Vancomycin-Resistant Enterococcus Treatment Guidance

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 treating of VRE bacteremia. Daptomycin has rapid bactericidal activity against enterococci and has evidence in the setting of VRE bacteremia, although not FDA-approved for that indication.

Treatment Recommendations

<table>
<thead>
<tr>
<th>CLSI Daptomycin MIC (mg/L) breakpoints for Enterococcus faecium\textsuperscript{14}</th>
<th>Susceptible (S)</th>
<th>Susceptible dose-dependent (SDD)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin MIC</td>
<td>≤4</td>
<td>≥8</td>
<td></td>
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<tr>
<td>Recommended Dosing</td>
<td>8-12 mg/kg Q24H</td>
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VRE bacteremia/invasive VRE infections:

<table>
<thead>
<tr>
<th>Susceptibility Profile</th>
<th>Treatment Recommendation</th>
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<tbody>
<tr>
<td>Daptomycin MIC &lt; 2 AND Linezolid Susceptible</td>
<td>Linezolid 600 mg bid OR Daptomycin 10 mg/kg IV daily</td>
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<tr>
<td>Daptomycin MIC &gt; 2 and &lt; 4 AND Linezolid Susceptible</td>
<td>Linezolid 600 mg bid OR Daptomycin 12 mg/kg IV daily</td>
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</tbody>
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Choice of linezolid or daptomycin is based on patient specific factors (tolerability, drug interactions, need for gram-positive treatment for pneumonia, other infections, etc.)

VRE endocarditis or other high-burden infections in which source control is not achievable:

Daptomycin 12 mg/kg IV daily
- Consider combination therapy with a B-lactam
- Choice of B-lactam to depend on patient specific factors

Dosing weight for daptomycin when using high dose regimens:

Total body weight should be used for non-obese patients
Obese patients (BMI ≥ 30) use adjusted body weight (AdjBW)
AdjBW = ideal body weight (IBW) + 0.4(TBW-IBW)
Literature Review

Monotherapy:
- 2 of the 4 most recent and robust 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

Combination Therapy9-13:
- B-lactams reduce the net positive bacterial surface charge of VRE, and thereby enhance the bactericidal effect of daptomycin
- In vitro data shows synergy between daptomycin and various B-lactams (ampicillin, ceftaroline, ertapenem, ceftriaxone, and cefepime)

References: