E009

4-hour Educational Workshop

Antimicrobial susceptibility testing with EUCAST breakpoints and methods

Susceptibility testing of new and revived antimicrobial agents

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Antimicrobial susceptibility testing (AST) has been the basis of effective infection chemotherapy, enhanced by the development of international standardized, reference methods. These methods have evolved since the 1960's via national AST committees/organizations and later harmonized through the efforts of standards groups (CLSI, EUCAST, ISO) to a high level of technical reproducibility. Reference dilution AST has generally focused on the broth microdilution method (BMD) to define drug potency and potential clinical MIC breakpoints with correlate disk diffusion (DD) methods enabling wider application of AST as therapeutic guidance.

AST of older agents (generally small molecules) had presented fewer technical challenges to adapt BMD or agar diffusion methods for clinical laboratory use; however in the past decade several investigational "new" drugs have encountered challenging AST development due to issues of poor drug solubility and agar diffusion, high binding to plastics, and needs for special medium supplements. The lipoglycopeptides and lipopeptides (daptomycin, dalbavancin, oritavancin, telavancin) can be used as examples. These agents require either supplements (calcium, polysorbate-80) to exhibit accurate activity in AST that can be correlated with clinical outcomes or PK/PD target attainment (TA). Such potency differences can be extreme (eight-to 32-fold) and the associated poor agar diffusion severely limits DD or stable-gradient test development. At regulatory approval of such agents, few commercial diagnostic products are available/possible leading to limited use of potentially important treatments that may have improved benefits to patients (prolonged T 1/2, high PK/PD parameters). Use of surrogate tests having high predictive values may become a common interim AST strategy.

Some "older" drugs have new therapeutic life when combined with enzyme inhibitors (so-called BLICs) that minimize hydrolytic effects of these resistance mechanisms. Challenges for testing these agents are focused on that concentration of the inhibitor correlating the MIC to clinical outcomes and PK/PD TA. Studies have emerged to measure PAE, post-beta-lactamase-inhibitor-effect (PBLIE) and BLI PD targets. Correlation of clinical outcomes to AST values has been achieved applying either fixed inhibitor concentrations or drug/inhibitor ratios. Examples of successful BLICs have been the recent approvals of ceftazidime-avibactam and ceftolozane-tazobactam, combinations developed for drug-resistant Gram-negative bacilli. New formulations of old drugs (tetracyclines, fosfomycin, etc.) also will require re-examination of AST methods and/or breakpoints.

In conclusion, contemporary development of AST methods and the assignment of relevant breakpoints has become more complex. Greater care to realize global harmonization of the process via regulatory agencies (EMA, FDA) needs more focus, and also to minimize the delayed introductions of newly approved drugs into diagnostic AST devices. Finally, such marketed devices or products also need to be vigorously validated against reference AST results through regulatory processes with results available in the public domain.