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Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Pilot Multicenter Randomized Controlled Trial

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Background. In vitro laboratory and animal studies demonstrate a synergistic role for the combination of vancomycin and antistaphylococcal β-lactams for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. Prospective clinical data are lacking.

Methods. In this open-label, multicenter, clinical trial, adults with MRSA bacteremia received vancomycin 1.5 g intravenously twice daily and were randomly assigned (1:1) to receive intravenous flucloxacillin 2 g every 6 hours for 7 days (combination group) or no additional therapy (standard therapy group). Participants were stratified by hospital and randomized in permuted blocks of variable size. Randomization codes were kept in sealed, sequentially numbered, opaque envelopes. The primary outcome was the duration of MRSA bacteremia in days.

Results. We randomly assigned 60 patients to receive vancomycin (n = 29), or vancomycin plus flucloxacillin (n = 31). The mean duration of bacteremia was 3.00 days in the standard therapy group and 1.94 days in the combination group. According to a negative binomial model, the mean time to resolution of bacteremia in the combination group was 65% (95% confidence interval, 41%–102%; $P = .06$) that in the standard therapy group. There was no difference in the secondary end points of 28- and 90-day mortality, metastatic infection, nephrotoxicity, or hepatotoxicity.

Conclusions. Combining an antistaphylococcal β-lactam with vancomycin may shorten the duration of MRSA bacteremia. Further trials with a larger sample size and objective clinically relevant end points are warranted.

Australian New Zealand Clinical Trials Registry: ACTRN12610000940077 (www.anzctr.org.au).

Keywords. *Staphylococcus aureus*; bacteremia; MRSA; clinical trial; vancomycin; β-lactam.

Invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infection imposes a substantial burden on healthcare systems throughout the world [1]. A recent national Australian study conducted over 1 year found that 450 of 1994 episodes (24%) of *S. aureus* bacteremia were caused by MRSA [2]. More importantly, this study found that the all-cause 30-day mortality was 30% for MRSA compared with 17.7% for methicillin-susceptible *S. aureus* (MSSA; $P < .001$). Studies from elsewhere have also reported infection with MRSA to have a higher mortality rate than MSSA [3]. The reasons for this difference in outcome are unclear but may relate to differences in host factors [4] or to the limitations of vancomycin, the most commonly used antibiotic for invasive MRSA infections [5]. Compared with the antistaphylococcal β-lactam oxacillin and its derivatives for treatment of MSSA infections, vancomycin demonstrates slower bacterial killing [6], poorer tissue penetration [7], and slower clearance of bacteremia [8] and is associated with higher mortality [9]. In recent years, several alternative agents to vancomycin have become available for the treatment of MRSA bacteremia, including linezolid, daptomycin, and ceftaroline. Each of these has been found to be noninferior to vancomycin for selected MRSA infections, but none have been shown to be superior for MRSA bacteremia [10], and are all associated with a high cost and/or a substantial risk of adverse effects.

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An alternative strategy to improve outcomes from MRSA bacteremia is to combine vancomycin with a second agent, aiming for synergistic bacterial killing. Unfortunately, neither daptomycin nor linezolid demonstrate in vitro synergy with vancomycin. In contrast, at least 17 in vitro studies have demonstrated synergy of vancomycin combined with various β-lactams against MRSA and vancomycin-intermediate *S. aureus* [11]. These studies varied in their methodology (checkerboard synergy testing or time-kill curves) and the β-lactams used but consistently found synergistic bacterial killing in the majority of tested strains. Animal studies have also demonstrated evidence of synergy between vancomycin and β-lactams [11]. The mechanisms for this observed synergy are not clear but may include β-lactam induced potentiation of host defense peptide activity against *S. aureus* [12], and a "see-saw" effect whereby reduced vancomycin susceptibility results in reduced transcription of *mecA* and increased susceptibility to β-lactams [13].

Thus, there is considerable in vitro and limited animal model evidence to suggest that the combination of vancomycin and an antistaphylococcal β-lactam may be more effective than vancomycin alone for MRSA bacteremia. In a retrospective analysis, Dilworth et al [14] described a higher rate of clearance of MRSA bacteremia in patients receiving empiric vancomycin plus a β-lactam than in patients receiving vancomycin alone. To our knowledge, however, no prospective human clinical studies addressing this question have been performed. We therefore conducted a pilot randomized controlled trial (RCT) to assess the feasibility, proof of concept, and safety of this strategy.

We hypothesized that the antistaphylococcal β-lactam flucloxacillin combined with vancomycin would have greater clinical efficacy than vancomycin alone in patients with MRSA bacteremia. The primary objective of this study was to determine and compare the average duration in days of MRSA bacteremia by allocated treatment.

METHODS

Study Design and Setting

We performed a pilot, multicenter, open-label, parallel-group RCT at 7 Australian hospitals (see Acknowledgments). Participants were recruited between January 2011 and May 2014. Institutional ethics approval was obtained at each site, and written informed consent was obtained from the participant or a surrogate decision maker before enrollment in the study. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000940077). The study protocol can be accessed at http://www.menzies.edu.au/page/Research/Projects/Staphylococcus/CAMERA_Protocols/.

Participants

Participants were hospital inpatients, and were eligible if they met all of the following inclusion criteria: (1) blood culture positive for MRSA; (2) ability to be randomized within 48 hours of the first positive blood culture obtained; (3) age ≥18 years; and (4) judged as likely to remain as a hospital inpatient for ≥7 days after randomization. Patients were excluded if they met any of the following criteria: (1) history of significant allergy to β-lactams or glycopeptides (defined as previous type 1 hypersensitivity reaction to any β-lactams or glycopeptides or definite history of rash or serious non–type 1 hypersensitivity reaction to flucloxacillin, any penicillin, or vancomycin); (2) renal failure with an estimated glomerular filtration rate <10 mL/min; (3) polymicrobial bacteremia; (4) previous participation in the trial; (5) known pregnancy; (6) unwillingness of treating clinicians for patient to be enrolled; or (7) currently treatment with β-lactam therapy that could not be ceased or substituted for with a non–β-lactam antibiotic.

Randomization and Masking

Randomization was stratified by site, with a 1:1 treatment allocation using permuted blocks of variable size. Randomization codes were computer generated by the trial statistician, who had no involvement in the day to day running of the trial. Allocation was concealed by using sequentially numbered opaque sealed double envelopes.

Procedures

Participants were randomized to receive either standard care (intravenous vancomycin dosed according to Australian guidelines [15] with adjustment to maintain mean (SD) trough vancomycin levels of 15 (3) mg/L), or combination therapy (vancomycin plus intravenous flucloxacillin 2 g 4 times daily for the first 7 days after randomization). Both groups also received standard management of MRSA bacteremia per the Australasian Society for Infectious Diseases 2006 guidelines [16]. The total duration of vancomycin was determined by the clinician.

Outcomes and Measurements

The primary end point was the duration of MRSA bacteremia in days. Secondary end points included (1) combined safety end point of nephrotoxicity (rise in serum creatinine of >50% from baseline) or hepatotoxicity (plasma alanine aminotransferase or γ-glutaryl transferase >2.5 times the upper limit of normal) within the first 10 days after randomization; (2) all-cause 28- and 90-day mortality rates; (3) relapsed bacteremia during index hospital admission (defined as a positive blood culture for MRSA ≥48 hours after a negative blood culture); (4) metastatic complications during the first 10 days; and (5) requirement for intensive care unit admission or development of septic shock after randomization. Post hoc secondary end points included duration of bacteremia >3 and >7 days. Blood cultures were collected daily for the first 7 days of the study in all patients. Those with a positive blood culture at study day 7 had ongoing blood cultures collected every 48 hours until they became negative. Blood was also collected for routine analyses and vancomycin levels on days 1–7 inclusive and on day 10.

Laboratory Methods

Oxacillin and vancomycin Etest (bioMérieux) minimum inhibitory concentrations (MICs) for each bacterial isolate were determined according to manufacturer's instructions. We genotyped the isolates using a coagulase gene polymerase chain reaction restriction fragment length polymorphisms assay with contour-clamped homogeneous electric field electrophoresis [17], binary typing [18], and *spa* sequence typing on selected isolates. These typing results were used to assign a predicted multilocus sequence type (ST). The binary typing method was also used to determine the presence of the gene encoding Panton-Valentine leukocidin [18].

Sample Size

A sample size of 60 was calculated to determine the duration of bacteremia in each group with a 95% confidence interval (CI) of ±2 days, assuming that the duration of bacteremia has a normal distribution with a standard deviation (SD) of 5.1 days (derived from Fowler at al [19]) and a 10% correction factor for dropouts.

Statistical Methods

The primary efficacy analysis compared the duration of bacteremia from randomization by treatment group. We defined the duration of bacteremia as the time in days from randomization until 1 day after the last positive blood culture. For example, if the last positive blood culture was on the third day after randomization, the duration of bacteremia was 4 days. If the blood culture obtained on the day of randomization was negative for bacterial growth, the duration of bacteremia was considered 1 day. Because the duration of bacteremia was not normally distributed, but rather had a negative binomial distribution, we analyzed these data using a generalized linear model with a negative binomial link. A negative binomial distribution can be thought of as the number of failures until the rth success. In our case it is the number of days of bacteremia before the first ($r = 1$) day of persistently negative blood cultures [20]. The estimate of the effect of the combination therapy is the ratio of the mean duration in the 2 interventions.

The duration of bacteremia was also assessed with a time-to-event analysis, including a Kaplan-Meier plot and a Cox model in which deaths, before the resolution of bacteremia, were treated as censored observations. A sensitivity analysis wherein the deaths were treated as a competing risk was also performed. Binary secondary outcomes were analyzed using a χ^2 test, with the result presented as a relative risk. Secondary analyses were done on a "per-protocol" data set that excluded patients in the standard therapy group who received ≥1 dose of any β-lactam and patients in the combination therapy group who received <12 doses of flucloxacillin.

The prespecified subgroups for assessment of the primary outcome were (1) complicated versus uncomplicated *S. aureus* bacteremia (complicated *S. aureus* bacteremia defined as any of the following: indwelling intravascular devices [cardiac valves, implantable cardiac devices, intravascular grafts] or a prosthetic joint; ongoing fever >38.0°C at days 3 and 4; a primary focus of infection of infective endocarditis, osteoarticular, intra-abdominal or central nervous system infection; and metastatic complications; duration of bacteremia was not included in

Table 1. Baseline Characteristics of Participants

Characteristic	Standard Therapy (n = 29)	Combination Therapy (n = 31)
Age, mean (SD), y	65 (21)	64 (19)
Male sex, No. (%)	17 (59)	22 (71)
Weight, mean (SD), kg	75.6 (14.3)	78.8 (15.5)
Comorbid conditions		
Charlson comorbidity index, median (IQR)	3 (1–5)	2 (1–6)
Charlson comorbidity index ≥3	16 (55)	15 (48)
Condition, No. (%)		
Diabetes mellitus	11 (38)	13 (42)
Chronic lung disease	10 (34)	6 (19)
Chronic renal impairment	5 (17)	7 (23)
Chronic liver disease	3 (10)	2 (6)
Hazardous alcohol use	2 (7)	4 (13)
Acquisition, No. (%)		
Nosocomial	4 (14)	11 (35)
Community onset, healthcare associated	15 (52)	9 (29)
Community acquired	10 (34)	11 (35)
Indwelling foreign material, No. (%)		
Central venous catheter	2 (7)	1 (3)
Permanent pacemaker	4 (14)	4 (13)
Prosthetic joint	5 (17)	3 (10)
Antibiotic use in 48 h before randomization, No. (%)		
Any antibiotics	26 (90)	25 (81)
Any vancomycin	13 (45)	13 (42)
Any β-lactam	23 (79)	20 (65)
Baseline investigations and illness severity		
SOFA score, median (IQR)	1 (1–3)	1 (0–2)
APACHE score, mean (SD)	11.0 (6.0)	10.2 (5.9)
Septic shock, No. (%)	7 (24)	8 (26)
C-reactive protein, median (IQR)	130 (67–255)	150 (49–290)
Total WBC count, median (IQR)	12.4 (9–16.2)	11.8 (8.3–14.8)
Primary focus of infection, No. (%)		
Primary blood stream	10 (34)	7 (23)
SSTI	6 (21)	7 (23)
Catheter related	2 (7)	6 (19)
Osteoarticular (native)	0 (0)	4 (13)
Osteoarticular (device)	1 (3)	2 (6)
Pleuropulmonary	3 (10)	0 (0)
Urinary tract	2 (7)	1 (3)
Endocarditis	0 (0)	1 (3)
Other[a]	4 (14)	2 (6)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; IQR, interquartile range; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SSTI, skin and soft-tissue infection; WBC, white blood cell.

[a] *Other* comprised "unknown" (n = 2), intra-abdominal (n = 1), central nervous system (n = 1), and surgical site infection (n = 2).

Table 2. Antibiotic Susceptibility and Genotypic Characteristics of Bacterial Strains

Susceptibility and Characteristics	Standard Therapy (n = 28)[a]	Combination Therapy (n = 31)
Antibiotic susceptibility		
Vancomycin MIC, median (IQR), μg/mL	0.75 (0.63–1.0)	0.75 (0.50–1.0)
Vancomycin MIC ≥1.5 μg/mL, No. (%)	4 (14)	2 (6)
Oxacillin MIC, median (IQR), μg/mL	256 (96–256)	256 (128–256)
Genotypic features, No. (%)		
Panton-Valentine leukocidin positive	8 (28)	10 (32)
ST22[b]	5 (18)	9 (29)
ST93[c]	4 (14)	5 (16)
ST239[b]	6 (21)	3 (10)
Other genotypes[c]	13 (46)	14 (45)

Abbreviation: IQR, interquartile range; MIC, minimum inhibitory concentration; ST, sequence type.

[a] One isolate could not be recovered.

[b] These are considered healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) genotypes.

[c] These are considered community-associated MRSA genotypes.

this definition, because this was the primary end point of the study); (2) *S. aureus* vancomycin MIC <1.5 versus ≥1.5 μg/mL; (3) received versus did not receive ≥1 dose of β-lactam in the 48 hours before randomization; and (4) healthcare-associated MRSA (based on genotype; specifically, ST239 and ST22) versus community-associated MRSA (not ST239 or ST22) [21]. *P* values were 2 sided, and no adjustment was made for multiple comparisons. Analyses were performed with SAS (version 9.3; SAS Institute) or Stata (version 13.1; StataCorp) software. We did not have a data monitoring committee. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000940077).

RESULTS

Between 6 January 2011 and 20 April 2014, a total of 380 patients were screened for eligibility, and 60 patients were enrolled (Supplementary Figure 1), including 20 at Royal Darwin Hospital, 12 at Nepean Hospital, 8 at Westmead Hospital, 7 at Royal Perth Hospital, 6 at Blacktown Hospital, 5 at Liverpool Hospital and 1 at Royal Prince Alfred Hospital; 29 were randomly assigned to vancomycin (standard therapy group), and 31 to vancomycin plus flucloxacillin (combination group). In the 7 days after randomization, 3 patients in the standard therapy group received ≥1 dose of a β-lactam, and 3 patients in the combination group received <12 doses of flucloxacillin. These were considered protocol violations, leaving 26 and 28 patients, respectively, in the per-protocol population.

The 2 treatment groups were well balanced in terms of baseline characteristics and focus of infection (Table 1). The mean (SD) serum vancomycin levels during the first 10 days were 19.2 (5.1) mg/L and 20.3 (4.2) mg/L, and the median (interquartile range) time to achieve levels ≥15 mg/L were 3 (2–4.5) and 3 (2–3) days, for the standard therapy and combination groups, respectively, The distribution of MICs for vancomycin and oxacillin and genotypic characterization of isolates were also similar (Table 2, Supplementary Figure 2).

In the intention-to-treat (ITT) population, the mean (SD) duration of bacteremia was 3.00 (3.35) days in the standard therapy group and 1.94 (1.79) days in the combination group (Table 3). The distribution of duration of bacteremia in both groups followed a negative binomial distribution (Figure 1*A*). The rate ratio of means was 0.65 (95% CI, .41–1.02; *P* = .06), indicating that the mean time to resolution of bacteremia in the combination group was 65% that in the standard therapy group. Results of the per-protocol analysis (Table 3) were similar, with mean durations of bacteremia of 2.92 (SD, 3.37) in the standard therapy group and 1.82 (SD, 1.59) in the combination group, and a rate ratio of means of 0.62 (95% CI, .38–1.01; *P* = .055). For the ITT population, the number of participants with bacteremia for >3 days was 8 of 29 (28%) in the standard therapy and 4 of 31 (13%) in the combination group (Fisher exact test, *P* = .20); and the number with bacteremia for >7 days was 4 of 29 (14%) in the standard therapy and 1 of 31 (3%) in the combination group (Fisher exact test, *P* = .19). In the combination

Table 3. Primary Outcome Measure

	Duration of Bacteremia, d[b]			
Population[a]	Standard Therapy	Combination Therapy	Ratio of Means (95% CI)	*P* Value
ITT population				
Mean (SD)	3.00 (3.35)	1.94 (1.79)	0.65 (0.41–1.02)	.06
Median (IQR)	1 (1–2)	1 (1–4)	. . .	. . .
Per-protocol population				
Mean (SD)	2.92 (3.37)	1.82 (1.59)	0.62 (0.38–1.01)	.055
Median (IQR)	1 (1–2)	1 (1–4)	. . .	. . .

Abbreviations: CI, confidence interval; IQR, interquartile range; ITT, intention-to-treat; SD, standard deviation.

[a] The ITT population included 29 patients in the standard therapy and 31 in the combination therapy group; the per-protocol population, 26 and 28 patients, respectively.

[b] Duration of bacteremia in days follows a negative binomial distribution.

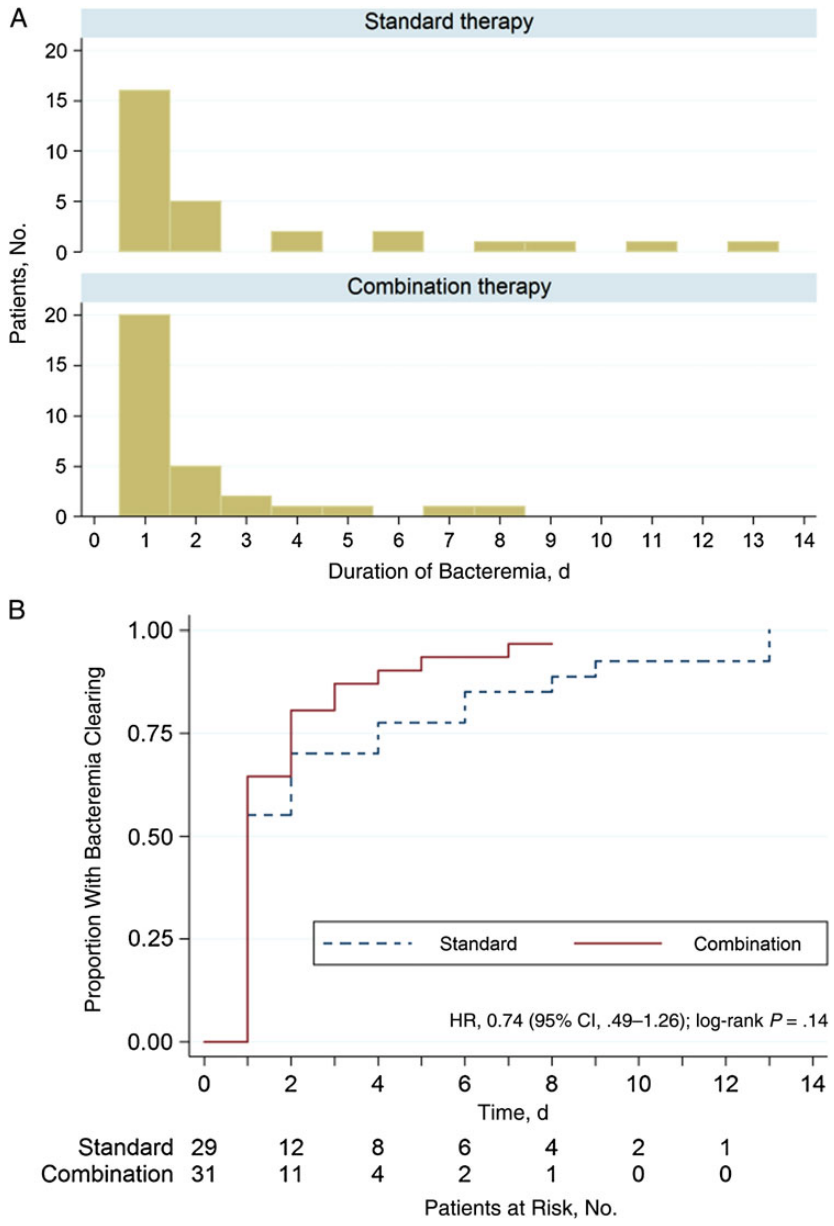

Figure 1. Comparison of duration of bacteremia according to allocated treatment group, represented as histograms (*A*) and cumulative hazard curve (*B*). CI, confidence interval; HR, hazard ratio.

group, 90% of patients had bacteremia cleared within 4 days, compared with 9 days in standard therapy group. Kaplan–Meier curves and a proportional hazards regression model also indicated that there was a nonsignificantly earlier time to clearance of bacteremia in the combination group (hazard ratio, 0.74; 95% CI, .43–1.26); (Figure 1*B*) (log-rank test, $P = .14$). When the 3 deaths before clearance of bacteremia were treated as a competing risk, the hazard ratio was 0.75 (95% CI, .50–1.13).

Analysis by prespecified subgroups did not reveal any statistically significant differences but suggested a greater benefit in the subgroup infected with *S. aureus* with a vancomycin MIC ≥1.5 (vs <1.5) μg/mL and in those with healthcare-associated (vs community-associated) MRSA genotypes (Supplementary Table 1). There were no significant differences between groups in hospital, 28- or 90-day mortality, relapsed bacteremia, the incidence of nephrotoxicity or hepatotoxicity, development of septic shock, need for intensive care unit admission, or metastatic complications (Table 4).

DISCUSSION

Our findings support the continued investigation of combining an antistaphylococcal β-lactam with vancomycin for MRSA bacteremia. We found a nonsignificant reduction of 1 day in

Table 4. Secondary Outcomes

Outcome	Patients, No. (%)		Relative Risk (95% CI)	*P* Value
	Standard Therapy	Combination Therapy		
ITT population				
Hospital mortality rate	5 (17)	5 (16)	0.96 (.48–1.90)	.91
28 d	5 (17)	5 (16)	0.96 (.48–1.90)	.91
90 d	6 (21)	5 (16)	0.86 (.46–1.59)	.65
Duration of bacteremia >3 d	8 (28)	4 (13)	0.47 (.16–1.39)	.16
Duration of bacteremia >7 d	4 (14)	1 (3)	0.23 (.03–1.97)	.14
Relapsed bacteremia	1 (3)	0 (0)	0	.30
ICU admission or development of septic shock after randomization	7 (24)	12 (39)	1.46 (.76–2.80)	.23
Grade ≥2 nephrotoxicity or hepatotoxicity	16 (55)	21 (68)	1.31 (.78–2.19)	.32
Metastatic complications during 1st 10 d	3 (13)	1 (4)	0.61 (.32–1.16)	.29
Per-protocol population				
Hospital mortality rate	3 (12)	5 (18)	1.33 (.52–3.41)	.52
28 d	3 (12)	5 (18)	1.33 (.52–3.41)	.52
90 d	4 (15)	5 (18)	1.10 (.50–2.42)	.81
Duration of bacteremia >3 d	7 (27)	5 (18)	0.78 (.43–1.39)	.43
Duration of bacteremia >7 d	3 (12)	1 (4)	0.61 (.32–1.16)	.29
Relapsed bacteremia	0 (0)	0 (0)		
ICU admission or development of septic shock after randomization	6 (23)	11 (39)	1.53 (.75–3.11)	.20
Grade ≥2 nephrotoxicity or hepatotoxicity	15 (58)	19 (68)	1.25 (.72–2.16)	.44
Metastatic complications during 1st 10 d	3 (13)	1 (4)	0.62 (.32–1.19)	.30

Abbreviation: CI, confidence interval; ICU, intensive care unit; ITT, intention-to-treat.

[a] The ITT population included 29 patients in the standard therapy and 31 in the combination therapy group; the per-protocol population, 26 and 28 patients, respectively.

the duration of bacteremia in the combination therapy group, and fewer patients in this group had persistent bacteremia at days 3 and 7 after randomization. Although the study was not powered to determine whether these differences were statistically significant, the differences warrant further investigation in larger numbers of patients.

Notably, participants in the 2 allocated treatment groups were well matched with regard to baseline demographics, comorbid conditions and clinical syndromes. There were more patients with catheter-related and native osteoarticular infections in the combination therapy group, and all 3 pleuropulmonary infections were in the standard therapy group. However, illness severity was similar in both groups. The groups were also balanced in terms of mean serum vancomycin levels, MRSA isolate MICs to vancomycin and oxacillin, and *S. aureus* genotypes.

The trend to reduction in duration of bacteremia with combination therapy was consistent in both the ITT and per-protocol groups. For the prespecified subgroups, the direction of effect was also toward a shorter duration of bacteremia with combination therapy in all subgroups. For the subgroup with infection due to MRSA with vancomycin MIC ≥1.5 μg/mL, the duration of bacteremia was 1, 2, 4, and 9 days for the 4 patients receiving standard therapy and 1 and 2 days for the 2 receiving combination therapy. If there is indeed a greater benefit for combination therapy in the group with vancomycin MIC ≥1.5 μg/mL, this would be consistent with findings of in vitro studies, where synergy is more consistently seen for isolates with higher vancomycin MICs [11].

Before this trial, there were retrospective reports suggesting that the addition of β-lactams for MRSA bacteremia may be beneficial. Patients with persistent MRSA bacteremia during treatment with daptomycin seem to experience quick clearance of bacteremia with the addition of nafcillin or oxacillin [22] or ceftaroline [23]. In a single-center retrospective cohort, Dilworth et al [14] compared 50 patients with MRSA bacteremia who received combination therapy with vancomycin and ≥24 hours of β-lactam and 30 patients who received vancomycin alone; they found a higher rate of microbiological eradication in the combination therapy group (96 vs 80%; $P = .02$). Thus, the results of our trial extend the existing clinical experience in combining β-lactams with standard therapy (either vancomycin or daptomycin) for MRSA bacteremia.

An additional therapeutic agent may increase the risk for adverse effects. Acute interstitial nephritis is a known, albeit uncommon, adverse effect of antistaphylococcal β-lactams [24]. In the setting of perioperative prophylaxis, Challagundla et al [25] found that high-dose compared with low-dose flucloxacillin (both with gentamicin) was associated with renal impairment. Although we found no statistically significant increase in renal impairment in the combination therapy group, there were 8 (28%) cases of a rise in serum creatinine of >50% over baseline with combination therapy, compared with 3 (11%) cases in the standard therapy group. Close monitoring

of renal impairment will be essential for future studies of combination therapy.

Strengths of our study include the randomized, multicenter design, well-matched groups, and inclusion of detailed bacterial genotypic and MIC investigations. Because this was designed as a pilot proof of feasibility study, the sample size is too small to make clinical recommendations. Even if we had found a statistically significant reduction in the duration of bacteremia with combination therapy, without clinically relevant end points there would be no cause to change practice. The experience with gentamicin is salutary. A trial demonstrating that adding gentamicin to standard therapy reduced the duration of bacteremia by 1 day but did not affect mortality rates [26] still led to a widespread practice of using gentamicin in this setting [27]. More recent data have confirmed a lack of mortality benefit [28] and indeed increased nephrotoxicity with the addition of gentamicin [29]. Hence, we believe it is important that β-lactam based combination therapy is not adopted as standard clinical practice for MRSA bacteremia until and unless stronger evidence of safety and efficacy emerges from subsequent RCTs.

In conclusion, our study provides an encouraging signal that the combination of vancomycin with an antistaphylococcal β-lactam may be useful for the treatment of MRSA bacteremia. This pilot RCT adds considerably to the growing literature from in vitro laboratory, in vivo animal, and retrospective clinical studies, and it provides the impetus for future clinical trials involving objective clinically relevant end points.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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