

Revised Abstract

Background: ESBL producing organisms continue to be a therapeutic dilemma for physicians as many currently marketed antimicrobials are ineffective against these isolates; however, carbapenems and tigecycline are effective against many of these strains. As part of the Tigecycline Evaluation Surveillance Trial (TEST), this report evaluates incidence and susceptibility trends of ESBL+ isolates in Asia/Pacific from 2004-2008. **Methods:** All clinical isolates identified as *E. coli*, *K. pneumoniae*, or *K. oxytoca* were classified as ESBL-positive or -negative using CLSI criteria. MICs were determined at each participating laboratory by CLSI broth microdilution. **Results:** In 2008, 99% of 78 ESBL+ isolates were susceptible to tigecycline and meropenem; the 2 next most active drugs were amikacin (85%) and pip-tazo (68%). **Conclusions:** Although other studies have reported significant increases in ESBL+ rates in Asia/Pacific in the past few years, due to sampling variations the present report cannot consistently confirm the high rates reported elsewhere. Incidence of ESBL+ isolates in Australia has clearly increased from 2004-2008. Tigecycline appears to offer an alternative to carbapenem therapy for treatment of infections caused by ESBL+ organisms.

Introduction

Extended spectrum beta-lactamase (ESBL) producing *Escherichia coli*, *Klebsiella pneumoniae*, and *K. oxytoca* have continued their inexorable increase worldwide [1-2]. Frequency of occurrence reported from various countries or even regions within any given country, has varied widely, but in almost all cases has increased each year. Since plasmids encoding ESBL production usually carry concomitant resistance determinants for aminoglycosides, tetracyclines, trimethoprim/sulfamethoxazole, and fluoroquinolones, increases in ESBL prevalence have a significant negative impact on therapeutic options.

The Tigecycline Evaluation Surveillance Trial (TEST) has been tracking the susceptibility patterns of gram-negative and -positive bacteria causing a variety of infections since 2004. The primary goals of the study are to ensure that current susceptibility patterns of these organisms are well-understood and widely disseminated, leading ultimately to the most effective choice of therapy and helping prevent further spread of resistance through inappropriate use of antimicrobials.

A previous report [3] indicated exceptionally high rates of ESBL-producing *E. coli* and *K. pneumoniae* in China and India, compared to other countries. The present report evaluates ESBL+ rates in Asia/Pacific from 2004 through 2008 as observed in the TEST program, and summarizes their antimicrobial susceptibility profiles against the drugs studied in TEST.

Materials & Methods

- Isolates were collected from clinical specimens (one isolate per patient only) according to site criteria and deemed clinically significant.
- Isolates were derived from blood, urine, wound, skin, fluids and other defined sources.
- Isolates were collected between 2004-2008 from 97 cumulative sites in 11 countries.
- Isolates were identified to the species level at each site using local laboratory criteria.
- Isolate collection, transport, confirmatory identification and database management were coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (Schaumburg, IL, USA)
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended microbroth dilution testing method (4). Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers; MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH, USA).
- The following agents were included on the gram-negative panel with expressed dilution ranges (mcg/ml): amikacin (0.5-64), amoxicillin-clavulanic acid (0.12/0.06-32/16), ampicillin (0.06-16), cefepime (0.5-32), ceftazidime (8-32), ceftriaxone (0.06-64), meropenem (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), tigecycline (0.008-16) and piperacillin-tazobactam (0.06/4-128/4).
- QC of broth microdilution panels followed manufacturers' and CLSI guidelines [5] using the following ATCC strains as needed and applicable: *E. coli* ATCC 25922, *E. coli* ATCC 35218, *K. pneumoniae* ATCC 700603 (ESBL positive control), and *Pseudomonas aeruginosa* ATCC 27853.
- ESBLs were initially screened using ceftazidime and/or ceftriaxone (microbroth panels) and confirmed using ceftazidime +/- clavulanic acid and cefotaxime +/- clavulanic acid as described by the CLSI [5].

References

- Paterson, D., Bonomo, R. *Extended-spectrum beta-lactamases: a clinical update*. Clin Microbiol Rev 2005; 18:657-686.
- Rossi, F., Baquero, F., Hsueh, P., Paterson, D., Bochicchio, G., Snyder, T., Satishchandran, V., McCarroll, K., DiNubile, J., Chow, J. *In vitro susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends)*. J Antimicro Chemother 2006. 58(1): 205-210.
- Hawser, S., Bouchillon, S., Hoban, D., Badal, R., Hsueh, P., Paterson, D. *Emergence of High Levels of Extended-Spectrum-Beta-Lactamase-Producing Gram-Negative Bacilli in the Asia-Pacific Region: Data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) Program, 2007*. Antimicrob. Agents Chemother. 2009. 53:3280-3284.
- CLSI, 2008. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition, in Document M7-A7*. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
- CLSI, 2009. *Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Infor Supplement*. CLSI document M100-S19. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.

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Results

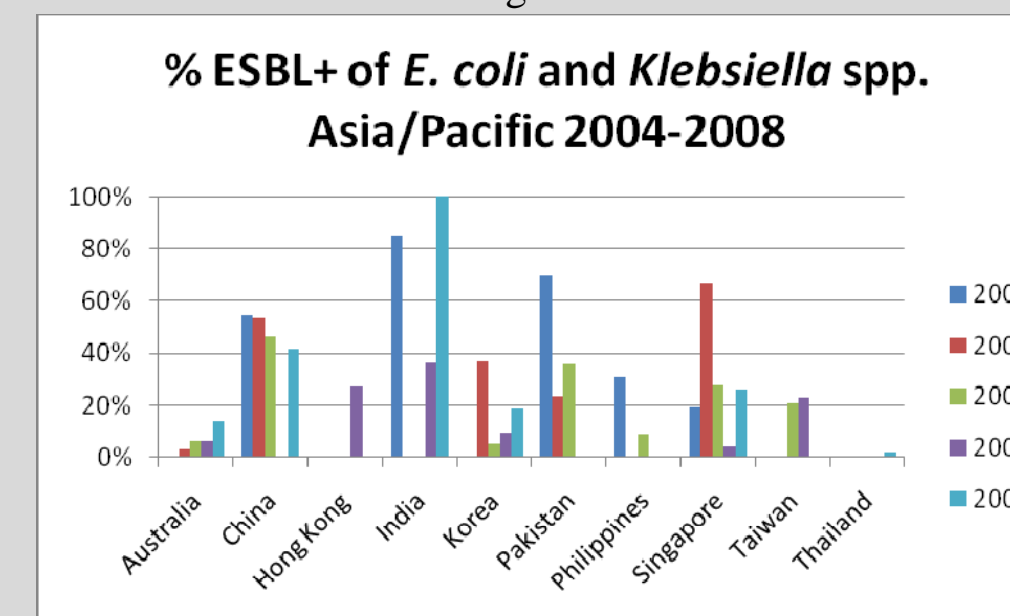
Table 1. Number of *E. coli*, *K. pneumoniae*, and *K. oxytoca* isolates contributed by each country each year of the TEST program.

# Total Isolates	2004	2005	2006	2007	2008
Australia	39	35	103	81	78
China	42	28	71	0	36
Hong Kong	0	0	0	63	0
India	39	0	17	115	14
Korea	0	49	97	248	103
Pakistan	13	34	95	0	0
Philippines	13	34	95	0	0
Singapore	98	3	47	97	50
Taiwan	0	0	203	146	0
Thailand	0	0	0	0	49
Totals	244	183	728	750	330

Table 2. Relative percentage of each year's isolates contributed by each country.

% of Total Isolates	2004	2005	2006	2007	2008
Australia	16%	19%	14%	11%	24%
China	17%	15%	10%	0%	11%
Hong Kong	0%	0%	0%	8%	0%
India	16%	0%	2%	15%	4%
Korea	0%	27%	13%	33%	31%
Pakistan	5%	19%	13%	0%	0%
Philippines	5%	19%	13%	0%	0%
Singapore	40%	2%	6%	13%	15%
Taiwan	0%	0%	28%	19%	0%
Thailand	0%	0%	0%	0%	15%

Figure 1.



Conclusions

- Although large increases in ESBL+ isolates in Asia/Pacific in the past few years have been reported elsewhere, the TEST study has not shown similar dramatic increases in Asia due to inconsistent representation of some key Asian countries (e.g., China, India, Pakistan), over the course of the study.
- It is noteworthy that Australia, which has participated in TEST with some consistency throughout the 5 years of the study, has shown increases in ESBL+ rates from 0% in 2004 to 14% in 2008 (P=0.015).
- The percentage of ESBL+ isolates susceptible to tigecycline was >99%. This *in vitro* activity was equal to or greater than the activities of either imipenem or meropenem against these therapeutically challenging strains.

Figure 2.

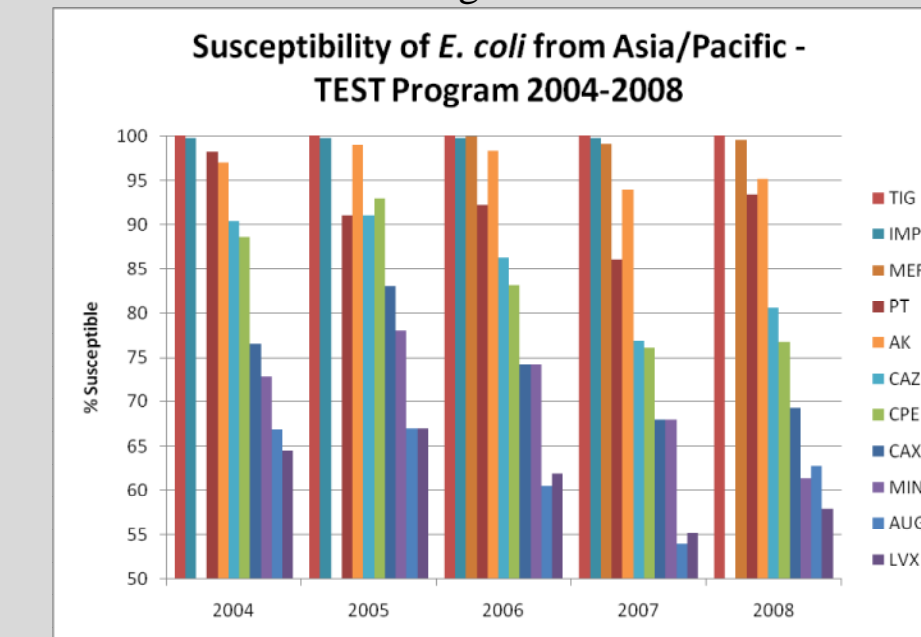


Figure 3.

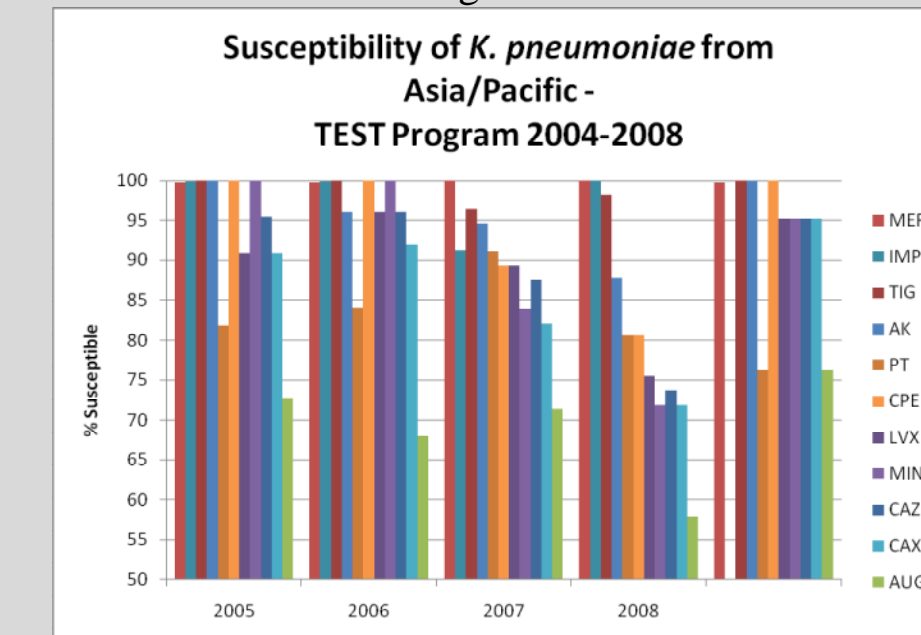


Figure 4.

