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ORIGINAL ARTICLE

Empirical combination of a β-lactam to vancomycin may not improve outcomes of methicillin-susceptible *Staphylococcus aureus* bacteremia, compared to vancomycin monotherapy

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Abstract To evaluate effect of empirical combination of a β-lactam to vancomycin and vancomycin monotherapy in *Staphylococcus aureus* bacteremia (MSSA-B), we conducted a retrospective cohort study. Electronic medical records of individuals who were diagnosed with MSSA-B between January 2005 and February 2015 at a tertiary care center were reviewed. Patients were classified into three groups according to empirical antibiotic regimen (BL group, β-lactam; VAN group, vancomycin; BV group, combination of β-lactam and vancomycin), and 30-day all-cause mortality of each group was compared. During the study period, 561 patients with MSSA-B were identified. After exclusion of 198 patients (36 with poly-microbial infection, 114 expired within 2 days, and 48 already received parenteral antibiotics) and a matching process, 46 patients for each group were included. Baseline characteristics were similar except for severity and comorbidity scores. The 30-day mortality for all three groups were not significantly different (BL 4.3%, VAN 6.5%, BV 8.7%; $P = 0.909$). In a multivariate analysis, type of empirical antibiotic regimen was not statistically associated with 30-day all-cause mortality. In comparison with the VAN group, the BV group yielded a HR of 0.579 (95% CI = 0.086–3.890, $P = 0.574$). Pitt bacteremia score was the only significant factor for mortality. The empirical combination of a β-lactam to vancomycin was not associated with lower mortality in treating MSSA-B, compared to vancomycin monotherapy.

Introduction

Due to increasing prevalence of methicillin-resistant *S. aureus* (MRSA), empirical coverage of methicillin-resistant strains in *S. aureus* bacteremia (SAB) became important [1–5]. To ensure MRSA coverage before identification of methicillin susceptibility, some clinicians recommend using a combination of β-lactam antibiotics to vancomycin as an empirical regimen for SAB [6], the benefit of which is still questioned in methicillin-susceptible *S. aureus* bacteremia (MSSA-B). To answer this question, we evaluated the empirical combination regimen and a de-escalation strategy in which empirical vancomycin was replaced with a definitive β-lactam, in comparison with β-lactam therapy in patients with MSSA-B.

Methods

Study design and population

A retrospective cohort study was conducted. We reviewed the electronic medical records of adult patients (age ≥ 18) who were diagnosed with MSSA-B between January 2005 and February 2015 at Samsung Medical Center, a 1,950-bed tertiary care university hospital in Seoul, Republic of Korea. Only the first bacteremia episode for each patient was included in the analysis. Identified patients were classified into three groups

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according to empirical antibiotic regimen (BL group, β-lactam; VAN group, vancomycin; BV group, combination of β-lactam and vancomycin) and matched by age and source of infection (1:1:1). The VAN and BV groups underwent de-escalation of their empirical regimen to definitive β-lactam antibiotics after identification of methicillin susceptibility. Patients who had poly-microbial infection, expired within 48 h of antibiotic treatment, and/or had already been on parenteral antibiotic therapy were excluded. The primary outcome was 30-day all-cause mortality. This study was approved by the Institutional Review Board of Samsung Medical Center.

Definitions

An episode of MSSA-B was defined as a positive culture in one or more sets of blood cultures with systemic manifestations of infection. Community-acquired infection was defined as MSSA-B occurring in the community or within 48 h after hospital admission in patients without healthcare-associated risk factors. Healthcare-associated infection was defined as community-onset MSSA-B in patients with previously described healthcare-associated risk factors [7]. Hospital-acquired infection was defined as MSSA-B that occurred longer than 48 h after admission in patients who did not have symptoms or signs of infection at the time of admission [2, 8, 9]. The source of bacteremia was determined according to the presence of clinical symptoms and signs, with isolation of MSSA from the presumed source. The development of acute kidney injury (AKI) as a complication of treatment was assessed 2 weeks from the onset of bacteremia according to the RIFLE classification system [10].

Microbiologic tests

Blood cultures collected before 2006 were processed in a BACTEC-9240 system (Becton Dickinson, Sparks, MD, USA), while the BacT/ALERT 3D system (bioMérieux Inc., Marcy l'Etoile, France) was used thereafter. For identification and antimicrobial susceptibility testing, including for methicillin, the VITEK II automated system (bioMérieux Inc.) was used with a standard identification card and the modified broth microdilution method. Minimum inhibitory concentration (MIC) breakpoints and quality control protocols were used according to the standards established by the Clinical and Laboratory Standards Institute (CLSI).

Statistical analysis

To compare clinical variables, the Mann–Whitney U test and Kruskal–Wallis test were used for continuous variables, and Chi-square and Fisher's exact tests were used for categorical variables. The Cox proportional hazard model was used to examine the association of the empirical antibiotic regimens with the 30-day mortality by adjusting potential confounding factors. All collected clinical variables with any relevance to prognosis underwent univariate analysis to find potential confounders. In addition to the type of empirical antibiotic regimen, the Pitt bacteremia score, Charlson's WIC, and variables with statistical significance in the univariate analyses were included in the multivariate analysis. All P-values were two-tailed, and those <0.05 were considered to be statistically significant. IBM SPSS Statistics version 20.0 for Windows (IBM, Armonk, NY, USA) was used for all statistical analyses.

Fig. 1 Selection of the study population among patients who were admitted and diagnosed with MSSA-B between January 2005 and February 2015 at a tertiary care center. Abbreviations: *MSSA-B* methicillin-susceptible *Staphylococcus aureus* bacteremia, *BL* β-lactam, *VAN* vancomycin, *BV* a combination of β-lactam and vancomycin
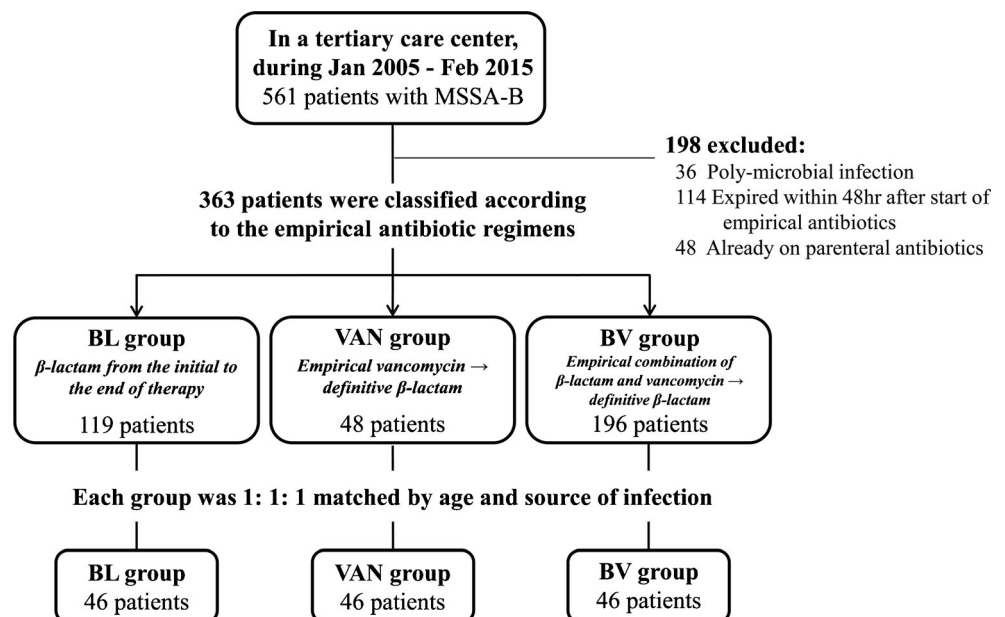
Results

Study population, baseline characteristics, and bacteremia acquisition

During the study period, 561 patients with MSSA-B were identified. After exclusion of 198 patients and a 1:1:1 matching process by age and infection source, 46 patients in each group were finally included in the analysis (Fig. 1). Baseline characteristics and bacteremia acquisition of patients in each group are presented in Table 1. The mean age of the patients was 60.4 years and was similar in all three groups. The BL and VAN groups showed a higher proportion of males to females than the BV group (BL 67.4%, VAN 65.2%, and BV 47.8%; $P = 0.004$). Patients in the VAN and BV groups had more comorbidities with higher Charlson's weighted index of comorbidity scores than patients in the BL group (BL 0, VAN 2, and BV 2, median values; $P = 0.003$). Patients in the

BL group had a higher proportion of community-acquired infections than patients in the VAN and BV groups (BL 56.5%, VAN 23.9%, and BV 34.8%; $P = 0.005$).

Clinical presentation, treatment, and outcomes

Clinical presentation, treatment, and outcomes of patients with MSSA-B according to empirical treatment group are presented in Table 2. The BV group had higher Pitt bacteremia score than the BL and VAN groups (BL 0.5, VAN 0, and BV 1, median values; $P = 0.018$) and proportion of ICU transfers within 48 h (BL 6.5%, VAN 8.7%, and BV 26.1%, median values; $P = 0.012$). The duration of empirical vancomycin administration in the VAN and BV groups and the total treatment duration in the three groups were similar. The vancomycin MIC in the VAN and BV groups and the oxacillin MICs in in all three groups were also statistically not different.

Table 1 Baseline characteristics and bacteremia acquisition in patients with MSSA-B according to empirical antibiotic regimen

Variables	Empirical antibiotic regimens			P value
	BL ($n = 46$)	VAN ($n = 46$)	BV ($n = 46$)	
Demographics				
Age, years	62.0 ± 12.9	59. 8 ± 15.74	59.5 ± 14.7	0.405
Male sex	31 (67.4%)	30 (65.2%)	22 (47.8%)	0.004
Underlying diseases				
Hypertension	14 (30.4%)	26 (56.5%)	17 (37%)	0.030
Diabetes mellitus	15 (32.6%)	20 (43.5%)	15 (32.6%)	0.457
Cardiovascular disease	1 (2.2%)	5 (10.9%)	4 (8.7%)	0.343
Chronic lung disease	0 (0%)	0 (0%)	0 (0%)	N/A
Chronic liver disease	3 (6.5%)	1 (2.2%)	6 (13.0%)	0.157
Chronic kidney disease	5 (10.9%)	14 (30.4%)	16 (34.8%)	0.019
on hemodialysis	4 (8.7%)	8 (17.4%)	9 (19.6%)	0.307
Neurologic disease	2 (4.3%)	5 (10.9%)	6 (13%)	0.433
Solid cancer	9 (19.6%)	11 (23.9%)	11 (23.9%)	0.847
Hematologic malignancy	3 (6.5%)	6 (13%)	4 (8.7%)	0.669
Charlson's WIC	0 (0–2)	2 (1–4)	2 (1–5)	0.003
Site of acquisition				
Community-acquired	26 (56.5%)	11 (23.9%)	16 (34.8%)	0.005
Healthcare-associated	12 (26.1%)	23 (50%)	15 (32.6%)	0.048
Hospital-acquired	8 (17.4%)	12 (26.1%)	15 (32.8%)	0.243
Source of bacteremia				
Primary bacteremia	3 (6.5%)	3 (6.5%)	3 (6.5%)	1.000
Skin and soft tissue	13 (28.3%)	13 (28.3%)	13 (28.3%)	1.000
Cardiovascular	24 (33.8%)	24 (33.8%)	23 (32.4%)	0.971
Lower respiratory tract	2 (4.3%)	2 (4.3%)	3 (6.5%)	1.000
Intra-abdominal	1 (2.2%)	1 (2.2%)	1 (2.2%)	1.000
Urinary tract	3 (6.5%)	3 (6.5%)	3 (6.5%)	1.000

Data are expressed as number (%) of patients, mean ± SD, or median (IQR)

MSSA-B methicillin-susceptible *Staphylococcus aureus* bacteremia, *BL* β-lactam, *VAN* vancomycin, *BV* a combination of β-lactam and vancomycin, *WIC* weighted index of comorbidity

Table 2 Clinical presentation, treatment, and outcomes of patients with MSSA-B according to empirical antibiotic regimen

Variables	Empirical antibiotic regimens			P value
	BL (n = 46)	VAN (n = 46)	BV (n = 46)	
Clinical presentations				
Body temperature, °C	38.1 (36.85–39)	38.2 (37.6–38.63)	38 (36.8–38.7)	0.612
Pitt bacteremia score	0.5 (0–2)	0 (0)	1 (1–3)	0.018
Transfer to ICU within 48 h	3 (6.5%)	4 (8.7%)	12 (26.1%)	0.012
WBC, ×10³/µl	11.0 (6.6–13.6)	11.5 (8.2–17.6)	10.8 (7.2–14.9)	0.346
ANC, ×10³/µl	8.4 (4.8–11.7)	9.9 (6.8–14.9)	9.0 (5.7–13.1)	0.213
Neutropenia	1 (2.2%)	0 (0%)	0 (0%)	1.000
CRP, mg/dl	11.8 (2.1–24.6)	10.7 (3.2–19.1)	14.9 (7.0–24.1)	0.461
Treatment				
Duration of vancomycin, days	N/A	2.5 (2.0–3.5)	2.8 (2.1–3.8)	0.628[a]
Duration of total treatment, days	14.2 (8.0–30.1)	13.7 (8.7–28.4)	15.1 (9.–23.6)	0.915
Oxacillin MIC, µg/ml	0.5 (0.25–0.5)	0.5 (0.25–0.5)	0.5 (0.25–0.5)	0.078
Vancomycin MIC, µg/ml	1 (1.0–1.0)	1 (0.5–1.0)	1 (0.5–1.0)	0.012
Outcomes				
30-day all-cause mortality	2 (4.3%)	3 (6.5%)	4 (8.7%)	0.909
30-day attributable mortality	0 (0%)	2 (4.3%)	0 (0%)	0.328
Bacteremia duration, days	2.2 (1.6–4.3)	3.7 (2.5–5.1)	2.8 (1.6–4.9)	0.010
Interval of 1st f/up culture, days	1.9 (1.4–2.5)	2.4 (1.7–3.1)	2.0 (1.5–2.9)	0.353
1st f/up within 3 days	33 (71.7%)	31 (67.4%)	38 (82.6%)	0.231
Bacteremia clear-up[b]	42/42 (100%)	43/43 (100%)	46/46 (100%)	N/A
No. of cultures before clear-up	1 (1–1)	1 (1–2)	1 (1–2)	0.259
Development of AKI[c]	1/42 (2.4%)	5/38 (13.2%)	4/37 (10.8%)	0.190

Data are expressed as number (%) of patients or median (IQR)

MSSA-B methicillin-susceptible *Staphylococcus aureus* bacteremia, *BL* β-lactam, *VAN* vancomycin, *BV* a combination of β-lactam and vancomycin, *ICU* intensive care unit, *WBC* white blood cell, *ANC* absolute neutrophil count, *CRP* C-reactive protein, *N/A* not available, *MIC* minimum inhibitory concentration, *f/up* follow-up, *AKI* acute kidney injury

[a] Patients in VAN and BV groups were compared

[b] Patients who did not perform follow-up culture within 7 days were excluded from the analysis

[c] Patients who were on dialysis from baseline were excluded from the analysis

Although the 30-day mortality rate was highest in the BV group, no statistically significant difference was observed among the groups (BL 4.3%, VAN 6.5%, BV 8.7%; P = 0.909). The duration of bacteremia was longer in the VAN group than in the BL and BV groups (BL 2.2, VAN 3.7, BV 2.8 days, median values; P = 0.010). However, the time interval before the first follow-up blood culture was also longer in the VAN group, which makes it difficult to interpret bacteremia duration (BL 1.9, VAN 2.4, BV 2.0 days, median values; P = 0.353). Numerically, more patients in the VAN and BV groups experienced AKI, but these numbers were not statistically significantly different (BL 2.4%, VAN 13.2%, and BV 10.8%; P = 0.190).

Multivariate analysis of 30-day all-cause mortality in MSSA-B

In the multivariate analysis, only Pitt bacteremia score was significantly associated with 30-day mortality in MSSA-B (HR 1.533, 95% CI = 1.054–2.229, P = 0.025, Table 3). Although the VAN and BV groups showed slightly higher HRs than the BL group, type of empirical antibiotic regimen was not associated with 30-day all-cause mortality (in comparison with the BL group: HR 1.844, 95% CI = 0.258–13.201, P = 0.542 for the VAN group; HR 1.541, 95% CI = 0.249–9.532, P = 0.642 for the BV group). In a subgroup analysis comparing the VAN and BV groups, type of empirical antibiotic regimen

Table 3 Multivariate analysis of 30-day all-cause mortality of MSSA-B

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Empirical antibiotics				
BL group	1		1	
VAN group	1.492 (0.249–8.932)	0.661	1.844 (0.258–13.201)	0.542
BV group	2.005 (0.367–10.949)	0.422	1.541 (0.249–9.532)	0.642
WBC	1.043 (1.014–1.073)	0.004	1.025 (0.992–1.058)	0.138
Charlson's WIC	1.082 (0.828–1.414)	0.565	1.016 (0.741–1.392)	0.923
Pitt bacteremia score	1.579 (1.172–2.127)	0.003	1.533 (1.054–2.229)	0.025

MSSA-B methicillin-susceptible *Staphylococcus aureus* bacteremia, *BL* β-lactam, *VAN* vancomycin, *BV* a combination of β-lactam and vancomycin, *WBC* white blood cell, *WIC* weighted index of comorbidity

was not associated with 30-day all-cause mortality (in comparison with the VAN group: HR 0.579, 95% CI = 0.086–3.890, $P = 0.574$ for the BV group), and only the Pitt bacteremia score showed statistical significance (HR 1.929, 95% CI = 1.097–3.391, $P = 0.022$, Table 4).

Discussion

In the present study, there was neither superiority nor inferiority of empirical combination regimen of β-lactam and vancomycin to the other two groups. The 30-day all-cause mortality was highest in the BV group, but BV group had also higher Pitt bacteremia score and proportion of ICU transfers within 48 h. This implies that physicians tended to choose combination therapy for severely ill patients, and such tendency was adjusted by the multivariate analysis. These findings imply that numerical difference of outcome variables in previous studies [11, 12] might be affected by disease severity and comorbidities, and emphasize that adjustment of confounding variables by multivariate analysis is essential. Our data give evidence that the combination of a β-lactam to vancomycin may not have additional

benefits compared to vancomycin monotherapy as an initial empirical therapy treating MSSA-B.

The inferiority of definitive vancomycin therapy to β-lactams in treating MSSA-B is well documented [6, 11, 13–17], but it is not clear whether short-term administration of vancomycin as an empirical treatment would also be inferior [12, 18]. In our data, there was no inferiority of empirical vancomycin therapy to β-lactam treatment. No statistically significant difference among three empirical antibiotic regimens was observed in the multivariate analysis of 30-day all-cause mortality. Duration of bacteremia was longer in the VAN group than in the BL and BV groups, but the time interval before the first follow-up blood culture was also longer in the VAN group. This finding is similar to that of a previous study by Khatib et al., which showed delayed clearance of MSSA-B in the VAN group without a difference in all-cause mortality [18]. However, time-to-antibiotics was significantly longer in the VAN group, and the time interval of the first follow-up blood culture was not evaluated in that study. Another study by Lodise et al. showed significantly increased MSSA-B-related mortality in the VAN group compared to the BL group in intravenous drug users with infective endocarditis [12]. However, the severity and comorbidity of patients

Table 4 Multivariate analysis of 30-day all-cause mortality in subgroups of VAN and BV

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Empirical antibiotics				
VAN	1		1	
BV	1.351 (0.302–6.037)	0.694	0.579 (0.086–3.890)	0.574
WBC	1.045 (1.014–1.077)	0.004	1.016 (0.981–1.053)	0.377
Charlson's WIC	1.101 (0.813–1.490)	0.534	1.028 (0.722–1.465)	0.879
Pitt bacteremia score	1.973 (1.301–2.991)	0.001	1.929 (1.097–3.391)	0.022

BL β-lactam, *VAN* vancomycin, *BV* a combination of β-lactam and vancomycin, *WBC* white blood cell, *WIC* weighted index of comorbidity

were neither evaluated nor adjusted in that study. As the clinical evidence to date is heterogeneous, more clinical data should be accumulated to assess the effects of a de-escalation strategy for replacing empirical vancomycin with definitive β-lactam.

Inherent to retrospective design, the three groups were different in severity and comorbidity. To compensate, we matched each group by age and source of infection, and conducted multivariate analysis to adjust for potential confounding factors. In addition, low mortality rates caused by strict exclusion limited our ability to detect statistically significant differences between groups.

In conclusion, for empirical coverage of methicillin-resistant strains, the combination of a β-lactam to vancomycin did not improve outcome of MSSA-B compared to vancomycin monotherapy.

Compliance with ethical standards

Conflicts of interest None of the authors have any conflicts of interest to report.

Ethical approval This study was approved by the Institutional Review Board of Samsung Medical Center.

Informed consent As a retrospective study, the Institutional Review Board waived informed consent in the present study.

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