General Consultation

Proposal to remove macrolide breakpoints for *Haemophilus influenzae* but include a note on possible clinical efficacy and ECOFFs to distinguish wild type from isolates with acquired resistance

Comments due by Friday, November 17, 2017

Detailed below is a proposal to remove macrolide breakpoints for *Haemophilus influenzae*. The proposal is open for comment until 17 November 2017. Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (john.turnidge@escmid.org). Please use the accompanying form for your comments.

Consultation

Wild type *H. influenzae* are currently categorised by EUCAST as Intermediate to macrolides with a very wide range of MICs in the Intermediate category. With the planned move to a new definition for Intermediate, this categorisation will no longer be appropriate. As a consequence, EUCAST has undertaken a review of the role of macrolides in the treatment of *H. influenzae* infections.

MIC Distributions

*H. influenzae* MIC distributions from EUCAST MIC distribution website (accessed October 7, 2017):

<table>
<thead>
<tr>
<th>Agent</th>
<th>0.03</th>
<th>0.06</th>
<th>0.12</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>32</th>
<th>64</th>
<th>⩾128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>0</td>
<td>64</td>
<td>299</td>
<td>887</td>
<td>5442</td>
<td>15658</td>
<td>8888</td>
<td>1181</td>
<td>118</td>
<td>354</td>
<td>37</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>112</td>
<td>72</td>
<td>229</td>
<td>1192</td>
<td>6679</td>
<td>14779</td>
<td>4258</td>
<td>418</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1</td>
<td>7</td>
<td>21</td>
<td>113</td>
<td>127</td>
<td>618</td>
<td>4500</td>
<td>15097</td>
<td>7781</td>
<td>808</td>
<td>100</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>68</td>
<td>91</td>
<td>19</td>
<td>3</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>6</td>
<td>4</td>
<td>16</td>
<td>54</td>
<td>279</td>
<td>1846</td>
<td>2662</td>
<td>486</td>
<td>38</td>
<td>14</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

*No ECOFF was originally designated as data were sparse. Current data suggest that the wild type should be 4-64 mg/L and the ECOFF 64 mg/L. Current Intermediate range is highlighted in yellow.*

Clinical efficacy

Macrolides are not considered to be first line therapy for acute upper or lower respiratory tract infections caused by *H. influenzae* (Wierzbowksi et al., 2005; Adamantia and Torres, 2014). Macrolides do have a role in some chronic lower respiratory infections, but the current consensus is that their efficacy relates to anti-inflammatory and not antibacterial effects (Adamantia and Torres, 2014).
*H. influenzae* appears to be a poor target for macrolides. For most *H. influenzae* even the maximum serum concentration of macrolides never exceeds the MIC for the majority of the wild type population, although the pharmacodynamic significance of this has never been explored. Many *H. influenzae* infections have a high spontaneous cure rate (Forrest et al, 1997, and this is a likely explanation for the clinical efficacy of this agent presented in some studies. Indeed, in serious infections caused by *H. influenzae* it may be harmful to give an impression that there is potentially useful activity.

With regard to the categorisation of wild-type *H. influenzae* as Intermediate, these agents do not have regular high dosage regimens. The original argument for categorising the wild type as Intermediate was to indicate uncertainty of outcome and to distinguish the wild type from isolates with acquired resistance. It is now felt that use of the Intermediate category may be misleading as it suggests that macrolides may have useful activity against *H. influenzae* and there is no convincing clinical evidence that this is the case, at least in terms of antibacterial effect. In the absence of a good argument for a clinical breakpoint it is suggested that the breakpoints are removed, but we will still provide a comment regarding the clinical data suggesting that there may be a role of these agents in treatment.

It is proposed that macrolide breakpoints for *H. influenzae* are removed and notes added about problems of relating MICs to outcomes in a traditional way. In the table we will also add ECOFFs to distinguish isolates with acquired resistance from those belonging to the wild type.

**Proposed Note for the Breakpoint Table (version 8.0)**

Clinical evidence for the efficacy of macrolides in *H. influenzae* respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFs) should be used to detect strains with acquired resistance. The ECOFFs for each agent are: azithromycin 4 mg/L, clarithromycin 32 mg/L, erythromycin 16 mg/L and telithromycin 8 mg/L. There are insufficient data available to establish an ECOFF for roxithromycin.

**References**

