EUCAST Steering Committee responses to the EUCAST Proposal on the modification of the definition of the Intermediate category 2nd consultation (consultation period ended 2017-09-15).

<table>
<thead>
<tr>
<th>Comment from (name, contact details)</th>
<th>Comments</th>
<th>Responses</th>
</tr>
</thead>
</table>
| John Turnidge on behalf of AusNAC (jturnidge@gmail.com) | In general, AusNAC supports the move to redefine Intermediate. However, there appears to be an inconsistency between the proposed definition and proposal 3 for UTI: the definition says “categorised as intermediate because the antimicrobial agent is concentrated at the site of infection” but proposal 3 is to categorise as susceptible “For uncomplicated UTI only”.

AusNAC favours the proposal part 3 solution for uncomplicated UTI although reporting has some challenges: we usually do not know with certainty whether we are reporting on an uncomplicated UTI. Do we leave it to the treating clinician (often junior medical staff in our case) to make the distinction? The labs generally have no idea whether it is a simple UTI or pyelonephritis except if there are corresponding blood cultures. For instance, is it possible to have favour just one call for AmoxyClav S (<8); I (16, 32); R (>32) and educate that I = S if a simple UTI? | The inconsistency has been noted and will be clarified in the final version of the proposal. The EUCAST Steering Committee will discuss removing the last part of the definition (the part referring to the increased concentration in certain sites almost exclusively referring to urine and urinary tract infections) and the consequences this would have on agents with exclusive and non-exclusive but important use in UTI. |
| Christoffer Lindemann pc-linde@online.no on behalf of NWGA | The NWGA supports the proposed definition of the intermediate category. | Noted |
| Kaisu Rantakokko-Jalava kaisu.rantakoko- | FiRe appreciates the detailed work EUCAST has done since the first consultation in 2015 and the possibility to comment on the new proposal. We admit that with increasing antimicrobial resistance, an unequivocal definition of the intermediate |
|  | Thank you for your positive comments about the proposal. | |
category becomes more and more necessary for the clinician who may need to choose between suboptimal (non-S) alternatives. We also accept the new concept of Area of Technical Uncertainty as a means to control variation and uncertainty of measurement where it may essentially affect the interpretation of a strain as susceptible or resistant.

We assume that the advantages and disadvantages of using the very SIR-system to mediate the need of enhanced exposure (as opposite of e.g. commenting the need of a higher dosing as a basis of S) has been carefully considered. We still have some specific concerns:

First, with the current suggestion, the AST interpretation for a wild-type *P. aeruginosa* will be “I” for all antipseudomonal drugs except meropenem (and maybe ceftolozane-tazobactam). This will unnecessarily discourage the use of old narrow-spectrum antimicrobials and increase the use of meropenem. Especially with this species, there is an evident risk of calling for resistance.

Concern has been raised by several groups about the proposal to report “I” for all antipseudomonal agents except meropenem. This will clearly bias the use of antimicrobials if the meaning of “I” is misunderstood. For this reason, the EUCAST Steering Committee has decided to retain “S” for the antipseudomonal agents, and instead will add a column to the Dosage tab in the Breakpoint Tables specifying that maximum dosing regimens were used when setting the “S” breakpoints for *Pseudomonas* spp. Further, the *Pseudomonas* spp. tab will carry a Note directing users to that column on the Dosage tab. This will also consistently apply to other situations where the wild-type category needs higher exposure to be treatable (these will no longer be called intermediate).
To minimize the harm, each laboratory report with an “I” should be followed by a comment explaining the new definition with phrasing that is both short and understandable to the clinician. For this purpose, the suggested new definition (especially the footnote) is too complicated, and maybe the practical phrasing would be closer to the previous suggestion.

Some minor points of concern:

- according to the definition, should not pneumococci with penicillin MIC<0.06 still be categorized as S, and only the dose-related area be I? Similar to *P. aeruginosa*, this has implications regarding antimicrobial stewardship.
- would trimethoprim or trimethoprim-sulfa really be recommended for systemic enterococcal infections, even with a maximal dosing?
- *H. influenzae* and macrolides?

We agree with the intent of this suggestion. As part of the roll out of the new “I” definition, EUCAST will develop educational tools, including tools to assist laboratories in informing clinicians about the changed definition of “I”.

With regard to these comments:

- As you are aware, pneumococcal interpretations are not just dependent on dosing regimen. There is also the issue of site of infection. Both of these are already accounted for in the current *S. pneumoniae* table and its accompanying Notes.
- The trimethoprim-sulfamethoxazole breakpoint for Enterococci pertains to UTI only. This will be addressed by the Steering Committee and most probably the breakpoints will be replaced by a Note describing the dilemma with variable folate concentrations in urine and listing ECOFFs (see similar solution below for macrolides vs. *Haemophilus influenzae*). The efficacy of macrolides against *H. influenzae* is controversial. EUCAST plans to remove macrolide breakpoints against this pathogen, after due
### Defining some results as being uncertain (within ATU) and requiring extra work before reporting

- It is likely that the breakpoints will be replaced by a Note (see similar solution above for trimethoprim +/- sulphonamide vs. Enterococci).
- EUCAST understands this issue but believes that, with adequate lead time, it will be possible to program LIS systems to flag ATUs back to the bench before the report is released. The key issue is that these problems cannot be solved by the recipient of the report and must remain the responsibility of the laboratory.

### Jesus Guinea Ortega on behalf of the AFST Subcommittee

<table>
<thead>
<tr>
<th>The EUCAST AFST SC discussed the proposal, main concerns were:</th>
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<tbody>
<tr>
<td>a) The proposed wording still doesn’t tell the clinician whether dose adjustment is necessary or not. This requires detailed PK/PD knowledge for the individual drug and infection focus in question.</td>
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<tr>
<td>b) For several drug bug combinations in mycology, WT and mutant populations overlap which in combination with a borderline exposure and variability in testing inevitably challenge correct and reproducible classification because the “S” BP is close to the WT population (to avoid misclassification of resistant isolates). In the absence of an intermediate category as a buffer zone, misclassification S/R will happen more often. One example is posaconazole, voriconazole and isavuconazole against <em>A. fumigatus</em> for which the MIC distribution for the most common resistance</td>
</tr>
<tr>
<td>In regard to the AFTST concerns:</td>
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<tr>
<td>a) While EUCAST agrees that the proposal does not directly address dose adjustment, it believes that dose adjustment <em>per se</em> is about therapeutic drug monitoring, and beyond the scope of the Intermediate proposal.</td>
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<tr>
<td>b) EUCAST is aware of the ‘overlap’ and the “S” no “I” problems. However, these problems are minimised if ECOFFs are set according to the newly codified ECOFF setting procedure. With this new procedure, variability in the</td>
</tr>
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</table>
mechanism TR34/L98H overlap with the WT population but is associated with increased failure rate. Another example is the echinocandins for which no I category exist and where the BP is very close to the WT population in order to reliably detect fks mutants. Here we see quite some random S and R classifications across the echinocandins as well as over time that is not clinically founded. This is further exaggerated when commercial tests are adopted that may not always be perfectly aligned with the ref method across all drug bug combinations.

For these reasons, the EUCAST AFST find that the revision of the “I” definition omitting the buffer zone does not match the non-ideal mycology world where susceptibility testing unfortunately does not always lead to a black and white result. The buffer zone does not go away just by being excluded from the definitions. Moreover, as the revision does not remove the clinician’s task of translating the “I” into if dose adjustment is needed (organism treatable at a higher dose) or if dose adjustment is not needed (e.g. urinary infection only and the compound is up-concentrated in the urine), the EUCAST AFST SC did not unanimously feel the intended pros out-weighted the cons.

A pragmatic explanation of the original definition is that

S means susceptible – the clinician can treat and expect an outcome similar to his/her experience with this type of infection in patient category.

I means Intermediate – Intelligence and further information required. Consult your microbiologist for advice.

R means Resistance – Refrain from using.

During the first consultation, concerns from many colleagues were raised regarding the omission of the buffer zone interpretation. The AFST SC would like to note that antifungal susceptibility testing is associated with technical variation that in real life implies, that there will be a group of isolates in a grey zone area independently on if we name them or not. A buffer zone of 1 to max 2 dilutions will increase the proportion of S and R results that are actually correct and trustworthy. Therefore, the AFST would recommend continuing allowing “I” for buffer zone for antifungal assay (including a lot of technical uncertainty) is factored into the pooling of distributions and subsequent ECOFF setting. The requirement that breakpoints should not be set within the wild-type distribution means that the “buffer zone” is already factored into breakpoint selection, and that ATU need only be applied in those few circumstances where the technical uncertainty cannot be fully overcome with ECOFF setting, such as in the first example you provided (azoles and Aspergillus). The Steering Committee reiterate that the major reason for a change is that having an Intermediate category with multiple meanings is not helpful unless its interpretation is explained in individual cases. As stated in the background documentation to the 1st and the 2nd consultation, and in the responses to the comments received, we find that there are major disadvantages with retaining Intermediate with multiple definitions, including that of a buffer zone.

EUCAST subcommittees need to adapt to the new terminology and in this case use “ATU” to reflect the need, in some cases, for a buffer
We welcome this EUCAST initiative to update the definition of the intermediate category. There has been confusion about the term intermediate since it has been used in completely different situations like 1) "dose increase required for treatment effect" and 2) "the result is methodologically uncertain". We appreciate that EUCAST has taken into account previous opinions and the problem of measurement uncertainty. It is important that the bacterial-antibiotic combinations where the uncertainty concept is relevant now will be clearly defined and that EUCAST suggests options for how uncertain results should be reported and used.

Change of definition is a major task that will require a lot of work and may implicate misunderstandings and patient risks. A future SIR system needs to be flexible and easy to adapt to future techniques and mechanisms.

We believe that the proposed concept "Area of technical uncertainty", ATU needs some clarification:
- Modern laboratories will not be able to handle some breakpoints (SIR) automated and some breakpoints (ATU) manually.
- How should ATU be implemented in laboratory information systems and processes?
- How do EUCAST recommend laboratories to register and report the corresponding uncertainty related to MIC determinations?
- The “Play it safe” option (no.3) include a possibility to change interpretation from “S” to “I” if results are within the ATU interval. Do EUCAST recommend a higher dose for some ATU results, if a higher dose will exclude technical uncertainty?

Alternative suggestion
One possible alternative to the proposed used of the intermediate group would be to report susceptibility in accordance with the proposal below. We believe it could be of great value before making a major change to consider pros and cons with this suggestion as compared to the current suggestion from EUCAST.

1) Define separate breakpoints for an antibiotic at standard dosage / exposure and for the same antibiotic in higher dosage / exposure. Antibiotics in higher dosage / exposure can then be presented as a

| Annika Carlsson Wisted and Håkan Hanberger on behalf of SRGA | We welcome this EUCAST initiative to update the definition of the intermediate category. There has been confusion about the term intermediate since it has been used in completely different situations like 1) "dose increase required for treatment effect" and 2) "the result is methodologically uncertain". We appreciate that EUCAST has taken into account previous opinions and the problem of measurement uncertainty. It is important that the bacterial-antibiotic combinations where the uncertainty concept is relevant now will be clearly defined and that EUCAST suggests options for how uncertain results should be reported and used. Change of definition is a major task that will require a lot of work and may implicate misunderstandings and patient risks. A future SIR system needs to be flexible and easy to adapt to future techniques and mechanisms. We believe that the proposed concept “Area of technical uncertainty”, ATU needs some clarification:
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| EUCAST agrees that it will be especially important to clearly explain the new definition of “I” and plans to develop educational materials for laboratories and clinicians, providing as much guidance as possible to assist with the transition.

EUCAST believes that with careful planning it will be possible for laboratories and LIS systems to handle ATU. EUCAST will spend the next few months working on suggestions about how this can be achieved, and including them in laboratory educational packages. We do not expect laboratories to report uncertainty in MIC determinations to the clinicians; instead we expect them to develop an understanding of them and how they affect laboratory testing. Two publications on this subject have been submitted recently.

EUCAST thanks the SRGA for its innovative suggestions, but believes that it has sufficient support for the proposed new definition and its application to move ahead without further major change. Moreover, the solution proposed will not work in...
separate line in the breakpoint table and on the response report.

Example Streptococcus pneumoniae (PCG MIC 1.0 mg/L, AMP MIC 1.0 mg/L)

Penicillin G……………………….R
Penicillin G (enhanced exposure)………S
Penicillin V……………………….R
Ampicillin……………………………R
Ampicillin (enhanced exposure)………S

The corresponding breakpoint table information would be as follows:

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Standard Exposure</th>
<th>High Exposure, Not Meningitis</th>
<th>High Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>0.06</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

2) Reserve the designation "I - intermediate" for measurement uncertainty only.

Proposed new definition:

Intermediate (I): A microorganism is defined as intermediate by a level of antimicrobial activity associated with an uncertain effect due to antimicrobial susceptibility testing results within the area of technical uncertainty.

The intermediate definition should be clarified regarding how the results should be handled by the laboratory prior to reporting according to the instructions in EUCAST's proposal on area of technical uncertainty. A change of term to "indeterminant" may be considered.

Some aspects of the alternative suggestion

1) Current I-intervals in the EUCAST breakpoint table are defined as "dose increase
required for treatment effect” and this interpretation is well-established in many (but not all) contexts and countries. Hence, an uncertain reported “I” may be misinterpreted as treatable with adjusted dosage. However, in accordance with the ATU recommendation an uncertain “I” should be hidden or annotated.

2) The clinically important situation where high dose can be used will be more clearly expressed also to the clinician who is uncertain about current definitions in the SIR system since “high exposure” (or high dosage) is stated together with the interpretation. However, more space and text are needed on the reports for resistant isolates.

3) The reporting system becomes flexible for future needs. For example, target levels for antibiotic exposure could be indicated instead of dosing regimens. When measurement uncertainty is low, EUCAST can choose to define breakpoints without intermediate interval. Uncertainty in the form of intermediate category may, if relevant, be defined even for high dosage situations.

3. The changes will be easier to implement. The structure of laboratory data systems and breakpoint tables may be kept unchanged. The same conceptual structure already used for infection site (“Ampicillin, UTI only” or “Penicillin G, meningitis”) will also be used for dosing / exposure. Brand new concepts such as “area of technical uncertainty” can be avoided. Confusion due to different definitions in different resistance determination systems can be avoided.

Sincerely
Annika Carlsson Wistedt
Member of NordicCast and SRGA
Chief physician
Clinical Microbiology, Laboratory,
Kalmar
annikawi@ltkralmar.se

Håkan Hanberger
Chair SRGA
Professor, Senior Physician
Infectious Diseases
Linköping University Hospital
hakan.hanberger@liu.se

Jane E. Ambler, PhD
VP Clinical Microbiology
Wockhardt Inc., USA

EUCAST thanks you for this feedback.
workshops (29 September 2016 and 13 September 2017) to facilitate discussion between key stakeholders, there has been much discussion regarding the variability of the broth microdilution (BMD) reference method (Ullery, 2017). Extensive mathematical modelling has questioned whether such variation should be considered realistic or extreme, and whether it is acceptable. In conclusion, it is unrealistic to consider that BMD can provide a single, absolute MIC value for a given organism/drug combination.

FDA’s Center for Devices and Radiological Health (CDRH) advises that assessment of the variability of the BMD reference method is an important consideration when planning a new AST device evaluation for clearance. FDA recommends AST device manufacturers should consider BMD variability of the new drug and define an analysis plan, e.g. replicate testing by the reference method (Conville, 2017).

When clinical breakpoints are set close to ECOFF’s, and/or intersect the wild-type distribution of target organisms including those species with a common resistance mechanism - such as methicillin resistance in *Staphylococcus aureus* mediated by mecA - the performance (accuracy and reproducibility) of the BMD method is further challenged. The prevalence and impact of sequence variability of PBP2a on the assessment of ceftaroline susceptibility exemplifies this (Lahiri, McLaughlin, Whiteaker et al., 2015 and Koeth, Apfalter, Becker et al., 2016).

Despite scientific advances in the field of pharmacokinetics (PK) and pharmacodynamics (PD) that have impacted antimicrobial drug development, detailed in the European Medicines Agency (EMA) guidelines (21 July 2016 EMA/CHMP/594085/2015), the use of PK-PD analyses to identify breakpoints is not addressed. The determination of the probability of target attainment (PTA) using simulations to support dose regimen selection requires adequate patient PK data, the use of population PK models and PD targets (PDTs) derived from *in vitro* and *in vivo* infection models with target pathogens relevant to the intended clinical use. Phase 3 registration trials by design commonly exclude desirable patients with infections caused by target organisms with high MICs, resulting in limited efficacy data for setting clinical breakpoints. Regulatory agencies are cautious to consider setting breakpoints outside clinical cutoffs.

EUCAST believes that many of the issues raised are dealt with by the new ECOFF setting procedure. The EUCAST tradition for more than 15 years is to avoid setting breakpoints within the wild-type distributions of important target organisms as they are defined by ECOFFs. The new procedure obviates the need for a “buffer zone” in most circumstances. Where is does not, the ATU concept has been introduced.

EUCAST is aware of the recent work on variability in MIC measurements and Steering Committee members have even initiated or contributed to publications that have recently been submitted for publication (including material presented at the recent FDA meeting).

With regard to the problem of changing and evolving breakpoints, this has been an issue to CLSI, the FDA, EUCAST and EMA for more than a decade. EUCAST understands the impact on device manufacturers, but believes that the new science behind breakpoint setting has mandated changes which are in the best interest of patient care. What is more, the
The Intermediate (I) category by CLSI definition includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies, especially for drugs with narrow pharmacotoxicity margins (Humphries RH, 2017). Much has work been done in recent years in an effort to reach international consensus to define drug resistance.

AST device manufacturer’s report they are already significantly challenged with recent breakpoint changes by standards organizations and the number of new antimicrobial agents in development that have Qualified Infectious Disease Product (QIDP) status. The EUCAST proposal to modify the definition of the intermediate category is likely to result in confusion and further delays in access to much needed commercial automated AST systems for clinical laboratories.

- CLSI June 2017 Agenda Book, Coordinated Development of ASTs and Antimicrobials Working Group; Broth-microdilution Variation and How it Affects AST Method Evaluations, M. Ullery, bioMérieux
- CLSI June 2017 Agenda Book, Coordinated Development of ASTs and Antimicrobials Working Group; Coordinated Development of New Drugs and AST Devices: FDA/CDRH Perspective, P.S. Conville, FDA CDRH

issue is essential about how the various 'systems' can adapt to those changes in a timely manner.

Iztok Štrumbelj on behalf of Slovenian National Antimicrobial Susceptibility Testing Committee (SKUOPZ)

National Laboratory of Health, Environment and Food, Department of Medical Microbiology Murska Sobota, Arhitekta Novaka 2b, SI-9000 Murska Sobota, Slovenia

Mobile: + 386 31 841 530 iztok.strumbelj@nlzoh.si

1a. We propose different symbol instead of “I” (one letter or two letters) for abbreviation of intermediate category if new definition will be adopted.

We think that: letter “I” in SIR is associated with different meanings and it would be difficult to associate new meanings with old symbol.

In any case, intense communication with clinicians will be necessary if new definition is adopted. However, if we start to use new symbol / letter, physicians will ask for explanation; if “I” would be used, they wouldn’t be alerted that new definition was applied to the category.

Possible options for replacement of “I” (other options may be used):

- S^H
- SH
- S_H
- H

1.b. We propose that short legend to the abbreviation is determined by EUCAST. e.g.:

SH (or H or S* or..) – sensitive by adjusting the dosing regimen to enhance exposure, or if the antimicrobial agent is concentrated at the site of infection.

Or something shorter, if possible (e.g. high dosing).

2.a. Agents used only for lower UTI.

We propose different symbol instead of “S” (one letter or two letters) for

2. See answer to 1. above

1. EUCAST has considered a large number of options for reporting symbols, especially “I”. EUCAST thanks the Slovenian NAC for its interesting suggestion. The Steering Committee is still debating whether or not to retain the “I” or to change it for something else. This discussion will continue until a final decision is taken. Should we decide to retain the “I”, we will, in the educational material to be developed, point out that “I” = “Intermediate” is also “I” = “Increased exposure” through dosing regimen adjustment. Even though introducing a new letter is tempting, it is an extremely complex issue since it involves reprogramming a large number of LIS systems and semiautomated machines for AST. It is likely to take a very long time to implement and there is a risk that different laboratories and different countries will be out of sync for many years after.
abbreviation of “sensitive with the caveat For uncomplicated UTI only”.

Possible options for replacement of “S” in this situation (other options may be used):

- SU
- SU
- SU
- U

(R remains R, there is no problem with that category in this situation).

2.b. We propose that short legend to the abbreviation is determined by EUCAST.

Maybe: “SU – sensitive if used for uncomplicated UTI”.

<table>
<thead>
<tr>
<th>3. Question regarding 4 A. - The wild type in the Susceptible category with a caveat concerning high dosing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In section 4 A. - regarding aminoglycosides, only Acinetobacter spp. is in section 4A.</td>
</tr>
<tr>
<td>However, in the Breakpoint tables, high dosing of aminoglycosides is also recommended in Enterobacteriaceae and Pseudomonas sections; a note is added in these sections too: Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages.</td>
</tr>
<tr>
<td>The questions:</td>
</tr>
<tr>
<td>- is high dose of aminoglycosides necessary only for Acinetobacter spp. or also for Enterobacteriaceae and Pseudomonas spp.</td>
</tr>
</tbody>
</table>

3. Breakpoints (and their associated dosing regimens) are currently under review by EUCAST. It is expected that this question will be addressed during the review process.

<p>| 3. Question regarding 4 B. Enterococcus spp. |
| See the response above |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>We would appreciate explanation regarding <em>trimethoprim-sulfamethoxazole</em> if the result of testing is &quot;I&quot;:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- is it to be regarded as susceptible for systemic infections if high dosing is used.</td>
</tr>
<tr>
<td></td>
<td>- is it to be regarded as susceptible with standard dose in lower urinary tract infections, where the drug is concentrated at the site of infection.</td>
</tr>
<tr>
<td></td>
<td>Currently, there is no comment that high dose is needed and meaning of intermediate category in this particular situation is not clarified.</td>
</tr>
</tbody>
</table>