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Emergence of High Levels of Extended-Spectrum-β-Lactamase-Producing Gram-Negative Bacilli in the Asia-Pacific Region: Data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) Program, 2007▽

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Of 3,004 gram-negative bacilli collected from intra-abdominal infections in the Asia-Pacific region during 2007, 42.2% and 35.8% of *Escherichia coli* and *Klebsiella* spp., respectively, were extended-spectrum β-lactamase (ESBL) positive. Moreover ESBL rates in India for *E. coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were 79.0%, 69.4%, and 100%, respectively. ESBL-positive *E. coli* rates were also relatively high in China (55.0%) and Thailand (50.8%). Ertapenem and imipenem were the most active drugs tested, inhibiting over 90% of all species, including ESBL-positive isolates with the exception of *Pseudomonas aeruginosa* isolates (<90% susceptible to all study drugs) and ESBL-positive *Klebsiella pneumoniae* isolates (<90% susceptible to all study drugs except imipenem). Quinolones achieved 90% inhibition levels only against ESBL-negative *K. pneumoniae* and ESBL-negative *K. oxytoca*. A decline in ampicillin-sulbactam activity was noted, with only 34.5% of all *Enterobacteriaceae* inhibited in this study.

Gram-negative bacilli (GNB) continue to be an important cause of health care-associated infections (8, 15). They are a common cause of sepsis, pneumonia, urinary tract infection, postsurgical infections in acute care hospitals, and intra-abdominal infections (16). Antimicrobial resistance among these bacilli is increasing on a worldwide basis, especially resistance against β-lactam antibiotics due to the development of β-lactamase enzymes, which can hydrolyze the β-lactam ring of such antibiotics (1). Various types of β-lactamases can confer resistance to expanded-spectrum cephalosporins, including chromosomally mediated β-lactamases, extended-spectrum β-lactamases (ESBLs), metallo-β-lactamases, and KPCs. ESBLs are known to confer resistance to all β-lactam drugs, but organisms typically remain susceptible to carbapenems (4, 12).

Large-scale surveillance studies demonstrate that the vast majority of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates, among others, are susceptible to carbapenems (9, 11, 17). However, antibiotic resistance in GNB is evolving globally, with different levels of regional resistance that can vary significantly. It is therefore increasingly important to monitor susceptibility trends in various regions of the world over time to detect, define, track, and communicate those trends so that effective therapeutic measures can be determined and customized to meet local needs.

The Study for Monitoring Antimicrobial Resistance Trends (SMART) program monitors the activity of ertapenem, imipenem, amikacin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, ciprofloxacin, levofloxacin, ampicillin-sulbactam, and piperacillin-tazobactam against GNB from intra-abdominal infections (IAI). This program has been ongoing since 2002 in most regions of the world, with nearly 120 hospitals participating in 2008. This report reviews the most current data from the SMART program from the Asia-Pacific region for isolates collected throughout 2007.

(Parts of this study were presented as posters at the joint 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious Diseases Society of America, 2008 [2] and at the 7th International Symposium on Antimicrobial Agents and Resistance, 2009 [3].)

MATERIALS AND METHODS

All isolates were derived from IAI. Only one isolate per patient was accepted into the study. Gram-negative aerobic and facultative bacteria were cultured from specimens from intra-abdominal body sites, e.g., appendix, peritoneum, colon, bile, pelvis, and pancreas. The majority of intra-abdominal specimens were obtained during surgery, though some paracentesis specimens were also accepted. Isolates from blood, urine, and perirectal abscesses were excluded. Overall, 3,004 clinical isolates from 35 laboratories in the following 11 locations in the Asia-Pacific region (numbers of laboratories are in parentheses) were collected and tested in 2007: Australia (1), China (6), Hong Kong (1), India (9), South Korea (2), New Zealand (2), Philippines (1), Singapore (2), Taiwan (7), Thailand (2), and Vietnam (2). Isolates were identified to the species level and tested at each site. Development of a centralized database of study results was managed by International Health Management Associates, Inc., located in Schaumburg, IL. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory methods.

MICs were determined using dehydrated MicroScan broth microdilution panels manufactured by Siemens Medical Solutions Diagnostics (West Sacramento, CA) by following Clinical and Laboratory Standards Institute (CLSI) guidelines

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TABLE 1. Frequency of ESBL-positive *E. coli*, *K. pneumoniae*, and *K. oxytoca*: location-specific data from the Asia-Pacific region during 2007

Location	No. of isolates of:						Total no. (%) of ESBL$^+$ isolates
	E. coli that were:		*K. pneumoniae* that were:		*K. oxytoca* that were:		
	ESBL^{+a}	ESBL$^-$	ESBL^{+a}	ESBL$^-$	ESBL$^{+a,b}$	ESBL$^-$	
Australia	1 (7.7)	12	0 (0)	3	0 (0)	0	1 (6.3)
China	158 (55.0)	129	25 (27.5)	66	1 (25.0)	3	184 (48.2)
Hong Kong	8 (17.8)	37	0 (0)	0	0 (0)	0	8 (17.8)
India	264 (79.0)	70	77 (69.4)	34	15 (100)	0	356 (77.4)
South Korea	10 (22.7)	34	12 (32.4)	25	1 (25.0)	3	23 (27.1)
New Zealand	3 (3.2)	91	1 (7.1)	13	1 (20.0)	4	5 (4.4)
Philippines	9 (17.0)	44	8 (40.0)	12	0 (0)	2	17 (22.7)
Singapore	17 (33.3)	34	12 (37.5)	20	0 (0.0)	1	29 (34.5)
Taiwan	33 (12.7)	227	30 (18.3)	134	2 (14.3)	12	65 (14.8)
Thailand	33 (50.8)	32	15 (45.5)	18	0 (0)	2	48 (48.0)
Vietnam	42 (34.4)	80	9 (39.1)	14	2 (50.0)	2	53 (35.6)
Total	578 (42.2)	790	189 (35.8)	339	22 (43.1)	29	789 (40.5)

[a] Percentages are in parentheses.
[b] Although these are denoted as ESBL positive, molecular characterization was not done; therefore, some strains may be K1 hyperproducers instead of ESBL producers.

(7). All antimicrobial agents were supplied by the panel manufacturer. The following antimicrobial agents, with their dilution ranges (expressed in μg/ml), were included on the panels: ertapenem, 0.03 to 4; imipenem, 0.06 to 8; cefepime, 0.5 to 32; ceftazidime, 0.5 to 128; ceftazidime-clavulanic acid, 0.12 to 16; cefoxitin, 2 to 16; ciprofloxacin, 0.25 to 2; amikacin, 4 to 32; levofloxacin, 0.5 to 4; cefotaxime, 0.5 to 128; cefotaxime-clavulanic acid, 0.12 to 16; piperacillin-tazobactam, 2 to 64 (piperacillin) and 4 (tazobactam); ampicillin-sulbactam, 2 to 16 (ampicillin) and 2 (sulbactam); and ceftriaxone, 1 to 32. MIC interpretive criteria followed published guidelines established by the CLSI (6).

E. coli, *K. pneumoniae*, and *Klebsiella oxytoca* strains were classified as ESBL producers if there was at least an eightfold reduction (i.e., three doubling dilutions) of the MIC for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when either drug was tested alone (7). Quality control (QC) testing was done by each testing site on each day of testing using the CLSI-recommended QC strains *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 (positive ESBL control), and *Pseudomonas aeruginosa* ATCC 27853. All participating labs used the same MIC panels manufactured by Siemens Medical Solutions Diagnostics and performed susceptibility testing and QC testing by the CLSI protocol as described in the MicroScan package insert. QC testing was performed each time a laboratory carried out batch testing of isolates. Only data from test days for which all pertinent CLSI-recommended QC results were in control were included in the database. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines (6).

RESULTS

Of the 3,004 GNB isolates collected, 82% were represented by seven species: *E. coli* (n = 1,368), *K. pneumoniae* (n = 528), *P. aeruginosa* (n = 245), *Enterobacter cloacae* (n = 150), *Enterobacter aerogenes* (n = 65), *Proteus mirabilis* (n = 61), and *Citrobacter freundii* (n = 51). Fifty-eight other species comprised the other 18% of the isolates. The most commonly isolated organism was *E. coli*, for which 578 of the 1,368 isolates (42.2%) were ESBL positive. Also ESBL positive were 35.8% of the *K. pneumoniae* isolates. Furthermore, although the number of *K. oxytoca* isolates was relatively small (n = 51), 22 (43.1%) were ESBL positive.

Table 1 and Fig. 1 show the distribution of ESBL isolates by location. While ESBL rates for the Asia-Pacific region as a whole were relatively high, several countries exhibited ESBL rates that were strikingly higher than 50%. For example, rates for India for ESBL-positive *E. coli*, *K. pneumoniae*, and *K. oxytoca* were 79.0%, 69.4%, and 100%, respectively. Furthermore, of the nine sites in India, none had an ESBL-positive rate for *E. coli* of less than 54.5% and the highest rate was 94.1% (data not shown). ESBL-positive *E. coli* rates were also high in China (55.0%) and Thailand (50.8%), making ESBL-positive isolates more common than ESBL-negative ones in all three countries. Furthermore, Thailand also exhibited relatively high rates of ESBL-positive *K. pneumoniae* isolates, whereby nearly one-half (45.5%) of isolates were ESBL positive (Fig. 1). The lowest rates of ESBL-positive isolates appeared in Australia and New Zealand; however, the numbers of *K. pneumoniae* and *K. oxytoca* isolates in these two countries were relatively small.

Table 2 describes the antimicrobial susceptibilities of the eight most commonly isolated organisms (those with $n > 50$), including ESBL-positive isolates of *E. coli*, *K. pneumoniae*, and *K. oxytoca*. The carbapenems, ertapenem and imipenem, were consistently the most active agents against all strains, with the exception of *P. aeruginosa* strains, for which 71% of isolates were susceptible to imipenem. The most active antipseudomonal antibiotic was amikacin, to which 85% of isolates were susceptible, followed by piperacillin-tazobactam (81% susceptible). The most active of the noncarbapenem antibiotics was generally amikacin: susceptibility of all organisms ranged from 73 to 100%. For all other agents, susceptibilities were typically considerably lower. Ampicillin-sulbactam exhibited notably poor in vitro activity against all species in this study (Table 1).

The susceptibilities to ertapenem and imipenem of non-ESBL-producing isolates ranged from 94 to 100% and 97 to 100%, respectively. ESBL-negative *E. coli* isolates exhibited 100% susceptibility to ertapenem and imipenem, and these drugs maintained most of their activity against ESBL-positive *E. coli*, with susceptibilities of 96% and 98%, respectively (Table 2). Furthermore, against ESBL-negative *K. pneumoniae*, ertapenem and imipenem exhibited susceptibilities of 99 and 100%, respectively. It is noteworthy that ertapenem exhibited marginally weaker activity against ESBL-positive *K. pneumoniae*, with 86% of isolates being susceptible. With imipenem, the susceptibility of ESBL-positive *K. pneumoniae* was

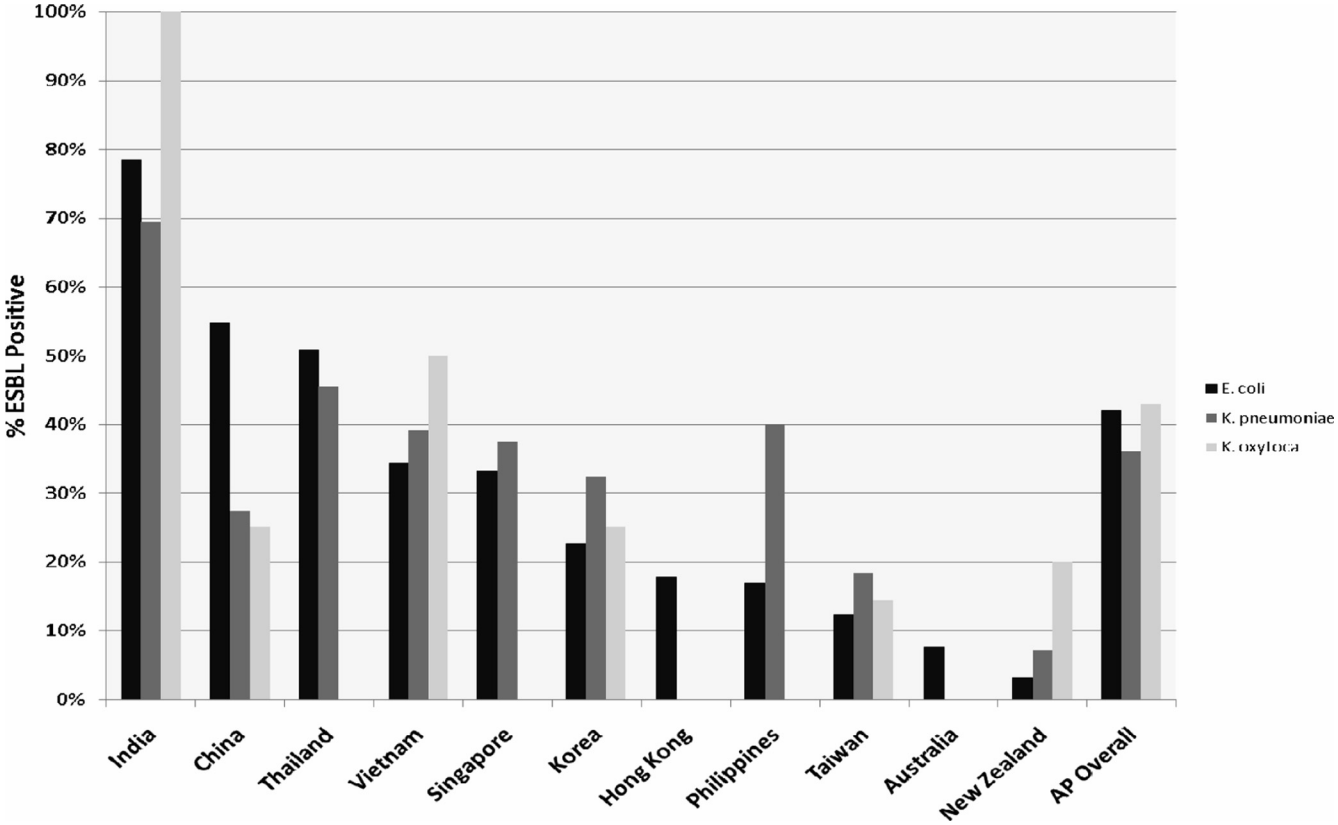

FIG. 1. Frequency distribution of ESBL-positive isolates by country in the Asia-Pacific (AP) region during 2007. Korea refers to South Korea.

3% lower than that of ESBL-negative isolates, representing a smaller drop in activity than that observed with ertapenem.

Table 3 summarizes rates of ESBL-positive *E. coli* and *K. pneumoniae* isolates from community-acquired and hospital-acquired infections in the Asia-Pacific region overall, China, India, and the Asia-Pacific region excluding those two countries. In the Asia-Pacific region excluding China and India, ESBL-positive *E. coli* rates for community-acquired and hospital-acquired infections were 13.7% and 31.5%, respectively. China's rates were roughly double those, at 36% and 64.7%, respectively, but showed approximately the same overall ratio of hospital-acquired infections to community-acquired infections: roughly twice as many hospital-acquired infections as community-acquired infections. In India, however, the community-acquired-infection rate of 79.0% was virtually identical to that of hospital-acquired infections (78.9%). ESBL-positive

TABLE 2. Antimicrobial susceptibilities of the eight most commonly isolated species to ertapenem, imipenem, and other comparator agents

Organism (no. of isolates)	% of isolates susceptible to[a]:											
	ETP	IMP	AK	CPE	CFT	CFX	CAZ	CAX	CP	LVX	P/T	A/S
C. freundii (51)	98	100	84	71	43	16	43	45	71	77	71	37
E. aerogenes (65)	97	97	83	77	48	22	46	55	75	83	69	31
E. cloacae (150)	94	98	92	79	49	7	53	48	77	79	71	17
E. coli ESBL$^+$ (578)	96	98	87	14*	5*	66*	29*	4*	17	21	83	5
E. coli ESBL$^-$ (790)	99	100	98	99	97	89	95	96	70	72	94	43
K. oxytoca ESBL$^+$ (22)	100[b]	100	86	41*	14*	64*	27*	9*	27	41	68	5
K. oxytoca ESBL$^-$ (29)	100	100	100	100	97	97	97	97	93	97	100	76
K. pneumoniae ESBL$^+$ (189)	86	97	73	28*	9*	61*	20*	10*	27	43	57	6
K. pneumoniae ESBL$^-$ (339)	99	100	99	99	97	87	97	97	93	94	94	76
P. mirabilis (61)	100	100	92	87	77	95	89	77	69	84	97	72
P. aeruginosa (245)	NA	71	85	69	14	NA	66	19	71	73	81	NA

[a] ETP, ertapenem; IMP, imipenem; AK, amikacin; CPE, cefepime; CFT, cefotaxime; CFX, cefoxitin; CAZ, ceftazidime; CAX, ceftriaxone; CP, ciprofloxacin; LVX, levofloxacin; A/S, ampicillin-sulbactam; P/T, piperacillin-tazobactam. *, CLSI standard M100-S17 recommends interpreting all cephalosporin results as resistant for ESBL$^+$ strains (4); NA, no CLSI breakpoint defined.

[b] While U.S. labels and prescribing information state that ertapenem and imipenem have been shown to be active against most strains of *K. oxytoca* both in vitro and for clinical infections, there is a notation in the "Clinical pharmacology" section of the ertapenem label that this activity excludes ESBL-producing strains.

TABLE 3. Frequency of ESBL-positive *E. coli* and *K. pneumoniae* isolates in community- and hospital-acquired infections in the Asia-Pacific region, China, and India

Type of infection[a]	% of ESBL$^+$ isolates of:							
	E. coli in[b]:				*K. pneumoniae* in:			
	A/P	A/P-	China	India	A/P	A/P-	China	India
CA	28	13.7	36	79	17.6	8.5	15.2	61.8
HA	55.4	31.5	64.7	78.9	50.2	42.8	40.0	72.7

[a] CA, community acquired (isolates recovered from a patient in a hospital for <48 h at the time of specimen collection; HA, hospital acquired (isolates recovered from a patient in a hospital for >48 h at the time of specimen collection).
[b] A/P, Asia-Pacific region including China and India; A/P-, Asia-Pacific region excluding China and India.

K. pneumoniae rates for hospital-acquired infections were three to four times higher than rates for community-acquired infections, the exception again being India, with rates of 72.7% and 61.8%, respectively.

DISCUSSION

Various country-based reports describing the incidence and susceptibility of ESBL-positive isolates of GNB are available in the literature, and each one reports quite different ESBL rates. For example, a one-center study in Vietnam reported that, of 350 isolates from clinical specimens, 87.4% were GNB. Of these GNB isolates, 88.9% were *Enterobacteriaceae*, of which 14.7% were ESBL positive (13). A study of 493 isolates from a single center in South Korea of *Enterobacter*, *Serratia marcescens*, *C. freundii*, and *Morganella morganii* revealed rates of ESBL-positive isolates of 12.8%, 12.4%, 4.9%, and 0%, respectively (5). Ko et al., from South Korea, described 22.4% of *K. pneumoniae* isolates and 10.2% of *E. coli* isolates as ESBL producers (14). In a recent study from Taiwan, 28.4% of *K. pneumoniae* isolates collected from various body sites were ESBL positive (4). Furthermore, in a study from India the percentage of ESBL-positive isolates was similarly elevated, with 23.1% of isolates being ESBL positive (18). Of the isolates from India, 48.4% of isolates were *E. coli* and 51.6% were *K. pneumoniae*. Notably, all of the ESBL-producing isolates were consistently susceptible only to carbapenems.

Asia is almost certainly a part of the world in which ESBLs have emerged de novo, with early antimicrobial resistance studies showing elevated levels of ESBL phenotypes, particularly among *Klebsiella* isolates and particularly in China, South Korea, Japan, and India (10). In most countries, there are mixtures of CTX-M types, with VEB appearing significantly in Vietnam and Thailand and ESBL isolates from India being completely dominated by the presence of $bla_{CTX\text{-}M\text{-}15}$ alone, with no other CTX-M types reported (10). The data from the SMART 2007 Asia-Pacific study show that *E. coli* and *Klebsiella* sp. ESBL frequencies are on the whole elevated in Asia compared both to previous years (2) and other regions of the world (2). Overall, ESBL frequencies in the Asia-Pacific region from 2007 were 40% compared with 30%, 17%, 10%, and 8% for Latin America, the Middle East and Africa, the European Union, and North America, respectively (2). Moreover, ESBL rates have markedly increased during the last few years in the Asia-Pacific region, with ESBL rates rising steadily from 2003 (15%) to 40% in 2007 (2, 3). However, there are two major features of the data from SMART 2007 (3) that are highly noteworthy. The first is that this is the first study demonstrating that, on the basis of the ESBL frequencies observed in India, China, Thailand, and Vietnam, the ESBL-positive phenotype has now become the dominant phenotype, alarmingly so in India, with *E. coli* and *K. pneumoniae* ESBL rates of 79.0% and 69.4%, respectively. Furthermore, the ESBL-positive *E. coli* rate in China was also notably high, running at 54.7%. India's near equivalence of rates of ESBL-positive isolates in community- and hospital-acquired IAI of both *E. coli* and *K. pneumoniae* is particularly significant. Additionally, these high rates were observed in all nine study centers in India, each representing distinct cities in various regions of India: New Delhi, Lucknow, Indore, Mumbai, Hyderabad, Bangalore, Chennai, Tamil Nadu, and Kolkata. The very high rates of ESBL-positive strains are seen all over the country and are not restricted to any single city or region. ESBL-positive *K. oxytoca* rates were also high in several countries. However, as molecular characterization of the strains was not performed, we are not able to distinguish K1-hyperproducing *K. oxytoca* from ESBL-producing *K. oxytoca*.

With the combined populations of India and China being circa 2.5 billion and with relatively high fecal carriage rates, these countries represent major ESBL gene reservoirs. Second, resistance to the majority of the antimicrobials used in the SMART 2007 study was high, with the exception of the carbapenems ertapenem and imipenem. It is important to mention, therefore, that, despite the high and increasing ESBL rates within Asia, and in particular in India, China, Thailand, and Vietnam, most ESBL-producing isolates remain susceptible to this important antibiotic class. Nevertheless, rates of resistance to ertapenem and imipenem in the current SMART study, albeit relatively low, may be creeping somewhat higher. Since almost all diminished ertapenem activity occurred in *K. pneumoniae*, we suspect it was due to the increasing incidence of KPC-producing strains; however, since study strains prior to 2008 were not saved or sent to a central laboratory for further testing, this supposition cannot be confirmed. Hence, further in-depth studies such as SMART and others are highly warranted in order to keep pace with the evolving clinical importance of ESBL producers and their susceptibility to currently available agents.

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