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Levofloxacin Susceptibility in *Escherichia coli* (EC): Asia 2005-2009

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Revised Abstract

Background: Fluoroquinolone resistance in *Escherichia coli* emerged quickly following the widespread use of fluoroquinolones in the 1980's. However, there are few studies that track the temporal trends in resistance to levofloxacin in *E. coli* in Asia. In order to more precisely describe such trends, large scale surveillance studies are useful. This report documents the rates of resistance to levofloxacin in *E. coli* collected in Asia from 2005 - 2009, as part of the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) study. **Methods**: A total of 1285 *E. coli* clinical isolates from various infection sources were collected in this study: 65, 321, 412, 216 and 271 isolates from 2005, 2006, 2007, 2008 and 2009, respectively. These originated from a cumulative total of 39 investigator sites in 11 Asian countries. MICs were performed and interpreted according to CLSI guidelines. **Results**: The table below illustrates the incidence of levofloxacin resistant *E. coli* with time.

Year	Total[a]	LVX^R	$\%LVX^R$
2005	65	30	46.2
2006	321	141	43.9
2007	412	207	50.2
2008	216	133	61.6
2009	271	136	50.2

[a], total EC isolates per each year; LVX^R, isolates exhibiting full resistance to levofloxacin (MIC breakpoint > 4 mcg/ml)

Conclusions: Taken together, this body of data shows that levofloxacin resistance in *E. coli* in Asia over the past five years remains persistently high. Although the levofloxacin resistance rate remains high, there has been no significant change in resistance in the five years monitoring of this study (p>0.05). The most active agents tested were tigecycline (100% susceptible), followed by meropenem (99%) and amikacin (90%)

Introduction

Escherichia coli is worldwide the most frequent pathogen isolated from uncomplicated urinary tract infections (UTI) (70 - 95%) and, in bacteremia of nosocomial or community origin, it represents about 15.5% and 42.1% of aetiologies, respectively (1). Fluoroquinolones such as levofloxacin are potent antimicrobial agents used for the treatment of a wide variety of community- and nosocomial- infections. However, increasing resistance to levofloxacin in *E. coli* isolated from community acquired UTI and other sources continues to restrict the use of this agent clinically. Moreover, infections due to extended-spectrum beta-lactamase (ESBL) - producing *E. coli* are an emerging problem in community and hospital settings, with increasing numbers being reported from various infection sources and countries in Asia (2). The current report describes susceptibilities and rates of levofloxacin resistance in *E. coli* clinical isolates collected as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) from Asia during 2005 – 2009 including ESBL-positive and ESBL-negative sub-populations.

Materials & Methods

Clinical isolates: A total of 1285 clinical isolates of *E. coli* were studied. 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 2005 – 2009, originated from various countries in Asia, and from multiple infection sources and clinical locations.

Susceptibility testing: Minimum inhibitory concentrations (MICs) were determined using plates manufactured by Trek Diagnostics, following manufacturer's and Clinical and Laboratory Standards Institute (CLSI) guidelines for broth microdilution testing (3). Susceptibility was determined using clinical breakpoints published by the US Food and Drug Administration package insert and CLSI (4, 5).

References

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Results

Figure 1. Distribution of 1,285 *E. coli* clinical isolates from Asia during 2005 – 2009 by country

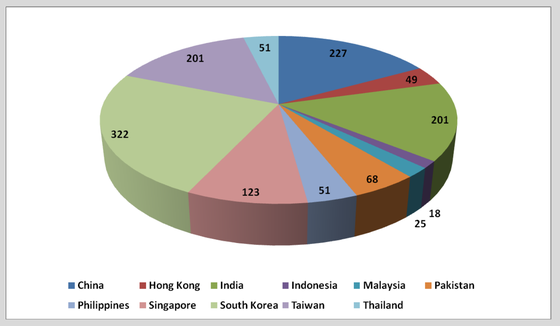

Figure 2. Percent of ESBL-positive *E.coli* clinical isolates isolated in Asia during 2005 – 2009 by country

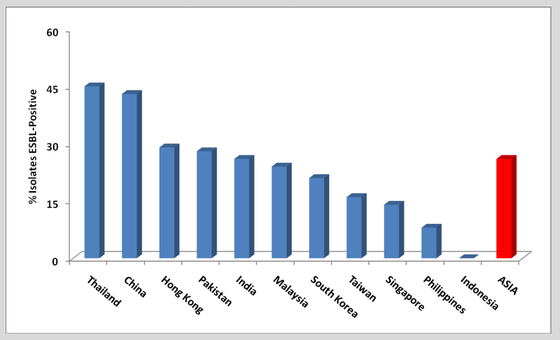

Figure 3. Percent of *E.coli* clinical isolates resistant to levofloxacin by country and by ESBL status

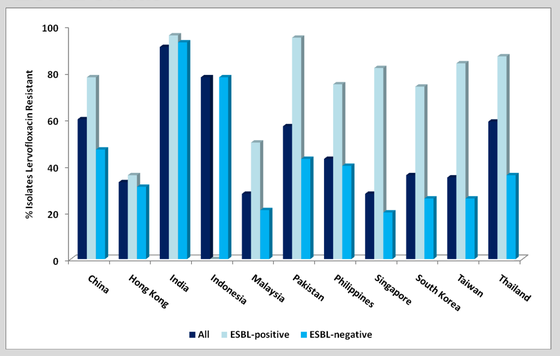

Table 1. Activity* of levofloxacin against all, ESBL-positive and ESBL-negative *E. coli* clinical isolates

Year	Organism	N	MIC_{50}	MIC_{90}	%S	%I	%R	MIN	MAX
2005	*E. coli*	65	2	> 8	50.8	3.1	46.2	≤0.008	> 8
	E.coli, ESBL	15	> 8	> 8	13.3	0.0	86.7	0.03	> 8
	E. coli, non ESBL	50	0.25	> 8	62.0	4.0	34.0	≤0.008	> 8
2006	*E. coli*	321	2	> 8	50.5	5.6	43.9	≤0.008	> 8
	E.coli, ESBL	85	> 8	> 8	14.1	4.7	81.2	0.015	> 8
	E. coli, non ESBL	236	0.25	> 8	63.6	5.9	30.5	≤0.008	> 8
2007	*E. coli*	412	8	> 8	47.6	2.2	50.2	≤0.008	> 8
	E.coli, ESBL	71	8	> 8	19.7	5.6	74.7	0.03	> 8
	E. coli, non ESBL	341	0.5	> 8	53.4	1.5	45.2	≤0.008	> 8
2008	*E. coli*	216	> 8	> 8	37.0	1.4	61.6	0.015	> 8
	E.coli, ESBL	68	> 8	> 8	10.3	2.9	86.8	0.03	> 8
	E. coli, non ESBL	148	4	> 8	49.3	0.7	50.0	0.015	> 8
2009	*E. coli*	271	8	> 8	45.0	4.8	50.2	≤0.008	> 8
	E.coli, ESBL	88	> 8	> 8	14.8	8.0	77.3	0.03	> 8
	E. coli, non ESBL	183	0.5	> 8	59.6	3.3	37.2	<= 0.008	> 8

*All MIC values are expressed in µg/ml. %S, %I, %R; percent susceptible, intermediate or resistant. MIN, minimum MIC; MAX, maximum MIC

Table 2. Activity* of levofloxacin and comparator agents AGAINST all isolates (n =1285) and levofloxacin-resistant (n = 647) *E. coli* clinical isolates

All Isolates (n = 1285)					**Levofloxacin-Resistant (n = 647)**				
Drug	**MIC $_{90}$**	**%S**	**%I**	**%R**	**Drug**	**MIC $_{90}$**	**%S**	**%I**	**%R**
Amikacin	8	94	1	5	Amikacin	32	90	2	8
Amox / Clav	32	54	27	19	Amox / Clav	> 32	30	39	32
Cefepime	> 32	72	5	23	Cefepime	> 32	50	9	41
Ceftazidime	32	75	7	17	Ceftazidime	> 32	54	14	32
Ceftriaxone	> 64	56	1	43	Ceftriaxone	> 64	28	1	72
Levofloxacin	> 8	46	4	50	Levofloxacin	> 8	0	0	100
Meropenem	0.12	99	0	1	Meropenem	0.12	99	1	1
Minocycline	16	64	15	21	Minocycline	> 16	53	18	28
Pip / Tazo	32	88	7	5	Pip / Tazo	64	79	12	9
Tigecycline	0.5	100	0	0	Tigecycline	0.5	100	0	0

*All MIC values are expressed in µg/ml. %S, %I, %R; percent susceptible, intermediate or resistant.

Conclusions

- Levofloxacin resistance in *E. coli* in Asia ranged from a low of 43.9% in 2006 to a high of 61.6% in 2008.
- In the majority of Asian countries, levofloxacin-resistance was higher in ESBL-positive populations as compared with ESBL-negative populations.
- Activity of levofloxacin (MIC_{50}) was higher against ESBL-negative populations as compared with ESBL-positive populations.
- Tigecycline was the most active comparator tested with 100% of isolates susceptible, followed by meropenem and amikacin.