Comparative Effectiveness of Ampicillin Versus Vancomycin or Daptomycin for the Treatment of Ampicillin-susceptible *Enterococcus* spp. Bacteremia

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BACKGROUND

- Enterococcal bloodstream infections (BSI) are associated with significant morbidity and mortality[1]
- Agents with activity against enterococci include penicillins, glycopeptides, and lipopeptides[2,3]
- Several studies have compared the efficacy of treatment options in *Enterococcus* spp. bacteremia with conflicting results[4-7]
- There are limited data on comparisons specifically between ampicillin (AMP), vancomycin (VAN), and DAP for ampicillin-sensitive *Enterococcus* spp. (ASE) BSI

OBJECTIVE

To compare the clinical outcomes of AMP, DAP, and VAN for the treatment of ASE BSI

METHODS

Study Design

- Single-center, retrospective, observational study
- Patients admitted to Baylor St. Luke's Medical Center (Houston, Texas) from January 2013 to December 2021
- Definitive treatment groups: AMP, DAP, and VAN
- In patients with multiple hospitalizations with enterococcal BSI, only the first BSI episode meeting the inclusion criteria during the study period was assessed

Study Criteria

Inclusion Criteria	Exclusion Criteria
• Age 18 years or older	• AMP-resistant *Enterococcus* spp. BSI
• ASE growth in index culture	• Polymicrobial BSI
• Definitive therapy with AMP, DAP, or VAN	• Received treatment for ≤24 hours

Study Endpoints

- **Primary outcome:** 28-day all-cause in-hospital mortality
- **Secondary outcomes:** 90-day hospital readmission due to microbiological recurrence and all-cause in-hospital mortality

Definitions

- **Empiric therapy:** therapy utilized while awaiting culture sensitivities
- **Definitive therapy:** therapy utilized for more than 50% of the total treatment duration while admitted following availability of susceptibility results
- **Index culture:** the first blood culture or set of blood cultures drawn that yielded *Enterococcus* spp.
- **Polymicrobial BSI:** isolation of one or more additional pathogens accompanying the enterococci yielded with the index culture. Clinically known contaminants, such as coagulase-negative *Staphylococcus* spp. or diphtheroids, grown only in one set of blood cultures were not considered polymicrobial

Statistical Analyses

- **Baseline characteristics and outcomes:** Kruskal Wallis test and Chi-squared test were utilized for continuous and categorical variables, respectively
- **Kaplan-Meier survival curves:** 28-day survival differences between the 3 groups were evaluated; a log-rank test was used to identify any significant differences between the survival curves
- **Multivariate Cox proportional hazards model**: Univariate analysis of all variables was performed. Variables found to have P<0.2 were included in a multivariate stepwise Cox regression analysis with backward elimination with P<0.2 set for retention in the final model. Definitive therapy was included in the final model regardless of significance
- **Statistical software:** all analyses performed using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria)

RESULTS

Table 1. Baseline characteristics

Variable	Definitive Antibiotic			P-value
	AMP (n=141)	DAP (n=17)	VAN (n=41)	
Age (years), mean (SD)	64.3 (15.1)	61.8 (18.0)	64.4 (13.9)	0.806
Race, n (%)				0.894
Caucasian	65 (46.1)	8 (47.1)	17 (41.5)	
African American	43 (30.5)	5 (29.4)	17 (41.5)	
Hispanic	25 (17.7)	3 (17.6)	6 (14.6)	
Other/Unknown	8 (5.7)	1 (5.9)	1 (2.4)	
Sex, males, n (%)	105 (74.5)	10 (58.8)	25 (61)	0.138
Hospital LOS (days), median (IQR)	17 (9-31)	18 (11-30)	12 (6-30)	0.458
ICU stay during index culture, n (%)	47 (33.3)	6 (35.3)	18 (43.9)	0.461
ICU LOS (days), median (IQR)	2 (0-10)	2 (0-16)	3 (0-22)	0.931
LOS prior to index culture (days), median (IQR)	0 (0-10)	0 (0-2)	1 (0-12)	0.939
Comorbidities, n (%)				
Cardiovascular	114 (80.9)	16 (94.1)	34 (82.9)	0.396
Central nervous system	29 (20.6)	5 (29.4)	12 (29.3)	0.413
Diabetes mellitus	48 (34)	9 (52.9)	14 (34.1)	0.299
Immunosuppression	19 (13.5)	3 (17.6)	1 (2.4)	0.108
Malignancy	33 (23.4)	2 (11.8)	9 (22)	0.550
Hepatic	22 (15.6)	2 (11.8)	6 (14.6)	0.913
Renal	43 (30.5)	7 (41.2)	19 (46.3)	0.145
Respiratory	24 (17)	2 (11.8)	7 (17.1)	0.856
RRT at time of treatment, n (%)	30 (21.3)	5 (29.4)	17 (41.5)	0.033
Combination therapy, n (%)	69 (49)	6 (35.3)	3 (7.3)	< 0.001
Ceftriaxone	69 (48.9)	2 (11.8)	1 (2.4)	
Ceftaroline	0 (0)	4 (23.5)	0 (0)	
Gentamicin	0 (0)	0 (0)	2 (4.9)	
Penicillin allergy, n (%)	8 (5.7)	10 (58.8)	18 (43.9)	< 0.001
Vancomycin resistance, n (%)	4 (2.8)	8 (47.1)	0 (0)	< 0.001
History of *Enterococcus* spp. BSI, n (%)	3 (2.1)	2 (11.8)	1 (2.4)	0.087
Infectious complication, n (%)				0.220
Endocarditis	26 (18.4)	2 (11.8)	1 (2.4)	
Osteomyelitis	5 (3.5)	1 (5.9)	1 (2.4)	
Septic arthritis	2 (1.4)	0 (0)	0 (0)	

AMP = ampicillin; DAP = daptomycin; VAN = vancomycin; BMI = body mass index; BSI = bloodstream infection; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; RRT = renal replacement therapy; SD = standard deviation

Table 2. Clinical outcomes

Outcome	Definitive Antibiotic			P-value
	AMP (n=141)	DAP (n=17)	VAN (n=41)	
28-day all-cause in-hospital mortality, n (%)	13 (9.2)	2 (11.8)	9 (22.0)	0.088
90-day readmission due to microbiological recurrence, n (%)	6 (4.3)	1 (5.9)	3 (7.3)	0.722
All-cause in-hospital mortality, n (%)	18 (12.8)	3 (17.6)	9 (22.0)	0.335

AMP = ampicillin; DAP = daptomycin; VAN = vancomycin

Figure 1. Kaplan-Meier survival curves based on definitive therapy

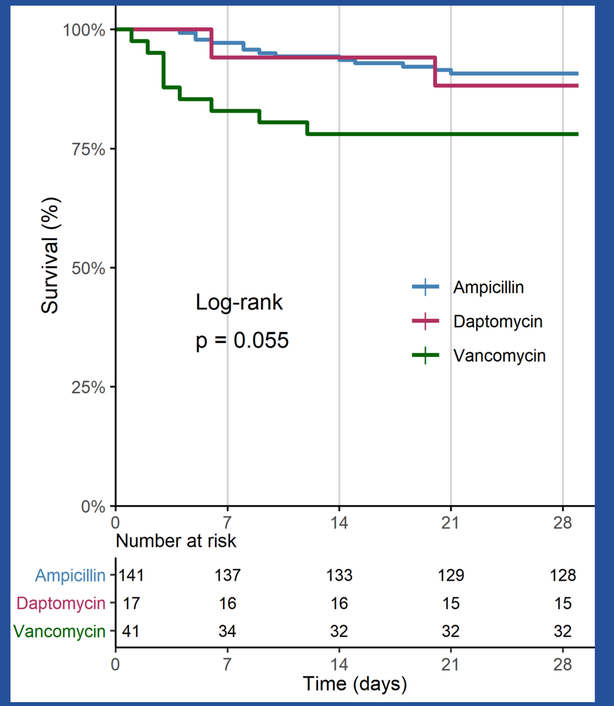

Table 3. Risk factors associated with 28-day all-cause in-hospital mortality

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.04 (1.01-1.08)	0.011	1.05 (1.02-1.09)	0.003
Combination therapy used	0.75 (0.32-1.74)	0.497		
Penicillin allergy	0.62 (0.19-2.09)	0.445		
Vancomycin resistance	0.64 (0.09-4.73)	0.661		
Index culture isolate				
E. faecalis	Reference	Reference	Reference	Reference
E. faecium	3.03 (1.13-8.12)	0.027	3.94 (1.39-11.1)	0.010
RRT at time of treatment	2.12 (0.94-4.77)	0.070	2.00 (0.84-4.75)	0.116
Definitive Antibiotic				
Ampicillin	Reference	Reference	Reference	Reference
Vancomycin	2.72 (1.16-6.37)	0.021	2.54 (1.04-6.21)	0.040
Daptomycin	1.28 (0.29-5.67)	0.745	0.87 (0.18-4.12)	0.862

HR = hazard ratio; CI = confidence interval; RRT = renal replacement therapy

CONCLUSIONS

- Treatment with VAN was found to be independently associated with 28-day all-cause in-hospital mortality in patients with ASE BSI compared to AMP or DAP
- Propensity score matching may be helpful to reduce treatment selection bias
- Prospective trials involving a larger cohort are necessary to confirm the findings of this study
- Further studies specifically comparing outcomes of DAP to AMP may be warranted, especially for infections, such as endocarditis and osteomyelitis

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