Treatment of Methicillin-Susceptible Staphylococcus aureus Osteoarticular and Prosthetic Joint Infections: Using the Oxacillin Minimum Inhibitory Concentration to Guide Appropriate Ceftriaxone Use

To the Editor—Methicillin-susceptible Staphylococcus aureus (MSSA) prosthetic joint infection (PJI) is difficult to treat even with surgical debridement and antimicrobial therapy. The antimicrobial agents of choice for MSSA are typically oxacillin, nafcillin, and cefazolin [1]. The use of ceftriaxone for MSSA PJI is controversial, as mentioned in the recently published Infectious Diseases Society of America (IDSA) guidelines on PJI management [2], in which it is recommended that ceftriaxone be dosed 1–2 g every 24 hours. We believe 2 g/day is appropriate but 1 g/day may give inadequate drug levels; thus, a higher risk for failure given ceftriaxone minimum inhibitory concentration (MIC) 90 values against MSSA is 4 µg/mL [3] (Table 1).

Current US Food and Drug Administration (FDA)–recommended ceftriaxone dosage for MSSA is 2–4 g/day [4]. This recommendation is based on pharmacokinetic-pharmacodynamic (PK/PD) analysis demonstrating that ceftriaxone 2 g/day will attain 25% free-drug time above MIC with 90% probability for a MIC at ≤4 µg/mL after considering ceftriaxone’s >90% protein binding, leading to lower drug level in tissue compared to serum [5]. Ceftriaxone given at 1 g daily will attain a target MIC at ≤2 µg/mL, but only 8% of MSSA in the SENTRY Antimicrobial Surveillance Program database in the United States has these MIC results (Table 1).

Clinical studies generally support a ceftriaxone dose of at least 2 g/day for osteoarticular and PJI infections. The IDSA PJI guidelines cited 2 cohort studies [6,7] and 1 registry trial [8] to support its ceftriaxone recommendation. On closer examination, both Tice et al and Guglielmo et al [6,7] used a ceftriaxone dosage of 2 g/day whereas Wynn et al [8] reported a mean of 1.85 g/day. A recent retrospective controlled study with a large number of MSSA PJIs, not cited by the guidelines, suggests that ceftriaxone 2 g/day and oxacillin 2 g every 6 hours have similar cure rates [9].

Table 1. Distribution of 14,335 Methicillin-Susceptible Staphylococcus aureus Isolates From the SENTRY Program, 2011–2012

<table>
<thead>
<tr>
<th>Ceftriaxone MIC, µg/mL</th>
<th>Oxacillin MIC, µg/mL</th>
<th>≤0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥16</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>&lt;0.1</td>
<td>39.3</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>300</td>
<td>163</td>
<td>74</td>
<td>4.3</td>
<td>53.2</td>
</tr>
<tr>
<td>4</td>
<td>4690</td>
<td>7106</td>
<td>747</td>
<td>74</td>
<td>88.0</td>
<td>6.5</td>
</tr>
<tr>
<td>2</td>
<td>774</td>
<td>206</td>
<td>19</td>
<td>2</td>
<td>7.0</td>
<td>1.1</td>
</tr>
<tr>
<td>1</td>
<td>76</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>39.3</td>
<td>53.2</td>
<td>6.5</td>
<td>1.1</td>
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</tr>
</tbody>
</table>
Because ceftriaxone is considered second-line therapy for MSSA, we believe ceftriaxone should be used cautiously in PJI and the dosage guided by the oxacillin MIC test result. Currently, the Clinical and Laboratory Standards Institute (CLSI) determines MSSA susceptibility based on oxacillin (MIC ≤2 µg/mL = susceptible) and cefoxitin results to detect the mecA gene [10]. CLSI no longer has ceftriaxone breakpoints (previously ≤8 µg/mL). We believe oxacillin is a good surrogate marker to predict ceftriaxone susceptibility from our analysis of the SENTRY Program database (Table 1). Current FDA ceftriaxone breakpoints are ≤4 µg/mL (susceptible), 8 µg/mL (intermediate), and ≥16 µg/mL (resistant). Using the oxacillin test result, the very major false susceptible error was <0.1% (oxacillin-susceptible/ceftriaxone-resistant) and minor errors were only 4.3% (oxacillin-susceptible/ceftriaxone-intermediate), both of which are well within CLSI’s acceptable limits. However, the probability of obtaining a ceftriaxone MIC ≥8 µg/mL dramatically increases at higher oxacillin MICs (eg, 1.6%, 3.9%, 17.5%, and 48.7% for an oxacillin MIC of ≤0.25, 0.5, 1, and 2 µg/mL, respectively). Therefore, we propose using ceftriaxone for serious MSSA infections only when the oxacillin MIC is ≤0.5 µg/mL and with a minimum dosing of 2 g/day. Although an oxacillin MIC of 1 or 2 µg/mL does not necessarily exclude ceftriaxone use, a dosage of 2 g every 12 hours would be preferred to ensure adequate drug levels and corresponding PK/PD target attainment.

We hope the authors of the IDSA PJI guidelines [2] will reconsider a ceftriaxone dosage of 2–4 g/day for MSSA to be consistent with current FDA product package insert recommendations and contemporary PK/PD and surveillance analyses.

**Note**

*Potential conflicts of interest.* All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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