Vancomycin monotherapy vs. combination therapy for the treatment of persistent methicillin-resistant *Staphylococcus aureus* bacteremia

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Persistent MRSA bacteremia is associated with complications such as infective endocarditis, leading to worse clinical outcomes including longer hospitalization and increased mortality.[1,2] Specific genotypes (e.g., accessory gene global regulator [agr] group II),[3] higher vancomycin minimum inhibitory concentration (MIC),[4] prior vancomycin use,[3] presence of heterogeneous vancomycin intermediate *S. aureus* (hVISA),[5,6] metastatic infections,[7] retained implants,[7] and inadequate source control[7] are associated with persistent MRSA (pMRSA) bacteremia. Predictors of mortality in MRSA bacteremia include higher MICs,[8-13] age greater than 65 y,[14] delay in appropriate antibiotic therapy,[14,15] inadequate vancomycin levels,[10] metastatic infections,[13] higher Charlson comorbidity index,[9] and presence of malignancy.[2,10]

Clinical and microbiologic failures are common when treating invasive MRSA infections.[16] There are limitations to the current antibiotics available. Vancomycin failures have been linked to its slow bactericidal activity, the emergence of strains with reduced susceptibility due to higher MICs or the presence of hVISA.[16] The Infectious Diseases Society of America 2011 MRSA treatment guidelines recommend considering modifying therapy when there is persistent MRSA bacteremia of 7 d or longer, with a change in antibiotic preferred rather than the addition of other antibiotics to vancomycin. This is mainly due to studies suggesting treatment successes with alternative salvage therapy such as daptomycin, coupled with the lack of published efficacy with combination therapy.[16] Nevertheless, none of the alternative antibiotics have been conclusively proven to be superior to vancomycin.[16]

Although there are limited studies that explored combination therapy in MRSA bacteremia,[13,17-19] it is still used in clinical practice. A survey of physicians in the United Kingdom found that almost half would consider adding rifampicin for complicated MRSA infections such as infective endocarditis or orthopedic infections.[20] Furthermore, a multicenter evaluation in the United Kingdom and Vietnam found that 40% of patients were treated with combination of antibiotics for at least part of their treatment course for MRSA bacteremia.[21]

Hence, this study aimed to evaluate the efficacy of add-on combination therapy vs. vancomycin monotherapy in adults with persistent MRSA (pMRSA) bacteremia. In addition, we assessed the risk factors associated with 30-d mortality in this group of patients.

We conducted a retrospective study at an acute care teaching hospital in Singapore. All patients more than 18 y old with persistent MRSA bacteremia (defined as repeated consecutive positive blood cultures after 7 d from the first positive blood culture[16]) from 1 January 2006 to 31 December 2009 who received either vancomycin monotherapy or add-on combination antibiotics were included. Excluded were patients whose index blood cultures were polymicrobial. Only the first episode of pMRSA bacteremia for each patient was studied. Patients were identified from the microbiology laboratory database, and relevant data extracted from medical charts, and electronic laboratory and pharmacy records. The institutional review board approved the study protocol.

Information collected included patient demographics (age, gender, ethnicity, prior hospitalization, surgery, and MRSA within 6 mo, prior nursing home residence), clinical (dates of admission, discharge, and death, intensive care unit [ICU] admission, mechanical ventilation, dialysis, presence of vascular, and orthopedic implants, Charlson co-morbidity index, Acute Physiology and Chronic Health Evaluation [APACHE] II score, Pitt bacteremia score, source of infection), management (duration of antibiotic use, removal of eradicable foci, vancomycin troughs), microbiologic (blood culture results, MRSA vancomycin MIC, hVISA screening), and outcome data. The primary physician (occasionally with an infectious disease consultation) decided on vancomycin monotherapy or additional combination antibiotics. There was no formal protocol in place for the treatment of persistent MRSA bacteremia during the study period.

Blood culture samples were collected and assayed in the BacT/Alert 3D system (bioMérieux,). Gram staining was done on broth from the bottles when these signaled positive, and those showing gram-positive cocci in clusters were sub-cultured onto blood agar and chocolate agar. A direct antimicrobial susceptibility testing

was also performed on Mueller Hinton agar incubated at 35 °C in ambient air.[22] After overnight incubation, staphylococci-like colonies were further identified using conventional tests to differentiate between *Staphylococcus aureus* and coagulase-negative staphylococci, and an antimicrobial susceptibility test repeated by conventional method.[23] Vancomycin MIC was determined using the Etest strips (AB Biodisk). The Etest macromethod was used for hVISA screening. Results were interpreted as positive for hVISA when vancomycin MIC was ≥4 mg/L with teicoplanin MIC ≥8 mg/L or, when the teicoplanin MIC was ≥12 mg/L.[24] *S. aureus* TTSH 48 (an in-house hVISA strain with a teicoplanin MIC of ≥12 mg/L), and ATCC 29213 (a vancomycin-susceptible *S. aureus* [VSSA] strain) were used as control strains.

The primary outcome was 30-d mortality. Secondary outcomes included in-hospital mortality, infection-related mortality, clinical improvement, microbiologic clearance, duration of bacteremia, length of hospitalization (overall and after positive MRSA bacteremia), and recurrence within 3 mo. Thirty-day mortality was defined as death within 30 d of first positive MRSA blood culture. Death was noted to be infection-related if so indicated on the death certificate. Microbiologic clearance at the end of treatment was defined as eradication of MRSA from blood during or on completion of antibiotic therapy. Microbiologic clearance at day 21 was defined as MRSA eradication within 21 d after the first positive blood culture. Day 21 was chosen to allow the completion of 2 more weeks of therapy, in view of the persistent bacteremia. Clinical improvement at day 14 was noted if there was resolution or improvement in the signs and symptoms of infection at 14 d after the first negative culture. Complicated MRSA infections included metastatic infections such as infective endocarditis, pneumonia, and bone and joint infections. The mean vancomycin trough was calculated using the sum of each measured trough concentration multiplied by the number of days at that level, then divided by the total number of treatment days.[25]

Categorical variables were compared using the Fisher exact test or the Pearson Chi-square test, as appropriate. Continuous variables were tested for normality with the Shapiro–Wilk test. Thereafter, comparison was done using the Student *t* test for variables with normal distributions, or the Mann–Whitney *U* test for non-parametric variables. Univariate analysis of variables associated with 30-d mortality was performed. Variables that were considered clinically relevant or had *P* values <0.1 were then entered into a multivariate logistic regression model, using a stepwise backward (likelihood ratio) method. All tests of significance were two-tailed, with the level of significance set at 0.05. SPSS statistical software version 19 (SPSS Inc.) was used for all statistical analyses.

A total of 86 cases with persistent MRSA bacteremia were identified during the study period and 76 patients were included in the analysis. Among the excluded cases, two were recurrent episodes, and the initial blood cultures of 3 patients were polymicrobial. Another 5 patients were switched to another antibiotic from vancomycin. All remaining 76 patients were initially treated with intravenous vancomycin. Fifty-five patients

Table 1. Combination therapies used in addition to vancomycin

Combinations used	Number	% of total
RIF + FA	12	57.1
RIF + SXT	2	9.5
RIF + GEN	1	4.8
RIF + CIP	1	4.8
RIF	3	14.3
DOX + SXT	2	9.5
Total	21	

RIF, rifampicin; FA, fusidic acid; SXT, sulfamethoxazole–trimethoprim; GEN, gentamicin; CIP, ciprofloxacin; DOX, doxycycline.

remained on vancomycin monotherapy, while 21 patients had other antibiotics added.

The majority of combination therapy included rifampicin, and the most common regimen was vancomycin, rifampicin, and fusidic acid (57.1%) (**Table 1**). The median time to additional combination antibiotics was 15 d (9–71 d).

The demographic and clinical characteristics of patients in both monotherapy and combination groups were shown in **Table 2**. The groups were comparable, with the only significant difference being that more patients in the monotherapy group had a previous MRSA infection in the past 6 mo. Patients had a mean age 64.7 y, 64.5% were males, 61.8% were Chinese, 47.4% were on dialysis, and 84.2% had been hospitalized in the past 6 mo. There were no differences in the proportion of patients with Charlson co-morbidity index ≥3, Pitt bacteremia score ≥4, and in mean APACHE II score. However, the combination group had higher proportions of patients with Pitt bacteremia score ≥4 and Charlson score ≥3, whereas the monotherapy group had more ICU admissions and patients on mechanical ventilation. The commonest sources of infection were infected vascular catheter (46.1%), and bone and joint infection (28.9%). Vancomycin MIC and hVISA screening were determined only for some cases. Samples with index culture vancomycin MICs ≥1.5 mg/L comprised 18.6% (13/70 samples), and only 2 patients had vancomycin MICs ≥2 mg/L. The combination therapy group had slightly more patients (13/21 [61.9%]) with complicated MRSA infections compared with the monotherapy group (23/55, [41.8%]).

Most patients (94.7%) were started on vancomycin within 1–2 d of positive blood culture, and all within the first 72 h. The majority (63.2%) had the infection foci removed within a median of 2.5 d. Mean vancomycin trough levels were similar between groups. The duration of inpatient MRSA antibiotic treatment was significantly longer in the combination group (35 d [15–81 d] vs. 23 d [7–146 d] monotherapy, *P* = 0.033) (**Table 2**).

Five patients who received combination therapy had microbiologic clearance before the addition, and were thus analyzed as part of the monotherapy group for microbiological outcomes (*n* = 60). This was due to a delay of 2–3 d in obtaining culture results. The addition of combination therapy did not significantly change microbiologic clearance rates at the end

Table 2. Demographic, clinical, and treatment characteristics of patients with pMRSA bacteremia

Characteristic	Combination (*n* = 21)	Monotherapy (*n* = 55)	Total (*n* = 76)	*P* value
Age, y, mean ± SD	63.4 ± 13.8	65.2 ± 15.2	64.7 ± 14.8	0.638
Male gender, *n* (%)	12 (57.1)	37 (67.3)	49 (64.5)	0.409
Race, *n* (%)				
Chinese	13 (61.9)	34 (61.8)	47 (61.8)	0.994
Malay	3 (14.3)	12 (21.8)	15 (19.7)	0.538
Indian	5 (23.8)	9 (16.4)	14 (18.4)	0.514
Charlson comorbidity index ≥3, *n* (%)	19 (90.5)	42 (76.4)	61 (80.3)	0.212
Hospitalization in previous 6 mo, *n* (%)	17 (81)	47 (85.5)	64 (84.2)	0.727
Nursing home resident, *n* (%)	1 (4.8)	4 (5.5)	4 (5.3)	1.000
Surgery in previous 6 mo, *n* (%)	10 (47.6)	32 (58.2)	42 (55.3)	0.408
MRSA infection in previous 6 mo, *n* (%)	1 (4.8)	17 (30.9)	18 (23.7)	*0.017*
Hospitalization days before index culture, median (range)	1 (0–37)	1 (0–113)	1 (0–113)	0.182
Source of infection[a]				
Vascular catheter, *n* (%)	11 (52.4)	24 (43.6)	35 (46.1)	0.494
Bone and joint, *n* (%)	8 (38.1)	14 (25.5)	22 (28.9)	0.277
Skin or soft tissue, *n* (%)	4 (19.0)	13 (23.6)	17 (22.4)	0.766
Other concurrent infections present, *n* (%)	15 (71.4)	44 (80.0)	59 (77.6)	0.539
Vascular catheters or orthopedic implants present, *n* (%)	14 (66.7)	37 (67.3)	51 (67.1)	0.960
APACHE II score, mean ± SD[b]	16.0 ± 3.6	15.1 ± 5.5	15.3 ± 5	0.364
Pitt bacteremia score ≥4, *n* (%)	2 (9.5)	2 (3.6)	4 (5.3)	0.305
Intensive care unit admission, *n* (%)	3 (14.3)	16 (29.1)	19 (25.0)	0.183
Mechanical ventilation, *n* (%)	1 (4.8)	13 (23.6)	14 (18.4)	0.095
Dialysis, *n* (%)	12 (57.1)	24 (43.6)	36 (47.4)	0.292
Vancomycin MIC for index culture greater than 1.5 mg/L[c], *n* (%)	3 (15.8)	10 (19.6)	13 (18.6)	1.000
Presence of hVISA[d], *n*	0	1	1	
Complicated MRSA infections, *n* (%)	13 (61.9)	23 (41.8)	36 (47.4)	0.117
Infection foci removed, *n* (%)	14 (66.7)	34 (61.8)	48 (63.2)	0.695
Days before infection foci removed, days, median (range)	2 (0–24)	3 (0–24)	2.5 (0–24)	0.319
Duration of inpatient MRSA antibiotics, days, median (range)	35 (15–81)	23 (7–146)	27 (7–146)	*0.033*
Mean VAN trough levels, mg/L, (± SD)	17.05 ± 4.3	16.3 ± 4.5	16.5 ± 4.4	0.534
Vancomycin continued after hospital discharge, *n* (%)	9 (42.9)	17 (30.9)	26 (34.2)	0.326
Continued on oral MRSA therapy, *n* (%)	6 (28.6)	7 (12.7)	13 (17.1)	0.169

VAN, vancomycin. [a]A patient may have multiple sources or sites of infection; [b]APACHE II score based on 75 patients, 1 patient had missing data; [c]Total of 70 samples; [d]Total of 21 samples.

of treatment (combination 14/16 [87.5%] vs. 47/60 [78.3%], *P* = 0.505) nor at day 21 (combination 10/16 [62.5%] vs. 37/60 [61.7%], *P* = 0.951). Failure to attain microbiologic clearance at the end of treatment was associated with lower vancomycin troughs (clearance 17.4 ± 4.1 mg/L vs. no clearance 13.6 ± 4.8 mg/L, *P* < 0.001). The median duration of bacteremia was longer in the combination group at 19 d vs. 14 d with monotherapy (*P* = 0.023), as patients with add-on combination antibiotics following vancomycin monotherapy took additional 1–21 d to achieve clearance (**Table 3**).

Thirty-day mortality was not statistically different (combination 2/21 [9.5%] vs. monotherapy 14/55 [25.5%], *P* = 0.208). All other reported clinical outcomes were also not significant between groups, although there was a trend to decreased in-hospital and infection-related mortality, improved clinical response and longer hospitalization with combination therapy (**Table 4**).

The overall 30-d mortality rate was 16/76 (21.1%). Univariate analysis showed significant between-group differences in ICU admissions (*P* = 0.019), microbiologic clearance at the

Table 3. Microbiologic outcomes of patients with pMRSA bacteremia

Outcome	Combination (n = 16)	Monotherapy (n = 60)	Total (n = 76)	P value
Microbiologic clearance at end of treatment, n (%)	14 (87.5)	47 (78.3)	61 (80.3)	0.505
Microbiologic clearance at day 21, n (%)	10 (62.5)	37 (61.7)	47 (61.8)	0.951
Duration of bacteremia, median (range)	19 (10–76)	14 (8–49)	15 (8–76)	*0.023*

VAN, vancomycin. Five patients had microbiologic clearance before the addition of combination therapy, and were included in the monotherapy group for analysis.

Table 4. Clinical outcomes of patients with pMRSA bacteremia

Outcome	Combination (n = 21)	Monotherapy (n = 55)	Total (n = 76)	P value
30-d mortality, n (%)	2 (9.5)	14 (25.5)	16 (21.1)	0.208
In-hospital mortality, n (%)	5 (23.8)	19 (34.5)	24 (31.6)	0.368
Infection-related mortality, n (%)	6 (28.6)	20 (36.4)	26 (34.2)	0.522
Clinical improvement at D14, n (%)	15 (71.4)	32 (58.2)	47 (61.8)	0.288
Recurrent MRSA culture[a], n (%)	4 (22.2)	7 (18.9)	11 (20.0)	1.000
Hospitalization days after index culture, median (range)	38 (18–98)	26 (9–147)	30.5 (9–147)	0.058
Total duration of hospitalization, median (range)	41 (20–128)	33 (11–223)	37.5 (11–223)	0.646

[a]Based on 55 patients who achieved microbiologic clearance and did not die during 6 mo of follow-up.

end of treatment ($P < 0.001$), and mean vancomycin trough levels ($P = 0.026$). No significant differences were noted in the proportion of patients on dialysis, the proportion with vancomycin MICs ≥1.5 mg/L, chronic and acute illness severity scores, presence of congestive heart failure or malignancy, or the presence of complicated or metastatic infections (**Table 5**).

Variables included in the multivariate analysis were age, intensive care unit admission, Charlson co-morbidity index of 3 or greater, vancomycin MIC for index culture greater than 1.5 mg/L, removal of infection foci, mean vancomycin trough levels, use of combination therapy, and microbiologic clearance. The multivariate analysis found that the lack of microbiologic clearance predicted 30-d mortality (odds ratio 69.3, 95% CI 9.8–492.0, $P < 0.001$).

This study showed that the addition of combination antibiotics did not significantly improve outcomes (mortality, microbiologic clearance, and clinical improvement) compared with vancomycin monotherapy, and that a failure to obtain microbiologic clearance at end of therapy affected 30-d mortality. The IDSA MRSA guidelines recommends a switch to alternatives, with daptomycin preferred as it is rapidly bactericidal.[16] However, in clinical practice, combinations of vancomycin with additional antibiotics are used for the treatment of pMRSA bacteremia or complicated MRSA infections. In a Korean study, adding aminoglycoside and/or rifampicin did not improve outcome, whereas switching from vancomycin to linezolid (with or without a carbapenem) resulted in improved microbiologic clearance and lower infection-related mortality.[19] Another study suggested that switching to linezolid or combination therapy did not reduce mortality. The only intervention that reduced mortality was complete eradication of infection foci.[13] Our results showed that combination therapy did not significantly influence various mortality measures.

Thirty-day mortality appeared lower with combination therapy, but the reduction may be attributable to other factors, as microbiologic clearance rates were similar between groups at day 21 and at the end of treatment. Furthermore, the use of combination antibiotics did not reduce recurrence rates.

Many studies have suggested different risk factors for mortality in MRSA bacteremia. In our study, appropriate therapy was not delayed as all patients were placed on vancomycin within the first 72 h of positive blood cultures. We included these reported risk factors in the univariate analysis (**Table 5**). The multivariate analysis model which included clinically and statistically significant variables indicated the lack of microbiologic clearance as the only independent predictor for 30-d mortality. This highlights the importance of achieving microbiological clearance.

Our study had several limitations in addition to its retrospective design and small sample size. First, we found that the 30-d mortality rate (21.1%) was lower than other studies, likely due to heterogeneity in patient population or standard of care. This could affect the generalizability of our results. Also, there was no fixed protocol for combination therapy, and the selection of combination antibiotic and trigger for starting combination therapy were individualized. However, most combinations in the study did include rifampicin, a common choice for add-on therapy.[20] In addition, blood cultures were not repeated at fixed intervals, although the majority was performed once every 2 d. This could potentially prolong the time to documented microbiologic clearance. Furthermore, there was a lag time between culture collection and results reporting, and some patients were put on combination therapy after microbiologic clearance. We addressed this by counting these cases as having a successful microbiological clearance with vancomycin monotherapy, whereas we considered them under

Table 5. Univariate analysis of potential factors associated with 30-d mortality in pMRSA bacteremia

Variable	30 d mortality		P value
	Deceased (n = 16)	Survived (n = 60)	
Age, years, mean ± SD	70.5 ± 11.5	63.1 ± 15.2	0.076
Charlson co-morbidity index ≥3, n (%)	15 (93.8)	46 (76.7)	0.17
Hospitalization in prior 6 mo, n (%)	15 (93.8)	49 (81.7)	0.442
MRSA infection in prior 6 mo, n (%)	4 (25.0)	14 (23.3)	1
Co-morbidities			
Congestive heart failure, n (%)	7 (43.8)	23 (38.3)	0.694
Malignancy, n (%)	1 (6.3)	7 (11.7)	1
Source of infection			
Vascular catheter, n (%)	6 (37.5)	29 (48.3)	0.44
Bone and joint, n (%)	5 (31.3)	17 (28.3)	1
Vascular catheters or orthopedic implants present, n (%)	11 (68.8)	40 (66.7)	0.875
APACHE II score[a], mean ± SD	16.2 ± 5.2	15.1 ± 5	0.445
Pitt bacteremia score ≥4, n (%)	1 (6.3)	3 (5)	1
Intensive care unit admission, n (%)	8 (50.0)	11 (18.3)	*0.019*
Dialysis, n (%)	7 (43.8)	29 (48.3)	0.744
Vancomycin MIC for index culture greater than 1.5 mg/L[b], n (%)	5 (31.3)	8 (14.8)	0.156
Complicated MRSA infections, n (%)	7 (43.8)	32 (49.2)	0.694
Infection foci removed, n (%)	8 (50.0)	40 (66.7)	0.219
Days before infection foci removed, median (range)	2 (0–5)	3.5 (0–24)	0.371
Combination therapy, n (%)	2 (12.5)	19 (31.7)	0.208
Mean VAN trough levels, mg/L (± SD)	14.3 ± 3.9	17 ± 4.4	*0.026*
Microbiologic clearance at end of treatment, n (%)	4 (25.0)	57 (95.0)	*<0.001*
Duration of bacteremia, median (range)	14 (10–22)	15.5 (8–76)	0.618

VAN, vancomycin. [a]APACHE II score based on 75 patients, 1 patient had missing data; [b]Total of 70 samples.

the combination group for clinical outcomes that were assessed at a later time period e.g., 30-d mortality. Lastly, tests for hVISA were not done for all patients and this test has become even less significant in our clinical practice. We would not draw any major conclusions about the impact of hVISA on our study results. The single patient who tested positive for hVISA responded to vancomycin monotherapy for all outcomes measures, i.e., achieved microbiological clearance, clinical improvement and did not experience 30-d mortality.

In conclusion, our study adds to the evidence against adding combination antibiotics to vancomycin when bacteremia persists, as no significant advantages in microbiologic and clinical efficacies were observed. We also showed that failure to achieve microbiological clearance was associated with mortality. Thus, alternative treatments should be considered along with adequate source control in the management of persistent MRSA bacteremia.

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