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 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 carbapenamase enzymes; therefore, the clinical significance of these changes has not yet been clearly determined. In conclusion, ongoing surveillance studies with in vitro minimum 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*

Les effets des changements au seuil de résistance des carbapénèmes sur les taux de susceptibilité des entérobactériacés : 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 *in 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 entérobactériacés 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 *in 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.

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 (third- and fourth-generation cephems and carbapenems), leading to elevated breakpoints and the subsequent risk of false-susceptible in vitro testing results when testing *Enterobacteriaceae*. Reports of clinical failures among cases caused by strains having minimum inhibitory concentration (MIC) values in the high susceptible range (1,2), and improved/updated PK/PD analyses (3) have forced re-evaluations of clinical susceptibility breakpoints established for several antimicrobials 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 E*nterobacteriaceae* in 2010 and 2013 for carbapenems

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

**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)

Enteric group (n tested)	% Susceptible (2012 criteria/2010 criteria)			
	Ertapenem	Imipenem	Meropenem	Doripenem
Enterobacteriaceae (19,382)	97.1/98.1	92.4/98.6	98.3/98.6	98.3/–*
Escherichia coli (6882)	99.6/99.8	99.8/100	99.9/99.9	99.9/–
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	99.8/–
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 morganii (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*

commonly used carbapenems (doripenem, ertapenem, imipenem and meropenem) in North America following CLSI document breakpoint modification (5-7).

These analyses used data from the SENTRY Antimicrobial Surveillance Program, an international resistance monitoring platform that reviews antimicrobial susceptibility data for a large number of agents and organisms each year since 1997. The strains, which come from many laboratories, are all tested using the same CLSI methodology (13) at JMI Laboratories (North Liberty, Iowa, USA). In this way, methodological and organism identification differences that may occur at primary testing laboratories are minimized or eliminated. It is also possible to temporally review changes to MIC values. This evaluation was performed to determine the effect of changing the breakpoints of four carbapenem agents on the perceived in vitro susceptibility of 19,382 strains of *Enterobacteriaceae* (seven species) isolated between 2008 and 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 morganii*, 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 (−35.3%) and M *morganii* 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 (≤60% 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 carbapenamase-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 *morganii*; 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.

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 changes made to breakpoints. It will be important, however, to continue to identify changes in susceptibility of the commonly prescribed broad-spectrum β-lactam agents and antimicrobial combinations in a global setting through ongoing surveillance networks (the SENTRY Program and the European Antimicrobial Resistance Surveillance Network).

REFERENCES

1. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: MIC matters. Clin Infect Dis 2013;56:488-95.
2. Weisenberg SA, Morgan DJ, Espinal-Witter R, Larone DH. Clinical outcomes of patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* after treatment with imipenem or meropenem. Diagn Microbiol Infect Dis 2009;64:233-5.
3. Andes D, Craig WA. Treatment of infections with ESBL-producing organisms: Pharmacokinetic and pharmacodynamic considerations. Clin Microbiol Infect 2005;11(Suppl 6):10-7.
4. EUCAST. 2013. Breakpoint tables for interpretation of MICs and zone diameters. Version 3.0, January 2013. <www.eucast.org/clinical_breakpoints/> (Accessed January 2, 2013).
5. Clinical and Laboratory Standards Institute. 2010. M100-S20. Performance standards for antimicrobial susceptibility testing: 20th informational supplement. Wayne: Clinical and Laboratory Standards Institute.
6. Clinical and Laboratory Standards Institute. 2013. M100-S23. Performance standards for antimicrobial susceptibility testing: 23rd informational supplement. Wayne: Clinical and Laboratory Standards Institute.
7. Dudley MN, Ambrose PG, Bhavnani SM, Craig WA, Ferraro MJ, Jones RN. Background and rationale for revised Clinical and Laboratory Standards Institute interpretive criteria (breakpoints) for *Enterobacteriaceae* and *Pseudomonas aeruginosa*: I. Cephalosporins and aztreonam. Clin Infect Dis 2013;56:1301-9.
8. Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? J Antimicrob Chemother 2012;67:1569-77.
9. Tamma PD, Powers JH. Do patient data really support the clinical and laboratory standards institute recommendation for lowering third-generation cephalosporin interpretive breakpoints? Clin Infect Dis 2013;57:624-5.
10. Tamma PD, Wu H, Gerber JS, et al. Outcomes of children with *Enterobacteriaceae* bacteremia with reduced susceptibility to ceftriaxone: Do the revised breakpoints translate to improved patient outcomes? Pediatr Infect Dis J 2013;32:965-9.
11. Thomson KS. Lowering of third generation cephalosporin breakpoints. Clin Infect Dis 2013; 57:1663-4.
12. Dudley MN, Ambrose PG, Jones RN. Commentary: Revised susceptibility breakpoints: Fear, loathing and good science. Pediatr Infect Dis J 2013;32:970-1.
13. Clinical and Laboratory Standards Institute. 2012. M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 9th edn. Wayne: Clinical and Laboratory Standards Institute.
14. Acar JF. Therapy for lower respiratory tract infections with imipenem/cilastatin: A review of worldwide experience. Rev Infect Dis 1985;7(Suppl 3):S513-S517.
15. Chiodini PL, Geddes AM, Smith EG, Conlon CP, Farrell ID. Imipenem/cilastatin in the treatment of serious bacterial infections. Rev Infect Dis 1985;7(Suppl 3):S490-S495.
16. Kager L, Nord CE. 1985. Imipenem/cilastatin in the treatment of intraabdominal infections: A review of worldwide experience. Rev Infect Dis 1985;7(Suppl 3):S518-S521.
17. MacGregor RR, Gentry LO. Imipenem/cilastatin in the treatment of osteomyelitis. Am J Med 1985;78:100-3.
18. Marier RL. Role of imipenem/cilastatin in the treatment of soft tissue infections. Am J Med 1985;78:140-4.
19. Shah PM. Clinical experience with imipenem/cilastatin: Analysis of a multicenter study. Rev Infect Dis 1985;7(Suppl 3):S471-S475.
20. Won SY, Munoz-Price LS, Lolans K, Hota B, Weinstein RA, Hayden MK; Centers for Disease Control Prevention Epicenter Program. Emergence and rapid regional spread of *Klebsiella pneumoniae* carbapenemase-producing *Enterobacteriaceae*. Clin Infect Dis 2011;53:532-40.
21. Zilberberg MD, Shorr AF. Prevalence of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Enterobacteriaceae* among specimens from hospitalized patients with pneumonia and bloodstream infections in the United States from 2000 to 2009. J Hosp Med 2013;8:559-63.
22. Jacob JT, Klein E, Laxminarayan R, et al. Vital signs: Carbapenem-resistant *Enterobacteriaceae*. MMWR Morb Mortal Wkly Rep 2013;62:162-70.