Evaluating Clinical Outcomes and Efficacy of Daptomycin in Combination with a Beta-Lactam for the Treatment of Vancomycin-Resistant Enterococcus (VRE) Bacteremia

Nerea Irusta, PharmD[1]; Ana D. Vega, PharmD, BCIDP[1]; Yoichiro Natori, MD, MPH[1,2]; Lilian Abbo, MD, FIDSA[1,2]; Kailynn J. DeRonde, PharmD, BCIDP[1,3]

[1]Jackson Memorial Hospital, Jackson Health System; [2]University of Miami; [3]Holtz Women and Children's Hospital, Jackson Health System (Miami, FL)

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BACKGROUND

- In vitro studies have demonstrated synergistic bactericidal activity with daptomycin plus ampicillin, ceftriaxone, ertapenem, cefepime, and ceftaroline in the treatment of vancomycin resistant enterococci (VRE). However, there is a paucity of literature presenting clinical outcomes.
- In early 2019, in light of the in vitro findings, our institution moved towards combination therapy for VRE bloodstream infections (BSI) in patients with elevated daptomycin MICs or complicated infections.
- The purpose of this study was to assess real world efficacy of daptomycin plus a β-lactam with in-vitro activity vs. other therapies for treatment of VRE BSI.

OBJECTIVES

- Primary outcome: time-to-microbiological clearance in days, defined as time between therapy onset to repeat negative blood cultures.
- Secondary outcomes: microbiological clearance within 3 days, recurrence of BSI within 30 days, infection related mortality; inpatient 30-day all cause mortality, duration of therapy (days), intensive care (ICU) length of stay (LOS) in days, and hospital LOS in days.

METHODS

- IRB approved, single center, retrospective study of adult patients with VRE BSI from 1/2018-9/2019.
- Excluded patients < 18 years old, pregnant, and/or incarcerated.
- Targeted daptomycin doses were based on MIC (µg/mL).
  - MIC < 2 = 8 mg/kg; MIC 2 = 10 mg/kg; MIC 3-4 = 12 mg/kg.
- In the primary analysis, combination therapy was defined as daptomycin plus ampicillin, ampicillin-sulbactam, ceftriaxone, ertapenem, cefepime, or ceftaroline for at least 24 hours; other therapy was defined as either daptomycin or linezolid monotherapy.
- In the post-hoc analysis, outcomes were evaluated for daptomycin combination therapy with any β-lactam vs. other therapy.
- Chi Square or Fischer's Exact Tests were performed as appropriate for nominal data; Mann-Whitney Tests were performed for ordinal and continuous variables; a 2 sided p value < 0.05 was considered significant. Factors associated with significance for outcomes, via univariate analysis, were evaluated with multivariable logistic regression (MLR), removed in a backward-step approach.

RESULTS: BASELINE CHARACTERISTICS

- 85 patients were evaluated; 23 in the combination arm and 62 in the other arm (25 patients daptomycin, 37 patients linezolid).
- Patients in the combination arm were significantly more likely to have a higher Charlson Comorbidity Index (CCI), be a transplant recipient, and have a primary source of infection other than a primary bacteremia or CLABSI (Table 1).
- Patients in the combination arm had numerically higher Pitt Bacteremia scores (PBS) (Table 1).

Table 1: BASELINE CHARACTERISTICS	Daptomycin + β-Lactam (n= 23)	Other therapy (n= 62)	*P value*
Age, median (range)	61 (35-76)	53 (25-84)	0.142
Race, n (%)			
Black	5 (22)	27 (44)	0.065
Caucasian	**11 (48)**	**13 (21)**	**0.014**
Hispanic	7 (30)	22 (35)	0.662
Transplant Recipient, n (%)	**14 (61)**	**14 (23)**	**< 0.001**
Pitt Bacteremia Score, median (range)	6 (0-12)	3 (0-13)	0.087
Charlson Comorbidity Index, median (range)	**6 (2-12)**	**5 (0-10)**	**0.013**
VRE colonization, n (%)	14 (88)[a]	17 (63)[a]	0.083
Beta-lactam, n (%)			
Ampicillin	8 (35)	N/A	N/A
Ampicillin-sulbactam	3 (13)		
Ceftriaxone	3 (13)		
Cefepime	2 (9)		
Ertapenem	5 (22)		
Ceftaroline	2 (9)		
Daptomycin dose <8mg/kg, n (%)	1 (4)	2 (8)[b]	0.601
Daptomycin dose considered appropriate, n (%)	18 (78)	19 (76)[b]	0.852
MIC of Daptomycin via E-test, n (%)			
<1 µg/mL	1 (4)	1 (4)[b]	0.951
1-2 µg/mL	10 (43)	10 (40)[b]	0.807
3 µg/mL	8 (35)	7 (28)[b]	0.612
4 µg/mL	2 (9)	2 (8)[b]	0.930
≥6 µg/mL	0 (0)	0 (0)[b]	N/A
Unknown	2 (9)	5 (20)[b]	0.267
Primary Source, n (%)			
Blood	**8 (35)**	**38 (61)**	**0.029**
Primary Bacteremia	**3 (13)**	**25 (40)**	**0.017**
CLABSI	5 (22)	13 (21)	0.938
Other	**15 (65)**	**24 (39)**	**0.029**
Pulmonary	3 (13)	3 (5)	0.189
Gastrointestinal	7 (30)	14 (23)	0.455
Hepatic/Biliary	**3 (13)**	**0 (0)**	**0.027**
Urinary	2 (9)	7 (11)	0.729
Polymicrobial, n (%)	10 (43)	24 (39)	0.690

[a]n= 16, n= 27; 16 patients had VRE screening in the daptomycin plus beta-lactam group; 27 patients had VRE screening in the other therapy group

[b]n= 25; 25 patients received daptomycin in the other group **without** a beta-lactam that has previously been cited in the literature as demonstrating in-vitro activity against VRE when combined with daptomycin

RESULTS: OUTCOMES

TABLE 2: PRIMARY AND SECODARY OUTCOMES	Daptomycin + in-vitro β-Lactam (n = 23)	Other (n = 62)	*P* value
Primary Outcome			
Days to microbiological cure, median (range)	2 (1-33)	2 (1-21)	0.213
Secondary Outcomes			
Microbiological cure ≤3 days, n (%)	13 (56.5)	42 (67)	0.336
Duration of therapy in days, median (range)	16 (1-86)	11 (11-49)	**0.001**
Length of stay in days, median (range)	77 (2-494)	46 (5-200)	**0.007**
Length of ICU stay in days, median (range)	34 (0-342)	9 (0-142)	**0.002**
In-patient 30-day mortality, n (%)	6 (26)	17 (27)	0.902
Infection-related mortality, n (%)	2 (8.7)	6 (9.68)	0.999
Recurrence within 30 days, n (%)	10 (43)	5 (8)	**< 0.001**

- No difference was found in the primary outcome between arms (p=0.213).
- The post-hoc analysis also demonstrated non-significance for in-patient 30-day mortality (p=0.322), infection-related mortality (p=0.999), and microbiological cure within 3 days (p=0.979). Unlike the primary analysis, there was no difference in recurrence within 30 days (p=0.166).
- The presence of polymicrobial infection (p=.008) and higher PBS (p=0.005) were significantly associated with infection-related mortality by MLR.
- Higher PBS was also significantly associated with 30-day in-patient mortality via univariate analysis (p < 0.001).
- A Mann Whitney test indicated the incidence of infection-related mortality was greater for patients with higher daptomycin MICs (U=20.5, p=0.06).
- An underlying source may be related to BSI recurrence (p=0.075).

DISCUSSION and CONCLUSIONS

- Although there wasn't a significant difference in time-to-microbiological clearance, patients treated with daptomycin plus a β-lactam with in-vitro activity had higher CCI and PBS. They were more likely to have an underlying source, be a transplant recipient, and received a significantly longer duration of therapy. This is consistent with our algorithm for combination therapy in complicated VRE BSI. Despite these differences, these patients did not appear to have an increased risk of death.
- Despite no difference in mortality, patients in the combination arm had a significantly longer LOS and ICU LOS, an indication they were surviving their infection and potentially favoring the combination arm.
- This study is limited by retrospective design, small sample size, and potential selection bias. Prospective, randomized controlled trials are needed to further validate these findings.