

UK

NEQAS

Susceptibility testing methods used in Europe

Does it make a difference?

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Susceptibility testing methods used in Europe

- Breakpoint guidelines followed
- Methods used

Does it make a difference?

- Performance of NEQAS participants related to guidelines and methods

Harmonisation of susceptibility breakpoints in Europe

- EUCAST

Participants in EARSS and UKNEQAS for Microbiology (2008)

	EARSS	NEQAS		EARSS	NEQAS
Austria	42	43	Italy	54	124
Belgium	110	4	Netherlands	24	18
Bulgaria	24	0	Poland	74	1
Croatia	27	6	Portugal	24	52
Czech Republic	47	0	Romania	37	2
Finland	13	23	Spain	40	0
France	68	0	Sweden	22	28
Germany	23	1	Switzerland	0	24
Greece	46	16	United Kingdom	54	278
Hungary	27	0	Other	111	82
Ireland	44	45			

Breakpoint guidelines used by participants in UKNEQAS 2007 and EARSS 2003

Guideline	NEQAS, No. (%) labs	EARSS, No. (%) labs
CLSI (NCCLS)	368 (53.7)	460 (62.4)
BSAC (UK)	203 (29.6)	25 (3.4)
SRGA (Sweden)	33 (4.8)	25 (3.4)
NWGA (Norway)	4 (0.6)	0
CRG (Netherlands)	5 (0.7)	5 (0.7)
DIN (Germany)	0	8 (1.1)
CA-SFM (France)	2 (0.3)	22 (3.0)
CZECH (Czech Republic)	0	8 (1.1)
FIRE (Finland)	0	2 (0.3)
MENSURA (Spain)	0	3 (0.4)
Others / >1 / no data	71 (10.3)	179 (24.3)
TOTAL	686	737

Methods used by participants in UKNEQAS 2008

Method	Portugal (%)	Other (%)
Disk diffusion	8 (16)	344 (51)
Automated	30 (60)	210 (31)
MIC	2 (4)	24 (4)
Breakpoint	2 (4)	21 (3)
Other/not stated	8 (16)	73 (11)
Total	50	672

Methods related to guidelines used by participants in UKNEQAS 2007

Method	CLSI n (%)	BSAC n (%)	SRGA n (%)
Disk diffusion	150 (41)	175 (86)	26 (79)
Automated	199 (54)	14 (7)	2 (6)
MIC	6 (2)	6 (3)	5 (15)
Breakpoint	12 (3)	6 (3)	0 (0)
Other/not stated	1 (1)	2 (1)	0 (0)

Compliance with CLSI method technical recommendations

Organism	No. labs	% compliance with CLSI recommendations
<i>S aureus</i>	153	50.6
<i>Enterococcus</i> spp	151	47.7
<i>S pneumoniae</i>	221	41.6
<i>H influenzae</i>	163	30.1
<i>N gonorrhoeae</i>	77	14.3

Do laboratories in Europe comply with recommendations in guidelines claimed to be used?

- Intermediate results in BSAC method for organism/antimicrobial combinations where there is no intermediate category (UKNEQAS)
 - Ceftazidime intermediate *E. coli* (before “I” introduced)
 - Tetracycline intermediate *S. aureus*
- Interpretations with agents not included in CLSI guidelines (UKNEQAS)
 - Fusidic acid with *S. aureus* (234 laboratories)
 - Mupirocin with *S. aureus* (108 laboratories)
- Failure to detect resistance when clearly demonstrated in UKNEQAS reference tests
 - MRSA



Performance related to breakpoint guidelines

Susceptibility testing of *E. coli* specimen 8508 to ampicillin (MIC 4-8 mg/L) by UKNEQAS participants

Method	Breakpoints	Susceptible		Intermediate		Resistant	
		Portugal	Other	Portugal	Other	Portugal	Other
CLSI	S _≤ 8 R>16	46	279	0	23	3	10
BSAC	S _≤ 8 R>16	1	172	0	3	0	13
SRGA	S _≤ 1 R>8	0	3	0	17	0	2

Susceptibility testing of *Neisseria gonorrhoeae* specimen 8482 to ciprofloxacin (MIC 0.5 mg/L) by UKNEQAS participants

Method	Breakpoints	Susceptible		Intermediate		Resistant	
		Portugal	Other	Portugal	Other	Portugal	Other
CLSI	S _≤ 0.06 R _{>} 0.5	16	57	10	107	8	85
BSAC	S _≤ 0.03 R _{>} 0.06	0	14	0	4	0	166
SRGA	S _≤ 0.03 R _{>} 0.06	0	2	0	0	0	28

Changes in breakpoints may affect reporting

S aureus 7240, Ciprofloxacin MIC 0.5 mg/L

Method	Breakpoints	Susceptible		Intermediate		Resistant	
		Portugal	Other	Portugal	Other	Portugal	Other
CLSI	$S_{\leq 1}$ $R_{>2}$	49	285	1	4	0	4
BSAC	$S_{\leq 1}$ $R_{>1}$	1	166	0	0	0	1
SRGA	$S_{\leq 0.06}$ $R_{>2}$	0	3	0	19	0	0

S aureus 7876, Ciprofloxacin MIC 0.25 mg/L

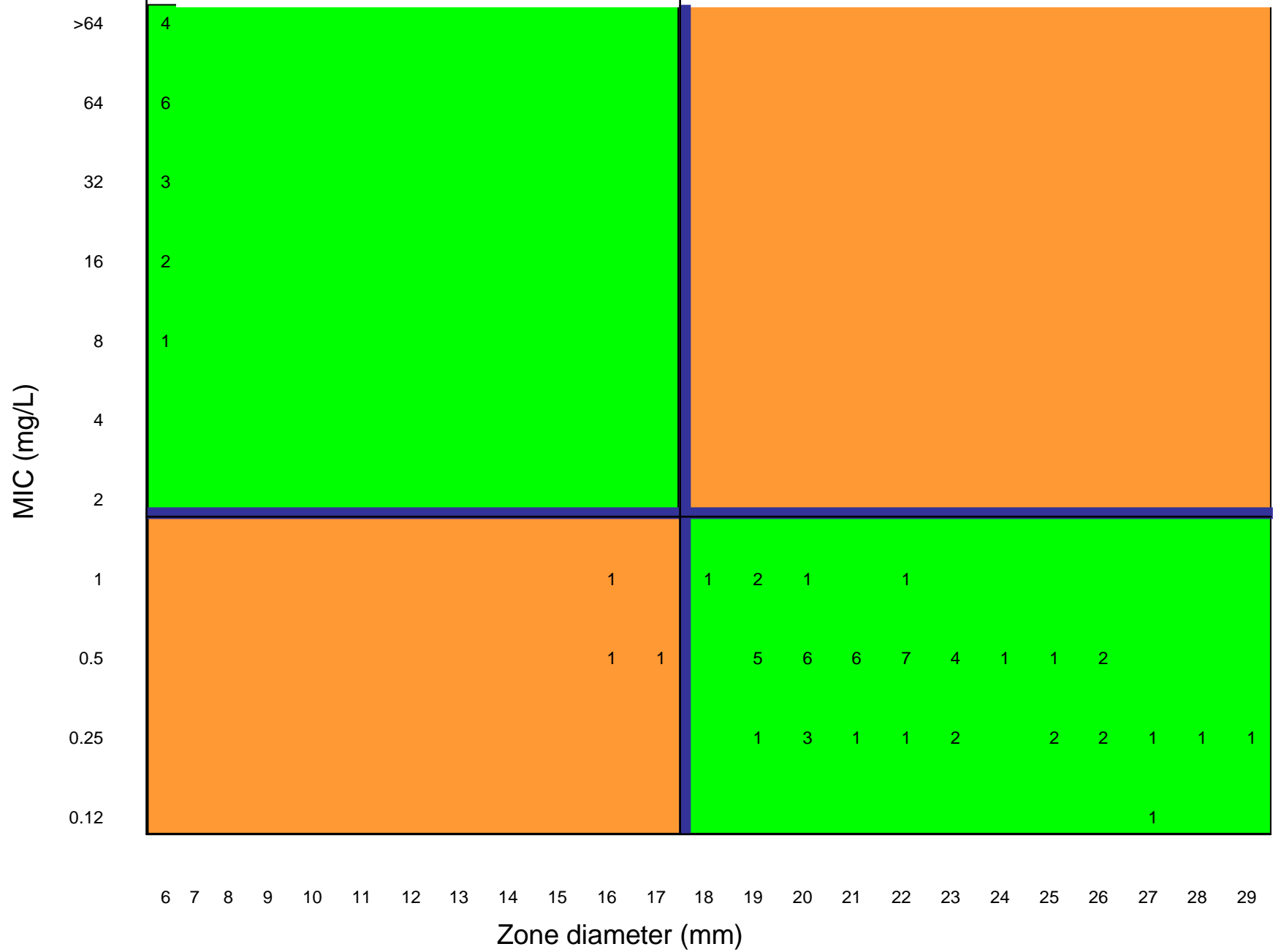
Method	Breakpoints	Susceptible		Intermediate		Resistant	
		Portugal	Other	Portugal	Other	Portugal	Other
CLSI	$S_{\leq 1}$ $R_{>2}$	46	304	0	0	0	0
BSAC	$S_{\leq 1}$ $R_{>1}$	1	175	0	0	0	1
SRGA	$S_{\leq 1}$ $R_{>1}$	0	23	0	2	0	1

Performance related to methods

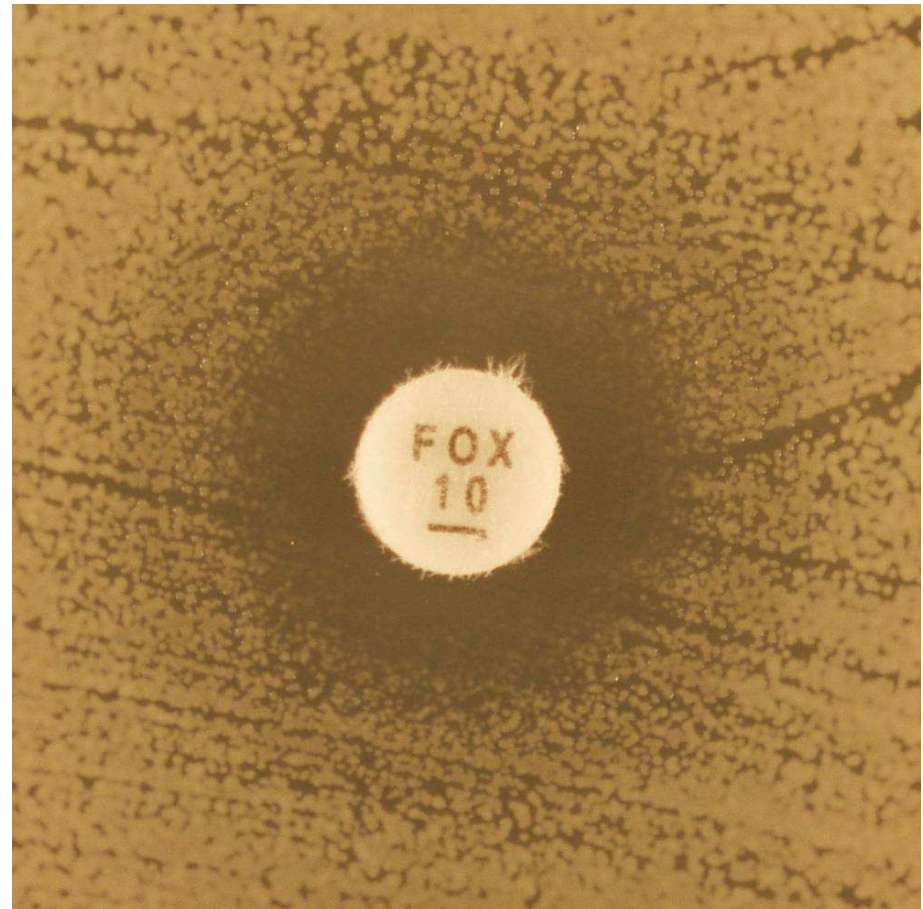
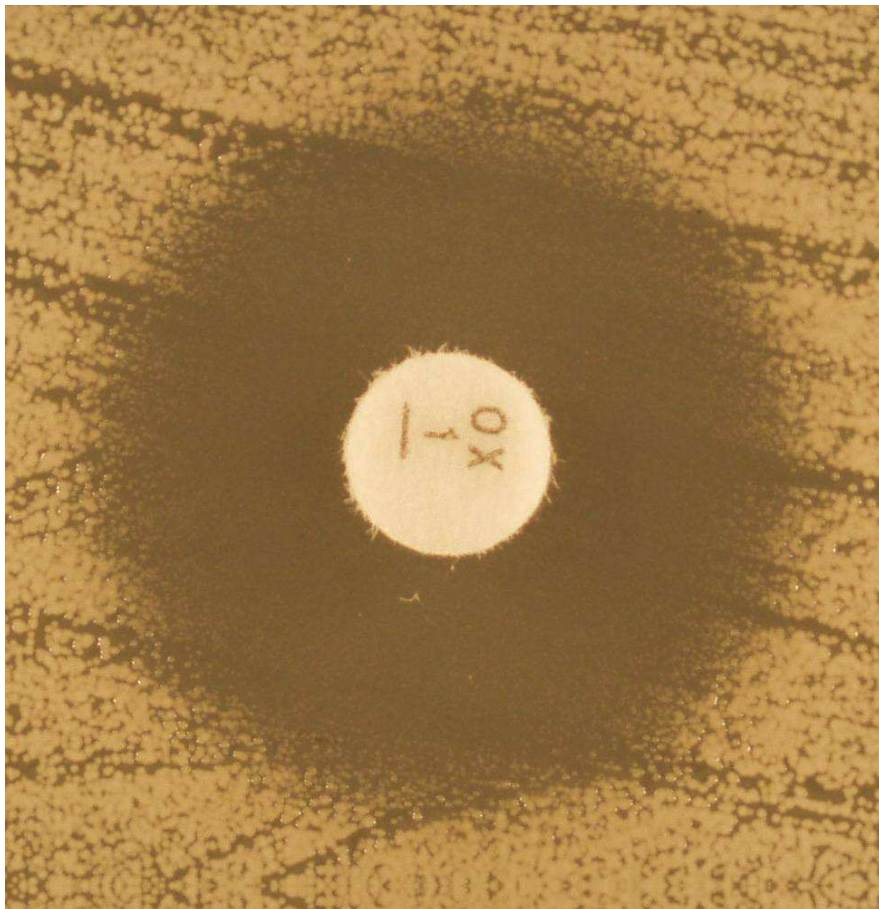
Susceptibility testing of *S. aureus* specimen 8578 to ciprofloxacin (MIC 1 mg/L)

Method	Breakpoints	Susceptible		Intermediate		Resistant	
		Portugal	Other	Portugal	Other	Portugal	Other
CLSI	S _≤ 1 R>2	42	286	0	20	1	3
BSAC	S _≤ 1 R>1	1	96	0	3	0	83
SRGA	S _≤ 1 R>1	0	19	0	1	0	1

S. aureus, ciprofloxacin, BSAC MIC v 1 µg disc



Detection of methicillin (oxacillin) resistance in *S. aureus* with cefoxitin



Detection of oxacillin/cefoxitin resistance in *mecA* positive *S aureus*

Organism	Oxacillin MIC (mg/L)	Oxacillin		Cefoxitin	
		n	%R	n	%R
7240	16->128	535	81	48	98
8248	64->128	609	94.9	162	99.4
7538	128->128	614	99	77	99
7597	>128	590	96	77	99
7659	>128	647	99.5	85	100
7703	>128	626	98.7	106	96.2

Penicillinase-hyperproducing *S. aureus*

S aureus 7876

oxacillin susceptible

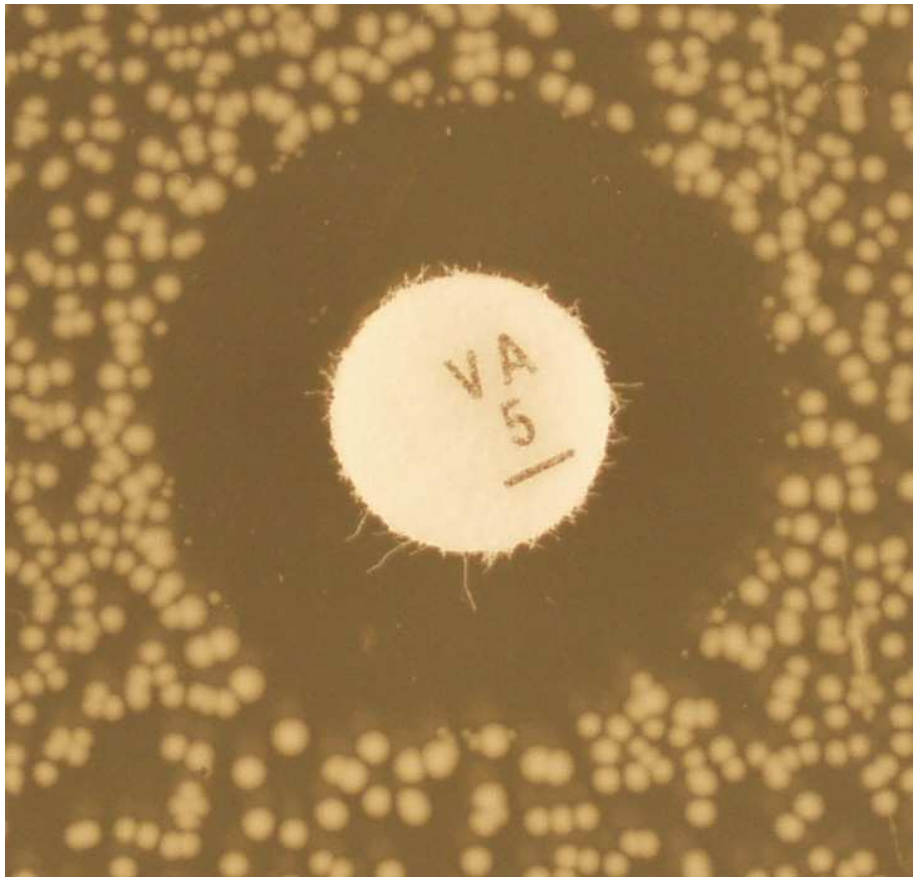
(MIC 0.5-1 mg/L)

mecA-ve)

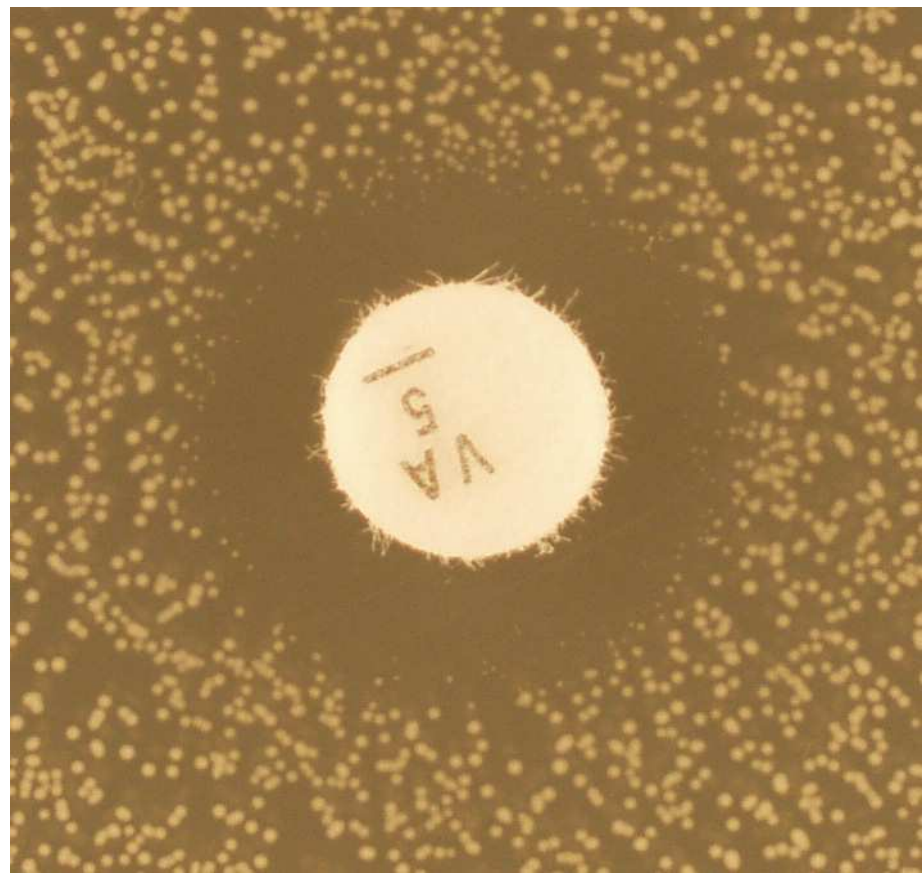


Organism	Oxacillin		Cefoxitin	
	n	%S	n	%S
7876	619	88	120	100

Detection of VanB glycopeptide resistance in enterococci



Vancomycin susceptible



VanB resistant

Detection of VanB glycopeptide resistance in enterococci by UKNEQAS participants

E. faecium 7826

Vancomycin MIC 8-16 mg/L, I/R

Method	Breakpoints	Susceptible		Intermediate		Resistant	
		Portugal	Other	Portugal	Other	Portugal	Other
CLSI	S _≤ 4 R>16	2	38	3	49	43	245
BSAC	S _≤ 4 R>8	0	84	0	8	1	107
SRGA	S _≤ 4 R>8	0	14	0	0	0	23

Methods used for detection of VanB glycopeptide resistance in enterococci

E. faecium 7826

Vancomycin MIC 8-16 mg/L, I/R

Method	Susceptible		Intermediate		Resistant	
	Portugal	Other	Portugal	Other	Portugal	Other
Disk	2	120	1	36	7	166
Automated	0	8	1	11	32	156
MIC	0	7	1	8	3	35
Breakpoint	0	3	0	2	3	16

Susceptibility testing methods used in Europe. Does it make a difference?

- No comprehensive data on guidelines/methods used and available data not entirely representative
- National guidelines largely followed in own countries, otherwise CLSI guidelines most widely used
- Disc diffusion methods most widely used but depends on the guidelines followed.
- Compliance with guidelines and methods unknown but some evidence that methods are not always strictly followed
- With some tests difference in performance in UK NEQAS can be associated with breakpoint guidelines or methods
- Does it make a difference?
 - Breakpoints – Yes
 - Methods – Mostly no, but some exceptions

EUCAST

European Committee on Antimicrobial Susceptibility Testing

Harmonisation of existing breakpoints

Setting clinical breakpoints for new antimicrobials

Revision of breakpoints

New antimicrobial agents are approved by regulatory authorities

- **Europe**

- National Medicines Agencies
- EMEA – European Medicines Agency

- **USA**

- FDA – Food and Drug Administration

EMA SOP for setting breakpoints through EUCAST



European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
PUBLIC		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

Available from the EUCAST (www.eucast.org) and EMA websites

CLSI / FDA

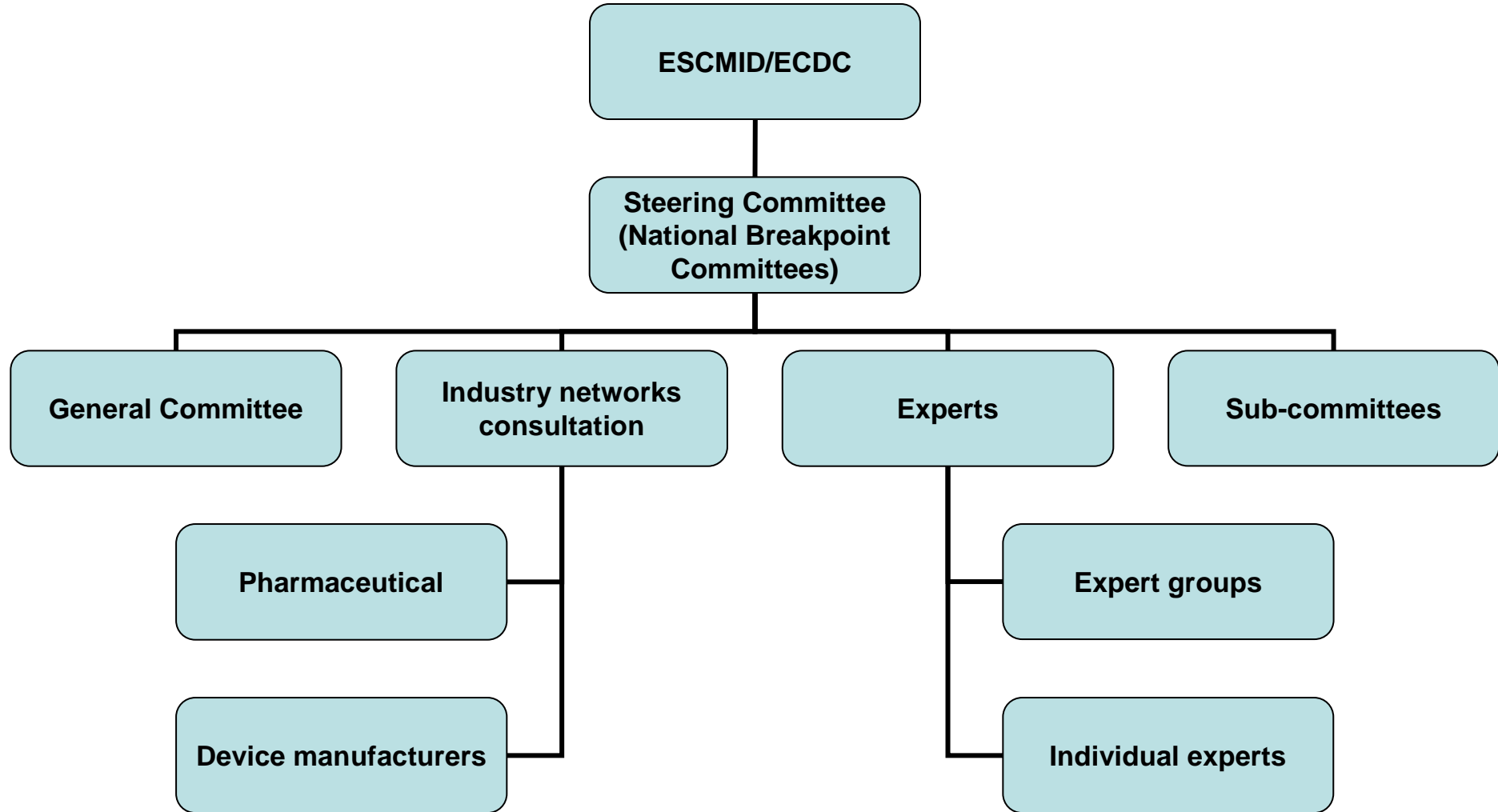
FDA has the legal authority to set breakpoints

CLSI has no legal status to determine breakpoints for new agents or to revise breakpoints for existing agents.

EUCAST compared with CLSI




EUCAST	CLSI
Committee representing the Profession with input from Regulatory authority.	Committee representing Industry, Profession and Regulatory authority
Industry consultative role	Industry major influence on decision process
Consensus process	Voting by committee members; several from industry
Five meetings per year	Two meetings per year
EUCAST functions as the breakpoint committee of EMEA	No agreement between CLSI and FDA
Transparent, rationale documents provided	No published rationale for decisions
All documents freely available	Documents for sale

Structure of EUCAST



EUCAST Steering Committee

- Chairperson Gunnar Kahlmeter
- Scientific Secretary Derek Brown
- Clinical data coordinator Rafael Canton

-  • BSAC (The UK) Alasdair MacGowan
-  • CA-SFM (France) Claude-James Soussy
-  • CRG (The Netherlands) Johan W. Mouton
-  • DIN (Germany) Arne Rodloff
-  • NWGA (Norway) Martin Steinbakk
-  • SRGA (Sweden) Christian Giske

- General Committee rep Antti Hakkanen (Finland)
- General Committee rep Paul Tulkens (ISC)

Previously: Czech republic, Greece, Spain, Russia, Poland , Italy

EUCAST General Committee

Austria Prof Helmut Mittermayer

Belgium Prof Jan Verhaegen

Bosnia Dr Selma Uzunovic-Kamberovic

Bulgaria Prof Krassimir Metodiev

Croatia Dr Arjana Tambic-Andrasevic

Czech Republic Dr Pavla Urbaskova

Denmark Dr Niels Frimodt-Møller

Estonia Dr M Ivanova

Finland Dr Antti Hakkanen

France Dr Luc Dubreuil

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Lithuania Prof Arvydsa Ambrozaitis

Netherlands Prof John Degener

Norway Dr Martin Steinbakk

Poland Prof Waleria Hryniewicz

Portugal Prof Jose Melo Cristino

Romania no official representative

Russia Dr Olga Stetsiouk

Serbia Dr Lazar Ranin

Slovak Republic Prof. Milan Niks

Slovenia Dr Jana Kolman

Spain Dr Francisco Soriano

Sweden Dr Barbro Olsson-Liljequist

Switzerland Prof Jaques Bille

Turkey Dr Deniz Gür

UK Prof Alasdair MacGowan

Yugoslavia no official representative

ISC – Prof Paul Tulkens

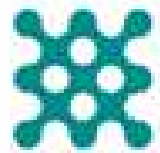
FESCI – Dr David Livermore

Chairperson Gunnar Kahlmeter, Sweden

Scientific Secretary Derek Brown, UK

Clinical data coordinator Rafael Canton, ES

<http://www.eucast.org>



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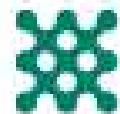
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[ESCMID - European Society of Clinical Microbiology and Infectious Diseases](#)

Finalised 2004-2005

Fluoroquinolones - EUCAST clinical MIC breakpoints 30 april 2004

Fluoroquinolone ¹	Species-related breakpoints (S</R>)										
	Enterobacteriaceae ²	Pseudomonas ³	Acinetobacter	Staphylococcus	Enterococcus	Streptococcus A,B,C,G	S.pneumoniae ⁴	H.influenzae M.catarrhalis ⁵	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes
Ciprofloxacin	0.5/1	0.5/1	1/1	1/1 ³	--	--	0.125/2	0.5/0.5	0.0	--	--
Levofloxacin	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1	--	--	--
Moxifloxacin	0.5/1	--	--	IE	--	IE	0.5/0.5	0.5/0.5	--	--	--
Norfloxacin	0.5/1	--	--	--	--	--	--	--	--	--	--
Ofloxacin	0.5/1	--	--	1/1 ³	--	--	0.125/4	0.5/0.5	0.1	--	--

- For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by national committees.
- Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case reports for other species.
- Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
- Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L, and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 mg/L. The breakpoints for levofloxacin relate to high dose therapy.
- Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC: s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. An Intermediate category was not

Aminoglycosides - EUCAST clinical MIC breakpoints 23 november 2004

Aminoglycosides ¹	Species-related breakpoints (S</R>)											Non-species related breakpoints ⁵ S</R>
	Enterobacteriaceae	Pseudomonas ²	Acinetobacter ²	Staphylococcus	Enterococcus ³	Streptococcus A,B,C,G	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes	
Amikacin	8/16	8/16	8/16	8/16 ⁴	--	--	--	IE	--	--	--	8/16
Gentamicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Netilmicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Tobramycin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4

- The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
- The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.
- Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and beta-lactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e. with gentamicin MIC>128 mg/L.
- Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.
- Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Glycopeptides - EUCAST clinical MIC breakpoints 30 april 2004

Glycopeptides	Species-related breakpoints (S</R>)										
	Enterobacteriaceae	Pseudomonas	Acinetobacter	Staphylococcus ¹	Enterococcus	Streptococcus A,B,C,G	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobe
Vancomycin	--	--	--	4/8	4/8	4/4	4/4	--	--	--	--
Telcoplanin	--	--	--	4/8	4/8	4/4	4/4	--	--	--	--

- Staphylococcus aureus* may be categorized as falsely susceptible to glycopeptides as glycopeptide MICs for strains with reduced susceptibility at the test conditions, in particular the medium used.
- Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-11-23, G Kahlmeter

Oxazolidinones - EUCAST clinical MIC breakpoints 30 april 2004

Oxazolidinone	Species-related breakpoints (S</R>)											Non-species related breakpoints ²
	Enterobacteriaceae	Pseudomonas	Acinetobacter	Staphylococcus ¹	Enterococcus ¹	Streptococcus A,B,C,G	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes	
Linezolid	--	--	--	4/4	4/4	2/4	2/4	--	--	--	--	2/4

- The S/I-breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild type MIC-distributions. Hence there is no intermediate category.
- Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-12-11, G Kahlmeter

Finalised 2006

Cephalosporins - EUCAST clinical MIC breakpoints 2006-03-31 (v 1.1)

Cephalosporins	Species-related breakpoints (S<R>)											Non-species related breakpoints ¹ S<R>
	Enterobacteriaceae ²	Pseudomonas ³	Acinetobacter	Staphylococcus ⁴	Enterococcus	Streptococcus A,B,C,G	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes	
Cefazolin	RD	--	--	note ⁴	--	--	--	--	--	--	--	1/2
Cefepime	RD	1/8	8/8	note ⁴	--	0.5/0.5 ⁶	1/2	0.25/0.25 ⁶	--	--	--	4/8
Cefotaxime	RD	1/2	--	note ⁴	--	0.5/0.5 ⁶	0.5/2 ⁶	0.12/0.12 ⁶	0.12/0.12 ⁶	0.12/0.12 ⁶	--	1/2
Ceftazidime	RD	1/8	8/8	--	--	--	--	--	--	--	--	4/8
Ceftriaxone	RD	1/2	--	note ⁴	--	0.5/0.5 ⁶	0.5/2 ⁶	0.12/0.12 ⁶	0.12/0.12 ⁶	0.12/0.12 ⁶	--	1/2
Cefuroxime	RD	8/8 ⁵	--	note ⁴	--	0.5/0.5 ⁶	0.5/1	1/2	--	--	--	4/8

1. Non-species related breakpoints for species where susceptibility testing is not recommended (marked with -- or IE in the table).
 2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some strains that produce ESBLs appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
 3. For cefepime and ceftazidime, the I/R-breakpoint for aztreonam in Pseudomonas aeruginosa was increased to avoid dividing the MIC wild type distribution. The I/R-breakpoint relates to high dose therapy.
 4. Susceptibility of staphylococci.
 5. The non-species related S/R-breakpoint for cefazolin.
 6. Strains with MIC values above the breakpoint have evidence regarding clinical use.
- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
 RD = rationale document listing data used by EUCAST for determining breakpoints.

Version*	Date
1.1	2006-05-17
1.0	2006-03-31

*The number before the point indicates breakpoint change.

Carbapenems - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.1)

Carbapenem	Species-related breakpoints (S<R>)											Non-species related breakpoints ¹ S<R>
	Enterobacteriaceae	Pseudomonas	Acinetobacter	Staphylococcus	Enterococcus	Streptococcus A,B,C,G	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes	
Ertapenem	RD	0.5/1	--	note ³	--	0.5/0.5 ^{4,7}	0.5/0.5 ^{4,7}	0.5/0.5 ^{4,7}	IE	--	1/1 ⁹	0.5/1
Imipenem	RD	2/8 ²	4/8 ⁶	2/8	note ³	4/8 ⁶	2/2 ^{4,7}	2/2 ^{4,7}	2/2 ^{4,7}	IE	--	2/8
Meropenem	RD	2/8	2/8	2/8	note ³	--	2/2 ^{4,7}	2/2 ^{4,7}	2/2 ^{4,7}	IE	0.25/0.25 ^{6,7}	2/8

1. Non-species related breakpoints for species where susceptibility testing is not recommended (marked with -- or IE in the table).
 2. Proteus and Morganella.
 3. Susceptibility of staphylococci.
 4. Imipenem and ertapenem.
 5. Meropenem breakpoint.
 6. The imipenem S/I breakpoint.
 7. Strains with MIC values above the breakpoint have evidence regarding clinical use.
 8. The ertapenem S/I breakpoint.
- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
 RD = rationale document listing data used by EUCAST for determining breakpoints.

Version*	Date
1.1	2006-06-20
1.0	2006-03-31

*The number before the point indicates breakpoint change.

Aztreonam - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.2)

Aztreonam	Species-related breakpoints (S<R>)											Non-species related breakpoints ¹ S<R>	
	Enterobacteriaceae ²	Pseudomonas	Acinetobacter	Staphylococcus	Enterococcus	Streptococcus A,B,C,G	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes		
Aztreonam	RD	1/8	1/16 ³	--	--	--	--	--	IE	IE	--	--	4/8

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).
2. The aztreonam breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some strains that produce ESBLs appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. The I/R-breakpoint for aztreonam in Pseudomonas aeruginosa was increased to avoid dividing the MIC wild type distribution. The I/R-breakpoint relates to high dose therapy.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
 IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
 RD = rationale document listing data used by EUCAST for determining breakpoints.

Version*	Date	Action
1.2	2006-06-20	This table rearranged in reversed chronological order
1.1	2006-06-12	Footnote 2, amended to include intermediate.
1.0	2006-03-31	Released by EUCAST

*The number before the point indicates breakpoint change. The number after the point indicates minor changes (footnotes, spelling, format, etc) without a change of breakpoints.

Finalised 2007-2008

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Penicillins - EUCAST clinical MIC breakpoints 2007-03-02 (version 0.6)

Penicillins (iv)	Species-related breakpoints (S≤/R>)											Non-species related breakpoints ¹⁸	
	Enterobacteriaceae ³	Pseudomonas	Acinetobacter ⁷	Staphylococcus ⁸	Enterococcus	Streptococcus A,B,C,G ¹²	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes		Gram-positive anaerobes
Benzylpenicillin	--	--	--	0.12/0.12 ⁸	Note ¹⁰	0.25/0.25 ¹³	0.06/1	IE ¹⁶	0.06/1 ¹⁶	0.06/0.25	0.25/0.5	0.25/0.25	0.25/1
Ampicillin ⁹	--	--	--	0.12/0.12 ⁸	Note ¹⁰	0.25/0.25 ¹³	0.06/1	IE ¹⁶	0.06/1 ¹⁶	0.06/0.25	0.25/0.5	0.25/0.25	0.25/1

Click on antibiotic name to see wild type MIC distributions.

2007-03-02 (version 0.6)

Macrolides, lincosamides, streptogramins - EUCAST clinical MIC breakpoints 2007-01-31 (v 0.4)

Macrolide	Species-related breakpoints (S≤/R>)											Non-species related breakpoints ¹⁸	
	Enterobacteriaceae	Pseudomonas	Acinetobacter	Staphylococcus	Enterococcus	Streptococcus	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes		Gram-positive anaerobes
Piperacillin	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Piperacillin/tazobactam ¹	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Ticarcillin	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Ticarcillin/clavulanate ¹	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Phenoxymethylpenicillin	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Pivmecillinam	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Oxacillin ²	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Cloxacillin	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Dicloxacillin	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1
Flucloxacillin	--	--	--	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1	0.06/1

Click on antibiotic name to see wild type MIC distributions.

2007-01-31 (v 0.4)

Miscellaneous antimicrobials - EUCAST clinical MIC breakpoints 2007-05-14 (v 0.2)

Wild type MIC distributions of bacteria and epidemiological cut-off values for measurement of resistance development.

Antimicrobial	Species-related breakpoints (S≤/R>)											Non-species related breakpoints	
	Enterobacteriaceae	Pseudomonas	Acinetobacter	Staphylococcus	Enterococcus	Streptococcus	S.pneumoniae	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram+ anaerobe bacteria		Gram- anaerobe bacteria
Doxycycline	note ²	--	--	1/2	--	1/2	1/2	1/2	1/2	--	?	?	IE
Tetracycline ⁴	0.25/4	--	--	1/2	--	1/2	1/2	1/2	1/2	--	?	?	IE
Minocycline	0.25/4 ³	--	IE	0.5/0.5	--	0.5/0.5	0.5/0.5	?	?	1/2 ⁵	?	?	IE
Fusidic acid	--	--	--	0.5/1	--	--	--	--	--	--	--	--	IE
Chloramphenicol	8/8	--	--	8/8	--	8/8	8/8	1/2	--	2/4	?	?	IE
Rifampicin	--	--	--	0.06/1	--	0.06/1	0.06/1	1/1 ⁵	--	0.5/1 ⁵	--	--	IE
Nitrofurantoin ⁷	64/64	--	--	64/64	64/64	64/64	--	--	--	--	--	--	IE
Trimethoprim ⁷	2/4	--	--	2/4	0.032/1 ⁸	--	--	--	--	--	--	--	IE
Trimethoprim-sulfamethoxazole (co-trimoxazole) ⁹	2/4 ⁹	Note ¹⁰	2/4 ⁹	2/4 ⁹	0.032/1 ^{8,9}	1/2 ⁹	1/2 ⁹	0.5/1 ⁹	--	--	--	--	IE
Fosfomicin iv	?	--	--	--	--	IE	IE	--	--	--	--	--	IE
Fosfomicin-trometamol	8/128	--	--	--	--	--	--	--	--	--	--	--	IE
Colistin	2/4	4/4	2/4	--	--	--	--	--	--	--	--	--	IE
Metronidazole ¹¹	--	--	--	--	--	--	--	--	--	--	4/4	4/4	--

1. Non-species related breakpoints have been determined not been given a species-specific breakpoint and not for Clarithromycin is used for the eradication of *H. pylori* an Erythromycin administered intravenously is active again mg/L.

2. Azithromycin is used in the treatment of *S. typhi* (S≤16 mg/L) respective wild type distributions (strains without any no inducible clindamycin resistance can only be detected i Erythromycin MIC values of 1-16 mg/L are typical for w are not given.

3. Erythromycin is no longer used in the therapy of *N. gon*

4. Quinupristin/dalfopristin breakpoints for *Enterococcus s*

5. Pharmacodynamic data for calculation of non-species n

-- = Susceptibility testing not recommended as the species IE = There is insufficient evidence that the species in questi RD =Rationale document listing data used for setting EUCA

Version*	Date	Action
0.5	2007-03-01	Preliminary table followin introduction of epidemiol
0.4	2007-01-30	Preliminary table after the EU
0.3	2006-11-21	Preliminary table after the EU
0.2	2006-09-09	Preliminary table for discussi
0.1	2006-04-06	Preliminary table for discussi

*The number before the point indicates breakpoint change. The

1. For susceptibility t

2. For susceptibility t

3. *Klebsiella* spp and

4. For systemic infec and some isolates

5. Pivmecillinam brea

6. Piperacillin and tic

7. Penicillin suscepti

8. Most staphylococ producers.

9. Susceptibility of st

10. For *Enterococcus*

11. Aminopenicillin bre international endo

12. For viridans strept

13. Strains with MIC v evidence regarding

1. Non-species related breakpoints are determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for i susceptibility testing is not recommended (marked with -- or IE in the table).

2. Doxycycline susceptibility is best determined using tetracycline.

3. Microorganisms susceptible to tetracycline are also susceptible to doxycycline and minocycline. Some staphylococci, streptococci and H.influenzae resistant to tetracycline may be susceptible to minocycline.

4. Tetracyclines are used in the treatment of brucellosis (MIC of wild type distributions:), *Pasteurella multocida* breakpoints for tetracycline is 2/4 mg/L. *Yersinia pestis* (), *Yersinia enterocolitica* () and *Burkholderia pseudomallei*.

5. For prophylaxis only. Refer to national guidelines for prophylaxis of bacterial meningitis.

7. For urinary tract infections only.

8. Enterococcus - find some more MIC-distributions.

9. Trimethoprim concentration in the presence of sulfamethoxazole in the ratio 1:19.

10. Trimethoprim-sulfamethoxazole (co-trimoxazole) breakpoint 4/4 mg/L for *Stenotrophomonas maltophilia* only (see 9).

11. Metronidazole is used for the treatment of *Helicobacter pylori* infections. The breakpoint is 4/4 mg/L.

EUCAST – the future

- Funding
 - ECDC contract for 3 years
 - Continued support from ESCMID
- Continuing collaboration with EMEA
- Continuing development of breakpoints and other susceptibility testing issues
- Implementation of breakpoints
 - Automated susceptibility testing systems with EUCAST MIC breakpoints (2009)
 - Disk diffusion
 - Use BSAC, CA-SFM or SRGA
 - A future International disk test with EUCAST zone diameter/MIC correlates
 - National Antibiotic Committees to be encouraged

The role of National Antimicrobial Committees?

Link to national microbiology in European countries

- To provide extended consultation
- As partners for developing, testing and implementing new methodology
- To provide experts for EUCAST and its subcommittees
- National forums for discussion of antimicrobial-related issues and education of medical and scientific staff

ECDC/ESCMID/EUCAST initiative 2009: to encourage European countries to identify or form National Antimicrobial Committees and to try to tie these to EUCAST through the EUCAST General Committee.