Can We have International Breakpoints? : EUCAST Perspectives

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The main parameters used to indicate whether the use of an antimicrobial will have a reasonable chance of success of treatment are the classifications 'resistant' (R) and 'susceptible' (S). The criteria used in the past to categorize bacteria as S or R in Europe were diverse, sometimes based on frequency distributions directed at discriminating between resistant (sub) populations, and sometimes using serum concentrations and other characteristics of the drug. Importantly, the methodology to identify resistant micro-organisms differed per country. In addition, the dosing regimens varied per country and per indication. As a result, the criteria for susceptible and resistant varied by country. For instance, the S breakpoint of cefotaxim for *E. coli* was $\leq$0.5 mg/L in Sweden, while it was 4 mg/L in France and The Netherlands. Similarly, the R breakpoint was >1 mg/L in Sweden and >32 in France. In addition, the definitions for susceptible and resistant itself, as well as the expressions used (e.g. >or$\geq$) were dissimilar as well. The interpretation of results within Europe was thus diverse and comparisons in resistance rates be interpreted with caution.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) was formed in 1996 and restructured at the ECCMID in Milan 2002. The prime purposes of the committee were to harmonize breakpoints in Europe for existing drugs and to determine common European breakpoints for new drugs. Over the last three years, EUCAST has developed procedures to that purpose and harmonized breakpoints for four classes of drugs (fluoroquinolones, aminoglycosides, glycopeptides and oxazolidinones). Currently, harmonized breakpoints for cephalosporins, aztreonam and the carbapenems are under development. In addition, the EUCAST finalized an EMEA (European Medicines Evaluation Agency) SOP detailing EUCAST involvement in breakpoint setting in the process for licensing new agents and initiated the process for setting breakpoints for two agents undergoing registration. All information, including breakpoints, frequency distributions and background material is freely available from the internet (www.eucast.org).

An important push in the whole process was the increasing understanding of dose-effect relationships of antimicrobials during the last decade. These have shown a clear correlation between pharmacokinetic/pharmacodynamic (PK/PD) index and effect, the AUC/MIC and Peak/MIC ratio for concentration dependent drugs and $T_{>MIC}$ for time-dependent drugs respectively. These relationships can be used to determine clincial breakpoints and thereby discriminate between high and low probabilities of successful outcome of treatment (S and R, respectively). This concept has been shown not only in numerous experimental studies but also in a number of clinical trials. Finetuning of breakpoints is further accomplished using Monte Carlo simulations. Alternatively, the EUCAST has recognized that clinical breakpoints based on PK/PD relationships confer a different meaning to resistance than early detection of micro organisms with acquired resistance mechanisms which do not belong to a natural

bacterial population. The EUCAST has therefore introduced wild-type cut-off values to clearly distinguish between the two denotations of resistance.

In a couple of years the EUCAST has shown that harmonization of breakpoints within Europe is possible and on its way. It is clear and obvious that international breakpoints are necessary and the tools, both the procedures as well as the scientific background, are available to achieve that goal.