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CLINICAL THERAPEUTICS

A Retrospective Analysis of Treatment and Clinical Outcomes among Patients with Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Isolates Possessing Detectable *mecA* by a Commercial PCR Assay Compared to Patients with Methicillin-Resistant *Staphylococcus aureus* Bloodstream Isolates

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ABSTRACT *mecA*-positive *Staphylococcus aureus* isolates phenotypically susceptible to cefoxitin (*mecA*-methicillin-sensitive *S. aureus* [MSSA]) have been identified. We describe the treatment and outcomes among patients with *mecA*-MSSA bloodstream infections (BSI) and MRSA BSI matched 1:1 for age, BSI origin, and BSI type ($n = 17$ per group). Compared to MRSA BSI patients, *mecA*-MSSA BSI patients more often experienced clinical failure (58.8% and 11.8%, $P = 0.010$), driven largely by persistent bacteremia (35.3% and 11.8%). *mecA*-MSSA BSI patients may be at higher risk for poor clinical outcomes.

KEYWORDS bacteremia, *mecA* PCR, *mecA*-positive methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus*, vancomycin

mecA-positive *Staphylococcus aureus* isolates (detected using molecular diagnostic assays) that exhibit cefoxitin susceptibility (*mecA*-methicillin-sensitive *S. aureus* [MSSA]) are being reported with increasing frequency; approximately 3% of *S. aureus* isolates may be *mecA*-MSSA (1). This phenotypic/genotypic discrepancy is concerning and may lead to the mischaracterization of methicillin susceptibility, which could expose patients to inferior antibiotic therapy (e.g., vancomycin for MSSA). We sought to characterize the treatment and outcomes of *mecA*-MSSA bloodstream infections (BSI) using methicillin-resistant *S. aureus* (MRSA) BSI as a comparator.

This was a retrospective comparative study of adult patients with *mecA*-MSSA and MRSA BSI within a single health system from 1 January 2010 through 30 August 2015. Patients <18 years of age, with polymicrobial BSI, who had an initial vancomycin MIC of ≥2 mg/liter, and/or who lacked 30-day follow up were excluded. Patients with *mecA*-MSSA BSI were matched 1:1 with MRSA BSI patients based on the following criteria shown to be predictive of mortality in *S. aureus* bacteremia: age (±15 years), primary type of BSI, and origin of bacteremia (2). *mecA*-MSSA was defined as an *S. aureus* isolate possessing detectable *mecA* by a modified commercial PCR assay (BD GeneOhm StaphSR assay; BD Diagnostics, Sainte-Foy, Quebec, Canada) but susceptibility to oxacillin (MIC, ≤2 mg/liter) by automated susceptibility testing (Vitek 2; bioMérieux, Durham, NC) and cefoxitin disk diffusion (zone of inhibition, ≥22 mm) (3, 4). MRSA was defined as *S. aureus* with an automated oxacillin MIC of >2 mg/liter, confirmed by cefoxitin disk diffusion (zone of inhibition, ≤21 mm), and detectable *mecA* by a modified commercial PCR assay (3, 4).

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Primary BSI type was classified as infective endocarditis (using the modified Duke criteria), uncomplicated bacteremia, or complicated bacteremia (5, 6). Uncomplicated bacteremia was defined by the isolation of *mecA*-MSSA or MRSA from blood cultures in patients without endocarditis, without implanted prostheses, having negative follow-up blood cultures obtained 2 to 4 days after the index culture, defervescence within 72 h of initiating effective therapy, and no evidence of metastatic sites of infection (5, 7). Patients not meeting the definition for uncomplicated BSI or infective endocarditis were classified as complicated BSI (5, 6). The source of bacteremia and severity of illness (Pitt bacteremia score) were categorized as previously described (8, 9). Clinical failure was a composite endpoint that included 30-day mortality, persistent bacteremia (≥7 days), and/or change of intravenous antibiotic(s) or addition of a second antibiotic targeted against *mecA*-MSSA or MRSA necessitated by a lack of infection resolution. Secondary outcomes of interest included length of stay and nephrotoxicity, as defined by the vancomycin consensus guidelines (10). This study was approved by the Wheaton Franciscan Healthcare institutional review board and was conducted in accordance with the Declaration of Helsinki. Continuous variables were summarized using the mean and standard deviation (SD) or the median and interquartile range (IQR). Two-sample *t* tests or Wilcoxon rank sum tests were used to compare the two groups. Categorical variables were summarized using frequencies and percentages and compared between the two groups using the likelihood ratio χ^2 or Fisher's exact test.

Twenty-six patients with *mecA*-MSSA BSI were identified. Of these, nine patients were excluded on the basis of: age ($n = 1$), irretrievable data in the medical record ($n = 7$), and insufficient follow-up data ($n = 1$). The 17 remaining *mecA*-MSSA patients were successfully matched with a MRSA BSI comparator ($n = 34$ total patients). No major differences between the two study groups in baseline characteristics were observed (Table 1). The proportion of patients with renal disease, a strong predictor of mortality in *S. aureus* bacteremia, was 29.4% in both groups; however, there were more patients on intermittent hemodialysis in the MRSA group (3 versus 1, respectively; $P = 0.601$) (2). All patients in the study were treated by an infectious diseases physician, and 94.1% of the patients received empirical vancomycin therapy in both groups.

Patients with *mecA*-MSSA BSI were more likely to experience clinical failure than those with MRSA BSI (58.8% versus 11.8%, respectively; $P = 0.010$), and patients with *mecA*-MSSA BSI tended to experience persistent bacteremia (35.3% versus 11.8%, respectively; $P = 0.225$). Salvage antibiotic therapy was employed in 10 (58.8%) and 2 (11.8%) of patients in the *mecA*-MSSA and MRSA groups, respectively (Table 2). Combination antibiotic therapy was used as salvage therapy in all of these cases, with the exception of one patient with *mecA*-MSSA BSI who received ceftaroline monotherapy. The median length of stay and infection-related length of stay both trended longer for the *mecA*-MSSA group than for the MRSA group. Nephrotoxicity was observed more frequently in the *mecA*-MSSA group than in the MRSA group (23.5% versus 0%, respectively; $P = 0.100$), despite similar rates of renal disease between groups.

In the current study, patients with *mecA*-MSSA bacteremia experienced clinical failure more often than matched patients with MRSA bacteremia. Failure was primarily driven by persistent bacteremia in the *mecA*-MSSA group, but clinical outcomes, such as mortality and length of stay, were similar between groups. Nearly all patients who experienced failure had complicated BSI. Given the well-matched groups, this difference in clinical failure is unlikely due to host-level factors, although it could be a result of an unmeasured host factor. It remains more plausible, based on our observations, that either vancomycin monotherapy contributed to the delayed bacterial clearance observed in the *mec*A-MSSA group, or intrinsic virulence differences between these two strains of *S. aureus* led to longer durations of bacteremia in the *mecA*-MSSA group. These results expose yet another limitation of vancomycin monotherapy for the treatment of MRSA bacteremia.

Almost all *mecA*-MSSA patients received vancomycin initially, likely because the CLSI recommends reporting *mecA*-positive *S. aureus* as cefoxitin resistant. During the study

TABLE 1 Patient demographics, clinical characteristics, antibiotic treatment, and clinical outcomes[a]

Variable	Treatment group		*P* value
	mecA-MSSA (*n* = 17)	MRSA (*n* = 17)	
Baseline characteristics			
Age (mean ± SD) (yr)	66 ± 15	63 ± 18	0.642
Male	12 (70.6)	9 (52.9)	0.481
Race			0.999
Caucasian	14 (82.4)	12 (76.5)	
Other	3 (17.6)	4 (23.5)	
Source of bacteremia			0.913
Bone/joint	6 (35.3)	6 (35.3)	
Skin and skin structure	6 (35.3)	5 (29.4)	
Other[b]	5 (29.4)	6 (35.3)	
Past medical history			
Previous hospitalization	7 (42.2)	11 (64.7)	0.303
Previous surgery	3 (17.6)	4 (23.5)	0.999
Previous *S. aureus* infection	0 (0)	2 (11.8)	0.485
Injection drug use	1 (5.9)	2 (11.8)	0.999
Prosthesis	9 (52.9)	5 (29.4)	0.296
Renal disease	5 (29.4)	5 (29.4)	0.999
Hemodialysis	1 (5.9)	3 (17.6)	0.601
Liver disease	2 (11.8)	0 (0)	0.485
Congestive heart failure	8 (47.1)	6 (35.3)	0.728
Diabetes mellitus	10 (58.8)	8 (47.1)	0.732
Cancer	3 (17.6)	1 (5.9)	0.601
Antibiotic exposures within 30 days of hospitalization	3 (17.6)	6 (35.3)	0.438
Pitt bacteremia score (median [IQR])	1.0 (0, 2.5)	1.0 (0, 2.0)	0.683
Complicated bacteremia	8 (47.0)	8 (47.0)	0.999
Vancomycin MIC (median [IQR]) (mg/liter)	1.0 (0.5, 1.0)	0.5 (0.5, 1.0)	0.563
Vancomycin MIC_{90} (mg/liter)	1.0	1.0	
Oxacillin MIC_{90} (mg/liter)	0.5	>4.0	
Concomitant site(s) of *S. aureus* infection	10 (58.8)	8 (47.0)	0.721
Procedure performed to mitigate complications of *S. aureus* bacteremia	9 (52.9)	10 (58.8)	0.999
Antibiotic therapy			
Vancomycin	16 (94.1)	16 (94.1)	0.999
Initial vancomycin trough (median [IQR]) (mg/liter)	12.9 (9.73, 18.48)	12.9 (10, 15)	0.696
Time to therapeutic vancomycin trough (median [IQR]) (days)[c]	4 (3, 8)	5 (3, 7)	0.796
Change in antistaphylococcal therapy	14 (82.4)	10 (58.8)	0.259
No. of changes in antistaphylococcal therapy (median [IQR])	1 (0, 2)	0 (0, 0.5)	0.007
Use of salvage antibiotic therapy	10 (58.8)	2 (11.8)	0.010
Salvage antibiotic therapy type			>0.999
Combination antibiotic therapy	9 (90.0)	2 (100)	
Ceftaroline monotherapy	1 (10.0)	0 (0)	
Clinical outcomes			
Clinical failure[d]	10 (58.8)	2 (11.8)	0.010
30-day, all-cause mortality	1 (5.9)	1 (5.9)	>0.999
Persistent bacteremia (≥7 days)	6 (35.3)	2 (11.8)	0.225
Change in antibiotic therapy due to lack of infection resolution	10 (58.8)	1 (5.9)	0.002
Duration of bacteremia (median [IQR]) (days)	3.5 (1.25, 7.75)	3 (3, 5)	0.901
Bacteremia clearance on vancomycin monotherapy	5 (29.4)	13 (76.5)	0.015
Recurrence of *S. aureus* infection within 1 yr	0 (0)	2 (11.8)	0.484
Readmission within 60 days of initial hospital discharge	6 (35.3)	6 (35.3)	0.999
Length of stay (median [IQR]) (days)	16 (10, 21)	14 (9, 18)	0.496
Infected-related length of stay (median [IQR]) (days)	14 (9, 18)	11 (9, 16)	0.357
Nephrotoxicity	4 (23.5)	0 (0)	0.103

[a]All data presented are as no. (%), unless otherwise noted. IQR, interquartile range.
[b]Includes endocarditis, intravenous catheter, genitourinary, central nervous system, and unknown source.
[c]Therapeutic serum vancomycin trough, 15 to 20 mg/liter.
[d]Clinical failure was a composite definition of 30-day, all-cause mortality, persistent bacteremia (≥7 days), and/or change in antibiotic therapy due to lack of infection resolution; some patients met more than one clinical failure criterion.

TABLE 2 Detailed antibiotic exposure, procedures, and outcomes among patients with *mecA*-MSSA and MRSA bacteremia

Patient age (yr)/sex[a]	BSI type[b]	Pitt score	MIC (mg/liter)[c]		Primary infection[d]	Antibiotic therapy and/or procedure to mitigate complications[e]				Reason(s) for clinical failure; outcome[f]
			VAN	OXA		1st line	2nd line	3rd line	4th line	
*mec*A-MSSA[g]										
89/M	Endocarditis	1	≤0.5	≤0.5	SSTI	LZD D2–4	CFZ+GEN D5–9	DAP+GEN D9–11; DAP+GEN D11–13	DAP D14	1, 2, 3; BSI cleared D12; expired D14
59/M	Complicated	2	1	≤0.5	Bone/joint	VAN+TZP+CLI D1–2	NAF+VAN D2–3; NAF D4–10; I&D joint D3	VAN D10–13; AKA D13	LZD+RIF D13–29	2, 3; BSI cleared D16
74/M	Uncomplicated	0	≤0.5	≤0.5	Bone/joint	VAN D2–4	VAN+MEM D4–10; VAN D10–17			3; BSI cleared D2
76/M	Uncomplicated	1	1	≤0.5	Bone/joint	VAN+CRO D1–3	VAN D4–9	CPT D9–16		3; BSI cleared D3
74/F	Complicated	1	1	≤0.25	Bone/joint	VAN+TZP D1–3	VAN+CPT+GEN D3–6; I&D, placement of antibiotic spacer D4	CFZ+DOX D6–9	VAN+DOX D9–13	3; BSI cleared D3
70/M	Complicated	2	1	≤0.25	GU	VAN D1–2	VAN+CPT D2–4	VAN+NAF+DOX D4–6; NAF+GEN+DOX D7–13	DOX+NAF D13–17	2, 3; BSI cleared D8
61/M	Endocarditis	1	≤0.5	≤0.5	SSTI	VAN D1–3	VAN+CPT D3–6	VAN+CFZ D6–17; AICD removed D7	VAN+TZP D17–54	2, 3; BSI cleared D9
60/F	Complicated	0	1	≤0.5	Bone/joint	VAN D1–6	DAP D6–10			3; BSI cleared D5
27/F	Endocarditis	6	≤0.5	≤0.25	IVDU	VAN+TZP D1–6	DAP+NAF D6–25			2, 3; BSI cleared D10
59/F	Complicated	0	≤0.5	≤0.25	CNS	VAN D1–3; spinal abscess drainage D2	VAN+CFZ+GEN D3–6	NAF+GEN D6–11		2, 3; BSI cleared D9
52/M	Uncomplicated	2	≤0.5	≤0.5	Bone/joint	VAN D1–8; AKA D3				None; BSI cleared D4
59/M	Uncomplicated	3	1	0.5	i.v. catheter (HD)	VAN+TZP D1–7; VAN D7–13; venous catheter changed D1, D2				None; BSI cleared D2
66/M	Uncomplicated	6	≤0.5	0.5	Bone/joint	VAN D1–19				None; BSI cleared D2
50/M	Uncomplicated	0	1	0.5	SSTI	VAN+GEN D1–7; VAN D7–16				None; BSI cleared D4
74/M	Endocarditis	5	≤0.5	≤0.25	Unclear source	VAN+TZP D1–7 (GEN ×1 D1)	VAN+GEN+RIF D7–14			None; BSI cleared D5
82/F	Uncomplicated	0	1	0.5	SSTI	VAN+TZP D1–2; VAN D2–6; myectomy, sacral ulcer debridement D3				None; BSI cleared D2
88/M	Uncomplicated	0	1	0.5	Bone/joint	VAN D1	VAN+CPT D2–4; removal of knee hardware D3	VAN+CFZ D4–5; CFZ D5–7		None; BSI cleared D4
MRSA										
55/M	Uncomplicated	1	≤0.5	≥4	Bone/joint	VAN D1–10				None; BSI cleared D3
63/M	Uncomplicated	2	1	≥4	i.v. cath (HD)	VAN D1–8; catheter change D1				None; BSI cleared D3
77/M	Endocarditis	1	≤0.5	≥4	SSTI	VAN D1–11				None; BSI cleared D2
54/M	Complicated	3	1	≥4	Bone/joint	VAN D1–2	VAN+CLI+NAF D2–3; I&D of knee, hardware not removed D3	VAN+CLI+CPT D3–5	VAN+DOX D5–14	None; BSI cleared D3
82/F	Uncomplicated	1	≤0.5	≥4	SSTI	VAN D1–11				None; BSI cleared D2
63/F	Uncomplicated	3	≤0.5	≥4	Bone/joint (HD)	VAN D1–16; leg/foot and bone removal D4; BKA D10				None; BSI cleared D2
62/M	Uncomplicated	0	1	≥4	Bone/joint	VAN D1–6				None; BSI cleared D4
38/F	Uncomplicated	0	≤0.5	≥4	SSTI	VAN D1–18; I&D D5				None; BSI cleared D3
84/F	Complicated	1	1	≥4	Bone/joint	VAN D–10; infected hardware not removed				None; BSI cleared D5
85/F	Endocarditis	0	1	≥4	IE	VAN D1–7	CPT+DAP D7–13	CPT D13–15; went to hospice D15		1, 2, 3; BSI never cleared, expired D16
69/M	Uncomplicated	2	≤0.5	≥4	SSTI	VAN D1–6; abscess I&D D3				None; BSI cleared D2
92/F	Uncomplicated	0	≤0.5	≥4	SSTI	VAN D1–7; abscess I&D D1				None; BSI cleared D3
70/M	Complicated	0	≤0.5	≥4	GU	VAN D1–9				None; BSI cleared D6

(Continued on following page)

TABLE 2 (Continued)

Patient age (yr)/sex[a]	BSI type[b]	Pitt score	MIC (mg/liter)[c]		Primary infection[d]	Antibiotic therapy and/or procedure to mitigate complications[e]				Reason(s) for clinical failure; outcome[f]
			VAN	OXA		1st line	2nd line	3rd line	4th line	
46/M	Endocarditis	1	≤0.5	≥4	i.v. cath	VAN D1–4; mitral valve replacement D3	DAP D4–12			None; BSI cleared D3
62/F	Complicated	2	1	≥4	Bone/joint	VAN D1–3	VAN+DAP D3–6; BKA D4	VAN D6–19		None; BSI cleared D2
23/F	Endocarditis	1	1	≥4	IVDU	VAN D1	DAP D2–8	DAP+DOX D9–16		2; BSI cleared D9
49/M	Complicated	1	1	≥4	CNS foci	VAN D1–4	CPT D4–21[h]; spinal surgery D14			None; BSI cleared D6

[a]M, male; F, female.

[b]Endocarditis, infective endocarditis; Complicated, complicated bacteremia; Uncomplicated, uncomplicated bacteremia.

[c]VAN, vancomycin; OXA, oxacillin.

[d]SSTI, skin and soft tissue infection; GU, genitourinary; IVDU, intravenous drug use; CNS, central nervous system; i.v., intravenous; HD, hemodialysis; cath, catheter; IE, infective endocarditis.

[e]D, day of therapy; LZD, linezolid; CFZ, cefazolin; GEN, gentamicin; DAP, daptomycin; TZP, piperacillin-tazobactam; CLI, clindamycin; NAF, nafcillin; RIF, rifampin; I&D, incision and drainage; AKA, above-knee amputation; MEM, meropenem, CRO, ceftriaxone, CPT, ceftaroline; DOX, doxycycline AICD, automated, implantable cardioverter-defibrillator; BKA, below-knee amputation.

[f]1, 30-day mortality; 2, persistent bacteremia (≥7 days); 3, change of intravenous antibiotic(s) or addition of a second antibiotic targeted against *mecA*-MSSA or MRSA necessitated by lack of infection resolution.

[g]*mecA*-MSSA result in the medical record accompanied by the following note: "*mecA* gene also detected within *Staphylococcus aureus* isolate. Detection of *mecA* gene (methicillin resistance) by PCR, in the context of methicillin-susceptible *Staphylococcus aureus* isolation (as determined by cefoxitin susceptibility testing), suggests the presence of partial *mecA* deletion in this isolate. Please contact the microbiology laboratory if you have additional questions."

[h]Change from vancomycin to ceftaroline was due to acute renal failure while on vancomycin, not a lack of infection resolution, as per the attending physician's note.

period, physicians were notified of positive *mecA* PCR results before susceptibility data became available. Antibiotic selection after vancomycin varied in this group, and the majority of patients improved on these regimens (Table 2). It is notable that of the 10 patients who experienced failure, all but one had complicated BSI. A higher bacterial inoculum is likely with complicated bacteremia, especially infective endocarditis (11). Given the 10^{-7} reversion rate from *mecA*-MSSA to MRSA demonstrated by Proulx and colleagues, there may be more MRSA involved with complicated *mecA*-MSSA infections (1). Our results do not demonstrate that the initial use of a β-lactam in combination with vancomycin or daptomycin improved outcomes for *mecA*-MSSA patients, but for complicated *mecA*-MSSA bacteremia, especially infective endocarditis, combination antibiotic therapy targeting MRSA and MSSA may be warranted. Additionally, cefoxitin has affinity for the low-molecular-weight penicillin-binding protein 4 (PBP4). PBP4 overexpression in *S. aureus* results in highly cross-linked cell walls and elevated β-lactam MICs (12). Conversely, lesser cross-linked *S. aureus* cell walls are associated with elevated vancomycin MICs (13). The cefoxitin-susceptible phenotype of the *mecA*-MSSA isolates may represent both reduced expression of PBP4 and vancomycin tolerance; interestingly, the median vancomycin MIC was higher in the *mecA*-MSSA group than the MRSA group. Given that the majority of patients in both groups received initial therapy with vancomycin, the difference in vancomycin MICs between groups may also explain the observed difference in persistent bacteremia between groups.

Our study is limited by its retrospective design, small sample, and restriction to a single health system in one geographic area of the United States. Additionally, bacterial isolates were not secured for additional laboratory analyses, nor did we have daptomycin and ceftaroline MICs for these isolates. However, the collected microbiological data represent what is available to clinicians, and this is the first clinical evaluation of *mecA*-MSSA to include more than two patients from a single center (1, 14). We believe these results should prove informative for clinicians confronted with *mecA*-MSSA BSI. It is clear from these data that the treatment of *mecA*-MSSA poses a unique challenge for infectious diseases clinicians and requires additional attention.

In summation, *mecA* PCR testing and the potential for a discrepancy between genotypic and phenotypic cefoxitin resistance results among *S. aureus* isolates have further complicated the treatment of *S. aureus* BSI. The description of *mecA*-positive *S. aureus* as cefoxitin resistant should be reevaluated, as this may predispose patients to vancomycin therapy, especially if physicians are notified of *mecA* PCR results before susceptibility results. Our data suggest that vancomycin monotherapy for *mecA*-MSSA BSI may place patients at risk for clinical failure.

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