ANTIBIOGRAMMA 2010

Criteri interpretativi per l'antibiogramma dei batteri Gram-positivi

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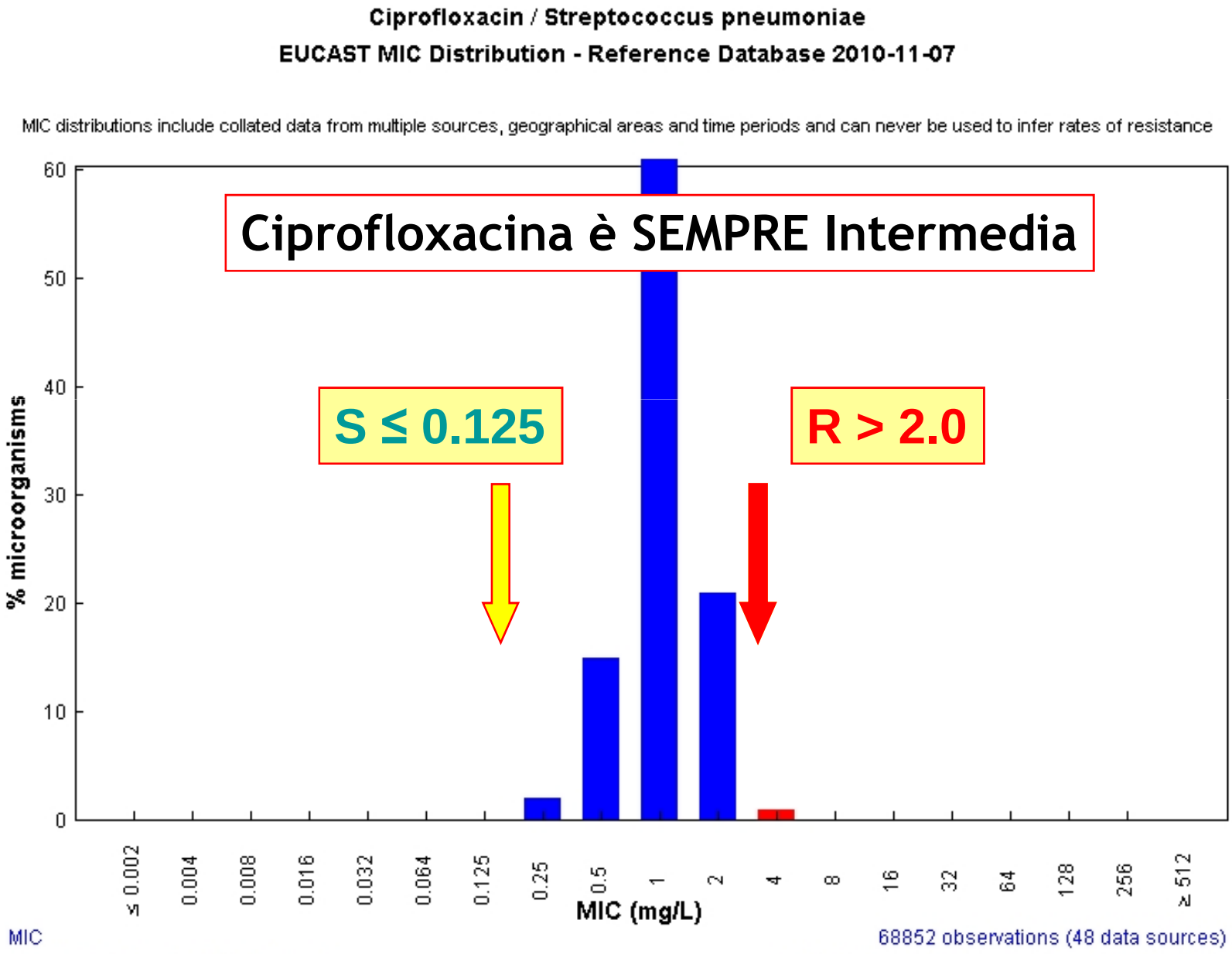
Streptococcus pneumoniae

Breakpoint EUCAST e CLSI

Antibiotico	EUCAST	CLSI
	S ≤ / R > (mg/L)	S ≤ / R > (mg/L)
Penicillina (polmonite)	2 (dose) / 2	2 / 4
Penicillina (meningite)	0.06 / 0.06	0.06 / 0.06
Oxacillina (screening)	- / -	- / -
Cefotaxime (polmonite)	0.5 / 2	1 / 2
Cefotaxime (meningite)	0.5 / 2	0.5 / 1
Ceftriaxone (polmonite)	0.5 / 2	1 / 2
Ceftriaxone (meningite)	0.5 / 2	0.5 / 1
Ciprofloxacina	0.12 / 2	- / -
Eritromicina	0.25 / 0.5	0.25 / 0.5
Clindamicina	0.5 / 0.5	0.25 / 0.5

Ciprofloxacina e *Streptococcus pneumoniae*



EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Pneumococchi

Regole interpretative per i Fluorochinoloni

Rule no.	Organism	Agent	Rule	Scientific basis	Evidence grade
13.4	*Streptococcus pneumoniae*	Ofloxacin Ciprofloxacin	If resistant to ofloxacin or ciprofloxacin, but not to moxifloxacin or levofloxacin, report warning: acquisition of a first mutation may lead to resistance development under therapy with other quinolones.	Acquisition of at least one target mutation in e.g. *parC (parE)*. First step mutations are better detected using norfloxacin.	C
13.5	*Streptococcus pneumoniae*	Levofloxacin Moxifloxacin	If resistant to levofloxacin or moxifloxacin, report as resistant to all fluoroquinolones.	Acquisition of combined mutations in e.g. *parC* and *gyrA* leads to complete or partial	B

Urban C et al *J Infect Dis*, 2001; 184:794-798

Varon E et al *Antimicrob Agents Chemother*, 2006; 50:572-579

Montanari MP et al *Microb Drug Resist*, 2004; 10:209-217

Davidson R et al *N Engl J Med*, 2002; 346:747-50

Perez-Trallero E et al *Clin Infect Dis*, 2005; 41:560-564

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Pneumococchi

Regole interpretative per i Fluorochinoloni

Occorre saggiare:	
Levofloxacina o Moxifloxacina	Se R → Refertare resistenti TUTTI i fluorochinoloni
Grado di evidenza B	Evidenze deboli e basate solo su pochi casi clinici o su modelli sperimentali. Si suppone che refertare il risultato come Sensibile possa condurre a fallimenti terapeutici.

Urban C et al *J Infect Dis*, 2001; 184:794-798

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Pneumococchi

Regole interpretative per i Fluorochinoloni

Rule no.					Evidence
13.4	Occorre saggiare:				
	Ofloxacina o Ciprofloxacina	Se R → nota di cautela *"Rischio di sviluppo di resistenza in corso di terapia con fluorochinoloni"*			
13.5	Grado di evidenza C	Non ci sono evidenze cliniche ma i dati microbiologici suggeriscono che l'uso clinico in questi casi dovrebbe essere scoraggiato.			

Urban C et al *J Infect Dis*, 2001; 184:794-798

Varon E et al *Antimicrob Agents Chemother*, 2006; 50:572-579

Montanari MP et al *Microb Drug Resist*, 2004; 10:209-217

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

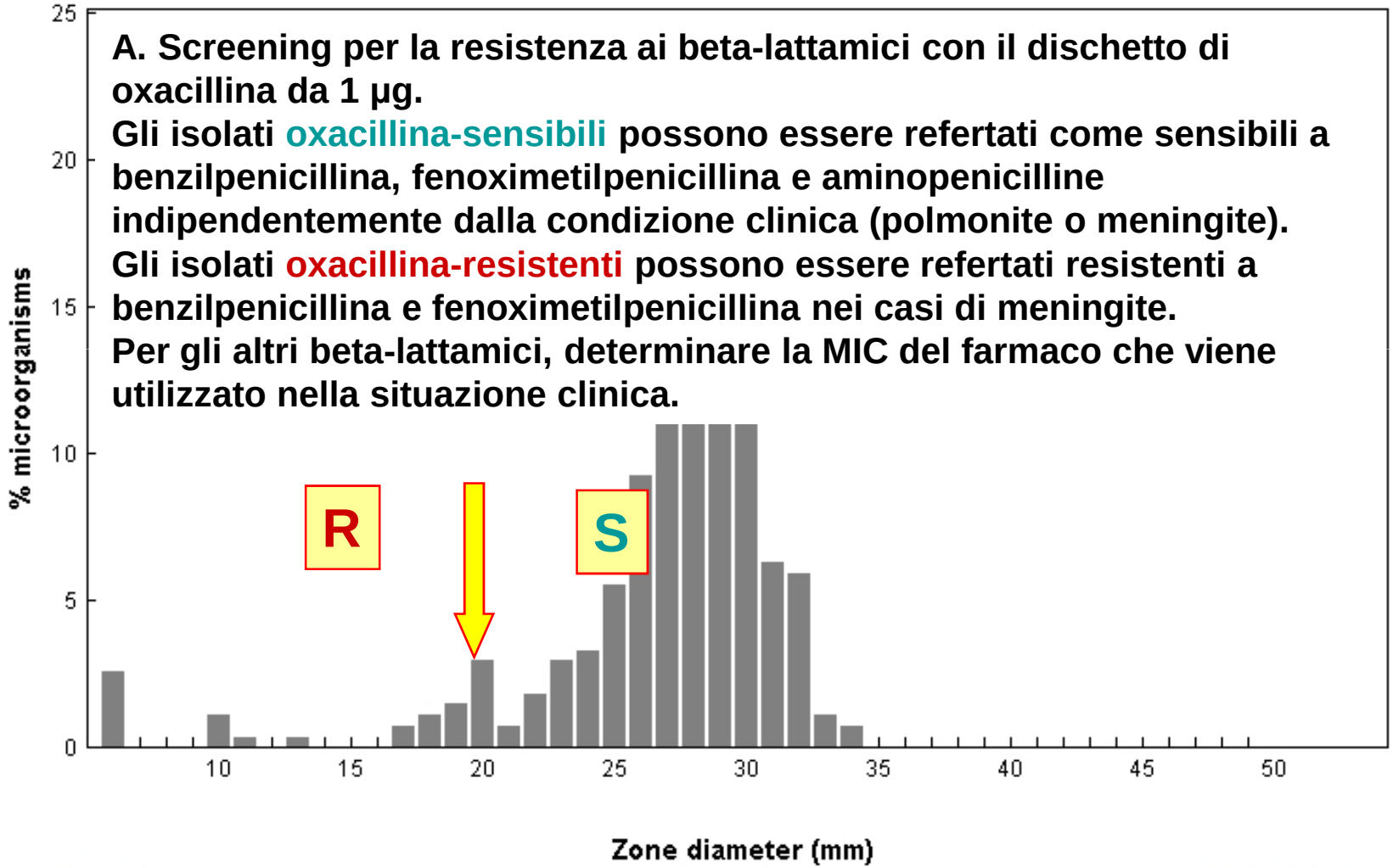
Oxacillin / Streptococcus pneumoniae

EUCAST zone diameter distribution - Reference database 2010-11-01

EUCAST disk diffusion method

Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

A. Screening per la resistenza ai beta-lattamici con il dischetto di oxacillina da 1 µg.
Gli isolati oxacillina-sensibili possono essere refertati come sensibili a benzilpenicillina, fenoximetilpenicillina e aminopenicilline indipendentemente dalla condizione clinica (polmonite o meningite).
Gli isolati oxacillina-resistenti possono essere refertati resistenti a benzilpenicillina e fenoximetilpenicillina nei casi di meningite.
Per gli altri beta-lattamici, determinare la MIC del farmaco che viene utilizzato nella situazione clinica.



Disk content: 1
Epidemiological cut-off: -

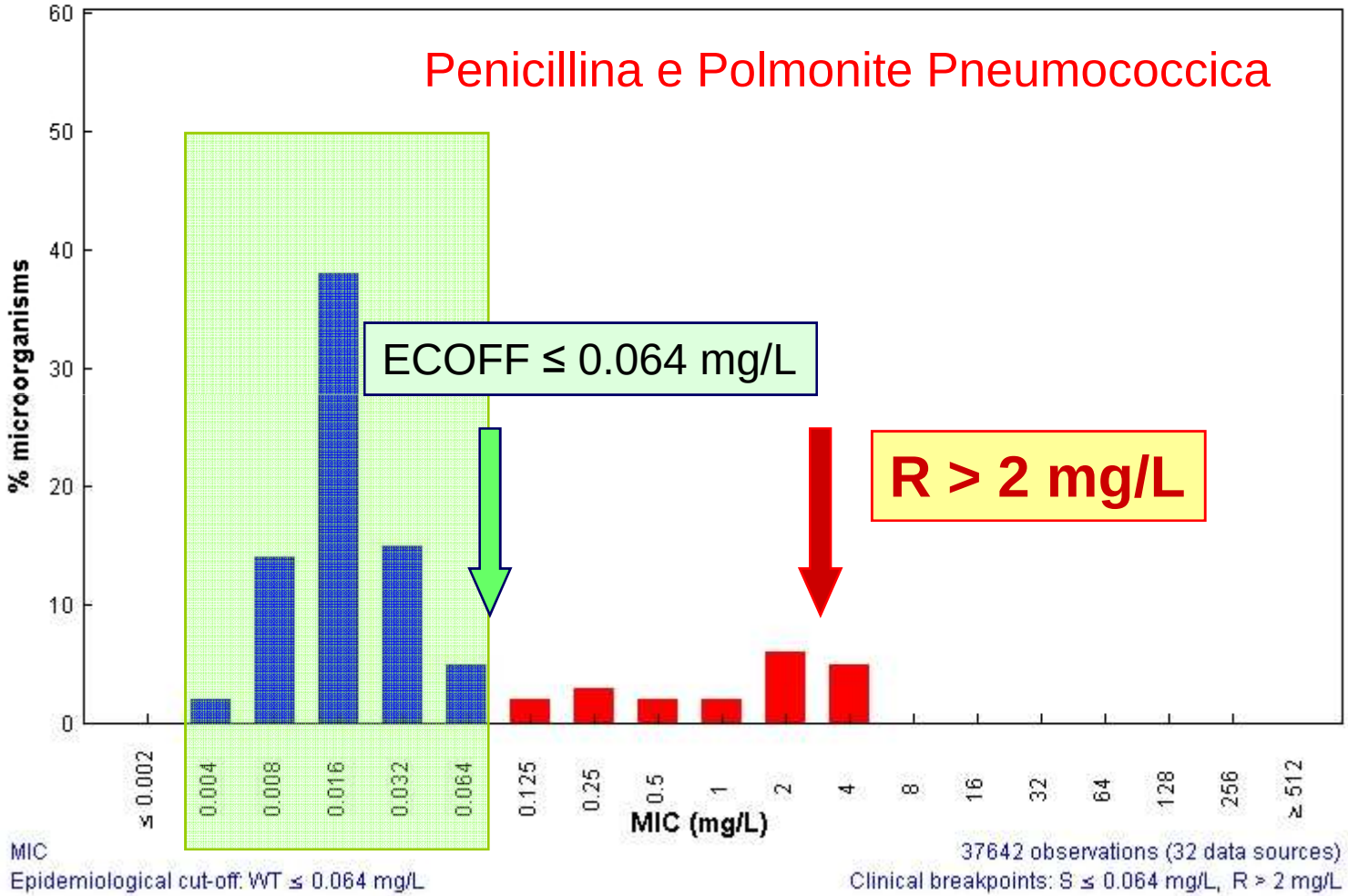
270 observations
Clinical breakpoints: S ≥ 18 mm, R < 18 mm

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Benzylpenicillin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database 2010-11-01

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

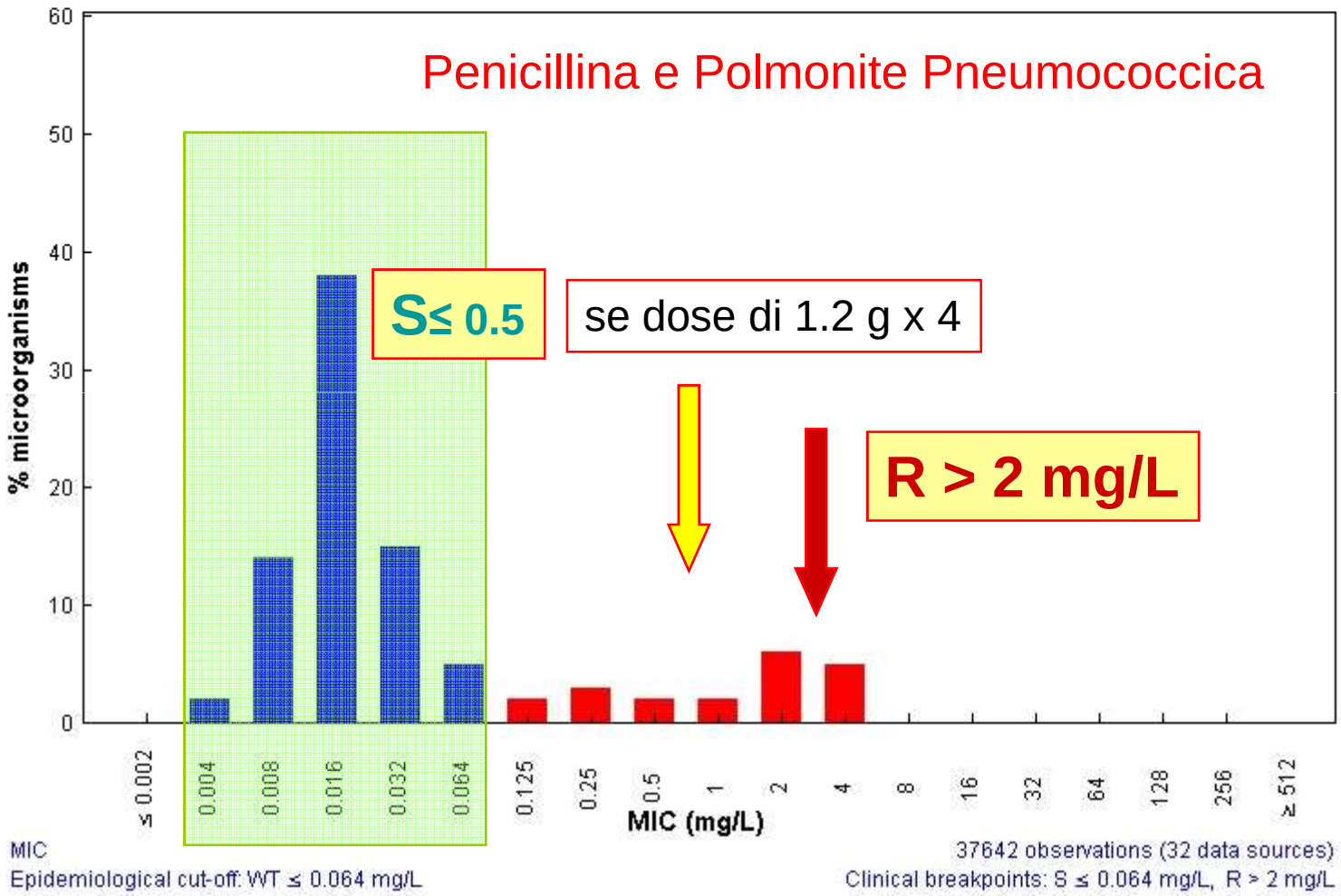


EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Benzylpenicillin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database 2010-11-01

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

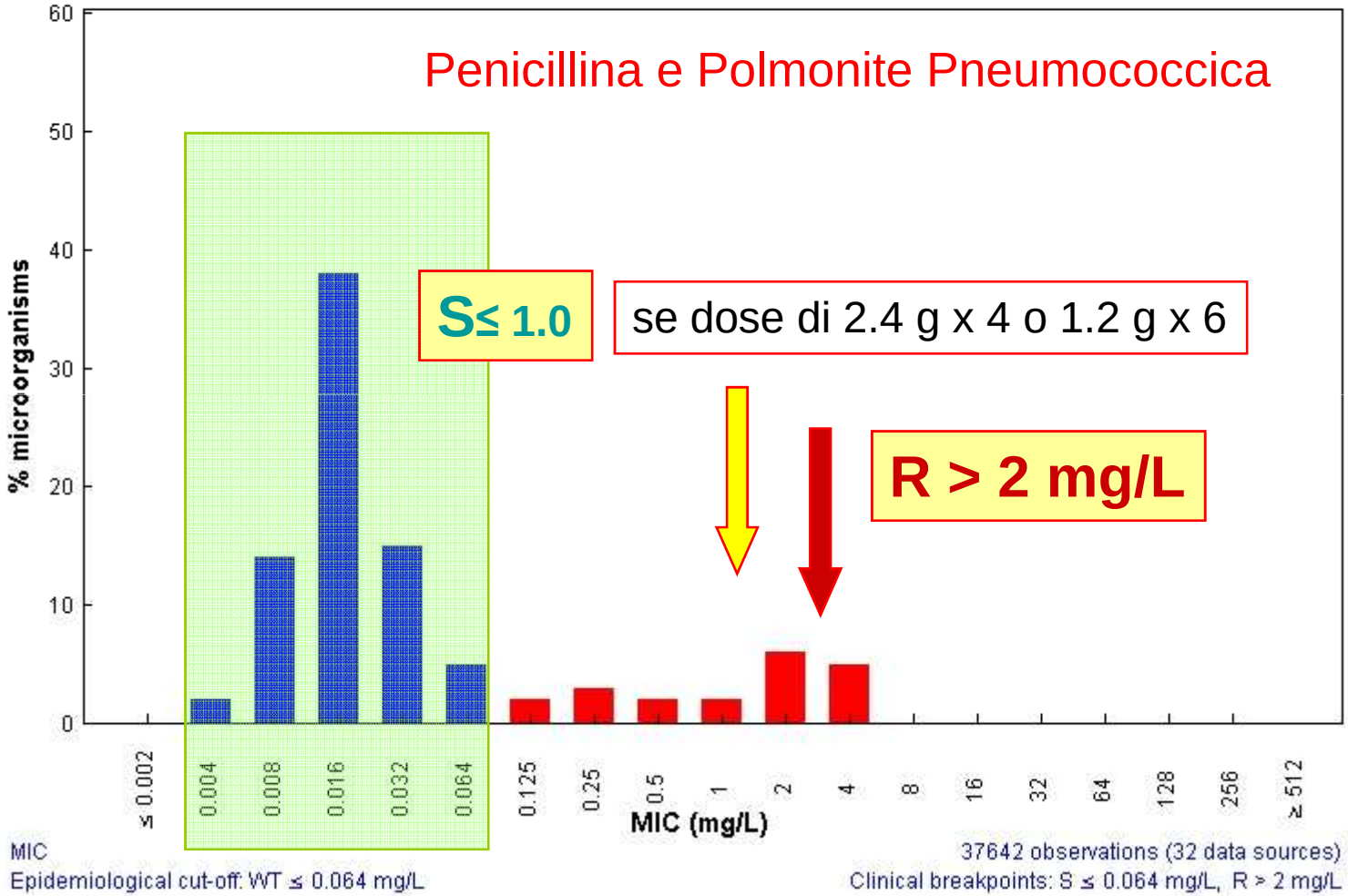


EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Benzylpenicillin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database 2010-11-01

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

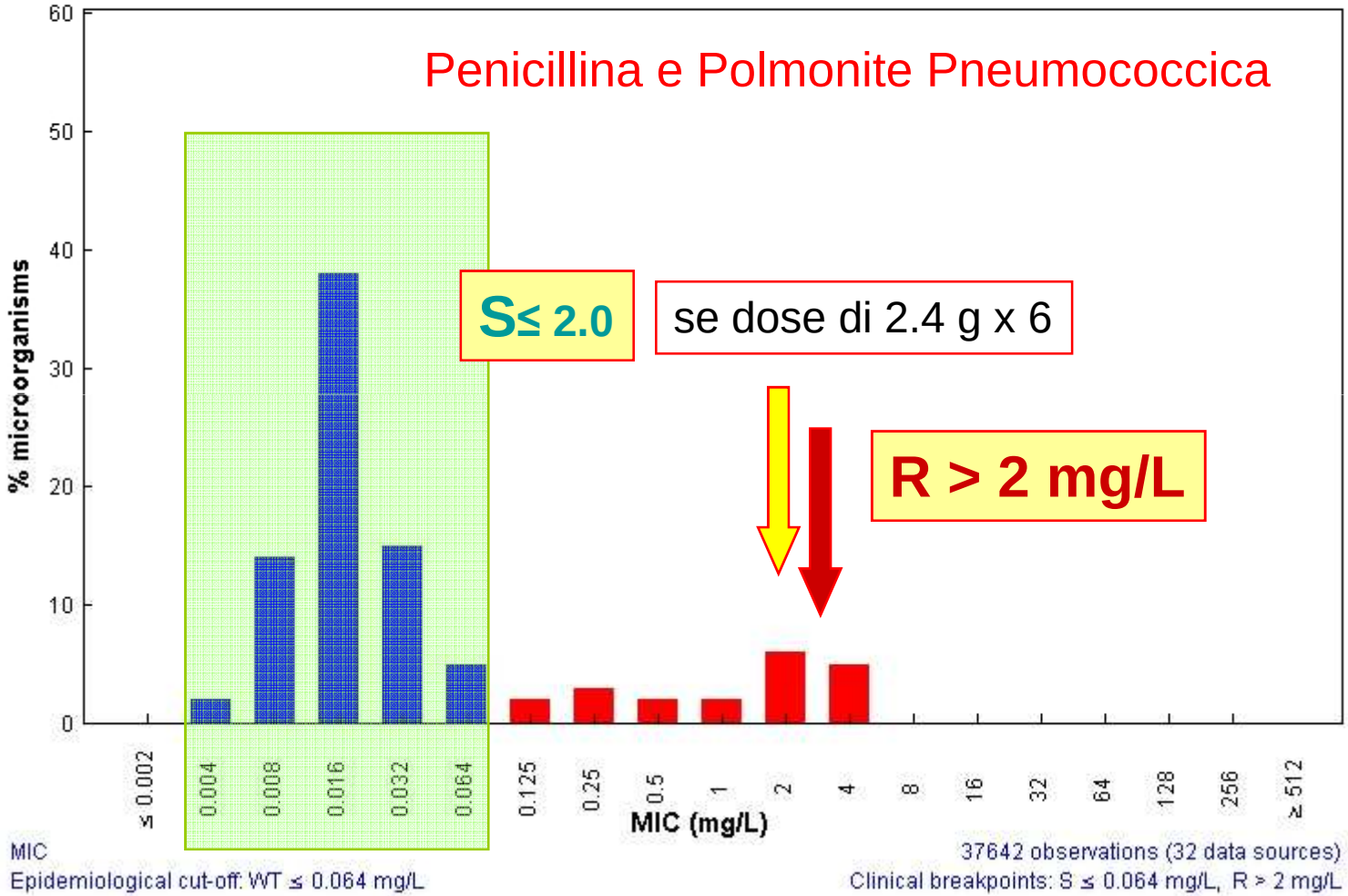


EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Benzylpenicillin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database 2010-11-01

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Emocoltura
Isolamento: *Streptococcus pneumoniae*

Break-point (EUCAST)

	MIC (mg/L)	S	**v.n. (mg/L)**	R		
Penicillina	1	≤ 0.064	**≤ 0.064**	> 2	S	*
Cefotaxime	1	≤ 0.5	**≤ 0.064**	> 2	S	*
Ceftriaxone	0.5	≤ 0.5	**≤ 0.064**	> 2	S	*
Meropenem	0.032	≤ 2	**≤ 0.064**	> 2	S	
Levofloxacina	1	≤ 2	**≤ 2**	> 2	S	
Vancomicina	0.25	≤ 2	**≤ 1**	> 2	S	
Linezolid	1	≤ 4	**≤ 2**	> 4	S	
Rifampicina	0.032	≤ 0.064	**≤ 0.064**	> 0.5	S	

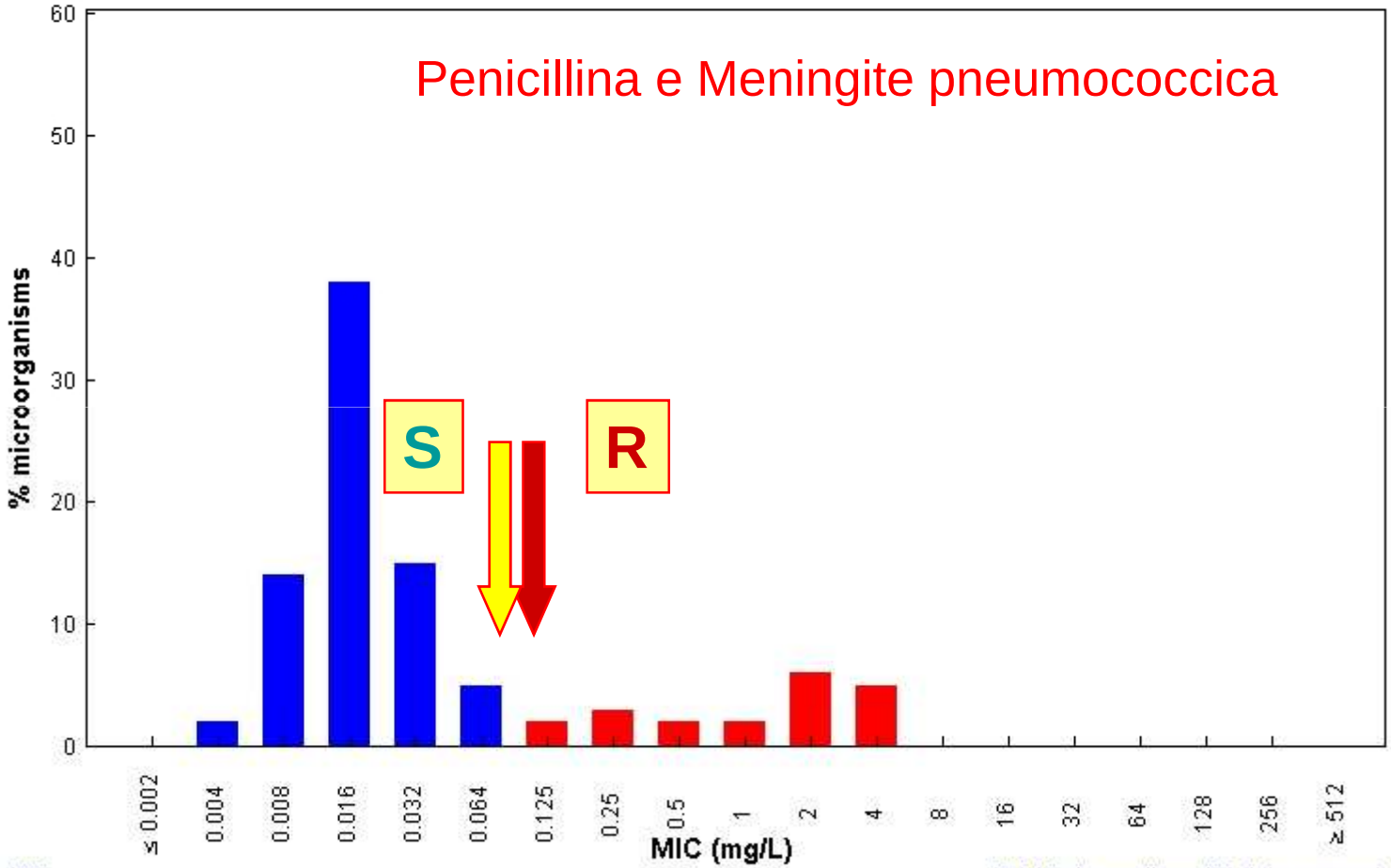
*** Per questi antibiotici sono necessari dosaggi più elevati della norma. Utile consulto infettivologico.**

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Benzylpenicillin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database 2010-11-01

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L

37642 observations (32 data sources)
Clinical breakpoints: S ≤ 0.064 mg/L, R > 2 mg/L

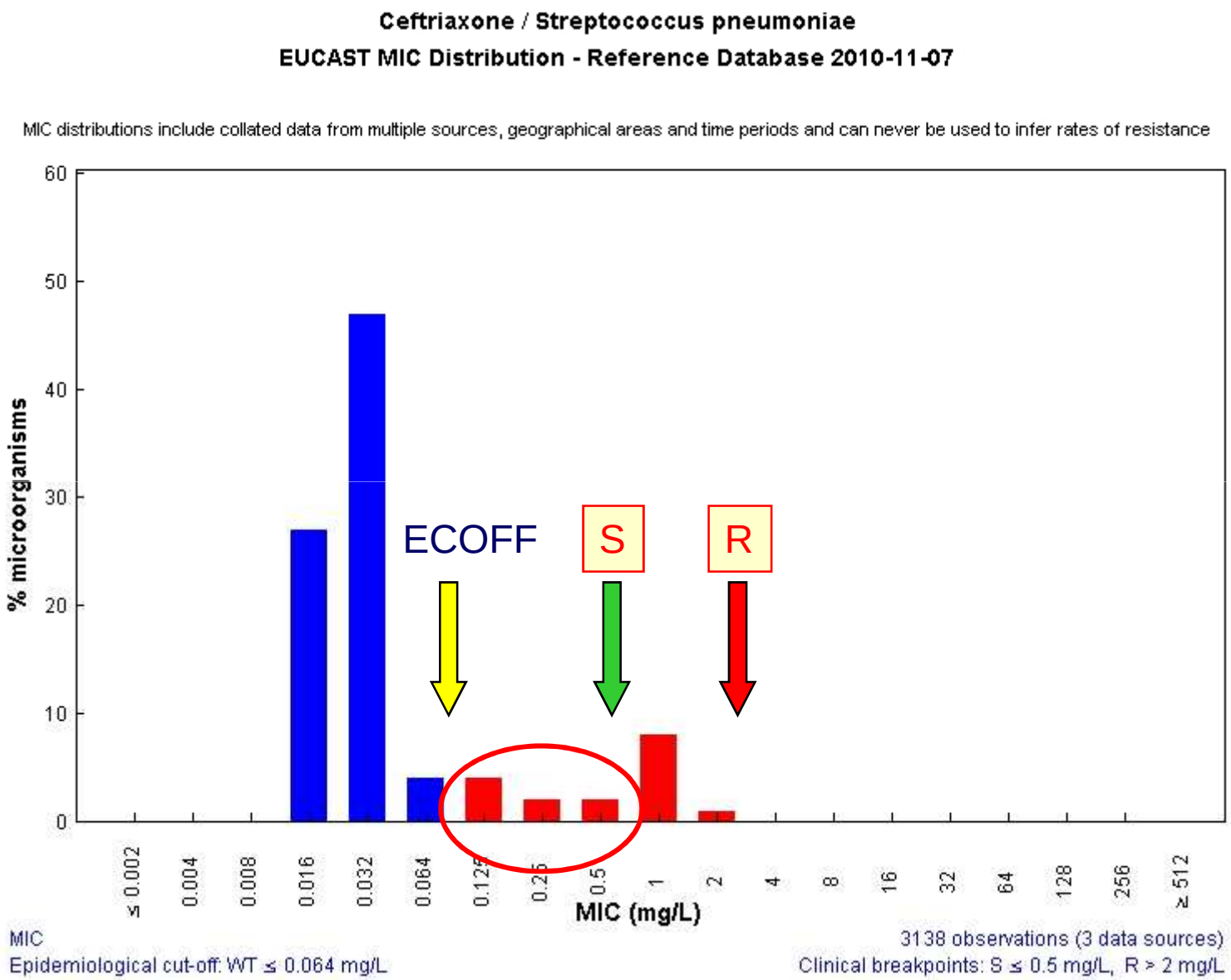
EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

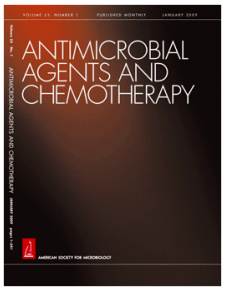
Beta-lattamici nella Meningite pneumococcica

	MIC breakpoint (mg/L)	
	S ≤	R >
Benzilpenicillina	0.06	2
Cefotaxime	0.5	2
Ceftriaxone	0.5	2
Meropenem	0.25	1

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Ceftriaxone e *S. pneumoniae*





Activities of Ceftobiprole and Other -Lactams against *Streptococcus pneumoniae* Clinical Isolates from the United States with Defined Substitutions in Penicillin-Binding Proteins PBP 1a, PBP 2b, and PBP 2x

Genotype[a]	Strain	MIC (μg/ml)[b]				
		BPR	CRO	CTX	AMC	PEN
wt	8865	0.008	0.03	0.03	0.03	≤0.015
	8869	0.008	0.03	0.03	0.03	≤0.015
	8621	0.008	0.03	0.03	0.03	≤0.015
	8625	0.008	0.03	≤0.015	0.03	≤0.015
	7876	≤0.004	0.03	0.03	0.03	≤0.015
	8626	≤0.004	≤0.015	≤0.015	0.03	≤0.015
	8025	≤0.004	0.03	0.03	0.03	0.03
1	8882	0.008	0.06	0.06	0.06	0.12
	8009	0.015	0.06	0.06	0.12	0.12
	7891	0.06	0.12	0.12	0.12	0.12
2	7877	0.12	0.5	0.5	2	1
	7879	0.25	0.5	0.5	1	1
	8006	0.25	0.5	1	2	1
	8010	0.25	0.5	0.5	1	1
	8617	0.25	0.5	0.5	1	1

Genotype[a]	Strain	MIC (μg/ml)[b]				
		BPR	CRO	CTX	AMC	PEN
3	8032	0.12	0.5	0.5	2	2
	8157	0.12	1	2	2	2
	8151	0.25	1	1	2	2
	7888	0.25	1	1	2	4
	7889	0.25	2	2	2	4
	8007	0.25	2	2	4	4
	8161	0.5	2	2	2	4
4	8867	0.25	1	2	8	8
	8024	0.25	2	2	8	8
5	7771	0.5	4	8	16	8
	8623	0.5	4	8	16	8
	8036	0.5	8	8	8	8
	8048	0.5	8	8	8	8
	8819	1	8	16	16	8
	8575	1	16	16	16	8

Davies TA et al *Antimicrobial Agents and Chemotherapy*, July 2006; 50:2530-2532

Enterococchi

Enterococcus spp.

Breakpoint EUCAST e CLSI

Antibiotico	EUCAST	CLSI
	S ≤ / R > (mg/L)	S ≤ / R > (mg/L)
Ampicillina	4 / 8	8 / 8
Amoxicillina	4 / 8	- / -
Vancomicina	4 / 4	4 / 16
Teicoplanina	2 / 2	8 / 16
Gentamicina HL	128 / 128	512 / 512

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

Enterococcus spp.

Penicillins[1,2]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ampicillin	4	8	2	10	8
Ampicillin-sulbactam[3]	4	8		Note[A]	Note[A]
Amoxicillin[3]	4	8		Note[A]	Note[A]
Amoxicillin-clavulanate[3]	4	8		Note[A]	Note[A]
Piperacillin[3]	Note[3]	Note[3]		Note[A]	Note[A]
Piperacillin-tazobactam[3]	Note[3]	Note[3]		Note[A]	Note[A]

1. Fare riferimento a linee guida nazionali o internazionali per i breakpoint per *Enterococcus* spp. nella endocardite.

2. *E. faecium* resistente alle penicilline può essere considerato resistente a tutti gli altri beta-lattamici inclusi i carbapenemi.

3/A. La sensibilità a ampicillina, amoxicillina e piperacillina con o senza inibitore delle beta-lattamasi può essere desunta dal test di sensibilità ad ampicillina.

European Heart Journal (2009) **30**, 2369–2413
doi:10.1093/eurheartj/ehp285

ESC GUIDELINES

Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009)

European Heart Journal (2009) **30**, 2369–2413
doi:10.1093/eurheartj/ehp285

Antibiotic	Dosage and route	Duration (weeks)	Level of evidence
Beta-lactam and gentamicin susceptible strain (for resistant isolates see[a,b,c])			
Amoxicillin *with* Gentamicin[e]	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses. ***Paediatric doses:***[f] Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses. Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses.	4–6[d] 4–6	I B
OR			
Ampicillin *with* Gentamicin[e]	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses ***Paediatric doses:***[f] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses. Gentamicin as above.	4–6[d] 4–6	I B
OR			
Vancomycin[g] *with* Gentamicin[e]	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses ***Paediatric doses:***[f] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above.	6 6	I C

European Heart Journal (2009) **30**, 2369–2413
doi:10.1093/eurheartj/ehp285

d 6-week therapy recommended for patients with > 3 months symptoms and in PVE.

e Monitor serum levels of aminoglycosides and renal function as indicated in Table 13.

f Paediatric doses should not exceed adult doses.

g In b-lactam allergic patients. Monitor serum vancomycin concentrations as indicated in Table 13.

Amoxicillin *with* Gentamicin[e]	200 mg/kg/day i.v. in 4–6 doses	4–6[d]	I B
	3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	4–6	

c. Multiresistance to aminoglycosides, beta-lactams, and vancomycin: suggested alternatives are

i. linezolid 2 x 600 mg/day i.v. or orally for ≥ 8 weeks (IIa, C) (monitor haematological toxicity),

ii. quinupristin–dalfopristin 3 x 7.5 mg/kg/day for ≥ 8 weeks (IIa, C) [for *Enterococcus faecium* only]

iii. beta-lactam combinations including imipenem plus ampicillin or ceftriaxone plus ampicillin for ≥ 8 weeks (IIb, C).

b beta-Lactam resistance:

(i) if due to beta-lactamase production, replace ampicillin with ampicillin–sulbactam or amoxicillin with amoxicillin–clavulanate (I, C);

(ii) if due to PBP5 alteration, use vancomycin-based regimens.

a High level resistance to gentamicin (MIC > 500 mg/L): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses (I, A).

Otherwise, use more prolonged course of b-lactam therapy.

The combination of ampicillin with ceftriaxone was recently suggested for gentamicin-resistant *E. faecalis*[148] (IIa, B).

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Regole interpretative per β-lattamici e Cocchi Gram-positivi

Rule no.	Organisms	Agent	Rule	Scientific basis	Evidence grade
8.6	*Enterococcus* spp.	Ampicillin	If resistant to ampicillin report as resistant to ureidopenicillins and carbapenems.	Alterations of PBP-5 lead to decreased affinity of β-lactams. Rare penicillinase-producing isolates have been reported in a few countries but not in Europe.	C

Weistein MP et al *J Clin Microbiol*, 2004; 8:3747-3751

Ono S et al *Antimicrob Agents Chemother*, 2005; 7:2954-2958

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
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Enterococcus spp.

Penicillins[1,2]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Benzylpenicillin	-	-		-	-
Phenoxymethylpenicillin	-	-		-	-
Ticarcillin[4]	-	-		-	-
Ticarcillin-clavulanate[4]	-	-		-	-
Oxacillin	-	-		-	-
Cloxacillin	-	-		-	-
Dicloxacillin	-	-		-	-
Flucloxacillin	-	-		-	-
Mecillinam (uncomplicated UTI only)	-	-		-	-

"-" indica che il test di sensibilità non è raccomandato perché la specie è un cattivo bersaglio per la terapia con quel farmaco.

Gli isolati possono essere refertati come R senza saggiarli.

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Enterococcus spp.

Carbapenems	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Doripenem	-	-		-	-
Ertapenem	-	-		-	-
Imipenem	4	8	10	21	18
Meropenem	-	-		-	-

Monobactams	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Aztreonam	-	-		-	-

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Enterococcus spp.

Cephalosporins	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefaclor	-	-		-	-
Cefadroxil	-	-		-	-
Cefalexin	-	-		-	-
Cefazolin	-	-		-	-
Cefepime	-	-		-	-
Cefixime	-	-		-	-
Cefotaxime	-	-		-	-
Cefoxitin	-	-		-	-
Cefpodoxime	-	-		-	-
Ceftazidime	-	-		-	-
Ceftibuten	-	-		-	-
Ceftriaxone	-	-		-	-
Cefuroxime	-	-		-	-
Cefuroxime axetil	-	-		-	-

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European Society of Clinical Microbiology and Infectious Diseases

Enterococcus spp.

Macrolides, lincosamides and streptogramins	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Azithromycin	-	-		-	-
Clarithromycin	-	-		-	-
Erythromycin	-	-		-	-
Roxithromycin	-	-		-	-
Telithromycin	-	-		-	-
				-	-
Clindamycin	-	-		-	-
Quinupristin-dalfopristin[1]	1	4	15	22[A]	20[A]

1/A. I breakpoint per Quinupristin/Dalfopristin sono validi solo per *E. faecium*.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
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Enterococcus spp.

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin	-	-		-	-
Levofloxacin	-	-		-	-
Moxifloxacin	-	-		-	-
Nalidixic acid	NA	NA		NA	NA
Norfloxacin	-	-		-	-
Ofloxacin	-	-		-	-

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Table 2D
Enterococcus spp.
M02 and M07

(13) These interpretive criteria apply to urinary tract isolates only.

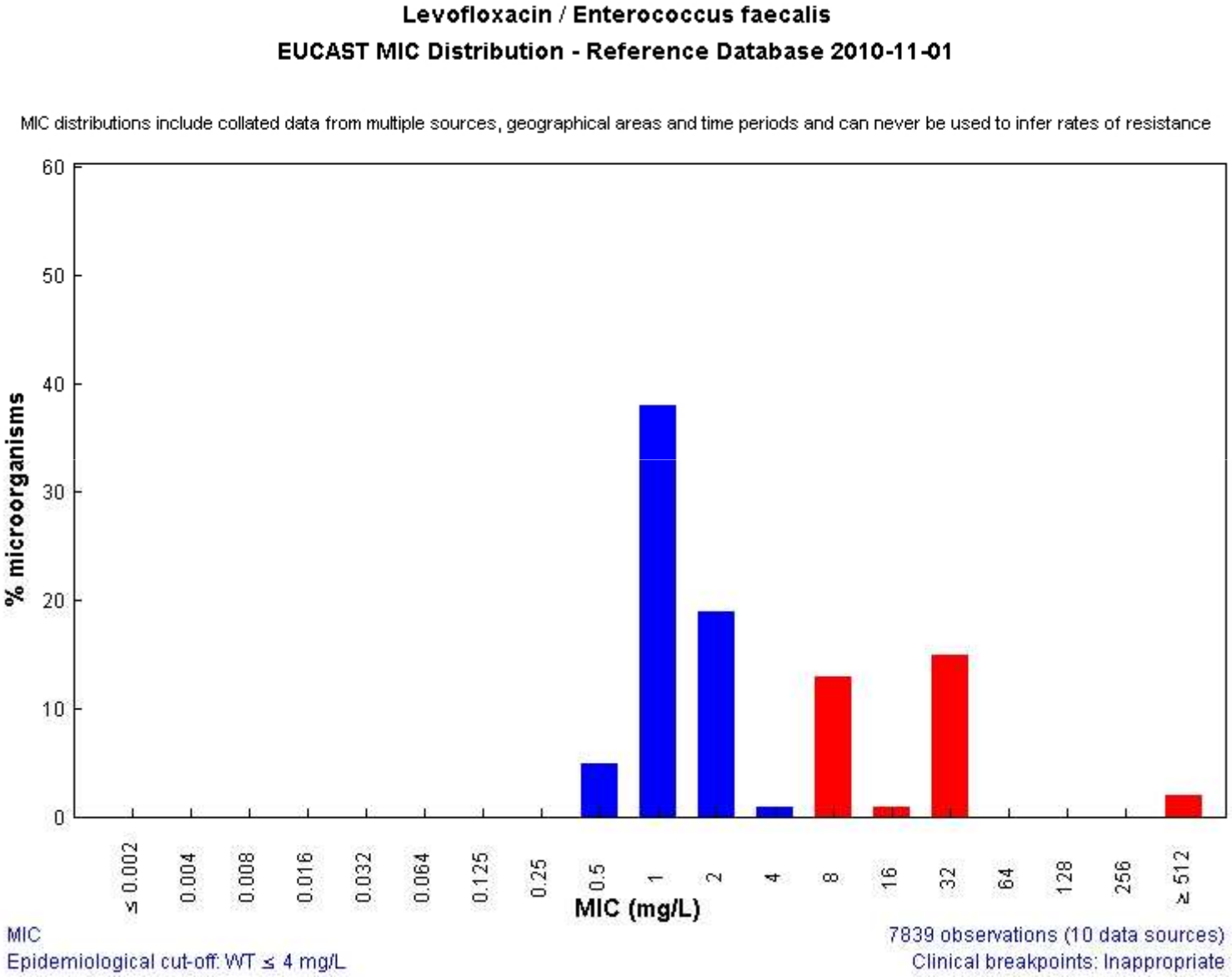
FLUOROQUINOLONES								
U	Ciprofloxacin	5 µg	≥ 21	16–20	≤ 15	≤ 1	2	≥ 4
U	Levofloxacin	5 µg	≥ 17	14–16	≤ 13	≤ 2	4	≥ 8
U	Norfloxacin	10 µg	≥ 17	13–16	≤ 12	≤ 4	8	≥ 16

Levofloxacin

Antimicrobial wild type distributions of microorganisms

	0.016	0.032	0.064	0.128	0.25	0.5	1	2	4	8	16	32	64	128	256	512
Staphylococcus aureus	0	111	1426	10540	8805	1472	308	358	2486	1781	130	39	2	1	0	0
Staphylococcus capitis	0	1	2	85	277	40	5	4	13	22	1	5	0	0	0	212
Staphylococcus coagulase negative	0	4	73	1655	1344	206	46	251	580	328	42	32	2	0	0	0
Staphylococcus epidermidis	0	17	28	2026	2579	272	121	783	1767	3581	144	402	0	0	0	216
Staphylococcus haemolyticus	0	0	13	92	14	5	3	14	77	12	9	12	1	0	0	0
Staphylococcus hominis	0	2	16	147	50	12	18	54	48	162	0	0	0	0	0	0
Staphylococcus saprophyticus	0	0	3	41	30	126	13	3	20	15	14	20	0	0	0	241
Staphylococcus warneri	0	0	1	40	134	10	3	1	4	9	2	16	0	0	0	249
Streptococcus group C	0	0	1	2	28	123	53	0	1	0	0	0	0	0	0	0
Streptococcus group G	0	0	1	2	103	351	64	5	0	0	0	0	0	0	0	0
Streptococcus agalactiae	0	0	1	26	914	399	982	87	11	3	1	2	0	0	0	195
Streptococcus pneumoniae	0	0	11	83	375	16689	64729	2570	122	186	373	66	23	4	2	231
Streptococcus pyogenes	1	0	1	23	1897	20366	2645	1577	8	10	9	0	0	0	0	238
Enterococcus faecalis	0	1	0	32	35	464	2999	1551	134	1065	117	1205	44	6	1	185
Enterococcus faecium	0	0	0	7	6	43	123	288	97	41	105	216	107	40	0	0
Streptococcus bovis	0	0	0	0	1	5	120	43	1	0	0	0	0	0	0	0
Streptococcus mitis	0	0	1	0	0	36	205	51	2	0	0	0	0	0	0	0
Streptococcus oralis	0	0	0	0	0	5	81	17	2	0	0	0	0	0	0	0
Streptococcus sanguis	0	0	0	1	2	47	49	16	0	0	0	0	0	0	0	0
Streptococcus viridans	0	0	0	2	16	109	188	70	11	3	3	0	1	0	0	0

Levofloxacina e *Enterococcus faecalis*



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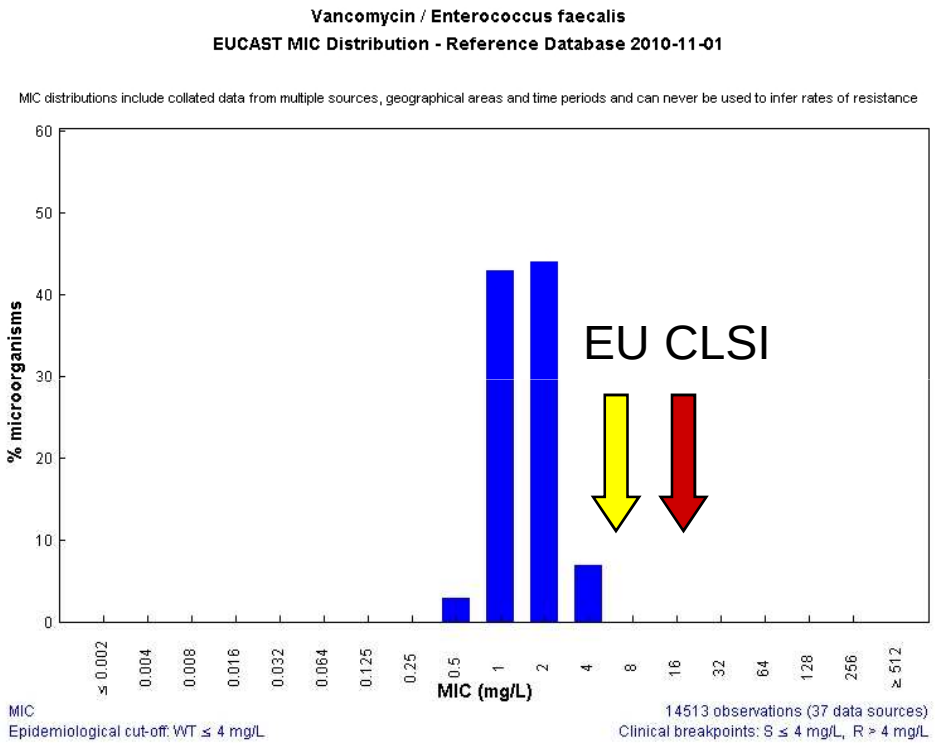
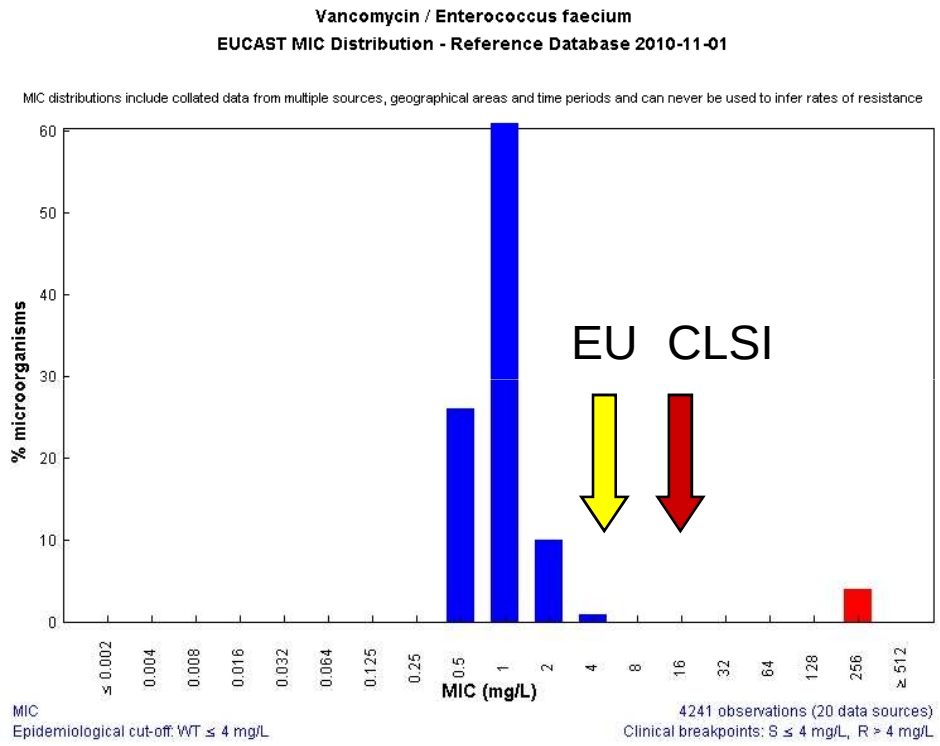
Vancomicina e *Enterococcus* spp.





1. The S/I breakpoint for vancomycin has been raised to 4 mg/L to avoid dividing the wild type MIC distributions of some species.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

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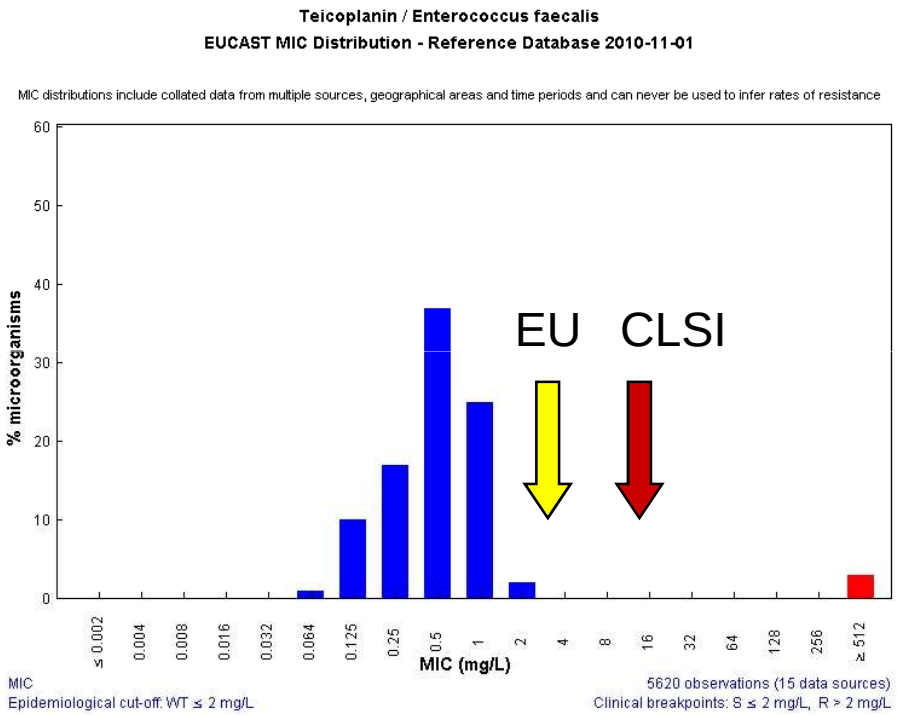
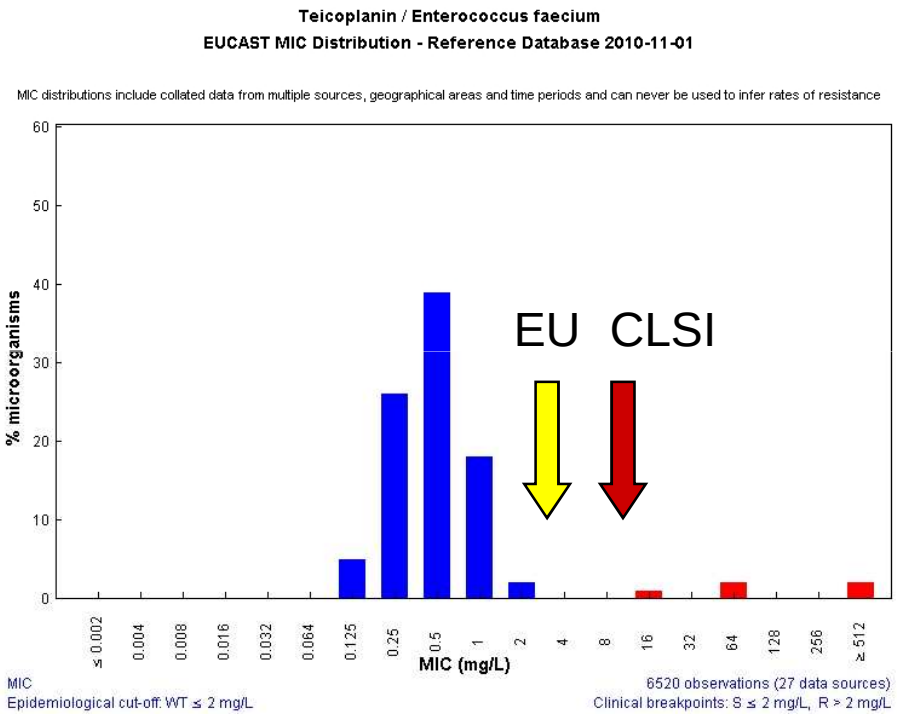
Teicoplanina e *Enterococcus* spp





1. The I/R breakpoint for teicoplanin has been reduced to 2 mg/L to avoid discrepant reporting of isolates with vanA-mediated resistance.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
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Enterococcus spp.

Miscellaneous	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Chloramphenicol	-	-		-	-
Colistin	-	-		-	-
Daptomycin	IE	IE		IE	IE
Fosfomycin iv	-	-		-	-
Fusidic acid	-	-		-	-
Linezolid	4	4	10	19	19
Metronidazole	-	-		-	-
Rifampicin	-	-		-	-
Spectinomycin	-	-		-	-

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Daptomycin

Rationale for the EUCAST clinical breakpoints,

version 1.0

5. Pharmacodynamics		
	Staphylococci	Streptococci
AUC/MIC for stasis	250-550	75-237
AUC/MIC for 2 log drop	800-4000	157-815

Table 1: Target attainment for 4mg/kg/day daptomycin

daptomycin MIC mg/L	% target attainment with an AUC/MIC target of		
	373 (- one standard deviation)	438 (mean)	503 (+ one standard deviation)
≥4	0	0	0
2	0	0	0
1	96.8	77.2	42.9
0.5	100.0	100.0	100.0
≤0.25	100.0	100.0	100.0

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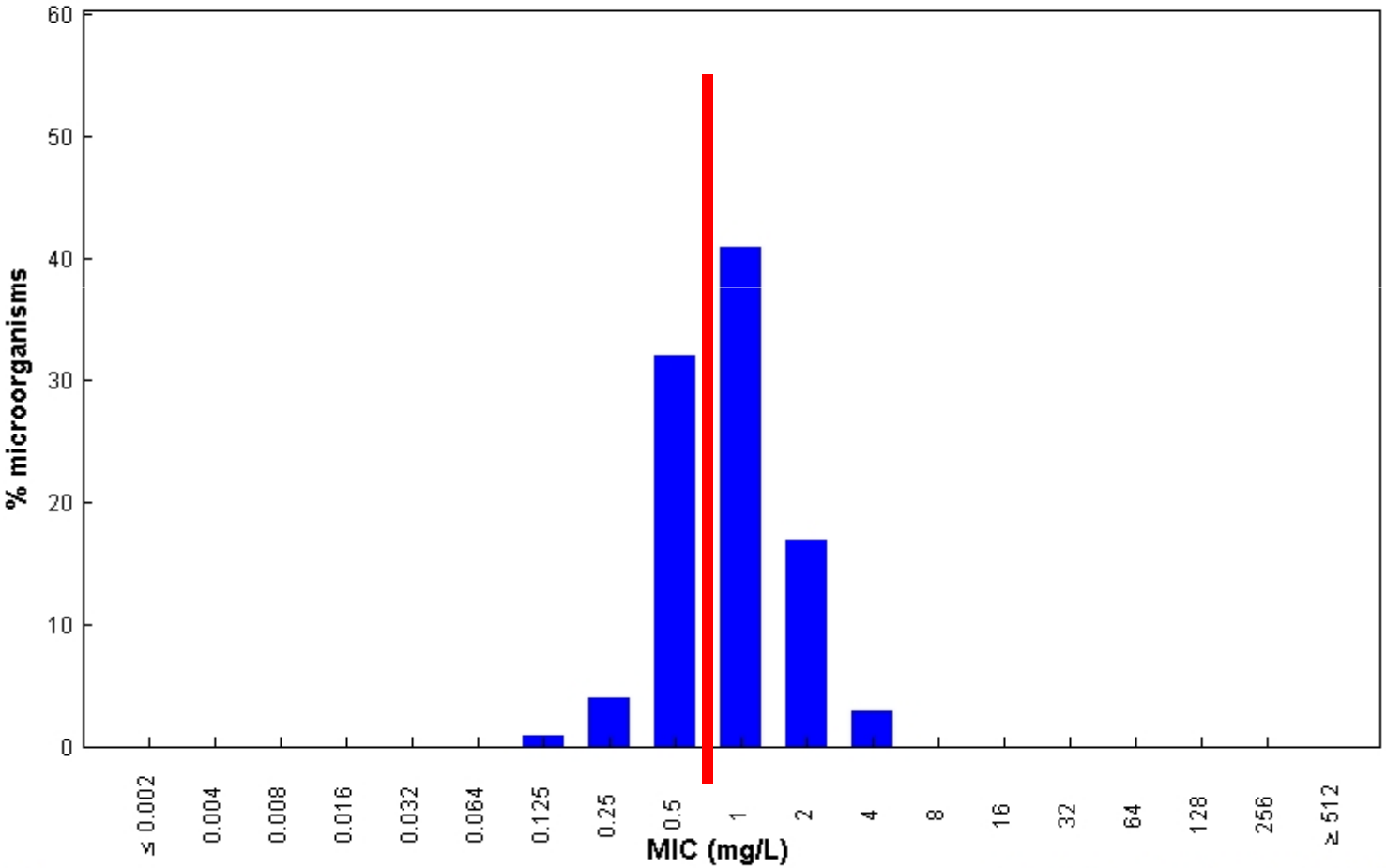
Daptomicina e *Enterococcus faecalis*

Daptomycin / Enterococcus faecalis

EUCAST MIC Distribution - Reference Database 2010-11-01

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC

Epidemiological cut-off: WT ≤ 4 mg/L

9698 observations (11 data sources)

Clinical breakpoints: IE

Resistenza emergente alla daptomicina in *Enterococcus* spp.

Failure of Daptomycin Monotherapy for Endocarditis Caused by an *Enterococcus faecium* Strain with Vancomycin-Resistant and Vancomycin-Susceptible Subpopulations and Evidence of In Vivo Loss of the *vanA* Gene Cluster

Cesar A. Arias,[1,2,6] Harrys A. Torres,[2,5] Kavindra V. Singh,[1,2] Diana Panesso,[6] Judson Moore,[1] Audrey Wanger,[4] and Barbara E. Murray[1,2,3]

Table 1. *Enterococcus faecium* isolates and MICs.

Strain	Date of isolation	Sample site	MIC, mg/L				Daptomycin MIC by Etest, mg/L
			Dapto[a]	Van[b]	Amp[c]	Gen[b]	
TX0133a	28 March 2006	Blood	4	512	32	8	6
TX0133b	9 May 2006	Blood	2	2	16	8	6
TX0133a.01	NA	Within the inhibition zone around the vancomycin Etest strip	2	1024	ND	8	6
TX0133a.04	NA	Outside the inhibition zone around the vancomycin Etest strip	4	1	ND	4	4
TX0133c	26 May 2006	Blood	2	512	64	4	3

NOTE. Amp, ampicillin; Dapto, daptomycin; Gen, gentamicin; NA, not available; ND, not determined; Van, vancomycin.
[a] Broth microdilution and macrodilution method.
[b] Agar dilution method.
[c] Automated method.

Infective endocarditis caused by daptomycin-resistant Enterococcus faecalis: A case report

Clin. Infect. Dis 2005; 41:565

ZEINA A. KANAFANI, JEROME J. FEDERSPIEL & VANCE G. FOWLER JR

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Enterococcus spp.

Antibiogramma per isolati urinari

	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Amoxicillina	4	8		Note[A]	Note[A]
Amoxicillina-clavulanato	4	8		Note[A]	Note[A]
Nitrofurantoina	64	64	100	15	15
Trimethoprim-sulfamethoxazolo	0.03	1	1.25-23.75	50	21

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Enterococcus spp.

Antibiogramma per isolati non-urinari

	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ampicillina	4	8	2	10	8
Teicoplanina	2	2	30	16	16
Vancomicina	4	4	5	12	12
Linezolid	4	4	10	19	19
Tigeciclina	0.25	0.5	15	18	15
Quinupristin-dalfopristin	1	4	15	22	20
Gentamicina HLR	Nota	Nota	30	Nota	Nota

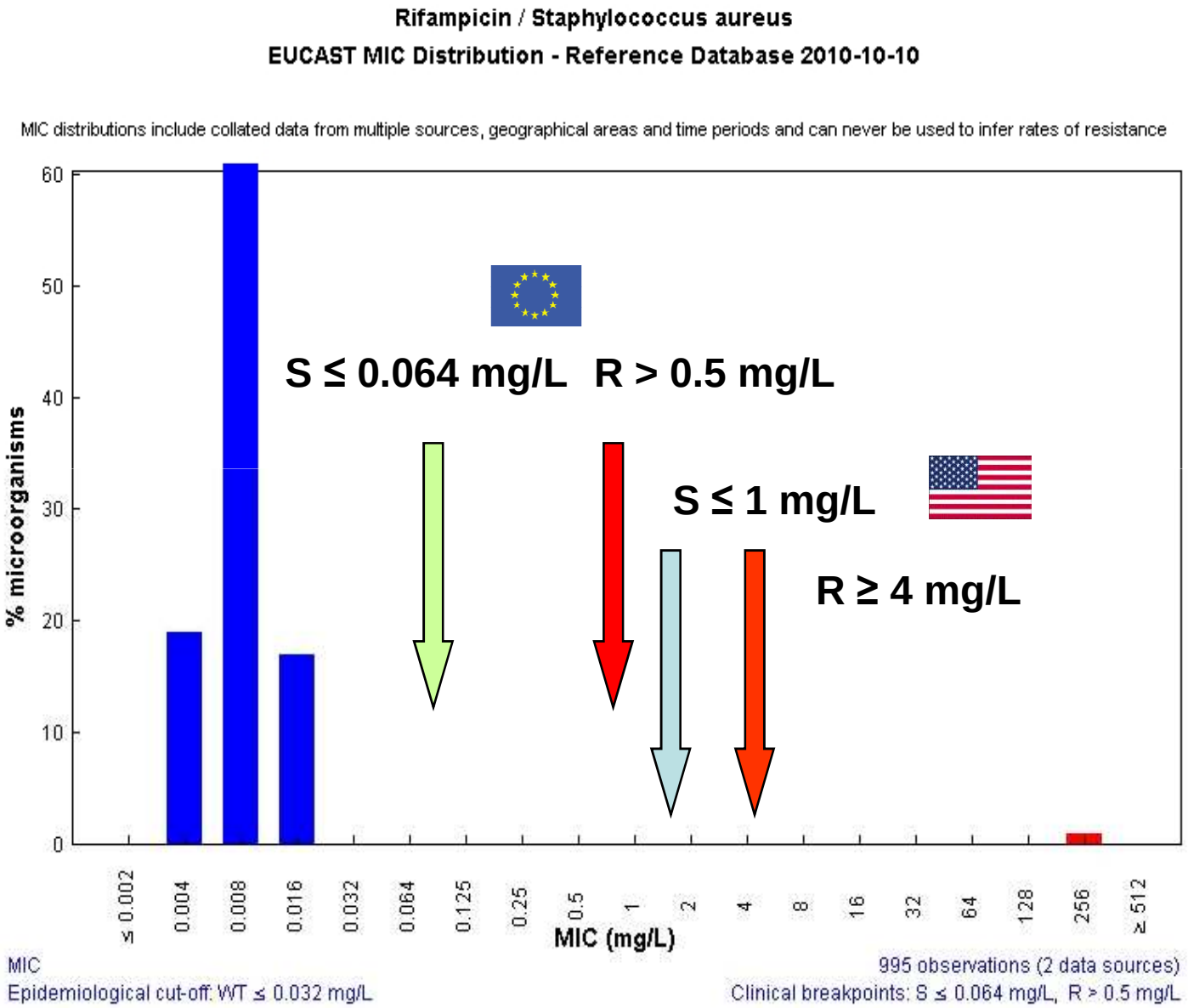
Staphylococcus spp.

Staphylococcus aureus

Breakpoint EUCAST e CLSI

Antibiotico	EUCAST	CLSI
	S ≤ / R > (mg/L)	S ≤ / R > (mg/L)
Penicillina	0.12 / 0.12	0.12 / 0.12
Oxacillina	2 / 2	2 / 2
Cefoxitina	4 / 4	- / -
Ciprofloxacina	1 / 1	1 / 2
Vancomicina	2 / 2	2 / 8
Teicoplanina	2 / 2	8 / 16
Eritromicina	1 / 2	0.5 / 4
Gentamicina	1 / 1	4 / 8
Tetraciclina	1 / 2	4 / 8
Acido fusidico	1 / 1	- / -
Rifampicina	0.06 / 0.5	1 / 2

Rifampicina e *Staphylococcus aureus*



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Staphylococcus spp.

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Benzylpenicillin	**0.12[1]**	**0.12[1,2]**	**1 unit**	**26[A]**	**26[A]**
Ampicillin	Note[1]	Note[1]	**2**	**15[A,B]**	**15[A,B]**
Oxacillin[2]	**Note[1,2]**	**Note[1,2]**		**Note[A]**	**Note[A]**

2. *S. aureus* and *S. lugdunensis* with oxacillin MIC values >2 mg/L are mostly resistant due to the presence of the mecA gene.

The corresponding oxacillin MIC for coagulase-negative staphylococci is >0.25 mg/L.

Oxacillina	S	R
S. aureus* e *S. lugdunensis	≤ 2 mg/L	> 2 mg/L
Stafilococchi coagulasi-negativi	≤ 0.25 mg/L	> 0.25 mg/L

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European Society of Clinical Microbiology and Infectious Diseases

Staphylococcus spp.

Cephalosporins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter Breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefoxitin (screen) ***S. aureus, S. lugdunensis***	**Note[3]**	**Note[3]**	**30**	**22[A]**	**22[A]**
Cefoxitin (screen) ***Coagulase-negative staphylococci***	**Note[3]**	**Note[3]**	**30**	**25[A]**	**25[A]**
Ceftazidime	**-**	**-**		-	-
Ceftibuten	**IE**	**IE**		IE	IE

3. *S. aureus* and S. *lugdunensis* con MIC a cefoxitin >4 mg/L sono in genere resistenti per la presenza del gene *mecA* mentre la MIC per gli stafilococchi coagulasi-negativi a parte *S. lugdunensis* è un peggior predittore di resistenza rispetto al test in disco-diffusione.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
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Staphylococcus spp.

Cefoxitina (metodi in MIC)	S	R
S. aureus* e *S. lugdunensis	≤ 4 mg/L	> 4 mg/L
Stafilococchi coagulasi-negativi	-	-

Ce				Zone diameter eakpoint (mm)	
					R <
Cefoxitin (screen) ***S. aureus, S. lugdunensis***	**Note[3]**	**Note[3]**	**30**	**22[A]**	**22[A]**
Cefoxitin (screen) ***Coagulase-negative staphylococci***	**Note[3]**	**Note[3]**	**30**	**25[A]**	**25[A]**
Ceftazidime	**-**	**-**		-	-
Ceftibuten	**IE**	**IE**		IE	IE

3. *S. aureus* and S. *lugdunensis* con MIC a cefoxitin >4 mg/L sono in genere resistenti per la presenza del gene *mecA* mentre la MIC per gli stafilococchi coagulasi-negativi a parte *S. lugdunensis* è un peggior predittore di resistenza rispetto al test in disco-diffusione.

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Staphylococcus spp.

Glycopeptides	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Teicoplanin ***S. aureus, S.lugdunensis***	2[1]	2[1]		Note[A]	Note[A]
Teicoplanin ***Coagulase-negative staphylococci***	4[1]	4[1]		Note[A]	Note[A]
Vancomycin[1]	2[1]	2[1]		Note[A]	Note[A]

1. *S. aureus* con valori di MIC a vancomicina MIC di 2 mg/L sono sul limite della distribuzione delle MIC wild type e può esservi una alterata risposta clinica.

Il breakpoint I/R è stato ridotto a 2 mg/L per evitare di refertare isolati di "GISA" come intermedi in quanto gravi infezioni da isolati "GISA" non sono trattabili con dosi aumentate di vancomicina o teicoplanina.

Le MIC per i glicopeptidi sono dipendenti dal metodo e dovrebbero essere determinate in microdiluizione in brodo (referenza ISO 20776).

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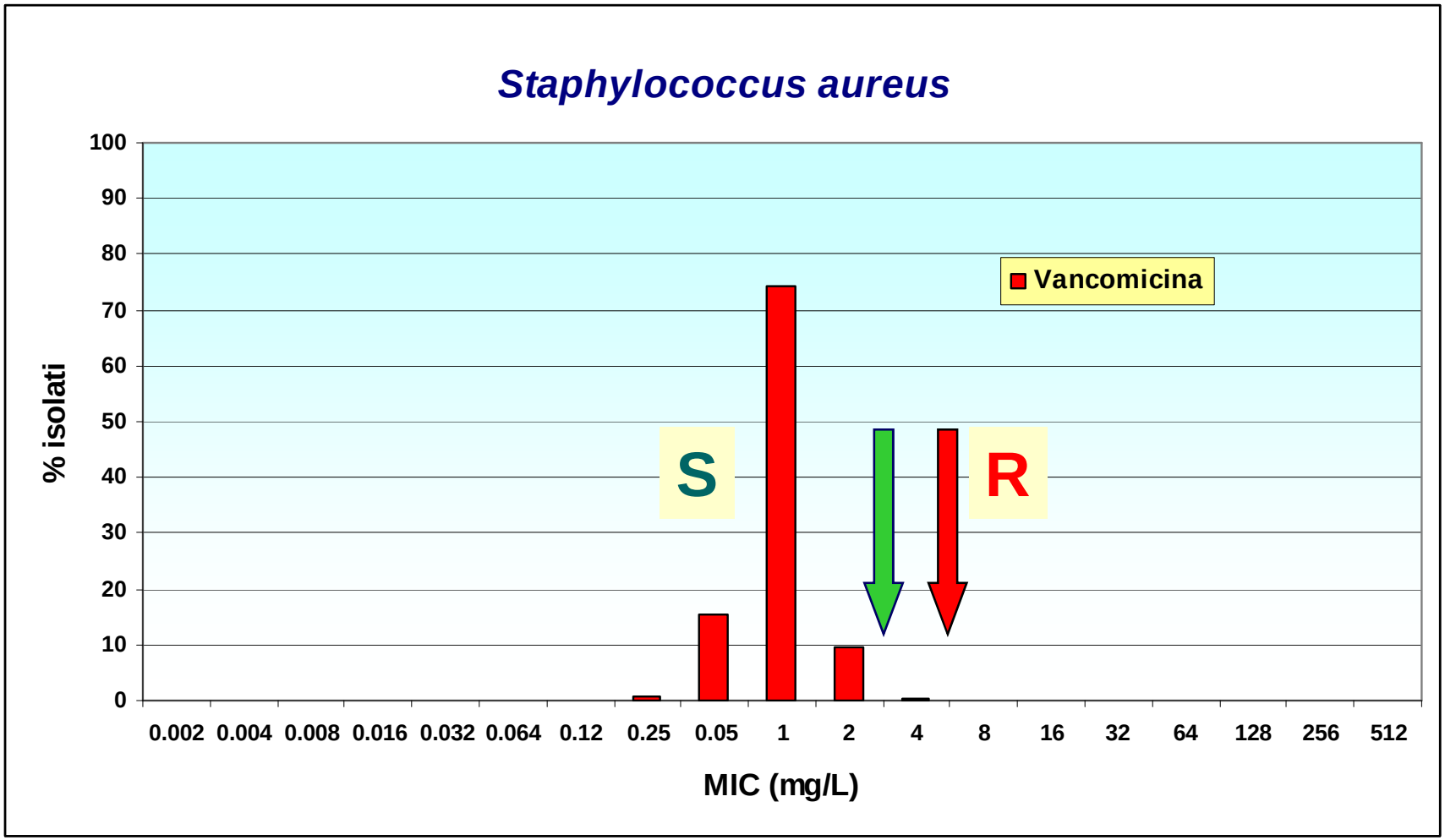
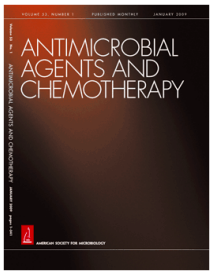
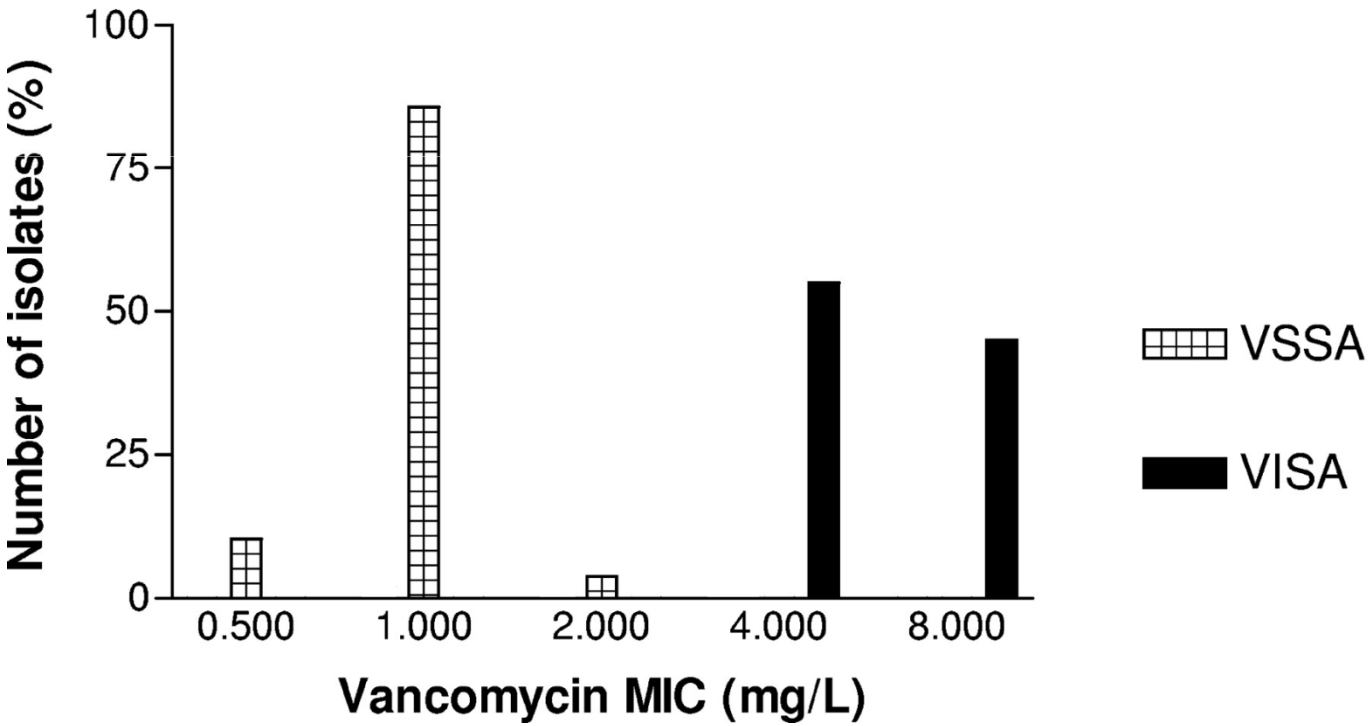
Antimicrobial wild type distributions of microorganisms



www.eucast.org accessed 10-31-2010



Evidence for Reduction in Breakpoints Used To Determine Vancomycin Susceptibility in *Staphylococcus aureus*



Wootton M et al *Antimicrobial Agents and Chemotherapy* (September 2005) 49:3982-3983

Influence of Vancomycin MIC on the Treatment of MRSA Bacteremia

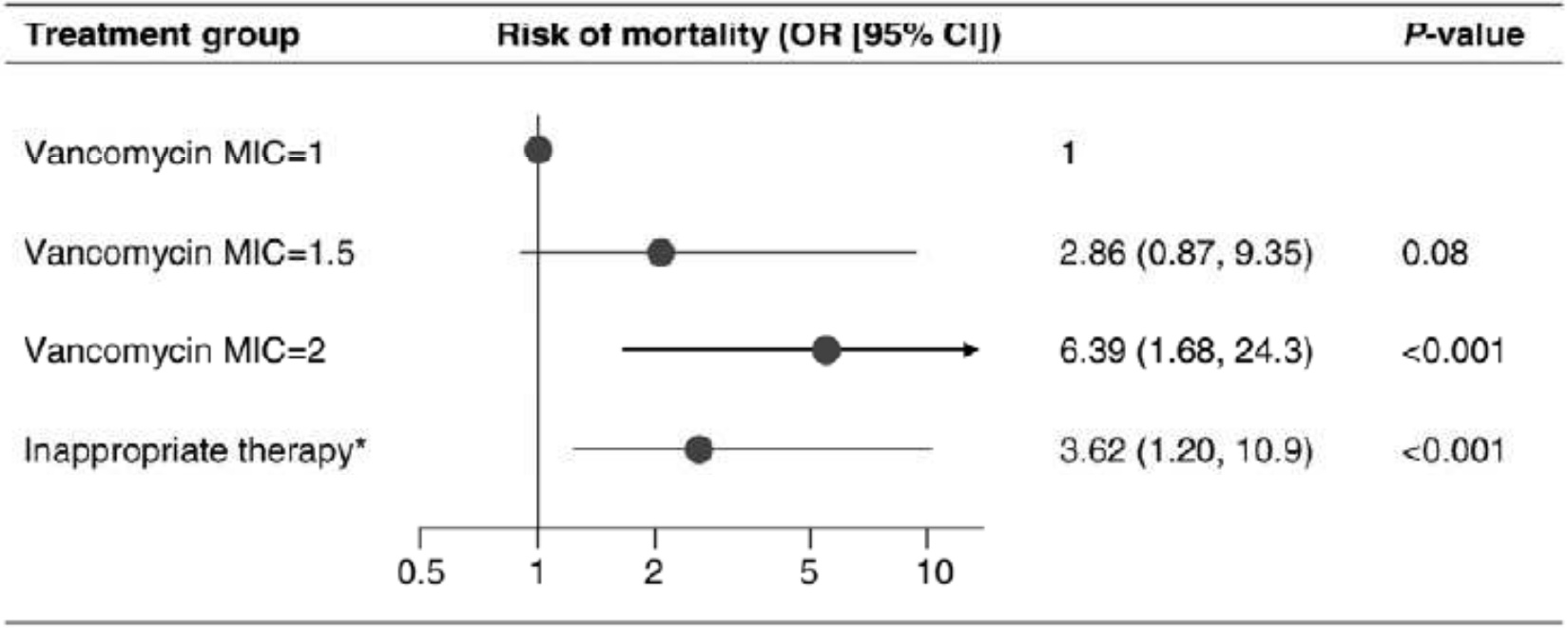
Factor	OR (95% CI)	*P*
Age, per year	1.02 (1.00–1.04)	.013
Receipt of corticosteroids	1.85 (1.04–3.29)	.034
Prognosis of underlying disease		
Nonfatal	1	
Rapidly fatal	1.81 (1.06–3.10)	.029
Ultimately fatal	10.2 (2.85–36.8)	<.001
Source of bacteremia		
Low risk	1	
Intermediate risk	2.18 (1.17–4.04)	.014
High risk	3.60 (1.89–6.88)	<.001
Treatment group		
VMIC1	1	
VMIC1.5	2.86 (0.87–9.35)	.08
VMIC2	6.39 (1.68–24.3)	<.001
NA	3.62 (1.20–10.9)	<.001
Shock	7.38 (4.11–13.3)	<.001

Factors independently associated with mortality (logistic regression model)

Soriano A et al, Clin Infect Dis 2008; 46:193-200

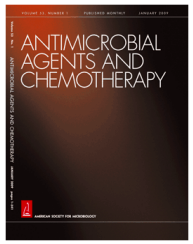
Staphylococcus aureus e Vancomicina
Fallimenti terapeutici

414 episodi di batteriemia da MRSA



Necessità di determinare e refertare una MIC precisa

Soriano A et al, *Clin Infect Dis* 2008; 46:193-200



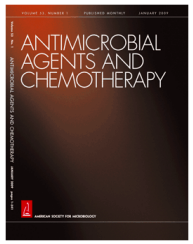
Vancomycin MICs for Methicillin-Resistant *Staphylococcus aureus* Isolates Differ Based upon the Susceptibility Test Method Used

Comparison of vancomycin MICs determined by broth microdilution, agar dilution, and Etest

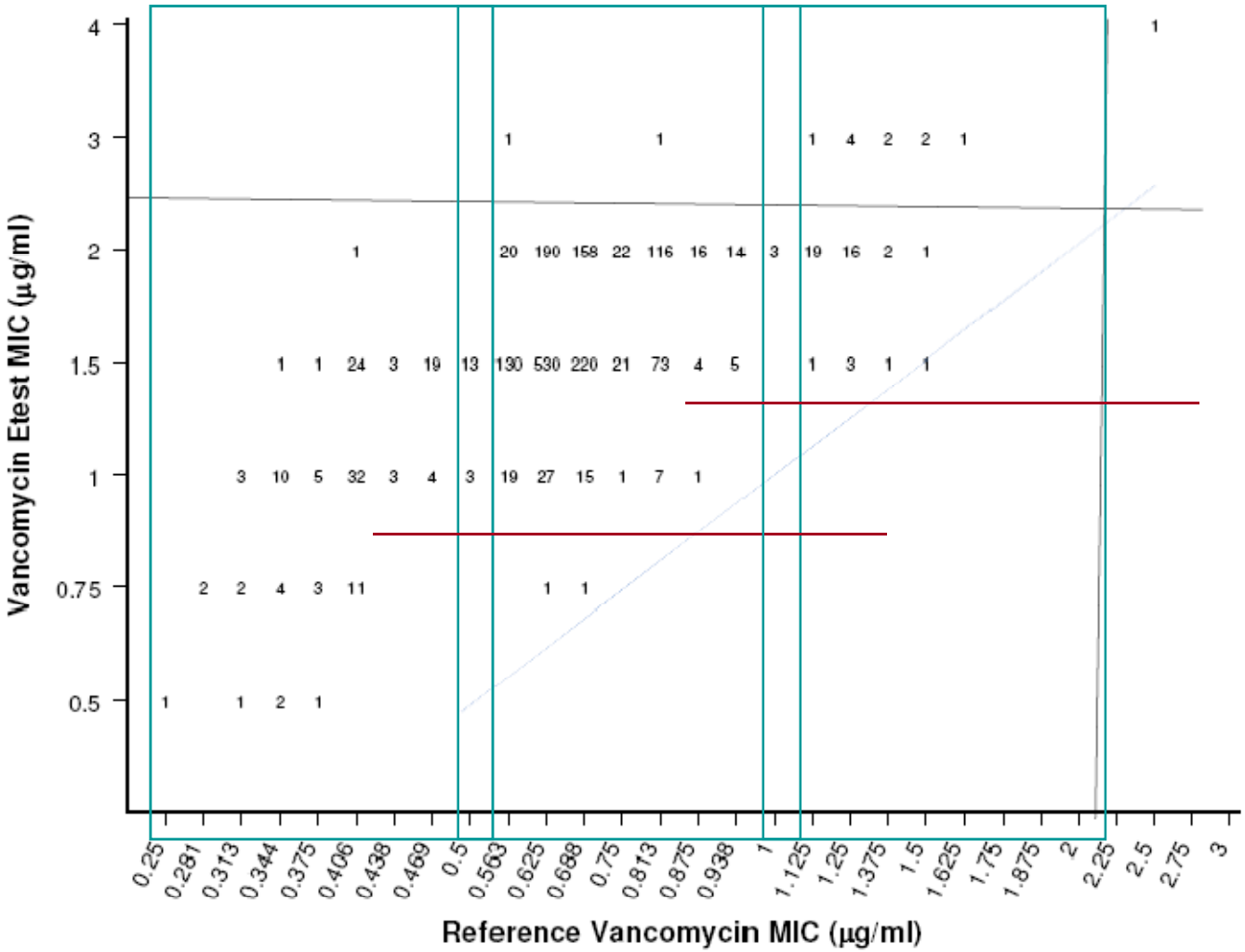
Vancomycin MIC (μg/ml)	No. of isolates (%) with MIC (μg/ml) determined by:			
	Broth microdilution	Agar dilution	Etest (Remel agar)	Etest (BBL agar)
0.5	21 (20.8)	1 (1)	0 (0)	0 (0)
0.75			1 (1)	1 (1)
1	77 (76.2)	88 (87)	11 (10.9)	1 (1)
1.5			69 (68.3)	62 (61.4)
2	3 (2.97)	12 (11.9)	20 (19.8)	37 (36.6)
Modal MIC (μg/ml)	1	1	2	2

[a] MICs were determined for 101 MRSA blood isolates obtained between 2002 and 2006.

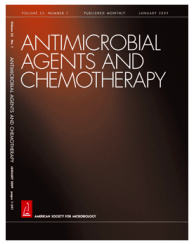
Prakash V et al *Antimicrobial Agents and Chemotherapy* (December 2008) 52:4528



Correlazione tra metodi per MIC Microdiluizione in brodo vs. Etest

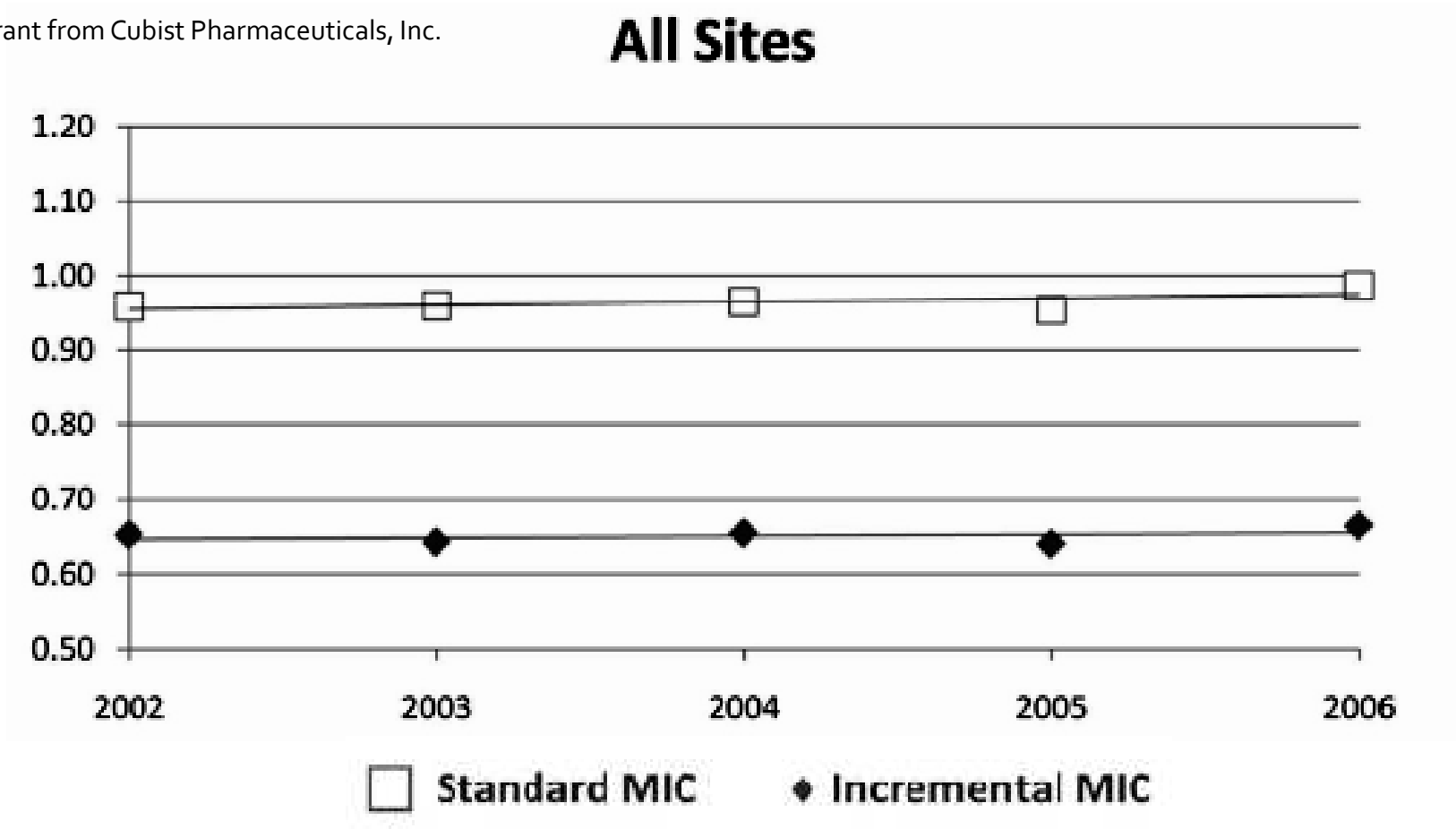


Sader HS et al *Antimicrob Agents Chemother* 27 April 2009

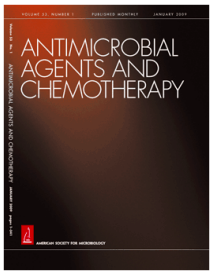


Evaluation of Vancomycin and Daptomycin Potency Trends (MIC Creep) against Methicillin-Resistant *Staphylococcus aureus* Isolates Collected in Nine U.S. Medical Centers from 2002 to 2006

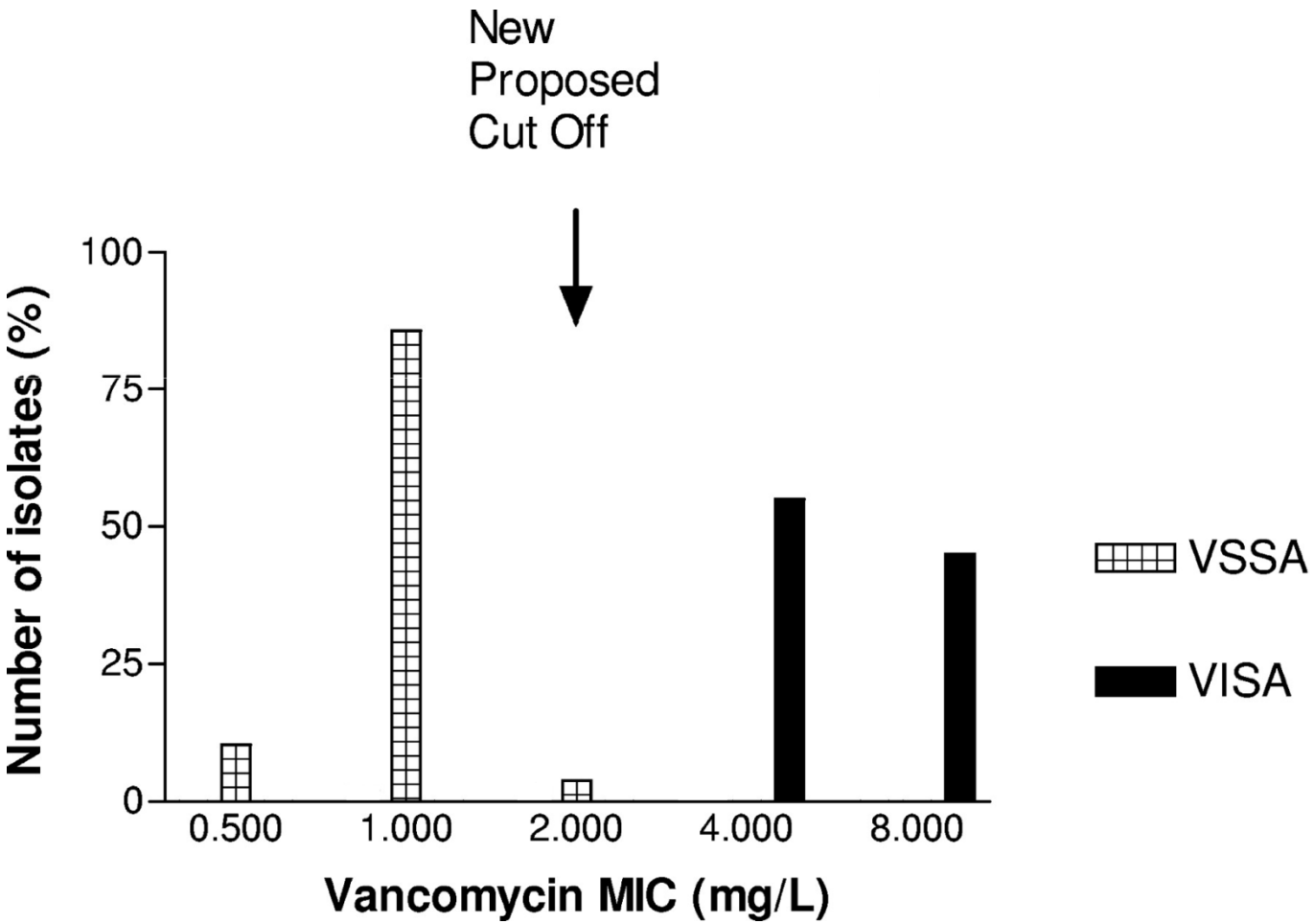
research grant from Cubist Pharmaceuticals, Inc.



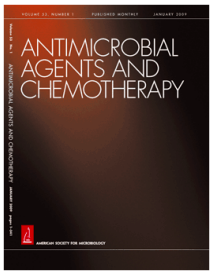
Sader HS et al *Antimicrobial Agents and Chemotherapy* (October 2009) 53:4127-4132



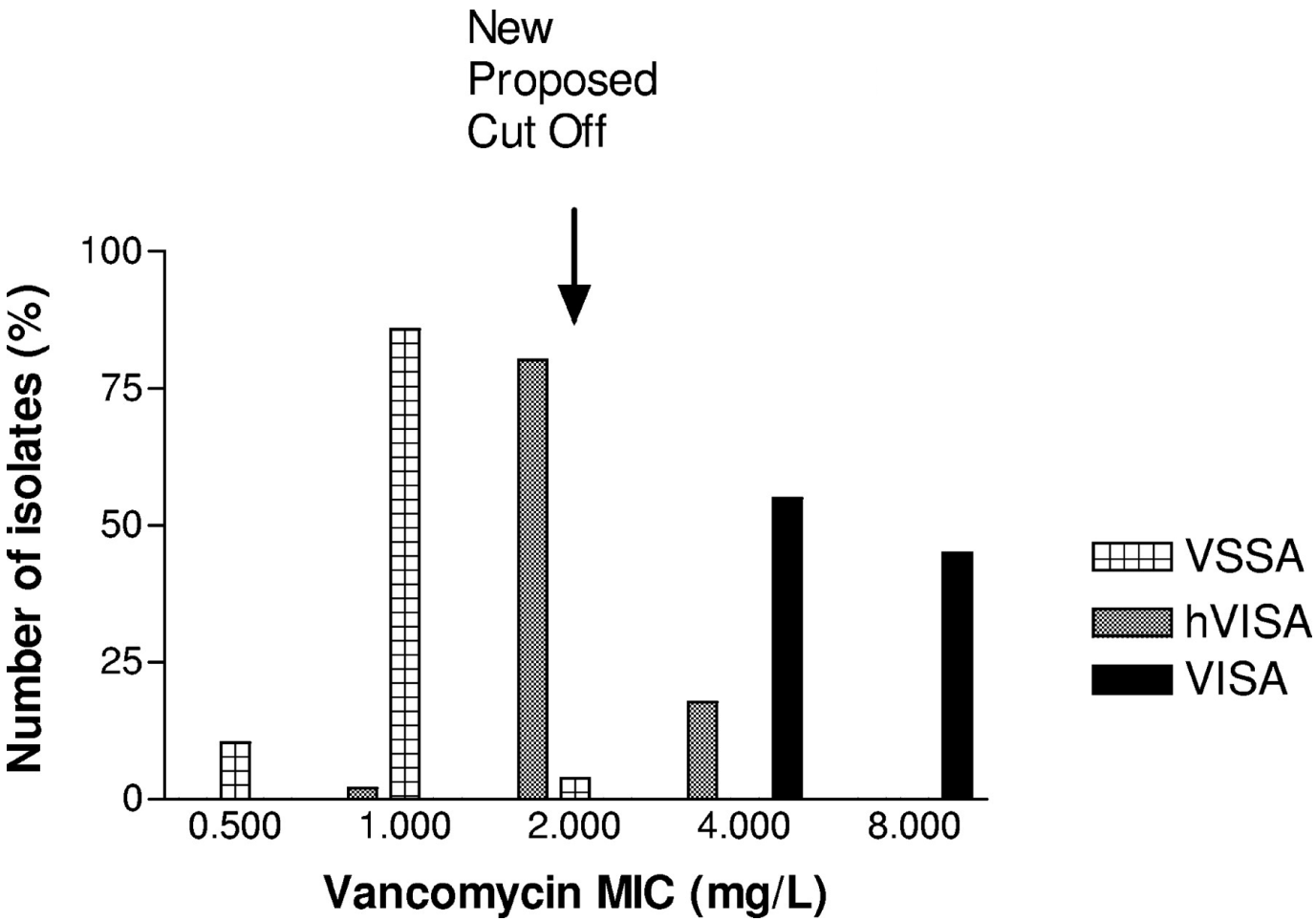
Evidence for Reduction in Breakpoints Used To Determine Vancomycin Susceptibility in *Staphylococcus aureus*



Wootton M et al *Antimicrobial Agents and Chemotherapy* (September 2005) 49:3982-3983



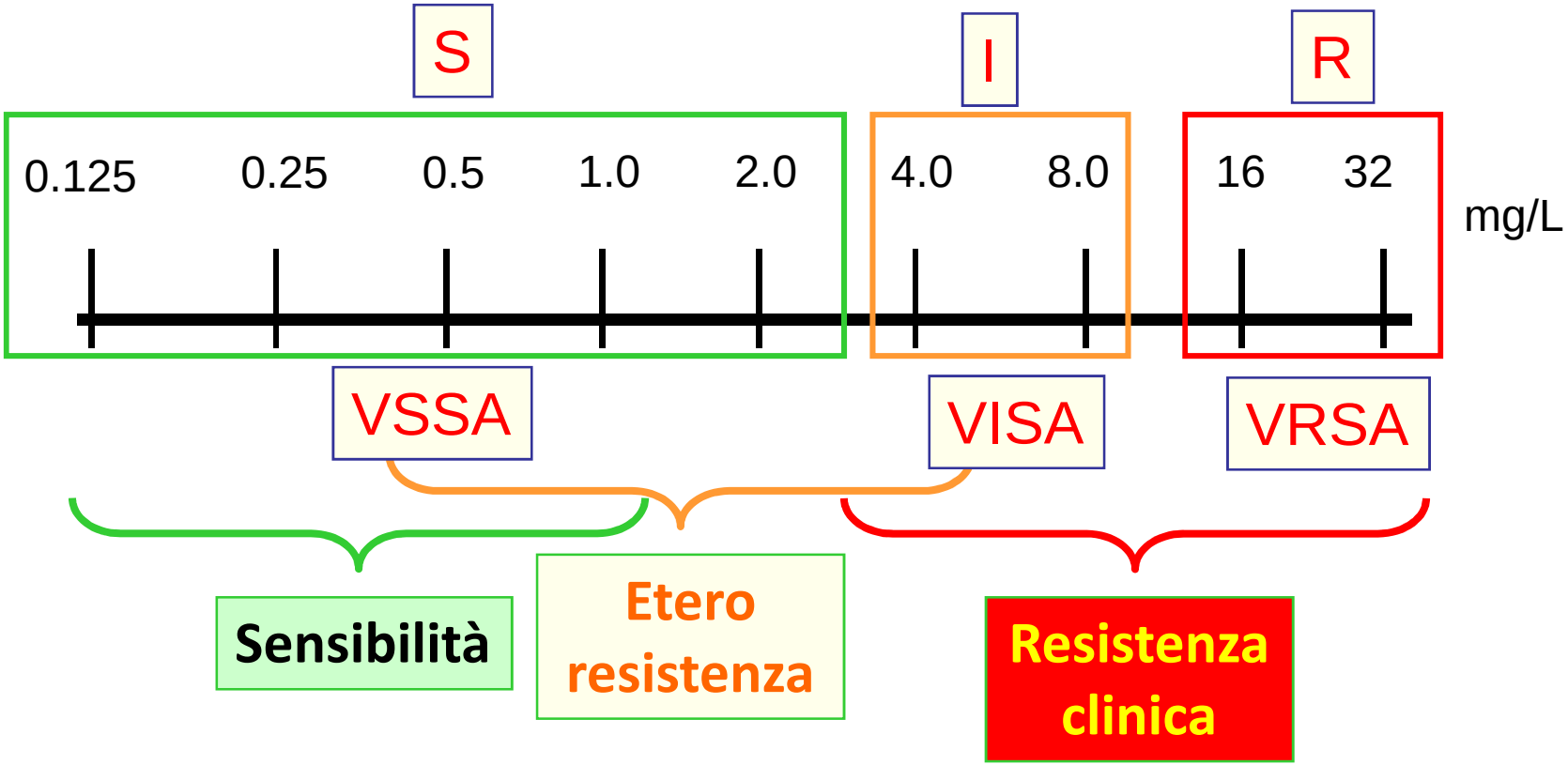
Evidence for Reduction in Breakpoints Used To Determine Vancomycin Susceptibility in *Staphylococcus aureus*

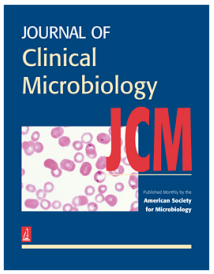


Wootton M et al *Antimicrobial Agents and Chemotherapy* (September 2005) 49:3982-3983

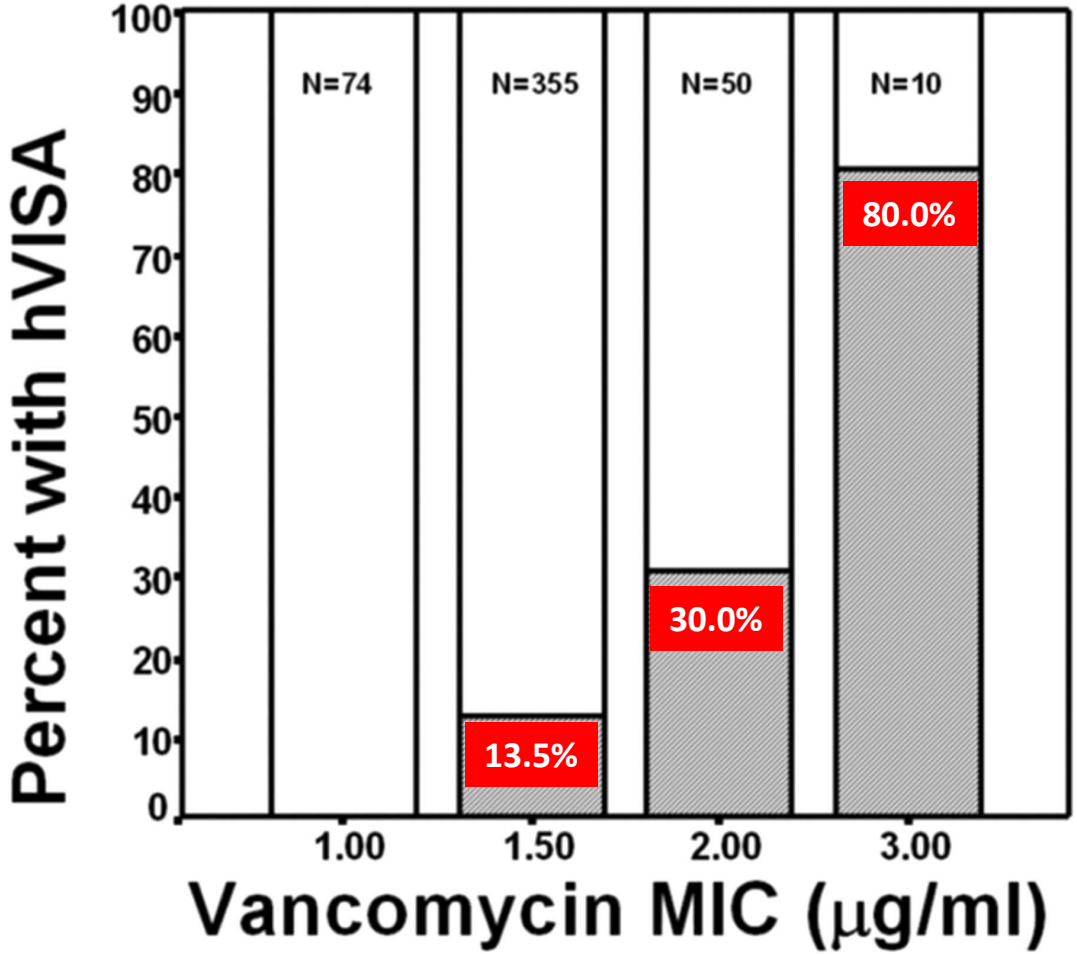
MIC a Vancomicina e *S. aureus*

Breakpoint CLSI

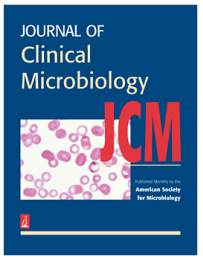




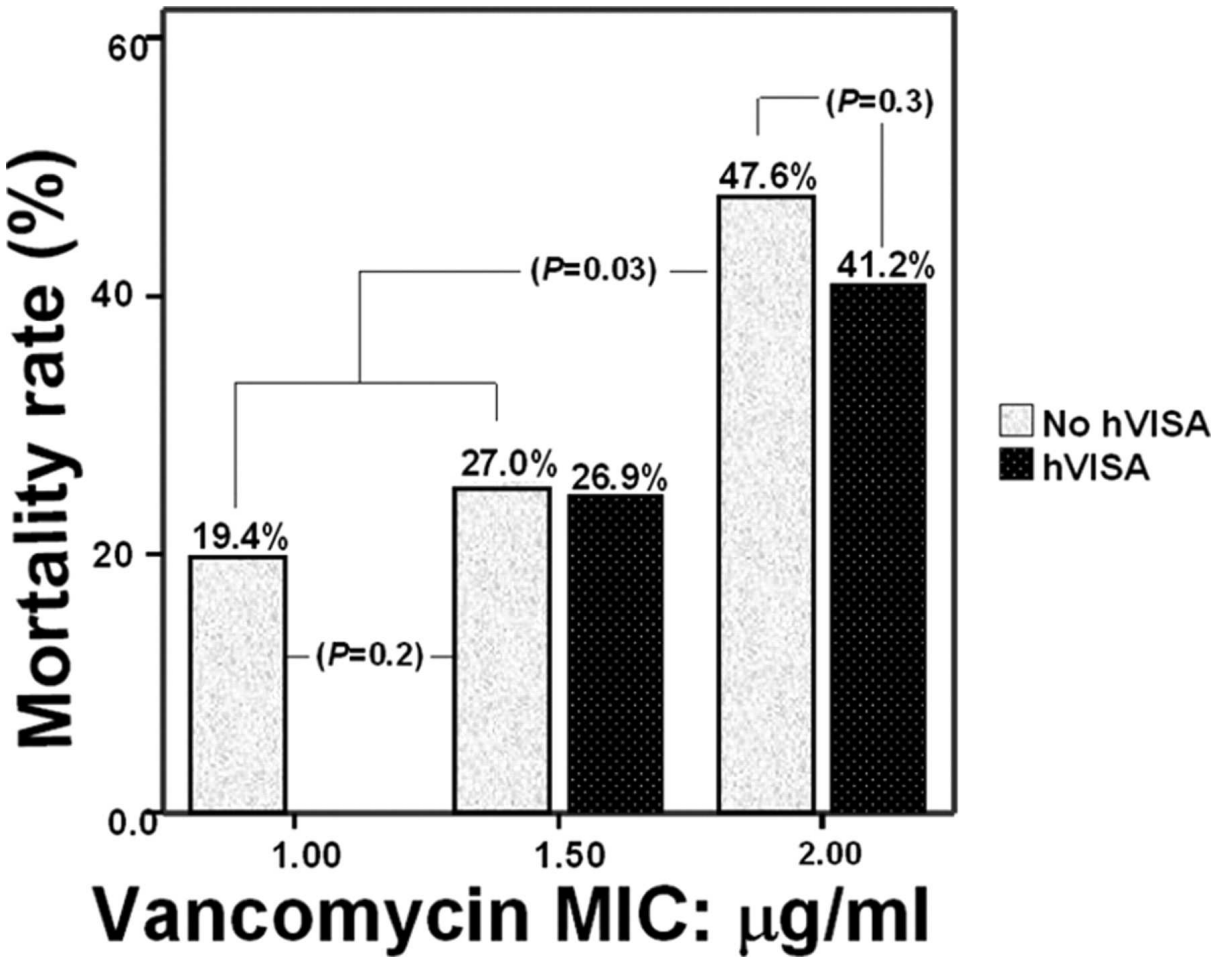
Frequency of hVISA (shaded area) among MRSA blood isolates saved intermittently between 1996 and 2006, stratified according to the vancomycin MIC.



Musta AC et al *Journal of Clinical Microbiology* (June 2009) 47:1640-1644



Mortality rate among patients with MRSA bacteremia stratified according to vancomycin MIC and hVISA infection status.



Musta AC et al *Journal of Clinical Microbiology* (June 2009) 47:1640-1644

Novel Screening Agar for Detection of Vancomycin-Nonsusceptible *Staphylococcus aureus*

Vancomycin MIC (mg/liter)[a]	Growth on BHI-V3 (no. of isolates)	No growth on BHI-V3 (no. of isolates)	Total
≥8	10	0	10
4	35	0	35
2	17	7	24
1	1	27	28
0.5	1	2	3

100% sensitivity

65% specificity

Vancomycin MIC determined by CLSI broth reference microdilution (BMD) using Difco Mueller-Hinton broth.

Burnham C-AD et al *Journal of Clinical Microbiology* (March 2010) 48:949-951

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

	MIC breakpoint (mg/L)		MIC breakpoint (mg/L)	
	S ≤	R >	S ≤	R >
	S. aureus e *S. lugdunensis*		Altri Stafilococchi Coagulasi-Negativi	
Beta-lattamasi	Negativa	Positiva	Negativa	Positiva
Oxacillina	2	2	0.25	0.25
Cefoxitina	4	4	NA	NA
Teicoplanina	2	2	4	4
Vancomicina	2	2	2	2
Levofloxacina	1	2	1	2
Eritromicina	1	2	1	2
Clindamicina	0.25	0.5	0.25	0.5
Rifampicina	0.06	0.5	0.06	0.5
Gentamicina	1	1	1	1
Tigeciclina	0.5	0.5	0.5	0.5
Daptomicina	1	1	1	1
Linezolid	4	4	4	4
Co-trimoxazolo	2	4	2	4

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	Dischetto (µg)	Breakpoint per diametro di alone (mm)		Breakpoint per diametro di alone (mm)	
		S ≥	R <	S ≥	R <
		S. aureus e *S. lugdunensis*		Altri Stafilococchi Coagulasi-Negativi	
Beta-lattamasi		Negativa	Positiva	Negativa	Positiva
Cefoxitina	30	22	22	25	25
Teicoplanina		NA	NA	NA	NA
Vancomicina		NA	NA	NA	NA
Norfloxacina (screen)	10	17	17	17	17
Eritromicina	15	21	18	21	18
Clindamicina	2	21	18	21	18
Rifampicina	5	25	22	25	22
Gentamicina	10	18	18	18	18
Tigeciclina	15	18	18	18	18
Daptomicina		NA	NA	NA	NA
Linezolid	10	17	17	17	17
Co-trimoxazolo	1.25-23.75	17	14	17	14

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Staphylococcus saprophyticus

Isolati urinari	**Dischetto (µg)**	**Breakpoint per diametro di alone (mm)**	
		S ≥	**R <**
Ampicillina	**2**	**15**	**15**
Co-trimoxazolo	**1.25-23.75**	**17**	**14**
Norfloxacina (screen)	**10**	**17[A]**	**17[A]**
Levofloxacina	*5*	*IP*	*IP*
Moxifloxacina	**5**	**22**	**19**
Nitrofurantoina	**100**	**13**	**13**