EV0537

Characterization and Profiling of Multi-Drug Resistant (MDR) *Enterobacteriaceae* from Europe 2013 - 2016 (TEST Program)

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Revised Abstract

Background: MDR Enterobacteriaceae are becoming more prevalent as various species continue to acquire and transfer genetic resistance elements. Multiple countries in Europe now document significant bacterial resistance problems, particularly in enteric species. To analyze the most recent situation in Europe, four years of data from the Tigecycline European Surveillance Trial (TEST) were analyzed for MDR rates and the impact on seven broad spectrum antimicrobial agents.

Methods: Five species of Enterobacteriaceae presented 9583 isolates with a MDR phenotype (R to ≥3 drugs) obtained from patients with numerous infection sources in 21 European countries during 2013-2016. MICs were determined using supplied broth microdilution panels. Susceptibility was interpreted according to EUCAST guidelines.

Results: The % of MDR isolates susceptible to tigecycline and comparative antimicrobial agents are shown for each of the five organism groups analyzed in the following table:

Drug	Organism (n)/%Susc.				
	C. freundii (485)	*E. coli* (2442)	*Enterobacter* spp. (3323)	*Klebsiella* spp. (2809)	*Serratia* spp. (524)
%MDR	34.9	27.8	40.6	33.1	15.6
AMK	97.3	93.7	96.0	79.6	88.0
FEP	67.2	30.6	43.9	12.4	64.1
CRO	8.3	26.2	8.1	7.7	23.5
LVX	63.3	8.2	62.4	22.4	51.7
MEM	96.5	98.8	96.3	76.3	94.3
TZP	40.0	70.6	30.3	34.6	54.2
TGC	96.5	98.9	82.4	73.6	60.3

AMK=Amikacin, FEP=Cefepime, CRO=Ceftriaxone, MEM=Meropenem LVX=Levofloxacin, TZP=Piperacillin-Tazobactam, TGC=Tigecycline

Conclusions: The MDR phenotype substantially impacts the % susceptibility for several different agents used to manage infections caused by Enterobacteriaceae, regardless of the genus or species being considered. The fluoroquinolones and advanced generation cephalosporins appeared to be most affected, while TGC, AMK, and MEM exhibited the highest level of activity against MDR phenotypes. The serious impact that the MDR phenotype can have on therapeutic choices warrants careful and continuous monitoring of this phenotype.

Introduction

Enterobacteriaceae species are important pathogens responsible for a wide variety of serious infections involving the bloodstream, the lower respiratory tract, the urinary tract, 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 European Surveillance Trial (TEST) program were analyzed to evaluate the profiles and characteristics of MDR populations from Europe.

Materials & Methods

- Between 2013 and 2016, 9583 MDR isolates of *Enterobacteriaceae* from Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland and the United Kingdom 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].
- MIC interpretive criteria followed published EUCAST guidelines [2].
- 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. *Enterobacteriaceae* and MDR *Enterobacteriaceae* Distribution by Country

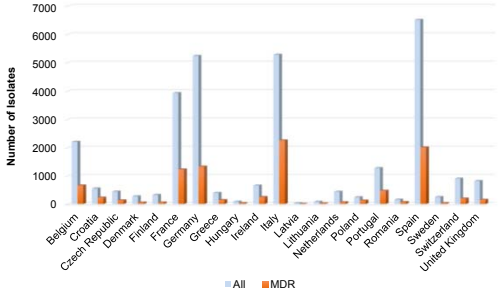
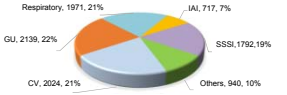


Table 1. Antimicrobial Susceptibility Profile for MDR *Enterobacteriaceae* by Patient Location

Location	Drug	%S	%I	%R	MIC_{50}	MIC_{90}
Inpatient	Tigecycline	83.2	9.6	7.2	0.5	2
7,119	Amikacin	90.1	5.8	4.1	2	8
	Cefepime	33.5	16.9	49.7	4	>32
	Ceftriaxone	12.1	2.8	85.1	>32	>32
	Levofloxacin	38.5	4.5	57.0	4	>8
	Meropenem	91.1	2.4	6.5	0.12	2
	Pip Tazo	42.3	12.0	45.6	16	>128
Outpatient	Tigecycline	84.3	8.2	7.5	0.5	2
1,480	Amikacin	92.0	4.7	3.3	2	8
	Cefepime	35.6	13.8	50.6	8	>32
	Ceftriaxone	19.5	2.5	78.0	32	>32
	Levofloxacin	27.7	2.9	69.4	8	>8
	Meropenem	92.5	2.6	4.9	≤0.06	1
	Pip Tazo	51.1	10.5	38.5	8	>128
Other	Tigecycline	84.9	8.7	6.4	0.5	2
984	Amikacin	88.4	7.1	4.5	2	16
	Cefepime	31.1	16.5	52.4	8	>32
	Ceftriaxone	13.4	1.4	85.2	>32	>32
	Levofloxacin	33.6	3.7	62.7	8	>8
	Meropenem	87.7	2.4	9.9	0.12	8
	Pip Tazo	41.8	11.5	46.8	16	>128

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*

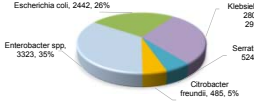


Figure 4. Patient Location Distribution of MDR *Enterobacteriaceae*

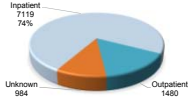


Table 2. Antimicrobial Susceptibility Profiles for MDR *Enterobacteriaceae* by Country (13 countries with > MDR 100 isolates)

Country	Drug	%S	%I	%R	MIC_{50}	MIC_{90}
Italy	Tigecycline	81.5	10.9	7.6	0.5	2
(2267)	Amikacin	77.3	13.6	9.1	4	16
	Cefepime	22.1	13.3	64.7	16	>32
	Ceftriaxone	11.0	1.8	87.2	>32	>32
	Levofloxacin	23.1	2.0	74.9	8	>8
	Meropenem	75.8	3.3	20.9	0.12	>16
	Pip-Tazo	38.9	9.5	51.7	32	>128
Spain	Tigecycline	83.5	9.0	7.5	0.5	2
(2018)	Amikacin	95.8	2.3	1.9	2	8
	Cefepime	40.7	15.5	43.8	4	>32
	Ceftriaxone	20.2	3.8	76.0	32	>32
	Levofloxacin	33.3	3.1	63.6	4	>8
	Meropenem	94.7	3.2	2.1	0.12	1
	Pip-Tazo	48.1	10.3	41.7	16	>128
Germany	Tigecycline	85.6	7.9	6.5	0.5	2
(1345)	Amikacin	95.6	2.3	2.1	2	8
	Cefepime	40.2	20.7	39.1	2	>32
	Ceftriaxone	14.0	2.6	83.4	32	>32
	Levofloxacin	47.5	4.2	48.3	1	>8
	Meropenem	96.7	1.8	1.6	0.12	0.5
	Pip-Tazo	45.0	11.6	43.4	16	>128
France	Tigecycline	84.6	9.0	6.4	0.5	2
(1243)	Amikacin	95.0	2.8	2.2	2	8
	Cefepime	29.8	18.3	52.0	8	>32
	Ceftriaxone	7.2	1.9	90.8	>32	>32
	Levofloxacin	42.2	6.3	51.5	2	>8
	Meropenem	98.8	0.5	0.7	0.12	0.25
	Pip-Tazo	44.4	14.8	40.8	16	>128
Belgium	Tigecycline	85.5	8.1	6.5	0.5	2
(667)	Amikacin	93.6	4.5	2.0	2	8
	Cefepime	44.4	18.1	37.5	2	>32
	Ceftriaxone	15.9	4.2	79.9	32	>32
	Levofloxacin	39.7	5.6	54.7	2	>8
	Meropenem	96.1	2.3	1.7	0.12	0.5
	Pip-Tazo	40.5	14.5	45.0	16	>128
Portugal	Tigecycline	79.9	10.1	10.1	0.5	4
(477)	Amikacin	94.6	3.8	1.7	4	8
	Cefepime	36.9	14.7	48.4	4	>32
	Ceftriaxone	15.9	2.1	82.0	>32	>32
	Levofloxacin	35.6	4.4	60.0	4	>8
	Meropenem	96.4	1.3	2.3	0.12	0.5
	Pip-Tazo	37.5	17.4	45.1	16	>128
Ireland	Tigecycline	86.1	7.6	6.4	0.5	2
(251)	Amikacin	95.6	2.8	1.6	2	4
	Cefepime	29.5	18.3	52.2	8	>32
	Ceftriaxone	9.6	2.8	87.7	>32	>32
Croatia	Tigecycline	79.3	15.5	5.2	0.5	2
(232)	Amikacin	89.7	8.2	2.2	4	16
	Cefepime	14.2	9.9	75.9	32	>32
	Ceftriaxone	6.0	0.4	93.5	>32	>32
	Levofloxacin	39.2	9.1	51.7	2	>8
	Meropenem	93.1	5.6	1.3	0.12	1
	Pip-Tazo	45.7	12.9	41.4	16	>128
Switzerland	Tigecycline	92.9	4.1	3.1	0.5	1
(196)	Amikacin	98.0	1.5	0.5	2	4
	Cefepime	55.1	14.8	30.1	1	>32
	Ceftriaxone	11.2	1.5	87.2	32	>32
	Levofloxacin	57.7	2.0	40.3	0.25	>8
	Meropenem	100	0.0	0.0	≤0.06	0.25
	Pip-Tazo	54.1	12.2	33.7	8	128
U. Kingdom	Tigecycline	80.9	4.6	14.5	0.5	4
(152)	Amikacin	94.7	0.7	4.6	2	8
	Cefepime	43.4	25.7	30.9	2	>32
	Ceftriaxone	14.5	5.3	80.3	32	>32
	Levofloxacin	67.1	4.6	28.3	0.5	>8
	Meropenem	96.1	3.3	0.7	0.12	1
	Pip-Tazo	53.3	5.3	41.5	8	>128
Greece	Tigecycline	81.3	9.7	9.0	0.5	2
(144)	Amikacin	66.7	20.8	12.5	4	32
	Cefepime	27.8	13.2	59.0	16	>32
	Ceftriaxone	16.0	4.2	79.9	>32	>32
	Levofloxacin	25.0	1.4	73.6	8	>8
	Meropenem	58.3	6.9	34.7	0.5	>16
	Pip Tazo	28.5	6.3	65.3	128	>128
Czech Republic	Tigecycline	88.6	5.3	6.1	0.5	2
(132)	Amikacin	94.7	3.8	1.5	4	8
	Cefepime	25.0	11.4	63.6	16	>32
	Ceftriaxone	7.6	1.5	90.9	>32	>32
	Levofloxacin	42.4	9.9	47.7	1	>8
	Meropenem	99.2	0.8	0.0	0.12	0.25
	Pip-Tazo	53.0	10.6	36.4	8	128
Poland	Tigecycline	78.2	16.1	5.7	0.5	2
(124)	Amikacin	79.0	9.7	11.3	4	>64
	Cefepime	25.0	11.3	63.7	16	>32
	Ceftriaxone	10.5	2.4	87.1	>32	>32
	Levofloxacin	16.9	11.3	71.8	8	>8
	Meropenem	99.2	0.8	0.0	0.12	0.25
	Pip-Tazo	41.9	12.9	45.2	16	128

Conclusions

- The MDR rate among *Enterobacteriaceae* is high in many European countries and approaches 41% in some countries.
- Meropenem, amikacin 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 European countries.

References

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Acknowledgment:

We gratefully acknowledge the contribution of the investigators, laboratory personnel, and all members of the Tigecycline European Surveillance Trial group. This study was sponsored by Pfizer Inc. IHMA is a clinical research organization that has been contracted by Pfizer to manage the TEST program. DH, DS, MR and BJ are employees of IHMA, Inc., which was paid by Pfizer to manage this study and to prepare this poster. HL-T is an employee of Pfizer.