Second Consultation
(25 October – 30 November 2018)

Oral amoxicillin breakpoints for Streptococcus pneumoniae

Background
Recently, the EUCAST SC consulted on revision of the clinical breakpoint for amoxicillin vs S. pneumoniae and H. influenzae. There were no major comments regarding the consultation, but the SC decided that the proposed I-group for S. pneumoniae was too wide, as normally only one dilution step can be achieved by increasing the dose. The proposed breakpoints were 0.5/2 mg/L in the previous consultation, but below we will state a case for changing this to 0.5/1 mg/L.

MIC-distributions
The wild type distribution and ECOFF for S. pneumoniae is shown in Figure 1.
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. Data from de Velde et al. (Figure 2) shows the %fT>MIC for some of the most used dosing regimens of amoxicillin. To achieve proper target attainment, isolates with an MIC of 0.5 mg/L would need to be treated with a dosing regimen of 500 mg x 3 while isolates with an MIC of 1 mg/L would need a minimum dosage of 750 mg x 3 (1). Increasing the dose to 1 g x 3 does not increase the target attainment, likely because of a maximum absorbtion being achieved already after 750 mg x 3 (1).

Figure 2 Monte Carlo simulations showing oral dosing of amoxicillin. (1). Target attainments are not improved by increasing from 750 to 1000 mg q8h.

Clinical data
*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 (2). There are few papers published where treatment of pneumococcal pneumonia with higher dose of oral amoxicillin (-clavulanic acid) is related to MIC of amoxicillin. Although the numbers are small, there is no certain correlation between elevated MIC and clinical failure.

<table>
<thead>
<tr>
<th>Trémolières et al. 1998:</th>
<th>24 cases of <em>S. pneumoniae</em> treated with amoxicillin 1000 mg x 3. Two of five patients with PRSP regarded as clinical failures. No MIC for amoxicillin. (3)</th>
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<td>Petitpretz et al. 2001:</td>
<td>49 cases of <em>S. pneumoniae</em> treated with amoxicillin 1000</td>
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mg x 3. MICs for amoxicillin-clavulanic acid was 0.016 – 2 mg/L. Five clinical failures, all susceptible to amoxicillin (MICs: <0.016, 0.016, 0.5, <0.016, <0.016 mg/L). (4)

Petitpretz et al. 2002: 22 cases of S. pneumoniae treated with amoxicillin-clavulanic acid 1000 mg x 3. One isolate with an amoxicillin-clavulanic acid of 4 mg/L, all other isolates had MICs ≤0.015 – 2 mg/L. Two treatment failures of which one case with amoxicillin-clavulanic acid MIC of 2 mg/L, the other had an MIC of 0.03 mg/L. (5)

Garau et al. 2003: 13 cases of S. pneumoniae treated with amoxicillin-clavulanic acid 875 x 3. Only one failure (penicillin and amoxicillin-clavulanic acid MIC ≤ 0.03 mg/L). No isolate in the group with amoxicillin-clavulanic acid MIC > 1 mg/L. (6)

Proposed clinical breakpoints

The ECOFF of S. pneumoniae is 0.064 mg/L and the proposed clinical breakpoints are set to cover the mostly used dosing regimens.

<table>
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<th>Agent</th>
<th>Breakpoints (mg/L)</th>
<th>S≤</th>
<th>R&gt;</th>
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<tr>
<td>Amoxicillin p.o.</td>
<td>0.5&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Amoxicillin-clavulanic acid p.o.</td>
<td>0.5&lt;sup&gt;2&lt;/sup&gt;</td>
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1. Minimum dosage related to MIC:  
MIC ≤ 0.5 mg/L: 500 mg x 3  
MIC 1 mg/L: 750 mg x 3

2. Minimum dosage related to MIC:  
MIC ≤ 0.5 mg/L: 500/125 mg x 3  
MIC 1 mg/L: 875/125 mg x 3

References


