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CLINICAL THERAPEUTICS

Adjuvant β-Lactam Therapy Combined with Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Does β-Lactam Class Matter?

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ABSTRACT We analyzed the impact of vancomycin (VAN) combined with adjuvant β-lactam therapy (Combo) on persistent (≥5 days) methicillin-resistant *Staphylococcus aureus* bacteremia versus VAN alone by using pooled data from two previously published observational studies ($n = 156$). Combo was inversely associated with persistent bacteremia (adjusted odds ratio, 0.460; 95% confidence interval, 0.229 to 0.923). Acute kidney injury was more common with Combo than with VAN (18.9% and 7.6%, respectively; $P = 0.062$).

KEYWORDS bacteremia, β-lactam, combination therapy, methicillin-resistant *Staphylococcus aureus*, vancomycin

Treatment with vancomycin (VAN) combined with a β-lactam (Combo) expedites methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia clearance compared with VAN alone (1–5). However, the impact of Combo on persistent MRSA bacteremia, using a contemporary definition of ≥5 days, is not well studied (6). There is also no consensus on which β-lactam(s) should be combined with VAN. We sought to assess persistent bacteremia rates among adults who received treatment with Combo or VAN alone and the impact of β-lactam class on persistent bacteremia.

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This was a retrospective analysis of pooled data from two previously published observational studies of adult patients with MRSA bacteremia in the United States (1, 2). The first was a single-center retrospective study of patients from January 2005 to December 2012 (1). The second was a multicenter retrospective study of patients from 1 January 2010 to 31 December 2014 (2). Patient cohorts in the two component studies were entirely distinct. Not all patients from the previous studies were included in the current study because the studies had different inclusion criteria. All patients included in the current study from the two previous studies had to meet the following criteria for study inclusion. All patients received VAN intravenously for ≥72 h. The Combo group received an intravenous β-lactam for ≥48 h with VAN, started within 24 h of VAN alone; the remaining patients comprised the VAN group. The primary outcome was persistent bacteremia (≥5 days of MRSA bacteremia). The impact of β-lactam class on persistent bacteremia was assessed. Acute kidney injury (AKI) (serum creatinine increase from baseline by 0.5 mg/dl or 50%) was also assessed throughout patient

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TABLE 1 Treatment assignment and persistent bacteremia, univariable analyses

Characteristic	Treatment assignment[a]			Bacteremia duration[a]		
	Combo[b] ($n = 90$)	VAN ($n = 66$)	*P* value	<5 days ($n = 103$)	≥5 days ($n = 53$)	*P* value
Age (yr, mean ± SD)	58 ± 16	61 ± 17	0.317	58 ± 16	60 ± 17	0.539
Male	50 (55.6)	35 (53.0)	0.871	57 (53.3)	28 (52.8)	0.865
Race/ethnicity			0.417			0.392
Caucasian	55 (61.1)	36 (54.5)		63 (61.2)	28 (52.8)	
Other	35 (38.9)	30 (45.5)		40 (38.8)	25 (47.2)	
Diabetes mellitus	43 (47.8)	27 (40.9)	0.419	45 (43.7)	25 (47.2)	0.735
Cancer	16 (17.8)	15 (22.7)	0.543	18 (17.5)	13 (24.5)	0.299
Lung disease	20 (22.2)	10 (15.2)	0.309	17 (16.5)	13 (24.5)	0.284
Congestive heart failure	14 (15.6)	8 (12.1)	0.644	16 (15.5)	6 (11.3)	0.628
End-stage renal disease	27 (30.0)	20 (30.3)	>0.999	32 (31.1)	15 (28.3)	0.854
Hemodialysis	15 (16.7)	15 (22.7)	0.412	19 (18.5)	11 (20.8)	0.831
PITT bacteremia score ≥4	19 (12.2)	12 (18.8)	0.690	23 (22.1)	8 (15.4)	0.397
Intensive care unit admission	41 (45.6)	22 (33.3)	0.140	43 (41.8)	20 (37.7)	0.731
Bacteremia source			0.167			0.156
Primary endovascular	27 (30.0)	24 (36.4)		32 (31.1)	19 (35.9)	
Secondary	50 (55.6)	27 (40.9)		56 (54.4)	21 (39.6)	
Catheter related	13 (14.4)	15 (22.7)		15 (15.0)	13 (24.5)	
Prosthesis	14 (15.6)	18 (27.3)	0.107	20 (19.4)	12 (22.6)	0.678
VAN MIC ≤1 mg/liter	74 (82.2)	57 (86.4)	0.517	84 (81.6)	47 (88.6)	0.357
Initial VAN level (mg/liter; median [IQR])	17.8 (14.0–23.4)	15.7 (11.3–20.2)	0.041	17.5 (14.0–23.0)	15.0 (11.1–23.2)	0.108
VAN therapy duration (days [range])	12 (8–26)	11.5 (7–22)	0.773	12 (7–31)	13 (9–19)	0.990
Persistent bacteremia	24 (26.7)	29 (43.9)	0.027			
In-hospital mortality	14 (15.6)	9 (13.6)	0.822	14 (13.6)	9 (17.0)	0.636
Acute kidney injury	17 (18.9)	5 (7.6)	0.062	13 (12.6)	9 (17.0)	0.474

[a]Data presented as *n* (%) unless noted otherwise.
[b]Piperacillin-tazobactam (60.0%), cefepime (15.6%), ceftriaxone (12.2%), meropenem (4.4%), imipenem-cilastatin (3.3%), ampicillin-sulbactam (2.2%), cefazolin (1.1%), and doripenem (1.1%).

exposure to antibiotic therapy while in the hospital (7). Patient characteristics, severity of illness (PITT bacteremia score), infection-related characteristics, and clinical outcomes were recorded (8). Bacteremia source was categorized as primary endovascular, secondary, or catheter related (9). Endocarditis was defined using modified Duke criteria (10).

We determined the association between treatment assignment and persistent bacteremia in the entire pooled study population. Then we assessed the impact of β-lactam class (penicillin, cephalosporin, and carbapenem) on persistent bacteremia. The same analyses were repeated only for those who received Combo. Nomenclature from both databases was harmonized to facilitate data analysis. Univariable analyses were used to compare patients in the VAN and Combo groups and patients with and without persistent bacteremia. Multivariable analyses of factors associated with persistent bacteremia were performed using forward, stepwise multiple logistic regression. The criterion for model entry was $\alpha = .20$, whereas the criterion for remaining in the model was significance at $\alpha \leq .05$. The Hosmer-Lemeshow test was utilized to evaluate goodness of fit. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

In total, 156 of the 177 potential patients (88.1%) were included (VAN, $n = 66$; Combo, $n = 90$). Patients were excluded for receiving β-lactam therapy for <48 h ($n = 9$), β-lactam therapy starting >24 h after VAN initiation ($n = 9$), >1 β-lactam ($n = 2$), and enteral β-lactam therapy ($n = 1$). The median (interquartile range [IQR]) duration of β-lactam therapy in the Combo group was 5 days (3 to 8 days). The groups were similar (Table 1), except that patients in the Combo group had a higher VAN exposure (initial median [IQR] trough level, 17.8 [13.9 to 23.6] versus 15.7 [11.3 to 20.6] mg/liter; $P = 0.039$). Persistent bacteremia was less common with Combo (26.7% versus 43.9%; $P = 0.027$). In a multivariable model, use of Combo was inversely associated with persistent bacteremia (adjusted odds ratio, 0.423; 95% confidence interval, 0.212 to

TABLE 2 Rates of persistent bacteremia and acute kidney injury by β-lactam class

Characteristic	Rate (*n* [%]) with:			
	Carbapenem (*n* = 8)	Cephalosporin (*n* = 25)	Penicillin (*n* = 56)	Vancomycin[a] (*n* = 66)
Persistent bacteremia	0 (0)	8 (32)	15 (26.8)	29 (43.9)
Acute kidney injury	1 (12.5)	4 (16)	12 (21.4)	5 (7.6)

[a]Vancomycin is listed for reference.

0.843). No other predictor variables were independently associated with persistent bacteremia. AKI was more common with the Combo treatment (18.9% versus 7.6%; $P = 0.062$). The rates of persistent bacteremia and AKI by β-lactam class are shown in Table 2.

These results suggest that Combo reduces the likelihood of persistent bacteremia when using the contemporary definition of ≥5 days (6). This is important because the treatment paradigm for MRSA bacteremia is changing toward a focus on antibiotic therapy escalation in response to persistence earlier in the disease course (6). Previous studies have used a 7-day persistent bacteremia definition and/or have analyzed the impact of Combo on composite microbiological and clinical outcomes showing favorable results with Combo (1–5). Truong et al. (4) recently evaluated Combo compared with VAN alone using a composite endpoint that included persistent bacteremia (>5 days) and found no difference in persistent bacteremia between groups. Davis et al. (3) found that Combo reduced the proportion of patients with positive blood cultures at day 3 compared with VAN alone. Combo has yet to show an impact on clinical outcomes beyond those included as part of a composite endpoint, with the notable exception of results from a study that used the combination of daptomycin plus ceftaroline as salvage therapy (11). However, the ongoing CAMERA-2 trial should provide more data on this important issue (12). Combo may reduce the need to escalate antibiotic therapy due to persistent bacteremia, which may prevent the overuse of last-line agents such as daptomycin and ceftaroline. However, the rate of AKI was higher with Combo than with VAN alone. Although our study was not designed to determine the impact of Combo on AKI, this finding is notable. The initial median VAN trough level was higher in the Combo group. Higher VAN exposure in Combo may be a consequence of AKI rather than a cause of AKI. Clinicians using adjuvant β-lactam therapy should be cognizant of the potential AKI risk with Combo. Most patients on Combo therapy (60%) received piperacillin-tazobactam, which, in combination with VAN, can increase the likelihood of AKI (13). It is prudent to avoid piperacillin-tazobactam use with Combo because it may be associated with nephrotoxicity. However, we cannot endorse use of other β-lactams for Combo based on our data alone. Additional, prospective clinical trial data are needed to determine which β-lactams may be safely used with VAN as Combo. The lack of persistent bacteremia among the small subgroup of patients receiving adjuvant carbapenem therapy ($n = 8$) is interesting but difficult to interpret. The impact of adjuvant β-lactam class on persistent bacteremia likely requires additional study with larger sample sizes.

We included a number of important data elements in this study, but the two data sets were not identical, preventing the use of certain variables (e.g., strain characteristics and more sensitive assessments of AKI). However, multiple patient and treatment-level data were included in this analysis, and patients in the Combo and VAN groups were well matched. Our study is limited by its retrospective nature and small sample size. We were unable to draw strong conclusions regarding the impact of β-lactam class used in Combo on persistent bacteremia or AKI. In conclusion, Combo reduced the likelihood of persistent bacteremia but was associated with a statistically nonsignificant trend toward a higher rate of AKI. Clinically, Combo may reduce persistent bacteremia rates and potentially prevent overuse of salvage antibiotic therapy. β-Lactam choice for Combo warrants further investigation.

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