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New definitions of susceptibility categories EUCAST 2019: clinic application

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ABSTRACT

In January 2019, the European Committee for the Study of Antimicrobial Susceptibility (EUCAST) introduced some changes in the definitions of clinical categories for antibiotic susceptibility. The objective of these changes was to improve the credibility of category "I", optimizing and lengthening the survival and use of available antibiotics in the face of increasing antimicrobial resistance. This article aims to describe and explain these changes in the EUCAST criteria as well as make a short review about the factors on which the antibiotic susceptibility criteria depend.

Keywords: breakpoints, antibiogram, new defintiions, EUCAST, pharmacokinetic

The European Committee for the Study of Antimicrobial Susceptibility (EUCAST), belonging to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), is the responsible of the analysis and study of the cut-off points and the technical issues for antimicrobial *in vitro* susceptibility tests. EUCAST establishes guidelines for the interpretation of antibiotic resistance. Following this purpose, EUCAST standardizes and collects the information provided by each National Antibiogram Committee and thus establishes the susceptibility cut-off points that are used to separate bacterial populations. Recently, the Steering Committee of EUCAST has decided to change the definitions of clinical categories for antibiotic susceptibility, valid since January 2019.

There are several factors that EUCAST analyses and takes into account to define cut-off points for each antimicrobial, including chemical formulation, dosage, pharmacokinetic and pharmacodynamics rules and behaviours, Monte Carlo modelling and others. To understand this complex process, it is useful to be familiar with some basic concepts (figure 1), such as minimum inhibitory concentration, clinical and epidemiological cut-off points and PK/PD parameters [1].

The clinical cut-off point expressed as minimum inhibitory concentration (MIC), distinguishes between a treatable and a non-treatable microorganism, susceptible or not to the antimicrobial. The term MIC is the minimum concentration of an antibiotic (expressed in µg/ml or mg/L) that inhibits the growth of a specific bacterial strain. The MIC pretends to evaluate the *in vitro* response of a microorganism to antimicrobial exposure in order to predict a therapeutic success or failure. Depending on the MIC values, bacteria could be assigned to three different clinical categories: susceptible, intermediate or resistant. It is important to know that MIC values are singular and must be interpreted differently for each antimicrobial and for each microorganism. So that, a lower MIC of one antimicrobial compared to another does not imply higher activity. To understand the MIC value, it is necessary to know how the antibiotic susceptibility techniques are performed. EUCAST considers two main techniques: the broth microdilution method, which provides quantitative results and the agar or disk diffusion test, which provides qualitative results.

Epidemiological cut-off points (ECOFF) distinguish microorganisms with or without phenotypically detectable acquired resistance mechanisms to the targeted microorganism. Wild-type strains are those without intrinsic neither acquired resistance mechanisms and will serve to determine clinical cut-off points. They are able to detect resistance (ie: oxacillin in S. pneumoniae, cefoxitin in MRSA).

PK/PD analyses help to define dose-response relationship in order to identify optimal dosing patterns. Pharmacokinetic (PK) parameters relate the actions of the human body on the antimicrobial and include absorption, distribution, metabolism and excretion. They study the time course of antimicrobial concentrations and their metabolites in different body fluids and tissues. PK parameters depend on the antimicrobial and the patient. Pharmacodynamical parameters (PD) include the

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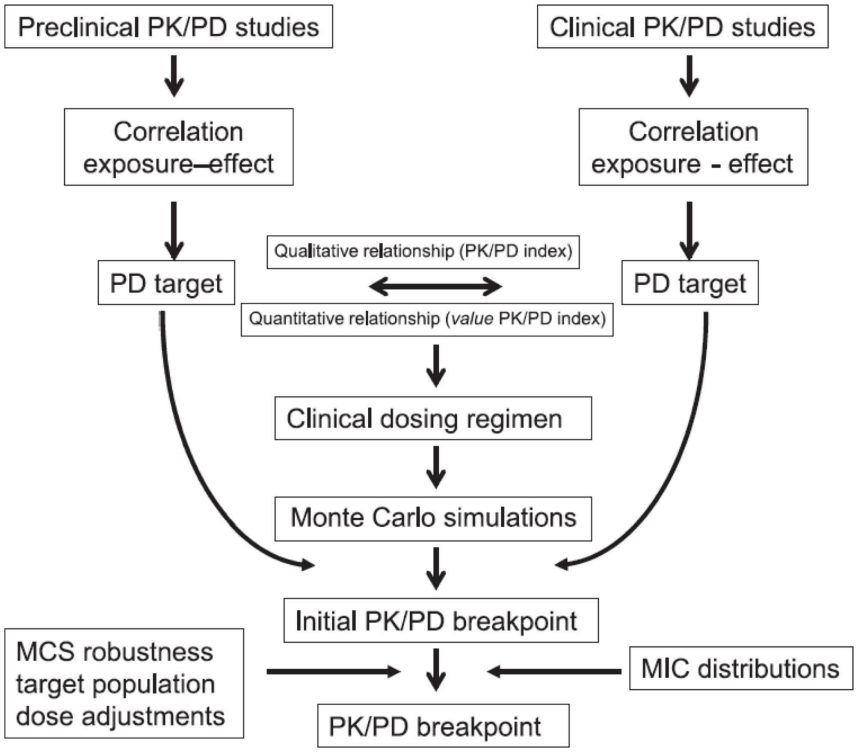

Figure 1 | **PK/PD parameters. Modified from Mouton JW, et al. [1].**

biochemical and physiological effects of the antimicrobial on microorganisms, and they also study the relationship between antimicrobial exposure and clinical or microbiological effects (response, toxicity). They depend on the causative pathogen. PK/PD values are unique and very important for identifying optimal antimicrobial doses and establishing PK/PD cut-off points. Antimicrobial treatment strategies based on PK/PD ratios are designed to maintain a useful concentration for an adequate time in the infective focus, maximizing both, bactericidal action and clinical efficacy, and reducing toxicity too.

Since 2002, EUCAST has used three definitions to categorise microorganisms as treatable or untreatable with each defined antimicrobial agent:

a) Susceptible (S): bacteria are in vitro inhibited by a concentration of an antimicrobial agent that is associated with a high probability of therapeutic success.

b) Intermediate (I): bacteria are in vitro inhibited by a concentration of an antimicrobial agent that is associated with an uncertain therapeutic effect.

c) Resistant (R): bacteria are in vitro inhibited by a concentration of an antimicrobial agent that is associated with a high probability of therapeutic failure.

In 2018, the pressure from a group of researchers and clinicians in favour of optimising antibiotic prescribing without cut-off points, just based only through tools that assess PK/PD targets, together with the indiscriminate rise of multidrug-resistant bacterial infections, made necessary to make some changes, modifying the classification of antibiotic susceptibilities, but keeping the letters "S", "I" and "R".

The previous definition of "Intermediate" generated some confusion and it was often interpreted by laboratories and clinicians as "Resistant", lumping "I" within the "R" category as non-susceptible, i.e. two *Resistant* categories versus a *Susceptible* one. This definition did not help clinical practice because it included some pharmacological, pharmacokinetic and microbiological inaccuracies: an uncertain therapeutic effect, susceptible if higher dosages are used, susceptible if the agent is concentrated at the site of infection, or a buffer zone to reduce miscategorization due to technical factors (natural assay variation [2]. The implementation of the new EUCAST criteria in 2019 had 2 main objectives: to signify and improve the usefulness of antimicrobial susceptibility studies, and to restore the credibility of category "I" to optimise and prolong the survival and use of available antibiotics (old and new).

The new definitions of S, I and R will emphasize the close relationship between the susceptibility of the isolated microorganism and the exposure of that organism to the antibiotic at the site of infection. With these changes there are two categories of *Susceptible* and only a *Resistant* one compared to the previous, and the term non-susceptible will be equated with Resistant.

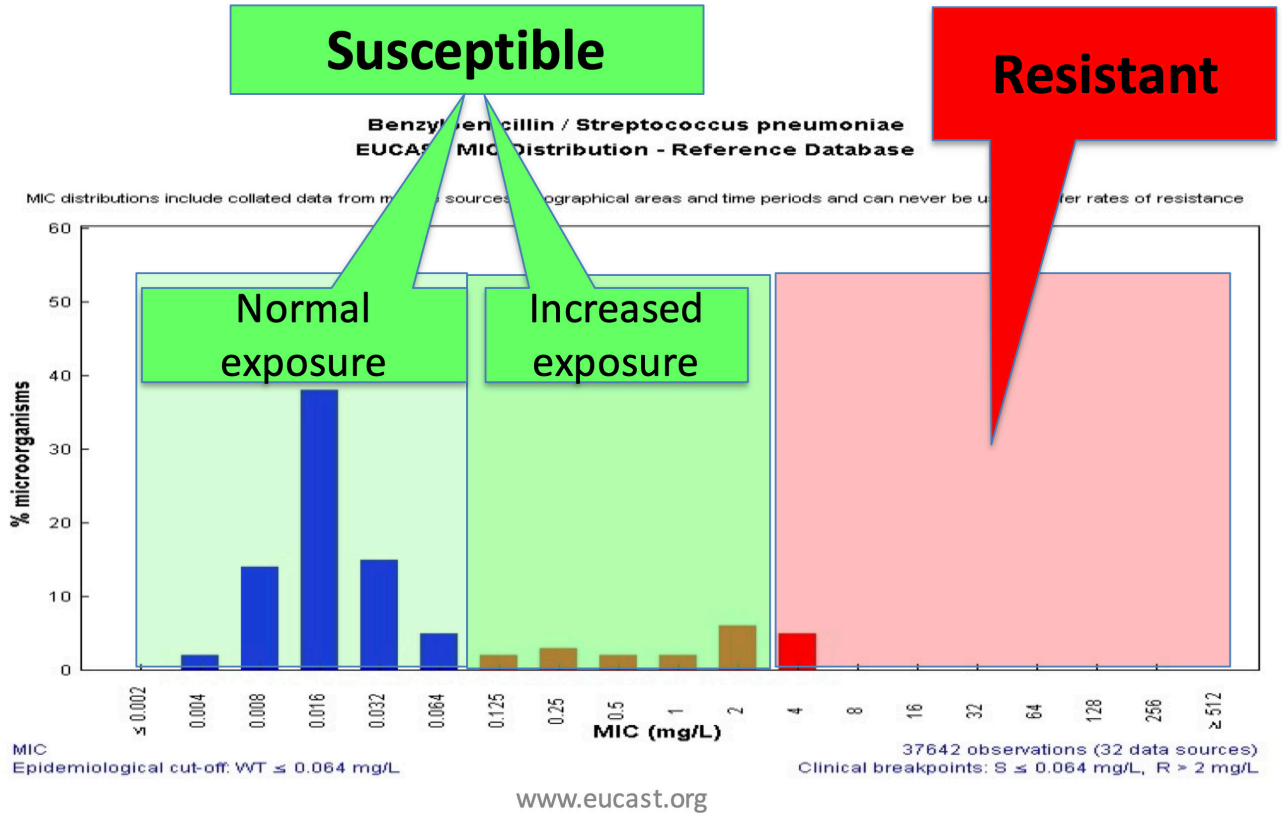

Figure 2 | **New EUCAST Susceptible (normal and increased exposure) and EUCAST Resistant categories (adapted from EUCAST [3]**

The categories of "Susceptible" and "Resistant" were easy to implement due to the changes to the definitions of both categories were minimal. They mainly emphasize the relationship between the clinical category and the level of exposure. S category implies susceptible to standard doses as long as the antimicrobial is the adequate for the type of infection to be treated. While R category discourages its use regardless of dose and mode of administration.

The new definition of the "I" Intermediate category includes situations where there is a high probability of therapeutic success if the exposure of the antimicrobial is increased by adjustment of the dosage regimen or by a higher concentration at the site of infection. The term "Intermediate" is changed to "susceptible-increased exposure"", but the letter "I" in the reports still appears and should be accompanied by an explanatory note [2,3]. With this new definition, the only difference between S and I is the amount of drug that is needed at the site of infection to reach an adequate clinical response (figure 2).

On the other hand, in 2019, the term "ATU" (Area of technical uncertainty) is introduced in susceptibility studies when a warning is needed to alert the laboratory about uncertainty in test results. The warning concerns the laboratory, not the clinician responsible for the patient, and the laboratory needs a strategy to ensure accuracy and to report the uncertainty of the result. This has improved EUCAST's ability to detect areas where technical uncertainty significantly affects the predictive value of the Antibiogram [3].

Because of these new definitions some microorganisms become intrinsically less susceptible to an antimicrobial, and they will never reach S category at standard doses, so it is necessary to remember that they are "Susceptible with increased exposure", i.e. more antimicrobial is needed at the site of infection to achieve clinical success with that strain. For example, treatment of *Pseudomonas* infections requires increased exposure for almost all active antimicrobials (piperacillin-tazobactam, ceftazidime, cefepime, imipenem, aztreonam, fluoroquinolones and aminoglycosides); therefore, wild-type *Pseudomonas* phenotypes fall into the clinical category of "Susceptible with increased exposure" for all relevant antimicrobials (except meropenem).

The recent work of the Swiss group of Munting et al [4] is a retrospective observational study in the hospital of Lausanne where they analyse antibiotic prescriptions, especially meropenem, before and after the new EUCAST criteria. The authors conclude that the new criteria led to increase the meropen-

Table 1 **Therapeutic objectives of the main antibiotics, according to new EUCAST definitions (modified from Cantón R. et al. [5])**

	Concentration-dependent		Time-dependent			
Bactericidal activity	Dependent on focus concentration		Dependent on the duration of exposure			
Post-antibiotiåc effect	Prolonged		Minimum			
PK/PD index	Cmax/CMI AUC24h/MIC		∫T > MIC (%) (% of time with concentration above MIC)			
Antibiotic	Aminoglycosides Fluoroquinolones Daptomycin		Beta-lactams			
Target PK/PD	Aminoglycosides	Cmax/CIM ≥25-30			Bacteriostatic effect	Bactericidal effect
	Fluoroquinolones	Levofloxacin AUC24h/MIC ≥25-30 (non-severe infections and *S. pneumoniae* respiratory infection)	Beta-lactams	Penicillins	<30%	>50%
		Ciprofloxacin AUC24h/CMI ≥125 (Serious infections and immunosuppressed)		Cephalosporins	>30-45%	>60-70%
				Aztreonam	>50%	>60%
	Daptomycin	AUC24h/MIC ≥666		Carbapenems	>20%	>40%
Comments	These antibiotics are used at high doses, and the prolonged PAE allows the use of wide dosing intervals (one dose per day).		- Time to efficacy: time during which concentrations are > MIC - Maximum bactericidal activity at concentrations 4-5 times the MIC value over the whole interval - The shorter the half-life, the higher the frequency of administration - Continuous perfusion is the most effective way of administering these antibiotics, especially if a high T>CMI value is required, and in case of increased clearance			

em prescriptions for the treatment of *Pseudomonas* infections (partially due to uncertain prescription and misinterpretation about other antibiotics defined with category "I" as if were non-susceptible but not due to the ignorance of dosing them according to the new definition). On the other hand, the authors highlighted the fact that consultation with an infectious disease specialist was a protective factor.

Another consequence of these changes requires a revision of the local, national and international antimicrobial susceptibility maps, based on these new definitions, which will be used as a tool to assist in prescribing in various settings and for different purposes.

These changes in Category "I" have a high clinical and technical impact on antimicrobial resistance surveillance and have required a change in some cut-off points. The new definitions reflect the need for correct exposure and for laboratories to take responsibility for technical difficulties and their resolution before finalising antibiogram reports.

These situations requiring "Increased Exposure" (EI) are generally infections that are difficult to treat, either because of the focus (high inoculum or difficult access for the antibiotic such as CNS or biofilms), because of the PK characteristics of the patient (increased volume of distribution, increased or decreased glomerular filtration rate as in burn patients or patients with renal failure), or because of the MIC.

Strategies to achieve IE may be by increasing the dose, in the case of concentration-dependent antibiotics such as quinolone, aminoglycosides or daptomycin, or by increasing the perfusion time or decreasing the interval in the case of time-dependent antibiotics such as beta-lactams (table 1). So the clues for antimicrobial prescription relay on adjusting the dose, the dosing interval, the infusion time or take advantage of concentration at the site of infection [5].

It is convenient to remember that it is important to make a good decision based on the antibiogram. Whenever possible, a beta-lactam should be chosen, especially in severe infections and since it has a better efficacy/toxicity profile, always discard safely a beta-lactam hypersensitivity. "R" antibiotics, consid-

ered resistant, should be ruled out and antibiotics reported as S-susceptible or susceptible-IE should be chosen. In addition, the antibiotic with the lowest possible spectrum should be selected with an adequate diagnostic approach, and a selective antibiogram report should be performed, especially in Primary Care [6,7].

It is important to choose the right dose and mode of administration, and to consult the antibiotic stewardship team in each sector if there is any doubt.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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