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Concise Communication

Methicillin-resistant *Staphylococcus aureus* bacteremia with elevated vancomycin minimum inhibitory concentrations

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Abstract

This case–control study of 25 cases with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia with vancomycin minimum inhibitory concentration (MIC) ≥ 2 µg/mL and 391 controls (MIC < 2 µg/mL) characterized the clinical characteristics, treatments, and outcomes associated with elevated vancomycin MIC. Elevated vancomycin MIC was associated with baseline hemodialysis, prior MRSA colonization, and metastatic infection.

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Bloodstream infection (BSI) with *Staphylococcus aureus* is associated with morbidity and mortality, posing significant management challenges.[1] Although vancomycin remains the standard of care for methicillin-resistant *S. aureus* (MRSA) BSI, treatment failures do occur, often associated with elevated vancomycin minimum inhibitory concentrations (MICs).[1,2] Although MRSA isolates with vancomycin MIC equal to 2 µg/mL are considered susceptible to vancomycin according to Clinical Lab and Standards Institute (CLSI) breakpoints,[3] they have been associated with treatment failure despite susceptibility.[1] Known risk factors for elevated MIC include prior vancomycin exposure, prolonged duration of bacteremia, and lack of source control.[2,4]

Management of MRSA BSI with elevated vancomycin MIC is not clearly defined.[1] Although source control is central to management, decisions to continue vancomycin, switch to alternative monotherapies, or attempt salvage combination therapy are made on a case-by-case basis with variability in practices.[1,5] Decisions are often multidisciplinary, between frontline providers, infectious diseases (ID) consultants, and ID pharmacists, along with established antimicrobial stewardship programs.

In this case–control study, we investigated risk factors and outcomes between those who do and do not develop MRSA BSI

with vancomycin MIC ≥ 2 µg/mL. Furthermore, we have described the treatments chosen by providers in this challenging situation.

Methods

This retrospective case–control study included adults (≥ 18 years) admitted to a quaternary care hospital in New York City with MRSA BSI over a 5-year period (2014–2019). The Clinical Microbiology Laboratory utilized matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Billerica, MA) for identification and Vitek 2 (bioMérieux) for susceptibilities. MICs of ≥ 2 µg/mL per Vitek 2 were verified by Etest (bioMérieux). Vancomycin MICs and interpretations were reported in the electronic medical record (EMR), with retesting of serially positive blood cultures every 72 hours.

Demographic and clinical data were extracted from the EMR for 416 consecutive adults (≥ 18 years) with MRSA BSI using previously described tools.[6] Colonization was determined by positive MRSA culture prior to BSI, or documented history of MRSA colonization; MRSA swab screening was not routinely performed.

Due to the exploratory nature of this study, we performed univariable logistic regression with the outcome defined as MRSA BSI with a vancomycin MIC ≥ 2 µg/mL. Cases were adults (aged >18 years) with MRSA BSI with a vancomycin MIC ≥ 2 µg/mL, and controls were adults (aged >18 years) with MRSA BSI with a vancomycin MIC < 2 µg/mL. For controls, duration of bacteremia was measured from the first date of positive blood culture until the first date of negative blood culture. Duration of bacteremia is associated with elevated vancomycin MIC; thus, we calculated the date of first positive blood culture until the date of vancomycin MIC ≥ 2 µg/mL for all cases. We also

Table 1. Univariable Analysis of Demographics and Clinical Characteristics of Cases with MRSA BSI with MIC ≥ 2 µg/mL Compared to Controls

Characteristic	Cases (n = 25), No. (%)	Controls (n = 391), No. (%)	Odds Ratio	95% Confidence Interval	P Value
Sex					
Male	15 (60)	245 (63)	0.89	0.39–2.04	.79
Female	10 (40)	146 (37)	Reference		
Age at infection					
18–54 y	9 (36)	124 (32)	Reference		
55–69 y	9 (36)	121 (31)	1.02	0.39–2.67	.96
≥70 y	7 (28)	146 (37)	0.66	0.24–1.83	.42
Race/Ethnicity					
Non-Hispanic White	9 (36)	155 (40)	Reference		
Non-Hispanic Black	7 (28)	100 (26)	1.21	0.44–3.34	.72
Hispanic	7 (28)	93 (24)	1.30	0.47–3.60	.62
Other	2 (8)	37 (10)	0.93	0.19–4.49	.93
Missing/Unknown	0	6			
History of injection drug use					
Yes	4 (20)	39 (10)	2.26	0.80–6.35	.12
No	20 (80)	352 (90)	Reference		
Body mass index, kg/m^2					
<18.5	1 (4)	49 (13)	0.32	0.03–2.55	.28
18.5–24.9	9 (36)	139 (36)	Reference		
25.0–29.9	8 (32)	94 (24)	1.1	0.49–3.53	.59
≥30.0	7 (28)	107 (28)	1.01	0.36–2.80	.98
Missing	0	2			
HIV diagnosis					
Yes	4 (16)	35 (9)	1.94	0.63–5.96	.25
No	21 (84)	356 (91)	Reference		
Admission source					
Home[a]	15 (60)	237 (61)	Reference		
NH/rehab/LTACH	3 (12)	102 (26)	0.4	0.13–1.6	.23
Outside hospital	7 (28)	52 (13)	2.13	0.83–5.48	.12
Prior hospital admission (90 d)					
Yes	21 (84)	255 (65)	2.80	0.94–8.32	.06
No	4 (16)	136 (35)	Reference		
Length of hospital stay prior to BSI					
CO-MRSA (≤ 3 days)	14 (5)	249 (64)	Reference		
HO-MRSA (> 3 days)	11 (44)	142 (36)	1.38	0.61–3.12	.44
Hemodialysis					
Yes	10 (40)	61 (16)	3.61	1.55–8.40	.003
No	15 (60)	330 (84)	Reference		
Presence of invasive device[b]					
Yes	22 (88)	286 (73)	2.69	0.79–9.18	.11
No	3 (12)	105 (27)	Reference		
Invasive procedures[c]					
Yes	13 (52)	165 (42)	1.48	0.66–3.34	.34
No	12 (48)	226 (58)	Reference		
Wound present[d]					
Yes	14 (56)	216 (55)	1.03	0.46–2.33	.94
No	11 (44)	175 (45)	Reference		

(*Continued*)

Table 1. (Continued)

Characteristic	Cases (n = 25), No. (%)	Controls (n = 391), No. (%)	Odds Ratio	95% Confidence Interval	P Value
Charlson comorbidity index[e]					
0–3	7 (28)	112 (29)	Reference		
4–5	3 (12)	90 (23)	0.53	0.13–2.12	.37
6–8	9 (36)	120 (31)	1.20	0.43–3.33	.73
>8	6 (24)	69 (18)	1.39	0.45–4.31	.57
History of transplant[f]					
Yes	3 (12)	49 (13)	0.95	0.27–3.30	.94
No	22 (88)	342 (87)	Reference		
History of MRSA colonization[g]					
Yes	19 (76)	137 (35)	5.87	2.29–15.05	<.001
No	6 (24)	254 (65)	Reference		
Presumed source of MRSA BSI					
Skin infection	7 (28)	136 (35)	0.73	0.30–1.79	.49
Pneumonia	1 (4)	42 (11)	0.35	0.05–2.63	.31
Vascular access	9 (36)	103 (26)	1.57	0.67–3.67	.30
Other[h]	7 (28)	115 (29)	0.93	0.38–2.29	.88
Bacteremic duration, median (IQR)[i]	5.0 (0.0– 13.0)	3.0 (1.0–5.0)	1.10	1.04–1.16	< .001
Polymicrobial					
Yes	3 (12)	44 (11)	1.08	0.31–3.74	.91
No	22 (88)	347 (89)	Reference		
ICU admission prior to BSI					
Yes	7 (32)	64 (17)	1.99	0.80–4.95	.14
No	18 (68)	327 (83)	Reference		
Intubated prior to BSI					
Yes	7 (28)	72 (18)	1.72	0.69–4.28	.24
No	18 (72)	319 (82)	Reference		

Note. BSI, bloodstream infection; HIV, human immunodeficiency virus; NH, nursing home; LTACH, long-term acute care hospital; MRSA, methicillin-resistant *Staphylococcus aureus*. CO, community-onset; HO, hospital-onset; IQR, interquartile range; ICU, intensive care unit; MIC, minimum inhibitory concentration.
[a]Included nonmedical residences such as home, group homes, assisted living facilities, and homeless shelters.
[b]Included pacemaker, implantable cardioverter defibrillator (ICD), left ventricular-assist device (LVAD), vascular access (excluding peripheral intravenous catheters), orthopedic hardware, nephrostomy, suprapubic catheter, ileal conduit, foley catheter, arteriovenous graft placement (AVG), percutaneous endoscopic gastrostomy (PEG) tube, or ostomy.
[c]Included any invasive procedures or surgery occurring within 1 month before first positive blood culture for MRSA, excluding electroencephalogram (EEG), electrocardiogram (EKG), and transthoracic echocardiogram (TTE).
[d]Included presence of a chronic skin wound overlying the sacrum, limb, abdomen, or other body part.
[e]Refer to standard definitions for CCI.
[f]Included solid organ and bone marrow transplant.
[g]Any positive culture from urine, sputum, tissue, or nares with MRSA prior to the positive MRSA blood culture or a documented history of prior MRSA infection or colonization.
[h]MRSA infection from urinary source, osteomyelitis, surgical site infection, spinal infection, septic arthritis or cardiac device infection, or an unknown/not reported source.
[i]Measured as time to development of elevated vancomycin MIC for cases and time to clearance of BSI in controls.

performed univariable logistic regression on outcome variables with being a case or control as a predictor. A *P*-value approximating $P \leq .05$ was considered notable for potential significance. Analyses were performed in R version 4.0.4 software.[7]

This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai (protocol nos. 13-00981 and 17-00825). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Results

Over the 5-year period (2014–2019), 25 (6%) of 416 of adults with MRSA BSI had an isolate with a vancomycin MIC ≥ 2 μg/mL. Overall, 9 patients had an MIC ≥ 2 μg/mL on initial cultures.

Among them, 4 patients were transferred from other hospitals; thus, culture information was not available. All 25 cases were previously exposed to vancomycin.

Cases had higher odds of baseline hemodialysis (odds ratio [OR], 3.61; 95% confidence interval [CI], 1.55–8.40; *P* = .003) and a history of MRSA colonization (OR, 5.87; 95% CI, 2.29–15.05; *P* < .001) (Table 1). Although only approaching significance, cases had higher odds of hospital admission in the prior 90 days (OR, 2.80; 95% CI, 0.94–8.32; *P* = .06). Ability to achieve source control did not differ between the groups. The frequency of elevated vancomycin MIC did not increase over the study period.

An outcome analysis revealed a 2.62 higher odds of recurrent MRSA BSI in cases (95% CI, 0.99–6.94; *P* = .05) (Table 2).

Table 2. Outcomes of Cases with MRSA BSI with MIC ≥ 2 µg/mL Compared With Controls

Outcome	Cases (n = 25), No. (%)	Controls (n = 391), No. (%)	Odds Ratio	95% Confidence Intervals	*P* Value
90-d mortality					
Yes	7 (28)	116 (30)	0.92	0.37–2.27	.86
No	18 (72)	275 (70)	Reference		
90-d mortality related to MRSA					
Yes	4 (57)	77 (66)	0.68	0.14–3.17	.62
No	3 (43)	39 (34)	Reference		
Missing	18	275			
> 50% rise in creatinine[a]					
Yes	10 (63)	140 (41)	2.42	0.86–6.80	.09
No	6 (37)	203 (59)	Reference		
Missing	9	48			
Recurrent bacteremia[b]					
Yes	6 (24)	42 (11)	2.62	0.99–6.94	.05
No	19 (76)	349 (89)	Reference		
ICU admission after BSI					
Yes	7 (28)	88 (23)	1.34	0.54–3.31	.53
No	18 (72)	303 (77)	Reference		
Intubated after BSI					
Yes	4 (16)	55 (14)	1.16	0.38–3.52	.79
No	21 (84)	331 (86)	Reference		
Missing	0	7			
Metastatic infection[c]					
Yes	10 (40)	74 (19)	2.86	1.23–6.61	.01
No	15 (60)	317 (81)	Reference		
Endocarditis					
Yes	5 (50)	32 (43)	1.31	0.35–4.92	.69
No	5 (50)	42 (57)	Reference		
Missing	15	317			
Days from BSI to discharge, median (IQR)	34 (15–47)	15 (8–24)	1.55	0.97–2.49	.07

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range
[a]Excluding patients on dialysis
[b]Positive blood culture over 30 days after the last positive blood culture
[c]Distal or secondary infection, anatomically unrelated to the primary site of infection, presenting during index admission of MRSA BSI. Includes infective endocarditis, septic pulmonary emboli, vertebral osteomyelitis, septic arthritis, iliopsoas abscess.

Cases also had a 2.86 (95% CI, 1.23–6.61) higher odds of developing metastatic infection during their index admission for BSI (*P* = .01). Median time to discharge after initial positivity reached borderline significance at 34 days for cases (IQR, 15–47) compared with 15 days (IQR, 8–24) for controls (95% CI, 0.97–2.49; *P* = .07). Mortality rates did not differ.

All 25 cases were initially treated with vancomycin monotherapy, and 7 patients (28%) completed treatment with vancomycin despite the elevated MIC because clinical response was achieved. For the remaining 18 patients (72%) who were switched from vancomycin, several reasons were documented: increasing MIC (n = 4), failure to clear cultures (n = 5), synergy of combination therapy (n = 5), persistent fevers (n = 1), difficulty dosing (n = 1), and lost parenteral access (n = 2). In 4 cases, regimens were adjusted due to detection of heterogeneous vancomycin-intermediate *S. aureus* (hVISA), but hVISA testing was stopped in 2016 and no longer influenced decision making.

Antibiotics utilized for the 18 cases (72%) that were switched from vancomycin therapy varied. Monotherapy was adjusted to daptomycin (n = 10), linezolid (n = 4), or telavancin (n = 1). Combination regimens included use of β-lactams (daptomycin-nafcillin, daptomycin-cefazolin, vancomycin-cefazolin, linezolid-cefazolin), and dual MRSA coverage (vancomycin-trimethoprim–sulfamethoxazole, vancomycin-daptomycin, linezolid-ceftaroline, vancomycin-ceftaroline, daptomycin-ceftaroline). Others included linezolid-tigecycline, and vancomycin-gentamicin. Adjunctive rifampin was used in 4 cases to clear bacteremia and reduce biofilm in disseminated infections. Three cases died or eloped prior to MIC elevation, and adjustments were not applicable.

Discussion

Management of invasive *S. aureus* is complicated by MRSA harboring elevated vancomycin MICs,[1] which were present in 6% of the population with MRSA BSI in this study. Cases had higher odds of a personal history of MRSA colonization and hemodialysis, consistent with prior findings.[4] Increased MRSA colonization in patients with frequent healthcare interactions has been established,[8] and frequent healthcare interaction in turn increases risk of cumulative antibiotic exposure, especially vancomycin, which is a known cause of elevated MIC.[4] Elevated vancomycin MIC was associated with metastatic infection but not increased mortality.

A survey of ID providers demonstrated variability in strategies for elevated vancomycin MICs.[5] In our case series, rationales differed, often attributed to the elevated MIC or to failure to clear bacteremia. The most common alternative treatment was switching from vancomycin to daptomycin. Although salvage combination therapy was also utilized, this practice is based on case reports and series and requires randomized controlled studies.[9] From the stewardship perspective, elevated MIC to vancomycin poses a unique challenge because, while susceptible, it prompts providers to adjust therapeutics. Minejima et al[10] did not find antibiotic choice a significant factor in duration of bacteremia or outcome, and changing antibiotics may have unintended consequences of increased antibiotic class exposures, leading to potential drug resistance and toxicities without clear benefit.

Because MICs may vary between testing platforms, we selected a stringent MIC cutoff for case identification (MIC $\geq$ 2 µg/mL) to minimize testing variability, although we may have missed isolates for lack of serial MIC testing. Single-center, retrospective series are predisposed to inaccuracies from chart abstraction. Although all study patients received vancomycin, total vancomycin days were difficult to determine; we could not account for prior vancomycin exposure or antibiotic discontinuation in conjunction with palliation. Lastly, it is challenging to determine directionality when there is increased MIC and metastatic complications, where the metastatic infection may be a risk factor for the elevated vancomycin MIC.

References

1. Liu C, Bayer A, Cosgrove SE, Daum RS. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* Infections in Adults and children: executive summary. *Clin Infect Dis* 2011;52:285–292.
2. Mwangi MM, Wu SW, Zhou Y, *et al.* Tracking the in vivo evolution of multidrug resistance in *Staphylococcus aureus* by whole-genome sequencing. *Proc Natl Acad Sci U S A* 2007;104:9451–9456.
3. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing.* 31st Ed. CLSI Supplement m100. Malvern, PA: CLSI; 2021.
4. Chen SY, Hsueh PR, Chiang WC, *et al.* Predicting high vancomycin minimum inhibitory concentration isolate infection among patients with community-onset methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Infect* 2014;69:259–265.
5. Liu C, Strnad L, Beekmann SE, Polgreen PM, Chambers HF. Clinical practice variation among adult infectious disease physicians in the management of *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2019;69:530–533.
6. Dupper AC, Sullivan MJ, Chacko KI, *et al.* Blurred molecular epidemiological lines between the two dominant methicillin-resistant *Staphylococcus aureus* clones. *Open Forum Infect Dis* 2019;6:ofz302.
7. Ripley BD, Others. The R project in statistical computing. *MSOR Connections The newsletter of the LTSN Maths, Stats & OR Network.* 2001;1:23–25.
8. Gorwitz RJ, Kruzon-Moran D, McAllister SK, *et al.* Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001–2004. *J Infect Dis* 2008;197:1226–1234.
9. Rose W, Fantl M, Geriak M, Nizet V, Sakoulas G. Current paradigms of combination therapy in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia: does it work, which combination and for which patients? *Clin Infect Dis* 2021;73:2353–2360.
10. Minejima E, Mai N, Bui N, *et al.* Defining the breakpoint duration of *Staphylococcus aureus* bacteremia predictive of poor outcomes. *Clin Infect Dis* 2020;70:566–573.