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

REPORT AS TESTED

ESCMID
EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

SaludMadrid

Dr. Rafael Cantón

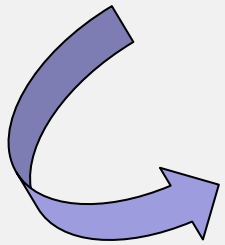
Hospital Universitario Ramón y Cajal
SERVICIO DE MICROBIOLOGÍA Y PARASITOLOGÍA

instituto ramón y cajal de investigación sanitaria irycis

Departamento de Microbiología II
Universidad Complutense. Madrid

Report as tested

- Strictly apply the recommended **breakpoints** for MIC or inhibition zone values for clinical categorization as susceptible (S), intermediate (I) or resistant (R)



- to achieve the goal of having breakpoints
- to avoid implementing expert rules
- to avoid delay in reporting

Although breakpoints are different, report “as tested” is currently recommended by both CLSI and EUCAST committees

Breakpoint definition (ISO 20776-1:2006)

… beyond CLSI and EUCAST

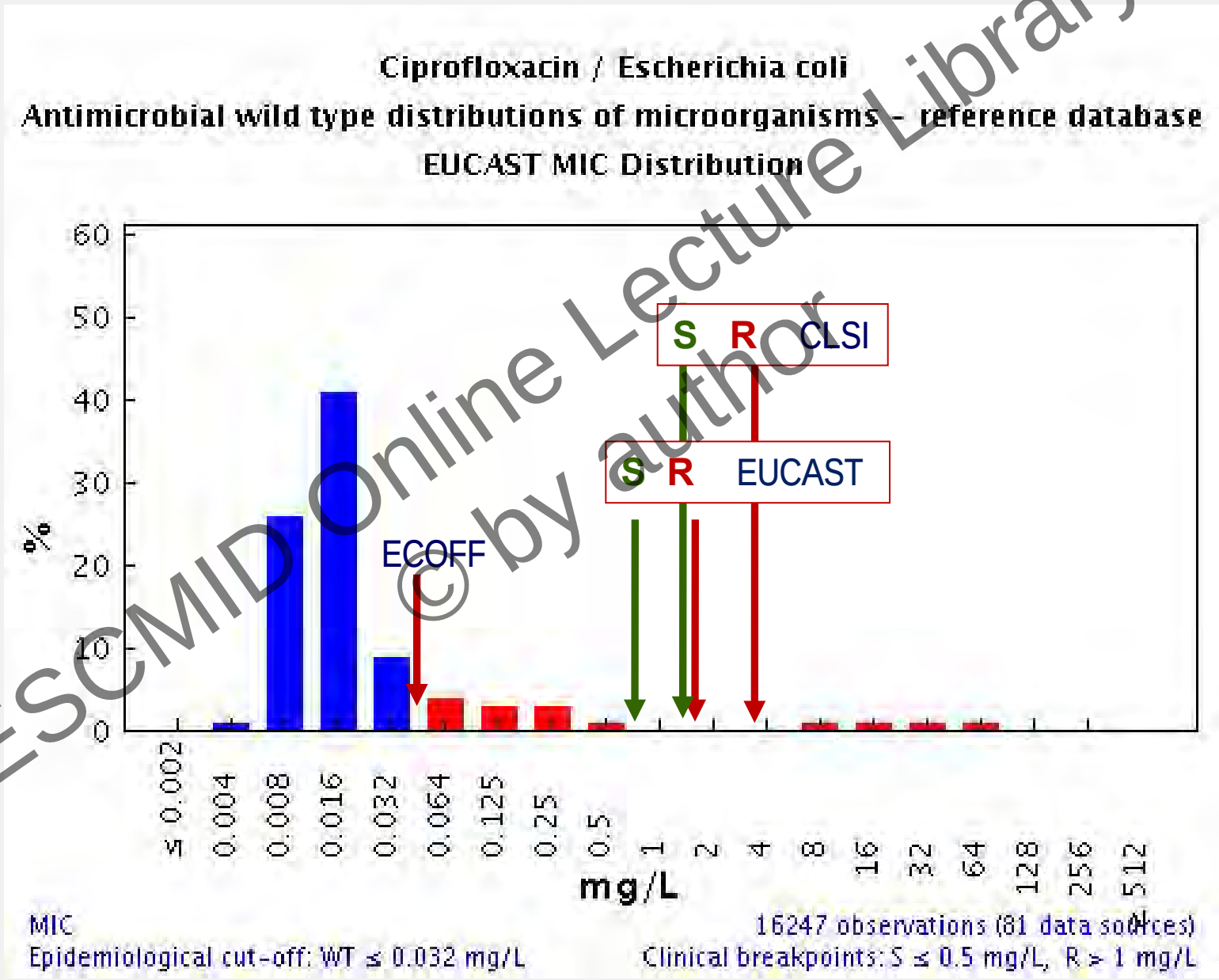
Values of parameters, such as MICs, on the basis of which bacteria can be assigned to the clinical categories "susceptible", "intermediate" and "resistant"

Susceptible bacterial strain inhibited *in vitro* by a concentration of an antimicrobial agent that is associated with a ***high likelihood of therapeutic success***

Intermediate bacterial strain inhibited *in vitro* by a concentration of an antimicrobial agent that is associated with uncertain therapeutic effect

Resistant bacterial strain inhibited *in vitro* by a concentration of an antimicrobial agent that is associated with ***a high likelihood of therapeutic failure***

Microbiological and clinical breakpoints



Clinical breakpoints: *the philosophy*

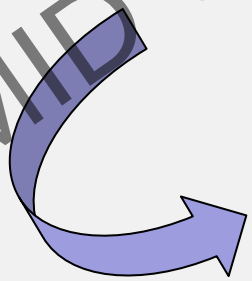
- The **aim of clinical breakpoints** is to use **MIC values …**
  - to separate strains where there is a high likelihood of treatment success from those where treatment is more likely to fail
  - to adequately **treat patients but not to detect resistance mechanisms** from a microbiological point of view
- They are ultimately derived from human clinical studies comparing outcomes with the MICs for the infecting pathogen
- If clinical breakpoints are well established no actions (expert rules) are needed beyond MIC interpretation (*interpretive reading*)

.. but this has not been the case in the past!

Interpretive reading of AST results

- During more than twenty 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!) previous clinical categorization

Courvalin P. ASM News 19921992;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

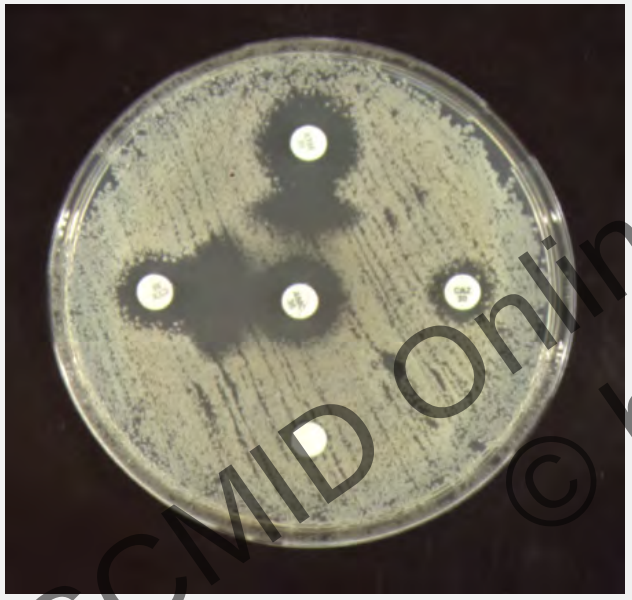


This approach was partially needed due to inadequate breakpoints!

*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 AST results

- **Interpretative reading:** ***the classical example***



ESBL positive isolate

expert rule

resistant to all
cephalosporins and aztreonam
(irrespective of MICs)

Report as tested

Q1

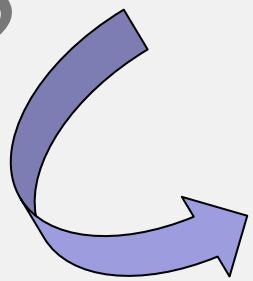
Report as tested

Q2

MIC testing *versus* detection of resistance

- Both **CLSI and EUCAST** decided in separate processes (2009-10) to modify breakpoints for **extended spectrum cephalosporins, based on**
  - harmonization process (only in EUCAST)
  - MIC distribution of isolates with and without ESBLs, pAmpC, …
  - animal infection models with isolates with and without ESBLs
  - PK/PD calculations (Monte Carlo simulation, …)
  - clinical results available at the time of setting breakpoints

MacGowan A. Clin Microbiol Infect 2008; 14 (Suppl 1):166-8
Kahlmeter G. Clin Microbiol Infect 2008; 14 (Suppl 1):169-74
Dudley et al. Clin Infect Dis 2013; 56:1301-9



NO ESBL CONFIRMATION IS NEEDED UNLESS FOR EPIDEMIOLOGICAL OR INFECTION CONTROL PURPOSES

3rd/4th gen. cephalosporin breakpoints in Enterobacteriaceae

Cefalosporins	CLSI (2010-13)			EUCAST (2009-13)	
	S	R		S	R
Cefotaxime	**≤1** (8)*	**≥4** (64)	=	**≤1**	**>2**
Ceftriaxone	**≤1** (8)	**≥4** (64)	=	**≤1**	**>2**
Ceftazidime	**≤4** (8)	**≥16** (32)		**≤1**	**>4** (8)
Cefepime	**≤8**	**≥32**		**≤1**	**>4** (8)
Aztreonam	**≤4** (8)	**≥16** (32)		**≤1**	**>4** (8)

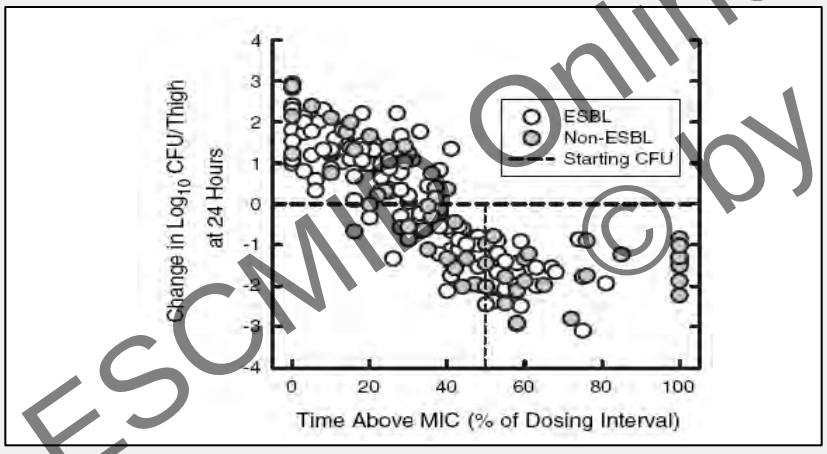
*2009

This approach was extended to breakpoints for carbapenems in Enterobacteriaceae

3rd/4th gen. cephalosporin breakpoints in Enterobacteriaceae

- CLSI and EUCAST "new" breakpoints were supported by PK/PD data, animal models and clinical outcome data

Enterobacteriaciae in a murine thigh infection model: Cephalosporin % T>MIC and microbiological efficacy



Andes & Craig. CMI 2005; 11(Suppl 6):10-7

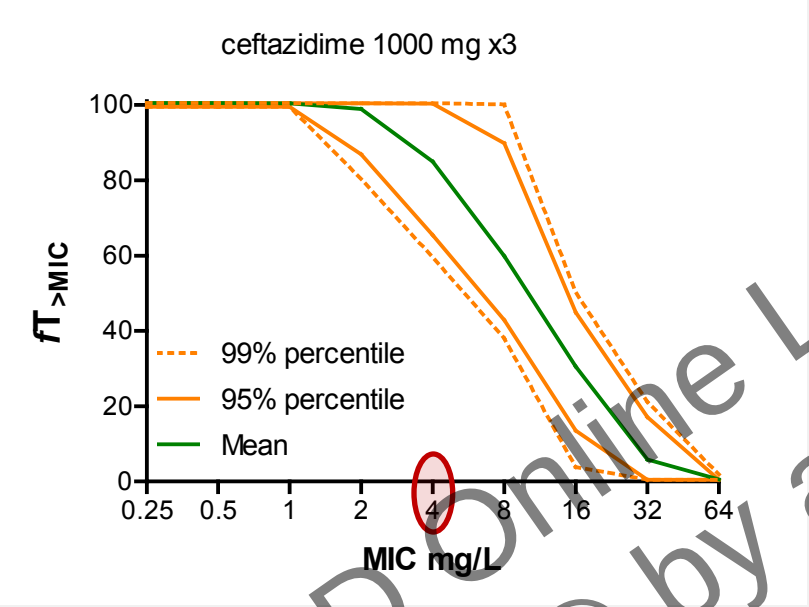
Monte-Carlo simulations and target attainment rate (TAR) for intravenous ceftriaxone 2 g every 24 h

	TAR at T>MIC rates of				
MIC (mg/L)	20%	30%	40%	50%	60%
0.25	100	100	97	55	6
0.5	100	100	72	9	0
1.0 S	100	90	16	0	0
2.0	99	29	1.0	0	0
4.0 R	54	0	0	0	0

MacGowan. CMI 2008; 14(Suppl 1):166-8

3rd/4th gen. cephalosporin breakpoints in Enterobacteriaceae

- Probability of target attainment (PTA) for **ceftazidime**



- 2 log drop in viable Gram-negatives requires 50% *f*T>MIC

dose	PTA achieved for MIC of	criteria
1 g x 3 IV	4 mg/L	S
2 g x 3 IV	8 mg/L	R

Ceftazidime rationale document, 2010

- EUCAST decreased ceftazidime and cefepime breakpoints due to evidence on clinical and MIC correlations:

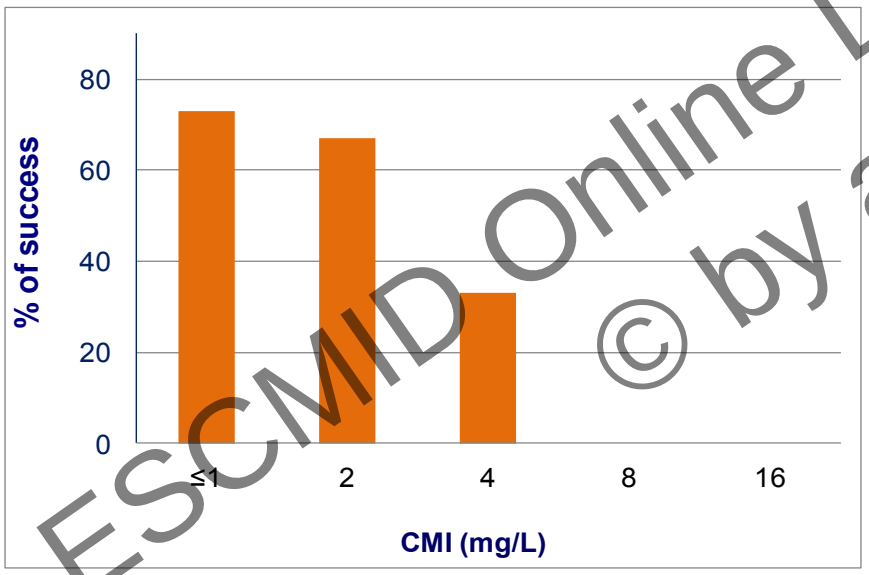
≤1 mg/L	no difference ESBL and non-ESBL producers
2-4 mg/L	variable successful outcomes
>4 mg/L	poor outcomes

Paterson et al. JCM 2001; 3; 9:2206-12; Andes & Craig. CMI 2005; 11 (Suppl. 6):10-7
Bin et al. DMID 2006; 56:351-7; Bhat et al. AAC 2007; 51:4390-5

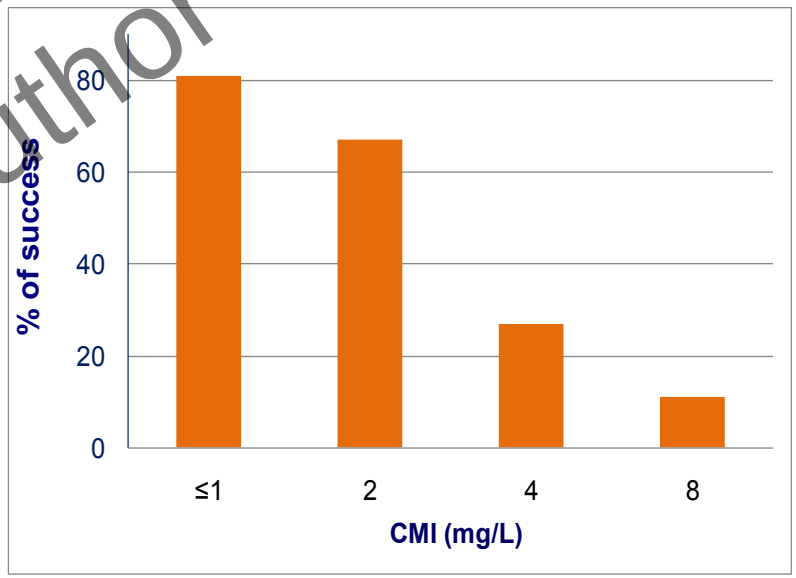
3rd/4th gen. cephalosporin breakpoints in Enterobacteriaceae

- **Clinical data for ESBL** producers indicates that outcome success decrease when 3rd gen ceph. MICs are ≥2 mg/L

Clinical outcome in patients with ESBL-producing *Klebsiella* spp. or *E. coli* bacteraemia and treated with 3rd gen. cephalosporin monotherapy



Paterson et al. JCM 2001; 39:2206-12



Andes & Craig. CMI 2005; 11 (Suppl. 6):10-7

What has been the impact of "report as tested"?

- **"Theoretical" calculations** (mainly on ESBLs) calculated microbiological impact on % of S-R isolates using CLSI or EUCAST breakpoints

  Howser et al. AAC 2010; 54:3043-6; Hoban et al. AAC 2010; 54:3031-4
  Howser et al. EJCMID 2011; 30:173-9; Rodriguez-Baño et al. CMI 2012; 18:894-900

- **Critical voices** alerting on **negative consequence** for no further detection and reporting of ESBLs and carbapenemases

  Livermore et al. JAC 2012; 67:1569-77: Nordmann, Poirel. JAC 2013; 487-9

- **Analysis and meta-analysis** of different **impact on mortality** for ESBL and carbapenemase producing organisms

  Bonten et al. JAC 2012; 67:1311-20; Falagas et al. AAC 2012; 4214-22

- **New publications on clinical outcomes**

  - carbapenemase producing organisms treated with carbapenems

  Quereshi et all. AAC 2011; 56: 2108-13; Tzouvelekis et al.CMR 2012; 25: 682-707
  Tumbarello et al. CID 2012; 55: 943-50

What has been the impact of "report as tested"?

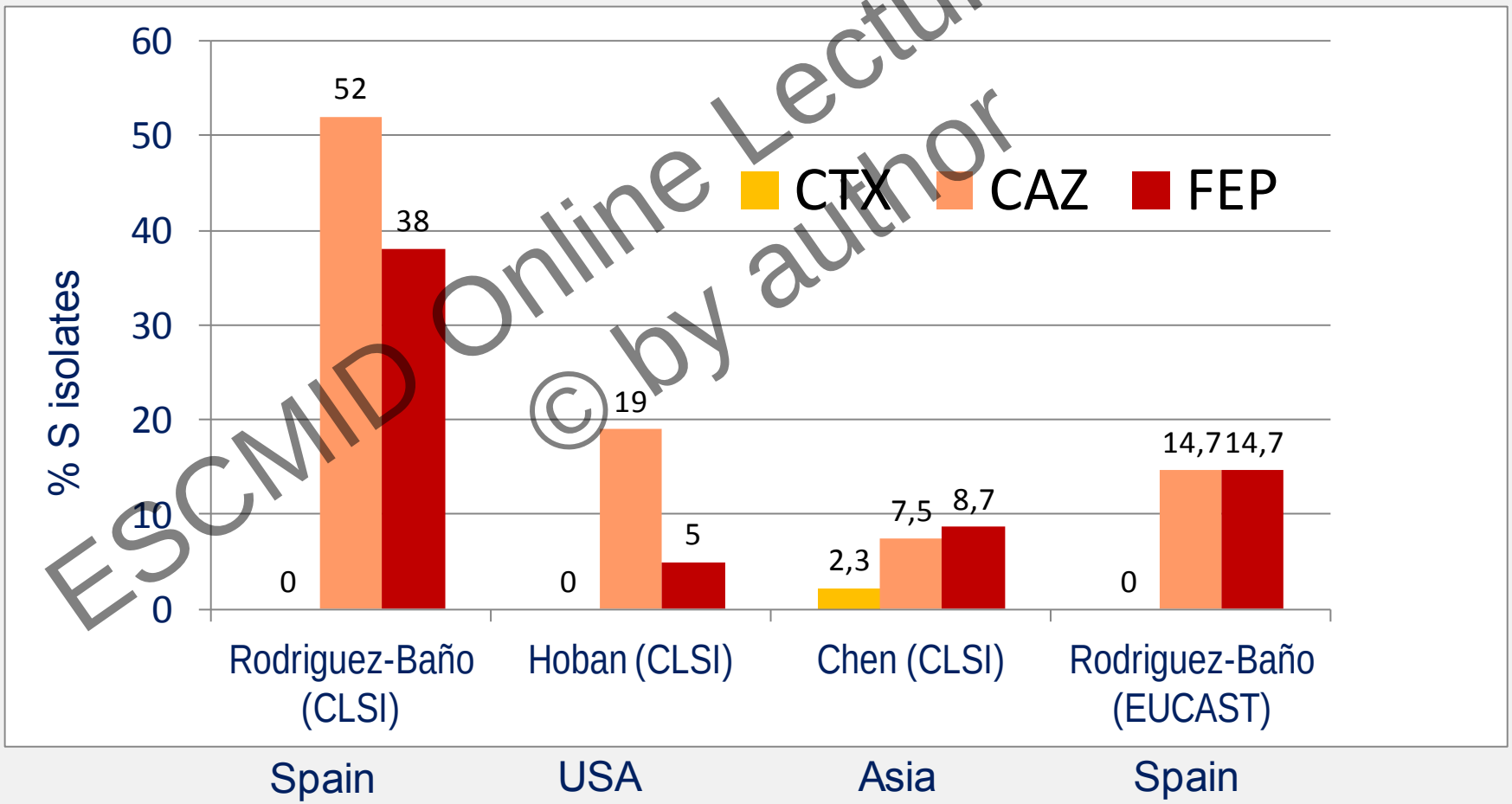
- "**Theoretical" calculations** (mainly on ESBLs) calculated microbiological impact on % of S-R isolates using CLSI and EUCAST breakpoints

Howser et al. AAC 2010; 54:3043-6; Hoban et al. AAC 2010; 54:3031-4
Howser et al. EJCMID 2011; 30:173-9; Rodriguez-Baño et al. CMI 2012; 18:894-900

- major impact when using CLSI rather than of EUCAST
- greater impact for ceftazidime and cefepime than for cefotaxime
- geographic dependent impact (different ESBL epidemiology)
- origin (hospital or community-onset) dependent impact

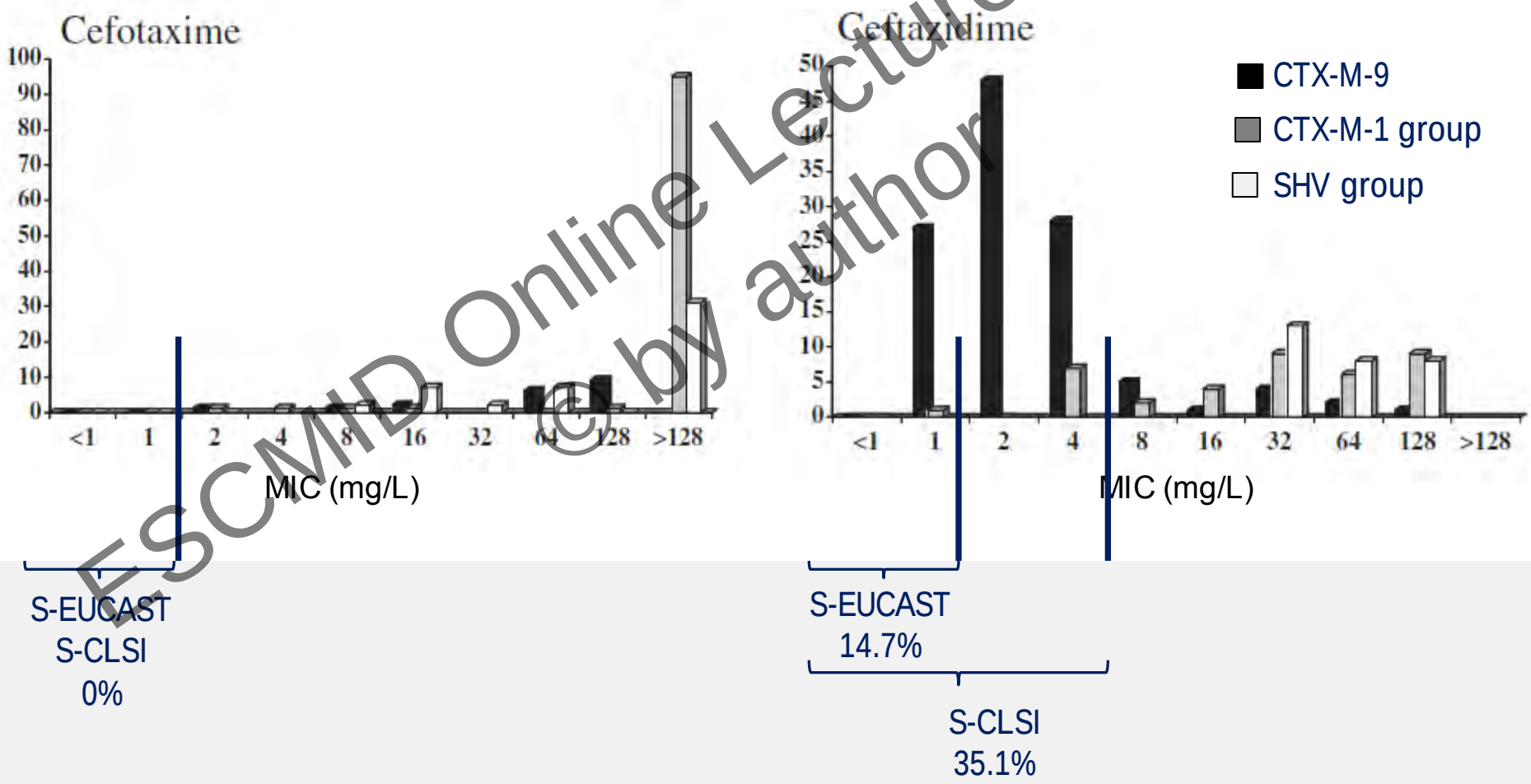
What has been the impact of these "new" breakpoints?

- % of ESBL-*E. coli* isolates susceptible to 3rd / 4th gen. ceph. when using CLSI and EUCAST breakpoints in different studies



What has been the impact of "report as tested"?

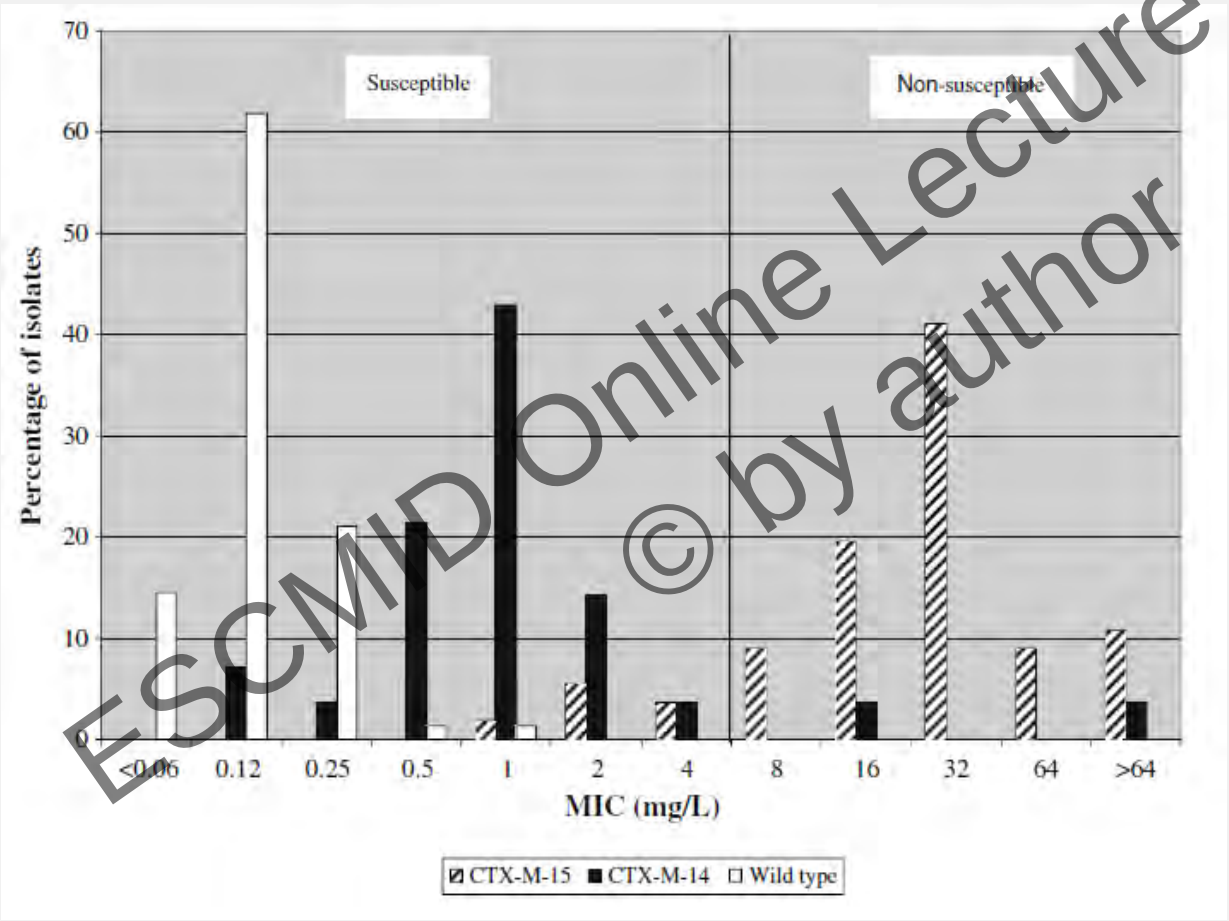
- Impact of CLSI & EUCAST breakpoints in ESBL-*E. coli* blood isolates



Rodriguez-Baño et al. Clin Microbiol Infect 2012; 18:894-900

What has been the impact of "report as tested"?

- Ceftazidime susceptibility of prevalent CTX-M producing *E. coli*



	% of CAZ-S isolates	
	CLSI	EUCAST
CTX-M-14	93	74
CTX-M-15	11	2

Willamson et al. EJCMID 2012; 31:821-4

Critical voices …

J Antimicrob Chemother 2012; **67**: 1569–1577
doi:10.1093/jac/dks088 Advance Access publication 29 March 2012

Journal of Antimicrobial Chemotherapy

Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly?

David M. Livermore[1,2*], Jenny M. Andrews[3], Peter M. Hawkey[4], Pak-Leung Ho[5], Yoram Keness[6], Yohei Doi[7], David Paterson[8] and Neil Woodford[2]

1.- Similar number of **clinical cases** on record where cephalosporins and carbapenems have proved effective and ineffective against infections due to low-MIC ESBL and carbapenemase producers, respectively

2.- Routine **susceptibility testing** is less precise than in research: ESBL and carbapenemase producers with MICs of 1–8 mg/L will oscillate between susceptibility categories according to who tests them and how.

3.- Although breakpoint committees advocate ESBL and carbapenemase detection for epidemiological purposes, some **laboratories will abandon seeking these enzymes** for treatment purposes, leading to a loss of critical infection control information

Critical voices …

J Antimicrob Chemother 2013; **68**: 487–489
doi:10.1093/jac/dks426 Advance Access publication 26 October 2012

Journal of Antimicrobial Chemotherapy

Strategies for identification of carbapenemase-producing Enterobacteriaceae

Patrice Nordmann* and Laurent Poirel

1.- Susceptibility to carbapenems is observed for several carbapenemase producers

2.- There is a **paucity** of **clinical successes of carbapenem-containing regimens** for treating infections due to carbapenemase producers that are susceptible to carbapenems *in vitro*.

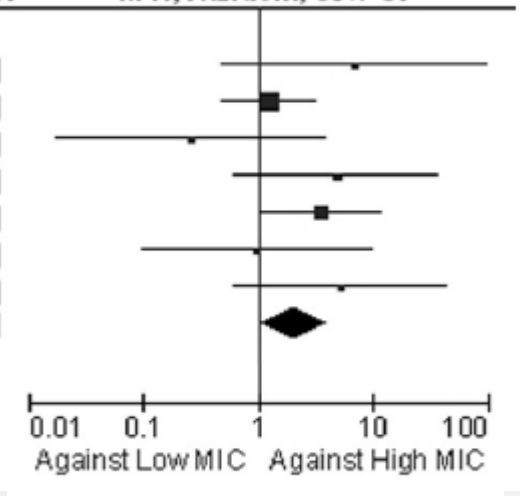
Detection will be useful for treating patients and for preventing nosocomial outbreaks of carbapenemase producers (and therefore MDR isolates), whatever the carbapenem resistance level is.

Impact of antibiotic MIC on infection outcome in patients with susceptible Gram-negative bacteria

- a higher all cause-mortality was observed for patients infected with strains with high MICs (Risk ratio 2.03; 95% CI, 1.05-3.92)

Study or Subgroup	High MICs Events	Total	Low MICs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Enterobacteriaceae						
Anthony 2008	2	2	0	3	6.0%	6.67 [0.47, 93.58]
Goethaert 2006 C	2	3	7	13	37.5%	1.24 [0.48, 3.19]
Goethaert 2006 CA	0	4	6	16	5.7%	0.26 [0.02, 3.88]
Paterson 2001	3	7	1	11	9.6%	4.71 [0.60, 36.81]
Qureshi 2011	1	1	3	15	24.6%	3.43 [1.01, 11.66]
Rodriguez-Bano 2012 A/C	2	25	1	12	7.8%	0.96 [0.10, 9.57]
Rodriguez-Bano 2012 P/T	3	13	1	22	8.8%	5.08 [0.59, 43.88]
Subtotal (95% CI)		**55**		**92**	**100.0%**	**2.03 [1.05, 3.92]**
Total events	13		19			

Heterogeneity: Tau² = 0.07; Chi² = 6.52, df = 6 (P = 0.37); I² = 8%
Test for overall effect: Z = 2.11 (P = 0.03)

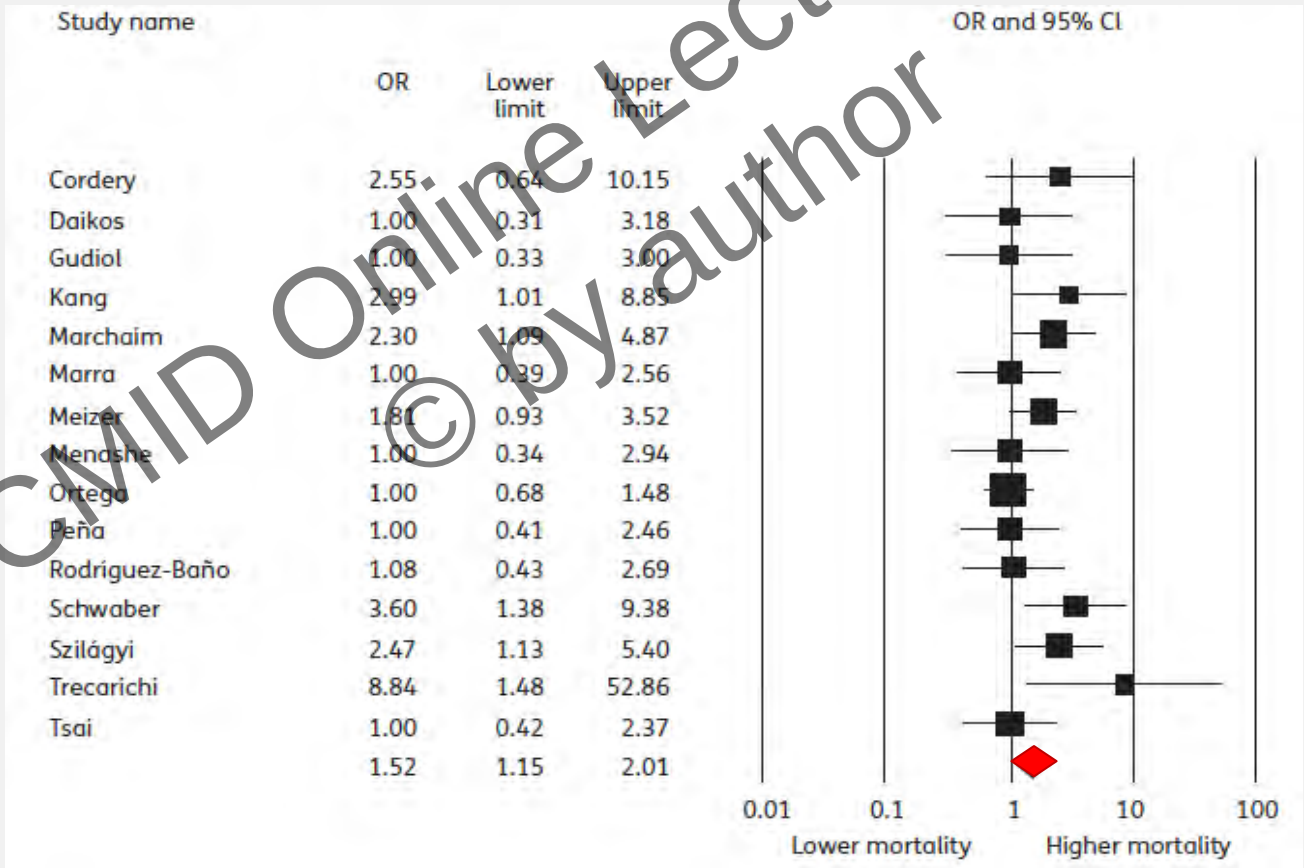


- differences in mortality were not statistically significant in patients infected with ESBLs (Risk ratio 1.89; 95% CI, 0.94-3.92)

Falagas et al. Antimicrob Agents Chemother 2012; 56 4214-22

Bacteraemia caused by ESBL-producing Enterobacteriaceae

- ESBL production in Enterobacteriaceae causing bacteremia is associated with higher mortality (OR 2.35; 95% CI, 1.90-2.91), but is reduced after adjustment for inadequate empirical therapy



Rottier et al. J Antimicrob Chemother 2012; 67:1311-20

Carbapenem breakpoints in Enterobacteriaceae

	FDA	CLSI (2010)		EUCAST (EMA) (2010)		
	S	S	R	S	R	ECOFF
Imipenem	**≤4**	**≤1** (4)*	**≥4** (16)	**≤2**	**>8**	**≤0.5; ≤1****
Meropenem	**≤4**	**≤1** (4)	**≥4** (16)	**≤2**	**>8**	**≤0.125**
Ertapenem	**≤2**	**≤0.25** (2)	**≥1** (8)	**≤0.5**	**>1**	**≤0.06**
Doripenem	**≤0.5**	**≤1** (ND)	**≥4** (ND)	**≤1**	**>4**	**≤0.12**

*2009; ***E. coli* y *K. pneumoniae*;** ND: not defined

EUCAST breakpoint are higher than those of CLSI !

What is the clinical impact?

REVIEW 10.1111/j.1469-0691.2012.03823.x

Interventional strategies and current clinical experience with carbapenemase-producing Gram-negative bacteria

M. Akova[1], G. L. Daikos[2], L. Tzouvelekis[3] and Y. Carmeli[4]

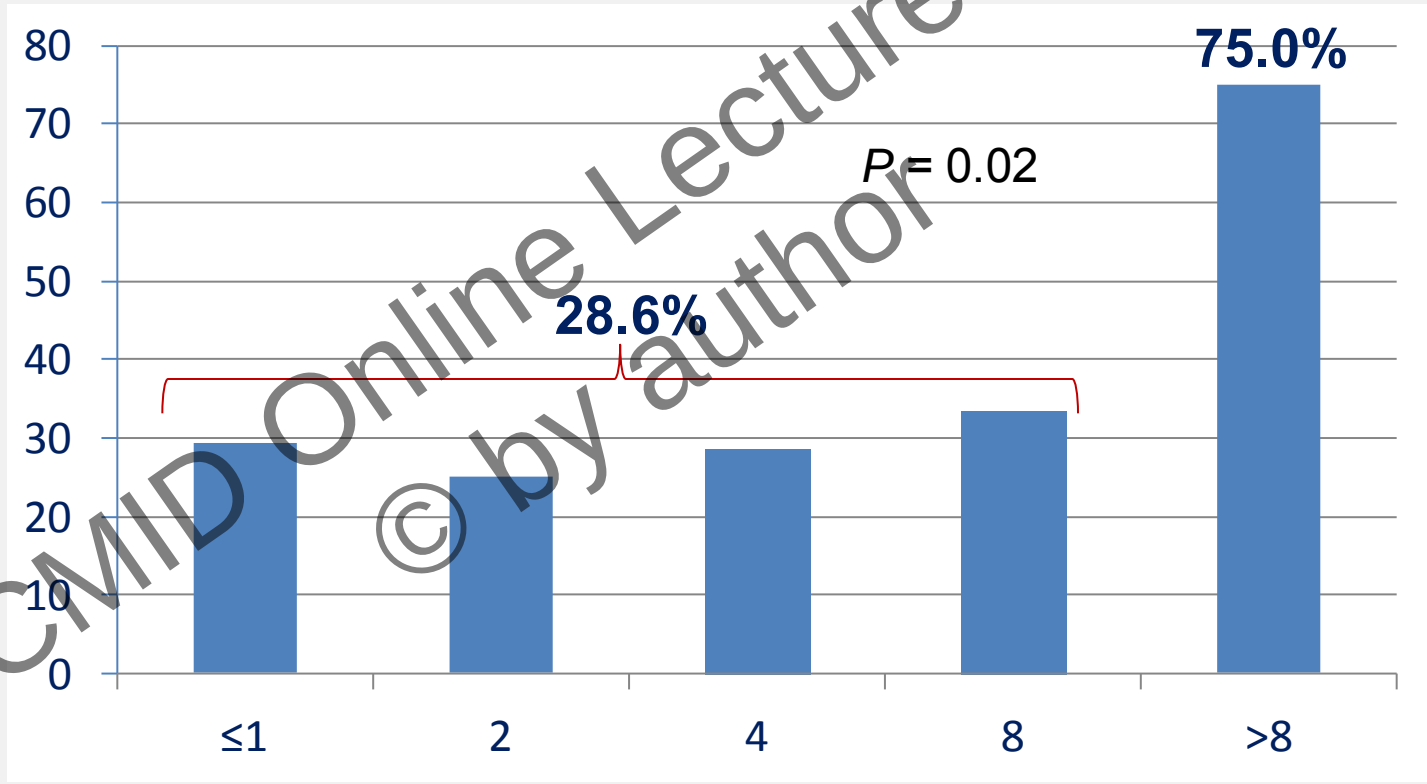
1) *Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey,* 2) *First Department of Propaedeutic Medicine, University of Athens, Athens, Greece,* 3) *Laboratory of Bacteriology, Hellenic Pasteur Institute, and Department of Microbiology, Medical School, University of Athens, Athens, Greece and* 4) *Division of Epidemiology, Tel-Aviv Sourasky Medical Centre, Tel-Aviv, Israel*

Efficacy of antimicrobial regimens used to treat infections caused by carbapenemase-producing *Klebsiella pneumoniae*

Antibiotic regimen	No. of patients (%)	Outcome success (%)	Failure (%)
Monotherapy			
Colistin	64 (24.2)	35 (54.7)	29 (45.3)
Tigecycline	8 (4.7)	5 (62.5)	3 (37.5)
Aminoglycoside	16 (6.8)	12 (75.0)	4 (25.0)
Carbapenem	23 (9.8)	18 (78.3)	5 (21.7)
Total	111 (47.5)	70 (63.1)	41 (36.9)
Combination therapy			
Two or more active drugs (carbapenem not included)	52 (22.2)	38 (73.1)	14 (26.9)
Two or more active drugs (carbapenem included)	30 (12.8)	28 (93.3)	2 (6,7)
Total	82 (35.0)	66 (80.5)	16 (19.5)
'Inappropriate' therapy	41 (17.5)	23 (56.1)	18 (43.9)
Total	234 (100)	159 (67.9)	75 (32.1)

Carbapenemase producing Enterobacteriaceae

Carbapenem monotherapy: 50 patients from 15 studies

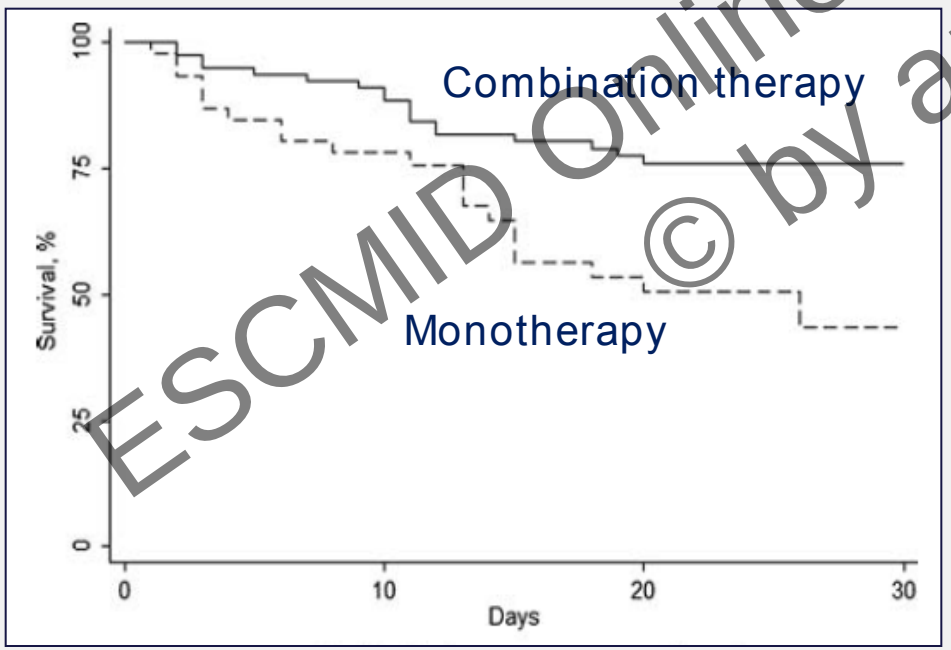


Tzouvelekis et al.Clin Microbiol Rev 2012; 25: 682-707

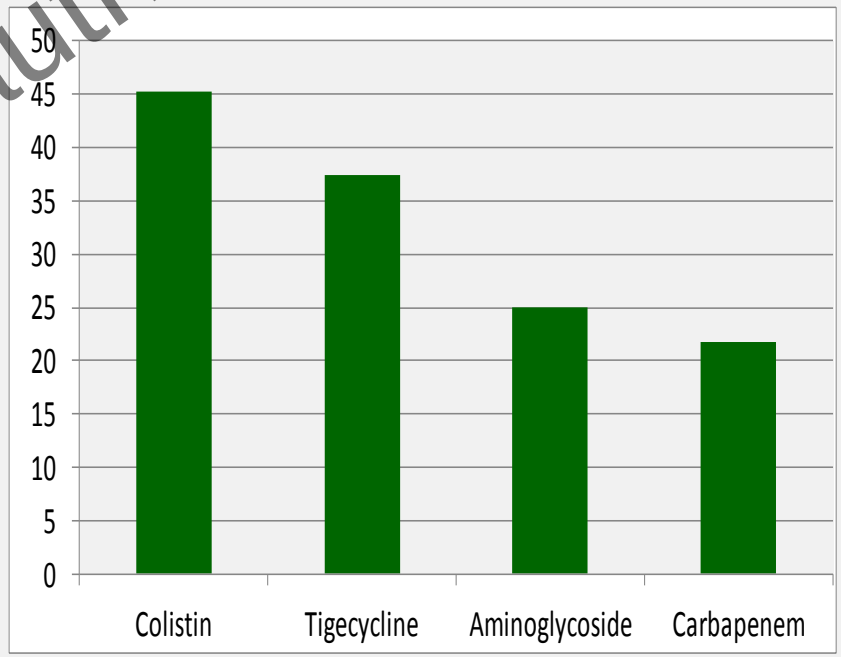
Mortality in bloodstream infections and KPC-*K. pneumoniae*

- Higher 30-day mortality rate in patients treated with monotherapy (54.3%) that those with combination (34.1%) therapy (*P*=0.02)
- Significant decreased of mortality in patients treated with combination therapy including meropenem

- Kaplan-Meier curves (survival)



- Mortality (%): monotherapy

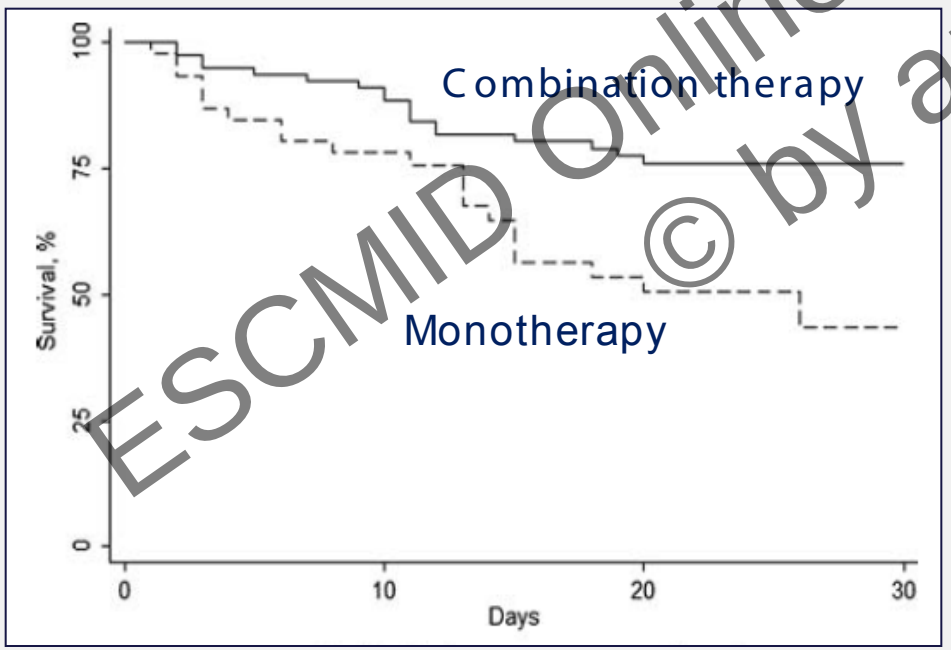


Tumbarello et al. Clin Infect Dis 2012; 55: 943-50

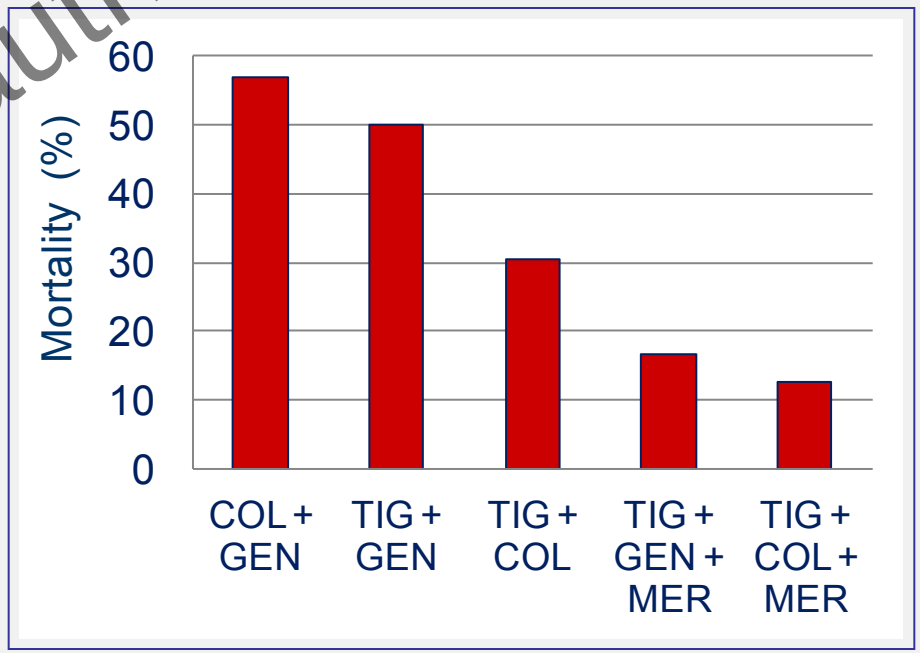
Mortality in bloodstream infections and KPC-*K. pneumoniae*

- Higher 30-day mortality rate in patients treated with monotherapy (54.3%) that those with combination (34.1%) therapy (*P*=0.02)
- Significant decreased of mortality in patients treated with combination therapy including meropenem

- Kaplan-Meier curves (survival)



- Mortality (%): combination therapy

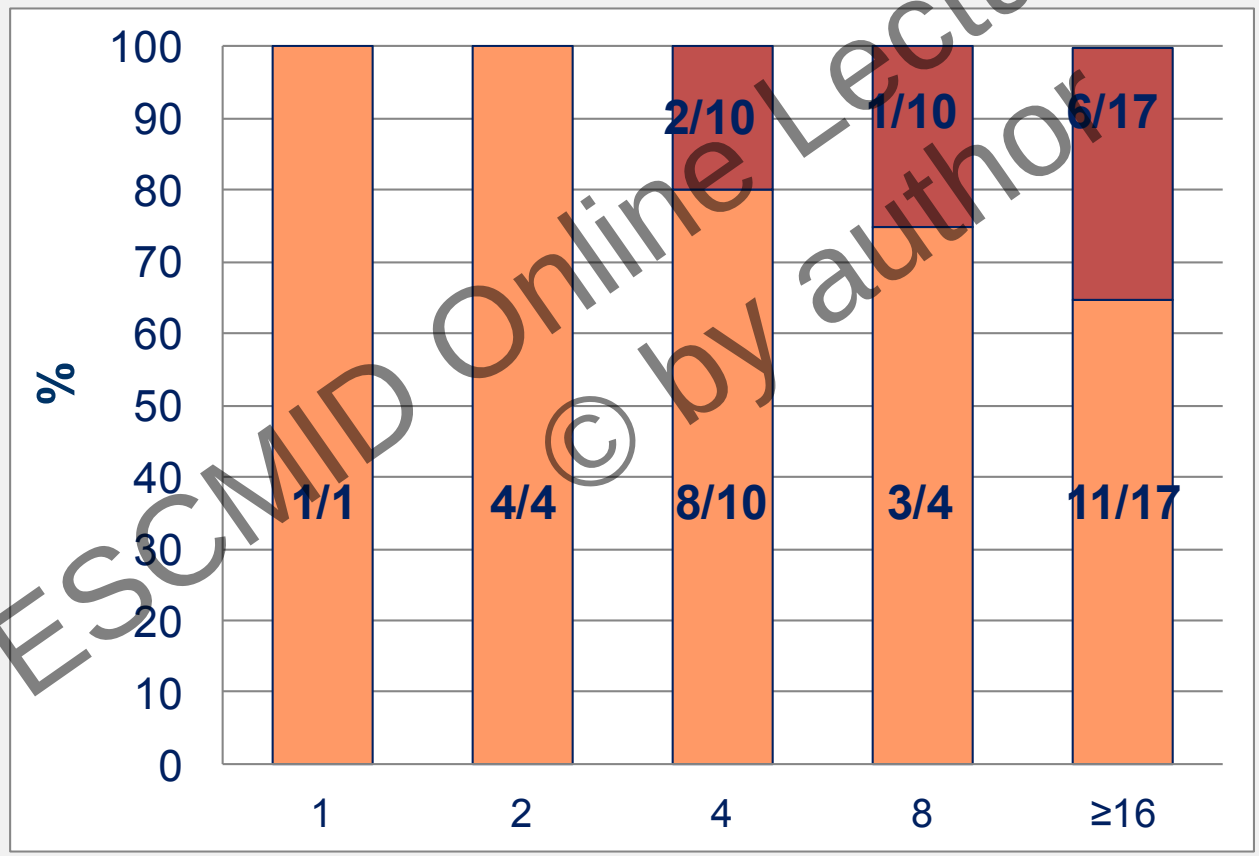


Tumbarello et al. Clin Infect Dis 2012; 55: 943-50

What is the impact of carbapenem MIC values?

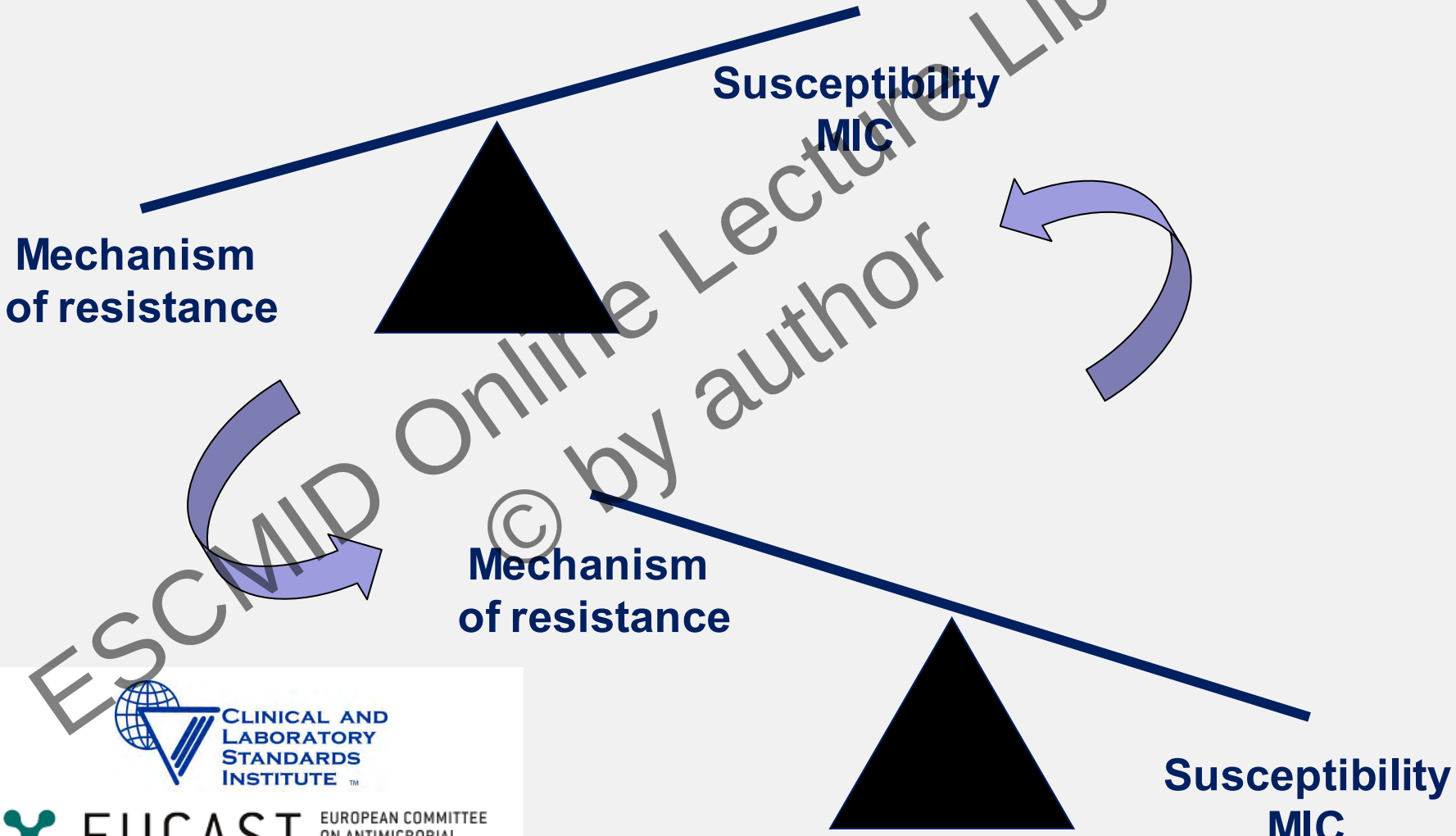
Mortality in bloodstream infections and KPC-*K. pneumoniae*

- 30-day mortality rate in patients treated with combination therapy including meropenem stratified by meropenem MIC values



Tumbarello et al. Clin Infect Dis 2012; 55: 943-50

MIC testing *versus* detection of resistance



CLINICAL AND LABORATORY STANDARDS INSTITUTE ™

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

MIC testing *versus* detection of resistance

Some additional issue

- Hetero-resistance, particularly in carbapenemase producers
- Different expression of ESBL and carbapenemase resistance genes
- Presence of ESBL and carbapenemase resistance genes in isolates within the wild type population (*silent expression*)
- Still waiting additional MIC correlations with clinical outcomes

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

REPORT AS TESTED

ESCMID
EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

SaludMadrid

Dr. Rafael Cantón

Hospital Universitario Ramón y Cajal
SERVICIO DE MICROBIOLOGÍA Y PARASITOLOGÍA

instituto ramón y cajal de investigación sanitaria irycis

Departamento de Microbiología II
Universidad Complutense. Madrid