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GP Study Webinar

Changes to susceptibility reporting

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Patient focused Collaborative Expert Caring

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EUCAST
EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Redefining susceptibility testing categories **S**, **I** and **R**.

Gunnar Kahlmeter and the EUCAST Steering Committee

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The EUCAST Steering Committee (SC) has decided to change the definitions of susceptibility testing categories but to retain the abbreviations S, I and R.

This decision was taken in June, 2018, following three general consultations (2015, 2017 and 2018). The results of the consultations are available on the EUCAST website (see Consultations)

New definitions are valid from 2019-01-01 (EUCAST breakpoint table v.9.0)

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Can I use co-amoxiclav?

Contrary to the often assumed paradigm that beta-lactam resistance is generally due to the presence/absence of specific beta-lactamases alone, mechanisms of resistance to amoxicillin-clavulanate seen regularly in a large unselected clinical dataset were multifactorial, resulting from combinations of multi-copy beta-lactamase genes, mutations in resistance gene-associated promoters, and inhibitor resistance mechanisms.

Davies, Timothy J et al. “Reconciling the Potentially Irreconcilable? Genotypic and Phenotypic Amoxicillin-Clavulanate Resistance in Escherichia coli.” Antimicrobial agents and chemotherapy vol. 64,6 e02026-19. 21 May. 2020, doi:10.1128/AAC.02026-19

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The individual effects of some of these features on MIC were small, variable and additive, resulting in only minor shifts around clinical breakpoints. This potentially explains inconsistencies on repeated phenotyping, and may be a consequence of the genetic basis of resistance rather than an inherent test weakness.

Davies, Timothy J et al. “Reconciling the Potentially Irreconcilable? Genotypic and Phenotypic Amoxicillin-Clavulanate Resistance in Escherichia coli.” Antimicrobial agents and chemotherapy vol. 64,6 e02026-19. 21 May. 2020, doi:10.1128/AAC.02026-19

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A further corollary is that discrepancies between genotypic predictions and phenotype are inevitable when using susceptible/resistant binary classifications. Finally, the phenotypic testing methodology significantly affected the magnitude of the effect of these resistance features on the MIC. These issues, when combined, resulted in inconsistent binary phenotypes despite reliable MICs, and consequently led to inevitable suboptimal concordance both between different phenotypic testing methodologies and also with WGS-based susceptibility/resistance predictions.

Davies, Timothy J et al. “Reconciling the Potentially Irreconcilable? Genotypic and Phenotypic Amoxicillin-Clavulanate Resistance in Escherichia coli.” Antimicrobial agents and chemotherapy vol. 64,6 e02026-19. 21 May. 2020, doi:10.1128/AAC.02026-19

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The 2002 – 2018 definitions of S, I and R
”The old definition”.

Since 2002, EUCAST has used the following definitions to categorise the microorganisms as treatable or not treatable with the agent in question.

Breakpoints in breakpoint tables are clinical, i.e. are meant to predict the clinical outcome in the infected patient.

S = Susceptible

I = Intermediate

R = Resistant

Definitions 2002 – 2018
("the old definition")

EUCAST definitions of clinical breakpoints and epidemiological cut-off values

Clinical resistance and clinical breakpoints

Clinically Susceptible (S)

- a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success
- a micro-organism is categorized as susceptible (S) by applying the appropriate breakpoint in a defined phenotypic test system
- this breakpoint may be altered with legitimate changes in circumstances

Clinically Intermediate (I)

- a micro-organism 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 drug can be used; it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.
- a micro-organism is categorized as intermediate (I) by applying the appropriate breakpoints in a defined phenotypic test system
- these breakpoints may be altered with legitimate changes in circumstances

Clinically Resistant (R)

- a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.
- a micro-organism is categorized as resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system
- this breakpoint may be altered with legitimate changes in circumstances

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The old definition of intermediate has four definitions rolled into one.

1. **uncertain therapeutic effect** (pharmacology/microbiology)
2. **where the drugs are physiologically concentrated** (pharmacokinetics)
3. **when a high dosage of drug can be used** (pharmacology/toxicology)
4. **a buffer zone to prevent technical errors …** (methodology)

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Intermediate results thus encompass both…

- **Uncertainty**
  - uncertain therapeutic effect
  - uncertain laboratory result
- **Exposure**
  - agent physiologically concentrated
  - Dosing strategy (dose, frequency, mode of administration)

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All clinical breakpoints are related to the achievable level of exposure* of the microorganism.

The achievable level of exposure* depends on many factors.
Individual differences in pharmacokinetics are allowed for in the calculations leading up to pharmacodynamic indices following population simulation. Others factors as follows are determined by the the site of infection or can be varied during therapy:

1. Site of infection
   - concentration in certain tissues and body fluids may be high (urine, bile, lymphatic tissues).
2. Dose and dosing frequency
3. Mode of administration (Oral, Intravenous, IV infusion etc)

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

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Dosing and mode of administration are in the EUCAST breakpoint table.

EUCAST breakpoints are related to the doses and modes of administration listed by EUCAST in rationale documents and in the breakpoint table, ”Dosing” tab.

With regimens other than those listed in the EUCAST tables, breakpoints may be invalid.

For this reason EUCAST has made every effort to consult with all countries to ascertain that the doses and modes of administration listed in EUCAST documents are representative of international practices.

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The new definitions of S, I and R

The new definitions reflect the need for correct exposure and for laboratories to take responsibility for technical difficulties and solve them prior to finalising AST reports.

The dosing strategies relevant to EUCAST breakpoints are available in the breakpoint table, “Dosing” tab.

These are the new definitions:

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Susceptible, standard dosing regimen (S)

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.

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

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Susceptible, increased exposure (I)

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.

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

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Resistant (R)

R - Resistant: A microorganism is categorised as *Resistant* when there is a high likelihood of therapeutic failure even when there is increased exposure*.

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

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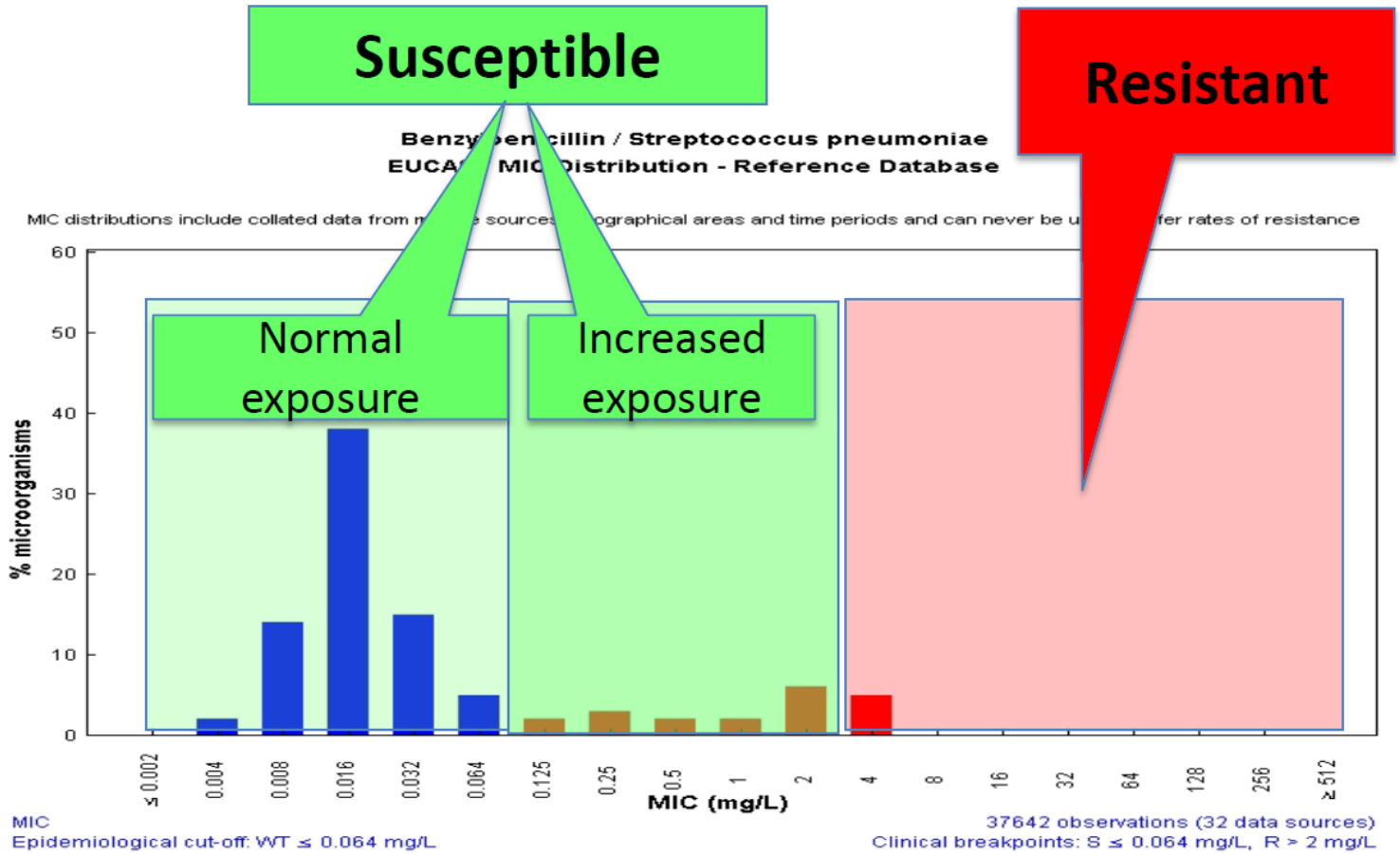
SIR - new definitions 2019



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With the modified definition of the ”I-category”....

....the only difference between ”S” and ”I” is the amount of drug at the site of the infection necessary to achieve an adequate clinical response.

The term ”intermediate” is replaced by the term ”Susceptible, increased exposure” but the abreviation in reports is still ”I”.