

**What to do when there are no
breakpoints?**

What to do when there is no method?

**Gunnar Kahlmeter
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Developing breakpoints (since 2002) and methods (since 2008/09 is a slow and painstaking process.

- Enterobacteriaceae
- 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
- Anaerobe bacteria
- Clostridium difficile

Organisms lacking breakpoints 2008

- Campylobacter
- Helicobacter
- Corynebacterium spp
- Listeria monocytogenes
- Pasteurella multocida
- Kingella kingae
- Aerococcus spp
- Aeromonas
- Plesiomonas
- Nocardia
- Bacillus
- Streptomyces
- Lactobacillus
- Leuconostoc
- Erysipelothrix rhusopathiae
- Mycobacterium spp
- ...

Organisms lacking breakpoints 2018

- ~~Campylobacter~~
- ~~Helicobacter~~
- ~~Corynebacterium spp~~
- ~~Listeria monocytogenes~~
- ~~Pasteurella multocida~~
- ~~Kingella kingae~~
- ~~Aerococcus spp~~
- ~~Aeromonas~~
- ~~Plesiomonas~~
- Nocardia
- Bacillus
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- ...

Organisms lacking breakpoints 2018

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- ~~Aerococcus spp~~
- ~~Aeromonas~~
- ~~Plesiomonas~~
- **Nocardia**
- Bacillus
- Streptomyces
- Lactobacillus
- Leuconostoc
- Erysipelothrix rhusopathiae
- Mycobacterium spp
- ...

AST - when there is no breakpoint?

EUCAST SOP 2016

1. The breakpoint is “IE”
2. The breakpoint is “—”
3. The agent is not in the table
4. The species is not in the table
5. The MIC breakpoints lack zone diameter correlates



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Clinical breakpoints

Organization

EUCAST News

Clinical breakpoints

About "Clinical breakpoints".

Splitting MIC wild type distributions

When there are no breakpoints?

Where clinical data is lacking!

EUCAST setting breakpoints.

Expert rules and intrinsic resistance

Resistance mechanisms

Guidance documents

Consultations

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.

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

1. Breakpoint table: “IE”

“IE”: insufficient evidence

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

2. Breakpoint table indicates “-”

“-”: intrinsic resistance

- EUCAST has evaluated the agent/species
- available evidence suggests that the agent is clinically ineffective irrespective of dose.
- In vitro data **not** encouraging.

3. The agent is not in the table

- **Older agent available only in few countries**
 - The “juice is not worth the squeeze” (streptomycin, josamycin, spiramycin, sparfloxacin)
- **New agent waiting for**
 - breakpoints as part of registration (EMA, FDA) process,
 - breakpoints in semi-automated systems (bioMerieux, BD, Siemens etc) waiting to be developed or approved.
 - zone diameter correlates to MIC breakpoints (EUCAST, CLSI) waiting to be developed.
- **Reliable AST difficult or not possible**
 - fosfomycin (agar dilution only and only for limited species),
 - caspofungin

4. The species is not in the table

1. Species/subspecies considered poor target for agent
 - *Pseudomonas spp* and tigecycline, *E. coli* and vancomycin, Enterococci and cephalosporins,
2. Species/Subspecies considered of doubtful/low clinical importance
 - *Bacillus spp.*, *Campylobacter laridis*, *Yersinia fredericksoniae*
3. Rare species
 - *Erysipelothrix rhusopathiae*,
4. Common species but rare subspecies in human medicine
 - *Haemophilus aphrophilus*
5. Clinical outcome data insufficient or not available
 - *Campylobacter laridis* vs. erythromycin
6. Reliable MIC determination not possible
 - *Acinetobacter* vs. cephalosporins, *Stenotrophomonas* vs. moxifloxacin m fl, *Burkholderia spp.*

Discussion

4. The species is not in the table

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There is no solution...

...unless a reproducible MIC can be
determined

Sometimes...

...there are species and agents not mentioned in EUCAST tables but present in CLSI tables.

CLSI needs to decide whether or not to take responsibility for these.

Example: Chloramphenicol breakpoints for Enterococci.

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.

Where there is no breakpoint

- Is there a breakpoint for a related organism?
- Is there a PK/PD breakpoint to guide?
- Is there an MIC wild type distribution for the species and agent? If so, determine if the isolate is wild type (devoid of resistance mechanisms) or non-wild type (with resistance mechanisms)

Breakpoints for related organisms

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

Isolates where there is no breakpoint

- Is there a breakpoint for a related organism?
- **Is there a PK/PD breakpoint to guide?**
- Is there an MIC wild type distribution for the species and agent? If so, determine if the isolate is wild type (devoid of resistance mechanisms) or non-wild type (with resistance mechanisms)

Isolates where there is no breakpoint

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[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

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

[QUICK NAVIGATION](#)

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](#)

Antimicrobial wild type distributions of microorganisms

Search

Method: MIC Disk diffusion

Antimicrobial: Species:

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

- Enterococcus casseliflavus
- Enterococcus cecorum
- 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
- Fusobacterium mortiferum
- Fusobacterium necrophorum
- Fusobacterium nucleatum
- Fusobacterium spp
- Fusobacterium varium

Erysipelothrix is completely missing

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 periods

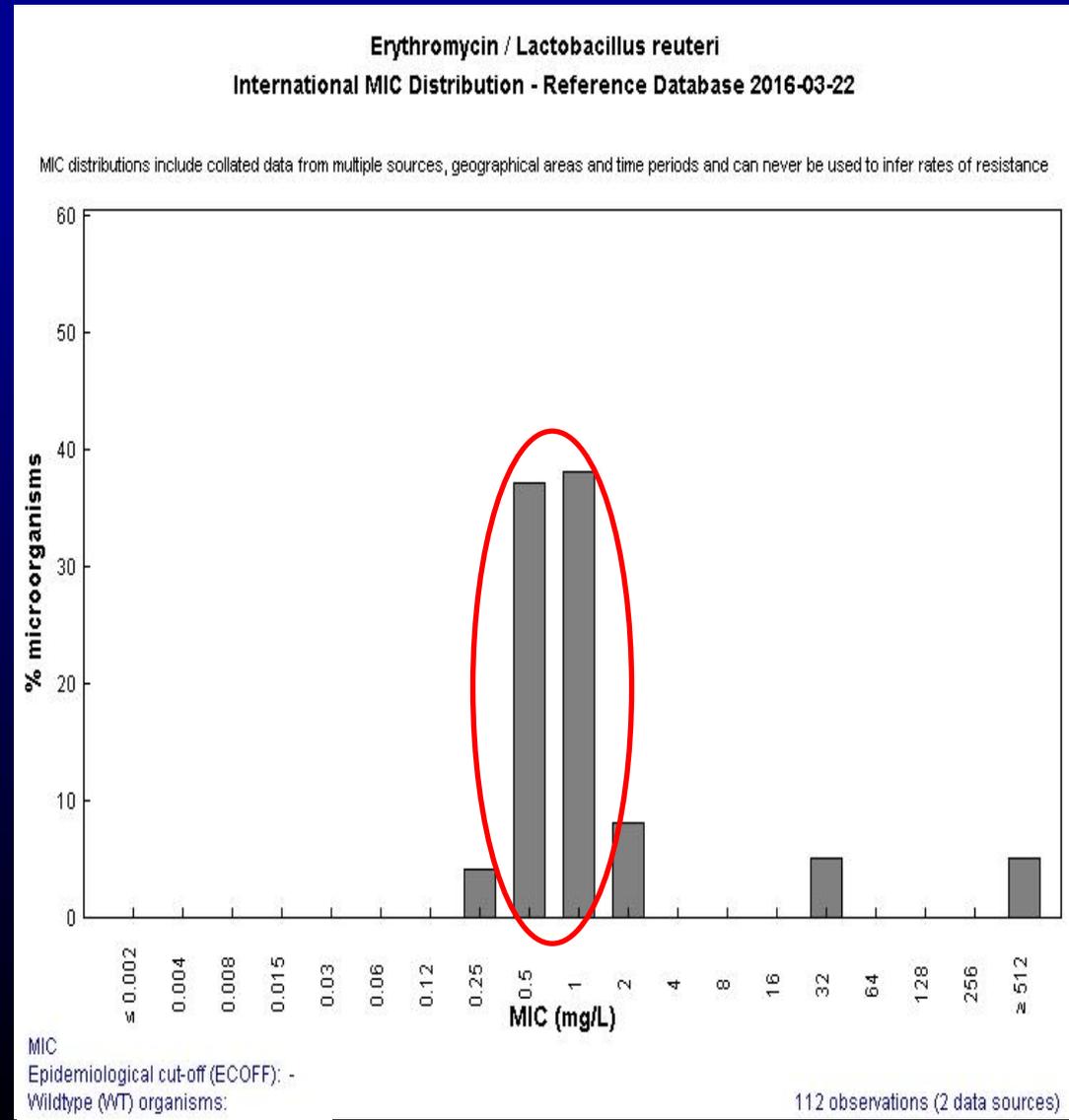
| | 0.002 | 0.004 | 0.008 | 0.016 | 0.032 | 0.064 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | EC |
|----------------------------------|-------|-------|-------|-------|-------|-------|-------|------|-----|----|----|---|---|----|----|----|-----|-----|-----|----|
| Ampicillin | 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 | 5 | 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 | |

- Enterococcus gallinarum
- 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

Check MIC against the wild type distribution for the species (or a closely related species)

If an MIC distribution is available check whether the organism is wild type

e.g. *Lactobacillus* spp.,
Erythromycin MIC 0.5 mg/L



How to report?

1. Breakpoint table “IE”

“IE”: insufficient evidence

- Compare the MIC with wild type distributions and the PK/PD breakpoint.
- Report the MIC (not essential) and a comment

2. Breakpoint table “-”

“-”: intrinsic resistance

- If a report is warranted, report “resistant” without testing.

3. Agent not in table

- Can a surrogate agent be used for testing and categorisation?
 - Erythromycin for macrolide (josamycin)
 - Ciprofloxacin for gramnegatives vs. fluoroquinolone; Norfloxacin for grampositives and a fluoroquinolone.
 - Vancomycin for a glycopeptide.
 - Colistin for polymyxin?

4. Species not in table

- 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**

A patient allergic to penicillins has a throat infection with *Arcanobacterium haemolyticum*. You would like to use erythromycin.

You wish to perform an MIC. **How?**

1. Gradient test on MH agar
2. Gradient test on MH-F-agar
3. Disk diffusion on MH agar
4. Disk diffusion on MH-F agar
5. Broth micro dilution in MH-F broth

A patient allergic to penicillins has a throat infection with *Arcanobacterium haemolyticum*. You would like to use erythromycin. You now know (?) the MIC = 0.5 mg/L.

How to report?

1. Use the PK-PD breakpoint – and report S, I or R.
2. Use the ECOFF – and report S, I or R.
3. Use the ECOFF and breakpoints for other gram-positive bacteria.
4. Compare to breakpoints for other gram-positive bacteria
5. Report an MIC-value without further guidance.

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.

Thank you!

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