GUIDANCE DOCUMENT

Important considerations for breakpoint setting of antibiotic-inhibitor combinations

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Scope

This document provides guidance on the EUCAST data requirements for the setting MIC clinical breakpoints for antibiotic-inhibitor combinations. The examples refer to beta-lactam and beta-lactamase inhibitor combinations, but may be generalized to any combination of microbiologically active agent and an inhibitor of a resistance mechanism.

Disk diffusion is not addressed in this document. In Europe, disk susceptibility breakpoint zones are not part of the registration process. For disk susceptibility testing, the disk drug content loads and the procedure should be discussed in advance with EUCAST. The EUCAST Development Laboratory (Växjö, Sweden) will provide the necessary guidance for this.

Introduction

EUCAST uses the following information in setting clinical breakpoint:

(1) the pharmacodynamic index (PDI) and its target size;

(2) the MICs of the microorganisms of interest (particularly the wild type population),

(3) the variation in pharmacokinetics in the target population (EUCAST SOP 1.2 on breakpoint setting, Mouton et al., 2012), and

(4) treatment outcome data from clinical trials.

For combinations of antimicrobials where one of the two compounds is developed specifically to counter beta-lactamases, the approach is identical. Usually, the dosing regimen of the active compound ('parent' drug) is developed assuming there is no resistance mechanism present, and clinical breakpoints are selected based in this
dosing regimen. It is further assumed that the activity of the beta-lactamase during treatment is countered by the inhibitor to restore the activity of the parent drug. Because of these assumptions, additional information is required for inhibitor combinations, including:

(5) the PDI of the inhibitor and its size for sufficient effect.

For informed decision making in setting clinical breakpoints by EUCAST, the following information is therefore required.

1. **MIC distributions of the parent drug and the inhibitor separately to evaluate the in vitro activity of both drugs**

The first will generally be available (e.g. on the EUCAST website) if the agents are already marketed. This will allow initial selection of the ECOFFs of both compounds, and determine whether the activity of the inhibitor is in a concentration range that is relevant in vivo.

2. **The concentrations of inhibitor required *in vitro* to inhibit relevant beta-lactamases**

To evaluate these concentrations, the inhibitory effect should be provided over a sufficiently broad concentration range for a number of strains that is large enough (e.g. 100) to fully evaluate the inhibitory effects, that is, the relationship between inhibitor and MIC value. These are essentially interaction experiments for determining the effective concentrations of the inhibitor. Strains tested should represent those of interest, that is, a variety of resistance mechanisms should be present that would be found if such strains were cultured from infection sites. This collection must include organisms producing well-characterized beta-lactamases that have shown been to be inhibited by the beta-lactamase inhibitor.

Of note, in the final test to be used in clinical laboratories, the concentration of the inhibitor will be fixed, unless firm evidence of superiority can be provided for a different approach. Previous inhibitor concentration studies from the development of other combinations with the inhibitor might also assist with the current combination.
3. The breakpoints of the active drug, the dosing regimens on which these are based and their justification

These can normally be found on the EUCAST website if the drug is already available as a single agent. However, if different dosing regimens are proposed than originally used for the justification of breakpoints by EUCAST, or if no EUCAST rationale document is available (which is eventually the case for some older drugs), a full justification needs to be provided. This justification should include PK-PD data in vitro and in vivo and, when possible, in man. Some guidance can be found in the EUCAST document on breakpoint setting (Mouton et al., 2012).

4. The pharmacodynamic index and its size for the inhibitor

An inhibitor may already be used with other active compounds. However, it cannot be assumed that the pharmacodynamic target of an inhibitor is the same if combined with another antimicrobial. Evidence should be provided that the pharmacodynamic target is similar, or if not, what the pharmacodynamic target is. Dose justification of the inhibitor should be provided. It should be noted that concentrations in vitro that are required for certain pharmacodynamic effects of the inhibitor are not necessarily similar to those in vivo. The relationship between concentrations required for effects of the inhibitor in vitro and in vivo should be provided.

Special considerations

1. Some inhibitors have intrinsic antimicrobial activity. For instance, avibactam is active at concentrations of 16 mg/L as demonstrated by MIC distributions for Escherichia coli and Klebsiella pneumoniae (Berkhout et al., 2015) as well as 16-32 mg/L for clavulanic acid in E. coli (Diez-Aguilar et al. 2015). As long as the active compound is more active than the inhibitor, there is no difference in approach to the above. In this case, efficacy will largely be determined by the active compound. If the inhibitor is as active or more active than the parent drug, the EUCAST approach to breakpoint setting will determined on a case-by-case basis.

2. Some drug combinations have clearly enhanced antimicrobial effects if given together; both in vitro and in vivo. In this situation EUCAST will set breakpoints on a
case-by-case basis. In general, what needs to be shown is clear antimicrobial activity 
in vivo and in vitro and that there is good correlation with in vitro testing results.

References

