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Point-Counterpoint: Differences between the European Committee on Antimicrobial Susceptibility Testing and Clinical and Laboratory Standards Institute Recommendations for Reporting Antimicrobial Susceptibility Results

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INTRODUCTION Antibiotic susceptibility test results are among the most important results issued by clinical microbiology laboratories because they routinely guide critical treatment decisions. Interpretations of MIC or disk diffusion test results, such as "susceptible" or "resistant," are easily understood. Clinical laboratories also need to determine whether and how their reports will reflect more complex situations. Such situations include, first, whether there is need to administer higher or more frequent doses of antibiotic than usual for clinical efficacy; second, whether an antimicrobial is likely to be effective at a body site where it concentrates; and third, whether there is some uncertainty in the test results due to technical variability that cannot be eliminated. Two leading organizations that set standards for antimicrobial susceptibility testing, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI), have taken different strategies to deal with these challenges. In this Point-Counterpoint, Gunnar Kahlmeter and Christian Giske discuss how EUCAST is addressing these issues, and Thomas Kirn and Susan Sharp discuss the CLSI approach.

KEYWORDS antimicrobial agents, susceptibility testing

POINT

In 2008, the first EUCAST breakpoint table was published, and subsequently, methods calibrated to the new breakpoints were developed (1). The relation between breakpoints and antimicrobial exposure was emphasized from the very beginning, and each breakpoint was related to dose, frequency, and mode of administration (2). These were published in the breakpoint decision rationale documents, available on the EUCAST Web pages (http://www.eucast.org). Presently, all European countries and many countries outside Europe have implemented EUCAST breakpoints and methodology.

Both EUCAST and CLSI use "susceptible" (S), "intermediate" (I), and "resistant" (R) and, until recently, also shared their definitions. During the international process of promoting EUCAST guidelines, it became evident that constructive interpretation of the meaning of "intermediate" was not possible. Dissecting the definition, it became clear that there were at least three unrelated parts rolled into one (3): (i) the drug has a level of antimicrobial activity associated with uncertain therapeutic effect, (ii) an infection due to an isolate may be appropriately treated in body sites where the drug is physically concentrated or when a high dosage of drug can be used, and (iii) a buffer zone should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations.

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TABLE 1 Definitions of the I group

Interpretive category (abbreviation)	Status	Definition
Intermediate (I)	EUCAST previous definition (in common with CLSI)	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 physically concentrated or when a high dosage of the drug can be used; it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.
Susceptible, increased exposure[a] (I)	EUCAST new definition (not shared with CLSI)	A microorganism is categorized as "susceptible, increased exposure" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

[a]Exposure is a function of how the mode of administration, dose, dosing interval, and infusion time as well as the distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

However, there was no system for informing clinical colleagues as to which part of the definition was valid in individual cases, and most colleagues were impressed by the words "uncertain" and "uncontrolled" and opted for the safest interpretation: to disregard "I" as a viable alternative. In effect, both microbiologists and clinicians largely regarded "I" as "R," thus skewing antimicrobial usage toward other antimicrobials.

As a result, EUCAST decided to revisit the old definitions (Table 1). EUCAST had from the beginning decided to avoid defining breakpoints that would divide MIC distributions of organisms lacking mechanisms of resistance to the agent (4). The reasons for this were, first, because EUCAST did not find evidence to suggest that there is a correlation between outcome and MIC inside the phenotypic wild-type distribution and, second, because reproducibility of the test results would not be achievable. Moreover, EUCAST had avoided defining an intermediate category if exposure could not be increased by changing either the dose, the frequency, or the mode of administration or because the agent would be concentrated at the site of infection as a result of its pharmacokinetics. Finally, EUCAST clarified that all breakpoints are dose dependent by publishing the dosing regimens on which breakpoints were based as part of the breakpoint table (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Dosages_EUCAST_Breakpoint_Tables_v_9.0.pdf). The dosages were subjected to a public international consultation where users of EUCAST breakpoints were asked to ascertain that national dosing guidelines and that traditions match or supersede the EUCAST guidance on "standard" and "high exposure."

As a logical conclusion of the preparatory work, we decided to follow through and change the definitions of S, I, and R. The proposal was subjected to three public consultations (comments and responses available on the EUCAST website, http://www.eucast.org/documents/consultations/) with input from societies, agencies (e.g., the European Medicines Agency and the European Centre for Disease Prevention and Control), and colleagues around the world. In this process, it was decided to retain the letter I but with a new definition: susceptible with increased exposure. Other letters were considered but found to be difficult to implement, as this would entail a number of changes in laboratory information systems and antimicrobial susceptibility testing (AST) devices. The CLSI definition "susceptible, dose dependent" was considered semantically imprecise, since all breakpoints are dose dependent. It was also considered confusing to EUCAST that in the CLSI system, the categories "I" (intermediate), SDD (susceptible, dose dependent), and "NS" (nonsusceptible) coexist with "S" (susceptible) and "R" (resistant), some of which have overlapping meanings.

For some species for which the breakpoints would classify the entire wild type as "I," we decided to opt for an interim solution, with a comment stating "susceptible with high exposure." The discussion is now whether we are ready to rebrand all of these to I. To exemplify, this would entail categorizing wild-type *Pseudomonas aeruginosa* as belonging to the I category rather than the S category for several agents, such as piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, imipenem, ciprofloxacin,

and levofloxacin. A decision was made by EUCAST in July 2019 to implement this change in January 2020.

Finally, what happened to the need for a "buffer zone that should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations"? First, the systematic avoidance by EUCAST of allowing breakpoints to split the MIC distributions of important target wild-type organisms (organisms lacking phenotypically detectable resistance) improves reproducibility *per se*. Also, with the MIC data and epidemiological cutoffs (ECOFFs) now available and the way that EUCAST analyzes the correlation between MIC and disk diffusion data, it is now largely possible to predict both technical and interpretative difficulties. For such situations, EUCAST in 2019 introduced a system through which laboratories, not clinicians, are warned against technical and interpretational difficulties. Most AST is straightforward when performed with calibrated and quality-controlled devices and material by well-trained staff. However, for situations where breakpoints are challenging methods (for example, colistin for *Pseudomonas aeruginosa* and beta-lactams for *Haemophilus influenzae* with mutations in penicillin-binding protein 3) or where there are technical difficulties with testing, such as with piperacillin-tazobactam versus *Enterobacterales*, laboratories are warned by EUCAST through the introduction of the area of technical uncertainty (ATU). ATUs are available in breakpoint tables and may pertain to MIC testing, disk diffusion, or both. The intention is to avoid unloading the responsibility for technical uncertainty on those who treat patients.

With rampant antimicrobial resistance development, there is a need to ascertain and develop the usefulness of antimicrobial susceptibility testing. By changing the definition and breakpoints to match, EUCAST aims to resurrect the credibility of the I category and thereby to optimize and prolong the survival and use of available antimicrobials.

Gunnar Kahlmeter and Christian G. Giske

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COUNTERPOINT

Over the past several decades, the Clinical and Laboratory Standards Institute (CLSI) Antimicrobial Susceptibility Testing Subcommittee has continuously refined its approach to categorical classification of antimicrobial susceptibility test results (see Table 2 for current categories and definitions). Historically, susceptible (S), intermediate (I), and resistant (R) categories have been used to interpret bacterial AST results. While most clinicians and laboratorians can easily understand and apply the results categorized as S or R, there is often considerable confusion over the I category, which conveys different information for different bug-drug combinations. For example, in some cases, the I category is utilized exclusively to account for technical variability in MICs or zone diameter measurements, especially when S and R breakpoints fall near the normal MIC or zone diameter distribution. In other cases, it has been used to identify organisms for which MICs are in a range where higher levels of drug exposure through alternative dosing/delivery or a drug concentration at a specific anatomical site would lead to reliable clinical efficacy. Without knowledge of the rationale for the inclusion of the I category for each bug-drug combination, it is difficult for clinicians to properly interpret I results and

TABLE 2 Current interpretive categories, abbreviations, and definitions used in the CLSI M100 document

Interpretive category	Category abbreviation	Definition
Susceptible	S	A category defined by a breakpoint that implies that isolates for which the MIC is at or below the susceptible breakpoint or whose zone diameters are above those associated with the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.
Intermediate	I	A category defined by a breakpoint that includes isolates for which MICs or zone diameters are within the intermediate range; the drug approaches usually-attainable blood and tissue levels, and response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated. An I with a "^" in document M100 Table 2 is used to describe agents that have the potential to concentrate at an anatomical site. The I category also includes a buffer zone for inherent variability in test methods, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.
Susceptible, dose dependent	SDD	A category defined by a breakpoint that implies that the susceptibility of an isolate depends on the dosing regimen that is used in the patient. To achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosing regimen (i.e., higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum, literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of an SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function. The SDD category may be assigned when doses well above those used to calculate the susceptible breakpoint are supported by the literature, widely used clinically, and/or approved and for which sufficient data to justify the designation exist and have been reviewed. This category also includes a buffer zone for inherent variability in test methods, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.
Resistant	R	A category defined by a breakpoint that implies that isolates for which the MIC is at or above the resistant breakpoint or whose zone diameters are at or below those associated with the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that the MICs or zone diameters for the isolate fall in the range in which specific microbial resistance mechanisms are likely; also, the clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.
Nonsusceptible	NS	A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above the susceptible breakpoint or whose zone diameters are below those associated with the susceptible breakpoint should be reported as nonsusceptible. An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates for which MICs are above the susceptible breakpoint and that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time that the susceptible-only breakpoint was set. The term "nonsusceptible" should not be used when describing an organism/drug category with intermediate and resistant interpretive categories. Isolates that are in the categories of "intermediate" or "resistant" may be called "not susceptible" rather than "nonsusceptible."

make appropriate clinical decisions. While it may seem that the simplest solution to this problem is to eliminate the I category altogether, this is simply not possible. Even though some antibiotics may not concentrate at specific anatomic locations or may be able to be delivered only as a single dose, inherent variability in AST determinations will always exist. Without a category such as I to provide a buffer zone between S and R, clinicians may be misled into believing that the drug is likely to lead to a successful outcome when it may fail (false susceptibility [very major error]) or may be dissuaded from using a drug that might be efficacious (false resistance [major error]).

There are numerous plausible options for addressing these complex issues: (i) continue the use of the I category to describe any result where variability exists and include modifiers that specify this, (ii) introduce the susceptible, dose-dependent (SDD)

category to clearly separate technical variation (I) from the possibility of using greater drug exposure to achieve reliable clinical efficacy (SDD), or (iii) include both I and SDD where appropriate.

In the January 2014 CLSI M100 document (1), an SDD category was used for the first time with regard to the *Enterobacteriales* and cefepime. Multiple cefepime dosing regimens are FDA approved, ranging from 0.5 g every 12 h to 2 g every 8 h (2). Part of the rationale for adding the SDD category at that time was to encourage the utilization of high-dose cefepime in cases where the MIC for a Gram-negative bacillus was above the achievable drug concentration using low-dose therapy but squarely within attainable levels when exposure was increased through higher doses. This would allow clinicians to select a narrower agent at a higher dose rather than abandoning the cephalosporin class for carbapenems. Notably, this was not the first time that the CLSI had made use of the SDD category; it was adopted in 1997 for the azole class of antifungals used to treat *Candida* spp., given the availability of multiple FDA-approved dosing regimens (400 mg per day to 800 mg per day for invasive candidiasis) (3). Following the initial introduction of SDD in document M100 for cefepime, it became clear that SDD could be useful to categorize results for other bug-drug combinations as well. For example, there are data that support the use of high-dose daptomycin to treat vancomycin-resistant *Enterococcus faecium*, which has prompted the recent addition of an SDD category into the CLSI M100 document for this bug-drug combination (4, 5). In the absence of an SDD category, most *E. faecium* isolates would be categorized as I, which may dissuade clinicians from using this first-line agent.

The addition of the SDD category has many advantages; it can specify test variability as well as the possibility of therapeutic effect with increased drug exposure. Most importantly, when well-established alternative dosing regimens are available, SDD is likely to instill confidence in selecting an antibiotic to treat an infection caused by bacteria for which MIC values are above the S category. It is reasonable to expect that this will have a positive impact on the decision to use narrower therapy when possible (such as cefepime for extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriales* for which MICs are in the 4- to 8-μg/ml range), contributing positively to antibiotic stewardship efforts. In addition, the SDD category creates an option for pharmaceutical companies that are developing new antibiotics to consider indications for two different doses of their drugs. Finally, with the addition of SDD, the unmodified I category takes on a narrower definition that clearly communicates to the clinician that he/she should proceed with caution. In addition, when modified with a "^," I indicates that the drug will accumulate at certain anatomical sites (typically in urine) and thus provides further data that can be used to formulate an accurate and well-informed clinical decision (the change is forthcoming in the 30th edition of document M100).

Adding a new interpretive category and modifying the definition of "I" do not come without challenges. Most notably, the potential benefit to clinical decision-making with these changes may be realized only if the results are efficiently and clearly communicated and the clinician receiving the results understands their meaning. Optimal reporting of SDD and I^ may require significant changes to laboratory and hospital information systems as well as testing instrumentation. It is expected that as SDD and I^ are used more frequently throughout the M100 document, these benefits/changes will occur. To ensure that clinicians are prepared to correctly interpret and apply SDD, I, and I^, educational efforts will need to be widely disseminated. Finally, since minor, major, and very major errors are currently calculated based on traditional S, I, and R categories, modifications to the method of calculation to include SDD will have to be made to ensure that instrument and reagent manufacturers are able to meet FDA performance criteria for clearance of their products.

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SUMMARY

Points of Agreement

1. If the "intermediate" interpretation of antibiotic susceptibility results has multiple meanings, it can confuse clinical staff who do not know which of the meanings is intended in a specific susceptibility report.
2. A report of "intermediate" makes it less likely that an antibiotic will be selected for administration by clinical staff.
3. It is important to communicate to clinical staff when increased exposure of an organism to an antibiotic, due to altered dosing or distribution of the antibiotic in the body, can be expected to result in successful treatment.

Points requiring further consideration

1. What is the best approach to addressing the problems raised by the multiple meanings with the antibiotic susceptibility test results of "intermediate"? Should this interpretation be replaced by or augmented by an interpretation indicating that increased exposure of the organism to the antibiotic can be expected to result in successful treatment?
2. How to deal with susceptibility test results when technical variability might lead to errors if reported as "susceptible" or "resistant." Should such uncertainty be adjudicated in the clinical laboratory and not reflected in the medical record, or should the medical record reflect this uncertainty?

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