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Impact Assessment of Revised CLSI Cephalosporin Breakpoints (M100-S20, 2010) Using 27,415 Enterobacteriaceae Isolates Tested in the SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

Abstract

Background: Following review of PK/PD properties and clinical data, CLSI modified interpretative breakpoints for susceptibility (S) and resistance (R) for ceftazidime (CAZ), ceftriaxone (CRO) and aztreonam (ATM) when testing Enterobacteriaceae (ENT). These lowered breakpoints now approximate EUCAST criteria. MIC data generated by the SENTRY Program was used to assess the overall S and R rates of these breakpoints.

Methods: 27,415 ENT isolates collected from 2007-2009 were tested by CLSI broth microdilution method against more than 30 agents including commonly used cephalosporins (CRO, CAZ and cefepime [CPM]) and ATM. Summary tables were generated using old (M100-S19; 2009) and new (M100-S20; 2010) CLSI criteria and current EUCAST (2010) breakpoints for comparison.

Results: CLSI M100-S20 breakpoints were reduced most for CRO (8X) and to a lesser extent for ATM (2X) and CAZ (2X), but unchanged for CPM. These revised CLSI criteria result in slightly decreased S rates for CRO (-3.2%), ATM (-2.2%) and CAZ (-2.0%). Revised CLSI breakpoints (2010) for S showed greater harmony with EUCAST than prior CLSI (2009) criteria for CRO (78.2/78.2 vs. 81.4/78.2%), ATM (82.5/79.3 vs. 84.7/79.3%) and CAZ 84.2/79.4 vs. 86.2/79.4%), respectively. Modified breakpoints did not change the rank order of coverage (%S) for CPM>CAZ>ATM>CRO. Among 867 ENT isolates with CRO MIC values of 2, 4 or 8 ug/ml, only 42.1% were *E. coli*, *Klebsiella* spp., or *P. mirabilis* (spp. subject to ESBL screen). These new CLSI breakpoints eliminate the need to perform supplementary ESBL testing or to change interpretations based on test results that would produce a majority of false-R reports.

Table	Susceptibility results (%S/R) for:[a]		
Antimicrobial	CLSI (2009)	CLSI (2010)	EUCAST (2010)
Ceftriaxone (CRO)	81.4 / 14.7	78.2 / 20.8[b]	78.2 / 20.8[b]
Ceftazidime (CAZ)	86.2 / 10.3	84.2 / 13.8	79.4 / 13.8
Aztreonam (ATM)	84.7 / 12.7	82.5 / 15.3	79.3 / 15.3
Cefepime (CPM)	89.1 / 8.6	89.1 / 8.6	83.3 / 10.9

a. SENTRY Program, M07-A8 (2009)
b. Underline notes same results for current (2010) breakpoints.

Conclusion: Recently, CLSI modified ENT cephalosporin breakpoints produced only minor decreases (≤3.2%) in S rates with an advantage of eliminating follow-up ESBL testing and showing greater harmonization with EUCAST interpretations and their R rates caused by a variety of non-ESBL mechanisms (identical for 3 of 4 agents).

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 decided to revise (2010) the interpretative breakpoints for susceptibility and resistance for cefazolin, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone and aztreonam. These lowered breakpoints are now more similar to those published by the EUCAST Group (2010).

This study was performed to evaluate the impact of the modified cephalosporin and monobactam breakpoints against Enterobacteriaceae as published by the CLSI in the M100-S20 (2010) document. These breakpoints now more closely harmonize with those utilized worldwide.

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 several cephalosporins 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 recently adjusted breakpoints in the M100-S20 document and the current EUCAST breakpoints for comparison purposes.

Concurrent testing of quality control (QC) strains assured proper test conditions were applied. These QC strains included *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.

Results

- The revised CLSI breakpoints for Enterobacteriaceae published in the M100-S20 document changed most for cefotaxime, ceftriaxone and ceftizoxime (8 or 16-fold) followed by cefazolin (8-fold), ceftazidime and aztreonam (2-fold). Breakpoints were not revised for cefuroxime, cefoxitin or cefepime.
- The overall susceptibility rates among the 27,415 Enterobacteriaceae strains were only slightly decreased for ceftriaxone (-3.2%), aztreonam (-2.2%) and ceftazidime (-2.0%) when applying the revised M100-S20 breakpoint criteria (Tables 1 and 3).
- Doripenem MIC distribution has been added to emphasize the wider spectrum of activity of the carbapenem class against this large collection of Enterobacteriaceae isolates (Tables 1 - 3).
- Greater harmonization was observed between the new M100-S20 and EUCAST (susceptibility/resistance rate difference) breakpoints for ceftriaxone (0.0/0.0%), ceftazidime (4.8/0.0%) and aztreonam (3.2/2.6%; Table 2).
- Prior M100-S19 and EUCAST susceptibility/resistance breakpoints showed larger rate differences for ceftriaxone (3.2/6.1%), ceftazidime (6.8/3.5%), and aztreonam (5.4/0.0%; Table 2).
- No change in the rank order of coverage (highest susceptibility rate) among the cephalosporins and aztreonam was observed when using M100-S19, M100-S20 or current EUCAST breakpoints (Table 4).
- When examining the collection of Enterobacteriaceae strains (n=867) with ceftriaxone MIC results at 2, 4, and 8 µg/ml, only 42.1% of these isolates were from the species where extended-spectrum β-lactamases (ESBL) are most commonly observed; *E. coli*, *Klebsiella* spp. and *P. mirabilis* (Table 5). All other strains/species (the majority) were harboring resistance mechanisms other than ESBL's, now categorized as non-susceptible.
- These revised cephalosporin breakpoints would eliminate the need for follow-up ESBL confirmation testing necessary to edit for cephalosporin, aztreonam and penicillin categorized results. ESBL testing may still be useful for epidemiological and/or infection control purposes (Table 5).

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

	% (cumulative %) at MIC (µg/ml)								
Antimicrobial	≤0.12	0.25	0.5	1	2	4	8	16	>
Ceftriaxone	-[b]	74.2 (74.2)	3.0 (77.1)	1.1 (78.2)	1.0 (79.2)	0.9 (80.1)	1.3 (81.4)	1.9 (83.3)	16.7 (100.0)
Ceftazidime	-	-	-	79.4 (79.4)	2.7 (82.2)	2.0 (84.2)	2.0 (86.2)	3.5 (89.7)	10.3 (100.0)
Cefepime	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)
Aztreonam	69.3 (69.3)	7.1 (76.4)	1.7 (78.1)	1.2 (79.3)	1.2 (80.5)	2.0 (82.5)	2.2 (84.7)	2.6 (87.3)	12.7 (100.0)
Doripenem[c]	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)	-[b]	0.4 (100.0)

a. All tests by CLSI reference methods.
b. - = not tested.
c. Doripenem results (newly published in M100-S20) are shown as a carbapenem example of spectrum.

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

	Susceptibility rate results (%S/R) for:		
Antimicrobial	CLSI (2009)	CLSI (2010)	EUCAST (2010)
Ceftriaxone	81.4 / 14.7	78.2[b] / 20.8	78.2 / 20.8
Ceftazidime	86.2 / 10.3	84.2 / 13.8	79.4 / 13.8
Cefepime	89.1 / 8.6	89.1 / 8.6	83.3 / 8.6
Aztreonam	84.7 / 12.7	82.5 / 15.3	79.3 / 12.7
Doripenem	- / -	98.7 / 1.0	98.7 / 0.7

a. SENTRY Program, M07-A8 (2009) methods.
b. Underline notes same results for all current breakpoints.

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

β-lactam	% variation
Ceftriaxone	-3.2%
Ceftazidime	-2.0%
Cefepime	NC[a]
Aztreonam	-2.2%
Doripenem	NC

a. NC = no change.

Table 4. Rank order changes in coverage of 27,415 SENTRY Program strains (2007-2009) for selected β-lactams.

Agents	CLSI (2009)	CLSI (2010)	EUCAST (2010)
Cephems	Cefepime (89.1%)	Cefepime (89.1%)	Cefepime (83.3%)
	Ceftazidime (86.2%)	Ceftazidime (84.2%)	Ceftazidime (79.4%)
	Aztreonam (84.7%)	Aztreonam (82.5%)	Aztreonam (79.3%)
	Ceftriaxone (81.4%)	Ceftriaxone (78.2%)	Ceftriaxone (79.3%)

Table 5. Analysis of organisms at each ceftriaxone MIC level (example).

	No. at ceftriaxone MIC (µg/ml) and (%):		
Species[a]	2	4	8
All (27,415)	269 (1.0)	243 (0.9)	355 (1.3)
E. coli (EC)	42	41	61
Klebsiella spp. (KSP)	46	61	85
P. mirabilis (PM)	13	9	7
	(101/269; 37.5%)	(111/243; 45.7%)	(153/355; 43.1%)
		(365/867; 42.1%)	

a. Species (EC, KSP, PM) at-risk to produce ESBLs by screening MIC criteria actually represent a minority of strains with these elevated MIC values, regardless of confirmatory test value e.g. interpreted false-susceptible, if confirmatory test (-) and MIC at ≤8 µg/ml by CLSI (2009) criteria were repeated.

Conclusions

- The revised cephalosporin and monobactam breakpoints found in the CLSI M100-S20 document produced only minor (≤3.2%) decreases in susceptibility rates among this large collection of Enterobacteriaceae strains.
- The revised CLSI M100-S20 breakpoints allows greater harmonization with the current EUCAST breakpoints for susceptibility and resistance rates; and has the advantage of elimination of necessary follow-up testing of ESBL-phenotype strains (MIC, ≥2 µg/ml) for definitive detection of ESBL-producing strains.

References

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