### EUCAST proposed breakpoints for *Burkholderia pseudomallei*.

Consultation (23 May - 30 June, 2019) – comments and EUCAST response.

<table>
<thead>
<tr>
<th>Comment from (name, contact details)</th>
<th>Comments</th>
<th>EUCAST Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>NWGA (the Norwegian working group on antibiotics) Christoffer Lindemann, <a href="mailto:pc-linde@online.no">pc-linde@online.no</a></td>
<td>The proposed breakpoints for <em>B. pseudomallei</em> are supported by the NWGA. In light of previous consultations and the new definition of the I-category, should the breakpoints from amox-clav and ceftazidime be 0.001/8? ECOFFs for the two agents are demonstrated to be at 8 mg/L, this is concordant with the “R pk/pd-bp”, indicating the need for high exposure to cover the entire wild-type.</td>
<td>Following the discussion in the EUCAST Steering Committee on how to handle wild-type distributions for agents where it is agreed that the species in itself is in need to of “high exposure”, it was decided to categorise wild-type organisms as “Susceptible, increased exposure” (I) for both amoxicillin-clavulanic acid and ceftazidime.</td>
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</tbody>
</table>
allergy, those who are intolerant of cotrimoxazole (particularly with neutropenia or gastrointestinal intolerance), in pregnant patients (where cotrimoxazole is relatively contraindicated) and in children (where doxycycline is contraindicated).

For eradication treatment (i.e. “step-down” oral treatment following initial intravenous therapy) of melioidosis, oral amoxicillin-clavulanate (coamoxiclav) is often used at a dose of 20/5 mg/kg three times a day. For adult patients < 60 kg, a dose of 1000/250 mg three times daily is suggested. In regions where co-amoxiclav is only available in fixed 2:1 combinations, 500 mg/250 mg three times daily with additional amoxicillin (500 mg three times daily). For patients >60 kg, a maximum dose of 1500/375 mg three times daily. We do not recommend twice daily regimens or formulations containing A:C ratios of > 4:1 (such as “Duo Forte” or “XR” formulations) because of inadequate clavulanate.

Checkerboard susceptibility testing suggests that clavulanate is key to the antimicrobial action of the combination, leading to the suggestion that more frequent oral dosing (6- or 4-hourly) may provide more optimal serum concentrations. David Dancea,b. Treatment
| Dominique BOISSINOT  
*Chef de Produit Applications  
Bactériologie/Product Manager Bacteriology Applications, I2A. dominique.boissinot@i2a.info* | Dear EUCAST, I have read your propositions.  
For your propositions, everything is ok. I just had some questions:  
1/ could we propose breakpoint for the complex "Burkholderia pseudomallei complex" and not only the species "pseudomallei"?  
the complex:  
*B. pseudomallei*  
*B. mallei*  
*B. thailandensis*  
*B. oklahomensis*  
*B. humptydooensis*  
Even B.mallei is isolated from veterinary (horse), it’s just a proposition to have breakpoint if we identify these species in humans susceptibility of B.mallei is similar to B.pseudomallei, the most important difference is susceptibility to | EUCAST: the breakpoints, ECOFFs and methods were developed with data on *B.pseudomallei* only. EUCAST avoid extrapolating to other species or subspecies when there is no data to support.  
**No action.**  
Intrinsic resistance to *B. pseudomallei*? We are not sure we know enough about the species to determine to which antimicrobials it is intrinsically resistant. For other species where experience is limited and only few agents are documented (such as *Kingella kingae*, *Listeria monocytogenes*, *Campylobacter* spp and others), EUCAST refrains from publishing recommendations for or against where solid evidence is lacking.  
**No action.** |
|  | aminoglycosides (Genta, Tobra) for *B.mallei*

2/ could we consider breakpoint diameters for *B.pseudomallei* complex and *B.cepcia* complex also ?

(as CLSI have made for *Burkholderia cepacia* complex) ?

3/ could you propose some intrinsic resistance for "*Burkholderia pseudomallei* complex" to complete the document? |
**Burkholderia pseudomallei**

<table>
<thead>
<tr>
<th>Antibiotics commonly used in the initial treatment of melioidosis.</th>
<th>MIC breakpoints (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoints (mm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>ATU</td>
<td>S ≥</td>
</tr>
<tr>
<td>Ceftazidime(^1)</td>
<td>0.001</td>
<td>8</td>
<td>10</td>
<td>50(^A)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Trimethoprim:sulfamethoxazole(^1,2)</td>
<td>0.001</td>
<td>4</td>
<td>1.25-23.75</td>
<td>50(^A)</td>
</tr>
</tbody>
</table>

**Antibiotics occasionally used in the treatment of melioidosis (confer with an expert before starting therapy, as dosing is critical).**

<table>
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<tr>
<th></th>
<th>MIC breakpoints (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoints (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanic acid(^1)</td>
<td>0.001</td>
<td>8</td>
<td>20-10</td>
</tr>
<tr>
<td>Doxycycline(^1)</td>
<td>0.001</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Chloramphenicol(^1)</td>
<td>0.001</td>
<td>8</td>
<td>30</td>
</tr>
</tbody>
</table>

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For the EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01

**MIC determination (broth microdilution according to ISO standard 20776-1).**

- **Medium:** Mueller-Hinton broth
- **Inoculum:** 5x10\(^5\) CFU/mL
- **Incubation:** Sealed panels, air, 35±1°C, 18±2h
- **Reading:** Unless otherwise stated, read MICs at the lowest concentration of the agent that completely inhibits visible growth.
- **Quality control:** *Pseudomonas aeruginosa* ATCC 27853.

**Disk diffusion (EUCAST standardised disk diffusion method).**

- **Medium:** Mueller-Hinton agar
- **Inoculum:** McFarland 0.5
- **Incubation:** Air, 35±1°C, 18±2h
- **Reading:** Unless otherwise stated, read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
- **Quality control:** *Pseudomonas aeruginosa* ATCC 27853.

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For agents with an arbitrary breakpoint of S≤0.001 (and the corresponding zone diameter breakpoint of S≥50 mm), there is no "Susceptible, standard exposure (S)" - only categories I and R ("Susceptible, increased exposure" and "Resistant"). This is to emphasise the need for the highest recommended dose when these agents are used in the treatment of melioidosis.

\(^1\) Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.