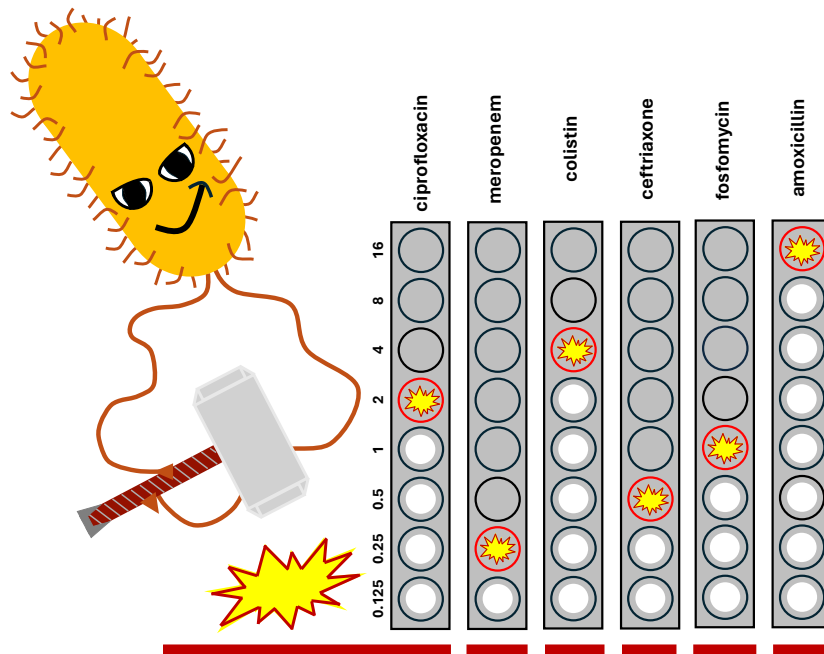


Antibiotic breakpoints and Minimum Inhibitory Concentration (MIC)

(Juan Antonio del Castillo Polo)



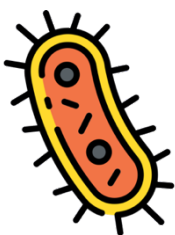
Are all antibiotics useful for all bacteria? How do we choose? Ever get curious about why some medicines fight illness while others don't? It's all about targeting the right enemy! Antibiotics fight infections caused by bacteria, but there are many different types of bacteria. Doctors choose the antibiotic that kills those bacteria more quickly and effectively and has less side effects and administration problems.

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Two important concepts: susceptible and resistant. When an antibiotic can kill a specific group of bacteria, making it suitable for treating infections caused by them, we say that those bacteria are susceptible (S) to this antibiotic with the dosage approved for human use. On the other hand, if the bacteria are not affected by the antibiotic and keep growing, we say these bacteria are resistant (R).

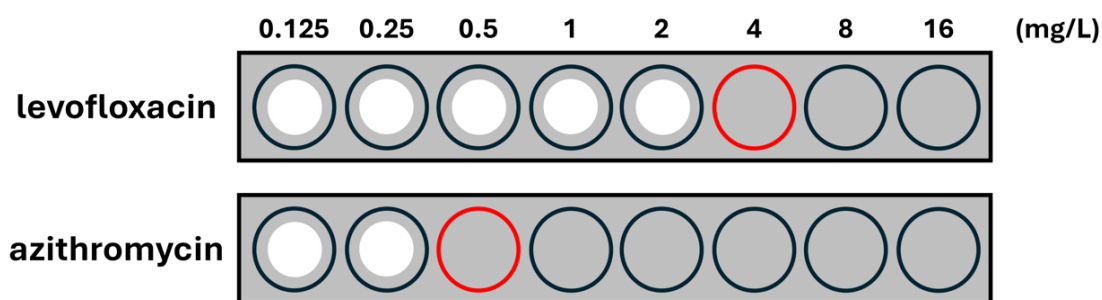


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What is an MIC? The term MIC stands for Minimal Inhibitory Concentration, which represents the lowest concentration of an antibiotic required to stop the growth of a specific bacterial strain. This value is determined in clinical microbiology laboratories through *in vitro* testing, where bacterial growth is observed in a panel with wells. For example, an *Escherichia coli* isolate with an MIC of 8 mg/L means that a concentration of antibiotic at 1 mg/L won't prevent its growth, while concentrations of 8 mg/L or 32 mg/L will.

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This cartoon shows how we determine the MIC. Black circles represent wells in a plastic plate containing the microbe to be tested, nutrient medium in which it can grow, plus the antibiotic being tested. The wells are identical except for the concentration of antibiotic, which increases as the wells go from left to right. After incubation to allow bacteria to grow and multiply, the plate is examined to see which wells show bacterial growth, indicated as white spots. Where no growth occurs, it means that the antibiotic concentration is sufficient to stop bacterial growth. The lowest antibiotic concentration that inhibits growth is the MIC and is indicated by a red circle. In the cartoon, the MIC for levofloxacin is 4 mg/L and for azithromycin 0.5 mg/L. Source: own elaboration.

A real MIC determination is shown below. The four left-hand wells contain a lot of bacteria that have grown and sedimented to the bottom of the wells, whereas the other wells have no visible bacterial growth (the antibiotic concentration was high enough to prevent it).



Source: partial figure from EUCAST guidance document on cefiderocol BMD (page 2). Real broth microdilution plate lecture, indicating MIC well in red. Available in: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Cefiderocol_MIC_testing_EUCAST_guidance_document_201217.pdf

What is a clinical breakpoint and why is it important?

Now that we have the MIC of the isolate, we need to compare the value with a reference to decide if an antibiotic can be given or not. Clinical breakpoints are like cut-off points that consider how well the antibiotic works inside the body; they are previously set and specific for bacterial species-antibiotic combinations. If the determined MIC is lower than or equal to the breakpoint, the antibiotic is strong enough at a safe dosage to kill the bacteria – we say that the isolate is susceptible (S). If it's higher, the antibiotic probably won't be strong enough to treat the infection – in this case, we call the strain resistant (R). Let's see that with some examples:

		S	R
<i>Staphylococcus aureus</i>	Azithromycin	≤ 2	> 2
	Doxycycline	≤ 1	> 1
<i>Streptococcus pneumoniae</i>	Azithromycin	≤ 0.25	> 0.25
	Doxycycline	≤ 1	> 1

Source: EUCAST Clinical Breakpoint Tables v 14.0

In these cases, the breakpoint for azithromycin is different in *S. aureus* (2) and *S. pneumoniae* (0.25). We require a higher concentration in the body of azithromycin to inhibit *S. aureus* growth than to inhibit *S. pneumoniae*. However, the breakpoint for doxycycline is similar for both. A *S.*

aureus isolate with a MIC=1 mg/L for azithromycin would be susceptible to it (breakpoint is 2); if the isolate was a *S. pneumoniae*, it would be resistant (breakpoint is 0.25).

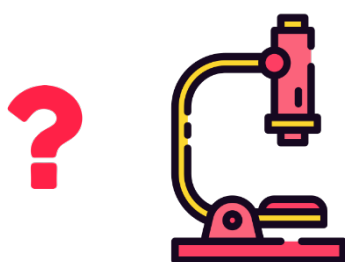
How are breakpoints set and how is it done? There are some institutions that set breakpoints and update them yearly. Two examples of them are EUCAST (The European Committee on Antimicrobial Susceptibility Testing, in the European Union) and CLSI (Clinical & Laboratory Standards Institute, in the United States of America).

Setting a breakpoint is a very complex procedure that involves clinical, pharmacological, and microbiological considerations, including pharmacokinetics (how the body affects the antibiotic) and pharmacodynamics studies (the effect of the antibiotic in the body). For example, when an oral antibiotic is prescribed, it is swallowed and goes into our digestive system before it is absorbed into our blood stream. Some of it may be inactivated by stomach acid, or inactivated by our gut microbiome, and what remains may not all pass into the blood stream. Once in the blood stream, not all will find its way to the infected tissue, and some may be metabolized by the liver. All these need to be considered.

Is it necessary to set a clinical breakpoint? Absolutely. When we want to use an antibiotic for treating a human infection caused by a specific bacterial strain, it is necessary to have a clinical breakpoint. Without a defined breakpoint, the MIC value obtained in the laboratory can't be evaluated against a reference. Consequently, we don't know if the bacteria in question are susceptible or resistant to the antibiotic.



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Is it necessary to determine the MIC in the laboratory? Not always. In many cases, bacteria very rarely develop resistance to the antibiotic that we want to use, allowing for its direct use without testing. In such cases, knowing the MIC value isn't essential, as it is inferred to be very low. The most common example of this is the use of a penicillin for tonsillitis. Doctors can directly prescribe a penicillin because tonsillitis is caused by a type of bacteria called *Streptococcus* that very infrequently develops resistance to penicillin.

Take-home messages

- MIC values indicate the lower value that inhibits bacterial growth in a laboratory setting, calculated for each specific bacterial isolate by microbiologists.
- Clinical breakpoint values give information about the likelihood of treatment success, evaluating if the MIC is below or above a threshold. They consider the interaction antibiotic-body, and are set by international institutions, not in the microbiology laboratory.
- While calculating MIC values may not be always mandatory, having a defined clinical breakpoint is essential, particularly when the antibiotic is used to treat an infection.

Further information about this topic, including specific examples of real-life cases, is available in the Topic Framework of the same name in the Section Our Wellbeing.