Lectura interpretada e interpretación del antibiograma

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RYC MICROBIOLOGÍA HOSPITAL RAMÓN Y CAJAL

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Lectura interpretada

Conflicts of interest

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

Clinical data coordinator (2007 – 2012, 2016 –)
Chairman (2012 – 2016)

CLSI

Member of the *Intrinsic Resistance Working Group* (2013 –)
Advisor (2016 – 2017)

CoESAnt

Member of *Comité Español del Antibiograma* (2014 – 2019)

Antimicrobial susceptibility testing (*Antibiogram*)

To evaluate in the laboratory the *in vitro* response of a microorganism to the action of one or several antibiotics

- To **predict the clinical success or failure** of an specific antibiotic treatment (either definitive or for empirical use)

Relevant for the patient

- To generate **epidemiological alerts** to establish accurate **control measures and prevention** of infection
- To know the **epidemiology of antibiotic resistance** (emergence, evolution and dispersion) mechanisms and to evaluate the control measures

Relevant for Public Health

Methods for antimicrobial susceptibility testing

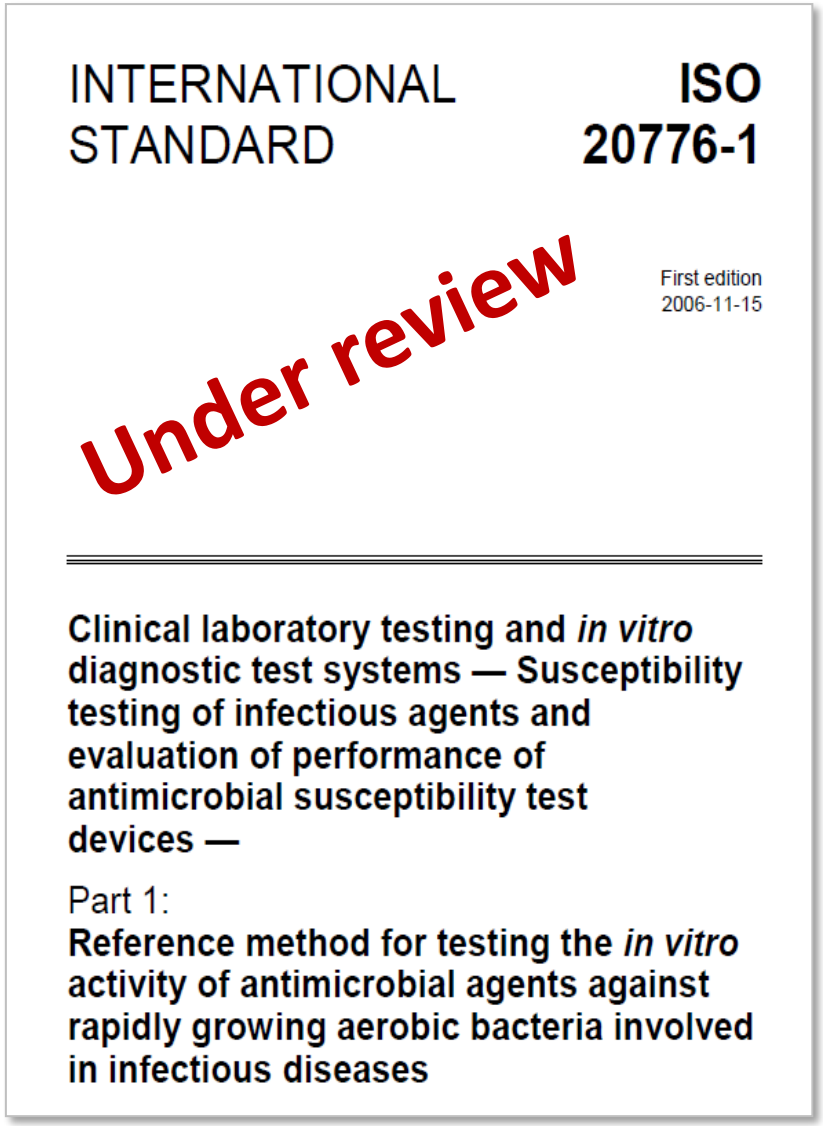
- **Phenotypic test methods:**
  *based on **antimicrobial activity** and **breakpoints***
  - MIC determination (broth, agar, gradient diffusion)
  - Disk diffusion (**EUCAST,** BSAC, CA-SFM, CLSI, SRGA, …)
  - Automated systems (Vitek, Phoenix, MicroScan, Sensititre, ...)

→ **MIC**

- **Genotypic test and proteomic methods**:
  *based on the detection of a **resistance gene** or its **product***
  - *mecA, vanA, vanB,* bla_{KPC}, …
  - PBP2a detection, β-lactamase detection, …
  - MALDITOF methods, …
  - PCR and whole genome sequencing (WGS)

- **By deduction** – "expert rules"
  - IF *mec*A-positive, THEN report β-lactam antibiotics as R, except …
  - IF erythromycin-R, THEN report azithromycin and clarithromycin as R
  - … …. …. …. …

Minimal inhibitory concentration (MIC)



INTERNATIONAL STANDARD

ISO 20776-1

Under review

First edition
2006-11-15

Clinical laboratory testing and *in vitro* diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices —

Part 1:
Reference method for testing the *in vitro* activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases

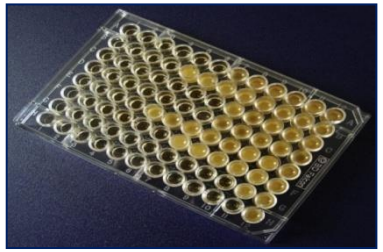
MICs…

- Well standardized biological method but highly influence by
  - Testing conditions (media, bacterial inoculum, growth phase, incubation period and temperature, …)
  - Double dilution system
- Slow procedure as a traditional overnight method (16-18 h)
- Included in regulatory procedures (EMA, FDA)

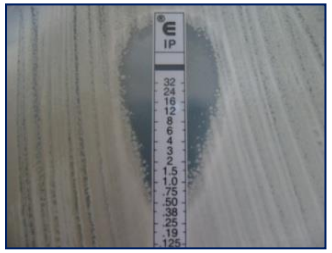
- **Phenotypic resistance** detection based in **MIC values**
- **PK/PD** analysis using **MIC values** as PD
- **Clinical outcome** correlation with **MIC values**

Minimal inhibitory concentration (MIC)

- **MIC:** The lowest concentration of an antimicrobial agent that inhibits the visible growth of a microorganisms after an overnight incubation







- **MIC values** are used **to predict clinical outcome** according to previously established **clinical breakpoints** (EUCAST & CLSI)

- **MIC values** are associated with the **absence or presence** of a **resistance mechanism (*interpretive reading*)**

Antimicrobial susceptibility testing committees

CLSI (NCCLS)

EUCAST

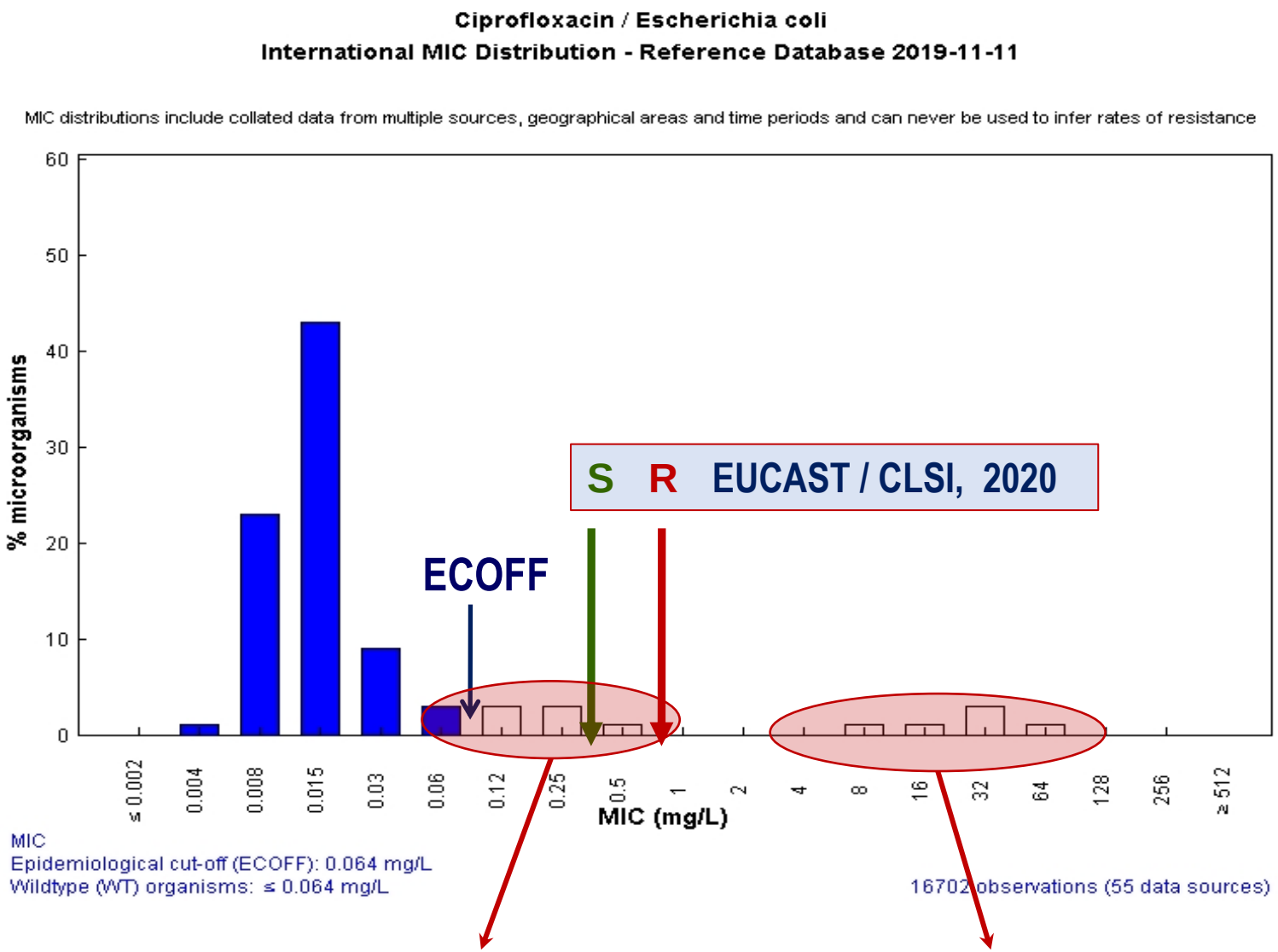
✓ **CLINICAL BREAKPOINTS**

✓ **CLINICAL BREAKPOINTS**
✓ **EPIDEMIOLOGYCAL CUT-OFF**

Breakpoints are defined for **clinical purposes** (to treat patients) and not with the specific aim to detect resistance mechanisms

Epidemiological cut-off values can be used to **detect resistance mechanisms**

ECOFFs / ECV and clinical breakpoints



Low level R mechanism
(*qnr, qyrA* single mutants)

High level R mechanism
(*qyrA, parC* double mutants)

- **The epidemiological cut-off value (ECOFF)** separates microorganisms without (**wild type**) and with **acquired resistance mechanisms** (**non-wild type**) to the agent

https://mic.eucast.org/Eucast2/

- The **clinical breakpoints** are used **to classify microorganisms** into **clinical categories (S/I/R)** to **predict clinical success or failure** when testing *in vitro* (antibiogram) an antimicrobial agent

Interpretive reading of the antibiogram

1.- To determine the susceptibility and resistance phenotype

2.- To infer the potential resistance mechanism behind the phenotype

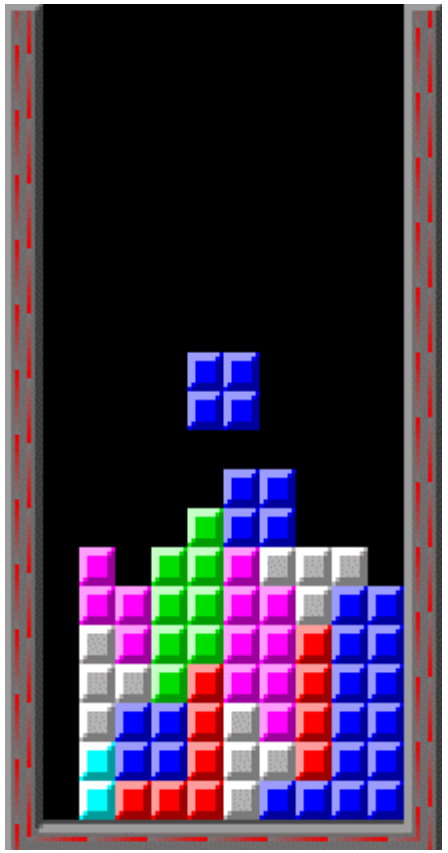
3.- To predict the phenotype previously determined from the resistance mechanism and to infer the activity of the different antimicrobials expressing the phenotype

Patrice Courvalin, ASM News, 1992

Susceptibility and resistance phenotype:

Conjunction of susceptibility testing results (MICs) of a microorganisms for a group of antimicrobial agents, normally belonging to a single family

Interpretive reading of the antibiogram



Requirements

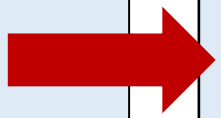
- Adequate identification of the microorganism
- Recognition of intrinsic resistances
- Analysis of susceptibility/resistance phenotype
- Use of antimicrobials as markers of resistance mechanisms
- Analysis of antibiotic + inhibitor combinations
- Determine quantitative susceptibility testing values (MIC / mm)
- Use of high inoculum in certain situations
- To know the local epidemiology / trends in antimicrobial resistance
- To implement ancillary tests and reference molecular techniques

Courvalin P. ASM News 1992;58:368-75; Livermore DM et al. J Antimicrob Chemother 2001;48(Suppl 1):87-102
Cantón R. Enferm Infecc Microbiol Clin 2002; 20: 176-86; Cantón R. Enferm Infecc Microbiol Clin 2010; 28:375-85;
Leclercq R et al. Clin Microbiol infect 2013; 19:141-60; Cantón R et al. Enferm Infecc Microbiol Clin 2020;38:182-7

Interpretive reading of the antibiogram

Relevance of bacterial identification

Antimicrobial	MIC (mg/L)
Ampicillin	>64
Amox/clav	>32/16
Ticarcillin	>64
Piperacillin	32
Piper/Tazo	16/4
Cefuroxime	>64
Cefoxitin	>32
Cefotaxime	4
Ceftazidime	8
Cefepime	1
Ertapenem	4



Organisms	Potential phenoype
E. coli	AmpC hyperproduction plasmid AmpC ESBL + porin deficiency
K. pneumoniae	ESBL + porin deficiency
E. cloacae	ESBL

Cantón R. Enferm Infecc Microbiol Clin 2010; 28:375-85

Intrinsic resistance

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

EUCAST Expert Rules Version 3.1

Intrinsic Resistance and Exceptional Phenotypes Tables

EUCAST Expert Rules version 2.0 was published on 29 October 2011(http://www
review over the past year and changes to the intrinsic resistance and exceptional
consultation (October-December 2015) and further discussion in the EUCAST St
exceptional phenotypes tables 1-7 (version 3.0), together with a summary of cha
Version 3.1includes corrections to typographical errors in ve 3.0.

Rule no.	Organisms	Ampicillin	Amoxicilin-Clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Cefazolin, Cefalotin Cefalexin, Cefadroxil	Cefoxitin[2]	Cefuroxime	Tetracyclines	Tigecycline	Polymyxin B, Colistin	Nitrofurantoin
1.1	*Citrobacter koseri,Citrobacter amalonaticus*[3]	R			R							
1.2	*Citrobacter freundii*[4]	R	R	R		R	R					
1.3	*Enterobacter cloacae* complex	R	R	R		R	R					
1.4	*Enterobacter aerogenes*	R	R	R		R	R					
1.5	*Escherichia hermannii*	R			R							
1.6	*Hafnia alvei*	R	R	R		R	R					
1.7	*Klebsiella pneumoniae*	R			R							
1.8	*Klebsiella oxytoca*	R			R							
1.9	*Morganella morganii*	R	R	R		R			R		R	R
1.10	*Proteus mirabilis*								R	R	R	R
1.11	*Proteus penneri*	R				R		R	R	R	R	R
1.12	*Proteus vulgaris*	R				R		R	R	R	R	R
1.13	*Providencia rettgeri*	R	R	R		R		R	R	R	R	R
1.14	*Providencia stuartii*	R	R	R		R		R	R	R	R	R
1.15	*Raoultella* spp.	R			R							
1.16	*Serratia marcescens*	R	R	R		R	R	R	R[5]		R	R
1.17	*Yersinia enterocolitica*	R	R	R	R	R	R					
1.18	*Yersinia pseudotuberculosis*										R	

R = resistant

Interpretive reading of the antibiogram: *K. pnueumoniae*

Antibiotic	MIC (mg/L)	Interpre-tation
Amoxicillin	>16	R
Amoxi-clav	≤4/2	S
Piper-tazo	≤8/4	S
Cefuroxime	≤0.5	S
Cefotaxime	≤0.06	S
Ceftazidime	≤0.06	S
Cefepime	≤0.06	S
Aztreonam	≤0.06	S
Ceftol-Tazo	≤0.5/4	S
Cefta-avib	≤0.5/4	S
Ertapenem	≤0.5	S
Imipenem	≤0.5	S
Meropenem	≤0.5	S

Wild type

Antibiotic	MIC (mg/L)	Interpre-tation
Amoxicillin	>16	R
Amoxi-clav	≤4/2	S
Piper-tazo	≤8/4	S
Cefuroxime	>16	R
Cefotaxime	>16	R
Ceftazidime	2	I
Cefepime	0.5	S
Aztreonam	0.5	S
Ceftol-Tazo	1/4	S
Cefta-avib	1/4	S
Ertapenem	2	S
Imipenem	≤0.5	S
Meropenem	≤0.5	S

ESBL

Antibiotic	MIC (mg/L)	Interpre-tation
Amoxicillin	>16	R
Amoxi-clav	>16/8	R
Piper-tazo	>64/4	R
Cefuroxime	>16	R
Cefotaxime	>16	R
Ceftazidime	>16	R
Cefepime	>16	R
Aztreonam	>4	R
Ceftol-Tazo	>8/4	S
Cefta-avib	4/4	S
Ertapenem	>8	R
Imipenem	<8	R
Meropenem	8	I

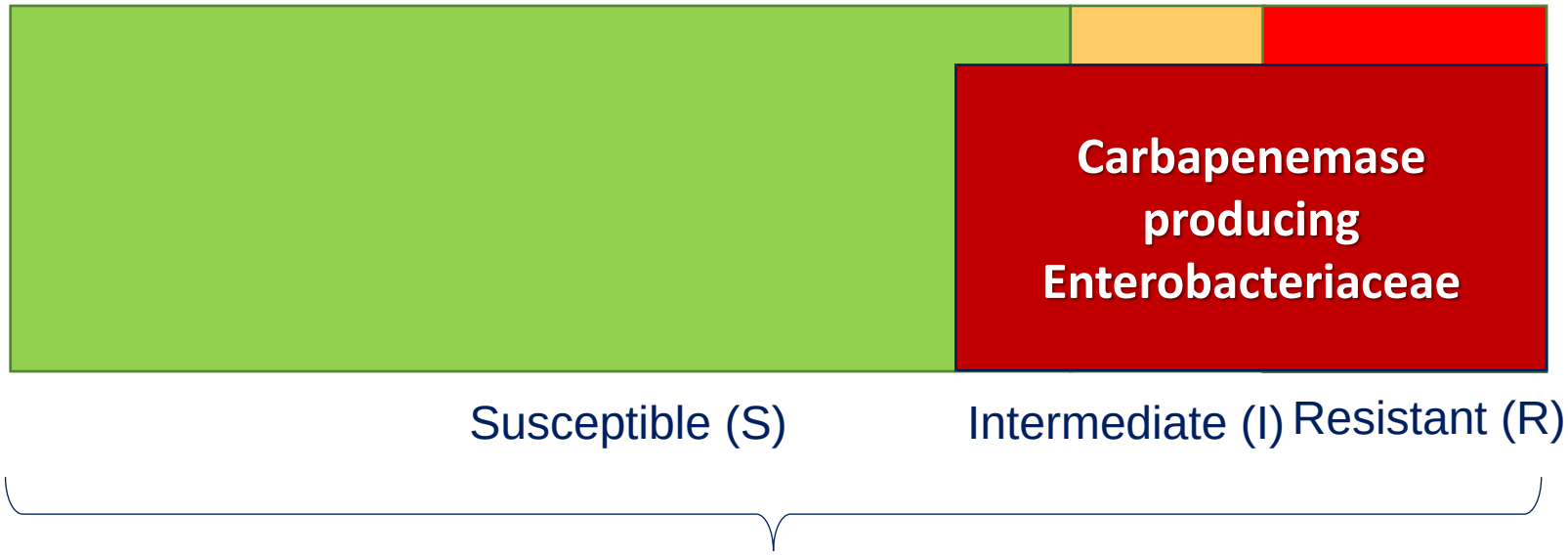
Carbapenemase

EUCAST, 2020 interpretive criterio (www.eucast.org)

Carbapenemase producing *Enterobacterales* (CPE)

- **Carbapenemases:** β-lactamases that hydrolyze penicillins, in most cases cephalosporins, and to varying degrees carbapenems and monobactams, the latter not hydrolyzed by metallo-β-lactamases)

- not all carbapenemases produce carbapemem (clinical) resistance



The antimicrobial resistance challenge: *the carbapenemases*

Carbapenemases

- Complex classification
- Variable expression of the enzyme
- Different phenotypes
- Superimposed with other resistance mechanism, even with other different carbapenemases
- Different inhibition profile of β-lactamase inhibitors

Cantón et al. Clin Microbiol Infect 2012; 18:413-31

Klebsiella pneumoniae

Antibiotic	MIC in mg/L (clinical interpretation)				
	Wild type	VIM-1	KPC -3	OXA-48	OXA-48 + CTX-M-15
Amoxicillin	>16 (R)	>16 (R)	>16 (R)	>16 (R)	>16 (R)
Amox./clav.	≤4/2 (S)	>16/2(R)	>16/2 (R)	>16/2 (R)	>16/2 (R)
Pip./taz.	≤16/4 (S)	>64/4 (R)	>64/4 (R)	>64/4 (R)	>64/4 (R)
Cefuroxime	8 (S)	>16 (R)	>16 (R)	8 (S)	>16 (R)
Cefoxitin	≤8(S)	>32 (R)	16 (R)	≤8(S)	16 (R)
Cefotaxime	≤1(S)	>16 (R)	>16 (R)	≤1(S)	>16 (R)
Ceftazidime	≤1(S)	>8 (R)	>8 (R)	≤1(S)	>8 (R)
Cefepima	≤1(S)	8 (R)	8 (R)	≤1(S)	8 (R)
Aztreonam	≤1(S)	1 (S)	>16 (R)	≤1(S)	>16 (R)
Imipenem	≤0.5 (S)	2 (S)	4 (R)	2(S)	2(2)
Meropenem	≤0.5 (S)	2 (S)	4 (R)	0.5(S)	0.5(2)
Ertapenem	≤0.5 (S)	4 (R)	>4 (R)	1 (R)	2 (R)

Data from Clinical Microbiology Dept. Hosp. Ramón y Cajal. Madrid. Spain

Interpretive reading of antimicrobial susceptibility testing results

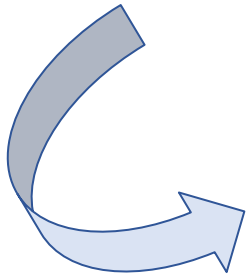
- During more than twenty-five years **interpretive reading of the antibiogram** has been used to:

  - infer resistance mechanisms behind resistant phenotypes

  - identify resistant organisms for infection control purposes

  - apply expert rules* and modify (when needed!) clinical categorization

Courvalin P. ASM News 1992;58:368-75
Livermore et al. J Antimicrob Chemother 2001;48(Suppl 1):87-102
Cantón R. Enferm Infecc Microbiol Clin 2002; 20: 176-86
Cantón R. Enferm Infecc Microbiol Clin 2010; 28:375-85
Leclercq et al. Clin Microbiol infect 2013; 19:141-60

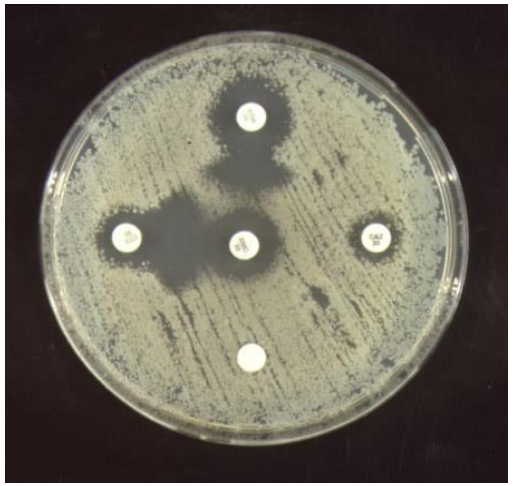


This approach was partially needed due to inadequate breakpoints!

*expert rule: action to be taken (normally S or I to R), based on current clinical or microbiological evidence, in response to specific AST results

Interpretive reading of antimicrobial susceptibility testing results

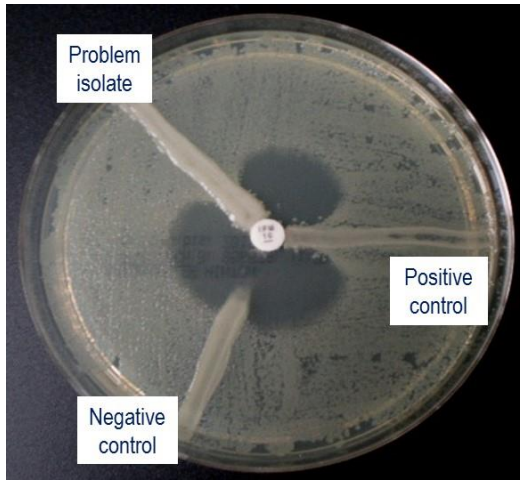
- **Interpretative reading, the classical examples: ESBLs and carbapenemases**



→ ESBL (+)

Expert rul

Intermedi /R stant to all c halosp s a aztreonam (irrespective of MICs)



→ carbapenemase (+)

Exper ru

Intermedia re tant to all c apene (i pective of MI

EUCAST Expert rules. V1 2008; Livermore et al. J Antimicrob Chemother 2012; 67:1569-77

ESBL and carbapenemase producers: current recommendations

Footnote recommendations in EUCAST breakpoint tables

The **cephalosporin breakpoints** for Enterobacteriaceae will detect all clinically important resistance mech (including **ESBL** and **plasmid me AmpC**). Some isolates tha lactamases are susceptible or int to 3rd or 4th gen. cephal breakpoints and **should be tested**, *i.e.* the presence or ab ESBL does not in itself influen categorisation of susceptibility.
ESBL detection and characterisation are recommended for public health and infection control purposes

Report as tested!

Th **carbapenem breakpoints** for obacte iaceae will detect all clinically resistance mechanisms (including **carbapenemases**). Some t produce carbapenemase are s susceptible with these and **should be reported as** e presence or absence of a penemase does not in itself influence the categorisation of susceptibility.
Carbapenemase detection and characterisation are recommended for public health and infection control purposes

EUCAST Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0.2020

Antimicrobial susceptibility testing committees

CLSI (NCCLS)

EUCAST

✓ **CLINICAL BREAKPOINTS**

✓ **CLINICAL BREAKPOINTS**
✓ **EPIDEMIOLOGYCAL CUT-OFF**

Breakpoints are defined for **clinical purposes** (to treat patients) and not with the specific aim to detect resistance mechanisms

Epidemiological cut-off values can be used to **detect resistance mechanisms**

EUCAST Breakpoints – 2020

European Committee on Antimicrobial Susceptibility Testing

Breakpoint tables for interpretation of MICs and zone diameters

Version 10.0, valid from 2020-01-01

This document should be cited as "The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0, 2020. http://www.eucast.org."

www.ecuast.org

EUCAST Breakpoints: dosages (… *a highly relevant part of the tables*)

Dosages — **EUCAST Clinical Breakpoint Tables v. 10.0, valid from 2020-01-01**

EUCAST breakpoints are based on the following dosages (see section 8 in Rationale Documents). Alternative dosing regimens which result in equivalent exposure are acceptable. The table should not be considered an exhaustive guidance for dosing in clinical practice, and does not replace specific local, national, or regional dosing guidelines. However, if national practices significantly differ from those listed below, EUCAST breakpoints may not be valid. Situations where less antibiotic is given as standard or high dose should be discussed locally or regionally.

Uncomplicated UTI: acute, sporadic or recurrent lower urinary tract infections (uncomplicated cystitis) in patients with no known relevant anatomical or functional abnormalities within the urinary tract or comorbidities.

Penicillins	Standard dose	High dose	Uncomplicated UTI	Special situations
Benzylpenicillin	0.6 g (1 MU) x 4 iv	1.2 g (2 MU) x 4-6 iv		**Meningitis caused by *S. pneumoniae*:** For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC≤0.06 mg/L are susceptible. **Pneumonia caused by *S. pneumoniae*: breakpoints are related to dosage:** For a dose of 1.2 g (2 MU) x 4 iv, isolates with MIC ≤0.5 mg/L are susceptible. For a dose of 2.4 (4 MU) g x 4 iv or 1.2 g (2 MU) x 6 iv, isolates with MIC ≤1 mg/L are susceptible. For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤2 mg/L are susceptible.
Ampicillin	2 g x 3 iv	2 g x 4 iv		**Meningitis:** 2 g x 6 iv
Ampicillin-sulbactam	(2 g ampicillin + 1 g sulbactam) x 3 iv	(2 g ampicillin + 1 g sulbactam) x 4 iv		
Amoxicillin iv	1 g x 3-4 iv	2 g x 6 iv		**Meningitis:** 2 g x 6 iv
Amoxicillin oral	0.5 g x 3 oral	0.75-1 g x 3 oral	0.5 g x 3 oral	~~***H. influenzae*: High dose only~~
Amoxicillin-clavulanic acid iv	(1 g amoxicillin + 0.2 g clavulanic acid) x 3-4 iv	(2 g amoxicillin + 0.2 g clavulanic acid) x 3 iv		
Amoxicillin-clavulanic acid oral	(0.5 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	(0.875 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	(0.5 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	Amoxicillin-clavulanic acid has separate breakpoints for systemic infections and uncomplicated UTI. When amoxicillin-clavulanic acid is reported for uncomplicated UTI, the report must make clear that the susceptibility category is only valid for uncomplicated UTI. ~~***H. influenzae*: High dose only~~
Piperacillin	4 g x 3 iv	4 g x 4 iv		~~***Pseudomonas* spp.: High dose only~~
Piperacillin-tazobactam	(4 g piperacillin + 0.5 g tazobactam) x 3 iv	(4 g piperacillin + 0.5 g tazobactam) x 4 iv		~~***Pseudomonas* spp.: High dose only~~
Ticarcillin	3 g x 4 iv	3 g x 6 iv		~~***Pseudomonas* spp.: High dose only~~
Ticarcillin-clavulanic acid	(3 g ticarcillin + 0.1-0.2 g clavulanic acid) x 4 iv	(3 g ticarcillin + 0.1 g clavulanic acid) x 6 iv		~~***Pseudomonas* spp.: High dose only~~
Phenoxymethylpenicillin	0.5-2 g x 3-4 oral depending on species and/or infection type	None		
Oxacillin	1 g x 4 iv	1 g x 6 iv		
Cloxacillin	0.5 g x 4 oral or 1 g x 4 iv	1 g x 4 oral or 2 g x 6 iv		
Dicloxacillin	0.5-1 g x 4 oral or 1 g x 4 iv	2 g x 4 oral or 2 g x 6 iv		
Flucloxacillin	1 g x 3 oral or 2 g x 4 iv (or 1 g x 6 iv)	1 g x 4 oral or 2 g x 6 iv		
Mecillinam oral	None	None	0.2-0.4 g x 3 oral	

Breakpoints are based in the **approved doses by EMA** and included in the Summary of Product Characteristics (SmPC)

Definitions / criteria used by the antibiogram committees

CLSI	EUCAST
Susceptible (S)	Susceptible (S)
Susceptible-dose-dependent (SDD)	Susceptible, increased exposure (I)
Intermediate (I)	
Resistant (R)	Resistant (R)
Non-susceptible (NS)	
	Area of Technical Uncertainty (ATU)
Epidemiological cut off value (ECV)	Epidemiological cut off value (ECOFF)

Definitions / criteria used by the antibiogram committees

CLSI	EUCAST
S - Susceptible a category defined by a breakpoint that implies that isolates with an MIC at or below 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.**	**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.

CLSI. 2020. Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA

EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0, 2020. http://www.eucast.org.

S = S

Definitions / criteria used by the antibiogram committees

CLSI	EUCAST
R – Resistant: A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are **not inhibited by the usually achievable concentrations of the agent with normal dosage schedules** and/or that demonstrate MICs that fall in the **range in which specific microbial resistance mechanisms are likely,** and **clinical efficacy of the agent against the isolate has not been reliably shown** in treatment studies.	**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 and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

CLSI. 2020. Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA

EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0, 2020. http://www.eucast.org.

R = R

Definitions / criteria used by the antibiogram committees

CLSI	EUCAST
Susceptible (S)	Susceptible (S)
Susceptible-dose-dependent (SDD)	Susceptible, increased exposure (I)
Intermediate (I)	
Resistant (R)	Resistant (R)
Non-susceptible (NS)	
	Area of Technical Uncertainty (ATU)
Epidemiological cut off value (ECV)	Epidemiological cut off value (ECOFF)

Definitions / criteria used by the antibiogram committees

CLSI	EUCAST
Intermediate (I) – a category defined by a breakpoint that includes **isolates with MICs within the intermediate range** that approach usually attainable blood and tissue levels and/or for which response **rates may be lower than for susceptible isolates** This category implies clinical efficacy in body sites where the **drugs are physiologically concentrated (I^)** or when **a higher than normal dosage of a drug can be used.** It also includes a **buffer zone**, which should prevent **small, uncontrolled, technical factors** from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.	**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 and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

CLSI. 2020. Performance standards for antimicrobial susceptibility testing, 29th ed. CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA

EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org.

S / I / R – Old definitions (*before 2018*)

Susceptible

Intermediate

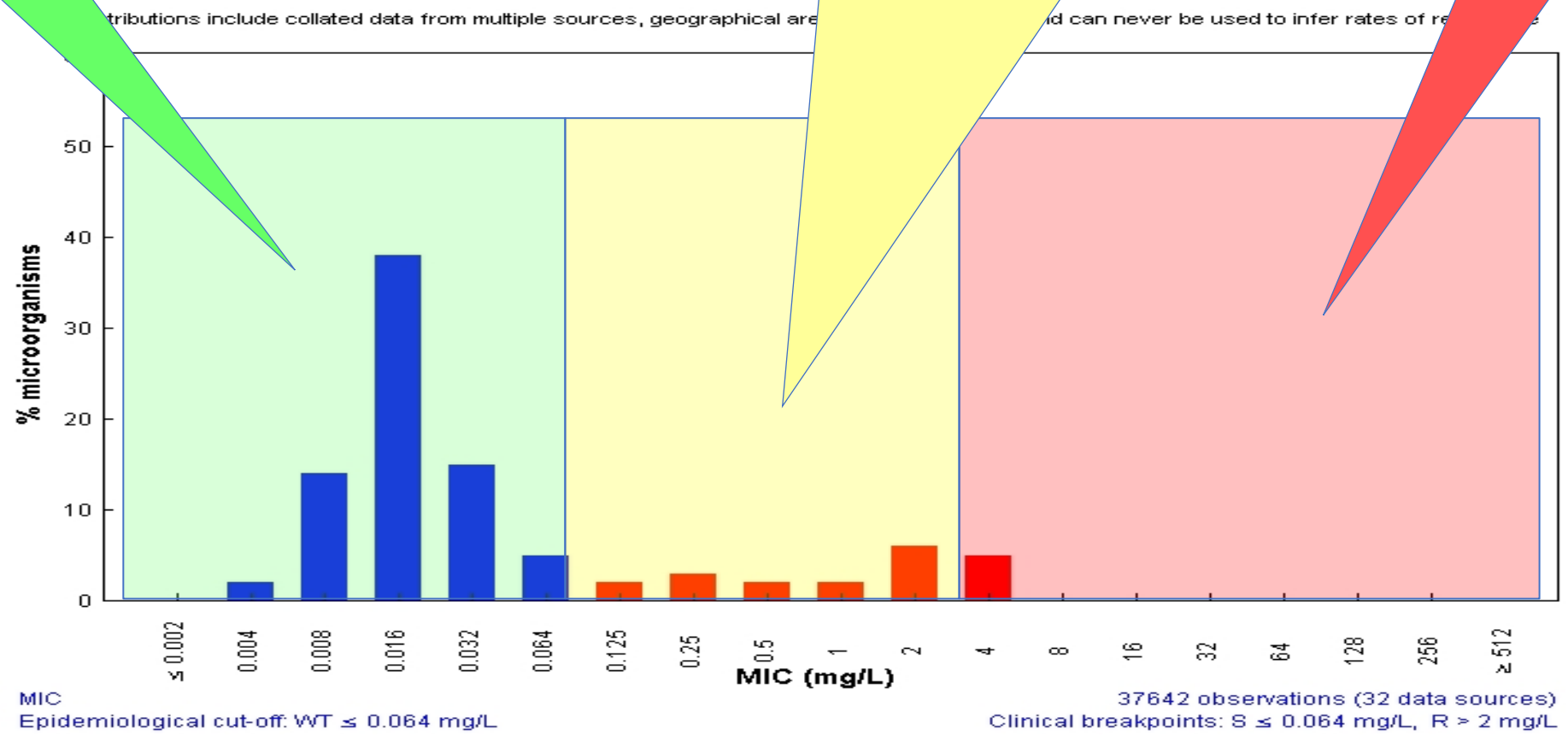
Uncertain effect

Buffer zone for technical variation

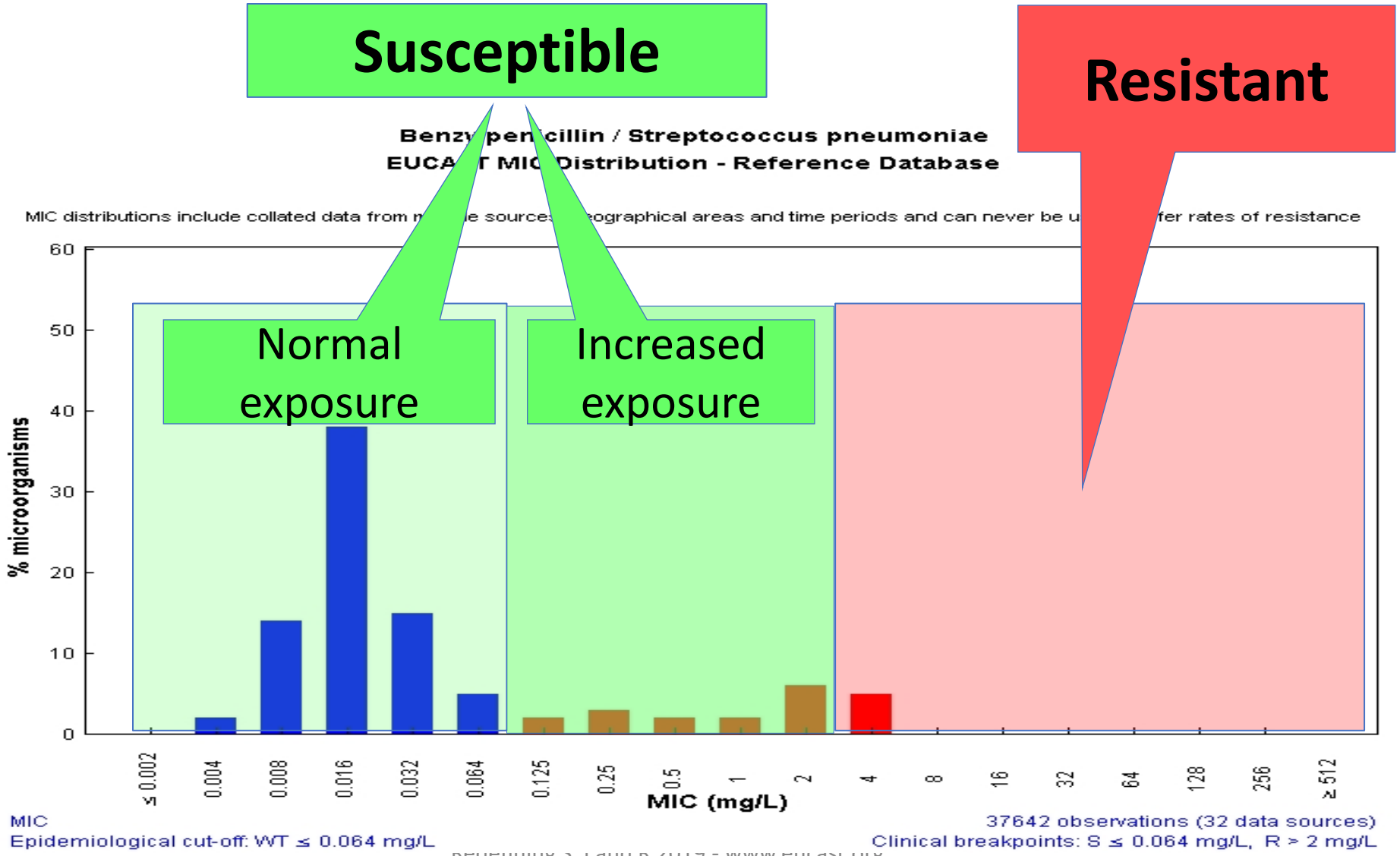
For a high dose

Where concentrated for pharmacokinetic reasons

Resistant



S / I / R – New definitions (*from 2019*)



S / I / R – New definitions (*from* 2019)

- **Implications for the laboratory**

  - maintenance of **S / I / R** letters in the laboratory report but with a more restricted meaning of the "I" not including MIC testing variability

  - avoid the use of "intermediate" and to substitute for **"I"** = *susceptible, increased exposure*

  - alert to the clinicians of the "new criteria" in the susceptibility testing report

  Suggests wordings (one longer, one shorter) to be included in laboratory reports:

  > A microorganism is categorised as ***Susceptible, increased exposure*** **("I")** when there is a high likelihood of therapeutic success because exposure to the agent can be increased at the site of infection by adjusting the dosing regimen, mode of administration or because the concentration is naturally high at the site of infection (see http://www.eucast.org/clinical_breakpoints/)
  >
  > An isolate may be categorized as ***Susceptible, increased exposure*** **("I")** to the agent provided higher exposure of the microorganism can be achieved (dose, frequency, mode of administration)

  - re-education on the process of **interpretive reading** (when only using interpretive categories)

S / I / R – New definitions (*from* 2019)

- **Implication for surveillance / cumulative reports in antimicrobial stewardship**

  - include separately **S / I / R** percentages

    - describe isolates as susceptible (S + I) or resistant (R).
    - when an isolate is described as susceptible (S + I), this excludes resistant (R)
    - when an isolate is described as resistant (R), this excludes susceptible (S + I)

  - combine **[S + I]** and not [I + R] as these reports are intended for the use of the antimicrobials and not for the detection of the resistance mechanisms

- **Implication for the treatment**

  - only antibiotics with different does have “I” category = antibiotics with a single dose do not have “I” category

  - to consider an antibiotic as a therapeutic option when categorized “I” but using the high dose when different doses are available

S / I / R – Old definitions (2002 – 2018)

Pseudomonas aeruginosa breakpoints v8.1

Betalactam agent	MIC breakpoints (mg/L)	
	S ≤	R >
Piperacillin*	16	16
Piperacillin-tazobactam*	16[1]	16[1]
Ticarcillin*	16	16
Ticarcillin-clavulanic acid*	16[2]	16[2]
Cefepime*	8	8
Ceftazidime*	8	8
Ceftazidime-avibactam	8[1]	8[1]
Ceftobiprole	IE	IE
Ceftolozane-tazobactam	4[1]	4[1]
Imipenem*	4	4
Meropenem	2	8
Meropenem-vaborbactam	8[3]	8[3]
Aztreonam	1	16

For susceptibility testing purposes, the concentration of the inhibitor is fixed at [1]4 mg/L, [2]2 mg/L or [3]8 mg/L

IE: insufficient evidence

***Breakpoints are based on high dose therapy**

S / I / R – New definitions (2019)

Pseudomonas aeruginosa breakpoints v9.0

Betalactam agent	MIC breakpoints (mg/L)	
	S ≤	R >
Piperacillin[HE]	16	16
Piperacillin-tazobactam[HE]	16[1]	16[1]
Ticarcillin[HE]	16	16
Ticarcillin-clavulanic acid[HE]	16[2]	16[2]
Cefepime[HE]	8	8
Ceftazidime[HE]	8	8
Ceftazidime-avibactam	8[1]	8[1]
Ceftobiprole	IE	IE
Ceftolozane-tazobactam	4[1]	4[1]
Imipenem[HE]	4	4
Meropenem	2	8
Meropenem-vaborbactam	8[3]	8[3]
Aztreonam[HE]	16	16

For susceptibility testing purposes, the concentration of the inhibitor is fixed at [1]4 mg/L, [2]2 mg/L or [3]8 mg/L

IE: insufficient evidence

HE = high exposure (= high dose, …)

Those with **only one (maximum possible) dose** are categorized as **S / R** with no **I** category

Those with **two doses, standard and high,** are categorized as **S / I / R**

S / I / R – New definitions (from 2020)

Breakpoints that categorise WT organisms (organisms without phenotypically detectable acquired resistance mechanisms to the agent) as **"Susceptible, increased exposure" (I)** instead of "Susceptible, standard dosing regimen (S)"

Previously listed as **agent^{HE}** to emphasize the need for high exposure (HE)

Categorization as I / R

Pseudomonas aeruginosa breakpoints v10.0

Betalactam agent	MIC breakpoints (mg/L)	
	S ≤	R >
Piperacillin	0.001	16
Piperacillin-tazobactam	0.001[1]	16[1]
Ticarcillin	0.001	16
Ticarcillin-clavulanic acid	0.001[2]	16[2]
Cefepime	0.001	8
Ceftazidime	0.001	8
Ceftazidime-avibactam	8[1]	8[1]
Ceftobiprole	IE	IE
Ceftolozane-tazobactam	4[1]	4[1]
Imipenem	0.001	4
Meropenem	2	8
Meropenem-vaborbactam	8[3]	8[3]
Aztreonam	0.001	16

For susceptibility testing purposes, the concentration of the inhibitor is fixed at [1]4 mg/L, [2]2 mg/L or [3]8 mg/L

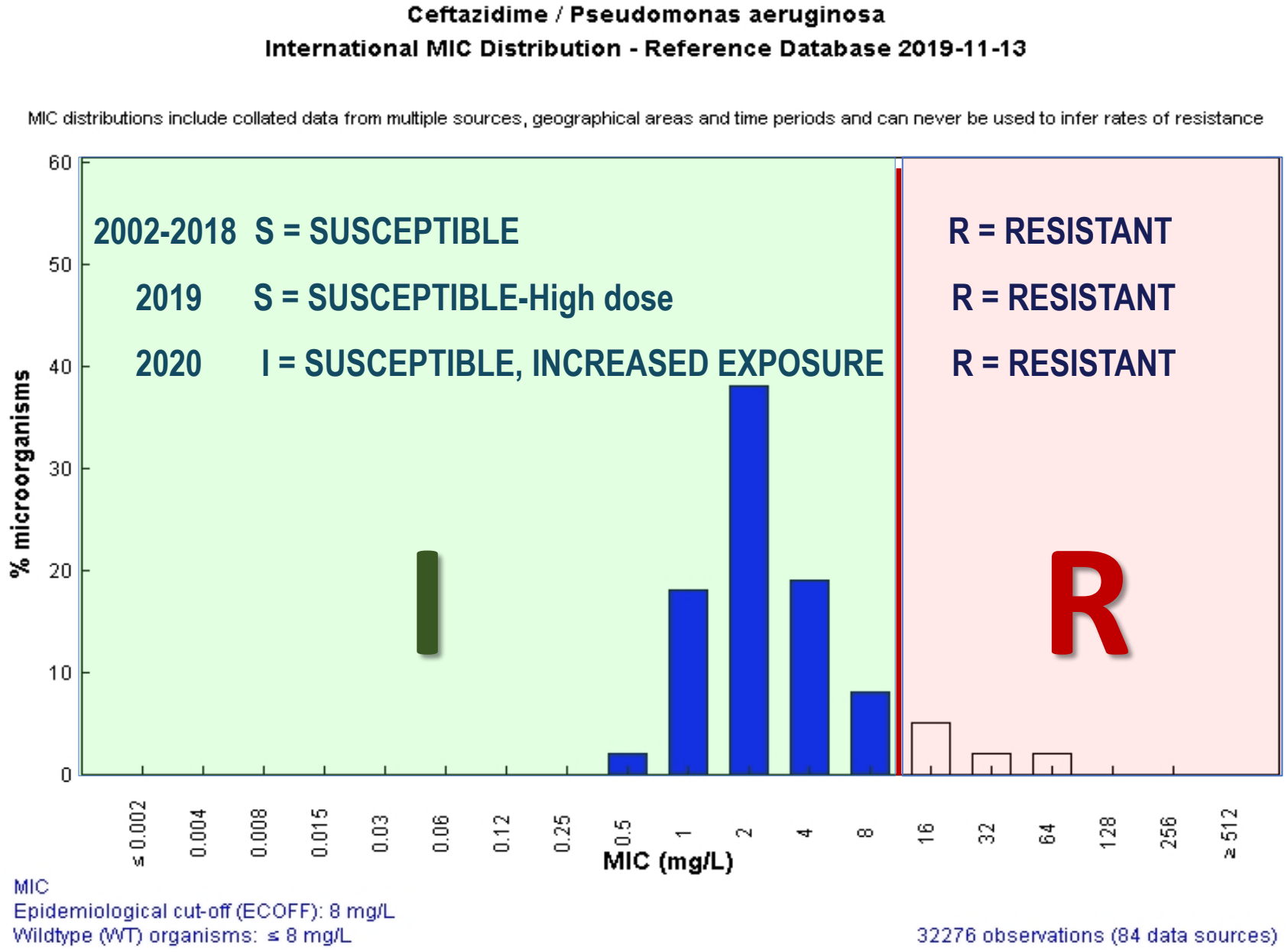
IE: insufficient evidence

Arbitrary valued to assure that all susceptible population is categorized as "I"

Those with **only one (maximum) possible dose** are categorized as **S / R** with no **I** category

Those with **two doses, standard and high,** are categorized as **S / I / R**

S / I / R – New definitions



Reporting with new "I" definition

Pseudomonas aeruginosa – new breakpoints and interpretive reading

Betalactam agent	MIC breakpoints (mg/L)		Wild type	AmpC derepressed	Porin deficiency (OprD⁻)	Efflux pump (MexAB-OprM)	Metallo-β-lactamase (VIM-2)	Carbapene-mase (GES-5)
	S ≤	R >	MIC (category)	MIC (category)	MIC (category)	MIC (category)	MIC (category)	MIC (category)
Piperacillin-tazobactam	0.001[1]	16[1]	4 (I)	>64 (R)	8 (I)	>64 (R)	>64 (R)	>64 (R)
Ceftazidime	0.001	8	1 (I)	>32 (R)	2 (I)	2 (I)	>32 (R)	>32 (R)
Cefepime	0.001	8	2 (I)	>16 (R)	4 (I)	4 (I)	>16 (R)	>16 (R)
Aztreonam	0.001	16	4 (I)	>16 (R)	8 (I)	8 (I)	4 (I)	>16 (R)
Ceftazidime-avibactam	8[1]	8[1]	1 (S)	1 (S)	2 (S)	2 (S)	>32 (R)	4 (S)
Ceftolozane-tazobactam	4[1]	4[1]	0.5 (S)	0.5 (S)	0.5 (S)	0.5 (S)	>16 (R)	>16 (R)
Imipenem	0.001	4	0.5 (I)	1 (I)	>8 (R)	1 (I)	>8 (R)	>8 (R)
Meropenem	2	8	0.5 (S)	0.5 (S)	2 (S)	8 (R)	>8 (R)	>8 (R)
For susceptibility testing purposes, the concentration of the inhibitor is fixed at [1]4 mg/L			I = *Susceptible, increased exposure* to the agent provided higher exposure of the microorganism can be achieved (dose, frequency, mode of administration).					

New S / I / R definitions: next stepts

- To adapt **cumulative reports** to the **new definitions**

PORCENTAJE DE AISLADOS SENSIBLES* (2019)

*Criterios EUCAST (www.eucast.org)

GRAMNEGATIVOS

	Betalactámicos									
Enterobacterias	AMP	AMC	PTZ	CTX	CAZ	FEP	ATM	IMP	ERT	MER
Escherichia coli	38	89	95	95	94	90	93	99	99	
Klebsiella pneumoniae		84	87	88	88	84	79	94	93	
Klebsiella oxytoca		89	93	95	95	92	89	99	99	
Klebsiella aerogenes			81	79	76	91	70	98	95	
Serratia marcescens			81	60	63	84	67	96	98	
Enterobacter cloacae			82	71	70	84	79	98	92	
Morganella morganii			97	70	65	98	82	60	99	
Proteus mirablis	50	92	93	100	100	100		97	100	
Salmonella spp.	52	91								
Bacilos gramnegativos no fermentadores										
Pseudomonas aeruginosa			81		83	79	84	76		84
Acinetobacter baumannii			94		91	91		91		94
Stenotrophomonas maltophilia					56					

[I]

[S + I]

84.3% = 78.9% + 5.3%

New S / I / R definitions: next stepts

- **To implement** a **new letter for the "I" category …?**
  - **HE** (High Exposure) S / **HE** / R
  - **I^{HE}** (Susceptible with High Exposure) S / **I^{HE}** / R
  - **SI** (Susceptible Increased exposure) S / **SI** / R

- To perform **educational efforts** in order to translate the **new definitions into clinics** and **stewardship programs**

- … … … … …

Colistin interpretive criteria: 2020 breakpoints

Microorganisms	Minimum inhibitory concentration (mg/L)						
	CLSI			EUCAST*			
	S	I	R	S	I	R	ATU
Enterobacterales	-	≤2	≥4	≤2	-	>2	-
Pseudomonas spp.	-	≤2	≥4	≤2	-	>2	4
Acinetobacter spp.	-	≤2	≥4	≤2	-	>2	-

CLSI: Clinical and Laboratory Standard Institute
S: susceptible; **I:** intermediate; **R:** Resistant
EUCAST: European Committee of Antimicrobial Susceptibility Testing
S: susceptible, standard dose; **I:** susceptible, increased exposure; **R:** Resistant;
ATU: Area of Technical Uncertainity

*Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive).

CLSI – Susceptible dose dependent category (SDD)

SDD

A category defined by **a breakpoint that implies that susceptibility of an isolate is dependent on the dosing regimen** that is used in the patient.

…it is necessary to **use a dosing regimen** (ie, higher doses, more frequent doses, or both) that results in **higher drug exposure** than the dose that was used to establish the susceptible breakpoint.

Consideration should be given to the maximum approved dosage regimen, because higher exposure gives the highest probability of adequate coverage of an SDD isolate.

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.

CLSI. 2020. Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA

CLSI – Susceptible dose dependent category (SDD)

- Susceptibility is dependent on the dosing regimen and it **only** applies **when multiple doses are used**
- **Initially only** proposed for **CEFEPIME and *Enterobacterales*** based on different dosing schemes (and site of infection)

Site/Infection Type	Dose	Frequency	Total Daily Dose
Mild to moderate UTI	0.5-1g	12h	1-2g
Severe UTI	2g	12h	4g
Mild to severe pneumonia	1-2g	12	2-4g
Moderate to sever SSTI	2g	12h	4g
Complicated IAI	2g	12h	4g
Neutropenic fever	2g	8h	6g

The non-UTI doses for cefepime range from 2 to 6 g/day

- Currently expanded to **CEFTAROLINE** and ***S. aureus***
  DAPTOMYCIN and ***Enterococcus spp.***

CLSI. 2020. Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI document M100. Clinical and Laboratory Standards Institute, Wayne, PA

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

POINT-COUNTERPOINT

2019, 57:e1129-19

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

Gunnar Kahlmeter,[a,b] Christian G. Giske,[a,c] Thomas J. Kirn,[d] Susan E. Sharp[e]

CLSI

S	susceptible
I	intermediate
SDD	susceptible dose dependent
R	resistant
NS	non susceptible

EUCAST

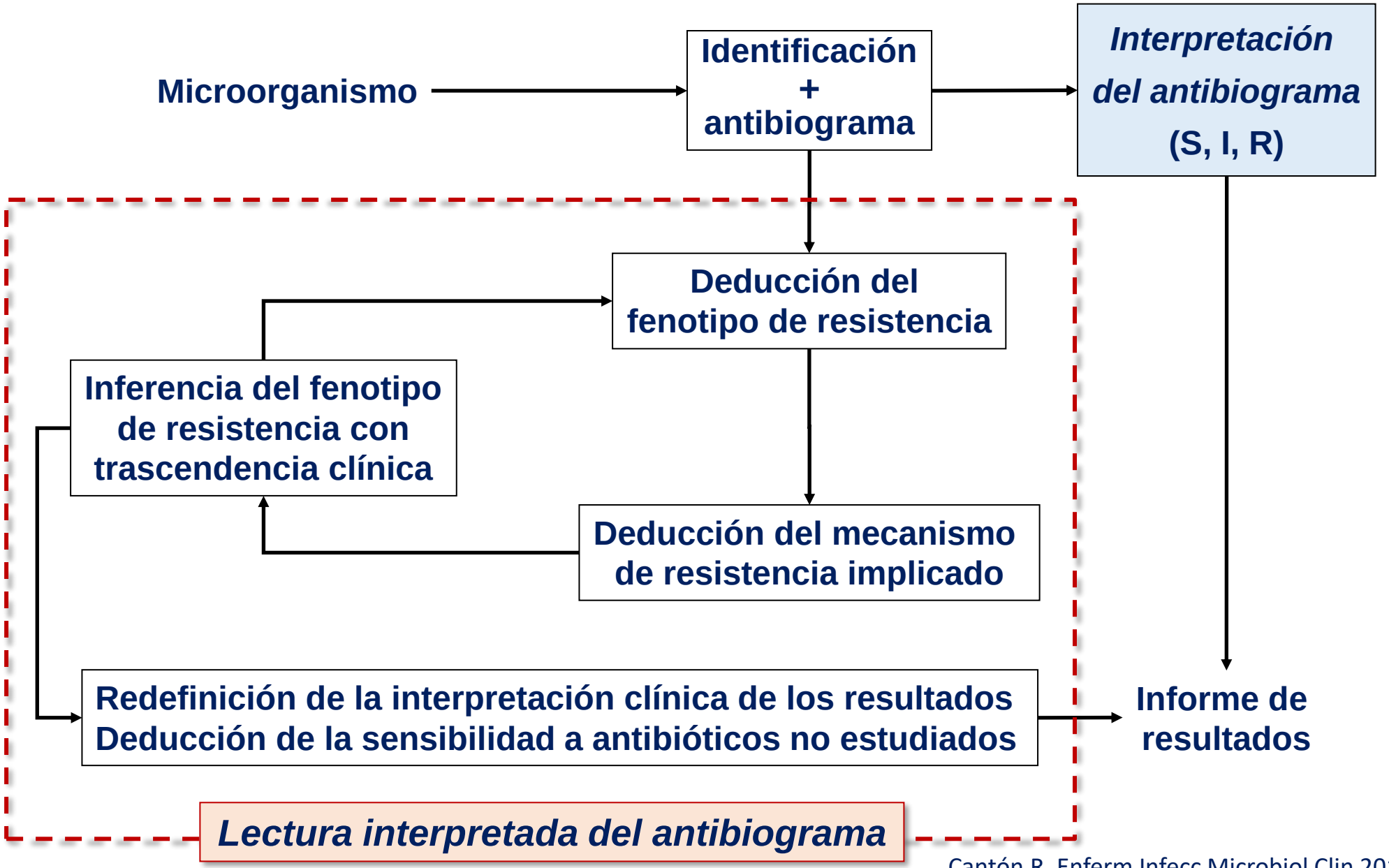
S	susceptible, standard dose
I	susceptible, increased exposure
R	resistant

ATU: area of technical uncertainty

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.

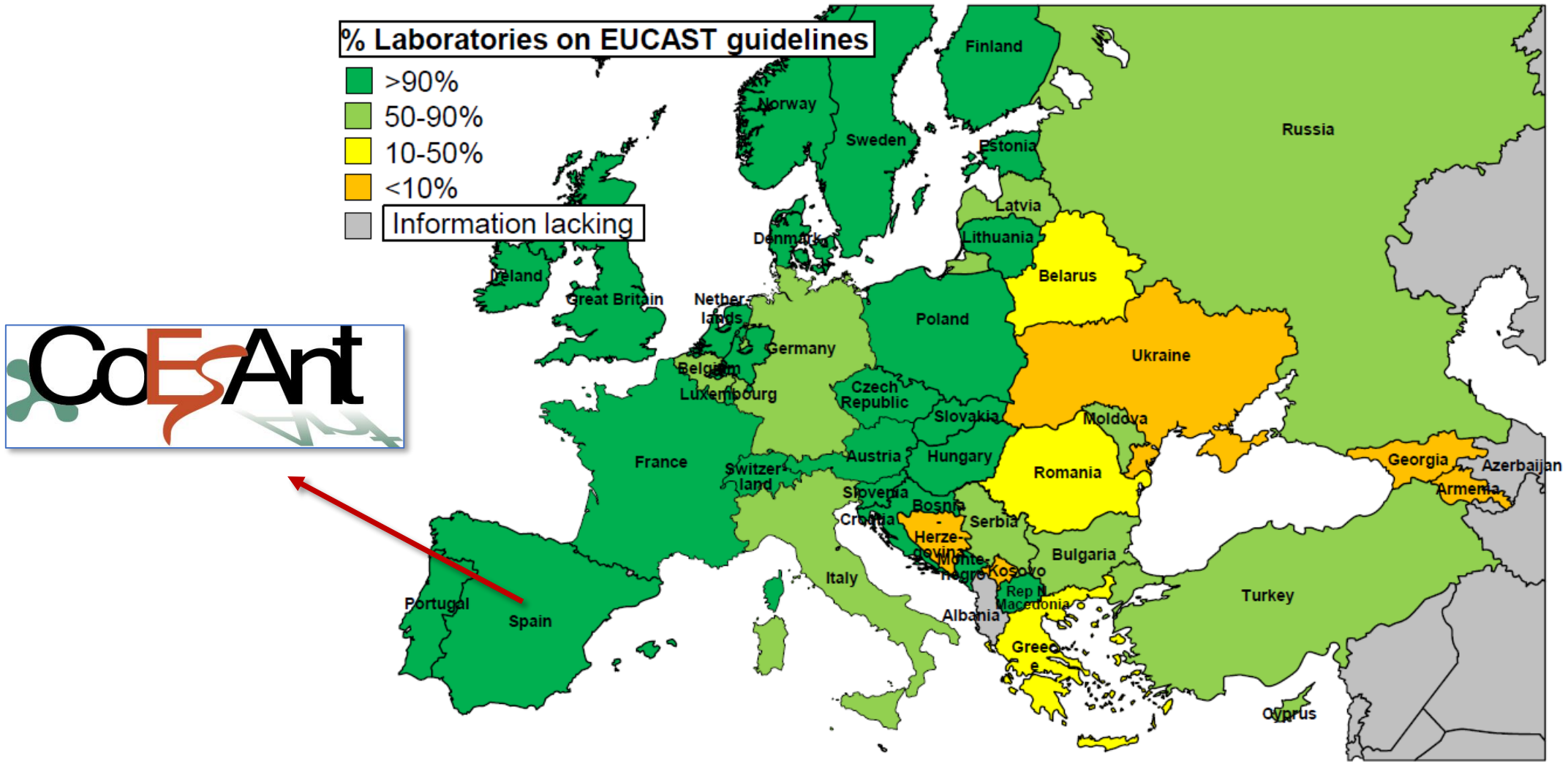
Interpretive reading of the antibiogram



Cantón R. Enferm Infecc Microbiol Clin 2010; 28:375-85

Implementation of EUCAST breakpoints/guidelines, February 2020

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



CoESAnt

Countries not on the map: Australia | Brazil | China | Canada | Iceland | Israel | Malta | Morocco | New Zealand | South Africa | USA

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_Presentations/2020/EUCAST_update_Gen_Comm_all_presentations.pdf

Lectura interpretada e interpretación del antibiograma

6 de julio de 2020

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