Guidance document on use of daptomycin to treat enterococcal bloodstream infection and endocarditis.

Updated April 2020

Introduction

Due to the lack of other effective agents, daptomycin has become increasingly used for the treatment of enterococcal infections, especially vancomycin-resistant strains (VRE). There is increasing evidence that the EMA-approved dosing regimens of daptomycin (4-6 mg/kg/day), designed originally for *Staphylococcus aureus* infections, are inadequate for treating enterococcal bloodstream infection [1].

When clinical breakpoints for daptomycin were originally set there was insufficient evidence to set a PK-PD breakpoint and MIC breakpoints for staphylococci and streptococci groups A, B, C, G were set at S≤1, R >1mg/L. It was considered that there was insufficient evidence to set a clinical breakpoint for enterococci for any indication.

If daptomycin is to be used for the treatment of enterococcal bloodstream infection or endocarditis and clinical breakpoints selected, there are two important considerations: selection of a dosing regimen and laboratory testing to support treatment.

Selection of a dosing regimen

There are several lines of evidence indicating that dosing regimens above 6 mg/kg/day are required for treating enterococcal bloodstream infection: PK-PD studies, MIC distributions, clinical outcome studies, studies examining the emergence of resistance during treatment and the safety of high doses.

PK-PD studies

The determinant of efficacy of daptomycin is the \( \frac{fAUC}{MIC} \) ratio [2]. In a recent study using the mouse thigh model, the target \( \frac{fAUC}{MIC} \) for a 1-log kill against *E. faecium* was 12.9 [3]. A 1-log reduction was not achieved against *E. faecalis*; a target of 7.2 achieved bacteriostasis with this species. With a human-simulated regimen of 6 mg/kg/day, a 1-log10-CFU reduction was observed in 3/3 *E. faecium* isolates with MICs of <4 mg/L and 0/3 *E. faecium* isolates with MICs of ≥4 mg/L.

A recent investigation undertook a CART analysis of clinical outcome data from enterococcal bloodstream infection treatment studies using published PK data [4]. An \( \frac{fAUC}{MIC} \) of 27.4 best predicted survival at 30 days. This value was statistically significant in patients with low acuity (\( n=77, \ p=0.006 \)) and nearly achieved statistical significance in all patients (\( n=114, \ p=0.051 \)). CART analysis of microbiological clearance identified an \( \frac{fAUC}{MIC} \) target of 19.9, although this did not reach statistical significance in all patients (\( n=66 \)) or the subset of those with low acuity (\( n=48 \)). The results of Monte Carlo simulations using the data generated from these analyses are shown in Table 1. Some small differences were noted for males versus females. Satisfactory target attainment rates were only seen with a dose of 12 mg/kg/day and then only for strains with MICs up to 2 mg/L.
Table 1: Probability of survival threshold (fAUC/MIC >27.43) attainment using Monte Carlo simulation [4]

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>6 mg/kg/day</th>
<th>8 mg/kg/day</th>
<th>10 mg/kg/day</th>
<th>12 mg/kg/day</th>
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<tbody>
<tr>
<td>0.25</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>91.0, 97.9</td>
<td>98.7, 99.9</td>
<td>99.9, 100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>32.4, 54.4</td>
<td>60.7, 80.4</td>
<td>80.4, 92.9</td>
<td>91.0, 97.9</td>
</tr>
<tr>
<td>4</td>
<td>1.5, 5.5</td>
<td>7.3, 18.1</td>
<td>18.1, 36.2</td>
<td>32.4, 54.4</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.0, 0.2</td>
<td>0.2, 2.0</td>
<td>1.5, 5.5</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Males and females were simulated separately. For MICs at which the probability differs, values are presented as ‘male, female’.

MIC distributions

MIC distributions for the wild-type populations of Enterococcus faecalis and Enterococcus faecium determined using EUCAST methods. ECOFFs are 4 mg/L and 8 mg/L, respectively (Table 2).

Table 2: MIC distributions and epidemiological cut-off values (mg/L) for Enterococcus spp.

<table>
<thead>
<tr>
<th>Species</th>
<th>Dist</th>
<th>≤0.06</th>
<th>0.125</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>≥16</th>
<th>ECOFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>E faecalis</td>
<td>16</td>
<td>9</td>
<td>99</td>
<td>524</td>
<td>3794</td>
<td>10066</td>
<td>5148</td>
<td>525</td>
<td>16</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>E faecium</td>
<td>16</td>
<td>5</td>
<td>39</td>
<td>66</td>
<td>198</td>
<td>988</td>
<td>11228</td>
<td>3308</td>
<td>230</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

Data from EUCAST MIC distribution website, April 2020

Clinical outcome studies in bloodstream infection

Foolad et al. reviewed the relationship between daptomycin dosing regimen and outcomes in patients with vancomycin-resistant enterococcal bloodstream infection [1]. These authors selected studies where ‘standard’ dosing regimens were compared to ‘high-dose’ regimens (>6-8 mg/kg/day). Reporting on six published studies, these authors concluded that earlier smaller studies were unable to demonstrate a mortality benefit from high-dose regimens, while later larger studies [5,6,7] showed a statistically significant benefit, particularly at doses of >9-10 mg/kg/day.

Microbiological clearance compared to dose was also examined by Foolad et al. Only one of the six studies showed a benefit for high doses in terms of clearance rates, although the numbers were small [8]. One study did show a more rapid clearance at high doses [6], while another did not [9]. A more recently published study did show more rapid clearance with doses of ≥9 mg/kg/day using a more sensitive method (PCR) for detecting clearance [10].

Earlier experience with higher dosing regimens for a range of enterococcal infections (70% were bloodstream infections) showed generally good responses, with 89% clinical success and 93% microbiological eradication [11]. The median daily dose of daptomycin was 8.2 mg/kg, with an interquartile range of 7.7 to 9.7 mg/kg. Higher rates of failure (14.4%) were observed in patients with E. faecium infections compared to other enterococcal species. This study also examined clinical success rates by MIC measured by broth microdilution and/or Etest® and are shown in Figure 1. Failure rates were similar across the MIC range of 1-4 mg/kg. Supporting this conclusion, Chong et al. showed no difference in microbiological response rates in haematopoietic stem cell transplant patients with VRE bloodstream infection [12].
Figure 1 
Clinical success rate stratified by daptomycin MIC [11]

The balance of evidence from these studies suggests that better outcomes are usually achieved with high dose regimens of ≥9-10 mg/kg/day.

Clinical outcome studies in endocarditis
Most enterococcal endocarditis is caused by *E. faecalis*. Published experience in treating endocarditis is more limited than that of bacteraemia. In a small series (n=6), Cerón et al. showed that daptomycin at 6-10 mg/kg/day was effective treatment [13]. Similar results were seen in another international study in *E. faecalis* endocarditis (n=9) with doses of 7.7-10.0 mg/kg/day [14]. Kullar et al. reported good success with vancomycin-resistant *E. faecium* endocarditis (n=5) when daptomycin was given as does of 8.2-10.0 mg/kg/day [15].

Safety of high doses
The main toxicity concern with daptomycin is elevation of creatinine phosphokinase (CPK) and, in its more severe form, rhabdomyolysis. Nevertheless, collective experience in 1097 patients treated with >6 mg/kg/day did not increase the risk of serious adverse reactions [16]. Britt et al. were unable to demonstrate a relationship between dose and CPK elevation in a cohort of 595 patients [6]. Chuang et al. had similar findings among 112 patients [7]. Furthermore, Britt et al. did not detect a relationship between dose and acute kidney injury, another of daptomycin’s potential side effects.

In short, the evidence to date suggests that adverse reaction rates are not increased when higher doses are used.

Emergence of resistance during treatment
Emergence of resistance in enterococci during daptomycin treatment, or as an accompanying phenomenon when daptomycin is used for treating conditions caused by other pathogens, is being increasingly reported [17,18]. Much of it is attributed to mutations in LiaFSR stress response system leading to amino acid substitutions [19], although a recent study suggests other stress response pathways may also be a cause [20]. In vitro data suggest that exposures achieved with doses of 10-12 mg/kg/day are needed to prevent these types of resistance emergence [21], including in strains with LiaFSR mutations but wild-type MICs [22].

Laboratory testing to support treatment
Susceptibility testing of daptomycin requires the presence of fixed concentrations of divalent calcium ions (Ca^{++}). Because Ca^{++} cannot be controlled in Mueller-Hinton agar, disk diffusion testing is not possible at present and an MIC method must be used. The ISO broth microdilution reference standard in cation-adjusted Mueller-Hinton broth is satisfactory for this purpose but must
be supplemented to ensure a final Ca\(^{++}\) concentration of 50 mg/L. MIC gradient diffusion strips are most widely used for routine testing and are effective because they control the Ca\(^{++}\) concentrations in the strip itself.

However, a recent study by Campeau et al. has shown that even reference MIC tests are subject to variability between laboratories and between manufacturers of Mueller-Hinton broth [17]. This was true of isolates with MICs across a wide range of values (≤0.15 to >16 mg/L). Further, many strains with LiaFSR mutations were included in this study, many of which yielded MICs in the putative wild-type range (Figure 1). There were similar findings with gradient diffusion MICs, namely interlaboratory variation, variation by Mueller-Hinton agar brand and many LiaFSR mutants having MICs inside the wild-type distribution. Thus, current susceptibility tests do not seem capable of distinguishing genetically wild-type isolates from those harbouring LiaFSR mutations.

**Figure 1** MIC distribution compared to the presence LiaFSR mutations [data from ref 11]

Forty strains, reference BMD, three labs, three lots of medium, replicate testing

If LiaFSR mutations are a predictor of resistance emergence, currently available phenotypic tests will not be helpful in detecting all of these since they are not properly expressed phenotypically.

**Summary**

High-dose daptomycin has been thought to be effective in the treatment on enterococcal bloodstream infection and endocarditis, although published experience with the latter condition is limited. Although daptomycin is increasingly used for these conditions, especially when caused by vancomycin-resistant isolates, the EUCAST Steering Committee recognises that there are remaining uncertainties, particularly the inability of even the highest published doses (12 mg/kg/day) to achieve adequate exposure against all wild-type isolates of *E. faecalis* and *E. faecium*. The documented variation in susceptibility testing amplifies these uncertainties. Therefore, EUCAST has not proposed clinical breakpoints for daptomycin and Enterococcus species, but rather listed the breakpoint as "IE" = Insufficient Evidence. In part, this decision is influenced by the dosing regimen that is required for bloodstream far exceeds that of the regimen licensed by EMA.

EUCAST has detailed its position on the use of daptomycin in infections caused by *Enterococcus faecalis* and *E. faecium* in a publication in CMI (currently available at [https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30235-4/pdf](https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30235-4/pdf)).
References


