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

What to do when there are no breakpoints?

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EUCAST – developing breakpoints (since 2002) and methods (since 2008)

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- Enterobacterales
- *Pseudomonas aeruginosa* (+ spp)
- *Stenotrophomonas maltophilia*
- *Acinetobacter* spp
- *Staphylococcus* spp
- *Streptococcus* A,B,C,G
- *Streptococcus pneumoniae*
- *Streptococcus*, viridans group
- *Enterococcus faecalis* and *E. faecium*
- *Haemophilus influenzae*
- *Moraxella catharralis*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- Anaerobic bacteria including *Clostridoides difficile*

Organisms lacking breakpoints 2008

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- *Campylobacter*
- *Helicobacter*
- *Corynebacterium* spp
- *Listeria monocytogenes*
- *Pasteurella multocida*
- *Kingella kingae*
- *Aerococcus* spp
- *Aeromonas*
- *Plesiomonas*
- *Nocardia*
- *Bacillus*
- *Streptomyces*
- *Lactobacillus*
- *Leuconostoc*
- *Erysopelothrix rusopathiae*
- *Mycobacterium* spp
- …

Organisms lacking breakpoints 2018

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- ~~*Campylobacter*~~
- ~~*Helicobacter*~~
- ~~*Corynebacterium spp*~~
- ~~*Listeria monocytogenes*~~
- ~~*Pasteurella multocida*~~
- ~~*Kingella kingae*~~
- ~~*Aerococcus* spp~~
- ~~*Aeromonas*~~
- ~~*Plesiomonas*~~
- *Nocardia (ongoing)*
- *Bacillus*
- *Streptomyces*
- *Lactobacillus*
- *Leuconostoc*
- *Erysopelothrix rusopathiae*
- *Mycobacterium* spp
- …

AST when there are no breakpoints – which scenarios can you encounter?

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1. The breakpoint is “IE” (insufficient evidence)
2. The breakpoint is “-” (intrinsic resistance)
3. The agent is not in the table
4. The species is not in the table
5. The MIC breakpoints lack zone diameter correlates (use MIC)

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Clinical breakpoints

Clinical breakpoints

Breakpoint tables for bacteria

- **Clinical breakpoints - bacteria (v 8.0) - pdf file for printing** (1 Jan, 2018)
- **Clinical breakpoints - bacteria (v 8.0) - excel file for screen** (1 Jan, 2018)

- **What to do when there are no clinical breakpoints!** Guidance from EUCAST 2016.

EUCAST instruction video on how to use the breakpoint table - **download here!**

The most important changes between **EUCAST Breakpoint Tables v 7.1** and v 8.0 are marked in pale yellow (or as underlined text in footnotes) in the tables and are listed here:

- EUCAST recommendations for MIC determination added.

- Enterobacteriaceae breakpoints validated for Plesiomonas shigelloides (except for aminoglycosides)

- Clarification that broth microdilution is the only approved method for colistin MIC determination.

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Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints

There are some bacterial groups and antimicrobial agents for which EUCAST has not determined breakpoints.

Breakpoints for new agents will be set as the agents go through the marketing approval application to the EMA and are released if the agent is granted approval. Breakpoints for some older agents may be set when a convincing need is established (e.g. nitroxoline and temocillin). There are also some less common organism groups (e.g. *Aeromonas* spp., *Vibrio* spp., *Kingella kingae*, *Aerococcus* spp., *Nocardia* spp.) for which breakpoints may eventually be determined. There are also some agents and organism groups where there may never be breakpoints. This mainly relates to older agents which have been replaced

Scenario 1: ”IE”, insufficient evidence

- EUCAST has evaluated the agent/species
- There is not enough evidence to support a clinical breakpoint
- In vitro data encouraging, but clinical data lacking

- IE is not meant to discourage from treatment if options are few

Scenario 2: ”-”, intrinsic resistance

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- EUCAST has evaluated the agent/species
- Available evidence suggests that the agent is clinically ineffective irrespective of drug exposure
- In vitro data are discouraging and clinical data absent

- Meant to discourage from attempts at testing and reporting

Scenario 3: Agent not in the table

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- **Older agent available only in few countries**
  - A lot of work needed, poor data quality, low expected impact
  - E.g. streptomycin, josamycin, spiramycin, sparfloxacin
- **New agent waiting for**
  - breakpoints as part of registration (EMA) process
  - zone diameter correlates to MIC breakpoints (EUCAST) waiting to be developed
- **Reliable AST difficult or not possible**
  - Fosfomycin (agar dilution only and only for limited species)
  - Trimethoprim and enterococci (folate concentration)

Scenario 4: Species not in the table

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1. Genus/species not given priority so far due to relative clinical importance
   -*Bacillus* spp., *Campylobacter laridis*, *Yersinia fredericksoniae*
   -Sometimes even a problem with access to good strain collections
2. Rare species
   -*Erysopelothrix rusopathiae*
3. Common genus but rare species in human medicine
   -*Haemophilus aphrophilus*
4. Clinical outcome data insufficient or not available
   -*Campylobacter laridis* vs. erythromycin
5. Reliable MIC determination not possible
   -*Acinetobacter* vs. cephalosporins, *Stenotrophomonas* vs. moxifloxacin and other drugs, *Burkholderia* spp.

Why not use CLSI breakpoints?

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- Many CLSI breakpoints have not been through a modern breakpoint setting process
  - A lot of the breakpoints would not survive if they were
- Some examples
  - Non-tuberculous mycobacteria: compare the CLSI breakpoints with PK-PD breakpoints or breakpoints for other species
  - Chloramphenicol and enterococci
- Reverse burden of evidence
  - Where is the proof that the breakpoints are dangerous?

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Some examples

Example 1

An orthopedic infection with *Bacillus cereus* isolated from several biopsies. Vancomycin MIC is 0.5 mg/L.

1. Use the PK-PD breakpoint, which is 2/2, and report S
2. Use the ECOFF, which is 2/2, and report S
3. Use the MIC and compare to the breakpoint for staphylococci and *Corynebacterium* spp. and write a comment.
4. Report an MIC-value without any further guidance, and leave the interpretation to the clinician.

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Breakpoints for related organisms

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- Find breakpoints for related organisms and interpret accordingly
- Campylobacter laridis, use *C. jejuni* and *C. coli; Haemophilus aphrophilus*, use *Haemophilus influenzae*, *Enterococcus bovis*, use *Enterococcus faecium*, etc

- Always check that no PK-PD breakpoint or ECOFF is available
- Proceed with caution!

Example 2

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Leuconostoc with benzylpenicillin MIC 0.25 mg/L

1. Use the PK-PD breakpoint
2. Use the ECOFF
3. Use the MIC and compare to the breakpoint for staphylococci and *Corynebacterium* spp. and write a comment.
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Example 2

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PK-PD (Non-species related) breakpoints

EUCAST Clinical Breakpoint Tables v. 9.0, valid from 2019-01-01

These breakpoints are used only when there are no species-specific breakpoints or other recommendations (a dash or a note) in the species-specific tables.
If the MIC is greater than the PK-PD resistant breakpoint, advise against use of the agent.
If the MIC is less than or equal to the PK-PD susceptible breakpoint, suggest that the agent can be used with caution. The MIC may also be reported although this is not essential.
Include a note that the guidance is based on PK-PD breakpoints only, and include the dosage on which PK-PD breakpoint is based.
More information is available in the guidance document "Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints".

Penicillins	MIC breakpoint (mg/L)		Notes
	S ≤	R >	
Benzylpenicillin	0.25	2	**1.** For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
Ampicillin	2	8	**2.** For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
Ampicillin-sulbactam	2[1]	8[1]	**3.** For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Amoxicillin	2	8	
Amoxicillin-clavulanic acid	2[2]	8[2]	
Piperacillin	4	16	
Piperacillin-tazobactam	4[3]	16[3]	
Ticarcillin	8	16	
Ticarcillin-clavulanic acid	8[2]	16[2]	
Temocillin	IE	IE	
Phenoxymethylpenicillin	IE	IE	
Oxacillin	IE	IE	
Cloxacillin	IE	IE	
Dicloxacillin	IE	IE	
Flucloxacillin	IE	IE	
Mecillinam	IE	IE	

Example 3

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Lactobacillus with erythromycin breakpoint of 0.5 mg/L

1. Use the PK-PD breakpoint
2. Use the ECOFF
3. Use the MIC and compare to the breakpoint for staphylococci and *Corynebacterium* spp. and write a comment.
4. Report an MIC-value without any further guidance, and leave the interpretation to the clinician

Example 3

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search term

Organization
EUCAST News
Clinical breakpoints
Expert rules and intrinsic resistance
Resistance mechanisms
Guidance documents
MIC distributions and ECOFFs
Zone distributions and ECOFFs
AST of bacteria
AST of mycobacteria
AST of fungi
AST of veterinary pathogens
Frequently Asked Questions (FAQ)
Meetings
Presentations and statistics
Documents
Translations
Information for industry
Links

The European Committee on Antimicrobial Susceptibility Testing – EUCAST

QUICK NAVIGATION

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST was formed in 1997. It has been chaired by Ian Phillips (1997 - 2001), Gunnar Kahlmeter (2001 - 2012), Rafael Canton 2012 - 2016) and Christian Giske (2016 -). Its scientific secretary is Derek Brown (1997 -). Its webmaster is Gunnar Kahlmeter (2001 -). From 2016, Rafael Canton is the Clinical Data Co-ordinator and Gunnar Kahlmeter the Technical Data Co-ordinator.

EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or 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 several subcommittees - see page Subcommittees.

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

EUCAST News

25 Apr 2016
Ceftobiprole Rationale Document published

17 Apr 2016
EUCAST Steering Committee changes

06 Apr 2016
EUCAST Posters at ECCMID 2016

06 Apr 2016
Updated maps of EUCAST uptake

30 Mar 2016
FAQ updated

About Newsfeeds

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

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Antimicrobial wild type distributions of microorganisms

Search

Method: MIC Disk diffusion

Antimicrobial: Antimicrobial...

Species: Enterococcus gallinarum

Species: **Enterococcus casseliflavus** (Method: **MIC**)

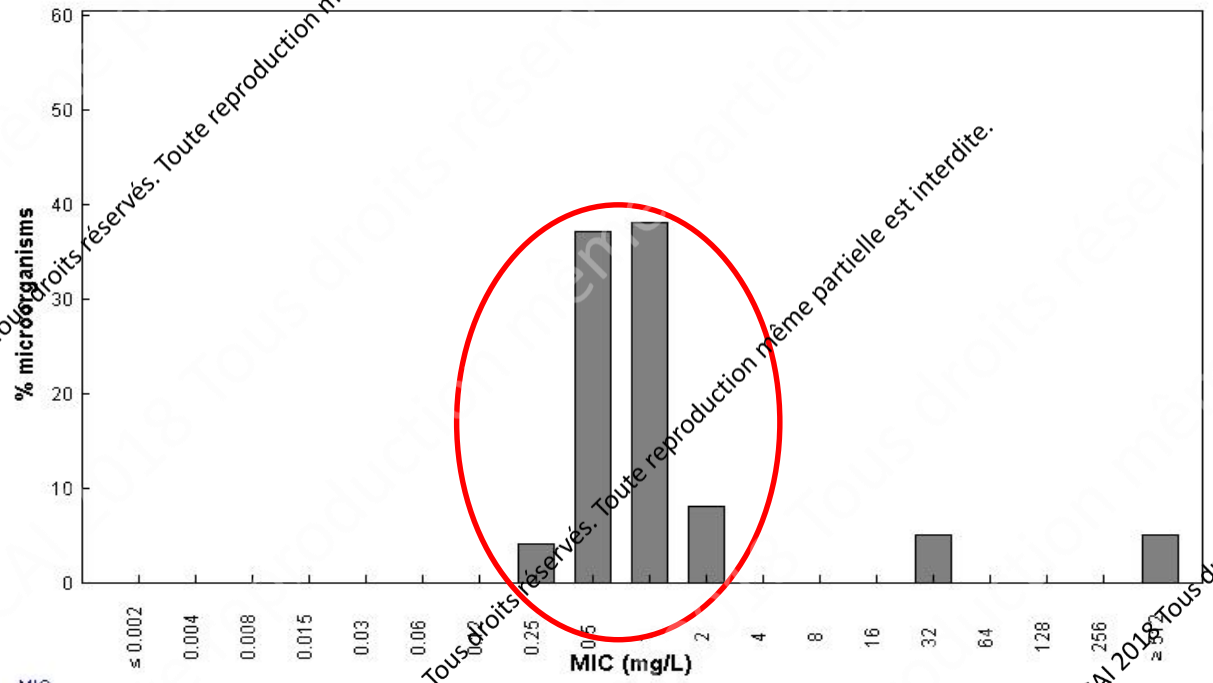
MIC distributions include collated data from multiple sources, geographical areas and time pe

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	EC
Ampicillin	0	0	0	0	0	0	0	0	12	22	19	0	1	0	5	0	0	0	0	
Benzylpenicillin	0	0	0	1	0	0	0	0	26	15	8	2	1	1	0	0	0	0	0	
Imipenem	0	0	0	0	0	0	0	5	30	7	8	5	1	5	0	0	0	0	0	
Tigecycline	0	0	0	0	8	64	25	6	0	0	0	0	0	0	0	0	0	0	0	

Enterobacter hormaechei
Enterobacter intermedium
Enterobacter sakazakii
Enterobacter spp
Enterobacter taylorae
Enterococcus avium
Enterococcus casseliflavus
Enterococcus durans
Enterococcus faecalis
Enterococcus faecalis ATCC 29212
Enterococcus faecalis ATCC 51299
Enterococcus faecium
Enterococcus gallinarum
Enterococcus hirae
Enterococcus spp
Escherichia coli
Escherichia coli ATCC 25922
Escherichia coli ATCC 35218
Eubacterium lentum
Eubacterium spp

Erythromycin / Lactobacillus reuteri
International MIC Distribution - Reference Database 2016-03-22

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 (ECOFF): -
Wildtype (WT) organisms:

112 observations (2 data sources)

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Reporting

Insufficient evidence

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- Compare the MIC with wild type distributions and the PK/PD breakpoint
- **Report the MIC (not essential) and a comment about probability of susceptibility**
- **Do not report SIR**

Intrinsic resistance

- If a report is warranted: report R without testing
- Remember that if you report R, some clinicians may think that the pathogen can sometimes be S…
- Even better to educate clinical colleagues
- Good SOPs in the lab can avoid a lot of unnecessary testing

Agent not in the table

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- Can a surrogate agent be used for testing and categorisation?
  - Erythromycin for macrolide (josamycin)
  - Colistin for polymyxin B
- Check MIC against breakpoints of a related species
  - Report the result of the comparison
- Check MIC against PK/PD breakpoints
  - Report as “below” or “above” the PK/PD breakpoints
- Check MIC against the wild type MIC distribution of the species or a related species
  - Report as without or with resistance mechanisms
- **Report MIC (not essential) + comment about likelihood of susceptibility**
- **Do not report SIR**

Take home message

When there are no breakpoints:

Do not report “S”, “I” or “R”

- These are susceptibility categories based on evidence for or against favorable clinical outcome
- Add a comment instead

Acknowledgments

- Colleagues in the EUCAST Steering Committee
- The EUCAST Development Laboratory
- More information: www.eucast.org

Karolinska Institute, South Campus

Karolinska University Hospital