Carolina Antimicrobial Stewardship Program | UNC Hospitals

Vancomycin-Resistant *Enterococcus faecium* Treatment

Vancomycin-resistant enterococci (VRE) has emerged as an important pathogen causing nosocomial infections and vancomycin resistance has been shown to be a principal predictor of mortality with regard to enterococcal bacteremia. While treatment options for VRE bacteremia are limited, linezolid is currently FDA-approved for VRE infection. However, because of its bacteriostatic nature, there are concerns about using linezolid for the treatment of VRE bacteremia. Daptomycin has rapid bactericidal activity against enterococci, and evidence supports the use of high doses for the treatment of VRE bacteremia, although not FDA-approved for that indication.

Table 1: CLSI Daptomycin MIC (mg/L) breakpoints for *E. faecium* and recommended dosing

	Susceptible	Susceptible Dose-Dependent (SDD)	Resistant (R)
Daptomycin MIC	-	≤ 4	≥ 8
Recommended Dosing	-	8-12 mg/kg Q24H	-

Note: Recommended dosing is for adult patients with normal renal function. See UNC Pharmacy Clinical Guidelines for dosing adjustments in patients with renal dysfunction:
https://unchcs.intranet.unchealthcare.org/dept/Pharmacy/mc/Pages/ClinicalGuidelines.aspx

Dose based on total body weight for non-obese patients. For BMI ≥ 30, use adjusted body weight.
AdjBW = IBW + 0.4(TBW-IBW)

Table 2: Treatment Recommendations

Treatment Recommendation	
VRE bacteremia and invasive VRE infections[1]	Daptomycin 10-12 mg/kg IV once daily OR Linezolid 600 mg IV or PO bid
VRE endocarditis or other high-burden infections in which source control is not achievable	Daptomycin 12 mg/kg IV once daily -Consider combination therapy with a B-lactam -Choice of B-lactam to depend on patient specific factors

[1] Choice of linezolid or daptomycin is based on patient specific factors (tolerability, drug interactions, need for gram positive treatment for pneumonia, other infections, etc.)

Literature Review

Monotherapy:

- 2 of the 4 meta-analyses showed improved survival with linezolid compared to daptomycin (the other 2 showed no difference)[1-4]
- Retrospective study in 2019 demonstrated increased clinical failure for daptomycin vs linezolid[5]
- VA study in 2015 is the only study demonstrating increased mortality with linezolid, even after adjusting for confounding factors[6]
- In almost every study reviewed, the median daptomycin dose was 6 mg/kg/day

Daptomycin Dosing:

- FDA-approved dose for BSI due to *S. aureus* is 6 mg/kg/day; however, VRE isolates generally demonstrate MICs 2- to 4-fold higher than those of *S. aureus*
- 2 cohort studies demonstrated lower mortality when higher doses of daptomycin were compared with lower doses.[7,8] There was no association between daptomycin dose and elevated CK in either study. A prospective observational study showed doses of 11 mg/kg/day or higher were associated with lower mortality in patients with higher MICs (≥2), but not in patients with lower MICs (≤1). Higher doses were associated with higher rates of CK elevations in this study.[9]

Combination Therapy:[10-15]

- B-lactams reduce the net positive bacterial surface charge of VRE, and thereby enhance the bactericidal effect of daptomycin.
- In vitro data show synergy between daptomycin and various B-lactams (ampicillin, ceftaroline, ertapenem, ceftriaxone, and cefepime).
- One retrospective cohort study of patients with VRE bacteremia showed lower mortality in patients receiving high dose daptomycin + beta-lactam combo compared to daptomycin monotherapy.

Resources

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