Susceptible Dose-Dependent Dosing Guidance: Daptomycin and Ceftaroline

Summary
The Clinical & Laboratory Standards Institute (CLSI) includes a susceptible dose-dependent (SDD) category for certain drug and organism combinations. The SDD is a breakpoint category for which the susceptibility of an isolate depends on the dosing regimen used. For isolates with SDD susceptibility results, dosing regimens that achieve higher drug exposure are necessary. For the highest probability of adequate coverage of an SDD isolate, consideration should be given to using the maximum, literature-supported dosing regimens.¹

UNC Medical Center’s Microbiology Lab includes an SDD category for *E. faecium*: daptomycin and *S. aureus*: ceftaroline.

SDD: *E. faecium*—Daptomycin

**Background**
The FDA-approved dosing for daptomycin was originally based on treatment of infections due to staphylococci. Though not a labeled indication, daptomycin is an important antibiotic for treatment of infections due to vancomycin-resistant *Enterococcus*. Daptomycin MICs for *E. faecium* are often higher than MICs for other Gram-positive organisms. Studies have found that applying labeled daptomycin dosing to severe infections due to *E. faecium* lead to poorer outcomes.² In two cohort studies, high-dose daptomycin was associated with lower mortality in patients with vancomycin-resistant *E. faecium* bacteremia. “High-dose” was considered to be ≥10 mg/kg daily and ≥9mg/kg daily, respectively. In both studies, the daptomycin MIC was 4 mg/L in ~ 70% of patients.³,⁴ Studies have also shown that high-dose daptomycin is generally well-tolerated and safe. It is recommended to monitor creatine kinase (CK) weekly in all patients receiving daptomycin.⁵

**Recommendations**

<table>
<thead>
<tr>
<th>Daptomycin MIC (mg/L) breakpoints for <em>Enterococcus faecium</em>¹</th>
<th>Susceptible (S)</th>
<th>Susceptible dose-dependent (SDD)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin MIC</td>
<td>-</td>
<td>≤4</td>
<td>≥8</td>
</tr>
<tr>
<td>Recommended dosing*</td>
<td>8-12 mg/kg Q24H</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Recommended dosing is for adult patients with normal renal function. Please 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 actual total body weight for non-obese patients. For BMI ≥ 30 use adjusted body weight. AdjBW = IBW + 0.4(TBW-IBW)

For serious infections caused by *E. faecium* reported as SDD (MIC ≤4 mg/L), dosing regimens of daptomycin 8-12 mg/kg per day are recommended. In these cases, consider consultation with Infectious Diseases. These recommendations apply to adult patients only. Equivalent high-dose daptomycin strategies have not been studied in children. Consider consultation with Pediatric Infectious Diseases. For serious infections due to other *Enterococcus* spp. or *S. aureus*, high-dose daptomycin strategies may also be appropriate. Contact the Antimicrobial Stewardship Program (ASP) for assistance with daptomycin dosing (pager 216-2398).

**References:**


Prepared by the UNC Medical Center Antimicrobial Stewardship Program
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**SDD: S. aureus: Ceftaroline**

**Background**
The FDA-approved adult dosing for ceftaroline is 600 mg IV every 12 hours given over 5-60 minutes. Most *S. aureus* isolates in the United States have a ceftaroline MIC of < 1 mg/L, however isolates with higher MICs have been reported.\(^1\) In the Phase 3 clinical trials using doses of ceftaroline 600 mg IV every 12 hours, the majority of *S. aureus* clinical isolates had ceftaroline MICs of < 1 mg/L.\(^2\) Pharmacokinetic/pharmacodynamics (PD/PD) modeling data support dosage regimens of 600 mg IV every 8 hours infused over 2 hours for *S. aureus* organisms with MICs of 2-4 mg/L.\(^2\) In a randomized controlled trial, this higher dosing regimen was shown to be safe and effective in patients with complicated skin and soft tissue infections with evidence of systemic inflammation.\(^3\)

**Recommendations**

<table>
<thead>
<tr>
<th>Ceftaroline MIC (mg/L) breakpoints for <em>Staphylococcus aureus</em>(^4)</th>
<th>Susceptible (S)</th>
<th>Susceptible dose-dependent (SDD)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline MIC</td>
<td>≤1</td>
<td>2-4</td>
<td>≥8</td>
</tr>
<tr>
<td>Recommended dosing*</td>
<td>600 mg every 12 hours over 5-60 minutes</td>
<td>600 mg every 8 hours over 2 hours</td>
<td>-</td>
</tr>
</tbody>
</table>

*Recommended dosing is for adult patients with normal renal function. Please see UNC Pharmacy Clinical Guidelines for dosing adjustments in patients with renal dysfunction: [https://unchcs.intranet.unchealthcare.org/dept/Pharmacy/mc/Pages/ClinicalGuidelines.aspx](https://unchcs.intranet.unchealthcare.org/dept/Pharmacy/mc/Pages/ClinicalGuidelines.aspx)*

For infections caused by *S. aureus* reported as SDD (MIC 2-4 mg/L), ceftaroline 600 mg every 8 hours (2 hour infusion) is recommended. In these cases, consider consultation with Infectious Diseases. These recommendations apply to adult patients only. Equivalent high-dose ceftaroline strategies have not been studied in children. Consider consultation with Pediatric Infectious Diseases.

**References:**