

Proposed modifications to EUCAST definition of the Intermediate category 2nd consultation 2017

In 2015, EUCAST proposed to change the definition of the Intermediate category. A general consultation generated numerous comments from colleagues (see the EUCAST webpage: <http://www.eucast.org/documents/consultations/>).

Conclusion of the consultation: The detailed and perceptive comments are appreciated. However, the current definition remains unsatisfactory since it harbours four different interpretations, but no indication to the clinician as to which interpretation applies in individual cases.

EUCAST has only rarely used intermediate as "a buffer zone", an area between S and R to avoid major and very major errors, and has rarely used the Intermediate category unless an increased exposure of the organism to the agent can be achieved (by adjusting the dosing regimen, or because the antimicrobial agent is concentrated at the site of infection). There is a need for clarification. Since the initial proposal and the ensuing discussions, the EUCAST Steering Committee and the National Breakpoint Committees have continued the discussion and agreed to the modified proposal to change the definition of the intermediate category.

The proposals are open for comment by 15 September 2017.

Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (john.turnidge@escmid.org) and use the accompanying form for your comments.

Please avoid repeating previous arguments by first checking comments and Steering Committee responses from the first consultation (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2016/20160919_1_intermediate_consultation_comments_and_responses.pdf).

Background

When the EUCAST harmonisation process started in 2001 the committee decided

- That all breakpoints should be related to the dosing regimen and that therefore all standard and high dosages should be made available in rationale documents and be listed in the EUCAST breakpoint table.
- To avoid splitting wild type MIC distributions of important target microorganisms since dividing the wild type distribution would lead to poor reproducibility of S, I and/or R results.
- To relate the Susceptible category to situations where a standard dose would give sufficient exposure.
- To reserve an Intermediate category for situations where drug exposure could be increased by significantly increasing the dose or by changing the mode of administration (frequency or infusion time), or because the agent is concentrated at the site of the infection (e.g. UTI).

For agents used only in UTI the Susceptible and Intermediate categories were merged and for these the breakpoint table lists “Uncomplicated UTI only” (or in a few cases “For UTI only”).

The Susceptible and Resistant categories are not in need of revision. However, the current definition of intermediate is problematic because it includes multiple interpretations:

Current definition of the Intermediate category.

Intermediate (I): A microorganism is defined as intermediate by a level of antimicrobial agent activity associated with uncertain therapeutic effect. It implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug can be used; it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.”

The inclusion of multiple interpretations results in this category being interpreted differently by different groups and has led to confusion regarding its meaning:

1. uncertain therapeutic effect (pharmacodynamics/microbiology)
2. where the agents are physiologically concentrated (pharmacokinetics)
3. when a high dosage of agent can be used (toxicology)
4. a buffer zone (methodology)

For meaning 1. It is unclear how the recipient of the susceptibility test result should apply or interpret the meaning of “**uncertain therapeutic effect**” – it could indicate that caution is needed irrespective of which dose is chosen or that one should probably refrain from using this agent as long as there is an alternative agent. Or it could mean that since the effect is uncertain it is best to give as much agent as possible or that there should be close monitoring of the therapeutic effect.

For meaning 2 and 3. These interpretations relate to **increased exposure**, the need for a higher than usual dose, which in turn can be achieved by giving a **larger amount** of the agent with the same frequency as the standard dose, or a standard dose with a **higher frequency** or by changing the **mode of administration** from oral to IV or from injection to infusion. The increased exposure related to the “physiological concentration” of agent at the site of infection is mostly related to agents used for treating lower urinary tract infections and refer to agents that are concentrated in urine.

For meaning 4. The use of the Intermediate category as a **buffer zone** because of technical variation or technical difficulties has an entirely different meaning to when Intermediate is used to signal the need for increased exposure.

The EUCAST emphasis on **avoiding the splitting of wild type populations of important target species when setting breakpoints has reduced the need for a buffer zone**, and for several years EUCAST has not used the concept of a buffer zone when setting new breakpoints or when revising breakpoints. Hence there are now many agents and species where there is only one approved dose/mode of administration and where EUCAST has not included an Intermediate category.

Were we to keep the concept of a buffer zone in the definition, it would be logical to introduce an Intermediate category with all breakpoints; currently only 50% of the breakpoints include an Intermediate category. There is always some technical variation in antimicrobial susceptibility tests. The idea of avoiding “major errors” (reporting S as R) and “very major errors” (reporting R as S) by including an intermediate category is attractive. The wider you make the intermediate category, the rarer such errors would be, but at the same time an increasingly larger proportion of results would be of limited or no use to the clinician. In practice, Intermediate becomes a “I don’t know” category that is most often interpreted as Resistant by clinicians.

In summary, the current definition of Intermediate has four interpretations rolled into one, but on reports there is no guidance as to which of the four apply. Interpretations related to “uncertainty” (uncertain activity and buffer zone) are the responsibility of the laboratory and should be handled by the laboratory as part of susceptibility testing. We believe that with education the recipients can be helped to understand that an Intermediate category is an unequivocal encouragement to increase exposure of the agent and that with time Intermediate may become a more useful category.

In 2015, we proposed the following modification:

Intermediate (I): A microorganism is defined as intermediate by a level of antimicrobial activity associated with a high likelihood of therapeutic success but only when a higher dosage of the agent than normal can be used or when the agent is physiologically concentrated at the site of infection.

We now propose the following further modification:

Intermediate (I): A microorganism is categorised as intermediate when there is a high likelihood of therapeutic success because exposure* is enhanced (1) by adjusting the dosing regimen, or (2) because the antimicrobial agent is concentrated at the site of infection.

*exposure refers to concentration-time profiles found in the pharmacokinetic-pharmacodynamic indices that are relevant to the drug class: that is, the area-under-the-curve of the unbound agent, divided by the MIC ($fAUC/MIC$ ratio), or the percentage of the dosing interval that the unbound agent is above the MIC ($\%fT > MIC$).

The following analysis of the consequences of changing the definition is based on breakpoints listed in the EUCAST breakpoint table 7.1.

Historically, with the development of harmonised European breakpoints since 2002, the main rationale for having an Intermediate category was that for some agents the exposure could be significantly increased (often doubling the dose or more) to allow the use of a breakpoint which was one or, for some β -lactams, several dilution steps higher than the standard S breakpoint.

Isolates categorised as S should respond to standard dosing, as specified in the Dosages Tab in the EUCAST breakpoint table. Isolates categorised R will normally not respond irrespective of exposure. With a few exceptions (listed below), the isolates categorised as Intermediate are a small percentage of isolates neither fully susceptible nor resistant. These should respond to the higher dose as specified in the Dosages Tab.

However, there are some situations where it is important to signal that the intrinsic susceptibility of the species to the agent is low and that the highest possible dose should be used even for wild-type isolates. For this situation EUCAST has until now used two alternative methods to emphasise that the dosing regimen which gives the highest exposure should be used to treat patient infected with wild-type organisms:

(1) all wild-type isolates are categorised as Susceptible but a note is added that the dosing regimen giving the highest exposure is required for successful therapy.

Cefuroxime iv vs. Enterobacteriaceae, piperacillin w/wo tazobactam vs. *Pseudomonas* spp., ticarcillin w/wo clavulanic acid vs. *Pseudomonas* spp., cefepime vs. *Pseudomonas* spp., ceftazidime vs. *Pseudomonas* spp., doripenem vs. *Pseudomonas* spp. and *Acinetobacter* spp., imipenem vs. *Pseudomonas* spp. and *Acinetobacter* spp., ciprofloxacin vs. *Pseudomonas* spp. and *Acinetobacter* spp., levofloxacin vs. *Pseudomonas* spp., aminoglycosides vs. *Acinetobacter* spp., cefaclor vs. *Staphylococcus aureus*, fluoroquinolones vs. *Staphylococcus* spp., penicillin and dose-related breakpoints for *Streptococcus pneumoniae*, levofloxacin vs. *Streptococcus pneumoniae*, colistin vs. Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp.

(2) all wild-type isolates are categorised as Intermediate, which signals the need for the highest exposure dosing regimen, and then no comment is needed. In these instances (listed below) the intermediate category is typically 3-5 two-fold MIC concentrations wide.

This was used for *Pseudomonas* spp. vs. aztreonam, *Enterococcus* spp vs. trimethoprim and trimethoprim-sulfamethoxazole, *Streptococcus pneumoniae* vs. cefaclor and for *Haemophilus* spp. vs. macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin, telithromycin).

In most cases the footnote in alternative (1) is not part of the AST report and hence the information is lost except to those with special knowledge or interest. With the new definition of Intermediate, situations where the outcome of therapy using standard dosing is questionable should be dealt with in the way shown for alternative (2). This is irrespective of whether or not a smaller or larger part of the wild type is encompassed by the breakpoint.

Analysing all breakpoints in breakpoint table 7.1 (2017) for *Acinetobacter* spp., Enterobacteriaceae, *Pseudomonas* spp., *Stenotrophomonas maltophilia*, *Staphylococcus* spp., Streptococcus A, B, C and G, Viridans group streptococci, *Streptococcus pneumoniae*, *Enterococcus* spp., *Haemophilus influenzae* and *Moraxella catarrhalis* (but not for *Neisseria gonorrhoeae*, *Neisseria meningitidis*, anaerobes, *Kingella kingae*, *Aerococcus* spp., *Mycobacterium tuberculosis* and some others) we identified 107 instances where an Intermediate category was used. In 90 of these there was either a defined standard and high dose or a second mode of administration (oral and intravenous; intravenous injection vs. intravenous continuous infusion) or, in a few instances, the whole wild type was placed in the intermediate category.

However, in 17 instances, the EUCAST table and rationale documents listed an Intermediate category despite there being only one dosing regimen, i.e. only one dose and one mode of administration – e.g. the Intermediate category was used because a buffer zone was considered important. In none of these 17 instances could we find evidence that a buffer zone had been discussed or needed.

Our proposal is therefore:

1. **To change the definition of Intermediate** as proposed above,
2. **To review breakpoints for the species-agent combinations** with no appropriate reason for an Intermediate category. This is irrespective of whether or not we change the definition:
 - Enterobacteriaceae: ertapenem, norfloxacin (concentrated in urine but not used for systemic infections), tigecycline, trimethoprim (concentrated in urine but used only for UTI).
 - *Staphylococcus* spp.: roxithromycin, telithromycin, minocycline, trimethoprim.
 - *Enterococcus* spp.: tigecycline.
 - Streptococcus A, B, C and G: roxithromycin, telithromycin, minocycline and tigecycline.
 - *Streptococcus pneumoniae*: roxithromycin, telithromycin and minocycline.
 - *Haemophilus influenzae*: erythromycin (and roxithromycin and telithromycin depending on the ongoing review of macrolide breakpoints for *H. influenzae*).
3. **To retain the strategy for agents used only for lower UTI, namely to merge what would under other circumstances have been S and I into the susceptible category with the caveat “For uncomplicated UTI only”.** For Enterobacteriaceae, this currently applies to the following agents:
 - amoxicillin-clavulanic acid (separate breakpoints for systemic infections)
 - mecillinam
 - cefadroxil, cephalexin, cefixime, cefpodoxime, ceftibuten, cefuroxime-axetil
 - norfloxacin
 - nitrofurantoin
 - nitroxoline
 - trimethoprim
4. **To signal the need for the high exposure dosing regimen even for wild-type isolates by placing the whole wild type in the Intermediate category** and not as now, where some are in the Susceptible category with a footnote indicating the need for the highest dose (list A below) and some in the Intermediate category (list B below).
 - A. The wild type in the Susceptible category with a caveat concerning high dosing
 - cefuroxime iv vs. Enterobacteriaceae
 - piperacillin w/wo tazobactam vs. *Pseudomonas* spp.
 - ticarcillin w/wo clavulanic acid vs. *Pseudomonas* spp.
 - cefepime vs. *Pseudomonas* spp.
 - ceftazidime vs. *Pseudomonas* spp.
 - doripenem vs. *Pseudomonas* spp. and *Acinetobacter* spp.
 - imipenem vs. *Pseudomonas* spp. and *Acinetobacter* spp.
 - ciprofloxacin vs *Pseudomonas* spp. and *Acinetobacter* spp.
 - levofloxacin vs. *Pseudomonas* spp.
 - aminoglycosides vs. *Acinetobacter* spp.
 - cefaclor vs. *Staphylococcus aureus*
 - fluoroquinolones vs. *Staphylococcus* spp.
 - penicillin and ‘dose-related’ breakpoints for *Streptococcus pneumoniae*
 - levofloxacin vs. *Streptococcus pneumoniae*
 - B. The wild type in the Intermediate category
 - aztreonam vs. *Pseudomonas* spp.
 - trimethoprim and trimethoprim-sulfamethoxazole vs. *Enterococcus* spp.
 - cefaclor vs. *Streptococcus pneumoniae*

- macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin, telithromycin and possibly solithromycin) vs. *Haemophilus* spp.
5. **To deal with the need for a buffer zone in such a way that it becomes the responsibility of the laboratory and not the recipient of the susceptibility test report.** We have analysed all EUCAST MIC distributions and MIC vs. zone diameter correlations and suggest that EUCAST introduce a new concept, an “**Area of Technical Uncertainty**” (**ATU**). For the EUCAST disk diffusion test it is a 2-4 mm technical buffer zone for about 20 agent-species combinations:

The following agents are in need of an Area of Technical Uncertainty (organised by species) in the EUCAST disk diffusion test:

Enterobacteriaceae (5)

- amoxicillin-clavulanic acid, piperacillin-tazobactam, ceftaroline, ceftazidime-avibactam, ciprofloxacin

Pseudomonas aeruginosa (7)

- piperacillin-tazobactam, cefepime, ceftazidime, ceftazidime-avibactam, aztreonam, ciprofloxacin and levofloxacin

Staphylococcus spp. (4)

- ceftaroline, ceftobiprole, amikacin, linezolid

Enterococcus spp. (1)

- vancomycin

Viridans group streptococci (1)

- benzylpenicillin

Haemophilus influenzae (6) – all related to PBP3 mutations causing poor correlation between MIC and zone diameters in the area around the breakpoint.

- ampicillin, amoxicillin-clavulanic acid, (and to some extent cefepime, cefixime, cefotaxime, ceftriaxone, cefuroxime).

The situations where an ATU would be needed are few. Even in the absence of IT support or redevelopment of the LIS, it is possible to implement these in the laboratory. In its simplest form, a printed page listing species and agents and the ATU can be made available at the workbench.

Results in the ATU must be handled by the laboratory prior to reporting susceptibility test results. There are several options, including:

1. **Report the result as “uncertain”**
- add a comment; report the result in brackets
2. **Repeat results falling within the ATU**
- repeat the test or use another test.
3. **“Play it safe”** – if not solved by other means, a result in the ATU is changed to a more resistant category (S to I or I to R).

4. **Exclude the result from the report with a comment** “Because of technical difficulties a susceptibility test result could not be given for agent X”

It may be that it is appropriate to use different solutions for different situations. This will be examined further.