Impact of Revised CLSI and Current EUCAST Carbapenem Breakpoints on Enterobacteriaceae Susceptibility Rates: Report from the SENTRY Program

RN JONES, HS SADER, DJ FARRELL
JMI Laboratories, North Liberty, IA, USA

SENTRY ANTIMICROBIAL SURVEILLANCE

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ronald-jones@jmilabs.com

ABSTRACT

Background: In mid-2010, CLSI revised ENT CARB (ertapenem [ER], imipenem [IP], meropenem [ME]) breakpoints (CBP), as well as providing initial doripenem (DO) criteria. These reduced MIC CBPs significantly to levels like those of EUCAST. Reference S testing results from SENTRY Program (2007-2009) were used to quantitate the impact of these CBP changes on perceived coverage (%S).

Methods: SENTRY Program ENT (27,415 strains), tested against CARBs were tabulated using CLSI (M100-S19 [2009], M100-S20-U [2010]) and EUCAST CBPs. Coverage changes and rank orders across five monitored continents were determined and compared to a potent cephalosporin (cefepime [CP]).

Results: CLSI (2010) CARB CBPs decreased for ER (8X), IP (4X) and ME (4X) with coverage reductions of 98.3 to 94.3%, 99.0 to 93.0% and 99.1 to 98.6%, respectively. DO coverage was 98.7% for both CBP sets. CLSI results were slightly lower than EUCAST S rates for ER (96.5%), IP (97.6%) and ME (98.7%). The rank order of perceived coverage was: for CLSI – DO (98.7%) > ME (98.6%) > ER (94.3%) > IP (93.0%) and for EUCAST – DO = ME (98.7%) > IP (97.6%) > ER (96.5%). CP-S varied from 83.3% (EUCAST) to 89.1% (CLSI). CLSI CBPs detected nearly all carbapenemase-producing strains.

Conclusions: Revised ENT CLSI and current EUCAST CARB CBPs significantly decrease perceived coverage (not rank orders); most impacted were ER (-4.0% S) and IP (-6.0% S). The new CLSI CBPs approach harmonization with EUCAST.

	S results (%S/R) for:[a]		
Antimicrobial	CLSI (2009)	CLSI (2010)	EUCAST (2010)
CP	89.1 / 8.6	89.1 / 8.6[b]	83.3 / 8.6
DO	- / -	98.7 / 1.0	98.7 / 0.7
ER	98.3 / 1.3	94.3 / 3.5	96.5[c] / 2.3
IP	99.0 / 0.6	93.0[c] / 2.3	97.6[c] / 1.0
ME	99.1 / 0.6	98.6 / 1.2	98.7 / 0.9

a. SENTRY Program, M07-A8 (2009) methods for 27,416 strains.
b. Underline = same results for current breakpoints.
c. Decrease driven by *P. mirabilis* and indole-positive *Proteae* strains.

INTRODUCTION

The Clinical and Laboratory Standards Institute (CLSI) working group reviewed the pharmacokinetic/ pharmacodynamic properties, microbiology potency/MIC distribution, and clinical data for several cephalosporin, monobactam and carbapenem antimicrobial agents. The subcommittee revised the interpretative breakpoints for susceptibility and resistance for cefazolin, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone and aztreonam against Enterobacteriaceae in January 2010 (M100-S20) and further revised the breakpoints for imipenem, meropenem and ertapenem, and introduced breakpoints for doripenem in June 2010 (M100-S20-U). These lowered breakpoints are now more similar to those published by EUCAST (2010).

This study was performed to evaluate the impact of the modified carbapenem breakpoints when tested against Enterobacteriaceae as published by the CLSI in the M100-S20-U (2010) document.

MATERIALS AND METHODS

Organism Collection: 27,415 Enterobacteriaceae isolates recovered from respiratory tract, skin and skin structure and bloodstream infections were collected from patients in Asia-Pacific, European, North American and Latin American medical centers between 2007 and 2009. Rank order of pathogen frequency was *Escherichia coli* (12,031), *Klebsiella* spp. (6,933), *Enterobacter* spp. (3,707), *Serratia* spp. (1,608), *Proteus mirabilis* (1,350), *Citrobacter* spp. (676), Indole positive *Proteus* spp. (557), *Salmonella* spp. (324), and other Enterobacteriaceae (229).

Susceptibility Testing: The isolates were tested for susceptibility in cation-adjusted Mueller-Hinton broth against up to 30 antimicrobial agents including multiple cephalosporins and carbapenems by reference broth microdilution methods as described by the CLSI M07-A8 (2009). Susceptibility and resistance interpretations were calculated based on the old CLSI M100-S19 breakpoints, the revised breakpoints in the M100-S20-U document, and the current EUCAST breakpoints for comparison purposes.

Concurrent testing of quality control (QC) strains assured proper test conditions were applied. The QC strains included *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

- The revised CLSI carbapenem susceptibility breakpoints for Enterobacteriaceae (M100-S20-U, 2010) changed most for ertapenem (eight-fold lower), and less for imipenem and meropenem (four-fold). Breakpoints were introduced for doripenem (≤1, 2, ≥4 mg/L; for S, I, R), similar to imipenem and meropenem.
- Cefepime MIC distribution has been added to emphasize the wider spectrum of activity of the carbapenem class agents against this large collection of Enterobacteriaceae isolates (Tables 1 - 4), regardless of current breakpoints.
- Revising the carbapenem breakpoints decreases the risk of treating patient infections with KPC-producing or other carbapenem-resistant strains with carbapenem MIC results currently in susceptible or intermediate categories.
- Greatest harmonization was observed between the new M100-S20-U and EUCAST breakpoints for doripenem (0.0% difference) followed by meropenem (-0.5%), ertapenem (-4.0%) and imipenem (-6.0%; Tables 2 and 3).
- The rank order of carbapenem activity against the 27,415 Enterobacteriaceae strains did not significantly change and was doripenem (98.8%) > meropenem (98.6%) > ertapenem (94.3%) > imipenem (93.0%; Tables 1 and 4).

Table 1. MIC distribution for Enterobacteriaceae (27,415 strains) from a worldwide SENTRY Antimicrobial Surveillance Program collection for 2007-2009[a].

	% (cumulative %) at MIC (mg/L)								
Antimicrobial	≤0.12	0.25	0.5	1	2	4	8	16	>
Cefepime[b]	74.1 (74.1)	4.4 (78.5)	2.6 (81.1)	2.2 (83.3)	2.0 (85.3)	1.9 (87.2)	1.9 (89.1)	2.3 (91.4)	8.6 (100.0)
Doripenem	92.7 (92.7)	4.6 (97.3)	1.0 (98.3)	0.4 (98.8)	0.3 (99.0)	0.3 (99.3)	0.3 (99.6)	-[c]	0.4 (100.0)
Ertapenem	91.5 (91.5)	2.8 (94.3)	2.2 (96.5)	1.2 (97.7)	0.6 (98.3)	0.4 (98.7)	0.3 (99.0)	-	1.0 (100.0)
Imipenem	28.9 (28.9)	38.1 (67.0)	15.8 (82.7)	10.2 (93.0)	4.7[d] (97.6)	1.4[d] (99.0)	0.4 (99.4)	-	0.6 (100.0)
Meropenem	96.8 (96.8)	1.2 (97.9)	0.4 (98.4)	0.3 (98.6)	0.2 (98.8)	0.3 (99.1)	0.2 (99.4)	-	0.6 (100.0)

a. All tests by CLSI reference methods.
b. Cefepime results are shown as a potent cephalosporin example of spectrum.
c. - = not tested.
d. 31-39% of these strains were *P. mirabilis.*

Table 2. Spectrum/coverage of Enterobacteriaceae by cefepime and carbapenems using recently approved breakpoint criteria (27,415 strains; 2007-2009)[a].

	Susceptibility rate results (%S/R) for:		
Antimicrobial	CLSI (2009)	CLSI (2010)	EUCAST (2010)
Cefepime	89.1 / 8.6	89.1 / 8.6	83.3 / 8.6
Doripenem	- / -	98.8 / 1.0	98.8 / 0.7
Ertapenem	98.3 / 1.3	94.3 / 3.5	96.5[c] / 2.3
Meropenem	99.1 / 0.6	98.6 / 1.2	98.8 / 0.9
Imipenem	99.0 / 0.6	93.0[c] / 2.3	97.6 / 1.0

a. SENTRY Program, M07-A8 (2009) methods.
b. Underline notes same results for all current breakpoints.
c. Decrease driven by *P. mirabilis* and indole-positive *Proteae* strains.

Table 3. Changes in spectrum (% susceptible) between CLSI (2009) versus CLSI (2010) when testing SENTRY Program Enterobacteriaceae worldwide (27,415 strains).

β-lactam	% variation
Cefepime	NC[a]
Doripenem	NC
Ertapenem	-4.0%
Imipenem	-6.0%
Meropenem	-0.5%

a. NC = no change.

Table 4. Rank order in coverage (% susceptible) of 27,415 SENTRY Program strains of five selected β-lactams.

Agents	CLSI (2009)	CLSI (2010)	EUCAST (2010)
Cephems	Cefepime (89.1%)	Cefepime (89.1%)	Cefepime (83.3%)
Carbapenems	Meropenem (99.1%)	Doripenem (98.8%)	Doripenem (98.8)
	Imipenem (99.0%)	Meropenem (98.6%)	Meropenem (98.8%)
	Ertapenem (98.3%)	Ertapenem (94.3%)	Imipenem[a] (97.6%)
		Imipenem[a] (93.0%)	Ertapenem (96.5%)

a. Includes *Proteus* and *Morganella* disclaimer.

CONCLUSIONS

- The revised carbapenem breakpoints found in the CLSI M100-S20-U (2010) document produced modest decreases in the perceived susceptibility rates (-0.5 to -6.0%) when tested against this large world-wide collection of Enterobacteriaceae strains (SENTRY Program, 2007-2009).
- The revised CLSI M100-S20-U breakpoints (most conservative) demonstrate greater harmonization with the current EUCAST carbapenem breakpoints for susceptibility and resistance rates, thus reducing the risk of selecting carbapenem therapy against strains producing carbapenemases.

SELECTED REFERENCES

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