Antibiotic Profile of 55 Carbapenem-Resistant *Serratia marcescens* (CRSm) – T.E.S.T. Program

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Revised Abstract

Background: *Serratia marcescens* is a serious nosocomial pathogen with various resistant mechanisms including extended-spectrum b-lactamases (ESBLs) and cephalosporinases (AmpC). CRSm have been identified even before the approval of the carbapenems in US (1985) but continue to remain relatively rare in spite of the common use of carbapenem therapy against this species. **Methods:** The T.E.S.T. program determined the *in vitro* activity of tigecycline and 9 comparators against 55 (0.8%) CRSm identified from a total of 6,520 *S. marcescens* collected between January 2004 and March 2009. The isolates were identified to the species level at the participating sites and confirmed by a central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results**: *In vitro* activities against CRSm (n=55):

Drug	%Sus	%Int	%Res	MIC_{50}	MIC_{90}
Tigecycline	80.0	10.9	9.1	1	4
Amikacin	60.0	5.5	34.6	8	>64
Amox-Clav	0	1.8	98.2	>32	>32
Cefepime	41.8	10.9	47.3	16	>32
Ceftazidime	50.9	5.5	43.6	≤8	>32
Ceftriaxone	29.1	10.9	60.0	>64	>64
Levofloxacin	61.8	5.5	32.7	2	>8
Meropenem	0	0	100	>16	>16
Minocycline	54.6	16.4	29.1	4	16
Pip-Tazo	34.6	10.9	54.6	128	>128

Conclusions: Tigecycline had the lowest $MIC_{50/90}$ of all study drugs against CRSm and inhibited 80% of all isolates at its FDA breakpoint of 2 mcg/ml; 9% were considered resistant to tigecycline. None of the commonly employed antimicrobials included in this study provided acceptable *in vitro* antibiotic profiles against CRSm. Tigecycline may prove useful against such carbapenem-resistant strains.

Introduction

Increased spread of extended-spectrum ß-lactamases (ESBLs) among members of the family *Enterobacteriaceae* has resulted in an increase in the use of carbapenems [1]. Carbapenems are among the few therapies available for serious infections caused by multidrug-resistant gram-negative bacteria, in particular, strains producing ESBLs. While the vast majority of ß-lactamases cannot hydrolyze carbapenems, several types of carbapenem-hydrolyzing enzymes have been described, mainly in the non-lactose-fermenting bacteria. In *Enterobacteriaceae,* carbapenem resistance usually requires additional mechanisms, such as porin loss, in conjuction with production of enzymes that are capable of hydrolyzing carbapenem. The most common are the molecular class B metalloenzymes that are found on mobile elements [3], however several types of class A carbapenemases have also been detected [2]. The first class A carbapenemase was identified in a *Serratia marcescens* strain isolated in 1982 [4]. More recently, KPC producing strains have emerged [5]. In this study we evaluated the *in vitro* activity of tigecycline and nine comparators against 55 carbapenem resistant *Serratia marcescens* identified from a total of 6,520 *S. marcescens* collected between January 2004 and March 2009 in the Tigecycline Evaluation Surveillence Trial (TEST) program.

Materials & Methods

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 and 2009 from 253 study centers in 54 countries. Isolates were identified to the species level and tested at each site by the participating laboratory.
- 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 were determined by the CLSI recommended broth microdilution testing method [6]. Panels were manufactured by MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) or Trek (TREK Diagnostic Systems, Cleveland, OH, USA).
- Quality controls (QC) were performed by each testing site on each day of testing using the following ATCC control strains: *E. coli* ATCC 25922; *Pseudomonas aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2008) guidelines [7].

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Results

Results are presented in the following figures and tables.

Table 1. Percentage of carbapenem-resistant *Serratia marcescens* (CRSm) by region.

Region	CRSm/ *S. marcescens* (%)
Europe	14/2099 (1)
Latin America	15/669 (2)
North America	25/3007 (1)
South Pacific	1/181 (1)
South Africa	0/108 (0)
Asia	0/352 (0)
Middle East	0/83 (0)

Table 2. *In vitro* activity of select antimicrobial agents against 55 carbapenem-resistant *Serratia marcescens*.

				MIC (mcg/ml)	
Drug	**%Sus [a]**	**%Int**	**%Res**	**MIC_{50}**	**MIC_{90}**
Tigecycline	80.0	10.9	9.1	1	4
Amikacin	60.0	5.5	34.6	8	>64
Amox-Clav	0	1.8	98.2	>32	>32
Cefepime	41.8	10.9	47.3	16	>32
Ceftazidime	50.9	5.5	43.6	≤8	>32
Ceftriaxone	29.1	10.9	60.0	>64	>64
Levofloxacin	61.8	5.5	32.7	2	>8
Meropenem	0	0	100	>16	>16
Minocycline	54.6	16.4	29.1	4	16
Pip-Tazo	34.6	10.9	54.6	128	>128

[a] Susceptibilities are defined in CLSI document M100-S18 (2008) where applicable. Tigecycline breakpoint is defined in FDA package insert (Tygacil®, 2005).

Table 3. *In vitro* activity of tigecycline and comparators against 55 carbapenem-resistant *Serratia marcescens* showing cumulative percent inhibited (%) at each MIC (mcg/ml).

MIC	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	
N														Total
Cumulative %														
Tigecycline				2	15	20	7	6	4	1				55
				3.63	30.9	67.27	80	90.9	98.18	100				
Amikacin						3	10	9	6	5	3	19		55
						5.45	23.63	40	50.9	60	65.45	100		
Amox-Clav										1	54			55
										1.81	100			
Cefepime					14		1	2	6	6	26			55
					25.45		27.27	30.9	41.81	52.72	100			
Ceftazidime									28	3	24			55
									50.9	56.36	100			
Ceftriaxone		1	4	4	4	1	2			2	4	33		55
		1.81	9.09	16.36	23.63	25.45	29.09			32.72	40	100		
Levofloxacin	1	3	6	7	2	7	8	3	18					55
	1.81	7.27	18.18	30.9	34.54	47.27	61.81	67.27	100					
Meropenem										55				55
										100				
Minocycline					1	2	13	14	9	16				55
					1.81	5.45	29.09	54.54	70.9	100				
PipTazo					1	4	8	4		2	4	2	30	55
					1.81	9.09	23.63	30.9		34.54	41.81	45.45	100	

Conclusions

- Carbapenem resistance in *Serratia marcescens* remains low worldwide, at less than or equal to 2%.
- Tigecycline had the lowest $MIC_{50/90}$ of all study drugs against carbapenem-resistant *Serratia marcescens* and inhibited 80% of all isolates at its FDA breakpoint of 2 mcg/ml.
- None of the commonly employed antimicrobials included in this study provided acceptable *in vitro* antibiotic profiles against carbapenem-resistant *Serratia marcescens.*