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Impact of new CLSI piperacillin/tazobactam breakpoints on reported susceptibility of *Pseudomonas aeruginosa* in North America - TEST 2009-2011

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Revised Abstract

Background: The Tigecycline Evaluation Surveillance Trial (TEST) has monitored the activity of tigecycline, piperacillin-tazobactam, and comparators globally since 2004. In January 2012, the CLSI lowered the piperacillin-tazobactam breakpoint (BP) for *Pseudomonas aeruginosa*. This report summarizes the impact of the BP changes on reported susceptibility levels for *P. aeruginosa* collected from 2009 to 2011 in North America. **Methods:** Between 2009 and 2011, 186 sites participated in TEST in North America. A total of 2,037 *P. aeruginosa* isolates were collected in Canada (n=269) and the United States (n=1,768). MICs were performed as specified by CLSI at each site using prepared broth microdilution panels and interpreted according to both M100-S21 (old BP, ≤S||≥R: ≤64/4 | -- | ≥128/4) and M100-S22 CLSI guidelines (new BP, ≤S||≥R: ≤16/4 | 32/4-64/4 | ≥128/4). **Results**: MIC (mcg/ml) and susceptibility results for piperacillin/tazobactam by specimen source are shown below.

		%S	%I	%R	MIC_{50}	MIC_{80}	MIC_{90}
Respiratory (n=875)	Old BP	82.5	--	17.5	8	64	> 128
	New BP	69.7	12.8	17.5			
Skin/skin structures (n=412)	Old BP	87.9	--	12.1	8	32	128
	New BP	77.4	10.4	12.1			
Blood (n=299)	Old BP	87.3	--	12.7	8	16	128
	New BP	80.9	6.4	12.7			
Genitourinary (n=268)	Old BP	86.4	--	11.6	8	32	128
	New BP	75.7	12.7	11.6			
Other (n=183)	Old BP	88.0	--	12.0	4	32	128
	New BP	76.5	11.5	12.0			
All (n=2,037)	Old BP	85.6	--	14.4	8	64	128
	New BP	74.3	11.2	14.4			

BP=breakpoint, S=susceptible, I=intermediate, R=resistant.

Conclusions: Overall, 11.2% of *P. aeruginosa* isolates shifted from the susceptible to the intermediate category using the new CLSI breakpoints (p<0.0001), with percentages for the different specimen sources ranging from 6.4% (blood) to 12.8% (respiratory and genitourinary). This interpretation of MIC data is now more consistent with EUCAST guidelines which use a susceptible breakpoint of ≤16/4 mcg/ml with no intermediate category.

Introduction

The Tigecycline Evaluation Surveillance Trial (TEST) has been tracking the susceptibility patterns of gram-negative and -positive bacteria causing a variety of infections since 2004. The primary goals of the study are to ensure that current susceptibility patterns of these organisms are well understood and widely disseminated, leading ultimately to the most effective choice of therapy and helping prevent further spread of resistance through inappropriate use of antimicrobics.

In January 2012, the Clinical Laboratory Standards Institute (CLSI) lowered the susceptible breakpoint for piperacillin-tazobactam against *Pseudomonas aeruginosa* from ≤64/4 µg/ml to ≤16/4 µg/ml and introduced intermediate breakpoints of between 32/4 and 64/4 µg/ml. Full resistance remained at ≥128/4 µg/ml [1, 2]. This change was necessary because both PK/PD target attainment analysis [4] and clinical trial data [5] indicate that isolates with piperacillin MIC of ≥32 µg/ml cannot be successfully treated with 'standard' dosing of piperacillin 3g every 6h.

Here we report on the activity of piperacillin-tazobactam against *P. aeruginosa* collected in North America from 2009 to 2011 and the effect of using the new breakpoints.

Materials & Methods

- Between 2009 and 2011, 195 cumulative sites participated in the TEST program in North America and provided *P. aeruginosa* isolates. For this report, 2,037 isolates of *P. aeruginosa* were identified to the species level and MICs determined at each participating laboratory using sponsor-supplied broth microdilution panels. Sources of infection included respiratory, skin and skin structures, blood and genitourinary (Figure 1). Only one isolate per patient was accepted into the study.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA) or Sensititre (TREK Diagnostic Systems, Cleveland, OH) panels [3]. All antimicrobics were supplied by the panel manufacturers.
- MIC interpretive criteria followed published guidelines of CLSI published in 2011 and 2012 [1, 2]. These are shown in Table 1.
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [1].
- Differences in percent susceptible between the 2012 (new) breakpoints [1] and the 2011 (old) breakpoints [2] were evaluated for significance using Fisher's exact test. A two-tailed p-value <0.05 was considered statistically significant.

References

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Results

- The cumulative MIC distributions for piperacillin-tazobactam against *P. aeruginosa* by specimen source are shown in Figure 2. MIC distribution was quite similar for each specimen source, but it was slightly lower for blood infections compared with respiratory sources.
- Summary susceptibility and MIC data for all North America and USA or Canada separately using the old and new breakpoints are given in Table 2. The effect of the new breakpoint is clearly shown by a reduction in percentage of isolates in the susceptible category and an increase in isolates considered of intermediate susceptibility. This reduction in susceptibility was seen to a greater extent in isolates from Canada compared to the USA. Also, overall, *P. aeruginosa* from blood infections were the least affected and respiratory sources the most.
- In most cases the reduction in percent susceptibility for each specimen source analyzed together or separately by country was statistically significant (p-values between <0.0001 and 0.0026). However, this reduction was not statistically significant for isolates from blood infections in Canada (p=0.6115) or the USA (p=0.0654) but it was significant for blood infections from both countries combined (p=0.0436).
- Similarly, the reduction in piperacillin-tazobactam susceptibility was not statistically significant in Canadian skin and skin structure isolates (p=0.1324) or Canadian isolates from 'other' infections (p=0.7043). However, this is due to low isolate numbers from these infection types in Canada.

Table 1: CLSI breakpoints published in 2011 and 2012 for piperacillin-tazobactam against *P. aeruginosa*

Year	Breakpoint (mcg/ml): Susceptible	Intermediate	Resistant
2011	≤64/4	-	≥128/4
2012	≤16/4	32/4-64/4	≥128/4

Table 2: Summary MIC and susceptibility data for piperacillin-tazobactam against *P. aeruginosa* from the USA and Canada broken down by specimen source.

Source	Country	N	BP	%S	%I	%R	MIC50	MIC90
Respiratory	All	875	Old BP	82.5%	-	17.5%	8	>128
			New BP	69.7%	12.8%	17.5%		
	United States	724	Old BP	82.7%	-	17.3%	8	>128
			New BP	70.6%	12.2%	17.3%		
	Canada	151	Old BP	81.5%	-	18.5%	8	>128
			New BP	65.6%	15.9%	18.5%		
SSTI	All	412	Old BP	87.9%	-	12.1%	8	128
			New BP	77.4%	10.4%	12.1%		
	United States	365	Old BP	89.9%	-	10.1%	8	128
			New BP	80.3%	9.6%	10.1%		
	Canada	47	Old BP	**72.3%[a]**	-	27.7%	8	>128
			New BP	**55.3%**	17.0%	27.7%		
Blood	All	299	Old BP	87.3%	-	12.7%	8	128
			New BP	80.9%	6.4%	12.7%		
	United States	270	Old BP	**86.3%**	-	13.7%	8	128
			New BP	**80.0%**	6.3%	13.7%		
	Canada	29	Old BP	**96.6%**	-	3.4%	8	32
			New BP	**89.7%**	6.9%	3.4%		
Genitourinary	All	268	Old BP	88.4%	-	11.6%	8	128
			New BP	75.7%	12.7%	11.6%		
	United States	242	Old BP	87.2%	-	12.8%	8	128
			New BP	75.6%	11.6%	12.8%		
	Canada	26	Old BP	100.0%	-	0.0%	8	32
			New BP	76.9%	23.1%	0.0%		
Other	All	183	Old BP	88.0%	-	12.0%	4	128
			New BP	76.5%	11.5%	12.0%		
	United States	167	Old BP	89.2%	-	10.8%	4	128
			New BP	77.8%	11.4%	10.8%		
	Canada	16	Old BP	**75.0%**	-	25.0%	8	>128
			New BP	**62.5%**	12.5%	25.0%		
All	All	2037	Old BP	85.6%	-	14.4%	8	128
			New BP	74.3%	11.2%	14.4%		
	USA	1768	Old BP	86.0%	-	14.0%	8	128
			New BP	75.4%	10.6%	14.0%		
	Canada	269	Old BP	82.9%	-	17.1%	8	>128
			New BP	67.3%	15.6%	17.1%		

[a]Percentages indicated in bold where difference is not statistically significant (p >0.05).

Figure 1: Breakdown of source of infection for 2,037*P.aeruginosa* isolates collected in North America between 2009 and 2011.

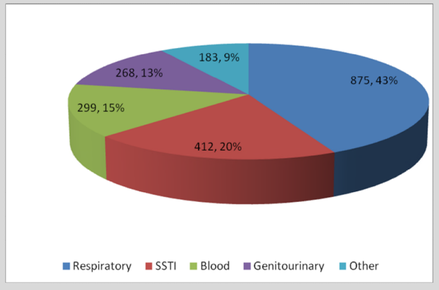
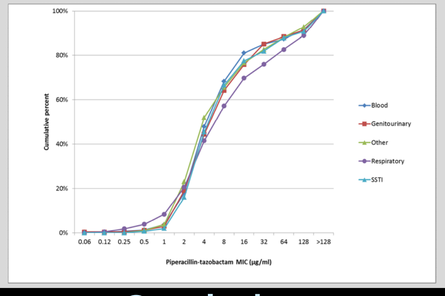


Figure 2: Cumulative MIC distribution for piperacillin-tazobactam against *P.aeruginosa* from varying infection sources.



Conclusions

- The change of CLSI breakpoints has a statistically significant effect on *P. aeruginosa* susceptibility to piperacillin-tazobactam, reducing overall susceptibility from 85.6% to 74.3% for all North American isolates combined.
- Reduced susceptibility was most profound in *P. aeruginosa* from respiratory sources (82.5% to 69.7% susceptible, p <0.0001).
- Piperacillin-tazobactam susceptibility was higher in blood infections compared with other sources of infection and as a consequence the effect of changed breakpoints was less in the blood isolates (87.3% to 80.9%, p=0.0436).
- The new breakpoints for piperacillin-tazobactam against *P. aeruginosa* are now more in line with other international breakpoints, eg. EUCAST [6].