NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

CLSI vs. EUCAST

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CLSI

A not-for-profit membership organization, the Clinical and Laboratory Standards Institute (CLSI) fostering excellence in laboratory medicine.
They develop clinical laboratory testing standards based on input from and consensus among industry, government, and health care professionals.

What is EUCAST?

Rafael Canton
Chairman of EUCAST

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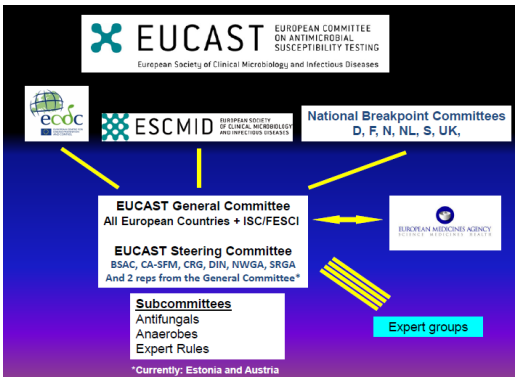
EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees.
EUCAST has a subcommittee on antifungal susceptibility testing and on methods for detection of resistance mechanisms of clinical and/or epidemiological importance.

Where they fit?



Structure of EUCAST

- Steering Committee- decision making body
- General Committee
- Subcommittees
- National Antimicrobial Susceptibility Testing Committees (NAC)
  - http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/Organisation_and_NACs/The_South_African_NAC.pdf


European Committee on Antimicrobial Susceptibility Testing 2013-2014

EUCAST functions

- 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 objectives

•To organize a network of established experts in the determination of antimicrobial breakpoints and in antimicrobial susceptibility testing.

•To determine, review and revise European clinical breakpoints and epidemiological cut-off values for surveillance of antimicrobial resistance in close collaboration with the European Medicines Agency (EMA) and ECDC.

Objectives continue

- To promote the development and standardization of in-vitro antimicrobial susceptibility testing methods used in Europe.
- To promote quality assurance of in-vitro antimicrobial susceptibility testing.
- To promote education and training in antimicrobial susceptibility testing.
- To advise ECDC and other European Union health agencies on issues related to antimicrobial susceptibility testing and detection of resistance determinants relevant to public health.
- To collaborate with international groups, ECDC and other European Union health agencies involved in antimicrobial susceptibility testing and/or the epidemiology of antimicrobial resistance in human pathogens.
- To work towards international consensus and harmonization of clinical breakpoints and antimicrobial susceptibility testing.

EUCAST breakpoints for new antimicrobial agents

- An agreement between the EMA, pharmaceutical industry and EUCAST, the role of EUCAST with respect to breakpoint determination is recognised as part of the official EMA process for approval of new antimicrobial agents (see EMA SOP/H/3043 14 February 2005, revised 23 January 2007).
- Only the applicant of the specific product under consideration will be part of the process, as outlined in the EMA SOP/H/3943

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
- Liaise with European regulatory organisations and NGOs and with international groups involved in breakpoints, methodology and surveillance of resistance.

European breakpoints harmonised!

- Harmonising break points for existing antibacterial drugs
- All break points revised!
- Review process started–glycopeptides and carbapenems

EUCAST and existing antimicrobials

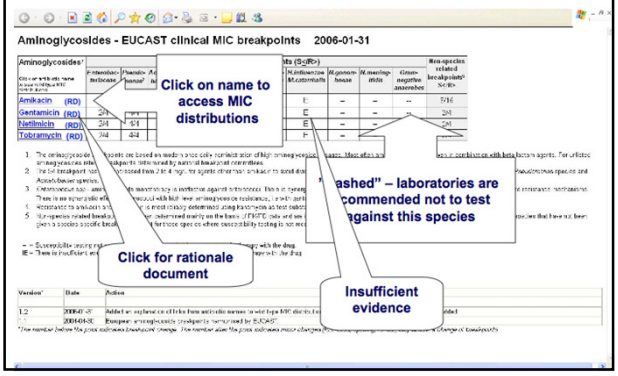
- Aminoglycosides √
- Carbapenems& aztreonam √
- Cephalosporins iv √
- Cephalosporins oral √
- Fluoroquinolones √
- Glycopetides √
- Macrolides and lincosamines √
- Miscellaneous antimicrobials √
- Penicillins √
- Tetracyclines √
- Antifungal drugs(flu-and voriconzole) √

EUCAST –break point 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 EUCAST breakpoint tables available at http://www.eucast.org



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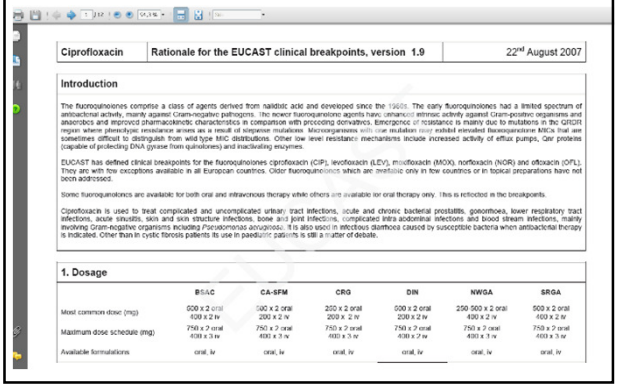

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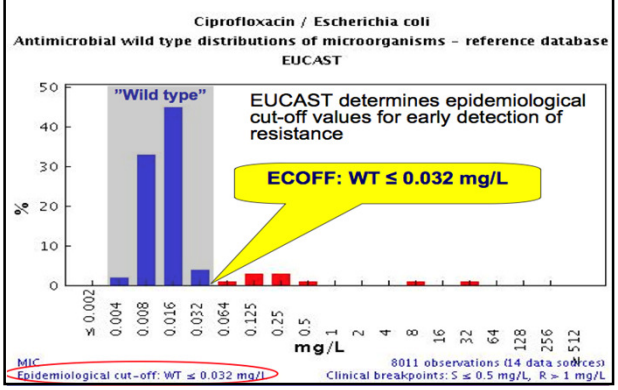

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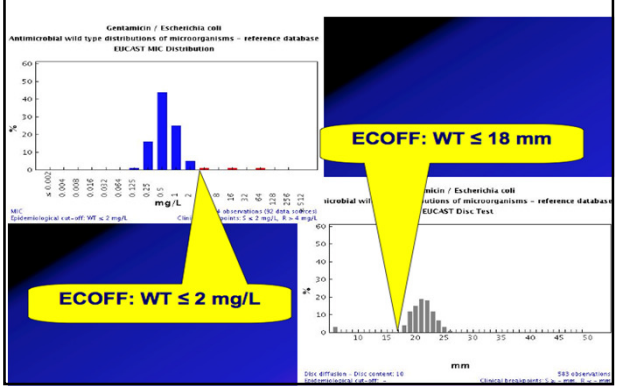


EUCAST and CLSI are different

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 vs. CLSI

EUCAST

- Funded by ESCMID, ECDC and nationals breakpoint committees
- Industry consultative role
- Five meetings per year
- EUCAST functions as the breakpoint committee of EMEA
- Rationale documents published on EUCAST website for free
- Clinical breakpoints and epidemiological cut-offs

CLSI

- Funded by member-national (industry, government institutions, societies, laboratories) and sale of documents
- Industry part of decision process
- Two meetings per year
- FDA determines breakpoints
- CLSI was recognized by FDA from 2010
- Breakpoints determined by FDA may be amended by CLSI after 2 yrs
- Rationale for decisions not published in an organized fashion and for sale
- Clinical breakpoints

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

EUCAST and CLSI breakpoints are different example Enterobacteriaceae

Enterobacteriaceae

EUCAST Clinical Breakpoint Table v. 3.1, valid from 2013-02-11

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1°C, 16±2h
Reading: Read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
Quality control: *Escherichia coli* ATCC 25922

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
Benzylpenicillin	-	-		-	-	
Ampicillin	8[1]	8	10	14[2,3]	14[4]	MA. Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S = 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 20 mm. B. Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agars.
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[2,3]	14[4]	2. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
Amoxicillin	8[1]	8	-	Note[5]	Note[5]	C. Susceptibility inferred from ampicillin.
Amoxicillin-clavulanate	8[1]	8[2]	20-10	14[2,3]	14[4]	3. For susceptibility testing purposes, the concentration of clavulanate is fixed at 2 mg/L.
Piperacillin	8	16	30	20	17	
Piperacillin-tazobactam	8[2]	16[2]	30-6	20	17	4. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Ticarcillin	8	16	75	23	23	
Ticarcillin-clavulanate	8[2]	16[2]	75-10	23	23	
Phenoxymethylpenicillin	-	-		-	-	
Oxacillin	-	-		-	-	
Cloxacillin	-	-		-	-	
Dicloxacillin	-	-		-	-	
Flucloxacillin	-	-		-	-	
Mecillinam (uncomplicated UTI only)	8[1]	8[1]	10	18[2,3]	18[2,3]	SE. Mecillinam (pivmecillinam) breakpoints relate to *E. coli*, *Klebsiella* spp. and *P. mirabilis* only. F. Ignore isolated colonies within the inhibition zone for *E. coli*.

Clinical BP for carbapenems in enterobacteriaceae

Enterobacteriaceae

EUCAST Clinical Breakpoint Table v. 3.1, valid from 2013-02-11

Cephalosporins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
						1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, i.e. the presence or absence of an ESBL does not in itself influence the categorisation of susceptibility. In many areas, ESBL detection and characterisation is recommended or mandatory for infection control purposes.
Cefaclor	-	-		-	-	
Cefadroxil (uncomplicated UTI only)	16	16	30	12	12	
Cefalexin (uncomplicated UTI only)	16	16	30	14	14	
Cefazolin	-	-		-	-	
Cefepime	1	4	30	24	21	
Cefixime (uncomplicated UTI only)	1	1	5	17	17	
Ceftibuten	1	2	5	20	17	
Cefoxitin (screen)[2]	NA	NA	30	19	19	2. The cefoxitin ECOFF (WT ≤ 8 mg/L) has a high sensitivity, but poor specificity for identification of AmpC-producing Enterobacteriaceae as this antibiotic is also affected by permeability alterations and some carbapenemases. Classical non-AmpC producers are wild type, whereas plasmid AmpC producers or chromosomal AmpC hyperproducers are non-wild type.
Cefpodoxime (uncomplicated UTI only)	1	1	10	21	21	
Ceftaroline	0.5	0.5	5	23	23	
Ceftazidime	1[1]	4	10	22	19	
Ceftibuten (UTI only)	1	1	30	23	23	
Ceftriaxone	1	2	30	23	20	
Ceftriaxone iv	0[3]	0	30	19	16	3. The breakpoint relates to a dosage of 1-2 g x 2 and to *E. coli*, *P. mirabilis* and *Klebsiella* spp. only.
Ceftriaxone oral (uncomplicated UTI only)	0	0	30	19	16	

Carbapenems[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
						1. The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases). Some isolates that produce carbapenemase are categorised as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorisation of susceptibility. In many areas, carbapenemase detection and characterisation is recommended or mandatory for infection control purposes.
Doripenem	1	4	10	24	18	
Ertapenem	0.5	1	10	25	22	
Imipenem[2]	2	8	10	22	16	2. Low-level resistance is common in *Morganella* spp., *Proteus* spp. and *Providencia* spp.
Meropenem	2	8	10	22	16	

SA

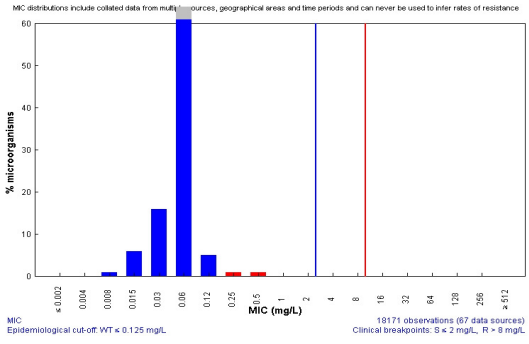
Staphylococcus spp.

EUCAST Clinical Breakpoint Table v. 3.1, valid from 2013-02-11

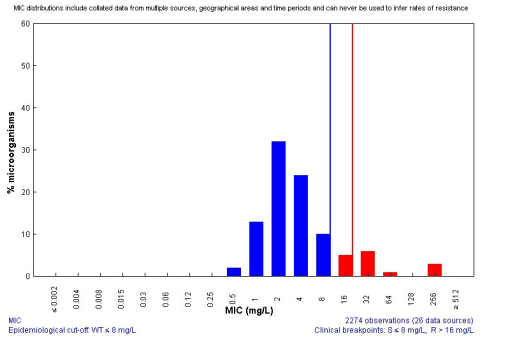
Cephalosporins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
						1. Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for ceftaroline, ceftolozane and ceftobiprole, which do not have breakpoints and should not be used for staphylococcal infections. Some methicillin-resistant *S. aureus* are susceptible to ceftaroline, see Note 9S.
Cefaclor[2]	Note[1]	Note[1]		Note[1]	Note[1]	2. High-dose therapy is required for treatment of staphylococcal infections.
Cefadroxil	Note[1]	Note[1]		Note[1]	Note[1]	A. Susceptibility inferred from cefoxitin.
Cefalexin	Note[1]	Note[1]		Note[1]	Note[1]	
Cefalotin	Note[1]	Note[1]		Note[1]	Note[1]	
Cefapirine	Note[1]	Note[1]		Note[1]	Note[1]	
Cefazolin	-	-		-	-	
Cefotaxime	Note[1]	Note[1]		Note[1]	Note[1]	
Cefoxitin (screen), *S. aureus*, *S. lugdunensis* and *S. saprophyticus*	Note[1]	Note[1]	30	22[3]	22[3]	3. *S. aureus* and *S. lugdunensis* with cefoxitin MIC values >4 mg/L are methicillin resistant, mostly due to the presence of the *mecA* gene. Disk diffusion reliably predicts methicillin resistance.
Cefoxitin (screen), Coagulase-negative staphylococci	Note[1]	Note[1]	30	25[4]	25[4]	4. For coagulase-negative staphylococci other than *S. lugdunensis* the cefoxitin MIC is a poorer predictor of methicillin resistance than the disk diffusion test.
Cefpodoxime	Note[1]	Note[1]		Note[1]	Note[1]	
Ceftaroline, *S. aureus*	1[5]	1[5]	5	20[5]	20[5]	9S. Methicillin-susceptible isolates can be reported susceptible to ceftaroline without further testing. For methicillin-resistant isolates with ceftaroline zone diameters 19-21 mm, determine the MIC to confirm the susceptibility.
Ceftazidime	-	-		-	-	
Ceftibuten	-	-		-	-	
Ceftizoxime	Note[1]	Note[1]		Note[1]	Note[1]	
Ceftriaxone	Note[1]	Note[1]		Note[1]	Note[1]	
Ceftriaxone iv	Note[1]	Note[1]		Note[1]	Note[1]	
Ceftriaxone oral	Note[1]	Note[1]		Note[1]	Note[1]	

Carbapenems[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
						MA. Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.
Doripenem	Note[1]	Note[1]		Note[1]	Note[1]	
Ertapenem	Note[1]	Note[1]		Note[1]	Note[1]	
Imipenem	Note[1]	Note[1]		Note[1]	Note[1]	
Meropenem	Note[1]	Note[1]		Note[1]	Note[1]	

KP MIC distribution



AB MIC distribution



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

Thank you for your attention!

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