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In vitro susceptibility of Multi-Drug Resistant (MDR) *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KPN) from Eastern and Western Europe During 2012-2015 Surveillance Years (TEST Program)

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Revised Abstract

Objectives: MDR gram-negative pathogens including EC and KPN are increasing in prevalence in many parts of the world including Europe. Europe is a continent with multiple countries dispersed geographically over long distances with varying antimicrobial resistance trends. 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 susceptibility that MDR has on seven broad spectrum antimicrobial agents. **Methods:** EC and KPN presented 3817 isolates with a MDR phenotype (R to >=3 drugs) obtained from patients with numerous infection sources in Eastern Europe (231) and Western Europe (3586) during 2012-2015. MICs were determined using supplied broth microdilution panels. Susceptibility was interpreted according to EUCAST guidelines. **Results**: The % susceptible for MDR isolates for tigecycline and comparative antimicrobial agents is shown for EC and KPN analyzed in the following table:

Organism (n) %Susceptibility

	Eastern Europe		Western Europe	
Drug	**EC (70)**	**KPN (161)**	**EC (1794)**	**KPN (1792)**
%MDR	**18.8**	**49.8**	**20.8**	**28.4**
AMK	85.7	79.5	91.6	67.2
FEP	15.7	6.2	13.2	7.4
CRO	2.9	4.4	12.4	5.6
LVX	4.3	6.8	3.5	8.4
MEM	97.1	85.1	98.8	64.6
TZP	62.9	28.0	63.2	22.2
TGC	94.3	73.3	98.8	68.9

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 EC and KPN. Susceptibilities were most affected in KPN isolates in comparison to EC isolates. Levofloxacin, cefepime and ceftriaxone appeared to be most affected, while TGC, AMK, and MEM exhibited the highest level of activity against MDR phenotypes. The MDR phenotype dramatically affects the activity of many first line antimicrobials used to treat serious infections and can limit therapeutic choices.

Introduction

The global increase and spread of multiple resistance mechanisms within many species of Enterobacteriaceae pose serious therapeutic challenges in treating patients with multi-drug resistant (MDR) pathogens. It is not uncommon today for species to possess and express 3 or more resistant mechanisms rendering many drug classes ineffective. In this study data from The Tigecycline European Surveillance Trial (TEST) program were analyzed to evaluate the antibiotic susceptibility profiles of MDR *E. coli* and *K. pneumoniae* from both Eastern and Western Europe.

Materials & Methods

- A total of 8977 and 6618 clinical isolates of *E.coli* and *K. pneumoniae,* respectively were collected in 1064 and 131 cumulative sites in Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom) and Eastern Europe (Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuiania, Poland, Romania, Serbia, Slovak Republic and Slovenia), respectively 2012-2015.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by 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 [1].
- 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 [2].
- MDR was defined as resistance to drugs from three or more of the tested drug classes (glycylcyclines, beta-lactam/inhibitor, cephems, penems, penicillins, quinolones, tetracyclines and aminoglycoside). MIC interpretive criteria followed published EUCAST guidelines [3].

Results

Table 1. Susceptibility of *E. coli* and *K. pneumoniae* in Eastern Europe 2012-2015

%Susceptible/MIC_{90}

Drug	MDR *E. coli*	All *E. coli*	MDR *K. pneumoniae*	All *K. pneumoniae*
N	70	373	161	323
AMK	85.7/16	96.5/8	79.5/32	89.2/16
FEP	15.7/>32	79.4/16	6.2/>32	38.1/>32
CRO	2.9/>32	75.6/>32	4.4/>32	37.2/>32
LVX	4.3/>8	65.7/>8	6.8/>8	48.9/>8
MEM	97.1/0.12	99.5/≤0.06	85.1/8	92.6/1
TZP	62.9/32	89.8/16	28.0/>128	58.8/>128
TGC	94.3/0.5	98.9/0.5	73.3/2	81.7/2

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

Table 2. Susceptibility of *E. coli* and *K. pneumoniae* in Western Europe 2012-2015

%Susceptible/MIC_{90}

Drug	MDR *E. coli*	All *E. coli*	MDR *K. pneumoniae*	All *K. pneumoniae*
N	1794	8604	1792	6295
AMK	91.6/8	97.6/8	67.2/32	90.3/8
FEP	13.2/>32	77.2/32	7.4/>32	65.3/>32
CRO	12.4/>32	76.5/>32	5.6/>32	64.5/>32
LVX	3.5/>8	64.4/>8	8.4/>8	69.8/>8
MEM	98.8/0.12	99.7/≤0.06	64.6/>16	89.9/4
TZP	63.2/128	89.2/≤0.06	22.2/>128	73.3/>128
TGC	98.8/0.5	99.5/≤0.008	68.9/4	85.2/≤0.008

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

Figure 1. MIC distribution of Comparator Antibiotics against MDR *E. coli* in Europe (Eastern & Western)

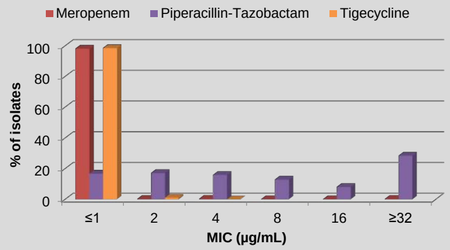


Figure 2. MIC distribution of Comparator Antibiotics against MDR *K. pneumoniae* in Europe (Eastern & Western)

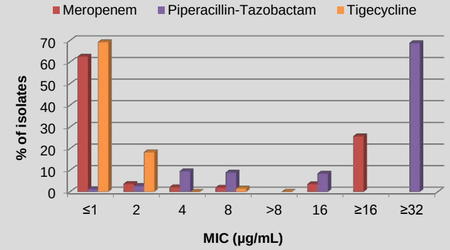


Figure 3. MIC distribution of Comparator Antibiotics against MDR *E. coli* in Eastern Europe

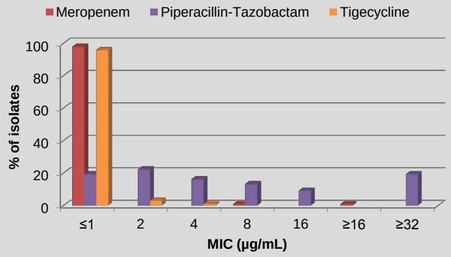


Figure 4. MIC distribution of Comparator Antibiotics against MDR *E. coli* in Western Europe

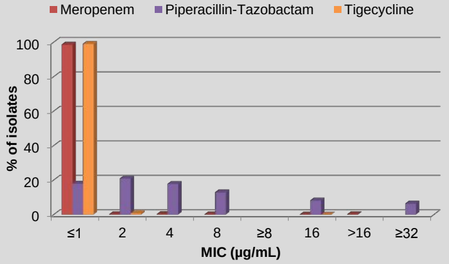


Figure 5. MIC distribution of Comparator Antibiotics against MDR *K. pneumoniae* in Eastern Europe

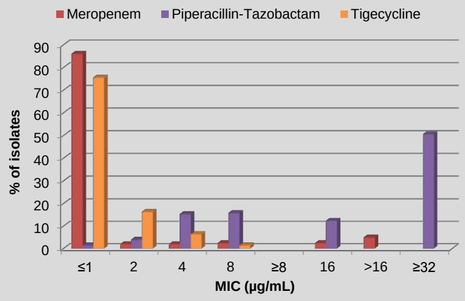
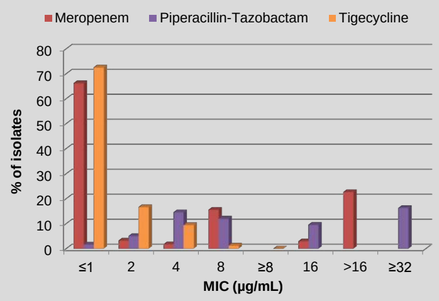


Figure 6. MIC distribution of Comparator Antibiotics against MDR *K. pneumoniae* in Western Europe



Conclusions

- Among the *E. coli* and *K. pneumoniae* collected, MDR rates were higher in *K. pneumoniae* than in *E. coli* and higher in Eastern Europe than Western Europe.
- The MDR phenotype in both *E. coli* and *K. pneumoniae* dramatically impacted the % susceptibility to most antimicrobials studied.
- Overall levofloxacin, cefepime, and ceftriaxone were most affected by the MDR phenotype while tigecycline, amikacin, and meropenem maintained the highest level of activity.
- MDR represents a growing threat to the activity of many agents used to treat multiple infections caused by Enterobacteriaceae as evidenced by European TEST data and should be carefully monitored going forward.

References and Acknowledgments:

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2. Clinical and Laboratory Standards Institute. 2016. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement. CLSI Document M1005. Wayne, PA.
3. European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2015. *Breakpoint tables for interpretation of MICs and zone diameters,* version 5.0 http://www.eucast.org.

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