Proposed introduction of oral amoxicillin breakpoints for *Haemophilus influenzae* and *Streptococcus pneumoniae*

General consultation, 7 February - March 23, 2018

Please send comments by 23 March 2018 to the EUCAST Scientific Secretary at jturnidge@gmail.com

**Background**

*Streptococcus pneumoniae* and *Haemophilus influenzae* are two of the most common organisms associated with respiratory tract infections. Non-invasive infections are often treated with oral amoxicillin. There are currently no breakpoints that take into account the oral dosing regimens and PK-PD data specific to this indication.

**MIC distributions**

The MIC distributions for *H. influenzae* and *S. pneumoniae* are shown in Figure 1 and Figure 2. They indicate that the ECOFF for *H. influenzae* is 2 mg/L, and for *S. pneumoniae* it is 0.06 mg/L.

![EUCAST MIC distribution of amoxicillin for H. influenzae](image)

**Figure 1. EUCAST MIC distribution of amoxicillin for H. influenzae**
Pharmacokinetics and pharmacodynamics

The standard dosing regimens used for oral amoxicillin varies between 750 and 3000 mg/day, divided into two to four doses. For amoxicillin-clavulanic acid, the standard dosing regimens are 500/125 mg x 3 or 875/125 mg x 2-3. The target for Monte Carlo simulations was set at 40% ft>MIC (1). This target is derived from clinical studies on children with acute otitis media or sinusitis, and support a PK-PD relationship for not only *S. pneumoniae* but also *H. influenzae*, indicating that the latter can act as a true pathogen. Data from de Velde et al. (2) presented the results of Monte Carlo simulations for some of the most used dosing regimens of amoxicillin (Figure 3). In order to achieve a target of 40% ft>MIC, patients infected by isolates with an MIC of 0.5 mg/L would need to be treated with a dosing regimen of 500 mg x 3 while patients infected by isolates with an MIC of 1 mg/L would need a dosage of 750 mg x 3.

Figure 2: EUCAST MIC distribution of amoxicillin for *S. pneumoniae*.
Clinical data

H. influenzae

There are publications comparing oral amoxicillin to other agents for treatment of respiratory tract infection. The result of these studies are not conclusive and do not include any information on treatment outcome related to MIC, although there is some support to the need of a higher dosage.

Hagberg et al. (3) reported 13 cases of community-acquired pneumonia with H. influenzae treated with amoxicillin 1000 mg x 3. The bacterial eradication rate was 11/13. There were no data on outcome related to amoxicillin MIC.

File et al. (4) reported 10 patients with community acquired pneumonia with H. influenzae and treated with amoxicillin-clavulanic acid 875/125 mg x 2. There were no clinical failures but no MICs were given.

Chatximanolis et al. (5) reported 19 patients with H. influenzae sinusitis randomized to treatment with roxithromycin or amoxicillin-clavulanic acid 500/125 mg x 3. All isolates were susceptible to the agents used and there were no clinical failures.

Gwaltney et al. (6) reported a comparative study of treatment for bacterial sinusitis. Cefdinir was compared with amoxicillin-clavulanic acid 500/125 mg x 3. In patients infected with H. influenzae and treated with amoxicillin-clavulanic acid the clinical response rate was 71/82 and the bacterial eradication rate was 4/7.

S. pneumoniae

Standard treatment with amoxicillin 500 mg x 3 has been thoroughly investigated and graded as A+ in for instance BTS Guidelines for treatment of hospital-acquired pneumonia (7). There are few publications where treatment of pneumococcal pneumonia with higher dose of oral amoxicillin (with or without clavulanic acid) is related to the MIC of amoxicillin. Although the numbers are small, there is no certain correlation between elevated amoxicillin MIC and clinical failure.

Trémolières et al. (8) reported 24 cases of S. pneumoniae infection treated with amoxicillin 1000 mg x 3. Two of five patients with penicillin-resistant S. pneumoniae (PRSP) were regarded as clinical failures. No MICs of amoxicillin were reported.
Petitpretz et al. (9) reported 49 cases of infection with *S. pneumoniae* treated with amoxicillin 1000 mg x 3. MICs of amoxicillin-clavulanic acid were 0.016-2 mg/L. There were five clinical failures, all with isolates susceptible to amoxicillin (MICs: <0.016, 0.016, 0.5, <0.016, <0.016 mg/L).

Petitpretz et al. (10) reported 22 cases of *S. pneumoniae* infection treated with amoxicillin-clavulanic acid 1000/125 mg x 3. There was one isolate with an amoxicillin-clavulanic acid MIC of 4 mg/L, and MICs for all other isolates were ≤0.015-2 mg/L. There were two treatment failures, one with amoxicillin-clavulanic acid MIC of 2 mg/L and the other 0.03 mg/L.

Garau et al. (11) reported 13 cases of *S. pneumoniae* infection treated with amoxicillin-clavulanic acid 875/125 mg x 3. There was one isolate with an amoxicillin-clavulanic acid MIC of 4 mg/L, and MICs for all other isolates were ≤0.015-2 mg/L. There were no isolates with amoxicillin-clavulanic acid MIC >1 mg/L.

**Proposed clinical breakpoints**

For *H. influenzae*, the lowest possible Susceptible breakpoint to avoid significant splitting of the wild-type would be 2 mg/L. This would not be fully covered by the dosing regimen 750 mg x 3 or 875/125 mg x 3 for amoxicillin with clavulanic acid. However, accepting a slightly lower target at 35% $fT>MIC$ would mean that the target is reached. These two dosing regimens should therefore be the standard doses for treatment of *H. influenzae* infections in order to achieve a target of 35% $fT>MIC$.

The ECOFF of amoxicillin for *S. pneumoniae* is 0.06 mg/L and the proposed clinical breakpoints are set to cover the most commonly used dosing regimens.

### *H. influenzae*:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Breakpoints (mg/L)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin oral</td>
<td>$S\leq$</td>
<td>1. Dosage to treat susceptible isolates:</td>
</tr>
<tr>
<td></td>
<td>$R&gt;$</td>
<td>750-1000 mg x 3.</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic</td>
<td>$2^1$</td>
<td>2. Dosage to treat susceptible isolates:</td>
</tr>
<tr>
<td>acid oral</td>
<td>$2^1$</td>
<td>875/125 mg x 3 (due to available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>formulations)</td>
</tr>
</tbody>
</table>

$^1$Most published data are with 1 g x 3, but newer data have shown that there is a significant saturation of absorption with higher dosages, such that increasing the dosage above 750 mg x 3 does not improve $fT>MIC$ in vivo.

### *S. pneumoniae*:

<table>
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<td>Amoxicillin oral</td>
<td>$0.5^1$</td>
<td>1. Minimum dosage related to MIC:</td>
</tr>
<tr>
<td></td>
<td>$2^1$</td>
<td>MIC ≤ 0.5 mg/L: 500 mg x 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MIC 2 mg/L: 750-1000 mg x 3</td>
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<tr>
<td>Amoxicillin-clavulanic</td>
<td>$0.5^2$</td>
<td>2. Minimum dosage related to MIC:</td>
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References