Tigecycline Activity Tested against Carbapenem-Resistant Enterobacteriaceae from European Hospitals: Results from the SENTRY Program (2010-2013)

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HS SADER, M CASTANHEIRA, DJ FARRELL, RK FLAMM, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

ABSTRACT

Objective: To evaluate the in vitro activity of tigecycline and comparators agents tested against carbapenem-resistant Enterobacteriaceae (CRE) isolated from European medical centres. Tigecycline is a glycylcycline with broad-spectrum antimicrobial activity that was initially approved by the European Medicines Agency in 2006 for the treatment of adults with complicated skin and soft tissue (cSSTI) and intra-abdominal infections (cIAI).

Methods: A total of 14,286 clinically-significant non-duplicate Enterobacteriaceae isolates from multiple types of infections were collected from 18 European countries from January 2010 to November 2013. Susceptibility testing was performed by reference broth microdilution method in a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) against a large panel of antimicrobials. Susceptibility interpretations were performed according to EUCAST breakpoint criteria. Isolates with meropenem MIC ≥4 mg/L (nonsusceptible by EUCAST criteria) were categorized as CRE. Fifty-one randomly selected CRE strains were screened for acquired carbapenemases by multiplex PCR.

Results: Overall, 1.9% (268/14,286) of Enterobacteriaceae strains were CRE. The highest CRE frequency was observed in Poland (16.1%; 65/405), followed by Italy (7.4%, 129/1,743), Greece (7.1%; 43/605) and Romania (5.0%; 8/157). No CRE (0.0%) was noted in Ireland (1,192 strains tested), Portugal (529), Slovakia (113), Slovenia (237), Sweden (418) and the United Kingdom (1,180). CRE rates were 0.2-2.6% in the remaining nations included in the investigation. Poland, Italy and Greece accounted for 88.4% of CRE strains. The most common CRE species were *Klebsiella pneumoniae* (237; 88.4%) and *Enterobacter cloacae* (18; 6.7%). CRE were isolated mainly from bacteremia (39.6%), pneumonia (24.3%), cSSTI (13.4%), urinary tract infections (12.7%) and cIAI (5.2%). Tigecycline (98.3% susceptible), imipenem (98.2%) and meropenem (98.1%) were the most active agents tested against Enterobacteriaceae overall; whereas only tigecycline exhibited good in vitro activity against CRE ($MIC_{50/90}$, 0.5/2 mg/L; 88.4% susceptible). Among carbapenem-resistant *K. pneumoniae*, 91.1% were susceptible to tigecycline ($MIC_{50/90}$, 0.5/1 mg/L). The most common carbapenemases identified were KPC-2/3 (80.4%) and VIM-1 (7.8%).

Conclusions: CRE has emerged and become a major problem of antimicrobial resistance in some European countries, mainly Poland, Greece, Italy and Romania. Tigecycline continues to demonstrate in vitro activity against Enterobacteriaceae, including CRE. Based on the potency and spectrum, tigecycline continues to have an important role for treating of infections caused by indicated Enterobacteriaceae organisms in Europe, including those caused by multidrug-resistant strains.

INTRODUCTION

The prevalence of carbapenem-resistant Enterobacteriaceae (CRE) remained extremely low for many years after the approval of the first carbapenem for clinical use in 1985. However, in recent years the occurrence of carbapenemase-producing Enterobacteriaceae has increased rapidly in some geographic regions. In particular, clonal *K. pneumoniae* strains with KPC (class A carbapenemases) have disseminated widely in the United States, Israel, and some European countries.

Tigecycline is a glycylcycline with broad-spectrum antimicrobial activity that was initially approved by the European Medicines Agency in 2006 for the treatment of adults with complicated skin and soft tissue (cSSTI) and intra-abdominal infections (cIAI). We evaluated the in vitro activity of tigecycline and comparators agents tested against CRE isolated from European medical centres.

METHODS

Organism collection: A total of 14,286 clinically-significant non-duplicate Enterobacteriaceae isolates from multiple types of infections were collected from 18 European countries from January 2010 to November 2013. Isolates were collected from patients with bloodstream infections, community-acquired and nosocomial respiratory tract infections, and wound or skin and skin structure infections. The Enterobacteriaceae species/genus included in this investigation were: *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp. and *Serratia marcescens.*

Methods: Susceptibility testing was performed by reference broth microdilution method in a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) according to Clinical Laboratory and Standards Institute (CLSI) methods using validated broth microdilution panels produced by ThermoFisher Scientific Inc. (Cleveland, Ohio, USA). Susceptibility interpretations were performed according to EUCAST breakpoint criteria (version 4.0, January 2014) and CLSI (M100-S14, 2014). Isolates with meropenem MIC ≥4 mg/L (non-susceptible by EUCAST criteria) were categorized as CRE. Fifty-one randomly selected CRE strains from the countries with the highest CRE rates (Greece [13 strains], Italy [21] and Poland [17]) were screened for acquired carbapenemases by multiplex PCR. Quality control was performed according to CLSI (M07-A9 and M100-S24) methods using *E. coli* ATCC 25922 and 35218 and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

- Overall, 1.9% (268/14,286) of Enterobacteriaceae strains were meropenem-non-susceptible (MIC, ≥4 mg/L; CRE). The highest CRE frequency was observed in Poland (16.1%; 65/405), followed by Italy (7.4%, 129/1,743), Greece (7.1%; 43/605) and Romania (5.0%; 8/157). Greece, Italy and Poland accounted for 88.4% of CRE strains (Table 1).
- No CRE (0.0%) was noted in Ireland (1,192 strains tested), Portugal (529), Slovakia (113), Slovenia (237), Sweden (418) and the United Kingdom (1,180). CRE rates were 0.2-2.6% in Belgium, Bulgaria, Czech Republic, France, Hungary, Netherlands and Spain (Table 1).
- The most common CRE species were *Klebsiella pneumoniae* (237 strains; 88.4%) and *Enterobacter cloacae* (18; 6.7%; Table 1).
- CRE were isolated mainly from bacteremia (39.6%), pneumonia (24.3%), cSSTI (13.4%), urinary tract infections (12.7%) and cIAI (5.2%).
- Tigecycline (98.3% susceptible [EUCAST]), imipenem (98.2% susceptible [EUCAST]) and meropenem (98.1% susceptible [EUCAST]) were the most active agents tested against Enterobacteriaceae, overall. Susceptibility rates for amikacin and colistin were 95.7 and 91.8%, respectively, according to the EUCAST breakpoint criteria (Table 2).
- Tigecycline was the only compound tested that demonstrated good in vitro activity against CRE ($MIC_{50/90}$, 0.5/2 mg/L; 88.4% susceptible). Colistin, the second most active compound, inhibited only 72.8% of CRE strains at the EUCAST susceptible breakpoint of ≤2 mg/L (Table 2).
- Among carbapenem-resistant *K. pneumoniae* (237 strains), 91.1% were susceptible to tigecycline ($MIC_{50/90}$, 0.5/1 mg/L) and 71.6% were susceptible to colistin ($MIC_{50/90}$, ≤0.5/1 mg/L; data not shown).
- The most common carbapenemases identified were KPC-2/3 (41/51 or 80.4%) and VIM-1 (4/51 or 7.8%; Table 3). KPC-2/3 accounted for 84.6, 81.0 and 68.8% of carbapenemases identified in Greece, Italy and Poland, respectively (Table 3).
- A large variety of carbapenemases were identified among CRE from Poland, including KPC-2/3 (11 strains; 68.8%), VIM-variants (four strains; 25.0%) and IMP-19 (one strain; 6.3%; Table 3).

Table 1. Frequency of occurrence of carbapenem-resistant Enterobacteriaceae (CRE) by country (Europe 2010-2013).

Country	No. tested	No (%) of CRE[a]	Species (no. of strains)[b]
Belgium	549	4 (0.9)	CF (1), EAE (1), KOX (2)
Bulgaria	79	1 (1.3)	KPN (1)
Czech Republic	306	1 (0.3)	KPN (1)
France	2,052	4 (0.4)	ECL (1), KPN (3)
Germany	1,965	7 (0.4)	KPN (7)
Greece	605	43 (7.1)	ECL (1), KPN (42)
Hungary	187	2 (1.1)	KPN (2)
Ireland	1,192	0	-
Italy	1,743	129 (7.4)	EAE (1), ECL (3), EC (1), KPN (124)
Netherlands	38	1 (2.6)	KPN (1)
Poland	405	65 (16.1)	CF (1), ECL (10), KOX (2), KPN (50), SM (2)
Portugal	529	0	-
Romania	157	8 (5.0)	ECL (3), KPN (4), SM (1)
Slovakia	113	0	-
Slovania	237	0	-
Spain	1,956	3 (0.2)	KPN (2), SM (1)
Sweden	993	0	-
UK	1,180	0	-
Overall	**14,286**	**268 (1.9)**	

a. CRE= carbapenem-resistant Enterobacteriaceae (meropenem MIC, ≥4mg/L) [EUCAST, 2014].
b. Abbreviations: CF = *Citrobacter freundii*, EAE = *Enterobacter aerogenes*, ECL = *Enterobacter cloaca*, EC = *Escherichia coli*, KOX = *Klebsiella oxytoca*, KPN = *Klebsiella pneumoniae* and SM = *Serratia marcescens* (4 strains).

Table 2. Activity of tigecycline and comparator antimicrobial agents when tested against of Enterobacteriaceae, including carbapenem-resistant strains, from European hospitals.

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S / %I / %R	EUCAST[a] %S / %I / %R
Enterobacteriaceae (14,286)[b]				
Tigecycline[b]	0.12	0.5	99.7 / 0.3 / <0.1	98.3 / 1.4 / 0.3
Ceftriaxone	≤0.06	>8	79.3 / 0.8 / 19.9	79.3 / 0.8 / 19.9
Ceftazidime	0.25	32	84.0 / 2.3 / 13.7	80.7 / 3.3 / 16.0
Cefepime	≤0.5	16	89.6 / 1.7 / 8.7	83.9 / 4.1 / 12.0
Imipenem	≤0.12	0.5	97.5 / 0.7 / 1.8	98.2 / 0.5 / 1.3
Meropenem	≤0.12	≤0.12	98.0 / 0.1 / 1.9	98.1 / 0.5 / 1.4
Piperacillin/tazobactam	2	64	86.7 / 6.1 / 7.2	82.2 / 4.5 / 13.3
Levofloxacin	≤0.5	>4	78.2 / 2.6 / 19.2	77.0 / 1.2 / 21.8
Amikacin	2	4	97.9 / 1.5 / 0.6	95.7 / 2.2 / 2.1
Colistin	≤0.5	2	--	91.8 / 0.0 / 8.2
Meropenem-non-susceptible (268)[c]				
Tigecycline[b]	0.5	2	96.6 / 3.4 / 0.0	88.4 / 8.2 / 3.4
Ceftriaxone	>8	>8	0.4 / 0.3 / 99.3	0.4 / 0.3 / 99.3
Ceftazidime	>32	>32	0.7 / 0.8 / 98.5	0.0 / 0.7 / 99.3
Cefepime	>16	>16	3.0 / 4.1 / 92.9	0.4 / 1.1 / 98.5
Imipenem	>8	>8	2.3 / 6.0 / 91.7	8.3 / 23.9 / 67.8
Meropenem	>8	>8	0.0 / 0.0 / 100.0	0.0 / 25.7 / 74.3
Piperacillin/tazobactam	>64	>64	1.1 / 0.8 / 98.1	0.4 / 0.7 / 98.9
Levofloxacin	>4	>4	6.3 / 1.9 / 91.8	3.7 / 2.6 / 93.7
Amikacin	32	>32	35.4 / 50.0 / 14.6	19.8 / 15.6 / 64.6
Colistin	≤0.5	>8	--	72.8 / 0.0 / 27.2

a. Criteria as published by the CLSI [2014] and EUCAST [2014].
b. Includes: *Citrobacter freundii* (332 strains), *Citrobacter koseri* (300 strains), *Enterobacter aerogenes* (416 strains), *Enterobacter cloacae* (1350 strains), *Escherichia coli* (7604 strains), *Klebsiella oxytoca* (738 strains), *Klebsiella pneumoniae* (2670 strains) and *Serratia marcescens* (876 strains).
c. Meropenem MIC, ≥4 mg/L. Includes: *Citrobacter freundii* (2 strains), *Enterobacter aerogenes* (2 strains), *Enterobacter cloacae* (18 strains), *Escherichia coli* (1 strain), *Klebsiella oxytoca* (4 strains), *Klebsiella pneumoniae* (237 strains) and *Serratia marcescens* (4 strains).

Table 3. Carbapenemase encoding genes detected among 51 randomly selected CRE strains from Greece, Italy and Poland (2010-2013).

Country (no. positive / no. tested)	no. of isolates						
	KPC-2/3	IMP-19	VIM-1	VIM-4	VIM-26	VIM-like	OXA-48
Greece (13/13)	11		1		1		
Italy (21/21)	19		1				1
Poland (16/17)	11	1	2	1		1	

CONCLUSIONS

- CRE has emerged and become a major problem of antimicrobial resistance in some European countries, mainly Greece, Italy, Poland and Romania.
- Tigecycline continues to demonstrate in vitro activity against Enterobacteriaceae strains isolated from European hospitals, including CRE.
- Based on the potency and spectrum, tigecycline continues to have an important role for treating infections caused by indicated Enterobacteriaceae organisms in Europe, including those caused by multidrug-resistant strains.

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