

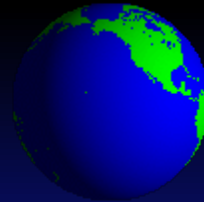


EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

EUCAST in Europe 2011



Gunnar Kahlmeter

Chairman of EUCAST



ESCMID

EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES



Methods for susceptibility testing

- **Phenotypic test methods**

based on **antimicrobial activity (MIC)** and **breakpoints**

- MIC, disk diffusion, automated systems like Phoenix, Vitek2, Microscan
- **Predicts susceptibility and resistance**
- **Quantifiable**

- **Genotypic test methods**

based on the detection of a **resistance gene** or its **product**

- mecA, vanA, vanB,PBP2, ... betalactamase detection....
- **Predicts resistance, not sensitivity**
- **Not quantifiable**
- **Useful for epidemiological purposes**

- **By deduction** – “expert rules”

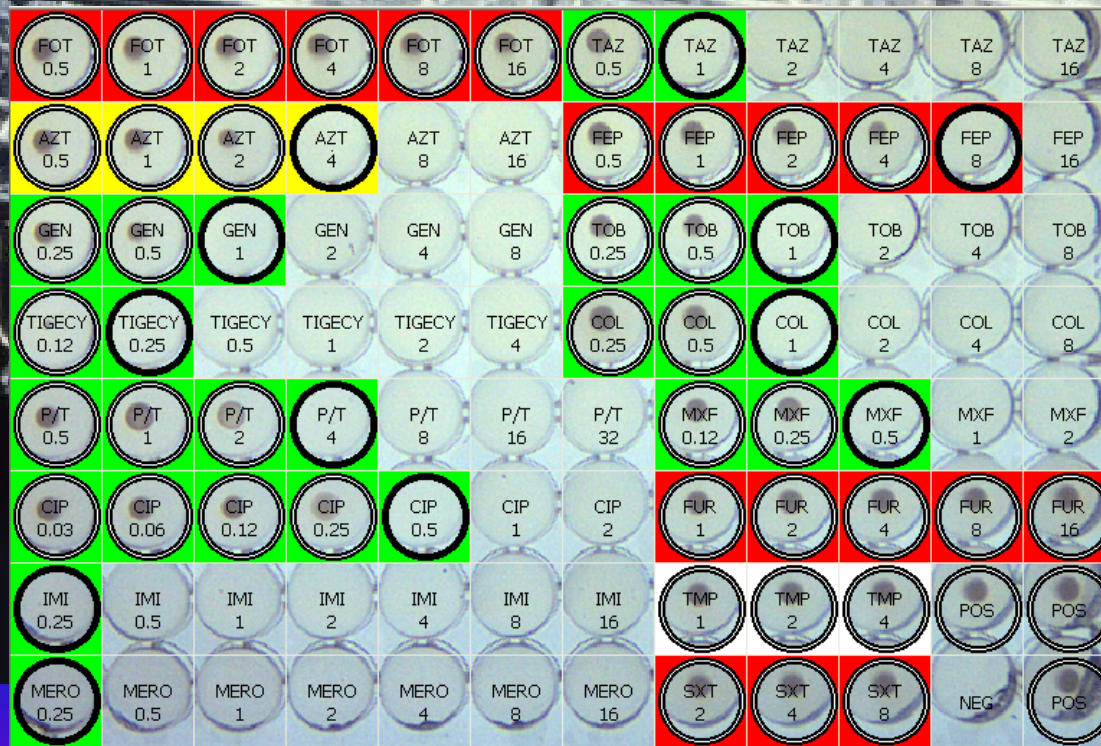
- If mecA-positive then report betalactam antibiotics R – or soon not?
- If ESBL-positive, then report betalactam antibiotics R – but not any longer!
- If erythromycin-resistant, then report roxithro- and clarithromycin R;
- **Some rules predict susceptibility, others resistance.**
- **Not reliable!**
- **Not quantifiable!**

Phenotypic susceptibility testing is
centred around

MIC

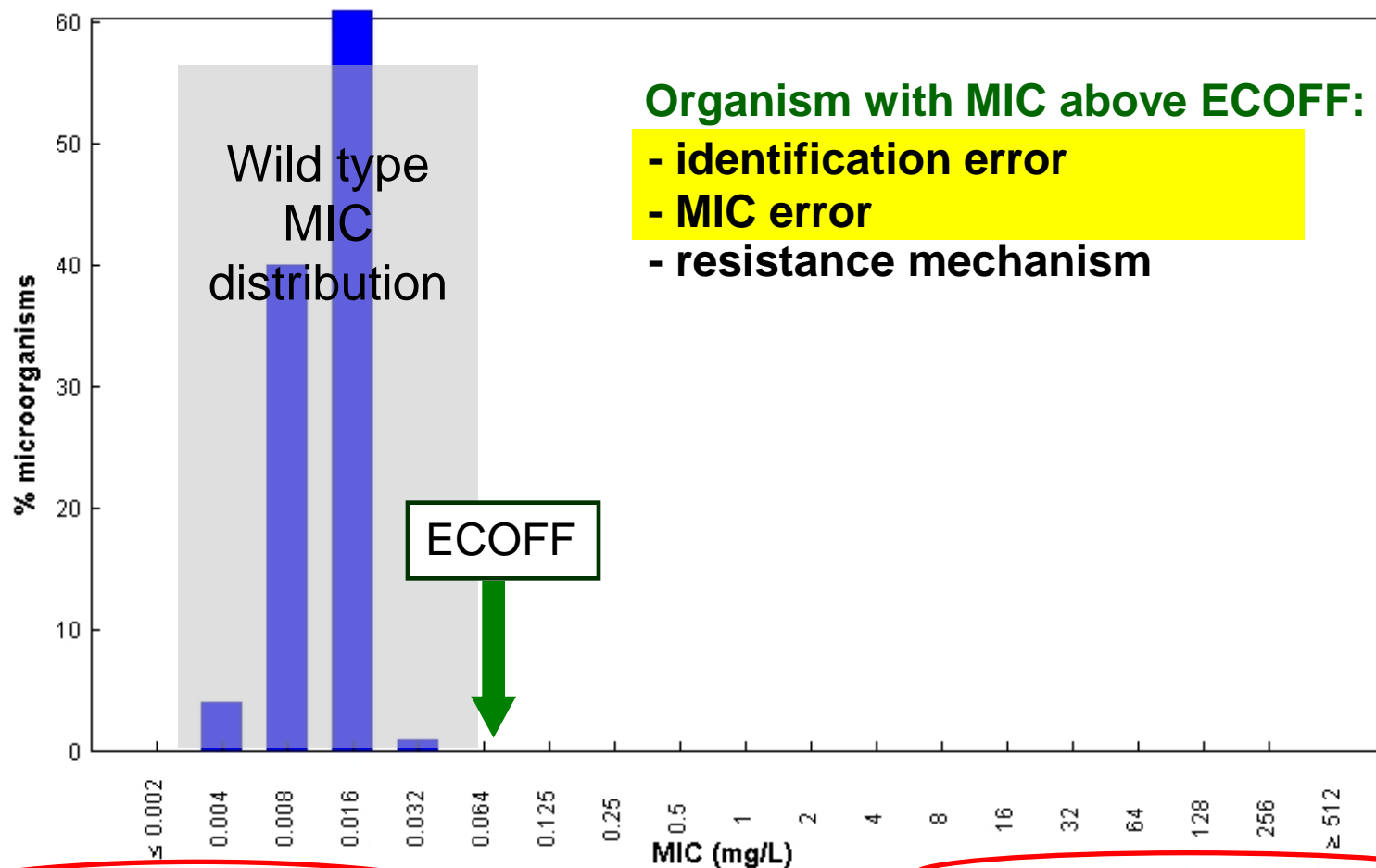
Breakpoints

From 2007 there is international agreement on an ISO-standard for MIC-determination of non-fastidious organisms in broth.



Benzylpenicillin / *Streptococcus pyogenes*
EUCAST MIC Distribution - Reference Database

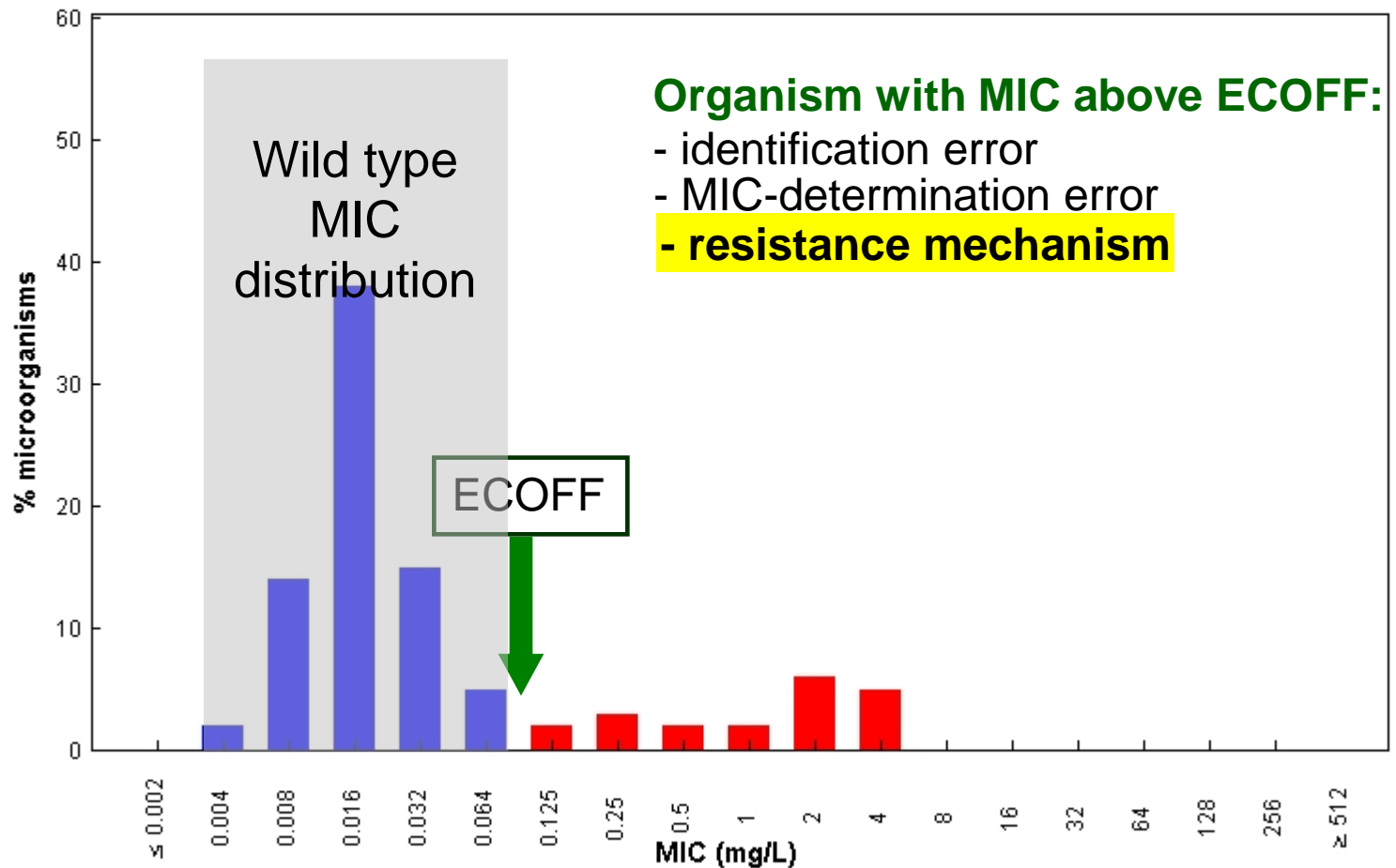
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



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

Benzylpenicillin / *Streptococcus pneumoniae*
EUCAST MIC Distribution - Reference Database

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



MIC

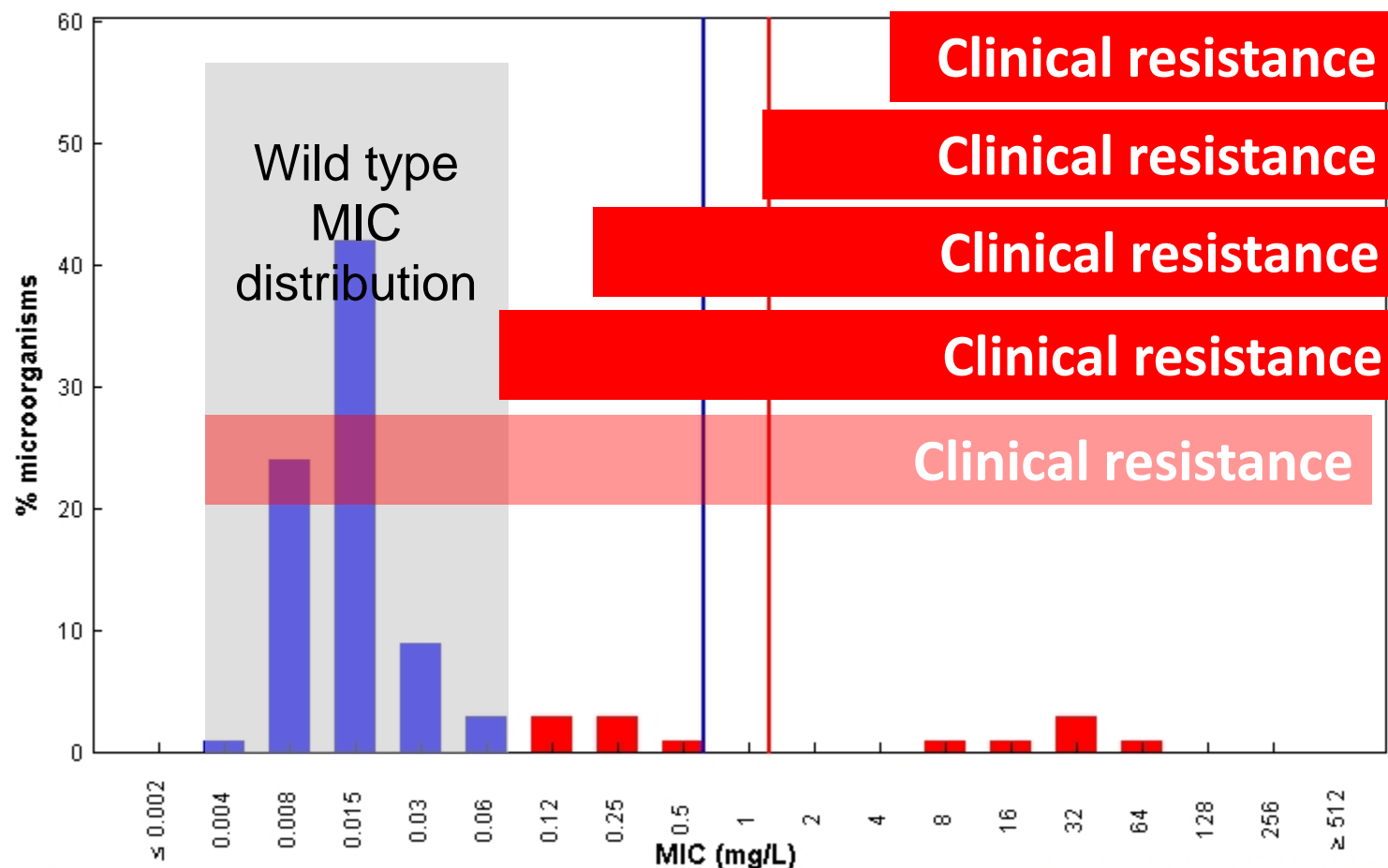
Epidemiological cut-off: WT ≤ 0.064 mg/L

37642 observations (32 data sources)

Clinical breakpoints: S ≤ 0.064 mg/L, R > 2 mg/L

Ciprofloxacin / *Escherichia coli* **EUCAST MIC Distribution - Reference Database 2011-12-01**

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

17877 observations (82 data sources)
 Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Breakpoints can fail in several ways!

- Fail to predict failure (undercall resistance)
 - CLSI piperacillintazobactam breakpoints in *Pseudomonas*
- Fail to predict success (overcall resistance)
 - Penicillin breakpoints in *S.pneumoniae* in pneumonia
- Fail to be useful (lack of correlation with either success or failure or fail to achieve reproducibility)
 - Breakpoints dividing WT populations – eg. previous Erythromycin breakpoints in *H.influenzae*

EUCAST was formed in 1996 and reformed in 2001.

Committee		Country	Disk Diffusion test?
EUCAST		Europe	Yes
CLSI		USA	Yes

*EUCAST is the umbrella for national breakpoint committees in Europe: BSAC, CA-SFM, CRG, DIN, NWGA & SRGA.



National Breakpoint Committees
D, F, N, NL, S, UK,



EUCAST General Committee
All European Countries + ISC/FESCI

EUCAST Steering Committee
BSAC, CA-SFM, CRG, DIN, NWGA, SRGA
And 2 reps from the General Committee*



Subcommittees

Antifungals
Anaerobes
Expert Rules

Expert groups
Neisseria
Helicobacter
C.difficile
etc...

*Currently: Estonia and Austria

EUCAST and CLSI are different

EUCAST

- Profession together with regulatory authorities
- Funded by ESCMID, ECDC and national breakpoint committees.
- Industry consultative role.
- Decision by consensus.
- Five meetings per year.
- EUCAST=EMEA brpt committee.
- Clinical breakpoints and ECOFFs
- Rationale for decisions published
- Documents free of charge (on web)

CLSI

- Industry, the profession, advisory regulators.
- Funded by industry and sales of output.
- Industry part of decision process
- Decision by vote.
- Two meetings per year.
- CLSI technical standing with FDA.
- Clinical breakpoints
- Rationale for decisions not published.
- Documents for sale

Tools for determining **CLINICAL BREAKPOINTS**

1. Dose or doses
2. Target organisms
3. Individual MIC-distributions for target organisms
 - breakpoints must not divide MIC-distributions of WT target organisms
4. Resistance mechanisms in target organisms
5. Clinical indications
6. Pharmacokinetics (C_{max}, AUC, T_{1/2}, Protein binding, V_d..)
7. Pharmacodynamic properties (peak conc/MIC, AUC/MIC, TA, MCs)
8. Clinical outcome (clinical outcome vs. MIC)
9. Epidemiological cutoffs, Pk/Pd-breakpoints and clinical data together determine the **CLINICAL BREAKPOINT**

EUCAST and CLSI breakpoints are different

	Antibiotics	Identical breakpoints		
	compared	S and R	Only S	Only R
Enterobacteriaceae	33	3	4	3
<i>Pseudomonas</i> spp.	16	1	5	2
<i>Acinetobacter</i> spp.	10	1	4	2
<i>Staphylococcus</i> spp.	27	4	6	2
<i>Enterococcus</i> spp.	6	0	2	3
Strept A, B, C and G	13	2	2	2
<i>S. pneumoniae</i>	24	3	2	5
Other streptococci	9	0	0	2
<i>Haemophilus</i> spp.	25	0	3	0

CLSI vs. EUCAST

All EUCAST breakpoints were determined AC

- EUCAST: Breakpoints must be reviewed at intervals
 - Extension of indications
 - Extension of target organisms
 - New resistance mechanisms
 - New drug in class
 - New clinical experience
 - New dosing or administration
 - Time

EUCAST

- breakpoints for new drugs with EMA

- Daptomycin ✓
- Tigecycline ✓
- Doripenem ✓
- Glycopeptides (two ongoing)
- Cefalosporine (activity against MRSA)
- Anti-Mtb (two agents to be started)

- Cefalosporine w. activity against MRSA (withdrawn)
- Fluoroquinolone (withdrawn)
- Diaminopyrimidine (withdrawn)

- Extensions of indications (currently none)

EMA = European Medicines Agency

EUCAST and the harmonisation process

Reviewed 2002 – 2009:

- Aminoglycosides
- Carbapenems & aztreonam (2nd review)
- Cephalosporins iv (2nd review)
- Cephalosporins oral
- Fluoroquinolones
- Glycopeptides (2nd review)
- Macrolides and lincosamines
- Miscellaneous antimicrobials
- Penicillins
- Tetracyclines

- Antifungal drugs (Candidae & Aspergillus)
 - fluconazole, voriconazole, posaconazole
 - anidulafungin, amfotericin B.

Topical agents:

Mupirocin (LLR/HLR)
Retapamulin (ECOFF)

Drugs being addressed:

Cefalothin (ECOFF)
Cefazoline (ECOFF)
Cefoperazone (ECOFF)
Sulbactam (alone)
Kanamycin
Streptomycin
Josamycin
Spiramycin
....

**Lack of data for
older drugs!**

Miscellaneous organisms

Consultation with expert groups on breakpoints and methods

- *Neisseria meningitidis* (review) - 2011
- *Moraxella catarrhalis* (finalized) - 2011 ✓
- *Helicobacter pylori* (finalized) - 2011 ✓
- *Clostridium difficile* (finalized) - 2011 ✓
- *Listeria monocytogenes* (finalized) - 2011 ✓
- *Campylobacter* (ongoing) - 2011
- *Pasteurella multocida* (ongoing) - 2012
- *Corynebacteria* (ongoing) - 2012
- *Legionella pneumophila* (ongoing) - 2012
- *Burkholderia cepacia* (started) - 2012
- ...

EUCAST expert rules

v 2.0 (2011)

- **Intrinsic resistance** – “don’t test, report resistant or not at all.
- **Exceptional phenotype** – “Don’t believe it if you see one!”
 - Exceptional resistance (ex. Penicillin resistance in *S. pyogenes*)
 - Exceptional susceptibility (ex. Ampicillin susceptibility in *K. pneumoniae*)
- **Interpretive reading (Expert Rules): IF - THEN**
 - IF mecA-positive, THEN report all betalactam antibiotics R (?!?)
 - IF ESBL-positive, THEN report betalactam antibiotics R (no longer valid!)

Expert rules are useful but may be unreliable!

EUCAST subcommittees

- **Expert rules and interpretive reading**
 - Major revision (v 2.0) now available
 - Published in CMI 2011
- **Antifungal susceptibility testing**
 - Candida and Aspergillus breakpoints for fluconazole, voriconazole, posaconazole, anidulafungin and amfotericin B.
- **Anaerobe susceptibility testing**
 - Finalised: drugs in need of breakpoints defined; breakpoints determined
 - Ongoing: Methodological development
- **Under discussion: Subcommittee on the detection of resistance mechanisms of clinical and/or epidemiological importance.**



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[MIC - distributions and QC](#)

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[EUCAST disk diffusion test](#)

[Frequently Asked Questions \(FAQ\)](#)

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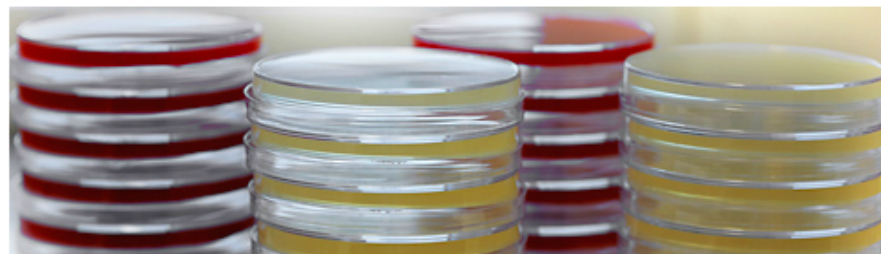
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The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and

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infection control. The Steering Committee is the decision-making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.

EUCAST has a subcommittee on antifungal susceptibility testing. Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and have been disbanded.

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST. Breakpoints for new agents are set as part of the licensing process for new agents through EMA. EUCAST breakpoints are available in devices for automated susceptibility testing but with some limitations, depending on the system. A disk diffusion susceptibility test method calibrated to EUCAST MIC breakpoints is also available.

EUCAST invites anyone with an interest in antimicrobial agents in general and antimicrobial breakpoints in particular to contact EUCAST, ESCMID or one of the

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Remember to activate your
free 2011 membership with
the newly-founded ESCMID

EUCAST News



01 Dec 2011

EUCAST breakpoint table 2.0

01 Nov 2011

**Consultation on Aspergillus
breakpoints for posaconazole**

 [Download](#)

01 Nov 2011

**Consultation on Aspergillus
breakpoints for itraconazole**

 [Download](#)

29 Oct 2011

**New EUCAST Expert Rules now
online**



Organization

Clinical breakpoints

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MIC - distributions and QC

Zone diameter distributions

EUCAST disk diffusion test

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Rationale Documents from EUCAST

The following Rationale Documents (see General Information on Rationale Documents) are currently available from EUCAST:

 [General Information on Rationale Documents](#)

 [Amikacin](#) v 1.2

 [Ciprofloxacin](#) v 1.9

 [Colistin](#) v 1.0

 [Daptomycin](#) v 1.0

 [Doripenem](#) v 1.0

 [Doxycycline](#) v 1.0

 [Ertapenem](#) v 1.3

 [Fluconazole](#) v 1.0

 [Gentamicin](#) v 1.2

 [Imipenem](#) v 1.3

 [Levofloxacin](#) v 1.5

 [Linezolid](#) v 1.0

 [Meropenem](#) v 1.5

 [Metronidazole](#) v 1.0

 [Minocycline](#) v 1.0

 [Moxifloxacin](#) v 2.3

 [Mupirocin](#) v 1.0

 [Netilmicin](#) v 1.1

Organization

Clinical breakpoints

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EUCAST disk diffusion test

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search term [Search](#)

... Disk diffusion methodology

EUCAST Disk Diffusion Test Methodology

EUCAST has developed a disk diffusion test based on MH-media and calibrated to EUCAST clinical breakpoints. The zone diameter breakpoints are tentative during 2010 and several are in preparation. Regular updates will be published during 2010.

Preparation of media for disk diffusion

[EUCAST Disk Diffusion - Manual](#) (v. 1.0 Dec 18, 2009)

[EUCAST Disk Diffusion - Slide Show](#) (v. 1.1 Jun 3, 2010)

[EUCAST Disk Diffusion - Reading Guide](#) (v. 1.0 Apr 30, 2010)

[Zubereitung der Medien](#) (2009)

[EUCAST Blättchendiffusionstest - Handbuch](#) (v. 1.0 Dec 18, 2009)

[EUCAST Blättchendiffusionstest - Diashow](#) (v. 1.1 Jun 3, 2010)

[EUCAST Blättchendiffusionstest - Ablesehilfe](#) (v 1.0, Jun 3, 2010)

[Preparación del medio para el estudio de sensibilidad con discos](#) (v 1.1)

[Descripción del método de disco](#) (v 1.1)

[EUCAST: método de difusión con discos para el estudio de la sensibilidad a los antimicrobianos](#) (v 1.1, Jun 3, 2010)

EUCAST tables

—

dash

Susceptibility testing not recommended – do not report or report “R” without testing.

Intrinsic resistance (or intrinsic insufficient activity).

EUCAST tables

IE

(insufficient evidence)

The susceptibility category (S, I or R) of organisms without resistance mechanisms cannot be determined.

Do not report or report “IE with an MIC” - categorical interpretation not possible.

Links in EUCAST breakpoint table

A B C D E F						
44						
45	Carbapenems					
46						
47						
48	Doripenem					
49	Ertapenem					
50	Imipenem ¹					
51	Meropenem	2	8	10	22	16
52						
53						
54	Monobactams	MIC breakpoint	Disk content	Zone diameter	Notes	
55		S ≤	R >	S ≥	R <	Numbers for comments on MIC
56						
57						
58						
59						
60	Fluoroquinolones	MIC breakpoint	Disk content			
61		S ≤	R >			
62						
63	Ciprofloxacin ¹	0.5	1	5		
64	Levofloxacin	1	2	5		
65	Moxifloxacin	0.5	1	5		
66	Nalidixic acid (screen)	Note ²	Note ²	30	16 ^A	16 ^A
67						2/A. Nalidixic acid may be used to screen for fluoroquinolone resistance. If other Enterobacteriaceae are resistant to all fluoroquinolones, the breakpoint correlates to an MIC value of 16 mg/L.
68	Norfloxacin	0.5	1	10	22	19
69	Ofloxacin	0.5	1	5		19
70						
71	Aminoglycosides ¹	MIC breakpoint				
72		S ≤				
73						
74	Amikacin	8				
75	Gentamicin	2				
76	Netilmicin	2				
77	Tobramycin	2				
78						
79						
80	Glycopeptides	MIC breakpoint	Disk content	Zone diameter	Notes	
81		S ≤	R >	S ≥	R <	Numbers for comments on MIC breakpoints

Click on antibiotic for Rationale Document

Click on MIC breakpoint for MIC distributions

Click on zone breakpoint for zone diameter distributions

Ciprofloxacin Rationale for the EUCAST clinical breakpoints, version 1.9 22nd August 2007

Introduction

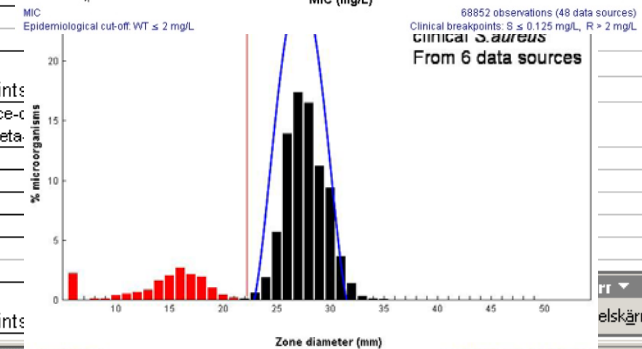
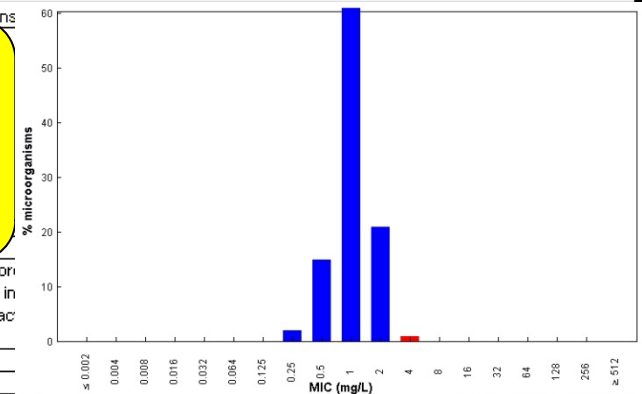
The fluoroquinolones comprise a class of agents derived from nalidixic acid and developed since the 1980s. The early fluoroquinolones had a limited spectrum of antibacterial activity, mainly against Gram-negative pathogens. The newer fluoroquinolones agents have enhanced intrinsic activity against Gram-positive organisms and extended and improved pharmacokinetic characteristics in comparison with preceding derivatives. Emergence of resistance is mainly due to mutations in the QRDR region where phenotypic resistance arises as a result of stepwise mutations. Microorganisms with one mutation may exhibit elevated fluoroquinolone MICs that are sometimes difficult to distinguish from wild-type MIC distributions. Other low-level resistance mechanisms include increased activity of efflux pumps, Gyr proteins (capable of protecting DNA gyrase from quinolones) and inactivating enzymes.

EUCAST has defined clinical breakpoints for the fluoroquinolones ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), norfloxacin (NOR) and ofloxacin (OFX). They are with few exceptions available in all European countries. Older fluoroquinolones which are available only in few countries or in topical preparations have not been addressed.

Some fluoroquinolones are available for both oral and intravenous therapy while others are available for oral therapy only. This is reflected in the breakpoints. Ciprofloxacin is used to treat complicated and uncomplicated urinary tract infections, acute and chronic bacterial prostatitis, gonorrhoea, lower respiratory tract infections, acute sinusitis, skin and soft tissue infections, bone and joint infections, complicated intra-abdominal infections and blood stream infections, mainly involving Gram-negative organisms including *Pseudomonas aeruginosa*. It is also used in infectious diarrhoea caused by susceptible bacteria when antibacterial therapy is indicated. Other than in cystic fibrosis patients its use in paediatric patients is still a matter of debate.

1. Dosage

	PSAC	CA-SEM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	750 x 2 oral 200 x 2 iv	500 x 2 oral 200 x 2 iv	250-100 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv
Maximum dose schedule (mg)	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 2 iv
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv



Disk diffusion methods

EUCAST vs. CLSI

- Both methods are based on Mueller-Hinton agar, but there are differences in:
 - **Disk potency**
 - Several disk contents are lower in EUCAST
 - **Medium**
 - EUCAST: **MH** and **MH-F**
 - CLSI: MH, HTM and Sheep blood.
 - **Incubation time**
 - EUCAST: **16-20 h** for all organisms
 - CLSI: 16-18 or 20-24 h

EUCAST susceptibility testing media

- **MH**

- Mueller-Hinton agar**

- Enterobacteriaceae*

- Acinetobacter* spp.

- Pseudomonas* spp.

- Staphylococcus* spp.

- Enterococcus* spp.



- **MH-F**

- Mueller-Hinton agar with 5% horse blood and 20 mg/L β -NAD**

- Haemophilus influenzae*

- Moraxella catarrhalis*

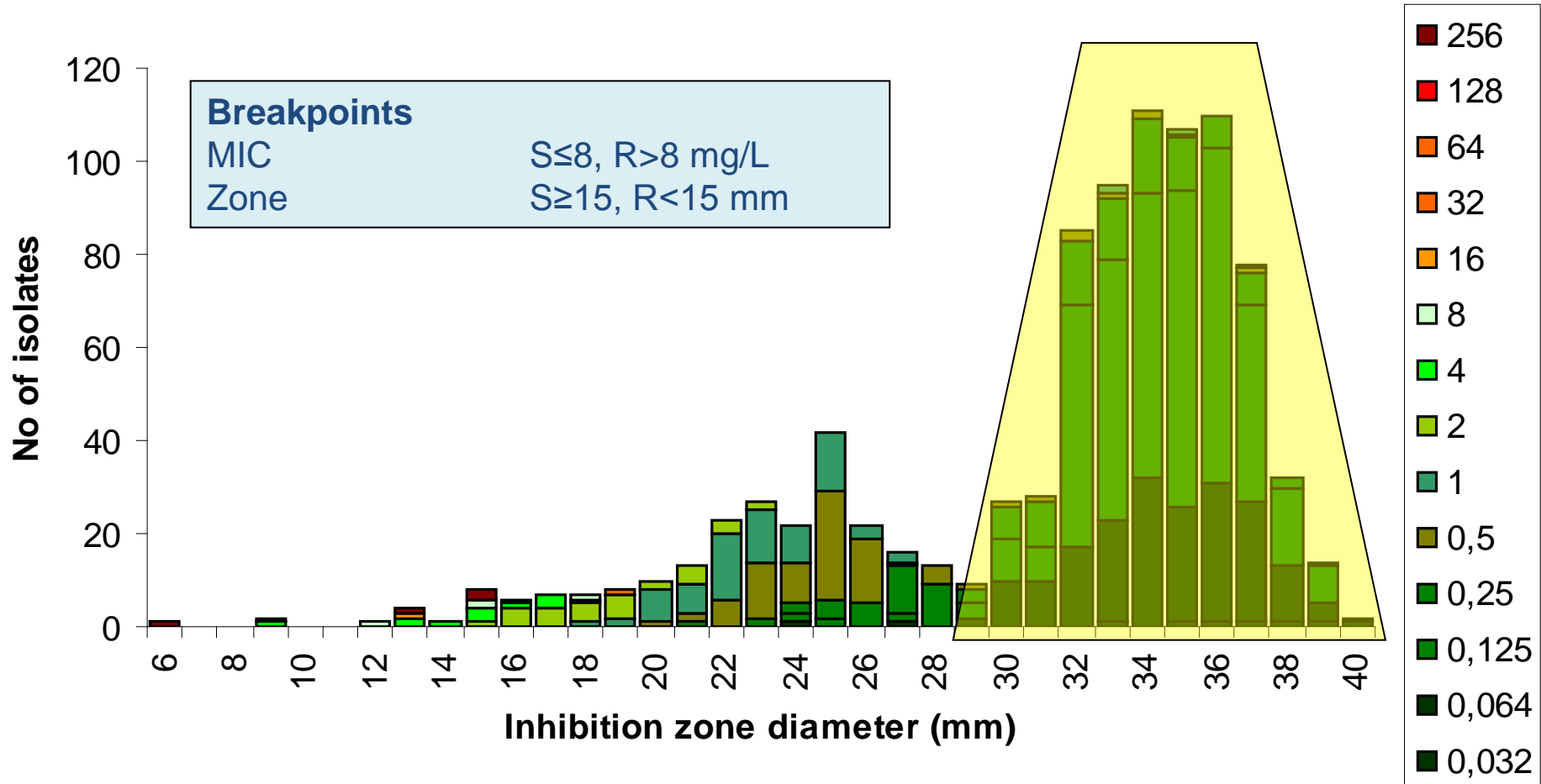
- Streptococcus pneumoniae*,

- Streptococci

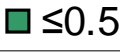
- Campylobacter*, *Listeria*, *Corynebacterium*, *Pasteurella*

Correlating MIC to zone diameters

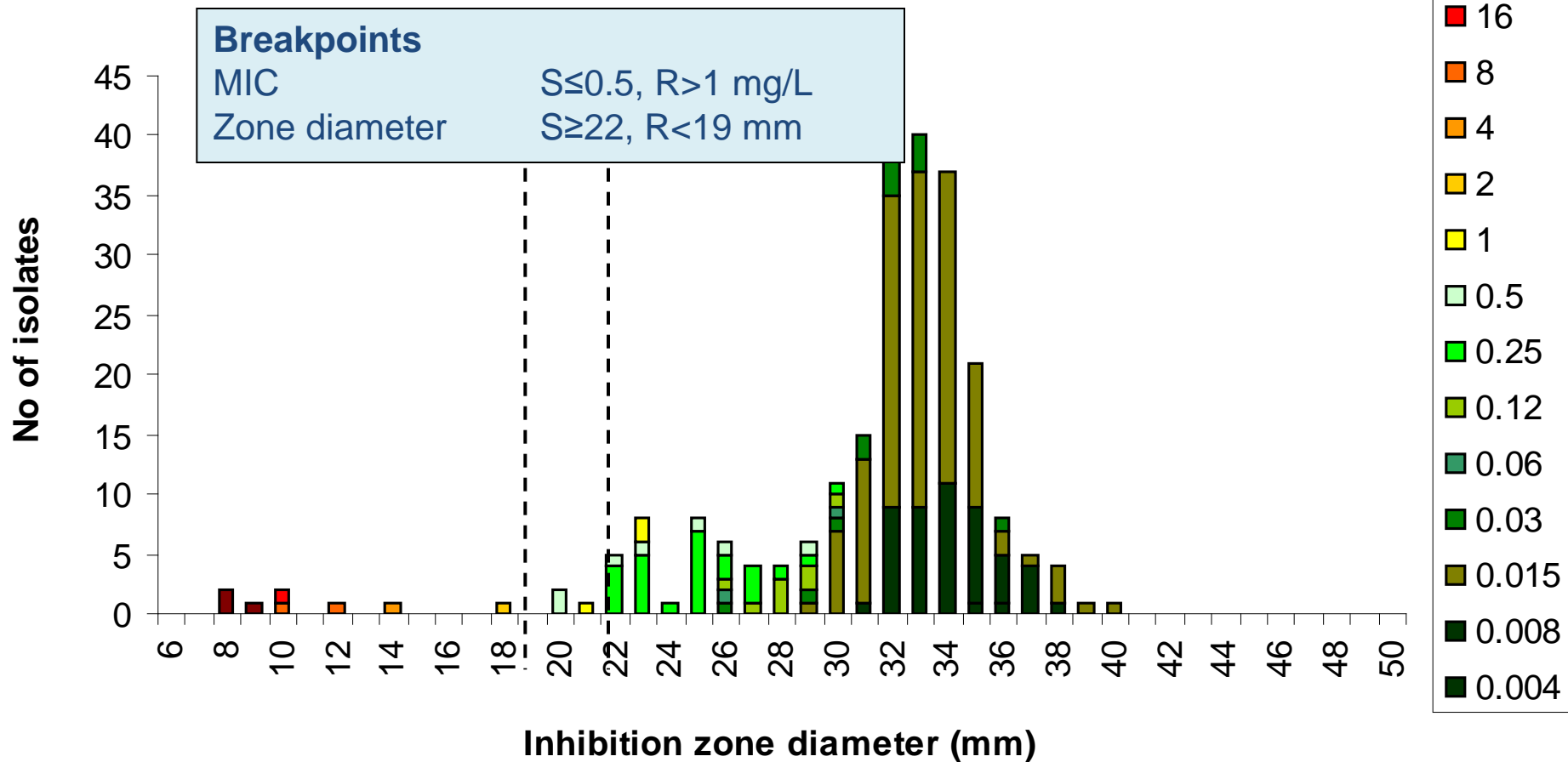
E. coli* vs. *mecillinam
931 isolates from the ECOSENS II Study



***E. coli*, 219 clinical isolates**



Ciprofloxacin 5 µg vs. MIC *E. coli*, 234 clinical isolates



Automated systems for AST

Phoenix, BD

- EUCAST breakpoints in 2009
- Evaluations (3): 2009 – 2010
- EUCAST panels/cards
- Several bugs and drugs are missing

Vitek2, BM

- EUCAST breakpoints in 2010 but in need of major software update 2011 (April – June)
- Cards containing mixture of breakpoints
- Problems with concept “EUCAST breakpoints”
- Evaluations ongoing
- Several bugs and drugs are missing

Microscan, Siemens

- EUCAST breakpoints 2010
- Launch April 2010
- no known evaluation
- Breakpoints panels and concept declared
- Several bugs and drugs are missing



Thank you!

Questions on EUCAST

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Derek.Brown@escmid.org

Rafael.Canton@escmid.org

Questions on the EUCAST disk diffusion test

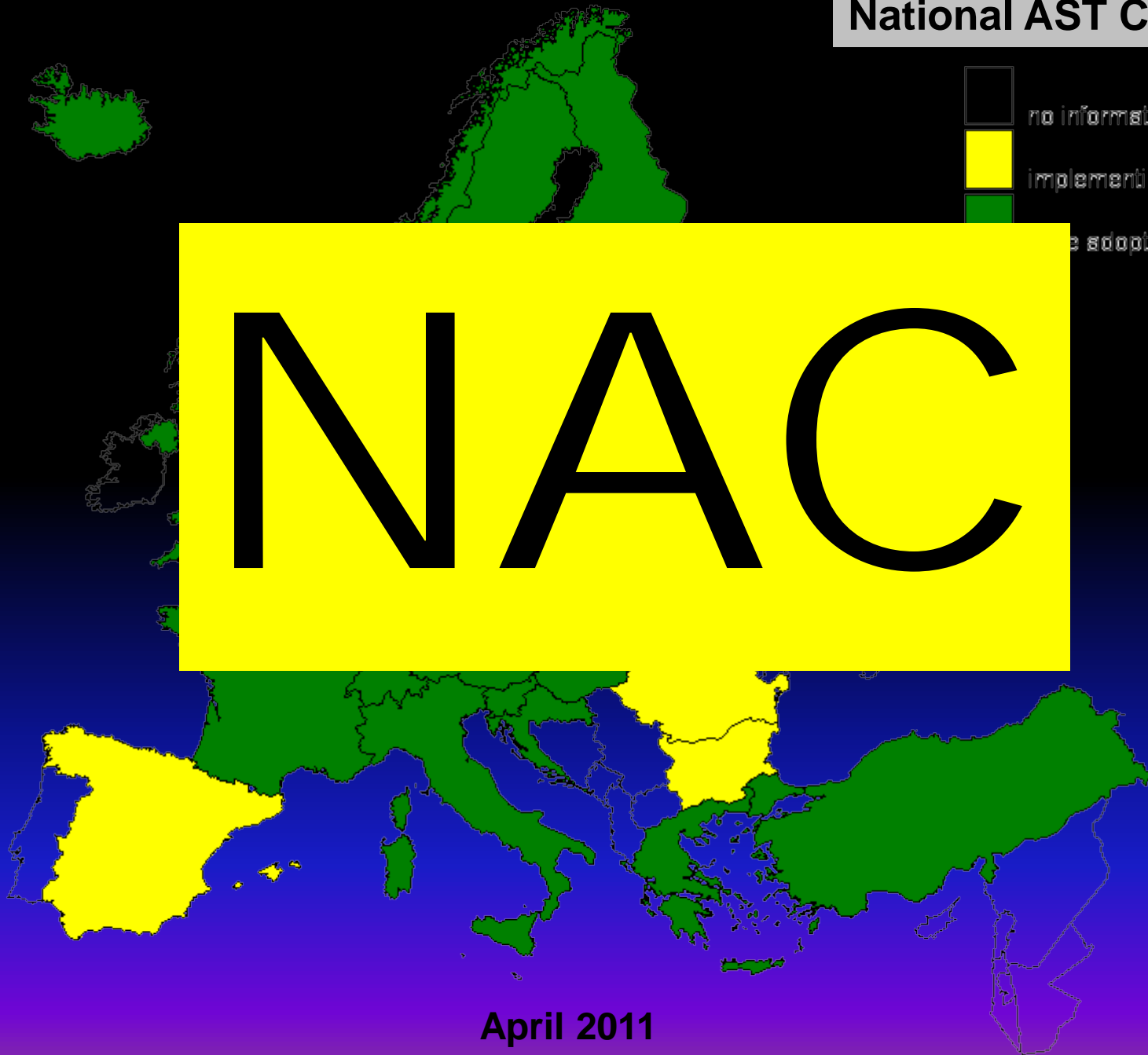
Erika.Matuschek@ltkronoberg.se

www.eucast.org

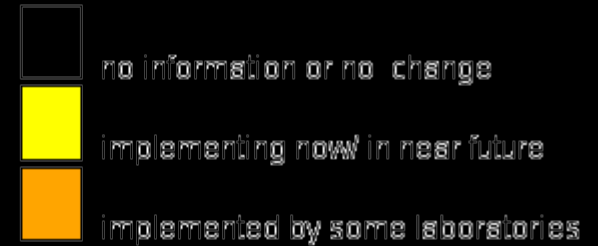
National AST Committees



NAC



April 2011



EUCAST breakpoints



April 2011