Antimicrobial Susceptibility of Urinary Tract Infection Pathogens in Asia – SMART 2009

35

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Revised Abstract

Background: The Study for Monitoring Antimicrobial Resistance Trends (SMART) has monitored susceptibility of intra-abdominal infection (IAI) pathogens since 2002, and began collecting data on urinary tract infections (UTI) in late 2009. This report summarizes Asian UTI data from SMART in 2009. **Methods**: 14 hospitals in 7 Asian countries each collected up to 30 consecutive non-duplicate isolates of gram-negative aerobic bacilli from UTI, including only one isolate per species per patient. Isolate identification and broth microdilution susceptibility testing was done at a central laboratory, and interpreted using CLSI M100-S20 (Jan. 2010) and M100-S20-U (June 2010) guidelines. **Results:** 405 isolates were collected (265 from females, 131 from males, 9 unspecified). *E. coli* was more common in females (69 vs. 41%; p<0.0001); *P. aeruginosa* and *M. morganii* were more common in males (12 vs. 4% and 5 vs. 1%, respectively; p<0.05). Thirty-three percent of *E. coli* were ESBL+, but significantly more *E. coli* were ESBL+ in males than in females (44 vs. 29%, p<0.05). Susceptibility of species with n≥10 is shown below using M100-S20 guidelines, with values ≥90% shaded.

Organism	N	AK*	AS	CPE	CFT	CFX	CAZ	CAX	CP	ETP	IMP	LVX	PT
E. coli	242	**95**	33	67	62	81	70	62	51	**100**	**100**	51	**93**
K. pneumoniae	51	**100**	51	75	65	86	75	67	73	**96**	**100**	82	82
P. aeruginosa	27	67	-**	48	-	-	52	-	48	-	70	48	81
P. mirabilis	23	83	61	78	70	**96**	87	70	65	**100**	**100**	78	**100**
A. baumannii	16	31	19	13	6	-	19	6	19	-	25	19	19
E. cloacae	14	**93**	7	71	57	0	64	57	64	**100**	**100**	64	79

*AK=amikacin, AS=Amp-sulbactam, CPE=cefepime, CFT=cefotaxime, CFX=cefoxitin, CAZ=ceftazidime, CAX=ceftriaxone, CP=ciprofloxacin, ETP=ertapenem, IMP=imipenem, LVX=levofloxacin, PT=piperacillin-tazobactam.
**no breakpoint.

Conclusions: The 33% ESBL+ rate of *E. coli* in UTI was similar to that reported previously for IAI in Asia, and was high enough to render a large proportion of isolates non-susceptible *in vitro* to the cephalosporins and fluoroquinolones studied in SMART. Nevertheless, carbapenems and, to a lesser extent, AK and PT were active vs. *Enterobacteriaceae* UTI pathogens, using either M100-S20 or M100-S20-U breakpoints. No drug exceeded 81% activity vs. *P. aeruginosa* or 31% vs. *A. baumannii*. Antimicrobial resistance in UTI pathogens continues to be a significant problem in Asia.

Introduction

The Study for Monitoring Antimicrobial Resistance Trends (SMART) has tracked susceptibility of aerobic gram-negative bacilli causing intra-abdominal infections (IAI) to ertapenem and several comparators since 2002. SMART has documented that antimicrobial resistance rates of many species have increased over the course of the study, as has incidence of extended spectrum beta-lactamase-producing (ESBL+) isolates of *Escherichia coli* and other species causing IAI. Since ertapenem is also indicated for use in complicated urinary tract infection (UTI) due to *E. coli* and *Klebsiella pneumoniae*, the scope of SMART was expanded in late 2009 to include isolates causing UTI. The data collected can be useful in identifying changes that may be needed in recommendations for empiric therapy of UTI, depending on local antibiograms.

This report summarizes the Asia/Pacific UTI susceptibility data from 2009 to ertapenem and other antimicrobial agents included in SMART. Furthermore, since the Clinical and Laboratory Standards Institute (CLSI) revised carbapenem susceptibility breakpoints in June 2010, we compared susceptibility percentages of ertapenem and imipenem using both M100-S20 [1] and M100-S20-U [2] to determine the impact of the changes on reported susceptibility.

Materials & Methods

- 13 hospitals in Asia/Pacific (AP) collected and identified 405 gram-negative aerobic bacilli from UTI in 2009. Only one isolate per species per patient was accepted into the study.
- All isolates were sent to a central laboratory (International Health Management Associates, Inc., Schaumburg, Illinois, USA) for confirmation of identification, antimicrobial susceptibility testing, detection of extended-spectrum beta-lactamase (ESBL) production, and long-term storage.
- Susceptibility testing and ESBL detection was done using custom MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, California, USA), following CLSI guidelines [3], and interpreted using both CLSI M100-S20 [1] and M100-S20-U [2] guidelines. The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): ertapenem 0.03-4, imipenem 0.06-8, cefepime 0.5-32, ceftazidime 0.5-128, ceftazidime/clavulanic acid 0.12-16, cefoxitin 2-16, ciprofloxacin 0.25-2, amikacin 4-32, levofloxacin 0.5-4, cefotaxime 0.5-128, cefotaxime/clavulanic acid 0.12/2-16/2, piperacillin/tazobactam 2/4-64/4, ampicillin/sulbactam 2/2-16/2, and ceftriaxone 1-32.
- Quality control was done on each day of susceptibility testing, using CLSI ranges for *E. coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *K. pneumoniae* ATCC 700603 (positive ESBL control) [1].
- *E. coli, K. pneumoniae, K. oxytoca,* and *Proteus mirabilis* isolates were classified as ESBL producers if there was at least an eight-fold reduction of MIC for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when tested alone [1].
- Development of a centralized database of study results was managed by International Health Management Associates, Inc. located in Schaumburg, Illinois, USA.
- Statistical significance was determined using Fisher's Exact Test, two-tailed.

References

1. Clinical and Laboratory Standards Institute, 2010. *Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement.* CLSI document M100-S20. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
2. Clinical and Laboratory Standards Institute, 2010. *Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement (June 2010 Update).* CLSI document M100-S20-U. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
3. Clinical and Laboratory Standards Institute, 2009. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Eighth Edition*, in Document M7-A8. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.

Acknowledgements

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Results

Figure 1. Percentage of UTI isolates from each species.

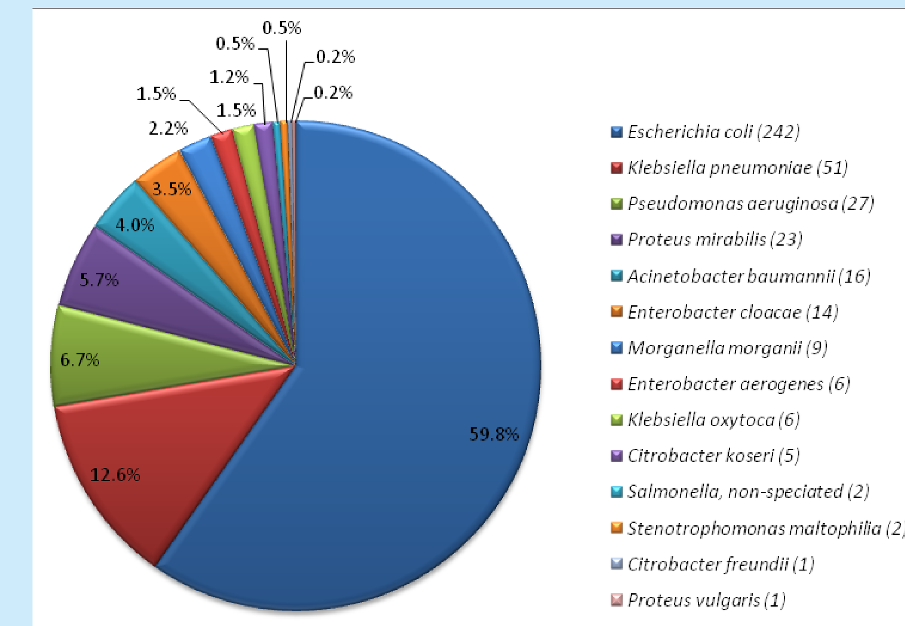
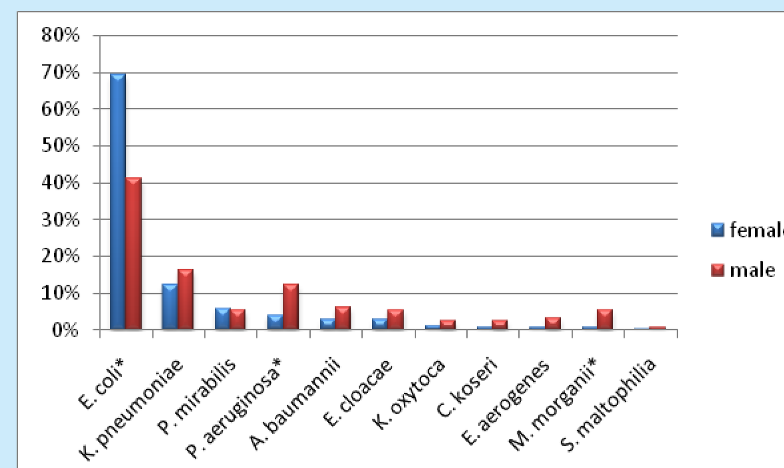


Figure 2. Relative percentage of each species found in UTI in female and male patients.



Asterisks indicate P<0.05.

Table 1. Antimicrobial susceptibility (M100-S20) of UTI isolates; only species with n>10 shown. Shading denotes values ≥90%.

Organism	N	AK	AS	CPE	CFT	CFX	CAZ	CAX	CP	ETP	IMP	LVX	PT
E. coli	242	95	33	67	62	81	70	62	51	100	100	51	93
E. coli, ESBL-	161	100	45	99	93	85	92	93	71	100	100	71	96
E. coli, ESBL+	81	85	10	4	0	73	26	0	11	99	100	11	88
K. pneumoniae	51	100	51	75	65	86	75	67	73	96	100	82	82
K. pneumoniae, ESBL-	38	100	74	100	88	88	94	91	88	97	100	88	91
K. pneumoniae, ESBL+	13	100	0	8	0	77	15	0	23	92	100	62	54
P. aeruginosa	27	67	0	48	0	0	52	0	48	0	70	48	81
P. mirabilis	23	83	61	78	70	96	87	70	65	100	100	78	100
P. mirabilis, ESBL-	17	100	71	100	94	94	100	94	82	100	100	94	100
P. mirabilis, ESBL+	0												
A. baumannii	16	31	19	13	6	0	19	6	19	0	25	19	19
E. cloacae	14	93	7	71	57	0	64	57	64	100	100	64	79

AK=amikacin, AS=ampicillin-sulbactam, CPE=cefepime, CFT=cefotaxime, CFX=cefoxitin, CAZ=ceftazidime, CAX=ceftriaxone, CP=ciprofloxacin, ETP=ertapenem, IMP=imipenem, LVX=levofloxacin, PT=piperacillin-tazobactam.

Figure 3. Comparison of UTI ESBL+ *E. coli* rates in males and females.

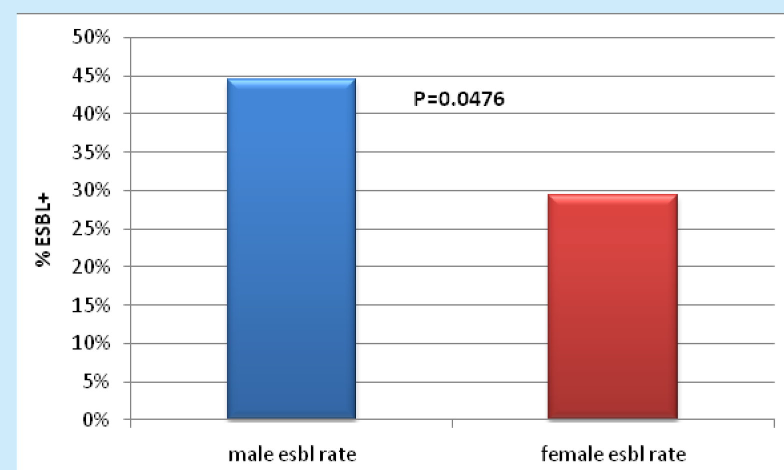
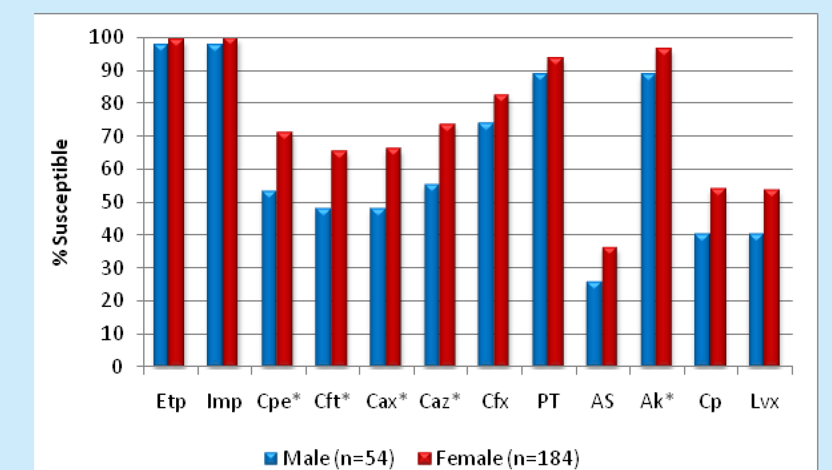


Figure 4. Susceptibility of *E. coli* from UTI in males and females.



Etp=ertapenem, Imp=imipenem, Cpe=cefepime, Cft=cefotaxime, Cax=ceftriaxone, Caz=ceftazidime, Cfx=cefoxitin, PT=piperacillin-tazobactam, AS=ampicillin-sulbactam, Ak=amikacin, Cp=ciprofloxacin, Lvx=levofloxacin.
Asterisks indicate significant differences (P<0.05).

Figure 5. Comparison of susceptibility to ertapenem using CLSI M100-S20 and M100-S20-U; only species with n ≥5 are shown.

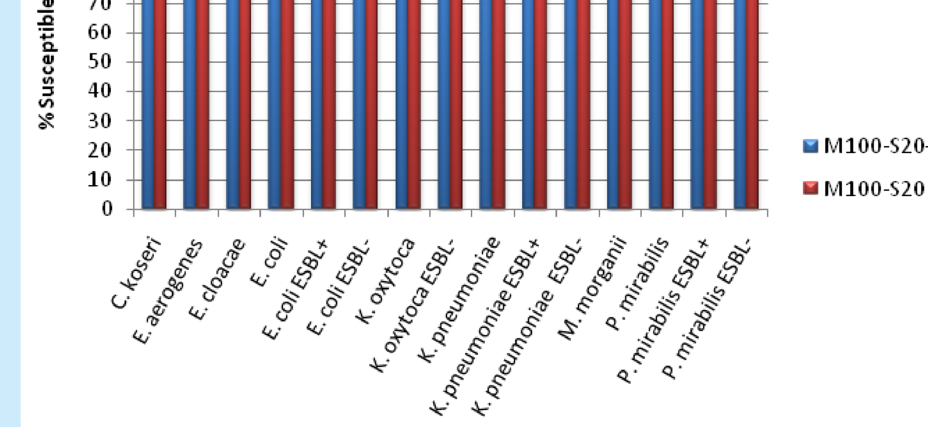
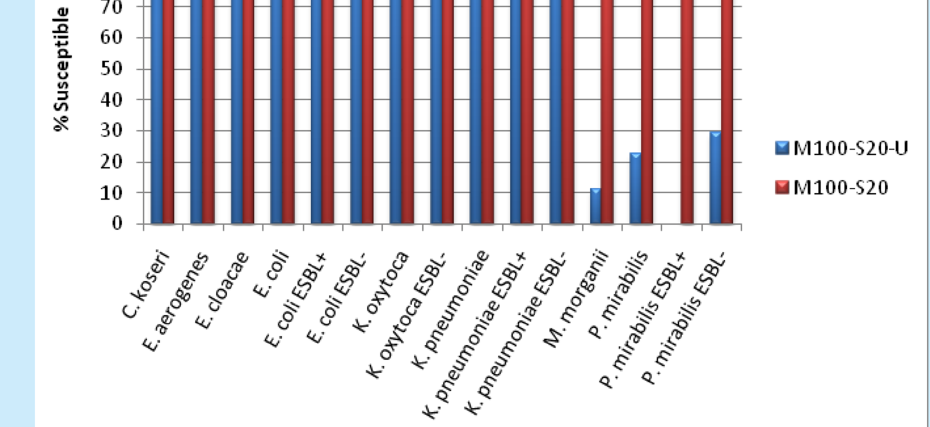


Figure 6. Comparison of susceptibility to imipenem using CLSI M100-S20 and M100-S20-U; only species with n ≥5 are shown.



Conclusions

- The ESBL+ rate among *E. coli* from UTI in Asia/Pacific was 32.8% overall, which is similar to rates reported previously for IAI in this region; however, the rate in males alone was 44.4%, vs. 29.3% for females. Given the significantly (P=.0476) higher ESBL rate seen in males, it is not surprising to see several drugs presenting lower (significantly, in many cases) susceptibility in males than females.
- Ertapenem and imipenem, along with piperacillin-tazobactam and amikacin to lesser extents, displayed good *in vitro* activity against *E. coli* overall; however, against ESBL+ isolates only the carbapenems inhibited >90%.
- Resistance rates among *P. aeruginosa* and *A. baumannii* were very high, with only piperacillin-tazobactam exceeding 80% inhibition vs. *P. aeruginosa*, and no drug exceeding amikacin's 31% inhibition vs. *A. baumannii.*
- The lower ertapenem breakpoints in CLSI M100-S20-U appear to affect primarily *Enterobacter* spp., causing about 15% of these isolates to be reported as non-susceptible. The lower imipenem breakpoints had almost no impact except for *P. mirabilis* and *M. morganii*; however, since imipenem is not indicated for treatment of *P. mirabilis* infections, and *M. morganii* only constitutes about 2% of gram-negative UTI pathogens, this diminishment of activity is unlikely to have any practical impact.
- Antimicrobial resistance in UTI in Asia/Pacific is a major problem, with 34% of UTI pathogens being resistant to multiple drugs (33% of *E. coli* and 25% of *K. pneumoniae* were ESBL+; and most *P. aeruginosa* and *A. baumannii* multiply resistant). Choices among drugs tested in SMART for empiric therapy of complicated UTI may be largely limited to carbapenems or piperacillin-tazobactam, pending definitive susceptibility reports from the laboratory.