Proposed modifications to EUCAST clinical breakpoints

Listed below are proposals to modify EUCAST clinical breakpoints. The proposals are open for comment by 15th November 2013. Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com). Please use the attached form for your comments.

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Proposal 1: Amoxicillin-clavulanic acid breakpoints for “uncomplicated UTI only” in addition to existing breakpoints for systemic infections

**Background**
In many countries amoxicillin-clavulanic acid is widely used to treat uncomplicated UTI caused by Enterobacteriaceae. EUCAST has received comments from several countries that current breakpoints do not take account of the high concentrations of amoxicillin-clavulanic acid in urine and categorise significant numbers of isolates as resistant when evidence suggests that uncomplicated UTI caused by these isolates can be successfully treated. This has been exacerbated by the adoption of a fixed concentration (2 mg/L) of clavulanic acid in MIC determinations rather than a 2:1 ratio of amoxicillin:clavulanic acid as MICs for some organisms are higher with the fixed concentration of amoxicillin-clavulanic acid.

The intermediate category is a category that can be used to allow for higher concentrations of agents in the urine, but the EUCAST amoxicillin-clavulanic acid breakpoints for systemic infections include no intermediate category because the susceptible breakpoint is already raised above the PK/PD breakpoint in order to avoid splitting the wild type of even the more susceptible species, such as *Escherichia coli*. Hence an intermediate category is not appropriate for amoxicillin-clavulanic acid breakpoints for systemic infections.

EUCAST has several breakpoints which are valid only for isolates from uncomplicated urinary tract infections (e.g. mecillinam, cefalexin, trimethoprim and nitrofurantoin for Enterobacteriaceae) but none of these agents have breakpoints for isolates for systemic infections. Fosfomycin and cefuroxime have separate breakpoints for oral and iv formulations, the oral formulations relating to uncomplicated UTI only. The current proposal is to introduce amoxicillin-clavulanic acid breakpoints for a category of “uncomplicated UTI only”. in addition to the breakpoints of susceptible ≤8 mg/L and resistant >8 mg/L for systemic infections, but without the distinction for oral and iv formulations.

**MIC distributions**
The MIC distributions for Enterobacteriaceae relevant to uncomplicated UTI are shown in the table (EUCAST MIC distribution website data). Based on these MIC distributions, breakpoints of susceptible ≤32 mg/L, resistant >32 mg/L for uncomplicated UTI would increase the proportion of *E. coli* isolates susceptible to amoxicillin-clavulanic acid from 79.6% to 97.4% (but note that with the fixed concentration of clavulanic acid the percentage susceptible would be lower as the current EUCAST MIC distribution is based on testing with a ratio of amoxicillin:clavulanic acid).

Table: EUCAST amoxicillin-clavulanic acid MIC distribution for Enterobacteriaceae relevant to uncomplicated UTI

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of isolates at different MIC (mg/L)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>≤0.5</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>42</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>347</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>8</td>
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</tbody>
</table>
**Pharmacokinetics**

For amoxicillin-clavulanic acid renal excretion is the primary method of clearance. Very high urinary concentrations of unchanged drug are reported from human studies when compared with those reported from serum. However, the amount of drug in urine will depend on a number of factors including dose, renal excretion, age and urine flow. Microbiological activity may also be changed by pH and assessment of antimicrobial activity is made more complex by the intrinsic antibacterial activity of urine.

Amoxicillin excretion is linear over the dose range 125mg to 1000mg with the mean urinary concentration being 580mg/L (50-1600mg/L) for a 250mg dose and 1100mg/L (115-1850 mg/L) for a 500mg dose (Sutherland et al, 1972). Around 30% of clavulanic acid is excreted unchanged in urine (Nilsson-Ehle et al, 1985), and mean concentrations in urine are 400mg/L at 0-4h. The concentration time profile for an amoxicillin 250mg dose in urine is 432mg/L, 516mg/L and 94mg/L at 0-2h, 2-4h and 4-6h respectively (Cole and Ridley 1978).

**Pharmacodynamics**

Antimicrobial pharmacodynamics have been studied using in vitro and murine infection models (Greenwood and O’Grady, 1978; Johnson et al, 1992).

The use of in vitro models illustrates that the high urinary concentrations associated with many β-lactams produce significant antibacterial effects in urine. Greenwood & O’Grady, 1977, even suggested that present doses may be too high for treatment of uncomplicated UTI. Animal models have indicated that for β-lactams (cefuroxime) antibacterial effects are more related to concentrations in urine than concentrations in serum or in bladder or kidney tissue. However, for treatment of kidney-based infection high serum concentrations of agents are required (Hvidberg et al, 2000). There are no published data on the dominant pharmacodynamic driver or magnitudes for urinary tract infection for any agent, though these data may soon be available.

**Laboratory studies relating MIC to antibacterial effect**

The impact of MIC on antibacterial effect in urine for amoxicillin was studied by Anderson et al (1975). Urine was collected from patients receiving amoxicillin three or four times a day and urinary concentrations of amoxicillin were 330-370mg/L. Enterobacteriaceae were classified into three groups on the basis of response to drug in urine and antimicrobial susceptibility tested by a disk diffusion method. Among amoxicillin susceptible isolates 31/31 showed >1 log reduction in viable count at 6h, but among amoxicillin resistant isolates only 10/26 showed >1 log reduction in count at 6h. It was also noted that strains with amoxicillin MIC 64-256mg/L responded to agents in the test system but when the amoxicillin MIC was >256mg/L no killing was observed.

**Clinical Data**

A number of studies with various agents indicate that urinary concentrations determine outcome in UTI (Gould et al, 1953, McCabe et al, 1966, Stamey et al, 1972). With amoxicillin-clavulanic acid, Martinelli et al (1981) showed that outcome was related to MIC...
and, although numbers were small, an MIC of ≤32mg/L had the best predictive value for cure.

There is a wealth of clinical trial data on amoxicillin-clavulanate to show efficacy, trials having been conducted in comparison with a range of other β-lactams, fluoroquinolones and trimethoprim-sulfamethoxazole. However, in most trials it is difficult to establish how susceptibility was determined as few details are given on methodology (reviewed by Todd and Benfield, 1990; Ball, 2007).

**Proposed breakpoints**

In summary:

Urinary concentrations of antimicrobial agents are often 100-500 fold higher than serum concentrations over a dosing interval; the pharmacodynamics of agents are not significantly different in urine to those in serum (i.e. the drug concentration and MIC determine microbiological outcomes)

Human data indicates urinary concentrations are more closely associated with clinical outcomes than serum concentrations for UTI

Where clinical data exists it suggests there is a relationship between MIC and outcome in UTI and that infections caused by isolates with higher MICs than systemic breakpoints can be treated in uncomplicated urinary tract infections.

It is therefore proposed that amoxicillin-clavulanic acid breakpoints restricted to Enterobacteriaceae and uncomplicated UTI are introduced as follows:

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC breakpoints (concentration of amoxicillin with a fixed 2 mg/L clavulanic acid)</th>
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<tr>
<td></td>
<td>S (mg/L)</td>
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<tr>
<td>Amoxicillin-clavulanic acid (uncomplicated UTI only)</td>
<td>≤32</td>
</tr>
</tbody>
</table>

**Reporting amoxicillin-clavulanic acid susceptibility**

One consequence of introducing separate breakpoints for uncomplicated UTI in addition to breakpoints for systemic infections is that an isolate initially reported susceptible on isolation from a urinary tract infection may subsequently be reported resistant if isolated from a systemic infection. Also the laboratory may not know whether the infection is uncomplicated or complicated. EUCAST therefore recommend that if laboratories use the “uncomplicated UTI only” breakpoint they should also report susceptibility according to the systemic breakpoints. Report format for amoxicillin-clavulanic acid will depend on the Laboratory Information System used but might appear as follows.

For an organism with amoxicillin-clavulanic acid MIC ≤8 mg/L:

- Amoxicillin-clavulanic acid for systemic use: S
- Amoxicillin-clavulanic acid for uncomplicated UTI: S
For an organism with amoxicillin-clavulanic acid MIC 16 or 32 mg/L:
- Amoxicillin-clavulanic acid for systemic use R
- Amoxicillin-clavulanic acid for uncomplicated UTI S

For an organism with amoxicillin-clavulanic acid MIC >32 mg/L:
- Amoxicillin-clavulanic acid for systemic use R
- Amoxicillin-clavulanic acid for uncomplicated UTI R

References


McCabe WR, Jackson GG, 1966. Treatment of pyelonephritis; Bacterial, Drug and Host factors in success or failure among 252 patients. NEJM 272; 1037-1044.


Proposal 2: Reduce the doripenem R breakpoint from >4 mg/L to >2 mg/L for
*Pseudomonas* spp., *Acinetobacter* spp. and Enterobacteriaceae

**Background**

In January 2012 the European Commission asked the Committee for Medicinal Products for human use (CHMP) to assess the results of a clinical trial and give an opinion on the impact of the study results on the benefit-risk balance of doripenem and whether the marketing authorisation should be maintained, varied, suspended or withdrawn. The trial was a prospective, randomised, double-blind, double-dummy, multicentre Phase 3 trial to assess the safety and efficacy of a fixed 7-day course of doripenem 1 g administered as a 4 h infusion every 8 h, compared with a fixed 10d course of imipenem-cilastin 1 g administered as a 1 h infusion every 8 h. The trial was terminated early on the recommendation of the independent data monitoring committee based on lower cure rates and higher mortality for subjects treated with doripenem compared with imipenem.

In June 2012 the CHMP adopted an opinion that the benefit-risk balance of doripenem in the treatment of pneumonia (including VAP) remains positive subject to changes to the product information as follows:

- For patients with augmented renal clearance and/or infections with non-fermenting gram-negative pathogens CHMP recommend increasing the dose to 1g every 8 h (the standard dose is 500 mg every 8 h).
- For nosocomial pneumonia (including VAP) a longer treatment period (10-14 d) is recommended in addition to the higher dose (the recommended treatment period is 5-14 d).
- If non-fermenting gram-negative pathogens are suspected or confirmed, combined treatment with an aminoglycoside should be considered (previously there was no recommendation for combined treatment with an aminoglycoside).


The CHMP also asked that EUCAST be consulted on whether breakpoints for doripenem need to be revised.

The decision to terminate the trial has prompted detailed reassessment of PK/PD data with the VAP-only Monte-Carlo simulation by EUCAST. The following points are made:

- There is some argument over interpretation of Monte-Carlo simulation data but EUCAST has used a target $f_{>\text{MIC}}$ of 40-50% and confidence limits of 95-99% for the target attainment rate for carbapenems. The target is stringent as these agents are used to treat serious infections.

- It has been suggested that supra-renal clearance should be taken into account when assessing PK/PD data. This was not accepted by the Steering Committee as the same could be claimed for many other agents and supra-renal clearance has never been taken
into account in setting breakpoints. As with other agents, this should be assessed by the clinician when choosing a dose for the individual patient.

The standard dose of 500 mg x 3 by intravenous infusion over 1 h is the basis of the susceptible PK/PD breakpoint of ≤1 mg/L. A high dose of 1 g x 3 by intravenous infusion over 4 h with the PK/PD criteria used by EUCAST would correspond to a resistant breakpoint of >2 mg/L. EUCAST previously had a resistant breakpoint of >4 mg/L based on the possibility of extended infusion time. In the current reassessment, it was considered that infusion over 4h rather than 1h improves the PK/PD performance but does not justify an R breakpoint of >4 mg/L.

A note should be added that a high dose (1 g x 3 by intravenous infusion over 4 h) should always be used for non-fermenters.

An additional consequence of review and reduction of the PK/PD resistant breakpoint is that there is no longer a justification for the R >4 mg/L clinical breakpoint for Enterobacteriaceae and Acinetobacter spp., and it is proposed that the resistant breakpoint is reduced to R > 2 mg/L.

**Proposed breakpoints**

- **PK/PD breakpoints** S ≤1 mg/L, R >2 mg/L.
- **Enterobacteriaceae** S ≤1 mg/L, R >2 mg/L.
- **Acinetobacter** spp. S ≤1 mg/L, R >2 mg/L.*
- **Pseudomonas** spp. S ≤1 mg/L, R >2 mg/L.*

*A dosage of 1 g x 3 by intravenous infusion over 4 h should be used for infections caused by these organisms.*
Proposal 3: Removal of the cefaclor breakpoints for *H. influenzae* and *M. catarrhalis*

Cefaclor breakpoints for *H. influenzae* and *M. catarrhalis* were originally included in breakpoint tables to emphasise the fact that activity is marginal, and as a consequence breakpoints were set deliberately to report almost all resistant.

Inclusion of breakpoints for organism-agent combinations where all isolates are intended to be reported resistant is inconsistent with convention used throughout the EUCAST breakpoint tables. As almost all isolates are resistant by current breakpoints it is proposed that the cefaclor breakpoints are removed and replaced with “-“.