

Meeting Report

Clinical and Laboratory Standards Institute (CLSI) and EUCAST

The Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) Sub-committee on Antimicrobial Susceptibility Testing (CLSI-AST) held their bi-annual meeting in Tampa, FL, USA from 8th to 11th January 2005.

On the 8th of January the CLSI, EUCAST and the Food and Drug Administration (FDA) had an ad hoc joint 2.5 hour session. Six members of the EUCAST Steering Committee attended as EUCAST representatives and the ESCMID Secretary General, Giuseppe Cornaglia attended on behalf of ESGARS. After initial presentations by EUCAST and CLSI, the two committees agreed that sharing data and co-ordinating the review process for breakpoints would be beneficial to both parties. Decision processes and their formal relationship to regulatory authorities were discussed including a description by Gunnar Kahlmeter (EUCAST) of the planned co-operation between EUCAST and EMEA, which allows EMEA to utilise EUCAST as a breakpoint committee in the formal registration process for new drugs. Much of the ensuing discussion related to the lack of a legal framework, which would allow CLSI a formal role in reviewing existing breakpoints in the USA.

During two sessions on 8th and 9th January the CLSI Working Group on *Enterobacteriaceae*, headed by Mike Dudley, reviewed the background to and the process for revising cephalosporin breakpoints for *Enterobacteriaceae*. It was pointed out that this work had been ongoing for over six meetings (3 years) and so far had neither led to any actual changes in breakpoints nor to the working group having convinced the majority of the voting sub-committee of the need for a change. The STMA (Susceptibility Testing Manufacturers Association), represented by Barbara Zimmer, described the difficulties faced by the manufacturers following a major revision of a large set of breakpoints. Some of them are related to the legal process to obtain necessary approval for new concentration ranges from the FDA. As on other occasions during the meeting, FDA representatives questioned the process by which CLSI could change breakpoints.

Much of the discussions centred on the problems inherent in reviewing breakpoints. CLSI pointed out the limitations of current screening tests for extended spectrum β -lactamases (ESBLs) and the difficulties in identifying resistance mechanisms (ESBLs, AmpC, permeability). Lowering of the breakpoints would obviate the need for screening with lower concentrations than current breakpoints. FDA representatives questioned the public health hazard of some ESBLs and called for more and better clinical data to prove that this problem was of a magnitude requiring any action from either FDA or CLSI.

At the full sub-committee meeting on 10th January ("voting-day") Gunnar Kahlmeter gave a 30-minute presentation on the structure of EUCAST, its relationship to national breakpoint committees, ESCMID and EMEA and of the process for setting breakpoints. The rationale documents for EUCAST breakpoints were described and also the EUCAST wild type MIC distribution programme was demonstrated.

At the full sub-committee meeting discussion on the need for revising CLSI breakpoints for cephalosporins continued after a summary presentation of the issues by Mike Dudley. Consensus was reached that a scientific process to review the current cephalosporin breakpoints in *Enterobacteriaceae* is needed, and that this should be done in collaboration with EUCAST. This review could be tied in with review of carbapenem and aztreonam breakpoints. The *Enterobacteriaceae* Working Group was charged with producing preliminary revised breakpoints and background data sheets including data such as wild type distributions of relevant bacteria, Pk/Pd data and simulations for relevant dosages and target attainment rates. These would be presented at the CLSI meeting in June 2005.

During the Staphylococcal Working Group meeting Fred Tenover presented data to support lowering the vancomycin breakpoints for *Staphylococcus aureus*. The current CLSI breakpoints are $S \leq 8$ mg/L and $R \geq 32$ mg/L (as compared to the recently revised EUCAST breakpoints of $S \leq 4$ mg/L and $R \geq 8$ mg/L). It was argued that *S. aureus*

with MICs of 4 mg/L isolated after long-term vancomycin therapy exhibited clear biological changes (thickened cell walls). After having reviewed a number of case reports with poor therapeutic outcome, the working group members voted to suggest to the full committee that a revision of the vancomycin breakpoint should be considered during 2005. This was subsequently endorsed by the full sub-committee on 11th January. The FDA representative, John Powers, again questioned the need for the change and the process by which CLSI could make the change.

From the EUCAST and ESCMID viewpoint the meeting was successful.

- The work performed by EUCAST was taken seriously by CLSI members. The EUCAST model for co-operating with EMEA, the wild type distribution programme, the EUCAST website including the way the breakpoint tables were presented and the rationale documents were viewed positively.
- The CLSI Working Group on *Enterobacteriaceae* was encouraged to work together with EUCAST in the quest for new breakpoints for cephalosporins.
- There was positive progress towards the goal set by EUCAST to find a way to work together with CLSI towards greater harmonisation of breakpoints between Europe and the USA.

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