LETTER TO THE EDITOR / EDİTÖRE MEKTUP

DOI: 10.4274/mjima.galenos.2019.2019.23
Mediterr J Infect Microb Antimicrob 2019;8:23
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2019.2019.23

Novel and Revised Terms in the EUCAST 2019 Guideline: Susceptible, Increased Exposure and Area of Technical Uncertainty

EUCAST 2019 Kılavuzundaki Yeni ve Güncellenen Kavramlar: İlaçla Artmış Maruziyette Duyarlılık ve Metodolojik Tampon Alan

Elif Seren TANRIVERDİ, Yücel DUMAN

İnönü University Faculty of Medicine, Department of Medical Microbiology, Malatya, Turkey

Keywords: European Committee on Antimicrobial Susceptibility Testing, antibiotic resistance, antibiotic susceptibility test, antimicrobial agent, rational antibiotic use
Anahtar Kelimeler: Antimikrobiyal Duyarlılık Testi Avrupa Komitesi, antibiyotik direnci, antibiyotik duyarlılık testi, antimikrobiyal ajan, akılcı antibiyotik kullanımı

Dear Editor,

Prior to the 2019 guideline, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) categorized antibiotic susceptibility test (AST) results into three main groups: susceptible (S), intermediate (I), and resistant (R)[1]. With this categorization, reporting a bacterium as susceptible to an antimicrobial agent meant there was a high likelihood of achieving a clinical response to treatment, while reporting as resistant indicated a low likelihood of treatment response. However, since the I label led to different approaches to treatment planning and interpreting AST results, EUCAST felt the need to update this category[2]. Therefore, EUCAST proposed a change in 2015 to redefine category I and eliminate uncertainties, and opened its official website to receive comments and suggestions[3]. After three general consensuses, EUCAST updated the definition of category I, to be applied as of 1 January 2019[4]. In addition, "areas of technical uncertainty" (ATU) was added as a new concept to the current guideline[5]. Herein, we aimed to explain the concept of ATU and the updated definition of category I.

In guidelines published between 2002 and 2018, EUCAST classified category S as susceptible, category I as intermediate, and category R as resistant. However, it was believed that category I being described as I caused uncertainties regarding the therapeutic efficacy of the antimicrobial agent and the dose and/or route of administration to be used with patients, leading to problems in the interpretation of AST results by clinicians. Hence, EUCAST felt the need to update this category. In the current guideline, the letters S, I, and R remain unchanged. An AST result of S still indicates high likelihood of therapeutic success with the antimicrobial agent used at a standard dose, while a result of R means that the likelihood of therapeutic success is low, even at higher doses. The definition of category I, on the other hand, has been updated as S with increased exposure to the drug, or susceptibility associated with the dose and route of administration (concentration) of the drug[4]. To date, the concept of increased drug exposure was more prominent in pharmacokinetic studies[6]. This concept means

Cite this article as: Tanrıverdi ES, Duman Y. Novel and Revised Terms in the EUCAST 2019 Guideline: Susceptible, Increased Exposure and Area of Technical Uncertainty. Mediterr J Infect Microb Antimicrob. 2019;8:23.

Address for Correspondence/Yazışma Adresi: Elif Seren Tanrıverdi MD, İnönü University Faculty of Medicine, Department of Medical Microbiology, Malatya, Turkey
E-mail: seren.tanriverdi@inonu.edu.tr
Received/Geliş Tarihi: 01.04.2019 **Accepted/Kabul Tarihi:** 17.07.2019 **ORCID ID:** orcid.org/0000-0002-0449-0356

Published: 22 July 2019

that the concentration of an antimicrobial agent at the site of infection may increase when its dose, route of administration, or frequency of administration is changed or, in some cases, due to the pharmacokinetic properties of the drug[7]. For instance, beta-lactam antimicrobials were found to reach higher concentrations at the site of infection when administered by intravenous infusion instead of bolus injection[8]. In contrast, there is a natural increase in concentration at the site of infection when using an antimicrobial agent that is excreted in the urine in lower urinary tract infections[7].

In the current guideline, the breakpoints used to differentiate between the S, I, and R categories are related to the dosage, route of administration, and natural concentration at the site of infection. In addition, the revised breakpoint tables show the dosage and route of administration that are associated with certain breakpoints[4].

The term "intermediate susceptibility" used in previous guidelines compelled clinicians to choose a different S antimicrobial agent for treatment[9]. This is one of the main reasons for updating the definition of category I, to prevent the rapid development of resistance to the antimicrobial agent that might be used. The current guideline is intended to ensure that available drugs are used instead of new, broad-spectrum antimicrobial agents with higher susceptibility rates[4].

Previous EUCAST guidelines (2002-2018) included warnings regarding certain technical uncertainties. These warnings include small, relatively uncontrollable technical and methodological factors, such as the materials used, the amount of inoculum, and reading differences, that may impact the determination of inhibition zone diameter during implementing disk diffusion method and the determination of minimal inhibitory concentration (MIC) with the broth microdilution method[7]. Kahlmeter's[9] proposed change in EUCAST category I can be considered a buffer zone, as mentioned in his description of a "buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations". For this reason, ATU has been translated into Turkish as a "methodological buffer zone/metodolojik tampon alan".

In the current guideline, situations that result from technical or methodological errors have been removed from the definition of category I[5]. The concept of ATU refers to a MIC value and/or inhibition zone diameter with uncertain interpretation or S, I or R categorization. EUCAST has identified the concept of ATU in order to reduce variations in AST results and eliminate/decrease the potentially suspicious S, I, and R category breakpoints[6]. With its 2019 guideline, EUCAST aims to reduce these methodological errors and the resulting discrepant interpretations. ATU values were determined based on accumulated data from EUCAST studies conducted over the years[5].

If AST results within the ATU value ranges, the following steps should be taken in the laboratory before reporting to the clinician[5]:

1. If a technical error is suspected in the AST result, it is recommended to repeat the test.
2. If S antimicrobial agent options for the patient are limited according to AST results, the antimicrobial agents within the ATU range should be confirmed with an alternative test (MIC, genotype identification, etc.). It is recommended to expand AST results and to determine the MIC values of different antimicrobial agents for multidrug-resistant bacterial strains. For example, AST should be expanded to include new cephalosporin-inhibitor combinations and colistin for multidrug-R Gram-negative bacteria[10]. In some cases, phenotypic or genotypic identification may be necessary to obtain more detailed information on the resistance mechanism of the bacterium.
3. If there are other S therapeutic alternatives in the AST report, reporting an antimicrobial agent in the ATU value range as R is a more correct approach.
4. If the AST result is still within the ATU boundary value range despite conducting these other steps, then the report should indicate the uncertainty of the susceptibility categorization of the antimicrobial agent. In serious cases, the clinician can be contacted.

Although these updates to the EUCAST 2019 (v.9.0) guideline may not be well-known among clinicians, we are of the opinion that they will be much more beneficial in terms of rational antibiotic use and will help prevent the rapid development of resistance to new antimicrobial agents. At the same time, they are essential guidelines for medical microbiology specialists in laboratory practice as well as for infectious disease and clinical microbiology specialists during treatment planning in clinical practice.

Ethics

Informed Consent: Not required.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.S.T., Y.D., Design: E.S.T., Literature Search: E.S.T., Writing: E.S.T., Y.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. EUCAST European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, Version 8.1, valid, 2018. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.1_Breakpoint_Tables.pdf.
2. EUCAST European Committee on Antimicrobial Susceptibility Testing. Proposed modifications to EUCAST definition of the Intermediate category 2nd consultation. 2017. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2017/Intermediate_category_-_2nd_consultation_2017.pdf
3. EUCAST European Committee on Antimicrobial Susceptibility Testing. Proposed modifications to EUCAST definition of the intermediate category. 2016. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2016/20160919_Intermediate_consultation_comments_and_responses.pdf
4. EUCAST European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 9.0, 2019. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf
5. EUCAST European Committee on Antimicrobial Susceptibility Testing. Area of Technical Uncertainty (ATU) in antimicrobial susceptibility testing, version 9.0, 2019. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Area_of_Technical_Uncertainty_-_guidance_2019-1.pdf
6. Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother. 2015;21:319-29.
7. EUCAST European Committee on Antimicrobial Susceptibility Testing. Redefining susceptibility testing categories S, I and R, version 9.0, 2019. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_Presentations/2018/EUCAST_-_Intermediate_category_-_information_for_all.pdf
8. Moehring R, Sarubbi C. Prolonged infusions of beta-lactam antibiotics. Last accessed date: 06.06.2019. Available from: https://www.uptodate.com/contents/prolonged-infusions-of-beta-lactam-antibiotics
9. Kahlmeter G; EUCAST Steering Committee. EUCAST proposes to change the definition and usefulness of the susceptibility category 'Intermediate'. Clin Microbiol Infect. 2017;23:894-5.
10. EUCAST proposes to retain susceptibility categories "S, I, and R" but to change the definitions to "Susceptible, standard dosing regimen", "Susceptible, increased exposure", and "Resistant". Consultation (3rd) February 23 – April 10, 2018. Last accessed date: 06.06.2019. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2018/EUCAST_intermediate_2018_February_23_General_Consultation.pdf