

EUCAST

update at CLSI, June 2009



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EUCAST

- Organised by ESCMID, ECDC and the national breakpoint committees in Europe.
Future: "ECDC External Expert Committee"
- Steering committee, General committee (European reps), and Consultation network
- Integrated part of EMEA process for approval of new antimicrobials (SOP)
- Advisors from EMEA and ECDC
- Funding from ECDC and ESCMID

EUCAST Steering Committee

2008 - 10

- **Chairperson** **Gunnar Kahlmeter** **2008 - 10**
- **Scientific Secretary** **Derek Brown** **2008 - 10**
- **Clinical data coordinator** **Rafael Canton** **2008 - 10**

-  • **BSAC (The UK)** **Alasdair MacGowan** **2008 - 10**
-  • **CA-SFM (France)** **Claude-James Soussy** **2008 - 10**
-  • **CRG (The Netherlands)** **Johan W. Mouton** **2008 - 10**
-  • **DIN (Germany)** **Arne Rodloff** **2008 - 10**
-  • **NWGA (Norway)** **A Sundsfjord** **2008 - 10**
-  • **SRGA (Sweden)** **Christian Giske** **2008 - 10**

- **General Committee rep*** **Antti Hakanen (Finland)** **2008 - 10**
- **General Committee rep*** **Paul Tulkens (ISC)** **2008 - 10**

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

EUCAST Tasks

- **Determine clinical breakpoints and epidemiological cutoffs for existing and new antimicrobials (bacteria, fungi)**
- **Provide standardised and harmonised methodology for AST in Europe (bacteria, fungi)**
- **Education of laboratory staff**
- **Liase with European regulatory organisations and NGOs and with international groups involved in breakpoints , methodology and surveillance of resistance.**

[Organization](#)

[Clinical breakpoints](#)

[Expert rules](#)

[Distributions of EUCAST MIC values
of wild type microorganisms](#)

[Distributions of EUCAST disk diffusion
susceptibility test inhibition
zone diameters](#)

[EUCAST disk diffusion test](#)

[Meetings](#)

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[Information for industry](#)

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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. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European countries, FESCI and ISC. The Steering Committee also consults experts within the fields of Infectious Diseases and Microbiology, pharmaceutical companies and susceptibility testing device manufacturers on EUCAST proposals.

EUCAST has subcommittees on antifungal susceptibility testing, expert rules for antimicrobial susceptibility testing, and antimicrobial susceptibility testing of anaerobes.

EUCAST has harmonized most antimicrobial MIC breakpoints in Europe. Breakpoints for new agents are set as part of the licensing process for new agents through EMEA. EUCAST breakpoints will be available in devices for automated susceptibility testing during 2009. A disk diffusion test calibrated to EUCAST MIC breakpoints is being developed for launch around the end of 2009.

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

search term

Search

News

EUCAST at ECCMID

At the 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2009) EUCAST will present several sessions

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EUCAST Presentation



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Why European breakpoints in Europe?

- breakpoints for European minimum and maximum dosages
- based on EMEA approved indications and outcome evaluation, Pk/Pd, multiple MIC distributions, and modern principles of determining breakpoints
- accepted by European regulatory authorities (EMA, ECDC) and the only breakpoints in European SPCs
- European (ECDC) "case definitions" for antimicrobial resistance surveillance
- rationale behind decisions transparent and published
- independent of commercial interests
- reviewed at intervals: with every new member of class and on the initiative of EMA, the Company, EUCAST
- in the public domain and free of charge

European breakpoints harmonised!

- Harmonising breakpoints for existing antibacterial drugs 2002 – 2009
- All breakpoints revised!
- 2008: review process started – glycopeptides and carbapenems

EUCAST and existing antimicrobials

- Aminoglycosides ✓
- Carbapenems & aztreonam ✓
- Cephalosporins iv ✓
- Cephalosporins oral ✓
- Fluoroquinolones ✓
- Glycopeptides ✓
- Macrolides and lincosamines ✓
- Miscellaneous antimicrobials ✓
- Penicillins ✓
- Tetracyclines ✓
- Antifungal drugs (flu- and voriconazole) ✓

EUCAST

– breakpoint committee for new drugs through EMEA*

- Daptomycin ✓
- Tigecycline ✓
- Garenoxacin (✓)
- Doripenem ✓
- Cefalosporine (1 ongoing)
- Glycopeptides (ongoing)
- Fluoroquinolone (1 ongoing)
- Diaminopyrimidine (1 ongoing)

- Extensions of indications

*EMEA = European Medicines Agency

EUCAST breakpoint tables available at <http://www.eucast.org>

Aminoglycosides - EUCAST clinical MIC breakpoints 2006-01-31

Aminoglycosides ¹	Enterobacteriaceae				Non-species related breakpoints ⁵			
	<i>Enterobacteriaceae</i>	<i>Pseudomonas</i> ²	<i>Acinetobacter</i>	<i>Stenotrophomonas</i>	<i>H.influenzae</i> <i>M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	Gram-negative anaerobes
Amikacin (RD)					IE	--	--	--
Gentamicin (RD)	2/4	4/4			IE	--	--	--
Netilmicin (RD)	2/4	4/4			IE	--	--	2/4
Tobramycin (RD)	2/4	4/4			IE	--	--	2/4

Click on name to access MIC distributions

Click for rationale document

'Washed' – laboratories are commended not to test against this species

Insufficient evidence

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides refer to breakpoints determined by national breakpoint committees.
 2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing by zero for *Acinetobacter* species.
 3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergistic effect with beta-lactams. There is no synergistic effect with enterococci with high level aminoglycoside resistance, i.e with gentamicin. Gentamicin is most reliably determined using kanamycin as test substance.
 4. Resistance to amikacin and netilmicin is most reliably determined using kanamycin as test substance.
 5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are given for those species where susceptibility testing is not recommended.
- = Susceptibility testing not recommended
IE = There is insufficient evidence

Version*	Date	Action
1.2	2006-01-31	Added an explanation of links from antibiotic names to wild type MIC distribution tables.
1.1	2004-04-30	European aminoglycoside breakpoints harmonised by EUCAST.

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

Introduction

The fluoroquinolones comprise a class of agents derived from nalidixic acid and developed since the 1960s. The early fluoroquinolones had a limited spectrum of antibacterial activity, mainly against Gram-negative pathogens. The newer fluoroquinolone agents have enhanced intrinsic activity against Gram-positive organisms and anaerobes 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, Qnr 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 (OFL). 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 skin structure 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.

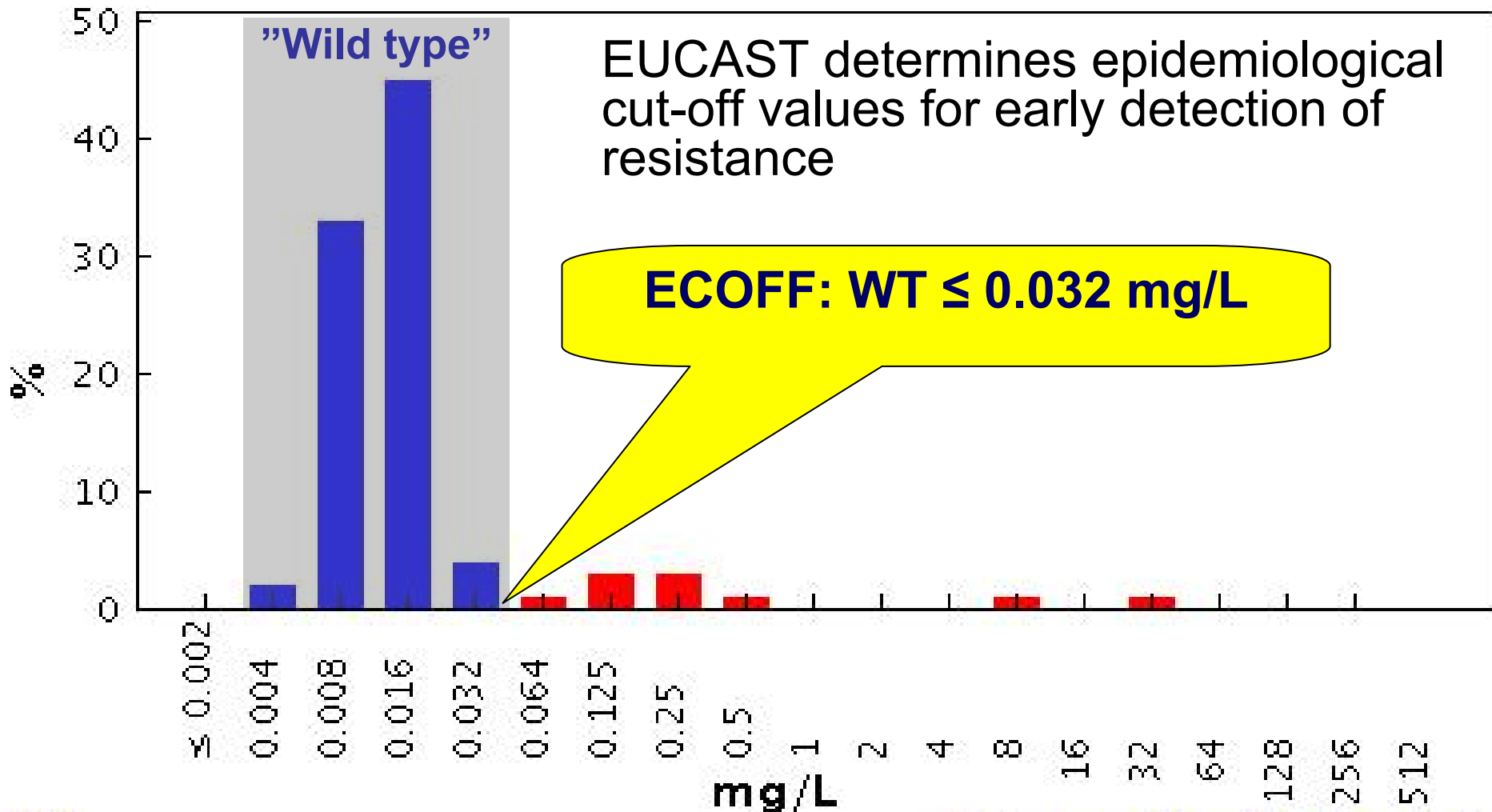
1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x 2 iv	500 x 2 oral 200 x 2 iv	250-500 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 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



MIC

Epidemiological cut-off: WT ≤ 0.032 mg/L

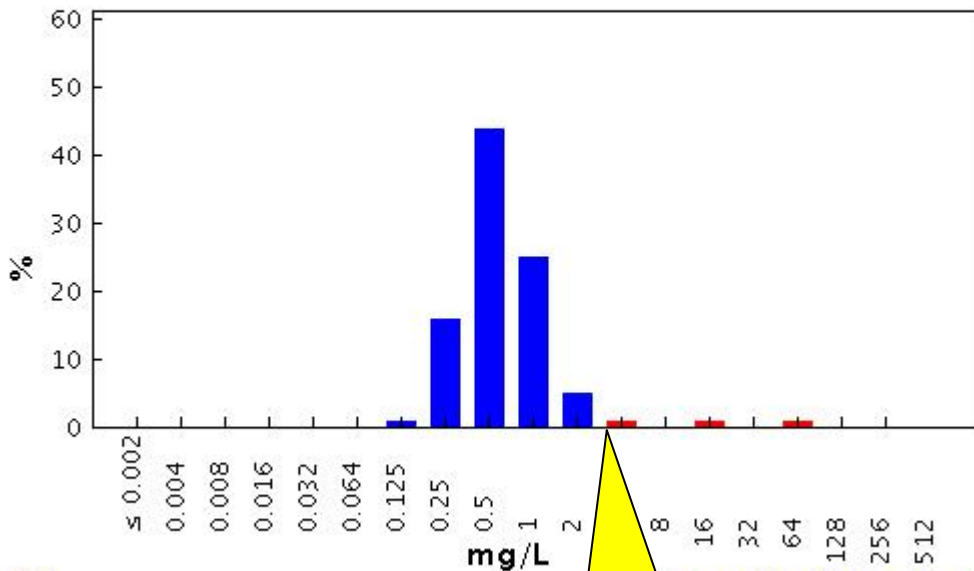
8011 observations (14 data sources)

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Gentamicin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST MIC Distribution

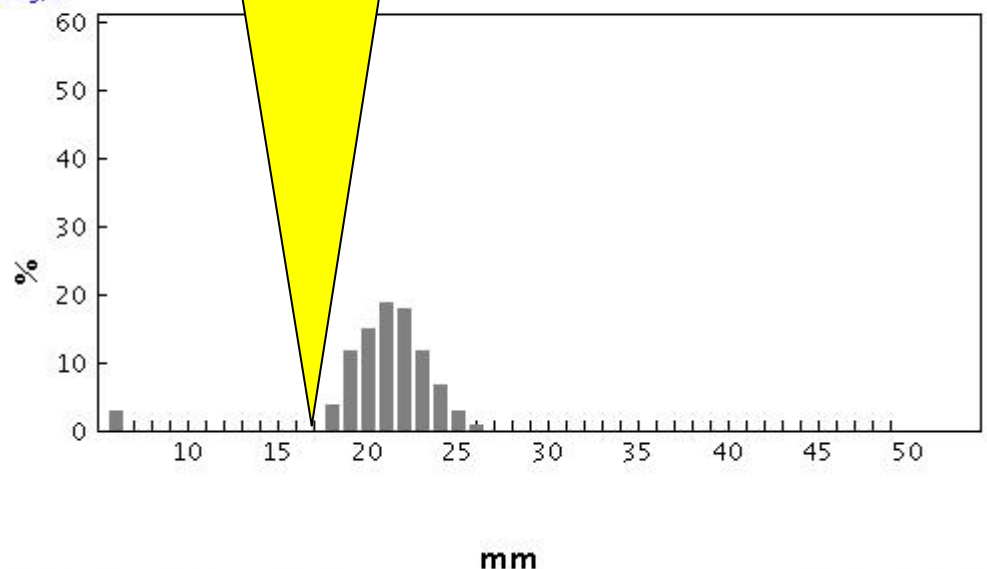


ECOFF: WT ≤ 18 mm

MIC Epidemiological cut-off: WT ≤ 2 mg/L Clinical breakpoints: S ≤ 2 mg/L, R > 4 mg/L

ECOFF: WT ≤ 2 mg/L

Gentamicin / Escherichia coli Antimicrobial wild type distributions of microorganisms - reference database EUCAST Disc Test



Disc diffusion - Disc content: 10 Epidemiological cut-off: - 583 observations Clinical breakpoints: S ≥ - mm, R < - mm

**EUCAST and CLSI
are different**

EUCAST and CLSI are different

EUCAST

- Committee of representatives of national breakpoint committees and the medical profession in European countries.
- In dialogue with regulatory authorities (ECDC, EMEA)
- In consultation with industry.
- Consensus decisions , no vote

CLSI

- Committee of representatives from the medical profession, science, industry and regulatory authorities
- Decisions by vote

EUCAST and CLSI are different

EUCAST

- Funded by ESCMID, ECDC and national breakpoint committees.

CLSI

- Funded by memberships (industry, government institutions, societies, laboratories) and sale of documents.

EUCAST and CLSI are different

EUCAST

- Industry consultative role

CLSI

- Industry part of decision process

EUCAST and CLSI are different

EUCAST

- Five meetings per year.

CLSI

- Two meetings per year.

EUCAST and CLSI are different

EUCAST

- EUCAST functions as the breakpoint committee of EMEA

CLSI

- FDA determines breakpoints
- CLSI will be recognized by FDA from 2010. Breakpoints determined by FDA may be amended by CLSI after 2 yrs.

EUCAST and CLSI are different

EUCAST

- Rationale documents published on EUCAST website

CLSI

- Rationale for decisions not published in an organised fashion.

EUCAST and CLSI are different

EUCAST

CLSI

- Documents for free.
- Documents for sale.

EUCAST and CLSI are different

EUCAST

CLSI

- Clinical breakpoints and epidemiological cut-offs

- Clinical breakpoints

EUCAST and CLSI breakpoints are different

Microbe	No of break-points	Same breakpoint(s) for		
		S and R	S	R
Enterobacteriaceae	36	0	3	3
Pseudomonas	18	1 (imipenem)	5	2
Acinetobacter	11	1 (colistin)	4	2
Staphylococci	31	4	5	2
Enterococci	14	0	2	3
Streptococci	25	2	5	2
S.pneumoniae	29	3	1	5
H.influenzae	27	0	3	0

Staphylococcus spp

EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Cefoxitin	4 / 4	4 / 4
Ciprofloxacin	1 / 1	1 / 2
Erythromycin	1 / 2	0.5 / 4
Clindamycin	0.25 / 0.5	0.5 / 2
Genta/Tobramycin	1 / 1	4 / 8
Daptomycin	1 / 1	1 / -
Linezolid	4 / 4	4 / -
Vancomycin	4 / 8	2 / 8
Vancomycin for consultation*	2 / 2	-

*Decision pending sept 2009

E.coli, Klebsiella, Proteus

EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ampicillin	8 / 8	8 / 16
Cefotaxime	1 / 2	8 / 32
Ceftazidime	2 / 8	8 / 16
Cefuroxime	8* / 8	4 / 16
Imi-/Meropenem	2 / 8	4 / 8
Ciprofloxacin	0.5 / 1	1 / 2
Gentamicin/Tobra	2 / 4	4 / 8
Amikacin	8 / 16	16 / 32
Trimethoprim	2 / 4	8 / 8
Nitrofurantoin	64 / 64	32 / 64

*Increased from 4 to 8 mg/L to avoid dividing the wild type MIC distribution

P. aeruginosa

EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ceftazidime	8 / 8	8 / 16
Piperacillin(tzb)	16 / 16	64 / 64
Imipenem	4 / 8	4 / 8
Ciprofloxacin	0.5 / 1	1 / 2
Genta/Tobra	4 / 4	4 / 8

Streptococcus pneumoniae

EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Benzylpenicillin ^{Meningitis}	0.064 / 0.064	0.064 / 0.064
Benzylpenicillin ^{Pneumonia}	0.064/ 2*	2 / 4**
Benzylpenicillin ^{Miscellaneous}	0.064/ 2	?
Penicillin V	PcG 0.064 / 0.064	0.064 / 1
Ampi/Amoxicillin	0.5 / 2	2 / 4
Cefotaxime	0.5 / 2	1 / 2
Moxifloxacin	0.5 / 0.5	1 / 2
Erythromycin	0.25 / 0.5	0.25 / 0.5
Azitromycin	0.25 / 0.5	0.5 / 1

*MIC-related (0.125 – 2 mg/L) variable dosing for pneumonia

**High dose for pneumonia

H. influenzae

EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ampicillin	1 / 1	1 / 2
Cefuroxime IV	1 / 2*	4 / 8
Cefuroxime oral	0.12/1**	4 / 8
Ciprofloxacin	0.5 / 0.5	1 / -
Erythromycin	0.5 / 16 (I)	- / -
Tetracycline	1 / 2	2 / 4

*Wildtype = S

**Wild-type = I

Implementation of EUCAST breakpoints

- MIC-testing of any kind ✓
- National systems for disk diffusion from France, UK or Sweden ✓
- Phoenix ✓
- Vitek2, MicroScan – ongoing
- Disk diffusion – ongoing (provisional breakpoints available by end of 2009)

Disc tests from EUCAST and CLSI

EUCAST

- Mueller Hinton
- Inoculum 0.5 McF
- Incubation 18 +/-2 h (24h for some organisms)
- **MH+5% Horse Blood and 20 mg β -NAD for streptococci, pneumococci & H.influenzae**
- Disk strengths
- QC strains and reference ranges

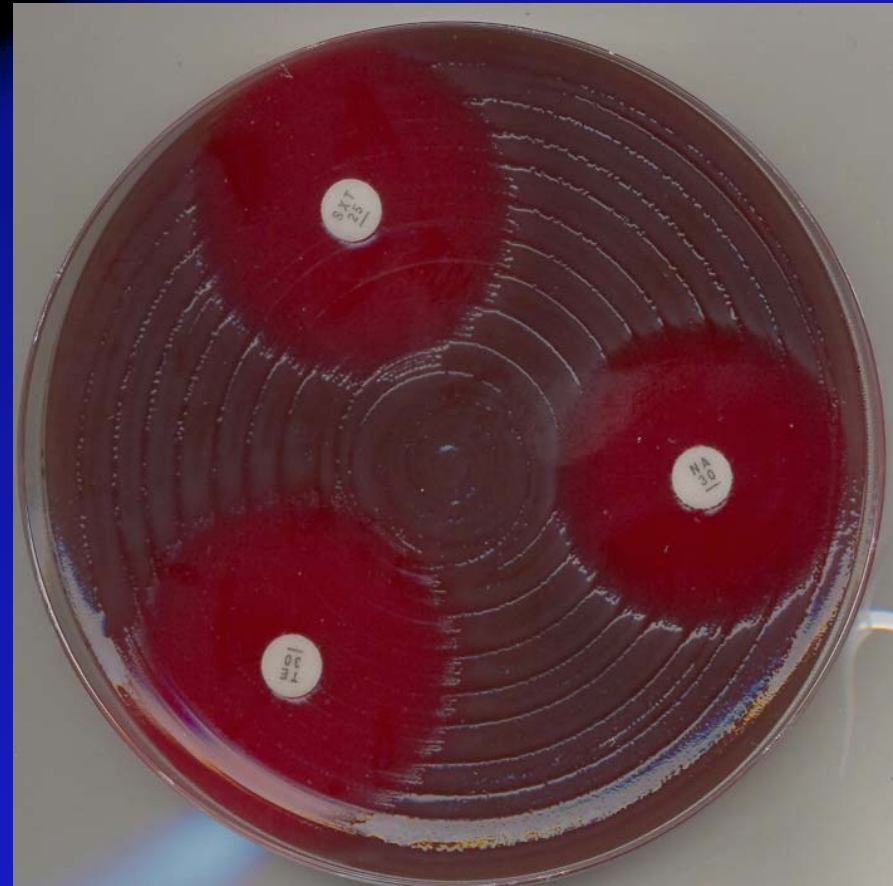
CLSI

- Mueller Hinton
- Inoculum 0.5 McF
- Incubation 18 +/-2 h (24h for some organisms)
- Two different plates for fastidious organisms
-
- Disk strengths
- QC strains and reference ranges

***S. pneumoniae* ATCC 49619**



***H. influenzae* NCTC 8468**

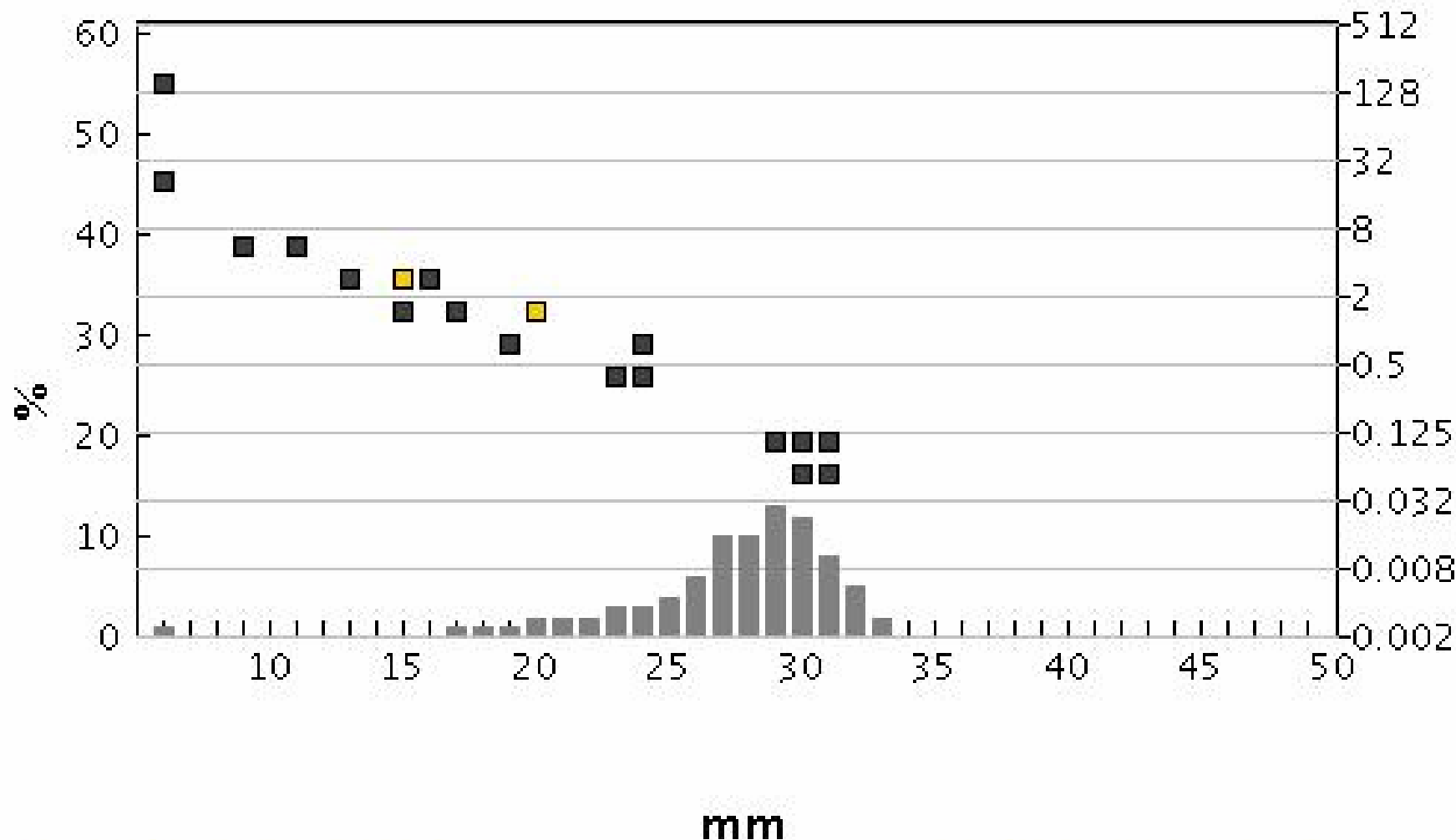


MIC and Zone Diameter Limits for Quality Control Strains						
<i>Escherichia coli</i> ATCC 25922						
Mueller-Hinton agar, McFarland 0.5, air, 35±1°C, 18±2 h. Read complete inhibition from the back of the plates against a black background illuminated with reflected light.						
Antimicrobial agent	MIC (mg/L)		Disk content (µg)	Inhibition zone size (mm)		Comments
	Target	Range ¹		Target	Range ²	
Amikacin	1-2	0.5-4	30	23	19-26	
Amoxicillin-clavulanic acid	4/2	2/1-8/4	20/10	21	18-24	
Ampicillin	4	2-8	10	19	16-22	Ignore faint growth that appears as inner zone.
Aztreonam	0.12	0.06-0.25	30	32	28-36	
Cefadroxil	-	-	30	18	15-21	EUCAST
Cefepime	0.03-0.06	0.015-0.12	30	34	31-37	
Cefotaxime	0.06	0.03-0.12	5	28	25-31	
Cefotaxime	0.06	0.03-0.12	30	32	29-35	
Cefoxitin	4	2-8	30	26	23-29	
Cefpodoxime	0.5	0.25-1	10	26	23-28	
Cefazidime	0.12-0.25	0.06-0.5	10	26	23-29	EUCAST
Cefazidime	0.2-0.25	0.1-0.5	30	29	28-32	
Ceftazidime	0.06	0.03-0.12	30	33	27-31	
Cefuroxime	4	2-8	30	23	20-26	
Chloramphenicol	4	2-8	30	24	21-27	
Ciprofloxacin	0.008	0.004-0.015	5	35	30-40	
Ertapenem	0.008	0.004-0.015	10	33	29-36	
Gentamicin	0.5	0.25-1	10	23	19-26	
Gentamicin	0.5	0.25-1	30	24	21-27	EUCAST
Imipenem	0.12	0.06-0.25	10	29	26-32	
Mecillinam	0.06-0.12	0.03-0.25	10	27	24-30	
Meropenem	0.015-0.03	0.008-0.06	10	31	28-34	
Moxifloxacin	0.015-0.03	0.008-0.06	5	32	28-35	
Nalidixic acid	2	1-4	30	25	22-28	
Nitrofurantoin	8	4-16	100	21	18-24	EUCAST
Nitrofurantoin	8	4-16	300	23	20-25	
Norfloxacin	0.06	0.03-0.12	10	32	28-35	
Piperacillin-tazobactam	2/4	1/4-4/4	30/6	24	21-27	EUCAST
Piperacillin-tazobactam	2/4	1/4-4/4	100/10	27	24-30	
Rifampicin	8	4-16	5	9	8-10	
Tetracycline	1	0.5-2	30	22	18-25	

Now available on www.eucast.org

Mecillinam / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database
EUCAST Disc Test



Disc diffusion - Disc content: 10
Epidemiological cut-off: -

1527 observations (2 data sources)
Clinical breakpoints: S \geq - mm, R $<$ - mm

EUCAST - 2009

- Harmonisation process finalised during 2009
 - Subcommittee on Antifungals – flu- and voriconazole finalised
 - Subcommittee on Anaerobes – finalised breakpoints 2008
 - Subcommittee on Expert Rules – finalised in 2008 (revision and CMI 2009)
- computer-aided expert rules 2009
- EUCAST Rationale documents on web and ETNs in CMI
- New drugs through EMEA (several ongoing)
- MIC distribution database >19 000 MIC distributions
- Zone diameter distribution database
- Breakpoints implemented in existing methods 2009.
- EUCAST breakpoints in Phoenix January 2009 and Vitek2 late 2009. Microscan ongoing.
- European disk test available before end of 2009
- Review of EUCAST breakpoints – ongoing for GP and Carbapenems.

Thank you!

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www.eucast.org



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING