

EUCAST guidance on **When there are no breakpoints in breakpoint tables?**

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In breakpoint tables, there are some species/species groups and antimicrobial agents lacking numerical breakpoints to allow categorical interpretation to S, I or R or a dash to allow the reporting of “resistant” without testing.

The most probable sequence of events in the laboratory is as follows (see also the flowchart):

1. A microorganism is found in a clinical sample and identified to species level. A decision of clinical relevance is taken, based on the pathogenicity of the species, the location, its relative abundance, and if it occurred in a single or in several samples. Not all cultured microorganisms are relevant. It is tempting to think a species which has only recently been possible to identify is important or relevant. This may not be the case, and when in mixed cultures, significance should always be questioned.
2. Once the clinical relevance has been established and a decision to perform antimicrobial susceptibility testing (AST) is taken, the EUCAST breakpoint table is consulted for relevant agents and testing conditions.
3. When guidance (breakpoints in the form of numerical values or dash) is lacking, a decision on which agents to investigate and which method and media to use is based on the species, growth characteristics, and on reviewing the literature.
4. When possible, consult the EUCAST MIC distribution website to identify the wild type distributions and ECOFFs or TECOFFs of the species and discover if there are any phenotypically detectable acquired resistance mechanisms (see addendum).
 - If non-wild type, include a comment in the report to discourage therapy.
 - If wild type, do not immediately consider the isolate susceptible to the agent, instead follow the guidance below.
 - If impossible to determine whether the isolate belongs to the wild type, follow the guidance below.

When numerical breakpoints are not in the table:

- There is a “dash” instead of numerical values: the microbe can be reported resistant without further testing.
- There is an “IE” instead of numerical values: use this guidance document to further assess the situation.

When the agent is not in the table:

- Breakpoints for **new agents** will be set as the agents go through the marketing approval application to the EMA and these are released if the agent is granted approval. When in doubt, contact EUCAST for advice about new agents.

- Breakpoints for some **older agents** may be determined when a convincing need is established (as was the case when colistin, nitroxoline and temocillin obtained breakpoints). Other older agents, replaced by more modern agents with clear advantages (improved activity, improved pharmacokinetics, or reduced toxicity), may never again have breakpoints. This is probably the case for the aminoglycoside kanamycin, the quinolone sparfloxacin, the macrolide josamycin and several cephalosporins.

When the species is not in the table:

- Breakpoints for rare species/species groups are lacking and may never be determined. This will depend on the perceived clinical need and on the frequency of identification and significance in clinical samples.

The literature. The literature will help determine (a) where a species may be of clinical importance and (b) which antimicrobials to include in the testing and for which a successful outcome may be expected, and (c) growth characteristics.

The MIC is the basis for any assessment. In the absence of a breakpoint, an assessment can only be made when an accurate and reproducible MIC value can be obtained. Determine the MIC using reference methods or validated surrogate methods.

- Broth microdilution is the reference method for aerobic bacteria using MH or MH-F broth depending on species.
- Agar dilution is the reference method for anaerobic bacteria using FAA-HB medium.
- Gradient tests are used in accordance with the manufacturer's recommendation. The test can only be relied on when validated for the species and agent, either by the manufacturer or by the user, and with simultaneous quality control. A gradient test developed and validated for one species cannot automatically be trusted with another species.
- Disk diffusion cannot be used since the value of an inhibition zone will depend on a predetermined correlation between inhibition zone and MIC-values.

Refrain from categorical reporting (especially "S" and "I") when there are no specific breakpoints. Reporting should instead be in the form of guidance as exemplified below. The numerical values in the tables predict poor outcome and are based on a conservative assessment of existing breakpoints for species listed in the regular breakpoint table, the most common MIC-distributions for these and their relation to clinical breakpoints and PK/PD cut-off values published in the rationale documents for various antimicrobial agents.

Reporting susceptibility when there are no breakpoints.

In general, avoid categorical (S, I and R) reporting when there are no breakpoints. Use alternative reporting strategies depending on outcome of testing and analysis. Below are likely alternative outcomes of your efforts and proposed comments for use in reports:

1. **An MIC could not be determined:**

Add the following comment to the report “An MIC could not be determined and characterising the susceptibility of the microorganism is impossible”.

2. **An MIC could be determined:**

- a. **The analysis suggests discouraging the use of the agent.** Add the following comment (in obvious cases, consider reporting “R”):
“Formal categorising of the susceptibility of the organism is not possible. The MIC suggests that the agent should not be used for therapy”. The MIC-value is added if appropriate.
- b. **The analysis suggests cautiously encouraging the use of the agent.** Add the following comment to the report:
“Formal categorising of the susceptibility of the organism is not possible. A cautious interpretation suggests that the agent may be considered for therapy.” The MIC-value is added if appropriate.

Table 1. Antimicrobial agents relevant for the treatment of aerobic bacteria with guidance for bacteria lacking breakpoints in standard EUCAST breakpoint tables.

Determine an MIC and compare with numerical values to assess the microbiological activity of the agent against the species. The clinical use of agents for which MIC-values are higher than those listed below should be discouraged, while agents for which the MIC is the same or lower can be considered for therapy. Avoid reporting isolates S, I or R – instead add a comment to discourage or consider therapy. The proposed values are based on (i) a compromise between current EUCAST susceptible (S or I) breakpoints for species already in the tables, (ii) wild type distributions for microorganisms when available and (iii) PK/PD cut-off values.

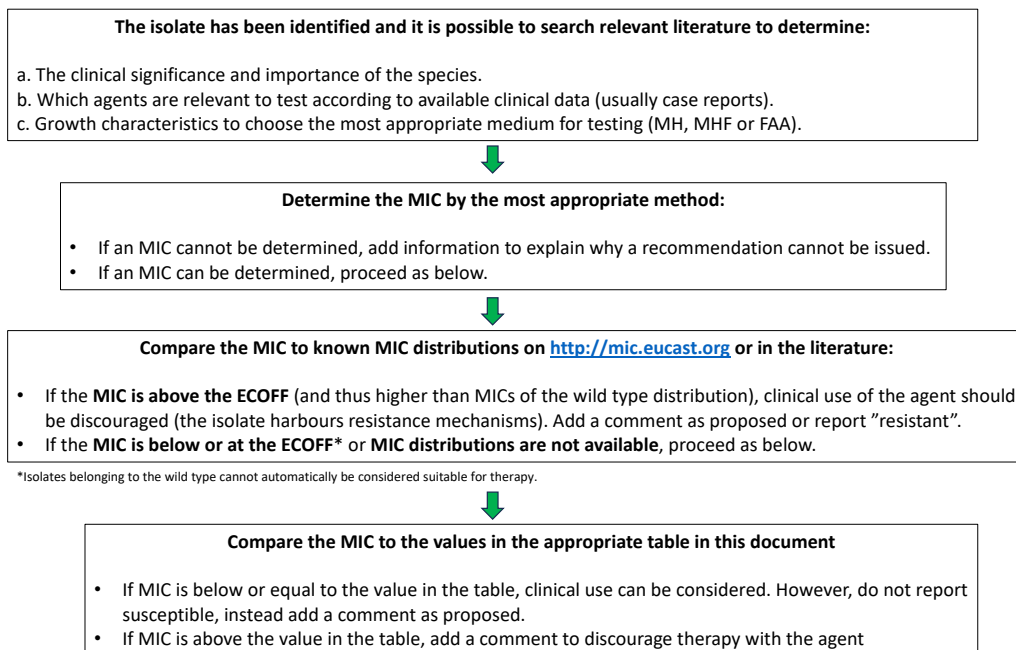
Agents and notes for aerobic bacteria	MIC-values above which therapy with the agent should be discouraged		Notes
	Gram-positive organisms	Gram-negative organisms	
Benzylpenicillin	0.25	0.5	If a beta-lactamase is detected, report resistant without further testing.
Ampicillin, Amoxicillin, Ampicillin-sulbactam, Amoxicillin-clavulanic acid (IV only)	0.5	8	The breakpoint of 8 mg/L pertains to intravenous high dose administration. If a beta-lactamase is detected, the value is only valid for amoxicillin-clavulanic acid and ampicillin-sulbactam.
Piperacillin-tazobactam	1	8	Species specific breakpoints for gram-positive organisms are 0.25 – 1 mg/L, and for gram-negative organisms 8 – 16 mg/L
Cefotaxime	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either excludes the use of both.
Ceftriaxone	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either excludes the use of both.
Ceftazidime	-	4	This is the Enterobacterales R-breakpoint.
Cefiderocol	-	2	This is the R-breakpoint for Pseudomonas, and other non-fermenters.
Imipenem	2	2	Species specific breakpoints are often 2 mg/L.
Meropenem	2	2	Species specific breakpoints are 0.25 – 2 mg/L
Ciprofloxacin	0.25	0.25	Species specific breakpoints are 0.25 – 1 mg/L.
Levofloxacin	0.5	0.5	Species specific breakpoints are 0.25 – 1 mg/L.
Moxifloxacin	0.25	0.25	Species specific breakpoints are 0.125 – 0.5 mg/L
Clindamycin	0.5	NA	Species specific breakpoints are 0.25 – 0.5 mg/L.
Tetracycline (test tetracycline, report doxycycline, minocycline)	2	2 For Gram-negative organisms other than Enterobacterales	Tetracycline (as a representative for tetracycline, doxycycline, and minocycline) species specific breakpoints are 0.5 – 2 mg/L.
Trimethoprim-sulfamethoxazole	1	1	Species specific breakpoints are 0.5 – 2 mg/L.
Tigecycline	0.5	NA	Species specific breakpoints are 0.125 – 0.5 mg/L.
Rifampicin	0.125	NA	Species specific breakpoints are 0.06 – 0.125 mg/L.
Linezolid	2	NA	Species specific breakpoints are 2 - 4 mg/L
Vancomycin	2	NA	Species specific breakpoints are 2 mg/L.
Dalbavancin	0.125	NA	Species specific breakpoints are 0.125 mg/L.
Daptomycin	1	NA	Species specific breakpoints are 1 mg/L.

Table 2. Antimicrobial agents relevant for the treatment of anaerobic bacteria with guidance for bacteria lacking breakpoints in standard EUCAST breakpoint tables.

Determine an MIC and compare with numerical values to assess the microbiological activity of the agent against the species. The clinical use of agents for which MIC-values are higher than those listed below should be discouraged, while agents for which the MIC is the same or lower can be considered for therapy. Avoid reporting isolates S, I or R - instead add a comment to discourage or consider therapy. The proposed values are based on (i) a compromise between current EUCAST susceptible (S or I) breakpoints for anaerobic species already in the tables, (ii) wild type distributions for microorganisms when available and (iii) PK/PD cut-off values.

Agents and notes for anaerobic bacteria	MIC-values above which therapy with the agent should be discouraged	
Benzylpenicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin-clavulanic acid	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.
Ampicillin-sulbactam	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.
Piperacillin-tazobactam	2	Breakpoints for anaerobic bacteria in the breakpoint table are 0.5 – 2 mg/L.
Meropenem	1	Breakpoints for anaerobic bacteria in the breakpoint table are 0.03 – 1 mg/L.
Imipenem	1	Breakpoints for anaerobic bacteria in the breakpoint table are 0.03 – 1 mg/L.
Ertapenem	0.25	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L.
Clindamycin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 mg/L.
Metronidazole	4	Breakpoints for anaerobic bacteria in the breakpoint table are 0.5 - 4 mg/L.
Vancomycin (Gram-positive)	2	Only relevant for a few gram-positive anaerobic bacteria. A breakpoint of 2 mg/L is common for targeted species.
Rifampicin (Gram-positive)	0.125	Breakpoints for species already in the EUCAST breakpoint tables are 0.06 – 0.125 mg/L.
Linezolid (mixed infections)	Pending	Linezolid has been used in the treatment of mixed infections where anaerobic bacteria were considered causative, but rarely for targeted therapy of anaerobic infections.
Moxifloxacin (mixed infections)	Pending	Moxifloxacin has been used in the treatment of mixed infections where anaerobic bacteria were considered causative, but rarely for targeted therapy of anaerobic infections.

Flowchart:



When the agent for use is not in the tables, and the last part of the flowchart cannot be applied, a decision can still be reached if a reliable MIC can be determined. Consult the literature for data to suggest a positive clinical outcome related to the MIC of this or a closely related species. Issue a cautious recommendation for use of the agent in the form of a comment, as proposed above, rather than a susceptibility category.

Addendum “How to identify the wild-type distribution”.

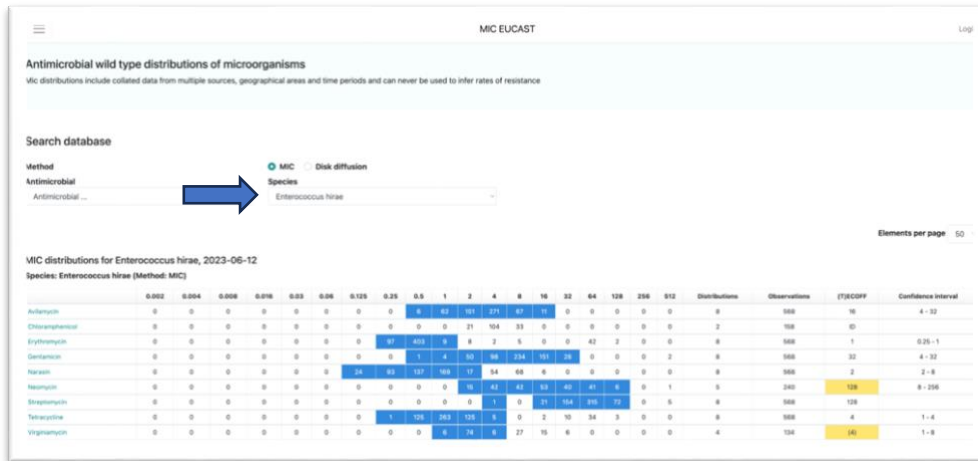
1. Access the EUCAST website (www.eucast.org)
2. Click on “MIC and zone diameter distributions and ECOFFs”.

The screenshot shows the EUCAST website interface. The left sidebar contains a list of navigation links, with 'MIC and zone distributions and ECOFFs' highlighted by a blue arrow. The main content area displays the title 'MIC and zone diameter distributions and ECOFFs' and a list of two links: '1. EUCAST MIC and zone diameter distributions and ECOFFs' and '2. Correlation between MIC values and inhibition zone diameters'. A blue arrow points to the first link. Below the links, there is a paragraph of text explaining the EUCAST software and its history, followed by a section titled 'Access to MIC and zone diameter distribution data.'

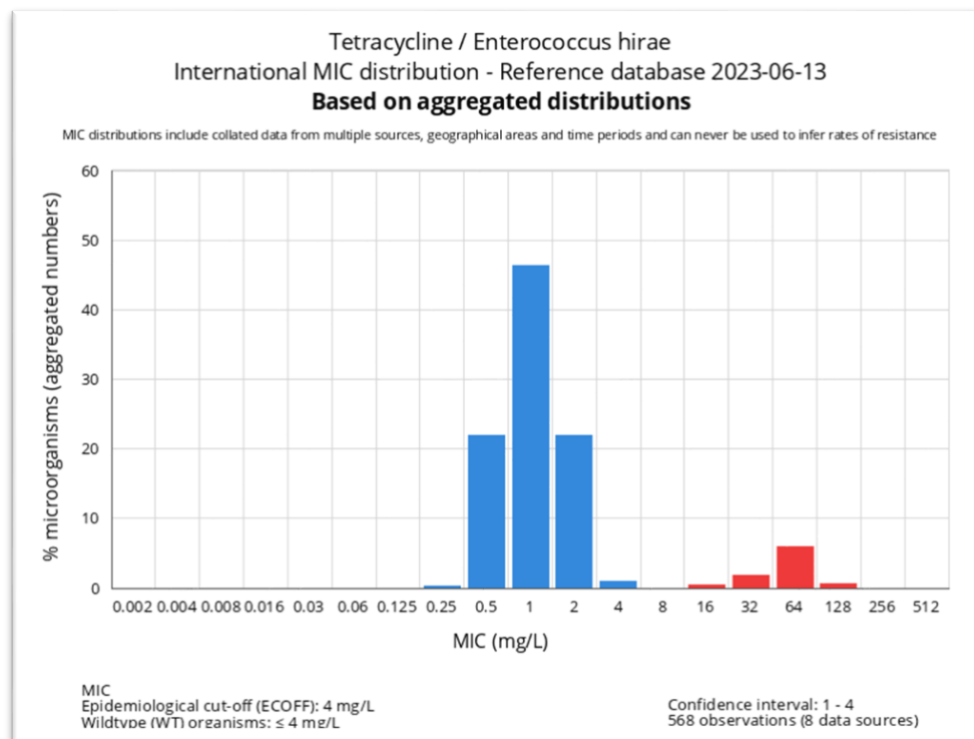
Click on “Search database”

The screenshot shows the 'Search database' section of the EUCAST website. The left sidebar contains a list of navigation links, with 'Search database' highlighted by a blue arrow. The main content area displays the title 'Antimicrobial wild type distributions of microorganisms' and a list of links: 'MIC and inhibition zone diameter distributions of microorganisms without and with phenotypically evident resistance mechanisms', 'MIC and inhibition zone diameter distributions', '1. MIC distributions', '2. Inhibition zone diameter distributions', 'Clinical MIC and Zone diameter breakpoints', 'Epidemiological cut-off values (ECOFF) and tentative epidemiological cut-off values (TECOFF)', and 'Limitations'.

...and search for the species in the pull-down list. If the species (or a closely related organism) is not in the list, a useful MIC distribution is not available. If MIC distributions are available, a table opens listing the agents for which MIC distributions can be viewed.



Click on the name of the agent (in the example “tetracycline”) to view the MIC distribution.



- If the organism can be shown to be non-wild type (MIC value above the ECOFF), include a comment in the report to discourage therapy.
- If the organism can be shown to be wild type (MIC value below the ECOFF), do not immediately consider the isolate susceptible to the agent, follow the guidance above.
- If not possible to determine whether the isolate belongs to the wild type or not, follow the guidance above.