Effects of breakpoint changes on carbapenem susceptibility rates of Enterobacteriaceae: Results from the SENTRY Antimicrobial Surveillance Program, United States, 2008 to 2012

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In the absence of clinical resistance, breakpoints for many antimicrobial agents are often set high. Clinical failures following use of the agents over time requires re-evaluation of breakpoints. This is based on patient response, pharmacokinetic/pharmacodynamic information and in vitro minimal inhibitory concentration data. Data from the SENTRY Antimicrobial Surveillance Program has shown that Clinical and Laboratory Standards Institute breakpoint changes for carbapenems that occurred between 2008 and 2012 in North America have resulted in decreased levels of susceptibility for some species. In particular, reduced susceptibility to imipenem was observed for Proteus mirabilis (35%) and Morganella morgani (80%). Minor decreases in susceptibility were also noted for Enterobacter species with ertapenem (5%) and imipenem (4.3%), and Serratia species with imipenem (6.4%). No significant decreases in susceptibility were observed for meropenem following the breakpoint changes. There were no earlier breakpoints established for doripenem. Very few of these Enterobacteriaceae produce carbapenemase enzymes; therefore, the clinical significance of these changes has not yet been clearly determined. In conclusion, ongoing surveillance studies with in vitro minimal inhibition concentration data are essential in predicting the need for breakpoint changes and in identifying the impact of such changes on the percent susceptibility of different species.

Key Words: Carbapenems; Surveillance; Susceptibility breakpoints

Antimicrobial susceptibility breakpoints are initially determined under statutes by regulatory agencies (United States Food and Drug Administration and European Medicines Agency) at the time of clinical approval based on accumulated microbiology, pharmacokinetic (PK)/pharmacodynamic (PD) and clinical trial outcome information. On their release, resistance to antimicrobials is often uncommon. This is especially true for broad-spectrum β-lactams, particularly the carbapenems. In the present article, we document the extent of spectrum/coverage impact for the four most approved from 1980 to 2000. These processes were initially addressed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (4) and later by the Clinical and Laboratory Standards Institute (CLSI) (5-7).

Responses to these lowered CLSI breakpoints have varied widely, from “there was no perceived adverse clinical signal and in fact the change would lead to unneeded applications of potentially toxic broader spectrum agents” to “the new lowered breakpoints without companion resistance enzyme screening would place patients at risk, or these recent changes were based on flawed science” (8-12).

Regardless of the ongoing debate, the CLSI breakpoint changes (6,7) have resulted in significantly decreased susceptibility rates for some β-lactams, particularly the carbapenems. In the present article, we document the extent of spectrum/coverage impact for the four most

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TABLE 1
Clinical Laboratory Standards Institute (CLSI) clinical breakpoint concentration (µg/mL) criteria for Enterobacteriaceae in 2010 and 2013 for carbapenems

| Susceptibility breakpoints | Carbapenem and CLSI year* |
|---------------------------|---------------------------|
|                           | Doripenem | Ertapenem | Imipenem | Meropenem |
|                           | 2010       | 2013       | 2010       | 2013       | 2010       | 2013       |
| Susceptible               | NC         | ≤ 1        | ≤ 2        | ≤ 0.5      | ≤ 4        | ≤ 1        |
| Intermediate              | NC         | 2          | 4          | 1          | 8          | 2          |
| Resistant                 | NC         | ≥ 16       | ≥ 16       | ≥ 16       | ≥ 16       | ≥ 16       |

*Criteria from CLSI, references 5-7. NC No criteria published

TABLE 2
Spectrum effects of Clinical Laboratory Standards Institute (CLSI) 2012 breakpoint criteria changes on carbapenems (results from the North America SENTRY Antimicrobial Surveillance Program, 2008–2012)

| Enterobacteriaceae (19,382) | Ertapenem | Imipenem | Meropenem | Doripenem |
|-----------------------------|-----------|----------|-----------|-----------|
| Escherichia coli (6882)     | 97.1/98.1 | 92.4/98.6| 98.3/98.6| 98.3/-     |
| Klebsiella species (5467)   | 94.7/95.1 | 95.3/95.9| 95.3/95.9| 95.3/-     |
| Enterobacter species (2662) | 92.9/97.9 | 94.7/99.0| 98.7/99.2| 98.7/-     |
| Proteus mirabilis (1244)    | 99.9/100  | 64.5/99.8| 99.9/100 | 99.9/-     |
| Serratia species (1119)     | 98.0/98.8 | 92.9/99.3| 98.8/99.2| 98.8/-     |
| Citrobacter species (746)   | 97.7/98.8 | 97.1/99.3| 98.8/99.3| 98.9/-     |
| Morganella morgani (490)    | 100/100   | 19.6/100 | 100/100   | 100/-      |

*No earlier breakpoints were published by CLSI; †Significant (lowering of susceptibility rate of >4%) decline in susceptibility rate
It is still uncertain what these changes (6,7) will mean clinically over time. The vast majority of these Enterobacteriaceae tested against the carbapenems do not produce clinically significant carbapenemases; otherwise, reduced susceptibility to meropenem and possibly doripenem would also be observed (Table 2). The current study was based only on MICs to the carbapenems to reflect the

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