Comparative Use of Vancomycin versus Ampicillin for Blood Stream Infections Caused by Ampicillin-Susceptible *Enterococcus faecalis*

Michaele Phan, PharmD[1]; Renee Ackley, PharmD, BCPS, BCIDP[1]; Jacqueline Meredith, PharmD, BCIDP[1]; Alex Ebied, PharmD, BCCCP[2]; Kristen Goodrich, PharmD Candidate[3]; Mindy Sampson, DO[1]
Atrium Health's Carolinas Medical Center[1], Charlotte, NC; High Point University Fred Wilson School of Pharmacy[2], High Point, NC; UNC Eshelman School of Pharmacy[3], Chapel Hill, NC

Introduction

- Enterococcus blood stream infections (BSI) have a high incidence of mortality (33%).[1,2] Although inappropriate antimicrobial therapy has been found as a risk factor for mortality, optimal antimicrobial therapy has not been well established.[3]
- Available studies assessing the efficacy of beta-lactam antibiotics compared to vancomycin have varying results and have not assessed the impact of rapid blood culture identification (BCID) diagnostic testing.[4,5,6]
- No studies have examined the association of a specific beta-lactam antibiotic and have included all Enterococcus spp (*Enterococcus faecalis* and *faecium)* and polymicrobial BSI.
- Per Atrium Health's BCID treatment algorithm for Enterococcus species without the vanA/B gene, it is recommended to treat with ampicillin and reserve vancomycin for those with a documented penicillin allergy.

Objective

To compare outcomes in adults with ampicillin-susceptible and vancomycin-susceptible *Enterococcus faecalis* BSI treated with ampicillin or vancomycin therapy where BCID was available.

Methods

Primary Outcome

- 30-day all-cause mortality

Secondary Outcomes

- 90-day all-cause mortality
- Hospital length of stay
- Incidence of treatment failure[a]
- Incidence of persistent BSI[b]
- Incidence of adverse drug reactions (ADRs)
- Incidence of antibiotic change from initial definitive therapy[c]
- Time to active treatment
- Time to BCID
- Time to definitive therapy
- Time to beta-lactam therapy
- Time to culture clearance

Study Design

- Multisite retrospective cohort study

Inclusion

- ≥ 18 years old
- Initial episode of *E. faecalis* BSI from January 2017 to October 2021
- At least four days of either ampicillin or vancomycin

Exclusion

- Polymicrobial BSI[d]
- ≥ 50% of definitive therapy with concomitant use of ampicillin and vancomycin

Statistical Analysis

- Estimated sample size of 208 patients would provide 80% power to detect a differential 30-day mortality rate of 15% between the groups
- All statistical tests were two-tailed, and a P-value < 0.05 was considered statistically significant

[a]Treatment failure: Recurrent BSI (positive *E. faecalis* blood culture 90 days since first negative blood culture) or disseminated infection (positive isolate of *E. faecalis* from any other sterile site within 90 days)
[b]Persistent BSI: Positive blood cultures > 5 days after initiation of antibiotic therapy
[c]Antibiotic change from initial definitive therapy: only included changes to alternative intravenous therapy
[d]Polymicrobial BSI: ≥ 1 additional bacteria or fungi isolated in the same blood culture; clinically known contaminants were not considered polymicrobial

Results

Figure 1: CONSORT-Style Flow Diagram

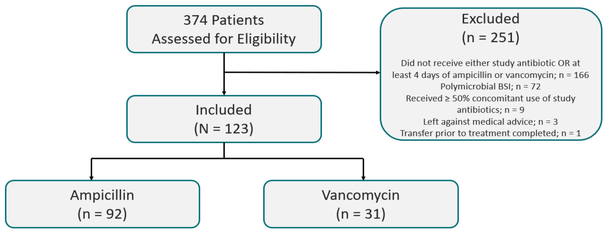


Figure 2: Baseline Characteristics

Characteristic	Ampicillin (n = 92)	Vancomycin (n = 31)	P-value
Age, year (SD)	67 ± 15	63 ± 17.8	0.237
Male sex, n (%)	69 (75.0)	12 (38.7)	< 0.001
Body mass index (kg/m^2), mean (SD)	28.02 ± 8.8	30.3 ± 11.3	0.303
Charleston Comorbidity Index, median	3	3	0.446
Pitt bacteremia score, median	3	1	0.862
Allergy to penicillin, n (%)	7 (7.6)	18 (58.1)	< 0.001
History of vancomycin infusion reaction, n (%)	1 (1.1)	0 (0)	1.000
Infectious Disease consultation, n (%)	75 (81.5)	21 (67.7)	0.109
Source of BSI, n (%)			
Urinary	40 (43.5)	8 (25.8)	0.081
Unknown	13 (14.1)	6 (19.4)	0.486
Intra-abdominal	12 (13.0)	4 (12.9)	1.000
Line-related	11 (12.0)	4 (12.9)	1.000
Bone and joint	9 (9.8)	3 (9.7)	1.000
Endocarditis	9 (9.9)	2 (6.5)	1.000
Skin and soft tissue infection	5 (5.4)	5 (16.1)	0.060
Other	5 (5.4)	3 (9.7)	0.414

Figure 3: Antibiotic Therapy Data

Characteristic	Ampicillin (n = 92)	Vancomycin (n = 31)	P-value
Initial active antibiotic[a], n (%)			
Vancomycin	69 (75.0)	28 (90.3)	0.080
Piperacillin-tazobactam	22 (23.9)	4 (12.9)	0.308
Ampicillin	19 (20.7)	0 (0)	0.003
Ampicillin-sulbactam	11 (12.0)	0 (0)	0.064
Meropenem	2 (2.2)	0 (0)	1.000
Other	5 (5.4)	3 (9.7)	0.414
Time to vancomycin goal trough[b], days (SD)	-	4.11 ± 1.7	-
Definitive oral antibiotic, n (%)	30 (32.6)	9 (29.0)	0.711
Initiation of timing			0.784
Inpatient	10 (10.9)	4 (12.9)	
Outpatient	20 (21.7)	5 (16.1)	
Oral antibiotic prescribed			
Amoxicillin	20 (21.7)	1 (3.2)	0.028
Amoxicillin-clavulanate	8 (8.7)	5 (16.1)	0.088
Other	2 (2.2)	3 (9.7)	0.101
Duration of total antibiotic therapy, days (SD)	24.2 ± 13.9	19.7 ± 12.9	0.105

[a]Patients may have multiple antibiotics for empiric therapy
[b]Vancomycin trough goal: 15 – 20 mg/L

Figure 4: Primary Outcome 30-Day All-cause Mortality

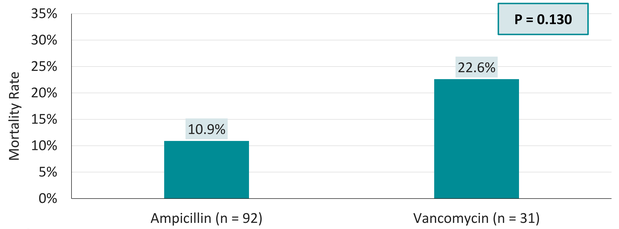


Figure 5: Secondary Outcomes

Outcome	Ampicillin (n = 92)	Vancomycin (n = 31)	P-value
90-day all-cause mortality	17 (18.5)	8 (25.8)	0.422
Adverse drug reactions, n (%)	13 (14.1)	7 (22.6)	0.270
Acute kidney injury	13 (14.1)	5 (16.1)	1.000
Itching	0 (0)	1 (3.2)	0.252
Vancomycin infusion reaction	0 (0)	1 (3.2)	0.252
Agranulocytosis	0 (0)	1 (3.2)	0.252
Treatment failure, n (%)	8 (8.7)	2 (6.5)	1.000
Recurrent BSI	6 (6.5)	2 (6.5)	1.000
Disseminated infections	2 (2.2)	0 (0)	1.000
Persistent BSI, n (%)	2 (2.2)	0 (0)	1.000
Change from initial definitive therapy, n (%)	11 (12.0)	6 (19.4)	0.302
Hospital length of stay, days (SD)	11.5 ± 10.5	8.9 ± 6.9	0.119

Figure 6: Microbiology Secondary Outcomes

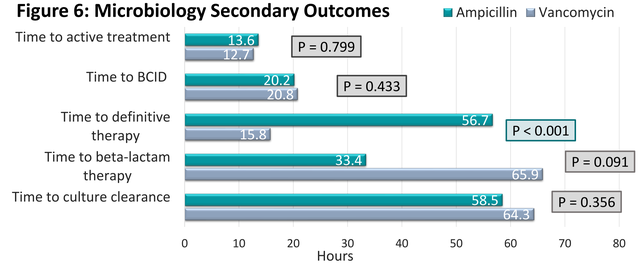
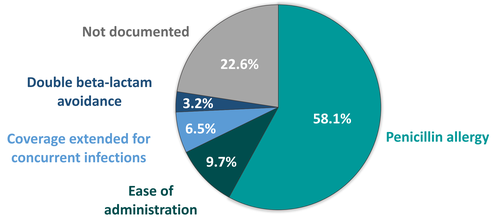


Figure 7: Reasons for Definitive Vancomycin Antibiotic, n = 31



Discussion

- Definitive therapy of ampicillin or vancomycin *E. faecalis* BSI was not associated with a difference in 30-day all-cause mortality.
  - There was a 12% mortality reduction observed in the ampicillin group. Although not statistically significant, this may be clinically significant.
  - This numerical difference is similar to the 15% mortality difference found in a prior study.[4]
- We hypothesized the use of rapid diagnostics would vastly reduce the time to ampicillin initiation, but this did not occur.
  - Although time to BCID was 20 hours for both groups, the time to definitive therapy for ampicillin was significantly longer. This difference may be due to providing extended coverage for other potential organisms or provider preference to wait for susceptibilities before narrowing therapy.
  - The time to ampicillin initiation was shorter than the time to beta-lactam initiation in a prior study at 83 hours.[5]
- 58.1% of patients remained on definitive vancomycin therapy for a documented penicillin allergy.
  - Although 10% of the U.S. population report a penicillin allergy, only 1 in 20 are confirmed.[7]
  - There is opportunity to challenge patients with a reported penicillin allergy and receiving vancomycin. This may increase the use of ampicillin over vancomycin.
- 30% of both treatment groups transitioned from intravenous antibiotics to oral antibiotics, but there is a paucity of data on the role of oral antibiotics in the treatment of *E. faecalis* BSI. Future research is warranted.

Limitations

- This was a retrospective design.
- Only the first *E. faecalis* blood stream infection episode was included.
- The sample size was too small to achieve 80% power subjecting to a type II error.
- Given there were more Infectious Disease consults in the ampicillin group, there may be selection bias for the choice of antibiotic given as ampicillin was recommended more often.

Conclusion

- There was no statistical difference in 30- and 90-day all-cause mortality or incidence of treatment failure in patients with *E. faecalis* BSI treated with ampicillin or vancomycin.
- There was no difference in ADRs between groups and rapid diagnostic testing did not shorten time to ampicillin initiation.
- Given our study was not sufficiently powered, larger prospective studies are warranted.

References

1. Low DE, Keller N, Barth A, Jones RN. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: Results from the SENTRY Antimicrobial Surveillance Program, 1997-1999. Clin Infect Dis. 2001;32(10 SUPPL. 2):1997-1999.
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39(3):309-317.
3. Suppli M, Aabenhus R, Harboe ZB, Andersen LP, Tvede M, Jensen JUS. Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy. Clin Microbiol Infect. 2011;17(7):1078-1083.
4. Foo H, Chater M, Maley M, Van Hal SJ. Glycopeptide use is associated with increased mortality in Enterococcus faecalis bacteraemia. J Antimicrob Chemother. 2014;69(8):2252-2257.
5. Petersiel N, Bitterman R, Manaa A, et al. β-lactam antibiotics vs. vancomycin for the early treatment of enterococcal bacteraemia: A retrospective cohort study. Int J Antimicrob Agents. 2019;53(6):761-766. doi:10.1016/j.ijantimicag.2019.03.023
6. Fletcher JM, Kram SJ, Sarubbi CB, Anderson DJ, Kram BL. Effectiveness of Vancomycin or Beta-Lactam Therapy in Ampicillin-Susceptible Enterococcus spp. Bloodstream Infections. J Pharm Pract. 2019;32(4):375-381.
7. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. Curr Allergy Asthma Rep. 2014;14(11):476.

Disclosures

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.

Contact Information
Michaele Phan | mxphan88@gmail.com