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Ed. Note: *Dr. Raoult felt that no response was necessary.*

Failure to Adopt New Interpretive Criteria for Ticarcillin-Clavulanic Acid Could Prove Fatal

We read with great interest the recent article by Barry et al. concerning interpretive criteria for disk tests with ticarcillin-clavulanic acid (1). Once again, a group of investigators outside of our own has confirmed that the interpretive criteria recommended by us 4 years ago are still the most accurate for detecting resistance to ticarcillin-clavulanic acid (as defined by an MIC of ≥128 μg/ml) among members of the family *Enterobacteriaceae*. This conclusion is inescapable since three independent studies have now shown our criteria to be the best for detecting resistance (1–3). That issue resolved, the only one left is one of philosophy: what are the repercussions of converting to our new criteria? According to Barry et al. there are "practical problems created by making changes in interpretive criteria." These problems were never specified, but the authors implied that adopting our criteria would cause more problems than they solved. The data presented do not support such implications.

We strongly agree with Barry et al. (1) that SmithKline Beecham Pharmaceuticals should now provide clinical data that will prove once and for all what susceptibility test (MIC or disk) and what interpretive criteria for disk tests are best correlated to a positive (or negative) clinical outcome. We requested such data from the company in 1988, as did the National Committee for Clinical Laboratory Standards (NCCLS) in 1990. However, these data have not been forthcoming. Until such data are available, we strongly recommend adoption of our criteria by all laboratories to avoid the potentially fatal error of false susceptibility. We perceive very major errors (false susceptibility) to be highly significant, and a reduction of this error from 10 to 2% among resistant strains is significant. We would rather risk loss of sales to a company that has made little attempt to correct a potentially fatal error than risk loss of life of a single patient who may receive inappropriate therapy due to an error in a laboratory test. It is clear from all of these studies that we do not know the correct way to test ticarcillin-clavulanic acid in the laboratory. Until this is resolved, we should either adopt conservative criteria that will avoid potentially fatal errors or not test it all. We would like to take this opportunity to thank all of the clinical laboratories that have helped us on this issue. It is clear that we must continue to urge the NCCLS to change their interpretive criteria. The science sends a very clear message, and this is not an issue that can be decided on philosophical, economic, or political bases.

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Author's Reply

Our recent manuscript (2) documented the true prevalence of discrepancies between disk diffusion and broth microdilution susceptibility tests with ticarcillin and ticarcillin-clavulanic acid (T/C). We did, indeed, confirm the findings of Sanders et al. (5) that some enteric bacilli were T/C resistant (MIC, ≥128 μg/ml) but were categorized as being susceptible by the current disk test criteria. By using the zone size breakpoints of Sanders et al. (5), many of those false-susceptible disk test results were eliminated. Unfortunately, those criteria miscategorized a significant number of susceptible strains. The relative importance of false-resistant disk test results is a subject of debate that will affect the selection of zone size criteria for a large number of agents, not just T/C. Realistically, how many false-susceptible and false-resistant disk tests can we tolerate? With most antimicrobial agents, both types of discrepant results can be minimized by increasing the intermediate category, but that often results in a fairly large number of equivocal or indeterminate disk test results. In clinical practice, how are moderately susceptible or intermediate test results actually used? How to deal with such philosophical questions realistically is the practical problem at hand.

The new T/C zone size standards may be preferred if one assumes that patients with infections due to strains that are inhibited by ≤16 μg/ml would all respond to T/C therapy and that strains for which MICs are higher are less likely to respond. The proper interpretive category for strains for which the MICs are intermediate (32 or 64 μg/ml) is a critical issue (3, 4) that has not yet been addressed. Dr. Sanders and colleagues have considered strains for which the MICs were ≥128 μg/ml to be resistant and have assumed that all others are susceptible clinically. They condemn any test criteria that fail to properly identify strains that are resistant by the dilution test. That assumes that the dilution test is an infallible predictor of resistance or susceptibility. At this time, we are unaware of any evidence of serious clinical problems arising from the interpretive criteria that have been in use for many years. However, we must keep sight of the fact that only 7% of all members of the family *Enterobacteriaceae* are resistant to the T/C combination by broth dilution tests and only 10% of that 7% will be considered susceptible by current disk test criteria. Clinical failures due to technical errors of that magnitude should be difficult to document.

It is possible that we are now seeing a new problem which is the result of a recent increase in the prevalence of strains for which the T/C MICs are elevated because of excess production of β-lactamase enzymes. That would explain why clinical problems did not appear in the early years of T/C usage. A recent study evaluated T/C susceptibility data collected in different medical centers during 1983, 1989, and 1991 (1). Over the 8-year time span, there was no evidence of a change in the prevalence of T/C resistance among *Enterobacteriaceae*. However, there were sporadic differences among institutions. In different medical centers, T/C-resistant *Escherichia coli* strains occurred at rates of 3 to 12%, and another 7 to 18% were moderately susceptible. Overall, T/C resistance rates have not changed substantially since 1983.

The NCCLS subcommittee on antimicrobial susceptibility tests has reviewed the evidence supporting the proposed changes in T/C zone size criteria and has decided not to change them. Their failure to accept the proposed changes in interpretive criteria was an informed decision that was made after extensive discussion and careful analysis of all available data.

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