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 morganii (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 inhibitory 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) and later by the Clinical and Laboratory Standards Institute (CLSI). 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

**Les effets des changements au seuil de résistance des carbapénèmes sur les taux de susceptibilité des entérobactéries : les résultats du programme de surveillance antimicrobienne SENTRY mené aux États-Unis de 2008 à 2012**

En l’absence de résistance clinique, la résistance de nombreux antimicrobiens est souvent fixée à un seuil élevé. En raison de l’échec clinique de certains de ces médicaments, il faut en réévaluer les seuils de résistance, d’après la réponse du patient, l’information pharmacocinétique et pharmacodynamique et les données relatives à la concentration minimale inhibitrice en vitro. Les données du programme de surveillance antimicrobienne SENTRY ont révélé que les changements au seuil de résistance des carbapénèmes établis par le Clinical and Laboratory Standards Institute entre 2008 et 2012 en Amérique du Nord ont entraîné une diminution de la susceptibilité de certaines espèces. Notamment, les chercheurs ont observé une susceptibilité réduite du Proteus mirabilis (35 %) et du Morganella morganii (80 %) à l’imipénem. Ils ont également remarqué de légères diminutions de la susceptibilité des espèces d’Enterobacter à l’ertapénem (5 %) et à l’imipénem (4,3 %), ainsi que des espèces de Serratia à l’imipénem (6,4 %). La susceptibilité du méropénem n’a pas diminué de manière significative, tandis qu’aucun seuil de résistance n’avait été établi auparavant pour le doripénem. Puisque très peu de ces entérobactéries produisent des enzymes de carbapénémase, la signification clinique de ces changements n’est pas encore claire. Bref, il est essentiel de poursuivre les études de surveillance pour colliger des données sur les concentrations minimales inhibitrices en vitro afin de prédire la nécessité de changer le seuil de résistance et de déterminer les conséquences de ces changements sur le pourcentage de susceptibilité des diverses espèces.

*Robert P Rennie PhD (ABMM) FCCM1, Ronald N Jones MD FCAP2*

**Results**

Les effets des changements au seuil de résistance des carbapénèmes sur les taux de susceptibilité des entérobactéries : les résultats du programme de surveillance antimicrobienne SENTRY mené aux États-Unis de 2008 à 2012

**Key Words:** Carbapenems; Surveillance; Susceptibility breakpoints

*Medical Microbiology, University of Alberta Hospital, Edmonton, Alberta; 2JMI Laboratories, North Liberty, Iowa, USA*
Escherichia coli Enterobacteriaceae (19,382) 97.1/98.1 92.4/98.6 98.3/98.6 species (5467) 94.7/95.1 95.3/95.9 95.3/95.9 species, 2662 Proteus from the USA). In all, there were 6882 from participating laboratories in North America (predominantly groups of presented in Table 1.

Comparing MIC values using the 2010 and 2013 CLSI-defined breakpoints of four carbapenem agents on the perceived in vitro susceptibility of 19,382 strains of Enterobacteriaceae (2008–2012). The determination was made by establishing the breakpoints of four carbapenem agents on the perceived in vitro susceptibility of 19,382 strains of Enterobacteriaceae (2008–2012). The determination was made by comparing MIC values using the 2010 and 2013 CLSI-defined breakpoints for these agents (5-7). The applied/compared breakpoints are presented in Table 1.

More than 19,000 strains representing seven species or genus groups of Enterobacteriaceae were included. These were strains isolated from participating laboratories in North America (predominantly from the USA). In all, there were 6882 Escherichia coli, 5467 Klebsiella species, 2662 Enterobacter species, 746 Citrobacter species, 1119 Serratia species, 1244 Proteus mirabilis and 490 Morganella morgani, ie, 96.0% of all enteric bacilli processed. Each strain was submitted to the monitor for storage and were then retested to confirm identity and perform susceptibility testing (6,11). Each carbapenem was tested in concentrations ranging from 0.06 µg/mL to 8 µg/mL using validated CLSI reference panels.

The results of the changes in breakpoints from 2010 to current criteria (6) are shown in Tables 1 and 2. Significant decreases or decline in susceptibility rates (defined as lowering of susceptibility of >4%) due to the reductions in breakpoints occurred for the following species – antimicrobial agent combinations: Enterobacter species for ertapenem (~5.0%) and imipenem (~4.3%), Serratia species for imipenem (~6.4%), P mirabilis for imipenem (~55.3%) and M morgani for imipenem (~80.4%). There were no notable changes for meropenem (all <1.0% reduction in susceptibility rates). No breakpoints for doripenem were published in 2010 (Table 1). For all species, susceptibility to doripenem was ≥98% using current breakpoint criteria. These revised breakpoints (6,7) were founded on solid PK/PD calculations for the most commonly used and indicated dosing regimens for doripenem (500 mg every 8 h), ertapenem (1 g every 24 h), imipenem (500 mg every 8 h or 1 g every 8 h) and meropenem (1 g every 8 h). These modified clinical breakpoints also efficiently separate carbapenemase-producing Enterobacteriaceae from wild-type susceptible populations (4,7,8) and more accurately predict clinical outcomes (2).

EUCAST carbapenem breakpoints are similar to those of the CLSI (4,6), and the European group also publishes a warning that “low-level resistance is common in Morganella spp., Proteus spp. and Providencia spp.” when tested against imipenem. This phenomenon appears to be detected more credibly (Table 2) using the revised CLSI criteria (6,7). Furthermore, review of the initial imipenem clinical trial results from 1985 demonstrated suboptimal outcomes (~50% eradications) for multiple types of infections caused by these indole-positive and -negative Proteae (14-19). Thus, one must conclude that these recent breakpoint modifications were appropriate, but also long overdue. Furthermore, the emergence of carbapenemase-mediated resistances, such as the KPC and NDM genes, in North America requires breakpoint changes to optimize choices of therapy among β-lactam agents (20,21), as well as initiating control interventions (22).

The lowering of breakpoints for the carbapenems has not had a profound negative effect on overall susceptibility for most species of Enterobacteriaceae when tested against the four carbapenem agents under surveillance. It is noteworthy that reduced susceptibility was observed for ertapenem and imipenem, but only for certain species. There has been no significant rate change for meropenem by reducing the breakpoints, and there has not been sufficient time or use of doripenem to identify whether breakpoints at this level will effectively identify strains that may fail therapy. Major reductions in breakpoint change-related susceptibility to imipenem have occurred in P mirabilis (35%) and M morgani; however, the rank order of carbapenem antimicrobial coverage remained the same in North America (doripenem = meropenem [98.3% to 98.3%] > ertapenem [97.1%] > imipenem [92.4%]) between 2010 and 2012.

**TABLE 1**

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

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<tr>
<td>Susceptible</td>
<td>NC</td>
<td>≤1</td>
<td>≤2</td>
<td>≤0.5</td>
<td>≤4</td>
<td>≤1</td>
<td>≤4</td>
<td>≤1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NC</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Resistant</td>
<td>NC</td>
<td>≥4</td>
<td>≥8</td>
<td>≥2</td>
<td>≥16</td>
<td>≥4</td>
<td>≥16</td>
<td>≥4</td>
</tr>
</tbody>
</table>

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

**TABLE 2**


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

*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 carbapenemases 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 works (the SENTRY Program and the European Antimicrobial Resistance Surveillance Network).

REFERENCES