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Fluoroquinolone Resistance among *Enterobacteriaceae* from U.S. Medical Centers Between 2011 and 2014

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Revised Abstract

Background: Since the introduction of quinolones in 1962, bacterial resistance has been on the rise. The development of fluoroquinolones (FQ) provided a broader spectrum of activity against both gram-negative and –positive pathogens. However, there has been a significant increase of resistance to FQ, particularly *Enterobacteriaceae* (ENT). This data from the Tigecycline Evaluation Surveillance Trial (TEST) program provides recent data on FQ resistance rates in ENT from isolates collected in hospitals located in the United States. **Methods:** A total of 1750 levofloxacin non-susceptible (LVX-NS) *Enterobacteriaceae* isolates from three species groups were collected from 130 U.S. hospitals between 2011 and 2014. $MIC_{50/90}$ and percent susceptible (%S) results were determined against LVX-NS isolates for cefepime (FEP), meropenem (MEM), piperacillin/tazobactam (TZP) and tigecycline (TGC) using CLSI broth microdilution methods and interpretative criteria. **Results:** The overall percentage of LVX-NS ENT during this four year study was 17.1%. The following table displays *in vitro* testing results for LVX-NS ENT against comparative agents.

	Species group (n/%LVX-NS)					
	Enterobacter spp. (153/4.9%)		*E. coli* (1171/32.4%)		*Klebsiella* spp. (426/12.1%)	
Drug	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
FEP	4/>32	40.5	≤0.5/>32	73.0	16/>32	32.6
MEM	0.12/4	86.7	≤0.06/0.12	98.6	0.12/>16	67.5
TZP	64/>128	42.5	2/16	90.0	128/>128	43.4
TGC	1/4	72.6	0.12/0.5	99.7	1/4	89.9

Conclusion: FQ resistance was much higher among *E. coli* compared to *Klebsiella* spp. and *Enterobacter* spp. TGC, TZP and MEM were most active against LVX-NS *E. coli* at a %S greater than or equal to 90%. TGC was also the most active agent tested against *Klebsiella* spp and *E. coli*. MEM and TGC had equivalent potency against *Enterobacter* spp. The increasing rate of FQ-NS ENT is concerning and requires continued monitoring of alternative therapeutic choices which are often co-resistant among this subset of bacterial pathogens.

Introduction

Since the introduction of quinolones in 1962, bacterial resistance has been on the rise. The development of fluoroquinolones provided a broader spectrum of activity against both gram-negative and –positive pathogens. However, there has been a significant increase of global resistance to fluoroquinolones, particularly among *Enterobacteriaceae*. This data from the Tigecycline Evaluation Surveillance Trial (TEST) program provides recent data on fluoroquinolone resistance rates in *Enterobacteriaceae* from isolates collected in hospitals located in the United States.

Materials & Methods

- A total of 1,750 levofloxacin non-susceptible *Enterobacteriaceae* isolates from three species groups were collected from 130 U.S. hospitals between 2011 and 2014.
- *Enterobacteriaceae* isolates were identified to the species level and MICs determined at each participating laboratory using supplied broth microdilution panels.
- Organism collection, transport, confirmation of organism identification, susceptibility testing, 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 using MicroScan (Beckman Coulter, West Sacramento, CA) or TREK (Thermo Fisher Scientific, Oakwood, OH) panels [1].
- Fluoroquinolone resistance was determined using guidelines issued by the Clinical and Laboratory Standards Institute (CLSI) on susceptibility and resistance to levofloxacin. MIC interpretive criteria followed published guidelines of the CLSI and the recent United States Food and Drug Administration package insert for tigecycline where applicable [2,3].
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [2].

Results

Figure 1. Four Year Trend of Levofloxacin Susceptibility Among *Enterobacteriaceae*.

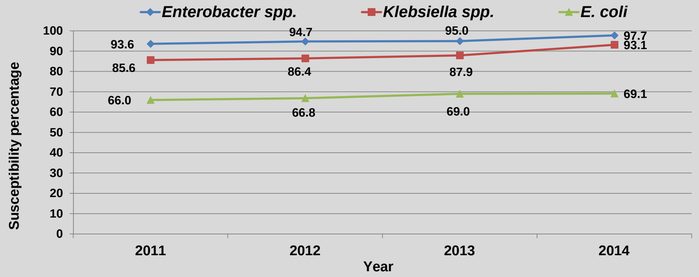

Table 1. Frequency Distributions of Tigecycline and Comparators Tested against 1,750 Levofloxacin-non-susceptible *Enterobacter* spp., *Klebsiella* spp. and *E. coli* Isolates.

		MIC (µg/mL)[a]									
Drug	**Value Type**	**≤0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**>128**
Cefepime	N	896	61	99	94	74	90	93	343[b]		
	Pct	51.2	54.7	60.3	65.7	69.9	75.1	80.4	**100**		
Meropenem	N	1553	16	11	17	20	44	83[c]			
	Pct	89.0	**90.0**	90.6	91.6	92.7	95.2	100			
Piperacillin-tazobactam	N	49	319	410	278	152	96	47	49	81	269
	Pct	2.8	21.0	44.5	60.3	69.0	74.5	77.2	80.0	84.6	**100**
Tigecycline	N	1342	203	116	55	29	5[d]				
	Pct	76.7	88.3	**94.9**	98.1	99.7	100				

[a] MIC_{90} values bolded. [b] Highest concentration tested was 32 µg/mL, MIC values were ≥64 µg/mL. [c] Highest concentration tested was 16 µg/mL, MIC values were ≥32 µg/mL. [d] Highest concentration tested was 8 µg/mL, MIC values were ≥16 µg/mL.

Table 2. Activity of Comparator Agents Tested Against Levofloxacin-susceptible and non-susceptible *Enterobacteriaceae* From Midwestern States.[a]

		Levo-S		Levo-NS	
Organism (n, Levo-S)/(n, Levo-NS)	**Drug**	**% Susceptible**	**MIC_{90}**	**% Susceptible**	**MIC_{90}**
***E. coli* (952)/(366)**	Cefepime	98.2	≤ 0.5	70.0	>32
	Meropenem	99.8	≤ 0.06	98.1	0.12
	Piperacillin-tazobactam	97.6	2	90.2	16
	Tigecycline	100	0.25	100	0.25
***Klebsiella* spp. (1,154)/(120)**	Cefepime	98.4	≤ 0.5	28.3	>32
	Meropenem	99.8	≤ 0.06	55.0	>16
	Piperacillin-tazobactam	97.4	4	39.2	>128
	Tigecycline	97.1	1	89.2	4
***Enterobacter* spp. (1,129)/(31)**	Cefepime	91.7	2	41.9	32
	Meropenem	99.5	0.25	96.8	1
	Piperacillin-tazobactam	88.6	32	38.7	>128
	Tigecycline	98.0	1	71.0	4

[a]States included Illinois, Indiana, Iowa, Kansas, Michigan, Missouri, Nebraska, North Dakota, Ohio, and Wisconsin.

Table 3. Activity of Comparator Agents Tested Against Levofloxacin-susceptible and non-susceptible *Enterobacteriaceae* From Southern States.[a]

		Levo-S		Levo-NS	
Organism (n, Levo-S)/(n, Levo-NS)	**Drug**	**% Susceptible**	**MIC_{90}**	**% Susceptible**	**MIC_{90}**
***E. coli* (573)/(319)**	Cefepime	98.3	≤ 0.5	80.6	32
	Meropenem	99.7	≤ 0.06	98.4	≤ 0.06
	Piperacillin-tazobactam	98.1	4	89.3	32
	Tigecycline	99.8	0.25	100	0.5
***Klebsiella* spp. (755)/(101)**	Cefepime	97.8	≤ 0.5	16.8	>32
	Meropenem	99.7	0.12	70.0	>16
	Piperacillin-tazobactam	97.4	8	32.7	>128
	Tigecycline	96.6	1	84.2	4
***Enterobacter* spp. (690)/(63)**	Cefepime	93.0	1	38.1	>32
	Meropenem	99.1	0.12	83.3	4
	Piperacillin-tazobactam	91.3	16	44.4	>128
	Tigecycline	96.5	1	73.0	4

[a] States included Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, South Carolina, Tennessee, and Texas.

Table 4. Activity of Comparator Agents Tested Against Levofloxacin-susceptible and non-susceptible *Enterobacteriaceae* From Western States.[a]

		Levo-S		Levo-NS	
Organism (n, Levo-S)/(n, Levo-NS)	**Drug**	**% Susceptible**	**MIC_{90}**	**% Susceptible**	**MIC_{90}**
***E. coli* (300)/(183)**	Cefepime	91.7	1	57.9	>32
	Meropenem	100	≤ 0.06	97.8	0.12
	Piperacillin-tazobactam	97.7	2	86.9	64
	Tigecycline	100	0.5	97.8	0.5
***Klebsiella* spp. (413)/(54)**	Cefepime	98.1	≤ 0.5	59.3	>32
	Meropenem	99.5	≤ 0.06	88.9	4
	Piperacillin-tazobactam	95.6	8	61.1	>128
	Tigecycline	94.9	1	87.0	4
***Enterobacter* spp. (407)/(22)**	Cefepime	90.7	2	40.9	8
	Meropenem	99.5	0.25	90.9	1
	Piperacillin-tazobactam	81.1	64	31.8	>128
	Tigecycline	96.8	1	50.0	8

[a]States included Arizona, California, Colorado, Oregon, and Washington.

Table 5. Activity of Comparator Agents Tested Against Levofloxacin-susceptible and non-susceptible *Enterobacteriaceae* From Northeastern States.[a]

		Levo-S		Levo-NS	
Organism (n, Levo-S)/(n, Levo-NS)	**Drug**	**% Susceptible**	**MIC_{90}**	**% Susceptible**	**MIC_{90}**
***E. coli* (619)/(303)**	Cefepime	97.1	≤ 0.5	77.9	>32
	Meropenem	99.8	≤ 0.06	99.7	≤ 0.06
	Piperacillin-tazobactam	96.9	4	92.4	16
	Tigecycline	100	0.25	100	0.25
***Klebsiella* spp. (770)/(151)**	Cefepime	97.1	≤ 0.5	37.1	>32
	Meropenem	99.6	≤ 0.06	68.0	>16
	Piperacillin-tazobactam	94.3	8	47.7	>128
	Tigecycline	97.1	1	95.4	2
***Enterobacter* spp. (730)/(37)**	Cefepime	92.5	2	43.2	>32
	Meropenem	99.6	0.12	81.1	8
	Piperacillin-tazobactam	83.3	64	48.7	>128
	Tigecycline	96.9	1	86.5	4

[a]States included Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, and Vermont.

Conclusions

- Fluoroquinolone resistance was higher among *E. coli* compared to *Klebsiella* spp. and *Enterobacter* spp. though all species or species groups showed increasing susceptibility to levofloxacin in 2014 compared to 2011 in the US medical centers surveyed (Figure 1).
- Tigecycline and meropenem were most active against levofloxacin-non-susceptible *E. coli* in all US regions with susceptibility percentages of ≥97% (Tables 2-5).
- Levofloxacin-non-susceptible *Klebsiella* spp. and *Enterobacter* spp. had lower susceptibility percentages to all drugs in all regions studied compared to levofloxacin-susceptible isolates (Tables 2-5)
- Fluoroquinolone-non-susceptible *Enterobacteriaceae* is concerning and requires continued monitoring of alternative therapeutic choices which are often co-resistant among this subset of bacterial pathogens collected in the US.

References and Acknowledgments:

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