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In vitro Activity of Tigecycline and Comparators against a North American Collection of *Enterobacteriaceae*-Update of the TEST program (2014-2016)

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Revised Abstract

Background: Infections caused by a variety of species of *Enterobacteriaceae* are problematic to treat empirically due to intrinsic and/or acquired resistance mechanisms that are in a steady state of flux. MIC data collected from the Tigecycline Evaluation Surveillance Trial (TEST) were analyzed to provide updated susceptibility results for seven commonly prescribed agents used to treat infections caused by common *Enterobacteriaceae*.
Methods: Isolates were identified and susceptibility determined using supplied broth microdilution panels according to CLSI guidelines at each participating institution in North America during The TEST program 2014-2016. CLSI breakpoint criteria were applied to define susceptibility rates. FDA breakpoints were used for tigecycline.
Results: Susceptibility to agents for all 6025 *Enterobacteriaceae*, species or species group are provided in the following table

Drug	Organism (n) * *Enterobacteriaceae (6025)*	*Enterobacter* spp. (1681)	*E. coli* (1844)	*Klebsiella* spp. (1825)	*Serratia* spp. (665)
Tigecycline	1/97.6	1/96.0	0.25/100	1/96.7	2/97.3
Amikacin	4/99.8	2/99.9	4/99.8	2/99.7	4/99.7
Cefepime	1/92.1	2/92.7	8/88.2	≤0.5/93.3	≤0.5/97.9
Ceftriaxone	16/84.6	32/75.6	>32/85.5	0.5/90.8	2/87.4
Levofloxacin	8/87.2	0.25/97.1	>8/68.8	0.5/93.3	1/96.2
Meropenem	0.12/99.0	0.12/99.4	≤0.06/99.9	0.12/97.6	0.12/99.0
Pip-Tazo	16/92.4	64/85.3	4/96.4	8/93.3	8/97.1

*Data presented as MIC_{50}/%S

ESBL rates were 11.5% and 7.1% for *E. coli* and *K. pneumoniae,* respectively.

Conclusions: Tigecycline, amikacin, and meropenem were the most active agents providing >90% susceptibility against all *Enterobacteriaceae* examined in this study. Variability in drug activity against certain species was observed, including lower levofloxacin susceptibility among *E. coli* and <76% susceptibility to ceftriaxone among *Enterobacter spp*. Given the ongoing changes in antimicrobial susceptibility profiles among *Enterobacteriaceae* it is important that the TEST program continue to monitor changes in the activity of these agents among these organisms isolated in North America.

Introduction

Enterobacteriaceae species are important pathogens responsible for a wide variety of serious infections involving the bloodstream, the lower respiratory tract, the urinary tract, skin and skin structure and other body sites. The tendency of these organisms to develop or acquire resistance to key antimicrobials can lead to multi-drug resistant (MDR) strains for which antibiotic therapeutic choices become limited. Tracking and profiling of the susceptibility of MDR strains is an important aspect of any surveillance initiative. In this study data from The Tigecycline Evaluation Surveillance Trial (TEST) program were analyzed to evaluate the profiles and characteristics of MDR populations from North America.

Materials & Methods

- Between 2014 and 2016, 926 MDR isolates of *Enterobacteriaceae* from North American hospital sites were locally collected from multiple infection sources, identified, and susceptibility determined at each participating laboratory using sponsor-supplied broth microdilution panels.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by International Health Management Associates, Inc., Schaumburg, IL, USA. The data were centralized at IHMA for analysis of the MDR populations. MDR was defined as resistance to drugs from three or more different antimicrobial classes.
- 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) panels [1] or FDA breakpoints for Tigecycline [2].
- Multi-drug resistance (MDR) was defined as resistance to ≥3 drug classes using the following classes: glycylcyclines, β-lactam/β-lactamase-inhibitors, cephems, carbapenems, penicillins (ampicillin), quinolones, and aminoglycosides.
- Quality control testing was performed on each day of testing using appropriate ATCC control strains and following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [3].

Results

Figure 1. MDR Rates Among Key Species of *Enterobacteriaceae*

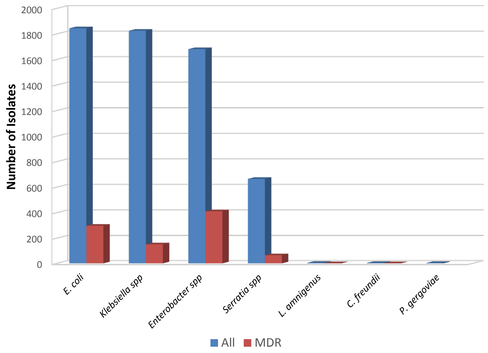
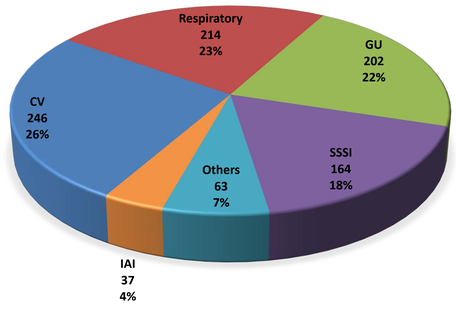


Figure 2. Source Distribution of MDR *Enterobacteriaceae



* CV: Cardiovascular; IAI: Intra-abdominal Infections; GU: Genitourinary; SSSI: Skin and Skin Structure Infections

Figure 3. Species Distribution of MDR *Enterobacteriaceae*

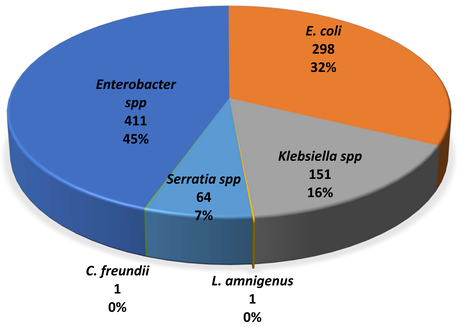


Figure 4. Patient Location Distribution of MDR *Enterobacteriaceae*

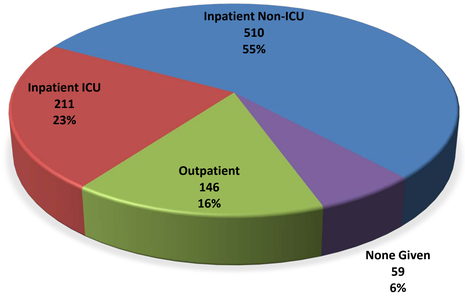


Table 1. Antimicrobial Susceptibility Profile for MDR *Enterobacteriaceae* by Patient Location

Location	Drug	% S	% I	% R	MIC_{50}	MIC_{90}
Inpatient Non ICU 510	Tigecycline	92.2	5.7	2.2	0.5	2
	Amikacin	99	0.2	0.8	2	8
	Cefepime	56.3	14.7	29	2	>32
	Ceftriaxone	18	2.4	79.6	32	>32
	Levofloxacin	48.8	2	49.2	4	>8
	Meropenem	93.5	0.4	6.1	≤0.06	0.5
	Pip-Tazo	59.4	18.8	21.8	16	>128
Inpatient ICU 211	Tigecycline	91	8	1	0.5	2
	Amikacin	99	1	0	2	8
	Cefepime	56.9	21.3	21.8	2	>32
	Ceftriaxone	12.3	2.4	85.3	32	>32
	Levofloxacin	69.2	2.4	28.4	0.25	>8
	Meropenem	93.4	0.5	6.2	0.12	0.5
	Pip-Tazo	42.7	28.4	28.9	32	>128
Outpatient 146	Tigecycline	93.8	5.5	0.7	0.5	2
	Amikacin	98.6	0.7	0.7	2	8
	Cefepime	54.1	18.5	27.4	2	>32
	Ceftriaxone	13	2.1	84.9	32	>32
	Levofloxacin	55.5	1.4	43.2	1	>8
	Meropenem	95.9	0.7	3.4	≤0.06	0.25
	Pip-Tazo	65.1	15.1	19.9	8	>128
Other Non Given 59	Tigecycline	83.1	13.6	3.4	0.5	4
	Amikacin	98.3	1.7	0	2	8
	Cefepime	49.2	20.3	30.5	4	>32
	Ceftriaxone	13.6	0	86.4	32	>32
	Levofloxacin	59.3	5.1	35.6	0.5	>8
	Meropenem	84.8	1.7	13.6	0.12	16
	Pip-Tazo	45.8	25.4	28.8	32	>128

Table 2. Antimicrobial Susceptibility Profiles for MDR *Enterobacteriaceae* by Organism Group

Organism	Drug	% S	% I	% R	MIC_{50}	MIC_{90}
Enterobacter spp (411)	Tigecycline	87.4	10.0	2.7	0.5	4
	Amikacin	99.5	0.2	0.2	2	4
	Cefepime	70.8	22.4	6.8	1	8
	Ceftriaxone	11.4	3.2	85.4	32	>32
	Levofloxacin	90.5	2.0	7.5	0.06	2
	Meropenem	97.3	0.5	2.2	0.12	0.5
	Pip-Tazo	40.2	37.0	22.9	32	128
E. coli (298)	Tigecycline	100	0	0	0.12	0.5
	Amikacin	99.0	0.7	0.3	4	8
	Cefepime	39.9	13.8	46.3	8	>32
	Ceftriaxone	21.5	0.3	78.2	>32	>32
	Levofloxacin	11.1	1.3	87.6	>8	>8
	Meropenem	99.3	0	0.7	≤0.06	0.12
	Pip-Tazo	84.2	6.7	9.1	4	64
Klebsiella spp (151)	Tigecycline	87.4	9.3	3.3	1	4
	Amikacin	96.7	1.3	2.0	2	16
	Cefepime	35.8	12.6	51.7	16	>32
	Ceftriaxone	15.2	2.7	82.1	>32	>32
	Levofloxacin	37.8	2.0	60.3	8	>8
	Meropenem	72.2	2.0	25.8	0.12	>16
	Pip-Tazo	33.1	6.0	60.9	>128	>128
Serratia spp (64)	Tigecycline	89.1	10.9	0	1	4
	Amikacin	100	0	0	2	4
	Cefepime	78.1	9.4	12.5	≤0.5	16
	Ceftriaxone	17.2	3.1	79.7	8	>32
	Levofloxacin	73.4	7.8	18.8	0.5	8
	Meropenem	89.1	0	10.9	0.12	4
	Pip-Tazo	75.0	18.8	6.3	8	64

Conclusions

- The MDR rate among *Enterobacteriaceae* was highest amongst inpatients vs. outpatients. It was also higher amongst patients from Non-ICU compared to ICU.
- Amikacin, meropenem, and tigecycline were the most active drugs *in vitro* against the MDR population.
- The MDR phenotype was prevalent among *Enterobacteriaceae* isolates from all sites of infection.
- The prevalence and critical importance of the MDR phenotype warrants careful and ongoing surveillance in North America.

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Disclosures

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