Updating Antimicrobial Susceptibility Testing Introduction

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LEARNING OBJECTIVES:

1. Identify the challenges of reporting and interpreting antimicrobial susceptibility testing results.
2. Describe the current methods utilized to determine AST results.
3. Discuss the correlation of AST results with patient outcome.

ABBREVIATIONS: MIC-minimal inhibitory concentration; AST-antimicrobial susceptibility testing; CLSI-Clinical and Laboratory Standards Institute; EUCAST-European Committee on Antimicrobial Susceptibility Testing; WT-wild type; NWT-non-wild type; UTI-urinary tract infection; MDR-multi-drug resistant; ESBL-extended-spectrum beta lactamase

INDEX TERMS: antimicrobial susceptibility testing, *Acinetobacter baumannii*, *Escherichia coli* ST131

Clin Lab Sci 2012;25(4):230

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Controversy exists concerning breakpoints or interpretive criteria, which are the values that determine the antimicrobial susceptibility testing (AST) categories susceptible, intermediate and resistant, the clinical predictive value of the minimal inhibitory concentration (MIC) criteria and the method of reporting AST results.[1,2,3]

Agreement between the physician and the clinical laboratory regarding the laboratory's interpretation, prediction and reporting of AST results is a potential source of conflict. While the physician's primary concern relates to the therapeutic dosing and the patient's clinical outcome, the latter is bound by the often inflexible type of standardization promoted by the Clinical and Laboratory Standards Institute (CLSI).[1,3]

Methods of testing, rigidity of quality control and adherence to the annually updated guidelines of the CLSI are paramount in the United States. A different concept is used by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). This system uses separate values and clinical breakpoints to note a microorganism as wild type (WT) or non-wild type (NWT). An organism lacking mechanisms of acquired or mutational resistance is used to define WT. The presence of one or more mechanisms of resistance defines NWT when an antibiotic is considered. The purpose of the EUCAST system is to detect small and large changes in susceptibility that will reflect the constantly evolving mechanisms of antimicrobial resistance. Variation in breakpoints from one system to another contributes to the complexity of interpretation and obscurity of prediction value most noted by physicians.[1]

In cases of acute infection, patients are treated empirically as bacterial identification and susceptibility reporting may take up to 48 hours. The significance of the results may considerably alter the treatment regimen. Polymicrobial infections (e.g. urinary tract, wounds, etc.) require multiple antibiotic agent therapy which may increase the risk of adverse effects (e.g. drug-drug interaction, renal impairment, etc.) as well as the cost of treatment.

Phenotypic AST molecular or genotypic detection performed from a specimen directly or from microbial isolate-growth can accurately determine the presence of resistance determinants (genes) of the pathogens responsible for the infection. Choosing the correct antimicrobial therapy in an emergent situation determined by this approach would seem to resolve

some of the problems encountered by AST. An increased demand for molecular technology has been created by misleading reporting systems and hospital antibiograms that lack a clinical predictive value.[1]

Correlation of breakpoints and patient outcome to account for therapeutic failure brings the question of AST validity to the forefront. In certain cases, molecular assays to detect *mec*A, *van*A, *van*B genes or extended-spectrum beta lactamase (ESBL) enzymes better predicts success and implements a faster turn-around-time than conventional culture and susceptibility methods. While there continue to be limitations that include false positive results due to non-specific products and contaminated material, as well as lack of reliable quality control guidelines, the main considerations are to improve, interpret and determine a better predictive value than the MIC result.[1,2,3]

In the article, Challenging Cases, case histories are presented to demonstrate the problems associated with antibiotic therapy based on AST and MIC breakpoints. The first example involves two patients with multiple comorbidities requiring surgical debridement and a lengthy antibiotic regimen. The eventual diagnosis of an infection due to *Acinetobacter baumannii*, a rare cause of necrotizing fasciitis, resulted in the death of both patients.[4]

The second example involves two patients, sisters suffering from alpha-1 -anti-trypsin deficiency, who were infected with the same multi-drug resistant (MDR) organism, a notorious strain ST131 of *Escherichia coli*. This was the first known case of within-household transmission of a UTI. Empiric treatment with a fluoroquinolone was cited as the main contributor to the younger sister's death.[5]

In the article, Methods, a general description is given of the standard phenotypic and genotypic AST methods commonly performed by clinical laboratories in the United States. The methods are based on standards annually updated by the CLSI and the antibiotic formulary used by the individual hospital or clinic. A discussion of antimicrobial agents and their breakpoints precedes the CLSI recommended procedure in this article.[6]

The Kirby Bauer disk diffusion method, a qualitative procedure, is the usual method performed in small hospitals and physician office clinics where considerations of adequate staffing and cost are foremost. Measurement of the zone sizes, where inhibition of bacterial growth occurs around the antibiotic disks, determines the susceptibility or resistance of an organism.

In contrast, quantitative procedures are based on the MIC and performed either as a manual or automated procedure. The reference method continues to be the broth dilution, which is followed by agar dilution and gradient diffusion or the E-test. Automated system testing, quality control and reference organisms are included in the discussion.[6]

To complete the series of articles is an overview, Present and Future Relevance in AST, which includes the "state of the art" critical factors involved in performing AST methods, the controversy affecting the present system, and challenges for the future. The AST state of the art in the clinical laboratory is exhibited in a number of parameters demonstrated by the accuracy of the method used (e.g. inoculum density, incubation, media requirements, etc.), the precision of performance, as well as the interpretive criteria and reporting of results.[1,2,3] Direct detection of resistant determinants to produce more rapid and accurate results has posed the question of AST relevance when results may be ambiguous and turn-around-time requires up to 48 hours.

Empiric therapy may subsequently fail due to the increase in resistant organisms that overwhelm therapeutic endeavors. The need for rapid results that lead to more successful antimicrobial therapy is mandated. If molecular technology surpasses AST in contributing to effective patient care and decreases extensive and costly hospitalization, the demand to incorporate these methods will prevail.[1,2,3]

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