

Activity of Levofloxacin and Comparators Against *Enterobacteriaceae* Causing Urinary Tract Infections in Asia: 2004-2010



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Revised Abstract

Background: *Escherichia coli* remain the most common cause of urinary tract infections (UTI) worldwide. However other members of the family *Enterobacteriaceae* are important especially in hospitalized patients. The Tigecycline Evaluation and Surveillance Trial (TEST) examines the susceptibility of pathogens isolated from patients with urinary tract infections in countries worldwide.

Methods: Clinically significant UTI pathogens from the family *Enterobacteriaceae* were obtained from 93 cumulative sites in 9 countries in Asia 2004-2010. MICs were determined for 740 isolates using supplied broth microdilution panels and interpreted according to FDA/CLSI guidelines.

Results: The % susceptible for the top 6 UTI species (n=727, 98%) *Enterobacteriaceae* spp. versus levofloxacin and comparative antimicrobial agents in shown in the following table:

Drug	% Susceptible					
	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>K. oxytoca</i>	<i>E. aerogenes</i>	<i>E. cloacae</i>	<i>S. marcescens</i>
Amikacin	94.2	89.5	95.2	89.6	87.2	92.6
Amox-Clav	48.3	58.0	52.4	0	3.4	5.6
Ampicillin	14.2	1.2	0	2.1	1.7	1.9
Cefepime	71.4	68.5	81.0	93.8	69.2	87.0
Ceftriaxone	52.6	52.5	66.7	50.0	36.8	61.1
Imipenem	100	100	92.9	100	100	100
Levofloxacin	39.4	59.9	85.7	85.4	65.0	83.3
Meropenem	97.7	95.2	100	100	90.8	93.5
Pip-Tazo	88.9	75.3	90.5	70.8	65.0	92.6
Tigecycline	100	98.8	95.2	100	88.9	98.2
N	325	162	21	48	117	54

Conclusions: Tigecycline, amikacin and meropenem were the most active agents overall against *Enterobacteriaceae* with %S of >90% for most species. The %S for each antimicrobial varied between species for each antimicrobial with *E. coli* generally the most susceptible. However, *E. coli* demonstrated the lowest susceptibility to levofloxacin. Overall, *Enterobacter* spp. was less susceptible to the studied agents than *Klebsiella* spp. and *S. marcescens*. The continued monitoring of Asian UTI pathogens in both in- and out-patients is warranted.

Introduction

Fluoroquinolone resistance in UTI pathogens has been increasing globally [1]. Poor health, urinary catheterization, recent hospitalization, and previous UTI are risk factors associated with increased fluoroquinolone resistance [2]. Independent risk factors also include prior exposure to antimicrobial agents including trimethoprim-sulfamethoxazole, metronidazole, cephalosporins, and fluoroquinolones. Additionally, the increasing prevalence of beta-lactamases with frequent co-resistance with fluoroquinolones has become a major concern [3]. The Tigecycline Evaluation and Surveillance Trial (TEST) has tracked resistance in gram-negative UTI pathogens since 2004. Evidence for increasing fluoroquinolone resistance and the *in vitro* activity of comparative agents in UTI is presented.

Materials & Methods

- ❖ **Clinical isolates:** Isolates were identified to the species level and tested at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria. All isolates were from the period 2004 - 2010 and collected from 93 cumulative sites in 9 Asian countries.
- ❖ **Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined using broth microdilution plates manufactured by MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and Trek Diagnostics (TREK Diagnostic Systems, Cleveland, OH, USA), following manufacturer and Clinical and Laboratory Standards Institute (CLSI) instructions for broth microdilution testing [4]. Susceptibility was determined using clinical breakpoints published by the CLSI [5] and the FDA (tigecycline) [6].
- ❖ **Quality Control:** QC of broth microdilution panels followed manufacturers' and CLSI guidelines using the following ATCC strains as needed and applicable: *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *Klebsiella pneumoniae* ATCC 700603 as ESBL-positive control.

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Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

Figure 1. Distribution of 740 UTI isolates from 9 Asian countries, 2004-2010.

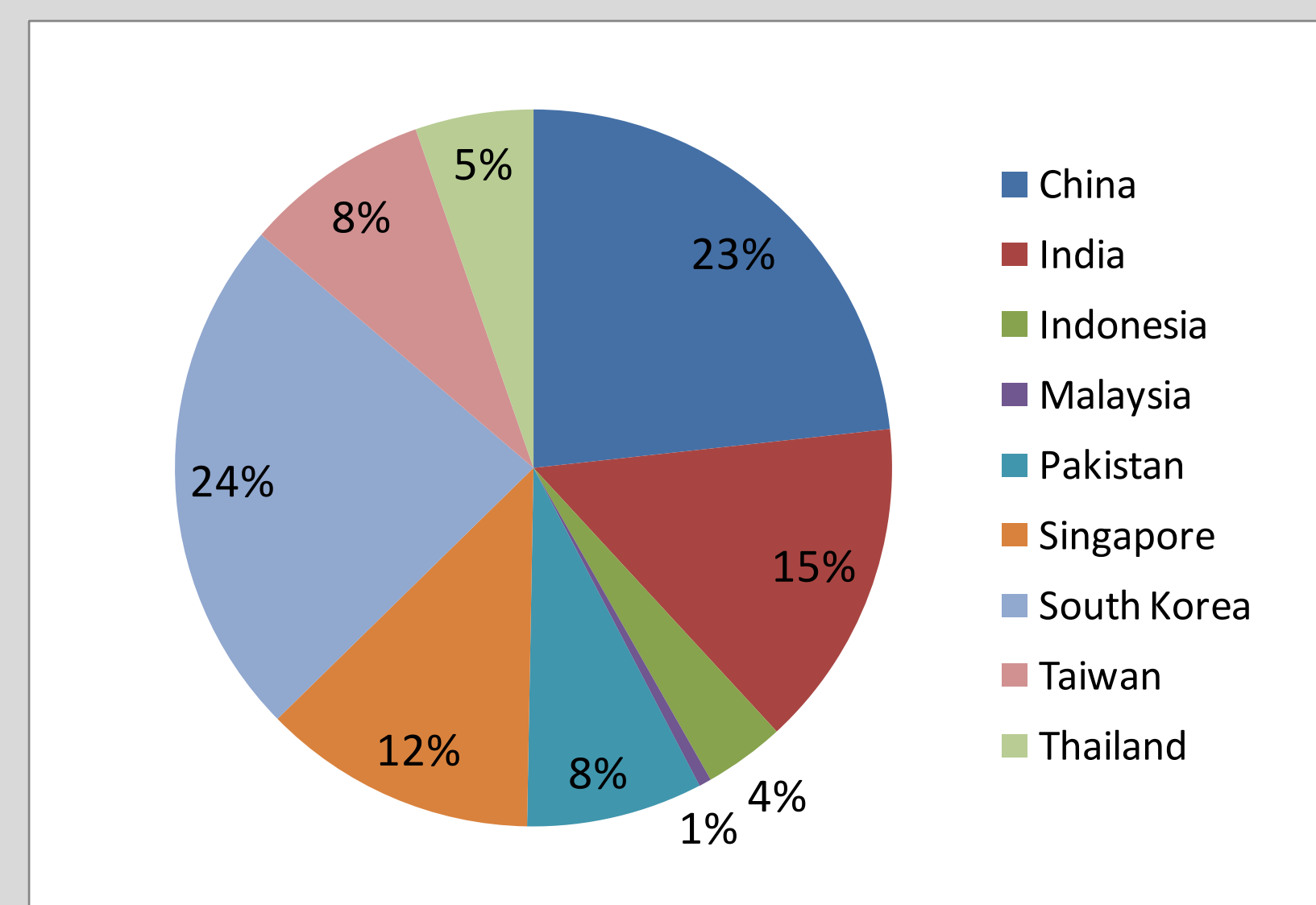


Figure 2. Distribution of 740 UTI isolates by species from Asia, 2004-2010.

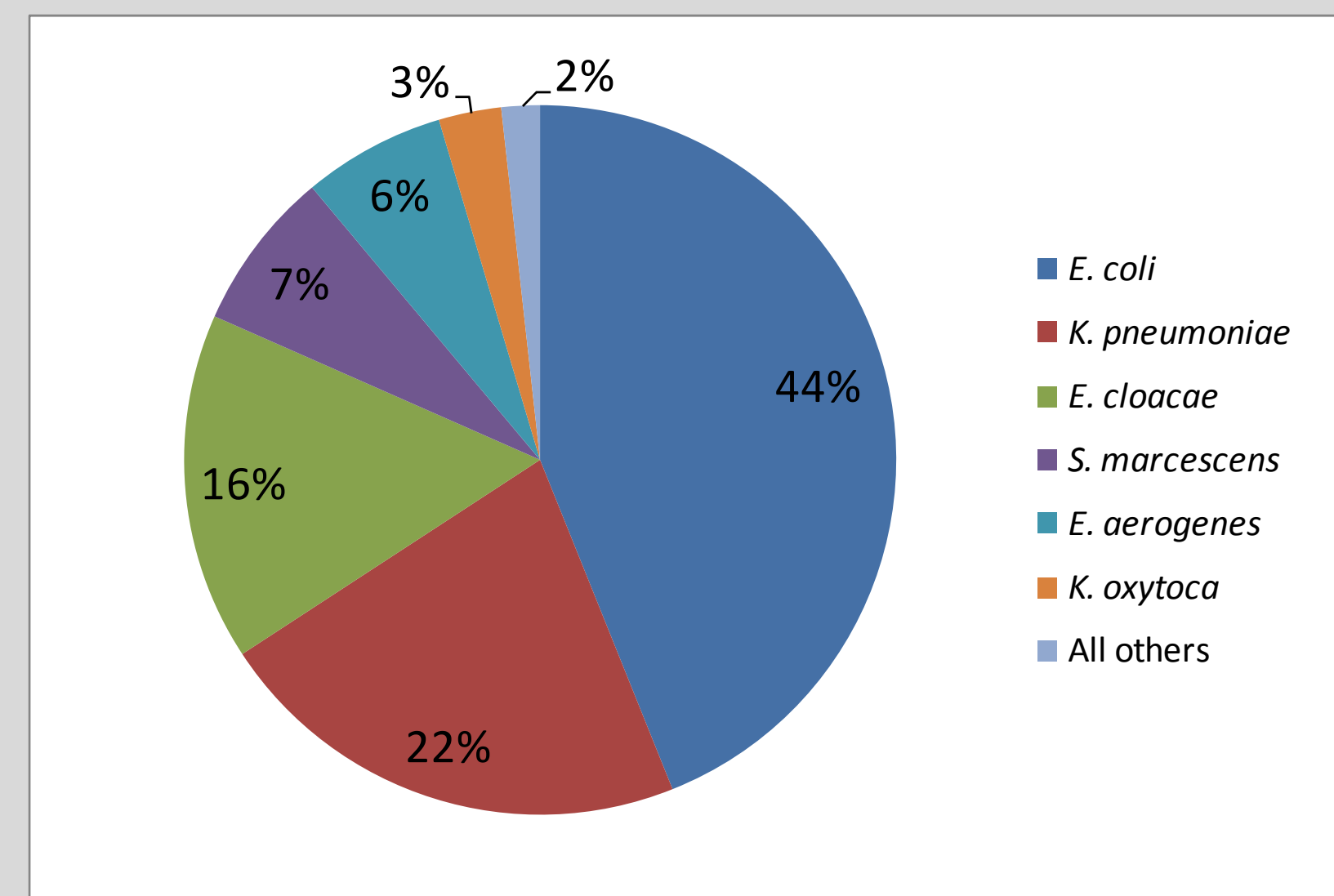


Figure 3. Levofloxacin resistant rate (%) and ESBL percentage (%) by year for UTIs in Asia, 2004-2010.

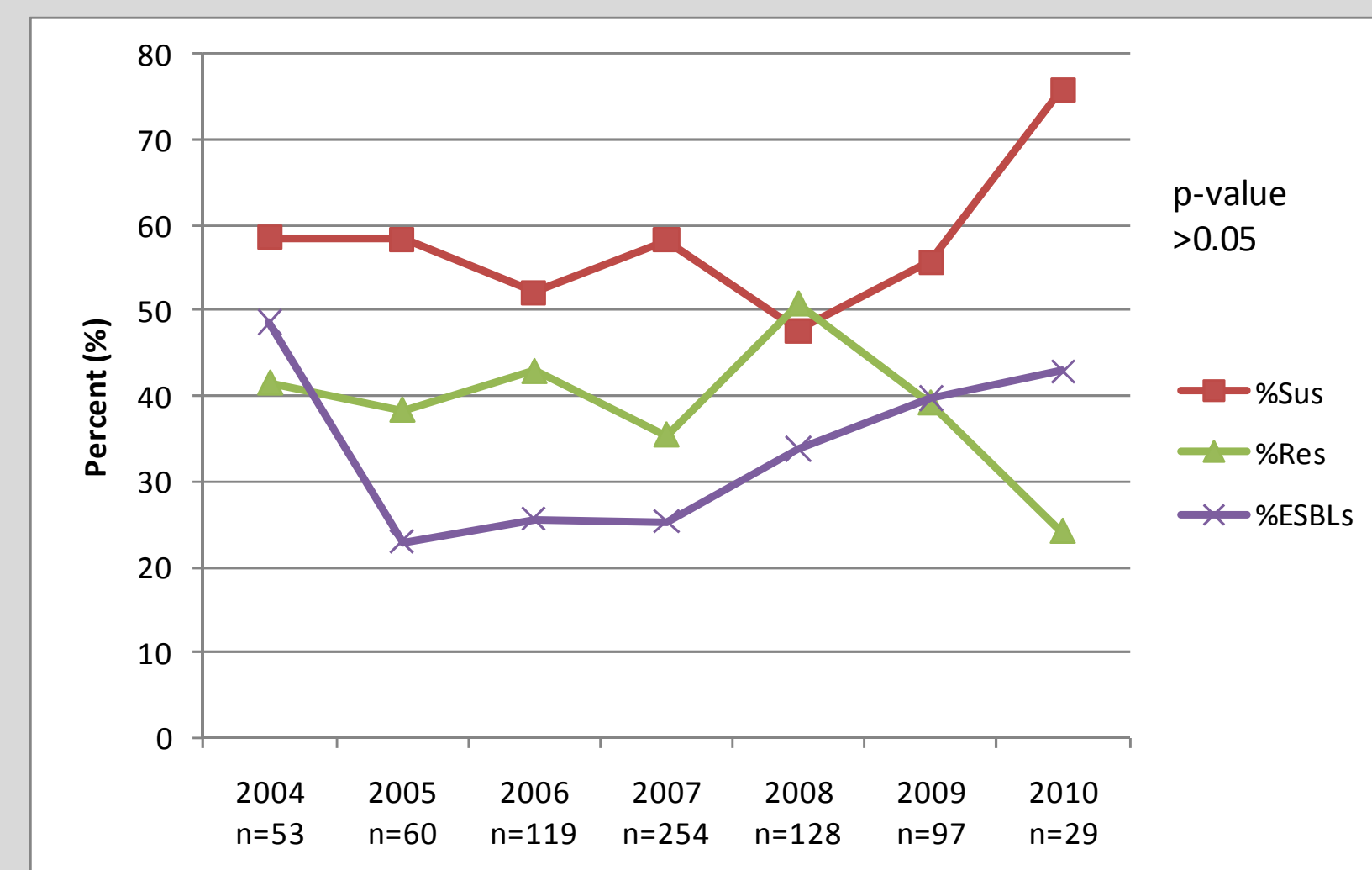


Table 1. *In vitro* activity of levofloxacin and comparators against 740 *Enterobacteriaceae* from UTIs in Asia, 2004-2010.

Drug	mcg/ml		%Sus*	%Int	%Res
	MIC ₅₀	MIC ₉₀			
Amikacin	2	16	91.4	0.8	7.8
AmoxClav	16	>32	36.8	19.2	44.1
Ampicillin	>32	>32	7.3	3.5	89.2
Cefepime	≤0.5	>32	72.8	5.4	21.9
Ceftriaxone	1	>64	50.5	3.0	46.5
Imipenem	0.25	0.5	99.5	0	0.5
Levofloxacin	1	>8	55.8	4.2	40.0
Meropenem	≤0.06	0.25	94.7	1.3	4.0
PipTazo	2	128	80.5	8.9	10.5
Tigecycline	0.5	2	97.3	1.9	0.8

* Interpretive criteria defined in CLSI document M100-S21 (2011), where available. Tigecycline breakpoints are defined by FDA (Tygacil®). 2010.

Table 2. *In vitro* activity of levofloxacin and comparators against 727 *Enterobacteriaceae* by species from UTIs in Asia, 2004-2010.

Organism*	Drug	mcg/ml		%Sus**	%Int	%Res
		MIC ₅₀	MIC ₉₀			
<i>E. aerogenes</i> n=48	Amikacin	2	32	89.6	4.2	6.3
	AmoxClav	32	>32	0	8.3	91.7
	Ampicillin	>32	>32	2.1	4.2	93.8
	Cefepime	≤0.5	8	93.8	2.1	4.2
	Ceftriaxone	2	64	50	2.1	47.9
	Imipenem	0.5	1	100	0	0
	Levofloxacin	0.06	>8	85.4	2.1	12.5
	Meropenem	≤0.06	0.12	100	0	0
	PipTazo	4	128	70.8	18.8	10.4
<i>E. cloacae</i> n=117	Amikacin	2	>64	87.2	0	12.8
	AmoxClav	>32	>32	3.4	6.8	89.7
	Ampicillin	>32	>32	1.7	6	92.3
	Cefepime	2	>32	69.2	4.3	26.5
	Ceftriaxone	8	>64	36.8	6	57.3
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	1	>8	65	4.3	30.8
	Meropenem	≤0.06	1	90.8	2	7.1
	PipTazo	8	>128	65	12	23.1
<i>E. coli</i> n=325	Amikacin	2	8	94.2	0.9	4.9
	AmoxClav	16	32	48.3	31.4	20.3
	Ampicillin	>32	>32	14.2	0.3	85.5
	Cefepime	≤0.5	>32	71.4	6.2	22.5
	Ceftriaxone	0.25	>64	52.6	0.9	46.5
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	8	>8	39.4	3.7	56.9
	Meropenem	≤0.06	0.12	97.7	0.5	1.9
	PipTazo	2	32	88.9	7.7	3.4
<i>E. coli</i> , ESBL n=93	Amikacin	4	16	93.6	2.2	4.3
	AmoxClav	16	>32	28	47.3	24.7
	Ampicillin	>32	>32	0	0	100
	Cefepime	16	>32	37.6	15.1	47.3
	Ceftriaxone	>64	>64	0	0	100
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	>8	>8	14	5.4	80.7
	Meropenem	≤0.06	0.12	100	0	0
	Minocycline	4	>16	57	17.2	25.8
<i>K. oxytoca</i> n=21	Amikacin	2	4	95.2	0	4.8
	AmoxClav	8	>32	52.4	28.6	19.1
	Ampicillin	>32	>32	0	9.5	90.5
	Cefepime	≤0.5	16	81	9.5	9.5
	Ceftriaxone	≤0.06	>64	66.7	0	33.3
	Imipenem	0.25	1	92.9	0	7.1
	Levofloxacin	0.06	4	85.7	4.8	9.5
	Meropenem	≤0.06	0.25	100	0	0
	PipTazo	2	16	90.5	0	9.5
<i>K. pneumoniae</i> n=162	Amikacin	2	32	89.5	0.6	9.9
	AmoxClav	8	>32	58	12.4	29.6
	Ampicillin	>32	>32	1.2	6.2	92.6
	Cefepime	≤0.5	>32	68.5	4.9	26.5
	Ceftriaxone	0.5	>64	52.5	2.5	45.1
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	0.5	>8	59.9	6.2	34
	Meropenem	≤0.06	0.25	95.2	0.8	4
	PipTazo	4	>128	75.3	7.4	17.3
<i>K. pneumoniae</i> , ESBL n=58	Amikacin	4	>64	79.3	0	20.7
	AmoxClav	16	>32	22.4	27.6	50
	Ampicillin	>32	>32	0	0	100
	Cefepime	32	>32	34.5	12.1	53.5
	Ceftriaxone	>64	>64	1.7	5.2	93.1
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	8	>8	29.3	8.6	62.1
	Meropenem	≤0.06	0.5	93.3	2.2	4.4
	PipTazo	16	>128	55.2	13.8	31
<i>S. marcescens</i> n=54	Amikacin	2	8	92.6	0	7.4
	AmoxClav	>32	>32	5.6	3.7	90.7
	Ampicillin	>32	>32	1.9	7.4	90.7
	Cefepime	≤0.5	32	87	1.9	11.1
	Ceftriaxone	0.5	64	61.1	11.1	27.8
	Imipenem	0.5	1	100	0	0
	Levofloxacin	0.12	8	83.3	3.7	13
	Meropenem	≤0.06	0.25	93.5	0	6.5
	PipTazo	2	16	92.6	5.6	1.9

* Species with n's <10 are not presented (Total N = 740).
** Interpretive criteria defined in CLSI document M100-S21 (2011), where available. Tigecycline breakpoints are defined by FDA (Tygacil®). 2010.

Conclusions

- ❖ Tigecycline, amikacin, imipenem, and meropenem were the most active antimicrobial agents *in vitro* against gram-negative *Enterobacteriaceae* from urinary tract infections (UTIs) in Asia with % Susceptible >90% against most species. Only ampicillin and ceftriaxone have overall lower susceptibility to UTI pathogens than levofloxacin.
- ❖ The % Susceptible for each antimicrobial varied from species to species with *E. coli* generally the most susceptible. However, *E. coli*, the most common UTI pathogen, demonstrated the lowest susceptibility to levofloxacin. Imipenem, meropenem, and tigecycline were unaffected by ESBL-producing *Enterobacteriaceae* (*E. coli* and *K. pneumoniae*).
- ❖ There has been an increase in levofloxacin susceptibility to UTI pathogens in the past two years (2009 and 2010) with a concomitant decrease in resistance in spite of a similar rise in ESBL activity; however, these changes were statistically insignificant (p >0.05). With <60% susceptibility of levofloxacin against the majority of UTI pathogens, particularly *E. coli* and *K. pneumoniae*, empiric therapy of UTIs with this and other fluoroquinolones should be reconsidered.