 (50)	Myocardial Infarction	4 (17)
CC5	11 (46)	Congestive Heart Failure	6 (25)
Other	1 (4)	Peripheral Vascular Disease	3 (13)
Male	14 (58)	Cerebrovascular Disease	4 (17)
Race/Ethnicity		Dementia	1 (4)
Non-Hispanic White	9 (38)	Chronic Pulmonary Disease	4 (17)
Non-Hispanic Black	7 (29)	Connective Tissue Disease	3 (13)
Hispanic/Latino/ Asian	8 (33)	Peptic Ulcer Disease	1 (4)
Age at Time of Infection		Diabetes (no complications)	3 (13)
18-54 Years	9 (38)	Diabetes with Organ Damage	7 (29)
55-69 Years	9 (38)	Hemi or Paraplegia	1 (4)
≥ 70 Years	6 (25)	Moderate/ Severe Renal Disease	12 (50)
History of IV Drug Use	5 (21)	Solid Tumor	1 (4)
Body Mass Index (BMI)		Leukemia	1 (4)
<18.5	1 (4)	Lymphoma/ Multiple Myeloma	3 (13)
18.5-24.9	8 (33)	Moderate/Severe Liver Disease	2 (8)
25.0-29.9	9 (39)	*Charlson Comorbidity Index (CCI)*	
≥ 30.0	7 (30)	0-3	7 (29)
HIV	4 (17)	4-5	4 (17)
Admission Source		6-8	8 (33)
Home	**17 (71)**	>8	5 (21)
NH/Rehab/LTACH	1 (4)	History of Transplant	3 (13)
Outside Hospital	6 (25)	**History of MRSA Colonization**	**16 (67)**
Prior Hospital Admission (90 Days)	**20 (83)**	*Presumed Source of MRSA BSI*	
Length of Hospital Stay Prior to BSI		Skin & Soft Tissue Infection	7 (29)
CO-MRSA	14 (58)	Diabetic Foot Infection	1 (4)
HO-MRSA	10 (42)	Vascular Access	9 (38)
Frequent Healthcare Interaction		Other/Unknown Source	7 (29)
Hemodialysis	10 (42)	**Persistent Bacteremia (≥ 5 Days)**	**19 (79)**
Infusion Center	2 (8)	Polymicrobial	2 (8)
None	12 (50)	ICU Admission Prior to BSI	6 (25)
Presence of Invasive Device	**21 (88)**		
Invasive Procedures	**12 (50)**		
Wound Present	**15 (63)**		

Table 1: Demographics and clinical characteristics of patients who developed MRSA bacteremia with MIC ≥ 2

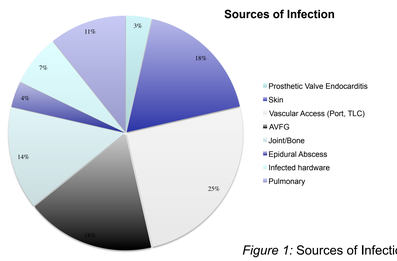

Figure 1: Sources of Infection

RESULTS:

Variable	Multivariate Analysis OR (95% CI)	*P* value
Admission from NH/Rehab/LTACH	**0.06 (0.002-0.60)**	**0.04**
History of MRSA Colonization	**6.77 (1.59-39.23)**	**0.02**
Persistent Bacteremia (≥ 5 Days)	**31.23 (6.32-258.73)**	**<0.001**

Table 2: Univariate and multivariate analyses were run comparing patients with MRSA bacteremia with MIC ≥ 2 (n=24) compared to the larger cohort of patients who developed MRSA bacteremia without elevated MIC to vancomycin (n=48), significant findings noted in table. Remainder of analysis insignificant (p>0.05). Abbrev: Nursing home (NH), long term acute care hospital (LTACH).

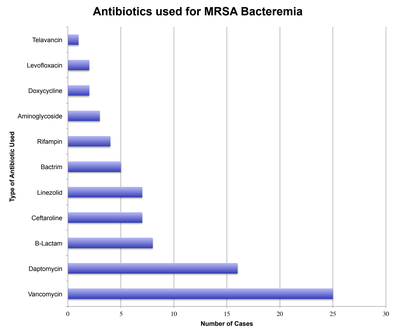

Figure 2: Aggregate use of antibiotics. Antibiotics were used both as monotherapy or in combination.

Outcome, n (%)	↑ MIC Levels (*n* = 24)
90 Day Mortality	5 (21)
90 Day Mortality Related to MRSA	2 (40)
Over 50% rise in creatinine	7 (47)
Recurrent bacteremia	9 (38)
Duration of Bacteremia, Mean ± SD	17.04 ± 16.48
Source Controlled	17 (71)
ICU Admission after MRSA BSI	7 (29)
Intubated After MRSA BSI	4 (17)
Metastatic Infection	9 (38)
Endocarditis (missing=15)	4 (44)
Medications, n (%)	**↑ MIC Levels (*n* = 24)**
Vancomycin	23 (100)
Linezolid	8 (33)
Daptomycin	14 (58)

Table 3: Outcomes of patients with elevated MIC

Variation in Individual Patient's MIC Over Time

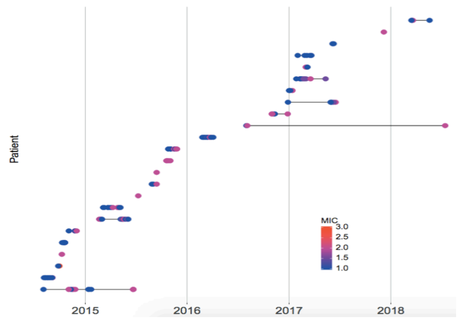

Figure 3: Vancomycin MICs for each patient plotted chronologically. Patients mostly started with MRSA bacteremia with MIC of 1 with several exceptions. There was significant variation in MIC with adjustment of antibiotic regimen.

Pt. #	Control ?	CC	# days	# Van	Regimens	Reason Switched	Clinical Description
1*	No	Other	32	30	Van (10), Van/TMP-SMX (12), Van/Dapto (13), Van/Rif (4), Van/TMP-SMX/Rif/Levo (6), TMP-SMX/Rif/Levo/Ceft (37)	Persistence, MIC	65 F with rheumatic heart disease s/p AVR and MVR found to have prosthetic valve endocarditis on TEE, unclear source
2*	Yes	CC8	5	?	Van at OSH, Ceft/Rif (13), Linez/Levo (24)	hVISA	41 F with IV drug use transferred from OSH for management MRSA BSI from skin source and repair of tricuspid valve
3	No	CC5	4	0	Van (12)	N/A	83 M with DLBCL c/b neutropenia with MRSA pneumonia and subsequent MRSA BSI.
4*	Yes	CC5	3	8	Van (14), TMP-SMX/Rif (42)	Fever	58 F with multiple myeloma, MRSA BSI from presumed PC
5*	No	CC5	18	28	Van at OSH, Dap (14), Van/Gent (28)	N/A	59 M with ESRD with MRSA BSI from infected AVF c/b MV endocarditis, transferred from OSH for MVR
6*	No	CC5	39	19	Van (21), Dapto (14), Linez/Rif (2), Linez/Ceft (2), Linez/Tige (7), Linez/Doxy (14)	hVISA	63 F with DM c/b neuropathy with hVISA BSI from metatarsophalangeal septic arthritis with OM c/b vertebral OM
7*	Yes	CC5	10, 29	7	Van (7), Dapto (30) // Dapto (15), Dapto/Unasyn (11), TMP-SMX/Unasyn/Telav (19), Telav (7)	Persistence	75 M with ESRD transferred from OSH with MRSA BSI from AVG, readmitted with MRSA BSI with metastatic infection including septic arthritis, venous thrombi
8*	Yes	CC5	69	47	Van (54), Dapto/Naf (27), Linez/TMP-SMX(43), TMP-SMX	hVISA	52 M with STEMI c/b cardiogenic shock s/p TAH who developed MRSA BSI from infected TAH c/b mediastinitis and sternal abscess
9	No	Not Done	-	0	Van (6)	N/A	85 M with CAD s/p VT arrest c/b MRSA pneumonia, transferred from OSH for management of cardiogenic shock and MRSA pneumonia
10	Yes	CC5	15, 4	13	Van (16), Dapto (26) // Dapto (30)	Difficulty dosing	45 M with fistulizing Crohn's on TPN admitted for abdominal abscess with course c/b multiple candidemia/MRSA line infections
11	Yes	CC5	1	0	Van (12)		49 M with HCV Cirrhosis s/p OLT admitted with SBO with course c/b respiratory failure and MRSA BSI from TLC.
12*	No	CC8	26	0	Van (9), Dapto (7), Dapto/ Cefaz (9), Linez (42)	hVISA	32 M with AIDS, recurrent cellulitis with MRSA BSI of unclear source but presumed episode of cellulitis
13*	No	CC8	32	19	Van (20), Dapto (15), Linez (7), Linez/Tige (12)	MIC	67 M with AIDS, admitted with MRSA BSI found to have hip OM on MRI
14	Yes	CC8	35	11	Van (31), Dapto (14), Linez (18)	MIC	56 M with ESRD newly on HD with MRSA BSI from PC infection, course c/b superinfection of IJ thrombus
15	Yes	CC5	-	5	Van (8)		36 M with HIV admitted for lower extremity OM s/p BKA course c/b MRSA BSI from OM, eloped
16*	Yes	CC8	13, 2	0	Van (3), Dapto (59) // Van/Ceft (9), Van/Cefaz (48)	MIC	45 M with ESRD, IV drug use, BSI from presumed skin source c/b endocarditis who presented again with back pain found to have pathologic fracture at site of vertebral OM
17*	Yes	CC8	15	10	Van (26), Van/Dapto (5), Van/ TMP-SMX(21), Doxy	Persistence	68 M with HIV who presented with LE weakness, found to have large thoracic and lumbar epidural abscess, source not identified
18*	Yes, No	CC8	42, 3	12	Van (15), Dapto (12), Van/Ceft (13), Van/Cefaz (17) // Van/ Cefaz (63)	MIC	59 F with HTN CVA c/b MRSA BSI from infected AVF. Re-admitted with hypoxemic respiratory failure from pneumonia c/b MRSA BSI, c/b vertebral OM.
19	Yes	CC8	8	34	Van (83)		77 F with ESRD, significant cardiac history s/p PPM with prior MRSA BSI from PC, BSI from PC c/b PPM thrombus
20*	Yes	CC8	25	39	Van (35), Van/Cefaz (60)	Persistence	72 F with ESRD, BSI from infected AVF
21*	No	CC8	-	13	Van (14), Dapto/Ceft (8)	Persistence	74 F with spinal stenosis with extensive surgical repair, BSI from spinal hardware infection
22	No	CC5	1	0	Van (30)		64 M with erythrodermic psoriasis, BSI due to skin source
23	No	CC5	8	5	Van (50)		81 F with ESRD, BSI due to infected AVG
24*	No	CC8	18	32	Van (28), Linez/Cefaz (5), Van/Ceftar (4)	Poor compliance, inability for source control	52 M with CAD, HFrEF s/p AICD with recurrent MRSA BSI 2/2 psoas abscess
25	No	CC5	7	1	Van (4), Dapto (4), Linez (1)	Transferred to hospice	61 F with multiple myeloma, MRSA BSI from likely PNA

Table 4: Clinical characteristics and antibiotic regimens of patients with MRSA bacteremia with MIC ≥ 2. Patient ID (No. 1-25) in left hand column. Patients who received combination therapy noted above with *. Duration of bacteremia noted in "# Days" column, two patients did not clear. Number of days of vancomycin exposure prior to developing elevated MIC (# Van) does not account for prior vancomycin exposure or vancomycin administration at outside hospital prior to transfer. Antibiotic regimen column denotes different regimens with cumulative duration of therapy in days. Abbreviations: Source Controlled (SC). Clonal complex (CC). Number of bloodstream infection days (#BSI days). Vancomycin (Van). Trimethoprim-Sulfamethoxazole (TMP-SMX). Rifampin (Rif). Levofloxacin (Levo). Ceftaroline (Ceft). Cefazolin (Cefaz). Linezolid (Linez). Daptomycin (Dapto). Tigecycline (Tige). Gentamicin (Gent). Doxycycline (Doxy). Telavancin (Telav). Nafcillin (Naf). Heteroresistant vancomycin-intermediate *S. aureus* assay (hVISA). Permacath (PC). Total artificial heart (TAH). Arteriovenous fistula or graft (AVFG). Outside hospital (OSH). Bacteremia (BSI). Mitral valve (MV). Mitral Valve Replacement (MVR). Diabetes mellitus (DM). Complicated by (C/b). Osteomyelitis (OM). End-stage renal disease (ESRD). Patients 7,10, 16, 18 had two episodes of bacteremia, regimens and duration of courses noted above.

CONCLUSIONS

- With few novel therapeutics under development, management of MRSA bacteremia, particularly with a rising MIC to vancomycin, is a clinical challenge for practitioners.
- In our case series we found that treatment is largely patient and practitioner-dependent, and not standardized.
- Further definition of the clinical risk factors for development and novel therapeutic strategies will enable understanding of how to best manage these challenging infections.

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