EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

To clinical colleagues:
On recent changes in clinical microbiology susceptibility reports - new interpretation of susceptibility categories S, I and R.

In 2019 and 2020 the European Committee on Antimicrobial Susceptibility Testing (EUCAST), after several years of discussion and consultation, changed the definitions of susceptibility categories S, I and R, but following consultations, decided to retain the acronyms. Each susceptibility category is defined by "breakpoints" specific for each species and agent". The breakpoints are minimum inhibitory concentrations (MIC) and describe the amount of agent needed to inhibit the growth of the bacteria and fungi.

Definitions of S and R are unproblematic – in principle susceptible (S) encourages therapy with the agent while resistant (R) is a strong recommendation to avoid the agent. Neither require much thought except as to the appropriateness of the agent for the infection at hand. It is implicit that an "S" stands for "Susceptible with standard dosing" whereas an "R" discourages from therapy irrespective of dose and mode of administration.

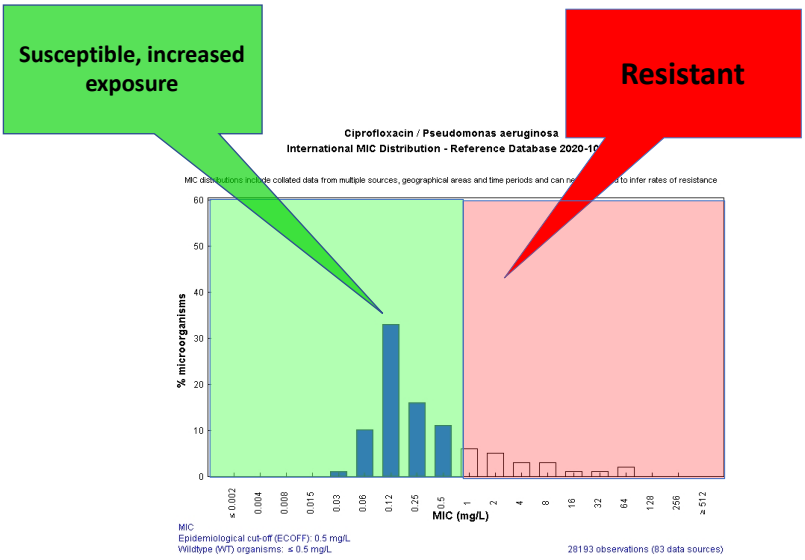
The previous definition of I (intermediate) was problematic. It failed to guide clinical practice and by most it was considered "just another R". In fact, clinicians, microbiologists, epidemiologists, and regulatory agencies would lump I and R together as "non-susceptible" so in real life practice the previous definitions offered two resistant categories, I and R, and just one susceptible category, S.

The new definitions of S, I and R emphasize the close relationship between the susceptibility of the organism and the exposure of the organism at the site of infection. Following the change there are two levels of susceptible and one of resistant, as compared to before when there were two levels of resistant and one of susceptible. The term "non-susceptible" now encompasses only resistant organisms.

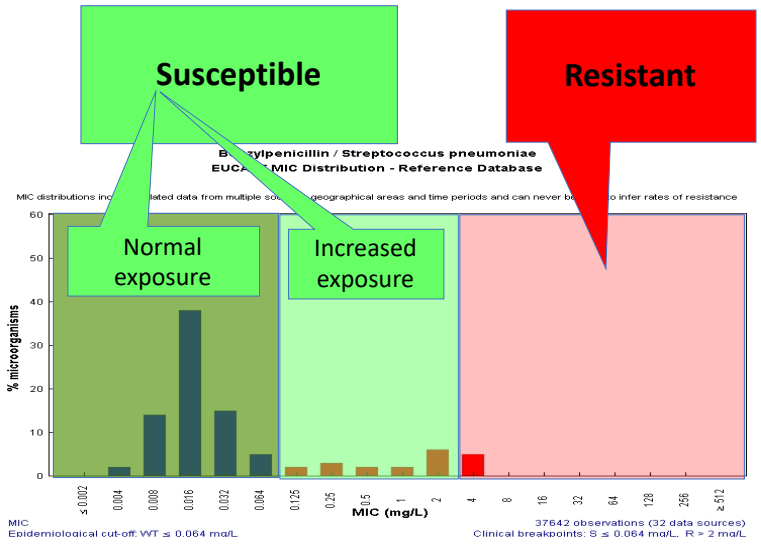
- **S - Susceptible, standard dosing regimen**: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- **I - Susceptible, increased exposure**: A microorganism is categorised as "Susceptible, 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.
- **R - Resistant:** A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

Dose is the amount of agent given to the patient whereas **exposure** includes dose, mode of administration, and both general pharmacokinetics and pharmacokinetics at the site of the infection. The doses against which breakpoints were reviewed and revised to match the new definitions are listed in a specific document (EUCAST: Clinical breakpoints and dosing of antibiotics), also part of the breakpoint table.

A typical characteristic of the new definitions is that some organisms, intrinsically less sensitive to an agent, will never attain a category of "Susceptible, normal dose". Instead, colleagues are reminded by EUCAST through the use of the category "Susceptible, increased exposure" of the need for more agent at the site of infection to achieve a successful clinical outcome with this species. This is exemplified by ciprofloxacin and *Pseudomonas aeruginosa* where isolates devoid of any resistance mechanisms to ciprofloxacin are categorised as "Susceptible, increases exposure". For more examples, see Table 1.



For most agent/species combinations, all three categories are used – below exemplified by *Streptococcus pneumoniae* and benzylpenicillin. Organisms with discrete resistance mechanisms may still be successfully treated provided they are exposed to enough agent. In this example organisms with MIC-values of 0.125 – 2 mg/L are reported "Susceptible, increased exposure" to remind colleagues of the need for increased exposure by one of the several means to achieve this.



So why are breakpoints for *Pseudomonas aeruginosa* different for ceftazidime (S≤0.001, R>8 mg/L) and ceftazidime-avibactam (S≤8, R>8 mg/L)? Both have the same active agent, the modes of administration are identical, and the inhibitor has no inherent activity? For ceftazidime there are two accepted levels of dosing whereas for ceftazidime-avibactam there is only one accepted dose and this corresponds to the high dose of ceftazidime. The logical result of this is that for *P. aeruginosa,* reports may contain either ceftazidime I or R whereas for ceftazidime-avibactam the report may be either S or R.

In conclusion, the new definitions and revised breakpoints to match require colleagues to accept that instead of two levels of resistance we now have two levels of susceptible. S and I both signal that successful therapy is possible, but with the latter one needs to consider how to best achieve "increased exposure".

For EUCAST

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Table 1. List of the most common agents and breakpoints where “Susceptible, increased exposure” is the routine susceptible category. An arbitrary S breakpoint of S≤0.001 ensures that isolates are never categorised as “Susceptible, standard dose” since MICs of relevant agents are always higher than the breakpoint.

Species	Agent	S≤	R>
Pseudomonas aeruginosa	Piperacillin and Piperacillin-tazobactam	0.001	16
	Ticarcillin and ticarcillin-clavulanic acid	0.001	16
	Cefepime	0.001	8
	Ceftazidime	0.001	8
	Aztreonam	0.001	16
	Imipenem	0.001	4
	Ciprofloxacin	0.001	0.5
	Levofloxacin	0.001	1
E. coli	Temocillin	0.001	16
	Cefazoline	0.001	4
	Cefuroxime	0.001	8
S. maltophilia	Trimethoprimsulfa	0.001	2
Acinetobacter	Doripenem	0.001	2
	Ciprofloxacin	0.001	1
Staphylococci	Ciprofloxacin	0.001	1
	Levofloxacin	0.001	1
Streptococcus A,B,C & G	Levofloxacin	0.001	2
S. pneumoniae	Cefaclor	0.001	0.5
	Levofloxacin	0.001	2
Haemophilus	Amoxicillin oral and Amoxicillin-clavulanic acid, oral	0.001	2