Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 26 (2020) 1692–1693

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Re: In the name of common sense: EUCAST breakpoints and potential pitfalls. National dissemination of EUCAST guidelines is a shared responsibility

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ARTICLE INFO

Article history:
Received 1 August 2020
Received in revised form
5 August 2020
Accepted 5 August 2020
Available online 20 August 2020

Editor: L. Leibovici

To the editor

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) acknowledges the difficulties encountered when attempting to disseminate new information concerning antimicrobial susceptibility testing (AST) [1]. This is especially true for colleagues outside our specialties. We also agree that unless colleagues have understood and accepted the rationale behind the new S (susceptible, standard dose), I (susceptible, increased exposure) and R (resistant) definitions, this may lead to an increased use of meropenem for the treatment of *Pseudomonas* infections since most other agents will be categorized as 'susceptible, increased exposure'. EUCAST had planned to use 2020 as the year during which all changes would be thoroughly explained and gradually implemented. COVID-19 put a spanner in everyone's works. It became very difficult to elicit much interest in anything but the pandemic.

The change was necessary. The old definition of 'intermediate' (I), crafted by EUCAST 2002–2018 [2] and embedded in the original 2006 version of ISO standard 20776-1 [3], had proved difficult to understand and nigh on useless in everyday practice. This was primarily due to its multiple meanings (italics): "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".

Most colleagues ignored an 'I' and looked for an 'S', and we learnt of colleagues who converted every 'I' to 'R' in the report. Surveillance systems lumped 'I' and 'R' under 'non-susceptible'. To make things worse, many colleagues liked wide 'intermediate' categories because these prevented or reduced very major (VMEs) and major errors (MEs) in AST: the wider the 'intermediate' category, the fewer VMEs and MEs. While this may seem attractive, the lack of clarity of the definition and an abundance of intermediate results would continue to drive the use of broader and more expensive antimicrobials. The assumption by Meylan and Guery [1] is most certainly correct: the gut reaction of most colleagues is to go looking for that 'S' because they do not trust 'I' to be useful. Which proves our point.

EUCAST is now resurrecting the usefulness of this susceptibility category. A discussion about changing definitions, and possibly the letters S, I and R, was started in 2014. During three public consultations (2015–2018), the arguments and proposals brought forward by Meylan and Guery, and many more, were discussed and commented on by EUCAST (see https://www.eucast.org/documents/consultations/ for three public consultations directly related to the change and two related to the consequences in reporting and dosing). All comments were discussed and responded to by EUCAST, as is evident when reading these. In

DOI of original article: https://doi.org/10.1016/j.cmi.2020.07.025.
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https://doi.org/10.1016/j.cmi.2020.08.008

preparation for all major decisions, EUCAST encourages National AST Committees (NACs) to discuss and inform national colleagues and to respond to consultations—all NACs were addressed, including the Swiss NAC—and their response will be among the others.

The 'susceptible dose-dependent (SDD)' category first appears in a 1997 article by Rex et al. and relates to fluconazole in antifungal AST [4]. It is later introduced by the Clinical and Laboratory Standards Institute (CLSI), primarily for antifungal susceptibility testing, but later also for a few antibacterial agents: cefepime, CLSI M100-S14 (2014) and subsequently ceftaroline and daptomycin. EUCAST evaluated SDD but decided against adopting it. The discussion between CLSI and EUCAST representatives was recently published as a point–counterpoint [5]. EUCAST took the view that all breakpoints are really dose-dependent, and that a three-letter category and a fourth category should be avoided (the CLSI system has S, I, SDD and R). Systems with difficulties changing one letter would have even more difficulties with a three-letter category and a fourth category. Neither antibacterial (as opposed to antifungal) susceptibility testing devices nor most laboratory information systems handle SDD or a fourth category. Through the EUCAST public consultations and distributed questionnaires we knew that >80% of colleagues were in favour of not changing the letter 'I'. These included the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), as well as the manufacturers of AST devices, all of which predicted lengthy and drawn-out procedures if a change of letter were to be managed. The delay in implementation and the confusion created by a change which would be impossible to synchronize needed to be avoided. To address the element of technical uncertainty built into the previous definition of 'I', the committee decided to carefully analyse where the major problems lay. Since the change laboratories are warned by the introduction in tables of the 'area of technical uncertainty' (ATU), often caused by a combination of natural variation in tests and poor separation between isolates without and with resistance mechanisms to the agent (e.g. piperacillin–tazobactam and Enterobacterales).

Implementation of EUCAST guidance is a shared responsibility. EUCAST, ESCMID, European agencies, NACs, national societies, and local stewardship teams and laboratories all have important roles in making sure colleagues have understood the meaning of the new 'susceptible, increased exposure' category and in adopting systems to cope. With the support of EUCAST, NACs have the most important role. We advise all concerned colleagues to contact their NACs to offer help and assistance, as well as to obtain updates on what has already been done and what is planned on a national level. NACs are encouraged to use the various materials made available by EUCAST for national translation and distribution to colleagues.

Author contributions

GK wrote the original draft; CGG, RC and JT performed review and editing. The entire EUCAST Steering Committee approved the final text.

Transparency declaration

Drs Kahlmeter and Turnidge have nothing to disclose. Dr Canton reports grants from BioMerieux, MSD, Pfizer, IMI-EU, and H2020-EU outside the submitted work. Dr Giske reports grants from 1928 Diagnostics, Spero Therapeutics, and H2020-EU outside the submitted work. No funding was received for this article.

Appendix

The EUCAST Steering Committee: Christian G. Giske (chair), John Turnidge (scientific secretary), Rafael Cantón (clinical data coordinator), Gunnar Kahlmeter (technical data coordinator and webmaster), Shampa Das (PKPD expert), Sören Gatermann (Germany), Gerard Lina (France), Christoffer Lindemann (Norway), Alasdair MacGowan (The United Kingdom), Joseph Meletiadis (PKPD expert), Gian-Maria Rossolini (Italy) and Jorge Sampaio (Brazil).

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