Tigecycline Disk Diffusion Breakpoints of *Acinetobacter* spp.: a Clinical Point of View

In the January 2007 issue of the *Journal of Clinical Microbiology*, Jones et al. reported a multicenter study of the tigecycline disk diffusion breakpoints of *Acinetobacter* spp., including multidrug-resistant (MDR) strains. The authors concluded that a breakpoint zone diameter of $\geq 16/\leq 12$ mm to define susceptibility/resistance, respectively, instead of those proposed by the U.S. Food and Drug Administration (FDA) for *Enterobacteriaceae* family organisms ($\geq 19/\leq 14$ mm, respectively), reduces the intermethod minor errors to an acceptable level (only 9.7% instead of 23.3%, with the FDA breakpoints proposed) (1).

We believe that this microbiological conclusion has major clinical relevance.

Tigecycline has been approved for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections. However, in Argentina, in the first month after the drug's launch, 61% of the tigecycline prescriptions were "off label," especially for patients with ventilator-associated pneumonia (VAP) due to MDR *Acinetobacter* sp. infection (D. Curcio, unpublished data). The high concentration of tigecycline in alveolar cells (77.5-fold higher than that in serum) (4), the increase of carbapenem-resistant *Acinetobacter* spp. in Argentina (54%) (5), the lack of medical evidence for the use of colistin in pulmonary infections (2), and the association between inappropriate initial antibiotic therapy and mortality in patients with VAP (defined as the susceptibility of cultured organisms to the antibiotics used) (3) seem to be the main reasons for using tigecycline in this indication.

We analyzed data from the Tigecycline Resistance Surveillance Program (Fulfillment) and found that a low proportion of infections due to *Acinetobacter* spp. were associated with the appropriate initial antibiotic empirical treatments compared with the proportion of infections due to microorganisms other than *Acinetobacter* spp. (27 versus 65%, respectively; $P < 0.00001$).

Besides, using FDA-proposed breakpoints, the *Acinetobacter* species resistance rate to tigecycline was 26%. The same resistance rate using a ≥ 16 -mm breakpoint was 3%.

In Argentina, over 90% of the clinical microbiology laboratories perform the antibiotic susceptibility test only through the disk diffusion method (unpublished data). That is why this is the only tool physicians have to prescribe antibiotics with microbiological documentation.

Regarding this point, Argentinean attending physicians are still expecting the definitive tigecycline breakpoints of *Acinetobacter* spp. and also the results of the phase 3 clinical trial about the clinical efficacy of tigecycline in nosocomial pneumonia (<http://www.clinicaltrial.gov>).

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Daniel Curcio is a speaker for Wyeth Laboratories, Argentina, for Tygacil. Francisco Fernández does not have a conflict of interest.

Both authors contributed to study concept, data analysis, interpretation of data, and manuscript preparation.

We had no sponsor.

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Authors' Reply

We read with some satisfaction that our recent publication on the topic of tigecycline intermethod (disk diffusion versus MIC results) accuracy for *Acinetobacter* species testing (3) was considered helpful in clarifying susceptibility among Argentinean clinical cases. As stated in our study results (3), numerous clinical microbiologists and infectious disease experts had reported elevated levels of suspected false intermediate and false resistant results when using the disk diffusion method (1) and the U.S. FDA MIC correlate breakpoints of $\leq 2/\geq 8$ $\mu\text{g/ml}$ (susceptibility/resistance, respectively) recommended for *Enterobacteriaceae* family organisms (Tygacil package insert [June 2005], Wyeth Pharmaceuticals Inc., Philadelphia, PA). Obviously, similar occurrences have negatively influenced the clinical outcome analyses of *Acinetobacter* sp. cases in Argentina, especially with "off-label" applications for treating ventilator-associated pneumonia.

Sadly, few parenteral antimicrobial agents are available for the therapy of MDR *Acinetobacter* sp. infections, and some of these drugs possess increased risks of adverse events or lack proven efficacy of use (4). The laboratories wishing to guide physicians' choices for MDR *Acinetobacter* disease must utilize validated, accurate methods (1, 2), realizing that definitive susceptibility breakpoints for this genus have not been published by either the FDA or the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS). Also, the prescription of this glycylcycline (tigecycline) for

treating *Acinetobacter* sp. disease remains a nonindicated use, to be selected when limited therapeutic options are present and supported by in vitro susceptibility test results as described by our working group (3). Measurable tigecycline activities (MIC, ≤ 2 $\mu\text{g/ml}$; zone diameter, ≥ 16 mm) assessed by CLSI methods (2) have consistent intermethod accuracy (3), giving physicians greater confidence in the laboratory susceptibility test result. However, we continue to encourage structured tigecycline clinical trials for the therapy of documented MDR *Acinetobacter* sp. infections (for respiratory, bacteremic, and other invasive indications), with clinical outcomes correlated to the susceptibility testing breakpoint criteria suggested in our intermethod analysis (3).

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