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Impact of Lowered CLSI Breakpoints on Reported Susceptibility Levels of Imipenem and Meropenem in the TEST Program

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Revised Abstract

Background: In June 2010, CLSI lowered carbapenem susceptibility breakpoints for *Enterobacteriaceae.* These changes will reduce reported susceptibility levels for these agents, and laboratory personnel should be prepared to explain the changes in susceptibility percentages that may be reported for these agents when the new breakpoints are published. The Tigecycline Evaluation Surveillance Trial (TEST) has been monitoring susceptibility levels of tigecycline and other drugs since 2004. This report evaluates the impact of the new carbapenem breakpoints on reported susceptibility of imipenem (Imp) and meropenem (Mer) in the TEST program. **Methods:** 25,458 and 53,986 isolates of *Enterobacteriaceae* were collected and tested vs. Imp and Mer, respectively, from 2004-2009 using broth microdilution following CLSI guidelines. Susceptibility to Imp and Mer was calculated using 2009 and 2010 CLSI breakpoints. **Results:** Imp and Mer %S/I/R values using 2009 (≤4/8/≥16) and 2010 (≤1/2/≥4) CLSI breakpoints are shown below for all *Enterobacteriaceae*.

Drug	Breakpoints (≤S|I≥R)	N	% Susceptible	% Intermediate	% Resistant
Imipenem	4 | 8 |16	25,458	99.68	0.15	0.18
Imipenem	1 | 2 | 4	25,458	97.17	1.92	0.91
Meropenem	4 | 8 | 16	53,986	98.42	0.43	1.15
Meropenem	1 | 2 | 4	53,986	96.76	0.96	2.28

Conclusions: Although the new CLSI S/I/R breakpoints for Imp and Mer appear to have minimal impact on %S reported for this collection of *Enterobacteriaceae* (a drop of 2.51% for Imp, and 1.66% for Mer; both remaining above 96%), the reported resistance to these two agents will show a "dramatic" increase in terms of year-over-year percentage change (over 500% for Imp and 98% for Mer). The change looks even more dramatic when calculating "non-susceptible" (NS) percentages, with Imp going from 0.33% NS to 2.83%, an increase of over 800%, and Mer NS increasing over 200%. Laboratories should be prepared to explain the "sudden" increase in non-susceptibility of *Enterobacteriaceae* to carbapenems that will be reported once they implement the new CLSI M100-S20-U breakpoints in their routine workload.

Introduction

The Clinical and Laboratories Standards Institute (CLSI) establishes susceptibility testing interpretive standards for antimicrobial agents. In the United States, the Food and Drug Administration (FDA) also establishes interpretive breakpoints for all new antimicrobics; however, the FDA does not have a well-established mechanism to routinely review its breakpoints to ensure that they accurately reflect the current body of knowledge about resistance mechanisms found in pathogens. The CLSI, on the other hand, can and does review the performance of its breakpoints periodically, and when new mechanisms of resistance are reported that were unrecognized when a drug was originally introduced for clinical use, the susceptibility breakpoints need to be reviewed to ensure they still accurately identify isolates with a high probability of treatment failure. Furthermore, as the science of pharmacokinetics/pharmacodynamics (PK/PD) has advanced over the past several years, it has been applied more and more by CLSI and other bodies such as the FDA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to identify more appropriate susceptibility breakpoints.

The advent and spread in bacteria of carbapenemases hydrolyzing one or more carbapenems (imipenem, meropenem, ertapenem, and doripenem) and the application of PK/PD information led the CLSI (and EUCAST before them) to lower the previously-established susceptibility breakpoints of *Enterobacteriaceae* to imipenem, meropenem, and ertapenem, and to select similar breakpoints for the more recently launched doripenem. However, changes of such magnitude will take a few years to be fully implemented by the manufacturers of antimicrobial susceptibility testing (AST) systems (bioMerieux Vitek, Siemens MicroScan, BD Phoenix, Trek Sensititre, etc.). As laboratories implement the new breakpoints either independently or when their AST provider releases new testing devices and software incorporating the new breakpoints, there will be a "sudden" increase in resistant or non-susceptible isolates to these carbapenems, almost entirely due to the lower breakpoints. This report shows the magnitude of change that most labs can expect to see, and can serve to help prepare laboratories and hospitals to explain the changes to their physicians, and differentiate between changes due to lower breakpoints and those due to a genuine increase in prevalence of carbapenemase-producing isolates.

Materials & Methods

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 and 2009 from 1,509 cumulative investigative sites in 59 countries globally. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) for imipenem and meropenem were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1], using panels manufactured by Trek Diagnostic Systems (Cleveland, OH) or Siemens Medical Solutions Diagnostics (West Sacramento, CA). Imipenem was replaced by meropenem during the 2005-2006 period. MIC interpretive criteria of the CLSI M100-S20 [2] and M100-S20-U [3] were applied to all data to compare percentages of susceptible (S), intermediate (I), and resistant (R) isolates.
- Quality controls (QC) were performed by each testing site on each day of testing using the CLSI-recommended ATCC control strains: *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853; results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI 2010 guidelines [2].

References

1. Clinical and Laboratory Standards Institute. 2008. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, 9th ed. Approved Standard M8-A8. Clinical and Laboratory Standards Institute, Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2010. Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. CLSI document M100-S20. Wayne, PA.
3. Clinical and Laboratory Standards Institute. 2010. Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. CLSI document M100-S20-U. Wayne, PA.

Acknowledgements

This study was sponsored by Pfizer Inc. We acknowledge the contribution of the investigators and laboratory personnel.

Results

Table 1. Imipenem and meropenem percent susceptible, intermediate, and resistant using CLSI M100-S20 and M100-S20-U breakpoints.

Drug	Breakpoints (≤S|I≥R)	N	% Susceptible	% Intermediate	% Resistant
Imipenem	4 | 8 |16	25,458	99.68	0.15	0.18
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Figure 1. Regional percentages of *Enterobacteriaceae* from 2004-2009 resistant to meropenem using M100-S20 and M100-S20-U breakpoints.

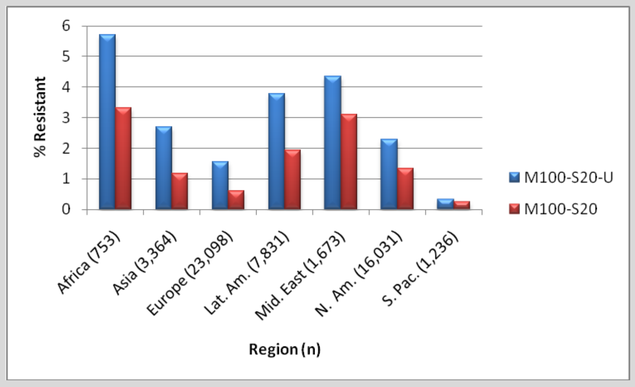


Figure 2. Regional percentages of *Enterobacteriaceae* from 2004-2009 resistant to imipenem using M100-S20 and M100-S20-U breakpoints.

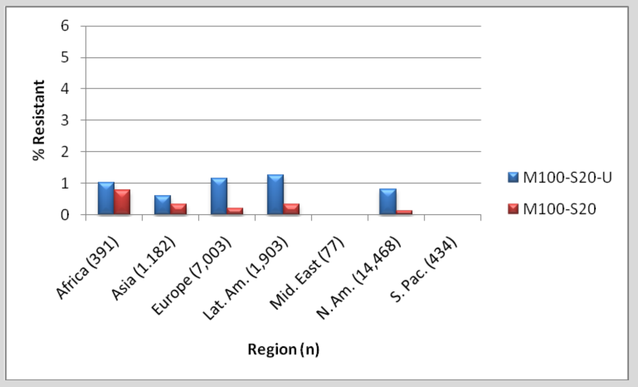


Figure 3. Relative worldwide percentages of 53,986 *Enterobacteriaceae* isolates reported as susceptible, intermediate, or resistant to meropenem using CLSI M100-S20 or M100-S20-U breakpoints.

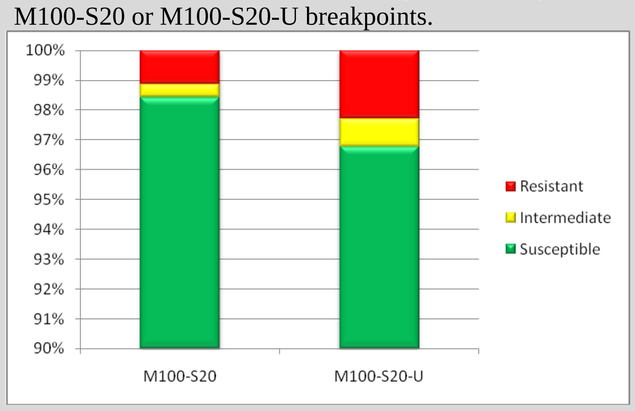


Figure 4. Relative worldwide percentages of 53,986 *Enterobacteriaceae* isolates reported as susceptible, intermediate, or resistant to imipenem using CLSI M100-S20 or M100-S20-U breakpoints.

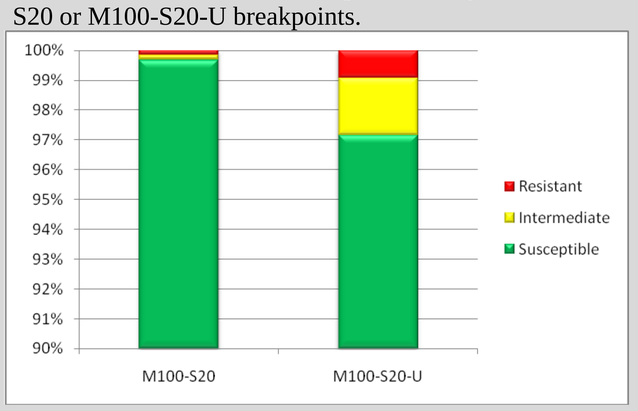
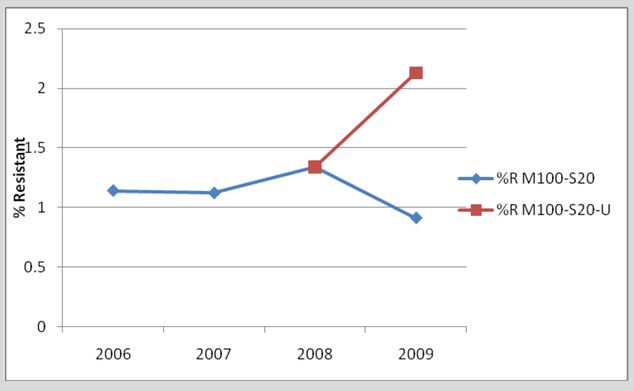


Figure 5. Impact on resistance trends of *Enterobacteriaceae* to meropenem using CLSI M100-S20 through 2008, then implementing M100-S20-U in 2009.



Conclusions

- Although the lower carbapenem breakpoints published in CLSI M100-S20-U in June 2010 only cause a drop in *Enterobacteriaceae* susceptibility percentages of 2.51 and 1.66% for imipenem and meropenem, respectively, the proportional increase in percentages reported as intermediate and resistant appear much larger due to their very small starting points.
- Other than South Pacific, most regions of the world will see their carbapenem resistance rates "significantly" increase upon implementation of the M100-S20-U breakpoints; however, the reported increases will be due almost entirely to the lowered breakpoints, not a genuine increase in rates compared to previous years.
- As AST manufacturers begin to introduce device and software updates incorporating the M100-S20-U breakpoints, antibiograms from hospitals will start to vary, depending on which AST system they use and when their manufacturer makes the update available. It will be important for investigators who aggregate susceptibility data to avoid mixing information from hospitals using different versions of the M100 guidelines.
- When presenting susceptibility reports of carbapenems using the lower breakpoints published in M100-S20-U, it may be prudent to either retrospectively apply the new breakpoints to previous years of data, or to include footnotes or comments in the reports explaining the cause of the sudden increase in rates of intermediate and resistant isolates compared to what physicians were used to seeing previously.