27th ECCMID
Vienna, Austria
22 – 25 April 2017

REPORTING ANTIBIOGRAM DATA

Reporting MICs or Clinical Categories?

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reipi-isciii

Vienna, April 22 2017

REPORTING MICs - - - CLINICAL CATEGORIES INDICATIONS

Microorganisms [likely] causing an infection

Bacteria cultured from colonized patients
Identification of microorganisms to genus/species level

Definition of breakpoints (clinical BP, ECOFF)
Research

REPORTING SUSCEPTIBILITY TESTING RESULTS

Methodological issues

Conceptual issues

REPORTING SUSCEPTIBILITY TESTING RESULTS

Methodological issues

IN VITRO SUSCEPTIBILITY TESTING: METHODOLOGIES

Phenotypic assays:

Microorganism-antimicrobial agents interaction

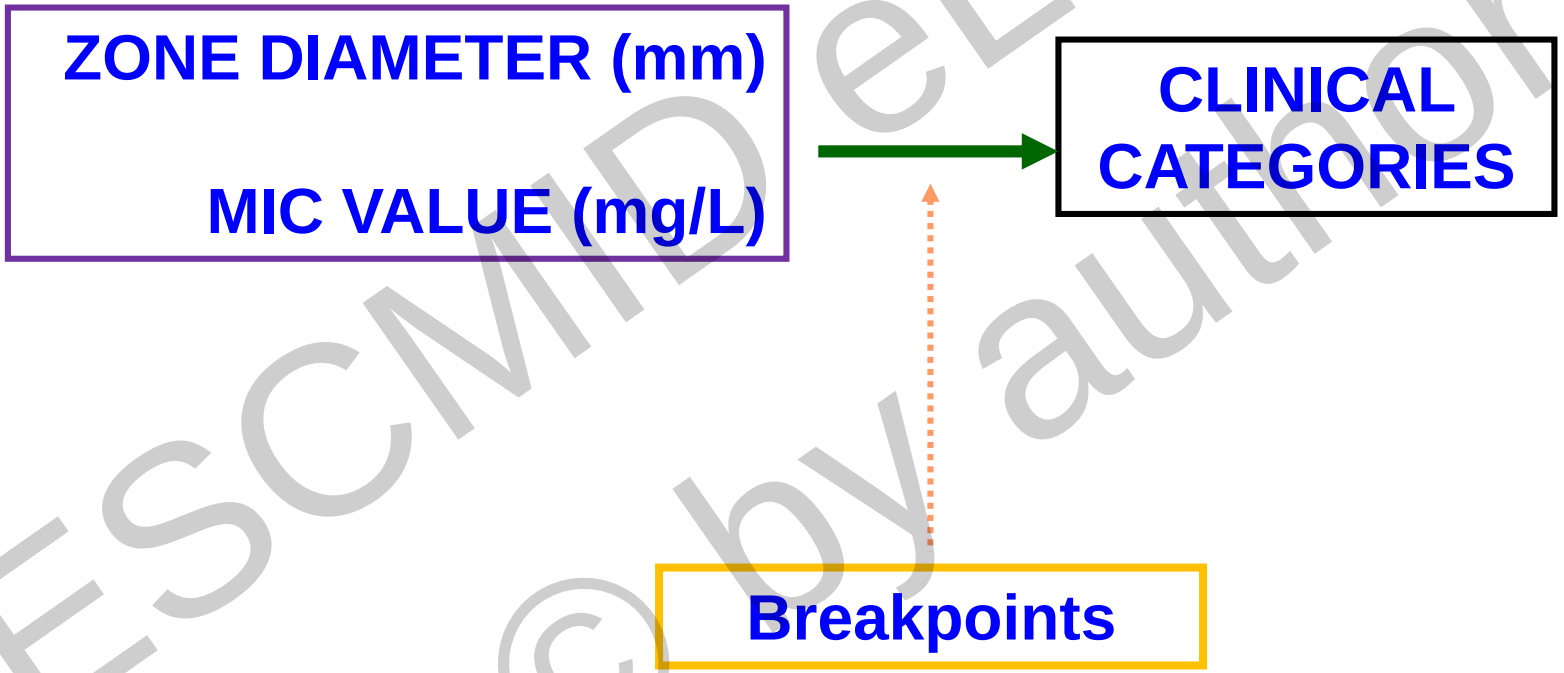
Dilution assays: Broth dilution
- **Macrodilution**
- **Microdilution**
  - **[(semi)-automated dilution devices]**

Agar dilution

Diffusion assays: Paper discs/Tablets
- **Gradient strips**

Detection of biochemical mechanisms

Detection of resistance genes

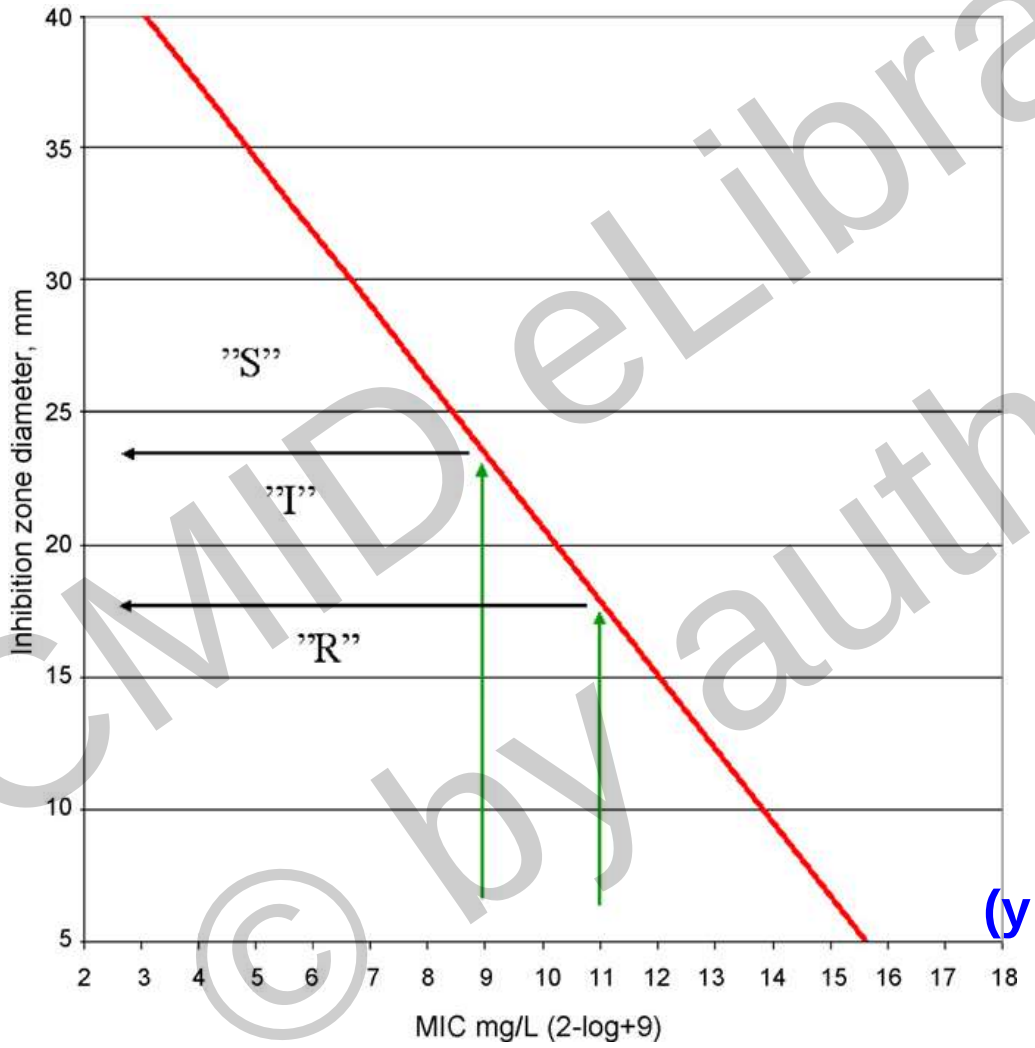


1. MICs are the simplest (semiquantitative) estimates of the antibacterial effect in vitro.
   MICs are currently the reference values measuring In vitro susceptibility testing.

2. All breakpoints defining clinical categories are either
   - MICs
   - Zone diameter values correlated with MICs

[Adapted from]Turnidge J & Paterson DL. CMR 2007, 391

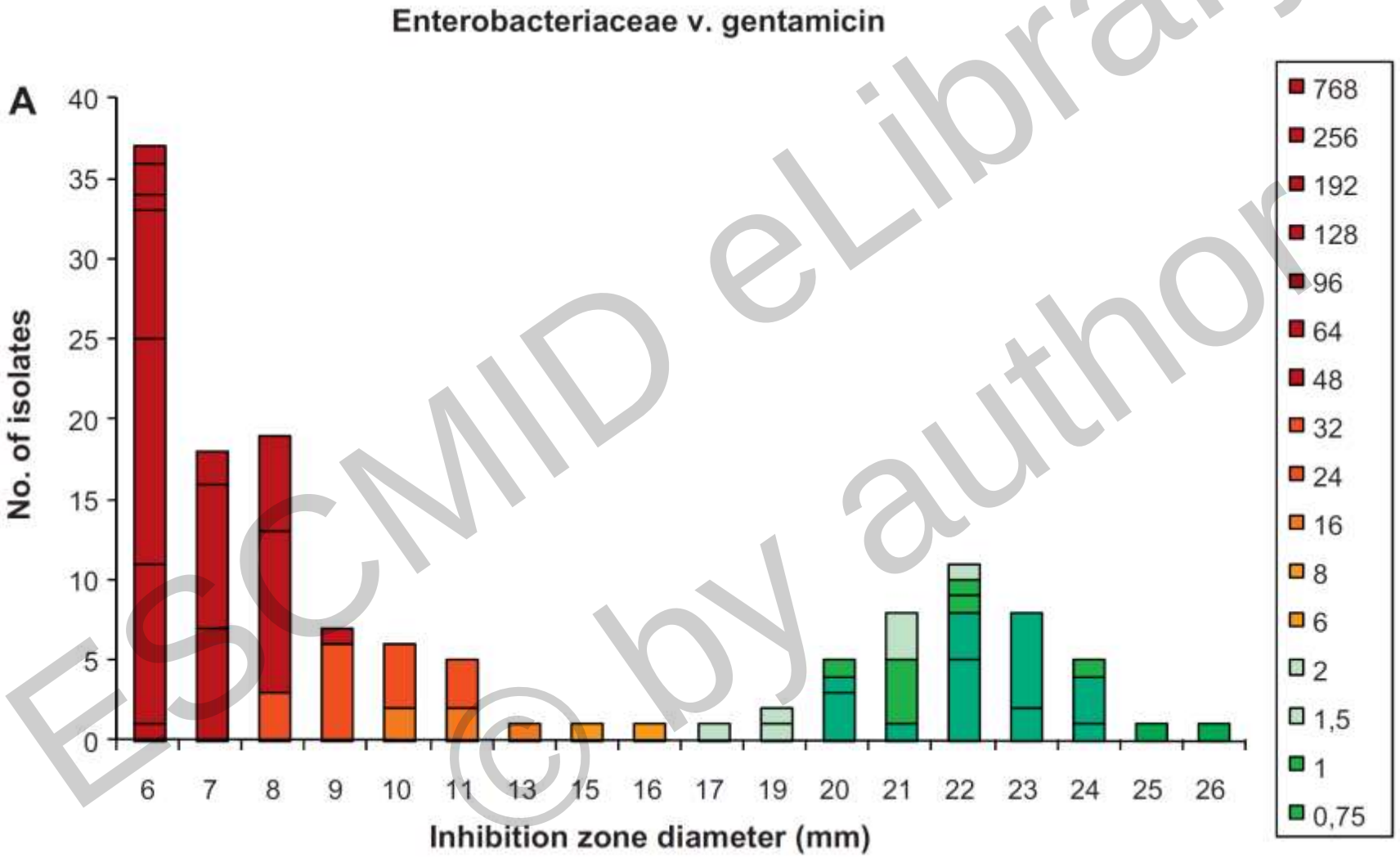
REGRESSION LINE FOR TETRACYCLINE



(y = −2.78x + 48.49)

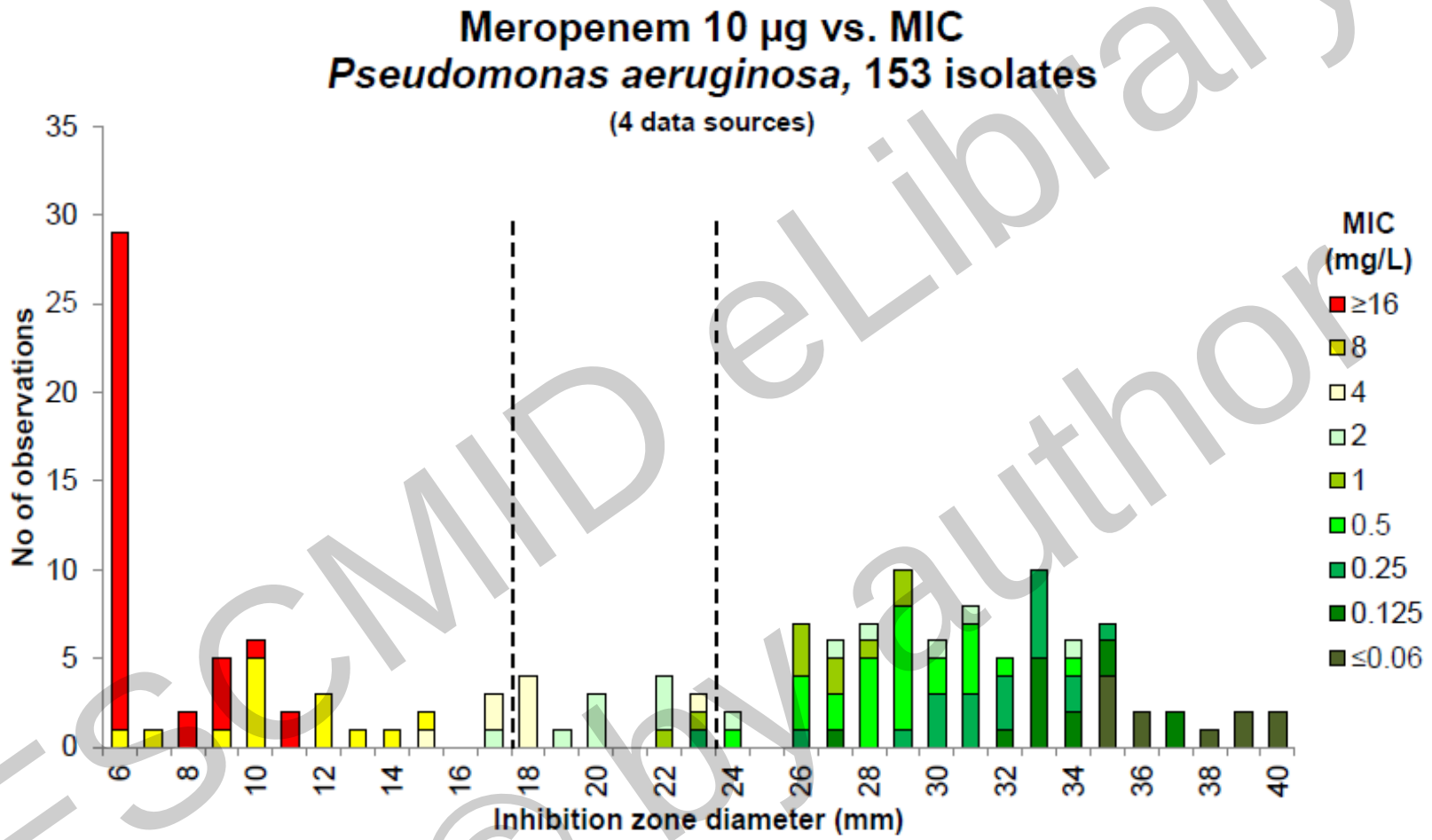
Kronvall G et al, IJAA 2011:281; Alestig K, et al., Scand J Infect Dis 1981:148

MIC-COLOURED ZONE DIAMETER HISTOGRAM TECHNIQUE



Kronvall G et al, IJAA 2011:281

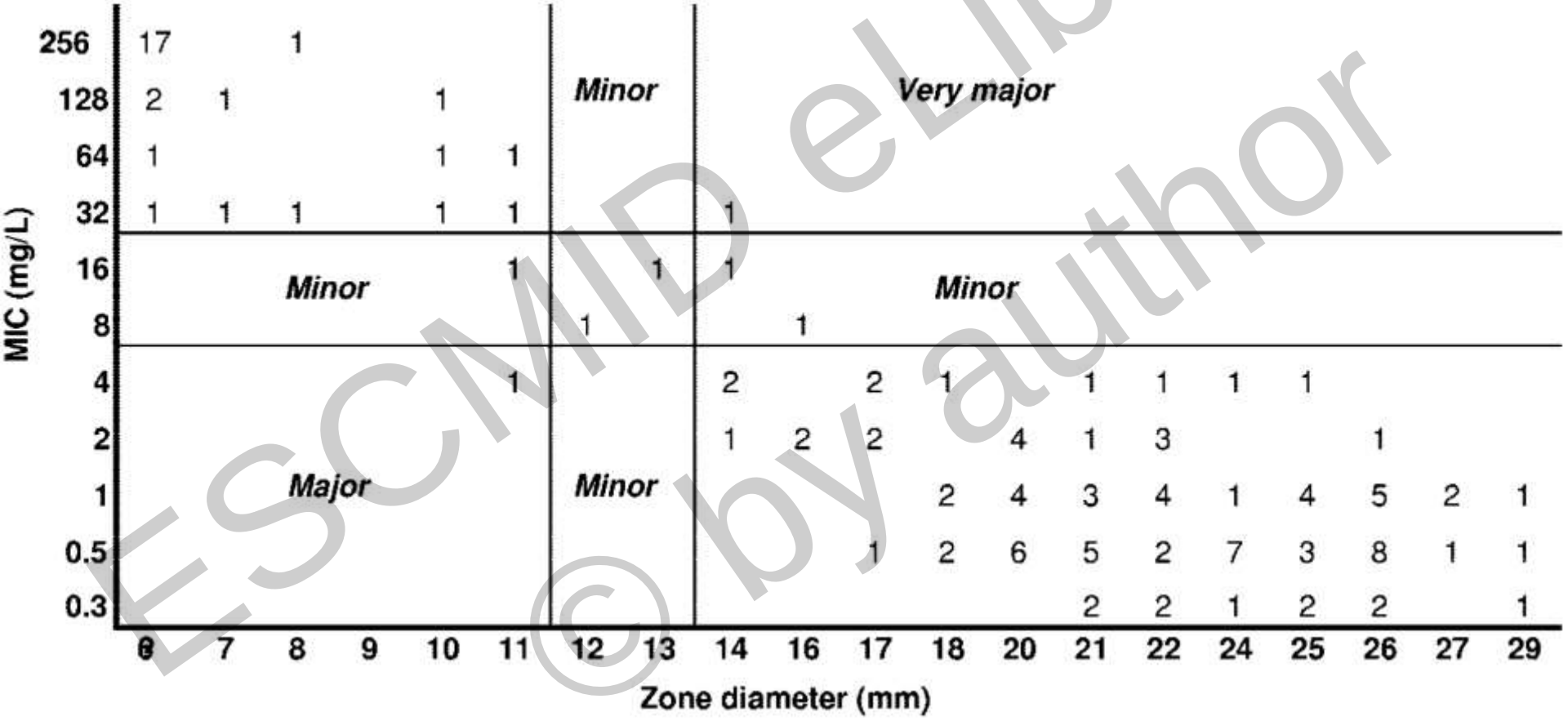
MIC-COLOURED ZONE DIAMETER HISTOGRAM TECHNIQUE



Breakpoints		ECOFF
MIC	S≤2, R>8 mg/L	2 mg/L
Zone diameter	S≥24, R<18 mm	

http://www.eucast.org/ast_of_bacteria/calibration_and_validation/

"SCATTERGRAM" OF MICs vs. IINHIBITION ZONE DIAMETERS



Turnidge J & Paterson DL. CMR 2007, 391

	STANDARDIZED	RESULT	CLINICAL CATEGORIES
MACRODILUTION	YES	MIC	YES
MICRODILUTION	YES	MIC	YES
[COMMERCIAL] MICRODILUTION	[☺]	[MIC]*	YES
AGAR DILUTION	YES	MIC	YES
GRADIENT DIFFUSION	[☺]	MIC	YES
DISC DIFFUSION	YES	Zone diameter	YES
DETECTION OF BIOCHEMICAL OF MECHANISMS	[☺]	Pos/Neg	Resistant vs. not Resistant
DETECTION OF RESISTANCE GENES	[☺]	Yes/Not	"Resistant" vs. "Not Resistant"

*Unprecise results are obtained for some agents depending on panels/cards composition

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Slide withheld at request of author

For some organisms, only MIC assays are indicated, or clinical breakpoints have only been defined for MIC assays

ENTEROBACTERIA: MICs vs DD
EUCAST 2017

	COMMENT
Mecillinam	AGAR DILUTION is the reference method for Mecilinam MIC determination.
Fosfomycin	Zone diameter breakpoints apply to *E. coli* only. For other Enterobacteriaceae, use an MIC method.
Tigecycline	Zone diameter breakpoints validated for *E. coli* only. For other Enterobacteriaceae, use an MIC method.
Colistin	Use an MIC method.

EVALUATION OF FIVE COMMERCIAL MIC METHODS FOR COLISTIN ANTIMICROBIAL SUSCEPTIBILITY TESTING FOR GRAM-NEGATIVE BACTERIA

”The correlation between gradient tests and reference MICs was poor, even when QC results were within range. This was probably related to the poor diffusion of colistin in agar.

Based on the results of this study, EUCAST recommends laboratories to use BMD methods for colistin MIC determination and advice against the use of gradient tests at this point.”

Matuschek E et al, ECCMID 2017 P161

Pseudomonas aeruginosa
EUCAST 2017

	MIC BP (mg/L)		Disc Content (µg)	Zone diameter BP (mm)	
	S<=	R>		S≤	R>
Ceftolozane-tazobactam	4	4	30	In preparation	In preparation

CLSI MIC BREAKPOINT FOR RESISTANCE IS DIFFERENT

([IN PRINCIPLE…] CLSI DIFFUSION BREAKPOINS SHOULD NOT BE APPLIED IF EUCAST METHDOLOGY AND CRITERIA ARE USED IN THE LAB!!!)

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COMPARATIVE GENERAL DISADVANTAGES OF PHENOTYPIC TESTING ASSAYS

DILUTION METHODS	1. (USUALLY) BASED ON GEOMETRIC SCALE 2. ACTUAL MIC VALUE SOMEWHERE BETWEEN THE OBTAINED MIC AND THE INMEDIATE LOWER DILUTION 1+2 : Major impact at high MICs!!! 3. INTRINSIC METHODOLOGICAL ERROR ACCEPTED TO BE ± 1 DILUTION (or even more, depending on the organism) 4. DIFFICULTIES FOR DETECTING CONTAMINATION IN DILUTION ASSAYS (TECHNICAL MISTAKE vs. EAGLE's EFFECT) 5. STANDARDIZED VERSIONS ARE DIFFICULT TO IMPLEMENT IN DAILY WORK OF CLINICAL LABORATORIES
GRADIENT DIFFUSION	1. UNRELIABLE RESULTS FOR SOME AGENTS […NOT A STANDARDIZED METHOD!!!]
DISC DIFFUSION	1. [MIC] and MBC NOT DEFINED 2. NOT A STANDARDIZED METHOD FOR SOME AGENTS/BACTERIA

REPORTING SUSCEPTIBILITY TESTING RESULTS

Conceptual issues

INTERPRETATIVE CLINICAL CATEGORIES

EUCAST	CLSI
SUSCEPTIBLE	SUSCEPTIBLE
	SUSCEPTIBLE-DOSE DEPENDENT
INTERMEDIATE	INTERMEDIATE
RESISTANT	RESISTANT
	NONSUSCEPTIBLE

EUCAST: CLINICALLY SUSCEPTIBLE (S)

A microorganism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success. The microorganisms is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

CLSI: SUSCEPTIBLE (S)

Isolates with an MIC at or below or zone diameters at or above the "susceptible breakpoint" are inhibited by usually achievable concentrations of antimicrobial agent when the dose recommended to treat the site of infection is used, resulting in likely clinical efficacy.

EUCAST: 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 by applying the appropriate breakpoint in a defined phenotypic test system

CLSI: RESISTANT (R)

Isolates with an MIC at or above or zone diammeters at or below the "resistant breakpoint" are not inhibited by usually achievable concentrations of the agent with normal dosaje 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.

EUCAST

CLINICALLY INTERMEDIATE (I) [TRADITIONAL]

- 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 drug can be used.

- It also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.
  [Impact on Major and Very Major errors in categorization!!!].

CLSI 2017

INTERMEDIATE (I)

- Isolates with MICs or zone diameters within the intermediate range, that approach usually attainable blood and tissue levels and for which response rates may be lower tan for susceptible isolates. It implies clinical efficacy in body sites where the considered drug is physiologically concentrated or when a higher tan normal dosage of a drug can be used.

- It includes a buffer zone, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretation, especially for drugs with narrow pharmacotoxicity margins.

EUCAST
Proposed new definition

INTERMEDIATE (I) (2016)

A microorganism is defined as intermediate by a level of antimicrobial activity associated with a high likelihood of therapeutic success but only when a higher dosage of the agent than normal can be used or when the agent is physiologically concentrated at the site of infection.

(2017) A microorganism is categorized as intermediate when there is a high likelihood of therapeutic success because exposure (activity) is enhanced (1) by adjusting the dosing regimen, or (2) because the antimicrobial agent is concentrated at the site of infection.

SHOULD LABORATORIES THAT PERFORM MIC TESTS REPORT ACTUAL MIC VALUES OR RATHER PROVIDE ONLY CATEGORY INTERPRETATIONS?

…Consensus view is that in all but selected situations, only the category interpretation should be reported routinely.

This view is predicated on the relatively obscure relationship that exists between individual MIC values and defined predictions of therapeutic response together with the inherent variability of MIC determinations.

Doern GV & Brecher SM, JCM 2011:S11

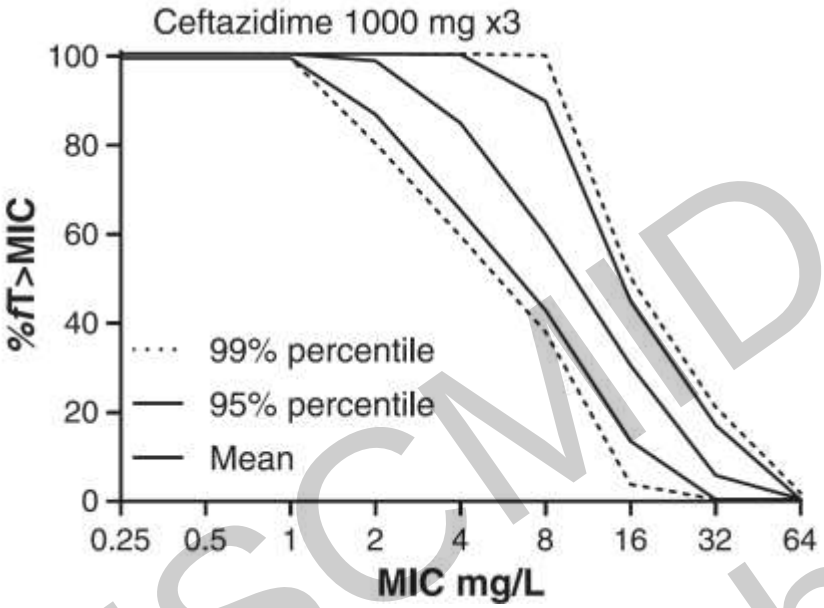
CLSI 2017

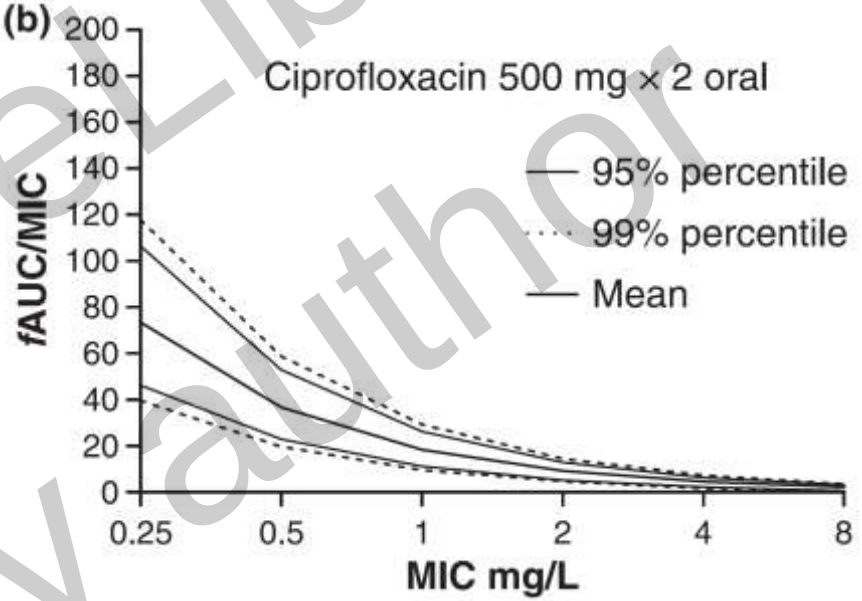
MIC values may be reported directly to clinicians for patient care purposes, AND an interpretative category results should also routinely be provided

When disk diffusion is used, zone diameters without an interpretative category should not be reported

It is not appropriate to apply disk diffusion or MIC breakpoints borrowed from a (breakpoint) table where the organism is not listed.

MIC IS CRITICAL FOR PD STUDIES





Mouton JW et al. CMI, 2012:37

(…A SIMILAR APPROACH WITH JUST CLINICAL CATEGORIES HAS NOT BEEN DEVELOPED)

Does resistance [always] predict failure and susceptibility predict success of antimicrobial therapy?

"90-60" RULE

Type(s) of infection	Drug(s) administered	Outcome measurement	Measurement used to determine susceptibility	Cases with successful outcome, % (no. of cases/total no. of cases), by susceptibility class		P
				Susceptible[a]	Resistant	
Bacteremia and fungemia	Various	Mortality	MIC[b]	73 (224/309)	48 (10/21)	.02
Bacteremia and fungemia	Various	Mortality	MIC[b]	89 (594/665)	77 (97/126)	<.001
Serious bacterial infections	Various	Clinical response	MIC	81 (219/271)	4 (1/27)	<.001
Pneumococcal otitis media	Amoxicillin/clavulanic acid	Clinical response	MIC	80 (149/186)	68 (15/23)	.26
Pneumococcal otitis media	Cefuroxime	Clinical response	MIC	94 (44/47)	78 (29/37)	.05
Pneumococcal otitis media[c]	Cefaclor or cefuroxime	Bacteriologic response	MIC	95 (55/58)	45 (9/20)	<.001
Pneumococcal otitis media[c]	Cefaclor or azithromycin	Bacteriologic response	MIC	89 (23/26)	24 (6/25)	<.001
Bacteroides bacteremia	Various	Bacteriologic response	MIC	88 (60/68)	57 (4/7)	.06
Moderate-to-severe bacterial infections	Ciprofloxacin	Bacteriologic response	AUC/MIC ratio	82 (37/45)	26 (5/19)	<.001
Bacterial infections	Aminoglycosides	Clinical response	Peak/MIC ratio	~90[d]	~55[d]	
Bacterial infections[e]	Cefotaxime	Bacteriologic response	Zone diameter	92 (1464/1591)	63 (31/49)	<.001
Bacterial infections[e]	Ciprofloxacin	Bacteriologic response	Zone diameter	91 (1652/1815)	62 (8/13)	.004
—	—	—	—	89 (4521/5081)	59 (215/366)	<.001

Successful outcome

Susceptible: 4521/5081 (89%)
Resistant: 215/536n(59%)

Rex JH, Pfaller MA. CID, 2002:982

For susceptible organism, is clinical response better for those with lower MICs?

OUTCOME AND MICs IN PATIENTS WITH INFECTION TREATED WITH CEFOTAXIME (1983!)

CEFOTAXIME MIC (mg/L)	CAT	Number of Patients	% Cured or improved	% Erradication
<=4	S	1003	94	91
8	S	273	90	86
16	I	151	77	75
32	I	70	84	71
>=64	R	19	64	50

EUCAST BP CEFOTAXIME-ENTEROBACTERIA (2017): ≤1 (S) ; >2 (R)

Murray P et al. 1983, 23rd ICAAC, abst. 545
[Doern GV & Brecher SM, JCM 2011:S11]

OUTCOMES OF PATIENTS WITH BACTEREMIA BY *K. pneumoniae* PRODUCING KPC-2/KPC-3 TREATED WITH MEROPENEM COMBINATIONS

MEROPENEM MIC (mg/L)*	Survivors %
1	100(1/1)
2	100 (4/4)
4	80 (8/10)
8	75 (3/4)
>=16	64.7 (11/17)
TOTAL	75 (27/36)

*MIC determined with Vitek2

Tumbarello M GL et al. CID, 2012:943

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- The carbapenem BP for Enterobacteriaceae will detect all clinically important resistance mechanisms (including most of carbapenemases).
- Carbapenemase-producing isolates should be reported as tested.
- Carbapenemase detection and characterisation recommended for public health and infection control purposes.

CLSI 2017

- MIC breakpoints in M100-S20 (January 2010): Perform the MHT, the Carba NP test, mCIM, and/or a molecular assay when […] imipenem or meropenem MICs of 2–4 µg/mL or ertapenem MIC of 2 µg/mL
- After implementation of the current breakpoints, these additional tests do not need to be performed other than for epidemiological or infection control purposes.

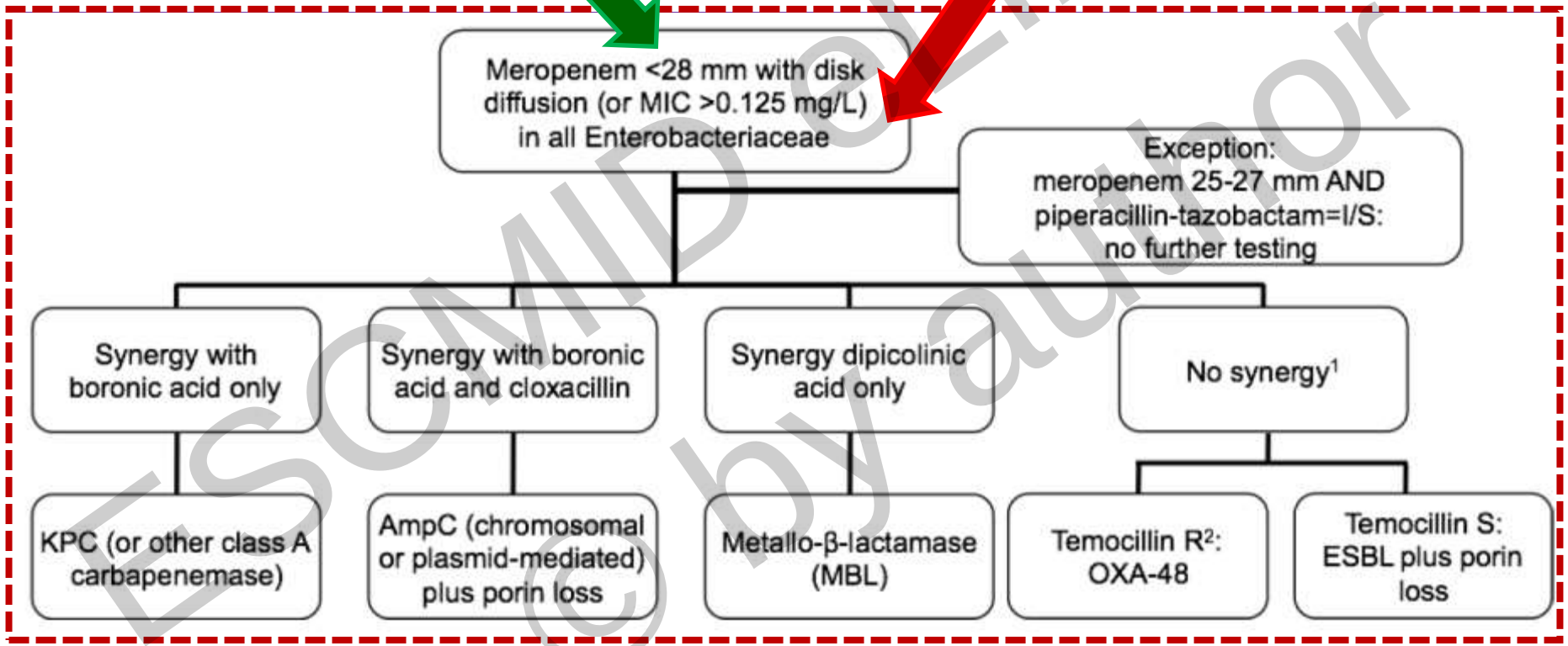
EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance

Version 1.0
December 2013

DETECTIÓN OF RESISTANCE MECHANISMS. CARBAPENEMASES (2017).

Disk diffusion

Commercial Panels?



PATIENTS WITH MRSA BACTEREMIA

VANCOMYCIN MIC AND MORTALITY

VANCOMYCIN MIC (mg/L)*	OR (95% CI)	P
1		
1.5	2.86 (0.87-9.35)	0.08
2	6.39 (1.68-24.3)	<0.001

VANCOMYCIN MIC AND SHOCK

VANCOMYCIN MIC (mg/L)*	OR (95% CI)	P
1		
1.5	0.59 (0.33-1.05)	0.07
2	0.33 (0.15-0.75)	0.012

*MIC determined with Etest®

Soriano A GL et al. CID, 2008:193

SYSTEMATIC REVIEW AND META-ANALYSIS

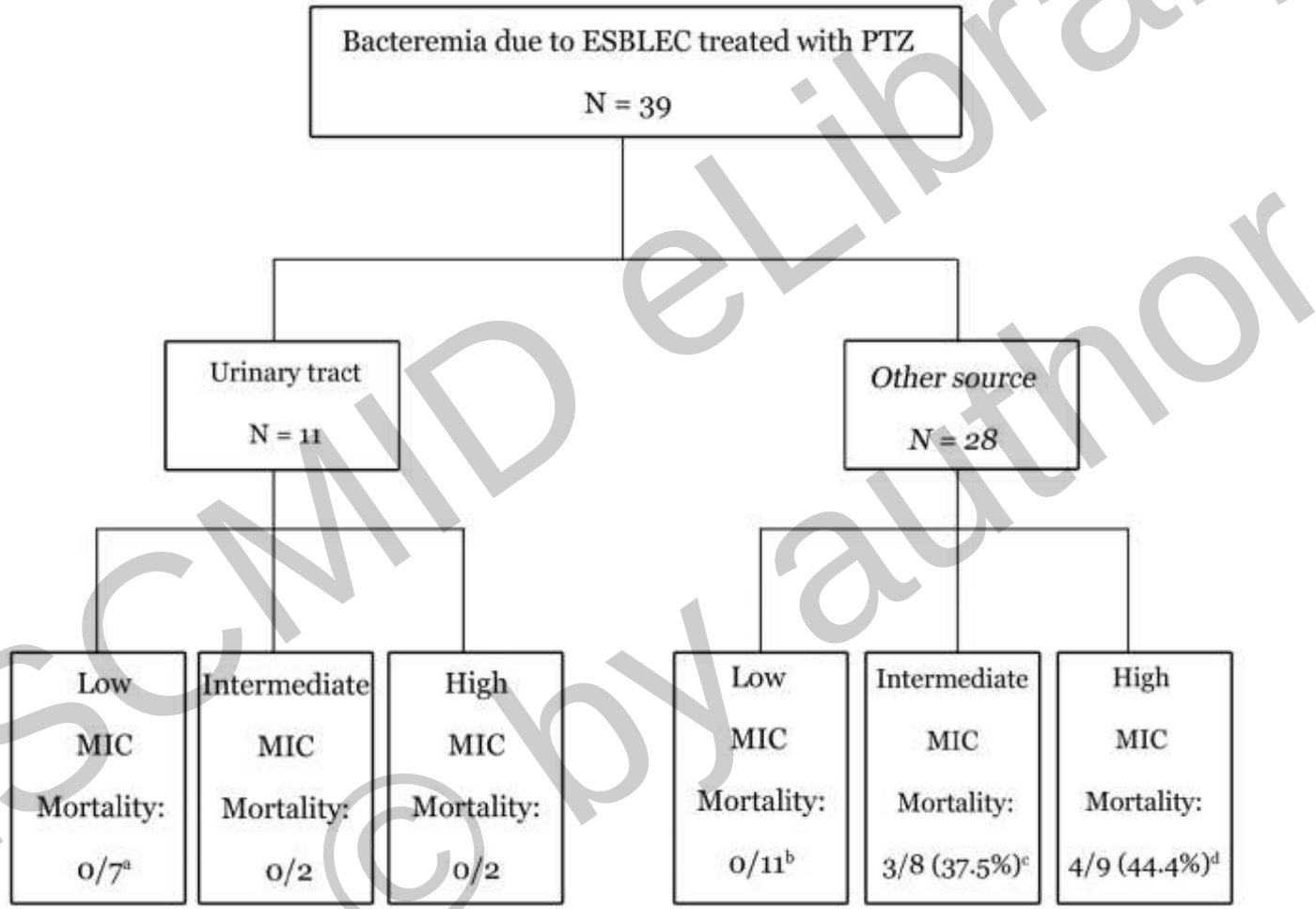
"No significant differences in risk death were observed in subgroups with high-vancomycin MIC vs low-vancomycin MIC values across different study designs, microbiological susceptibility assays, MIC cutoffs, clinical outcomes, duration of bacteremia, previous vancomycin exposure, and treatment with vancomycin"

VANCOMYCIN MICs: ≥1.5mg/L vs. <1.5mg/L

EUCAST VANCOMYCIN BREAKPOINTS FOR *S. aureus*: ≤2 (S) ; >2 (R)

Kalil AC et al. JAMA, 2014:1552

MICs OF PIP-TZB AND OUTCOMES IN PATIENTS WITH BACTEREMIA DUE TO ESBL(+) *E. coli*



No mortality

Lower mortality among patients with low-MIC isolates

Retamar P et al. AAC, 2013:3402

URINARY CONCENTRATIONS OF CIPROFLOXACIN AFTER ORAL ADMINISTRATION

	Urinary Cmax (mg/L)	Urinary through Conc. (mg/L)
Ciprofloxacin 500 mg	268 (130–967)	13 (5.1–37)
Ciprofloxacin 1000 mg	892.52 ± 476.4	32.80 ± 22.01

	Clinical Breakpoints Enterobacteria	
	EUCAST	CLSI
Ciprofloxacin	0.25-0.5	1-[2]-4

PATIENTS WITH BACTEREMIA CAUSED BY ENTEROBACTERIACEAE TREATED WITH PIP-TZB

EUCAST BREAKPOINTS FOR PIP/TZB: ≤8 (S), 16 (I), >16 (R)

A borderline (S/I) MIC (8-16 mg/L) of PIP/TZB was NOT associated with a worse outcome than a lower (S) MIC (<1-1-2-4 mg/L)

IF the organism is SUSCEPTIBLE, the actual MIC of PIP/TZ has no significant impact on clinical outcome

Delgado-Valverde M et al. JAC, 2016:521

MICs vs CLINICAL CATEGORIES WITHIN THE CLINICAL MICROBIOLOGY LAB

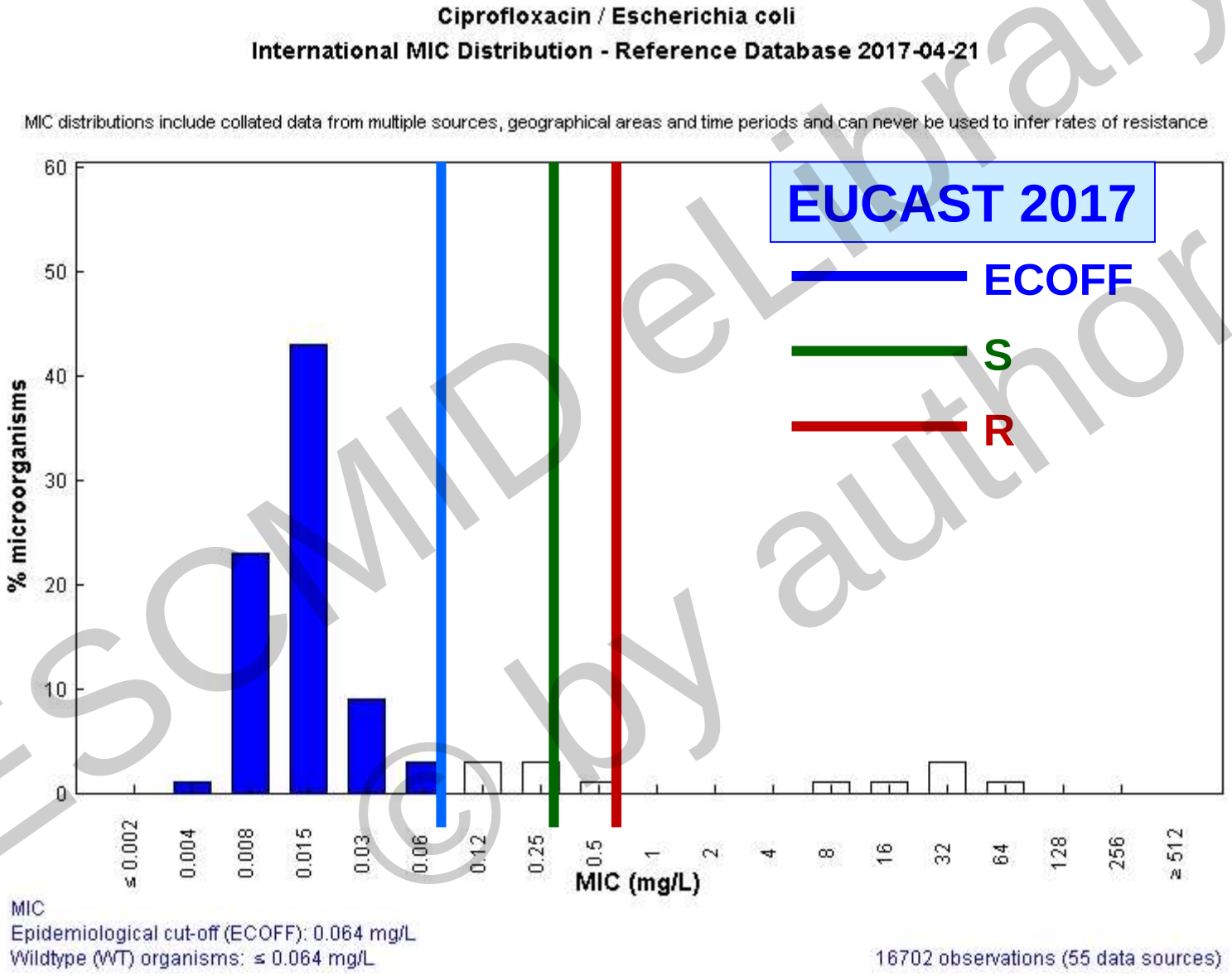
Detection of resistance mechanisms

- Low vs. high level resistance
- Emerging mechanisms
- Screening cut-off MIC values

Interpretative reading of antibiograms

Microorganisms identification (intrinsic resistance)

MICs FOR DEFINING BREAKPOINTS



SETTING BREAKPOINTS FOR NEW ANTIMICROBIAL AGENTS
IMPORTANCE OF MICs

EMA-Central registration procedure
The company will provide:

- Proposed indications for the agent
- Proposed dosing regimens for the agent (by indication) and the available formulations
- Proposed target organisms
- **MIC distributions for relevant species**
- Pharmacokinetic data
- **Pharmacodynamic data**
- **Modelling data, such as Monte Carlo simulations**
- Clinical trial data, including **outcome related to MIC** where available

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_SOPs/EUCAST_SOP_1.2_Setting_breakpoints_new_agents_20161121.pdf

(PERSONAL) CONCLUSIONS

CLINICAL CATEGORIES SHOULD BE ALWAYS REPORTED

IF MIC HAS BEEN OBTAINED, IT WOULD BE PREFERABLE ALSO REPORTING IT, NOT ONLY FOR BEING USEFUL TO (MANY) CLINICIANS, BUT ALSO BECAUSE OF ADEQUATE INFORMATION IN CLINICAL CHARTS

CONTINUING EDUCATIONAL ACTIVITIES EXPLAINING THE ACTUAL MEANING, ADVANTAGES AND SHORTCOMINGS OF ANTIBIOGRAM METHODS, MICs AND CLINICAL CATEGORIES SHOULD BE CONSIDERED