Antimicrobial resistance in major pathogens of hospital-acquired pneumonia in Asian countries

Evelina N. Lagamayo, MD
Manila and Quezon City, Philippines

Antimicrobial resistance is a worldwide problem. For patients with hospital-acquired or ventilator-associated pneumonia, resistant pathogens pose a significant challenge to successful treatment outcomes and to the cost-effective delivery of health care. In the developing world, antibiotic resistance may be relatively more prevalent compared with Western countries. Common resistant pathogens include methicillin-resistant *Staphylococcus aureus*, multidrug resistant *Pseudomonas aeruginosa*, multidrug resistant *Acinetobacter* species, and extended-spectrum β-lactamase-producing strains of *Escherichia coli* and *Klebsiella pneumoniae*. The emergence of these strains has provided a major impetus toward development of the present consensus treatment recommendations of the Asian HAP Working Group. The following review provides summary data regarding the incidence and prevalence of antibiotic-resistant pathogens in 10 Asian countries. (Am J Infect Control 2008;36:S101-8.)

The present consensus treatment recommendations represent the findings of an expert panel. The intent of the article is to provide useful, practical information to assist the clinician in the treatment of patients with hospital-acquired pneumonia (HAP) and ventilator-acquired pneumonia (VAP). It is hoped that this information will help in the development of effective treatment regimens for these patients.

Nosocomial infection is an important cause of morbidity and mortality worldwide, a problem made worse when nosocomial pathogens acquire antibiotic resistance. The emergence of resistant microorganisms has a significant impact on treatment outcomes and also poses a challenge to the provision of health care and its cost-effectiveness. This is especially true in the developing world, where antibiotic-resistant pathogens may have a higher prevalence and incidence. In Asian countries, antimicrobial resistance for common pathogens of hospital-acquired pneumonia (HAP), including methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) *Pseudomonas aeruginosa*, MDR *Acinetobacter* species, and extended-spectrum β-lactamase-producing (ESBL[+]) strains of *Escherichia coli* and *Klebsiella pneumoniae* has been documented.[1-5] In Singapore, it has been noted that antibiotic resistance is increasing among gram-negative bacilli and *S aureus*, both common pathogens in HAP.[6] Very high rates of MRSA, at least 70% of all *S aureus* isolates, have also been reported in Hong Kong and Japan.[7] Other common resistant pathogens include imipenem-resistant *P aeruginosa*, ceftazidime-resistant *A baumannii*, third-generation cephalosporin-resistant *K pneumoniae*, and fluoroquinolone-resistant *E coli*.[5] The prevalence of drug-resistant organisms has been a major rationale for development of the present consensus treatment recommendations for HAP in Asia. The following summarizes the findings of clinical microbiologists representing 10 Asian countries, relevant to the emergence of antibiotic-resistant pathogens of HAP.

From the Department of Laboratory Medicine, University of Santo Tomas, Espana, Manila; and St. Lukes Medical Center, E. Rodriguez Avenue, Quezon City, Philippines.

Address correspondence to Evelina N. Lagamayo, MD, Associate Professor, Department of Laboratory Medicine, University of Santo Tomas, Manila, Philippines. E-mail: evelagamayo@yahoo.com.

0196-6553/$34.00

doi:10.1016/j.ajic.2007.10.020

METHODS

An expert panel (Appendix) was convened comprising clinical microbiologists representing 10 Asian countries. The panel members exchanged and critically analyzed information regarding the etiologic distribution and antimicrobial resistance patterns of nosocomial pathogens causing HAP and ventilator-acquired pneumonia (VAP) in Asian hospitals. National and local surveillance data, where available, were analyzed on an individual hospital or individual country basis. Areas of incomplete knowledge were identified, and this, it is hoped, will be useful to define the direction of future surveillance and microbiologic studies.

Table 1. Overall incidence of HAP by major resistant pathogens methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Acinetobacter species, ESBL(+) *Klebsiella pneumoniae*, and ESBL(+) *Escherichia coli*

	Incidence (%) of HAP by specific pathogen					
	HAP (including VAP)			VAP		
Pathogen	Overall	Early	Late	Overall	Early	Late
MRSA	1-78	6-30	12-60	14.2-80	NR	NR
Ceftazidime-resistant P aeruginosa	0-30	0-10	1.5-30	12.9-35	NR	NR
Imipenem-resistant P aeruginosa	0-31	0-10	1.5-30	9.7-30	NR	NR
Ciprofloxacin-resistant *P aeruginosa*	0-39	1.2-30	0.8-40	9.7-40	NR	NR
MDR* *P aeruginosa*	0-20	0-10	0-20	16.1-25	NR	NR
Ceftazidime-resistant *Acinetobacter* species	0-76.3	0-15	2.7-40	40-87.3	NR	NR
Imipenem-resistant *Acinetobacter* species	0.9-30	0-5	1.1-30	14.5-70	NR	NR
MDR *Acinetobacter* species	1.2-87	0-10	1.5-40	35-96.4	NR	NR
ESBL(+) *K pneumoniae*	0.9-40	1.2-10	1.1-40	20-52.4	NR	NR
ESBL(+) *E coli*	2.3-40	1.2-10	2.7-40	11-55	NR	NR

MDR, multidrug resistant; *NR*, not reported.
*MDR means resistance to ≥3 classes of antibiotics.

OVERALL INCIDENCE OF HAP BY MAJOR RESISTANT PATHOGENS

Methicillin-resistant *S aureus*

For HAP, including data for VAP, the overall range of MRSA incidence was 1% to 78%. For early-onset HAP, the range was 6% to 30%, and, for late-onset HAP, an incidence of 12% to 60% was reported. For VAP cases, the incidence was 14.2% to 80% overall. No data were available regarding the incidence of MRSA in early- and late-onset VAP (Table 1).

The proportion of all *S aureus* clinical isolates that were MRSA was 29% to 70%. Among nosocomial infections, MRSA represented 8% to 80% of all clinical infections by *S aureus*, and, among intensive care unit (ICU) infections, MRSA represented 41% to 100%. For HAP cases, including VAP, the incidence of MRSA was 10.8% to 78% and, for VAP cases, 14.2% to 15%. Among MRSA strains, <5% exhibited reduced susceptibility to vancomycin and none exhibited resistance to linezolid (Table 2).

Table 2. Resistance in *Staphylococcus aureus*: MRSA

Incidence of MRSA	%
Per all clinical isolates of *S aureus*	29-70
Per nosocomial infections	8-80
Per ICU infections	41-100
Per HAP cases (including VAP)	10.8-78
Per VAP cases	14.2-15
MRSA with reduced susceptibility to vancomycin* (VISA or VRSA)	<5
MRSA with linezolid resistance†	0

VISA, vancomycin-intermediate *S aureus*; *VRSA*, vancomycin-resistant *S aureus*.
*Frequency of MRSA strains among all clinical infections by *S aureus*.
†Frequency of MRSA strains among all clinical isolates of MRSA.

P aeruginosa

In cases of HAP, including VAP, strains of *P aeruginosa* resistant to ceftazidime were reported to cause 0% to 30% of overall cases, 0% to 10% of early-onset cases, and 1.5% to 30% of late-onset cases. *P aeruginosa* resistant to imipenem was reported to cause 0% to 31% of overall cases, 0% to 10% of early-onset cases, and 1.5% to 30% of late-onset cases. *P aeruginosa* resistant to ciprofloxacin was reported to cause 0% to 39% of overall cases, 1.2% to 30% of early-onset cases, and 0.8% to 40% of late-onset cases. MDR *P aeruginosa* was associated with 0% to 20% of overall cases, 0% to 10% of early-onset cases, and 0% to 20% of late-onset cases (Table 1).

For VAP cases, the overall incidence of *P aeruginosa* resistance to ceftazidime was 12.9% to 35%, resistance to imipenem was 9.7% to 30%, resistance to ciprofloxacin was 9.7% to 40%, and resistance to multiple drugs was 16.1% to 25%. No data were available regarding the incidence of drug-resistant *P aeruginosa* in early- and late-onset VAP (Table 1).

The proportion of all *P aeruginosa* clinical isolates that were resistant to ceftazidime ranged from 3% to 48%. For cases of HAP (including VAP), the proportion ranged from 0% to 52% and, for VAP cases, 12.9% to 30%. Imipenem resistance was reported in 3% to 35% of all isolates of *P aeruginosa* overall, 0% to 31% of HAP cases (including VAP) and 0% to 31% of VAP cases. Ciprofloxacin resistance was reported in 4% to 44% of all clinical isolates of *P aeruginosa*, 0% to 39% of HAP cases (including VAP) and 9.7% to 40% of VAP cases. Resistance to piperacillin/tazobactam was reported in 2% to 30% of all isolates of *P aeruginosa*, 9.3% to 30% of all HAP cases (including VAP) and 9.7% to 30% of all VAP cases. Strains of *P aeruginosa* resistant to multiple drugs represented 14% to 23% of all clinical

Table 3. Resistance in *Pseudomonas aeruginosa*

Resistance in *Pseudomonas*	Incidence	%
Ceftazidime resistance	Per all isolates of *P aeruginosa*	3-48
	Per HAP cases (including VAP)	0-52
	Per VAP cases	12.9-30
Imipenem resistance	Per all isolates of *P aeruginosa*	3-35
	Per HAP cases (including VAP)	0-31
	Per VAP cases	9.7-30
Ciprofloxacin resistance	Per all isolates of *P aeruginosa*	4-44
	Per HAP cases (including VAP)	0-39
	Per VAP cases	9.7-40
Piperacillin-tazobactam resistance	Per all isolates of *P aeruginosa*	2-30
	Per HAP cases (including VAP)	9.3-30
	Per VAP cases	9.7-30
MDR (≥3 classes)	Per all isolates of *P aeruginosa*	14-23
	Per HAP cases (including VAP)	0-25
	Per VAP cases	16.1-30

isolates, 0% to 25% of HAP cases (including VAP) and 16.1% to 30% of VAP cases (Table 3).

Acinetobacter species

Overall, ceftazidime-resistant *Acinetobacter* species accounted for 0% to 76.3% of HAP cases (including VAP), 0% to 15% of early-onset cases and 2.7% to 40% of late-onset cases. Imipenem-resistant strains of *Acinetobacter* species represented 0.9% to 30% of overall HAP cases (including VAP), 0% to 5% of early-onset cases and 1.1% to 30% of late-onset cases. Multiple-drug resistance was reported in 1.2% to 87% of overall HAP cases (including VAP), 0% to 10% of early-onset cases and 1.5% to 40% of late-onset cases (Table 1).

Overall, VAP cases caused by ceftazidime-resistant *Acinetobacter* species ranged from 40% to 87.3%, those caused by imipenem-resistant strains ranged from 14.5% to 70%, and those caused by MDR *Acinetobacter* species ranged from 35% to 96.4%. No data were available regarding the incidence of drug-resistant *Acinetobacter* species in early- and late-onset VAP (Table 1).

The percentage of all *Acinetobacter* species clinical isolates resistant to imipenem ranged from 2% to 77%. For cases of HAP (including VAP), the percentage ranged from 0% to 68% and, for VAP cases, 14.5% to 20%. Ciprofloxacin resistance was reported in 23.2% to 92% of all isolates of *Acinetobacter* species overall, 0% to 86% of HAP cases (including VAP) and 40% to 92.7% of VAP cases. MDR *Acinetobacter* species was found in 25% to 66% of all clinical isolates, 1.2% to 87% of HAP cases (including VAP) and 30% to 96.4% of VAP cases. Pan-drug resistance (resistance to all antibiotic classes) was found in 0% to 30% of all clinical isolates, 0% to 46% of HAP cases (including VAP) and 3.6% to 20% of VAP cases (Table 4).

Table 4. Resistance in *Acinetobacter* species

Resistance in *Acinetobacter*	Incidence	%
Imipenem resistance	Per all isolates of *Acinetobacter*	2-77
	Per HAP cases (including VAP)	0-68
	Per VAP cases	14.5-20
Ciprofloxacin resistance	Per all isolates of *Acinetobacter*	23.2-92
	Per HAP cases (including VAP)	0-86
	Per VAP cases	40-92.7
MDR (≥3 classes)	Per all isolates of *Acinetobacter*	25-66
	Per HAP cases (including VAP)	1.2-87
	Per VAP cases	30-96.4
PDR (all antibiotic classes)	Per all isolates of *Acinetobacter*	0-30
	Per HAP cases (including VAP)	0-46
	Per VAP cases	3.6-20

MDR, multidrug resistant; *PDR*, pan drug resistant.

K pneumoniae

The overall incidence of ESBL-producing *K pneumoniae* was 0.9% to 40% of cases of HAP (including VAP). The incidence ranged from 0% to 10% for early-onset cases and from 1.1% to 40% for late-onset cases. For VAP cases, the overall incidence of *K pneumoniae* producing ESBL was 20% to 52.4%. No data were available regarding the incidence of ESBL(+) *K pneumoniae* in early- and late-onset VAP (Table 1).

The proportion of all *K pneumoniae* clinical isolates that were resistant to ceftriaxone ranged from 4% to 60%. For cases of HAP (including VAP), the proportion ranged from 0.3% to 40% and, for VAP cases, 50% to 60%. Imipenem resistance was reported in 0% to 24% of all isolates of *K pneumoniae* overall, 0% to 50.9% of HAP cases (including VAP) and 1% to 57.1% of VAP cases. Ciprofloxacin resistance was reported in 13% to 68% of all clinical isolates, 0.3% to 18% of HAP cases (including VAP) and 10% to 40% of VAP cases. Resistance to piperacillin/tazobactam was reported in 10% to 37% of all isolates of *K pneumoniae*, 0.3% to 8% of all HAP cases (including VAP) and 5% to 15% of all VAP cases. ESBL-producing *K pneumoniae* represented 11% to 45% of all clinical isolates, 0.9% to 35% of HAP cases (including VAP) and 20% to 52.4% of VAP cases (Table 5).

E coli

The overall incidence of ESBL-producing *E coli* was 2.3% to 40% of cases of HAP (including VAP). The incidence ranged from 1.2% to 10% for early-onset cases and from 2.7% to 40% for late-onset cases. For VAP cases, the overall incidence of *E coli* producing ESBL was 11% to 55%. No data were available regarding the incidence of ESBL(+) *E coli* in early- and late-onset VAP (Table 1).

Table 5. Resistance in *Klebsiella pneumoniae*

Resistance in *K pneumoniae*	Incidence	%
Cefriaxone resistance	Per all isolates of *K pneumoniae*	4-60
	Per HAP cases (including VAP)	0.3-40
	Per VAP cases	50-60
Imipenem resistance	Per all isolates of *K pneumoniae*	0-24
	Per HAP cases (including VAP)	0-50.9
	Per VAP cases	1-57.1
Ciprofloxacin resistance	Per all isolates of *K pneumoniae*	13-68
	Per HAP cases (including VAP)	0.3-18
	Per VAP cases	10-40
Piperacillin-tazobactam resistance	Per all isolates of *K pneumoniae*	10-37
	Per HAP cases (including VAP)	0.3-8
	Per VAP cases	5-15
ESBL (+)	Per all isolates of *K pneumoniae*	11-45
	Per HAP cases (including VAP)	0.9-35
	Per VAP cases	20-52.4

Table 6. Resistance in *Escherichia coli*

Resistance in *E coli*	Incidence	%
Cefriaxone resistance	Per all isolates of *E coli*	10-60
	Per HAP cases (including VAP)	2.3-53
	Per VAP cases	50-60
Imipenem resistance	Per all isolates of *E coli*	0-10
	Per HAP cases (including VAP)	0-10
	Per VAP cases	0
Ciprofloxacin resistance	Per all isolates of *E coli*	26-80
	Per HAP cases (including VAP)	2.6-55
	Per VAP cases	50-80
Piperacillin-tazobactam resistance	Per all isolates of *E coli*	5-39
	Per HAP cases (including VAP)	0-13
	Per VAP cases	10
ESBL (+)	Per all isolates of *E coli*	8-50
	Per HAP cases (including VAP)	2.3-40
	Per VAP cases	50-60

The proportion of all *E coli* clinical isolates resistant to ceftriaxone ranged from 10% to 60%. For cases of HAP (including VAP), the proportion ranged from 2.3% to 53% and, for VAP cases, 50% to 60%. Imipenem resistance was reported in 0% to 10% of all isolates of *E coli* overall and 0% to 10% of HAP cases (including VAP). No imipenem resistance was reported for VAP cases. Ciprofloxacin resistance was reported in 26% to 80% of all clinical isolates, 26% to 55% of HAP cases (including VAP) and 50% to 80% of VAP cases. Resistance to piperacillin/tazobactam was reported in 5% to 39% of all isolates of *E coli*, 0% to 13% of all HAP cases (including VAP) and 10% of all VAP cases. ESBL-producing *E coli* represented 8% to 50% of all clinical isolates, 2.3% to 40% of HAP cases (including VAP) and 50% to 60% of VAP cases (Table 6).

DISCUSSION

In general, *P aeruginosa*, *Acinetobacter* species, MRSA, and ESBL(+) *E coli* and *K pneumoniae* are the most common pathogens of HAP and VAP in Asian countries. In the present analysis, the 2 most common drug-resistant pathogens causing HAP are methicillin-resistant *S aureus* and MDR *Acinetobacter* species. In Korea and Taiwan, MRSA was most common, representing 50% to 70% of all *S aureus* isolates in Korea[4,8] and 53% to 83% of all *S aureus* clinical isolates in Taiwan.[9] In Taiwan, *S aureus* isolates have been reported that are resistant to oxacillin (66% of all isolates) and penicillin (8% of all isolates).[10] In a recent analysis[11] of 215,501 isolates from 44 Korean hospitals, *S aureus* (20.0% of all isolates) was found to be resistant to oxacillin (68%), clindamycin (59%), and cotrimoxazole (16%). Resistance to erythromycin, tetracycline, gentamicin, and ciprofloxacin has also been documented.[12]

Previously, it has been reported that Hong Kong has one of the highest prevalence rates of MRSA among hospitals within the Asia-Pacific region.[13,14] The panel estimated that, in ICU respiratory isolates, 9% are identified as *S aureus*, and up to 80% of these are MRSA. Other countries reported a lower incidence of MRSA (as a proportion of *S aureus* isolates), 18% in the Philippines in 2004[15] and 31% overall in 2005, 31% in India,[16] 42% in Pakistan,[17] and 38% in Malaysia.

S aureus strains with intermediate resistance to vancomycin have been reported in Korea and, in the past, in Hong Kong.[18] In Thailand, heterogeneous resistance to vancomycin or reduced susceptibility to vancomycin have been reported. Reports exist from 3 Thai hospitals,[19] a 2001 report from Eastern Thailand (2 hospitals) and a 2005 report from southern Thailand[20,21] and from the ANSORP study group. Data from the ANSORP study group documented the emergence of 2 hetero-VISA strains in Thailand between 1997 and 2000.[22] Recently, a Korean strain having a minimum inhibitory concentration of 4 μg/mL has been reported.[23] The panel also noted the existence in Singapore of a small number of unpublished cases of hetero-VISA strains of *S aureus*, typically in patients receiving long-term vancomycin therapy.

MDR *Acinetobacter* species were found to be highly prevalent in many Asian countries, in particular Thailand and India. In Thailand, one study reported that *Acinetobacter* species caused 44% or 69% of cases of nosocomial pneumonia in ICU neonates,[24] and another prospective study in ICU patients with device-associated nosocomial infections reported that the incidence of ceftazidime-resistant *A baumannii* was 69%.[5] The panel noted that, in Thailand, approximately 70% to 80% of *Acinetobacter* species are MDR, and, in 2003, the prevalence of pan-drug resistant strains was

estimated to be 46%. In Thailand, the sensitivity of *A baumannii* to amikacin was noted to be low, and netilmicin and cefoperazone/sulbactam are the preferred treatments. If MDR or pan-drug resistant strains are suspected, treatment options include colistin or polymyxin B. As in Thailand, in India, *Acinetobacter* species have been found to be an important nosocomial pathogen in ICU patients, accounting for 25% of all infections (46% of which were respiratory infections)[25] and displaying a high resistance to most antibacterial agents.[26] MDR *Acinetobacter* species are very common in India, and the panel noted the routine use of colistin in many Indian hospitals. The use of colistin for the treatment of MDR *Acinetobacter*-associated VAP has been described[27] and was recently reviewed.[28] In Korea, KONSAR data[11] shows that *Acinetobacter* species (7.4% of all isolates) were resistant to all antimicrobial agents except cefoperazone-sulbactam (15%) and imipenem (13%). Overall, 18.3% of *Acinetobacter* species was resistant to all drugs tested. A recent Korean study described *Acinetobacter* isolates from sputum that were nonsusceptible to imipenem.[29]

In China, a study[30] in 2004 reported that all *A baumannii* isolates were resistant to multiple antibiotics including meropenem. In that study, 72% to 78% were resistant to third- and fourth-generation cephalosporins. In Taiwan, a published study reported that 6% of *Acinetobacter baumannii* isolates were resistant to all available drugs, and 22% were resistant to imipenem.[10] Current estimates are that, in cases of HAP or VAP, approximately 80% of *A baumannii* isolates are resistant to ceftazidime or fluoroquinolone, and less than 15% are resistant to imipenem. In Singapore, data presented by the panel indicate that, among *Acinetobacter* species, approximately 50% was susceptible to aminoglycosides, yet only approximately 20% was susceptible to carbapenems. The overall rate of drug resistance in *Acinetobacter* species is 84%, whereas that in VAP cases is 60% to 70%. In Pakistan, the panel reported that there has also been a recent rise in the incidence of MDR *Acinetobacter* species. On the other hand, a multicenter study[31] reported that *Acinetobacter* species in the Philippines were yet highly susceptible (87.5% each) to the fourth-generation cephalosporins cefepime and cefpirome.

Gram-negative bacilli producing ESBL appear to be on the rise in some Asian countries and pose a serious problem in pulmonary infections. Often, these strains are cross-resistant to other classes of drugs, such as fluoroquinolones and aminoglycosides. The incidence of ESBL-producing bacilli appears to be highest in India. Published studies have reported that the proportion of *Klebsiella* species producing ESBL range from 71% to 87%,[32,33] and, for *E coli* strains, the proportion is 64%.[33] Studies from Thailand[34,35] report that, overall, ESBL production among gram-negative bacilli is 30%. Among *K pneumoniae*, 44% to 57% are ESBL producers, and, among *E coli* strains, 5.1% are ESBL producers. Data presented from the panel report a higher incidence of ESBL-producing *E coli* in Thailand, 15% to 40%, and a higher incidence of quinolone resistance, approximately 50%, than reported in the literature. A multicenter study[10] in Taiwan showed that 12% of *E coli* was ESBL producing, and 11% of *Klebsiella* was ESBL producing. In recent years, this percentage has been rising, increasing to 15% of *E coli* isolates and 29% of *Klebsiella* species isolates as of 2005. Data presented at this workshop, albeit representing 1 hospital, showed that ESBL-producing *Klebsiella* in Taiwan represents 15% of all clinical isolates, 25% of *Klebsiella* in HAP cases and 15% of *Klebsiella* in VAP cases. A limited number of HAP cases because of infection with *E coli* were available for analysis, and these indicated that approximately one third of isolates were ESBL producers. A Chinese multicenter study[36] reported that the prevalence of ESBL production in *E coli* and *K pneumoniae* increased from 11% to 34% from 1994-2001. Studies from Hong Kong report that 11% to 14% of *E coli* and *Klebsiella* species were ESBL producers,[37,38] and data presented by the panel show that ESBL-producing *E coli* accounts for 2.3% of HAP cases, whereas *Klebsiella* species account for 0.9% of HAP cases. In Malaysia, the incidence of ESBL-producing *E coli* is estimated at 7% to 8%. From Pakistan, only general information was available. Studies in local Pakistani journals have shown that the proportion of ESBL-producing organisms among nosocomial gram-negative bacilli is currently 36% to 52% and continues to rise.[39]

Resistance to multiple drugs among ESBL(+) gram-negative bacteria appears to be quite high in some Asian countries. A study[32] from a major hospital in New Delhi found that 39% to 88% of *K pneumoniae* isolates were resistant to third- and fourth-generation cephalosporins, whereas 51% to 90% were resistant to aztreonam, piperacillin, chloramphenicol, or trimethoprim-sulfamethoxazole. In a multicenter Indian surveillance study,[40] resistance was reported to piperacillin/tazobactam (23%), ciprofloxacin (57%), aminoglycosides (60%-65%), and other β-lactam drugs (60%-70%). The indiscriminate use of third-generation cephalosporins has been proposed as a reason for the rise of ESBL-producing strains in India.[33] Increased antibiotic use may be related to the introduction, in 2003, of less expensive, more widely available generic formulations into the market.

In Taiwan, published data show that 70% of ESBL(+) *E coli* strains and 63% of ESBL(+) *Klebsiella* species were resistant to ciprofloxacin.[41] Resistance to amikacin was 19% for *E coli* and 28% for *Klebsiella*. In a prospective study in Thailand[5] of ICU patients (including

VAP cases), 38% of *E coli* was resistant to quinolones, and 45% of *K pneumoniae* was resistant to third-generation cephalosporins. In Korea, KONSAR data[11] shows, similarly, that *E coli* (18.9% of all isolates) is resistant to cefotaxime (11%), cefoxitin (8%), fluoroquinolone (33%), and piperacillin-tazobactam (5%). *K pneumoniae* (8.6% of all isolates) was reported to be resistant to ceftazidime (25%), cefoxitin (23%), and piperacillin-tazobactam (14%). Based on data from Hong Kong in 2000,[37] ESBL-producing bacilli were highly susceptible to third-generation cephalosporins (>98% to cefpodoxime and ceftriaxone), yet the panel noted that resistance has since increased markedly and estimated the rate at 25% for ceftriaxone versus *E coli* and 16% versus *Klebsiella* species. Resistance to ciprofloxacin was noted to be approximately 36% in *E coli* and 13% in *Klebsiella* species. Resistance to piperacillin/tazobactam in *Klebsiella* species was estimated to be 12%. A multicenter study[31] in the Philippines reported that ceftazidime-resistant *E coli* and *Klebsiella* species occurred at rates of 13.3% and 31.1%, respectively. Cefepime and cefpirome were 97.8% to 100% active in vitro against these ESBL phenotypes.

To date, resistance to imipenem among ESBL(+) bacilli has not been noted in the literature to an appreciable extent in Asian countries. In Korea, resistance to imipenem was reported in 0.1% of *E coli* isolates and 0.3% of *K pneumoniae* isolates.[11] In Hong Kong,[37] no imipenem resistance was noted in *E coli* strains, but 1% of *Klebsiella* species strains was found to be resistant. An Indian multicenter surveillance study[40] reported that 99.1% of organisms was susceptible to meropenem. A Chinese multicenter study[42] reported that susceptibility to imipenem was 95% to 100% for *K pneumoniae* and 99% to 100% for *E coli*. In Malaysia, resistance to imipenem is estimated at <1%. Resistance has not been observed in Thailand, Taiwan,[41] or the Philippines.[31] In Pakistan, the panel reported that overall resistance to antibiotics is very high, especially as observed over the past 2 to 3 years. Overall, 12% to 13% of *Klebsiella* species were resistant to carbapenems and tazobactam; *E coli* strains were found to be resistant to ceftriaxone, imipenem, and ciprofloxacin.

Resistance in *P aeruginosa* to 1 or more antimicrobial agent has been documented in the literature. Studies from Thailand,[43] Taiwan,[10] and Korea[11] report that 19% to 24% of *P aeruginosa* isolates were resistant to ceftazidime and that 15% to 20% were resistant to imipenem[10,11] Members of the panel noted that, in Thailand, MDR *P aeruginosa* also demonstrates resistance to carbenem (approximately 30%), ciprofloxacin (20%-25%), and piperacillin-tazobactam (20%). In Hong Kong, the prevalence of MDR *P aeruginosa* was noted to vary between different medical centers. Overall drug resistance in *P aeruginosa*, as of 2005, was reported to be generally low, ranging from 0% to 4% for cefotaxime, ceftazidime, imipenem, piperacillin/tazobactam, or ciprofloxacin but may be higher in some hospitals. In one large hospital in Singapore, the susceptibility of clinical isolates of *Pseudomonas* species to carbapenem, ceftazidime, or amikacin ranged from approximately 60% to 70% and remained high (at least 30%) when evaluating total cases, ICU cases, or HAP cases. A multicenter study[31] in the Philippines reported that piperacillin/tazobactam was most effective against *P aeruginosa* (80% susceptible). The panel reported that, recently, in the Philippines, resistance has arisen in *P aeruginosa* against cefoperazone when used as a single agent. In current practice, combination treatment with cefoperazone/sulbactam is preferred.

Despite the importance of the findings presented in this study, there are several limitations that should be taken into consideration when assessing our conclusions. First, our results center around the findings of a collective expert panel, which can be very subjective, wherein the individually analyzed national and local surveillance data may not be free of bias. Without the reliance on formal or structured evaluation methods, the data gleaned from this exchange may not be uniformly measured.

In addition, there are inherent difficulties in compiling and comparing different sources of data from individual hospitals and local and national surveillance across many nations. Because of the varied availability and nature of the data collected, the surveillance data between countries are not comparable, and the comparisons we make are not always justified, which creates problems with the reliability, homogeneity, and generalizability of the data. Future studies would benefit from collaboration networks in the Asian-Pacific region.

Last, a discussion of antibiotic use patterns and antibiotic control programs is absent because such topics were not addressed by this panel. These key subjects are critical to our understanding of HAP/VAP epidemiology and etiology and should be included in future antimicrobial resistance studies in this region.

SUMMARY

An informal survey of etiologic pathogens in Asian countries revealed that MRSA is most common in Korea and Taiwan, whereas *Acinetobacter* species are most common in Malaysia, Thailand, Pakistan, and India. National surveillance data are lacking in many countries, and very little data exist that are specific to nosocomially acquired pneumonia, be it HAP or VAP. Overall, MRSA, *Acinetobacter* species, ESBL-producing *E coli* and *Klebsiella*, and *P aeruginosa* were found to be the most common pathogens causing HAP and

VAP in Asian countries. Better knowledge of local patterns of pathogen distribution can help facilitate treatment choices.

References

1. Prashanth K, Badrinath S. Epidemiological investigation of nosocomial Acinetobacter infections using arbitrarily primed PCR and pulse-field gel electrophoresis. Indian J Med Res 2005;122:408-18.
2. Lee K, Yum JH, Yong D, Lee HM, Kim HD, Docquier JD, et al. Novel acquired metallo-β-lactamase gene, bla(SIM-1), in a class 1 integron from *Acinetobacter baumannii* clinical isolates from Korea. Antimicrob Agents Chemother 2005;49:4485-91.
3. Hughes AJ, Ariffin N, Huat TL, Abdul Molok H, Hashim S, Sarijo J, et al. Prevalence of nosocomial infection and antibiotic use at a university medical center in Malaysia. Infect Control Hosp Epidemiol 2005; 26:100-4.
4. Lee HJ, Suh JT, Kim YS, Lenz W, Bierbaum G, Schaal KP. Typing and antimicrobial susceptibilities of methicillin-resistant *Staphylococcus aureus* (MRSA) strains isolated in a hospital in Korea. J Korean Med Sci 2001;16:381-5.
5. Thongpiyapoom S, Narong MN, Suwalak N, Jamulitrat S, Intaraksa P, Boonrat J, et al. Device-associated infections and patterns of antimicrobial resistance in a medical-surgical intensive care unit in a university hospital in Thailand. J Med Assoc Thai 2004;87:819-24.
6. Lim TK. Emerging pathogens for pneumonia in Singapore. Ann Acad Med Singapore 1997;26:651-8.
7. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J, Jones RN, et al; SENTRY Partcipants Group. Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. Clin Infect Dis 2001;32(Suppl 2):S114-32.
8. Kim HB, Park WB, Lee KD, Choi YJ, Park SW, Oh MD, et al. Nationwide surveillance for Staphylococcus aureus with reduced susceptibility to vancomycin in Korea. J Clin Microbiol 2003;41:2279-81.
9. Hsueh PR, Liu CY, Luh KT. Current status of antimicrobial resistance in Taiwan. Emerg Infect Dis 2002;8:132-7.
10. Hsueh PR, Liu YC, Yang D, Yan JJ, Wu TL, Huang WK, et al. Multicenter surveillance of antimicrobial resistance of major bacterial pathogens in intensive care units in 2000 in Taiwan. Microb Drug Resist 2001;7:373-82.
11. Lee K, Park KH, Jeong SH, Lim HS, Shin JH, Yong D, et al. Further increase of vancomycin-resistant *Enterococcus faecium*, amikacin- and fluoroquinolone-resistant *Klebsiella pneumoniae*, and imipenem-resistant *Acinetobacter* species in Korea: 2003 KONSAR surveillance. Yonsei Med J 2006;47:43-54.
12. Lee K, Kim YA, Park YJ, Lee HS, Kim MY, Kim E-C, et al. Increasing prevalence of vancomycin-resistant enterococci, and cefoxitin-, imipenem- and fluoroquinolone-resistant gram-negative bacilli: a KONSAR Study in 2002. Yonsei Med J 2004;45:598-608.
13. Bell JM, Turnidge JD. High prevalence of oxacillin-resistant *Staphylococcus aureus* isolates from hospitalized patients in Asia-Pacific and South Africa: results from SENTRY Antimicrobial Surveillance Program, 1998-1999. Antimicrob Agents Chemother 2002;46:879-81.
14. Ip MD, Lyon DJ, Chio F, Cheng AF. A longitudinal analysis of methicillin-resistant *Staphylococcus aureus* in a Hong Kong teaching hospital. Infect Control Hosp Epidemiol 2004;25:126-9.
15. Carlos CC. The 2004 Antimicrobial resistance surveillance data in the Philippines. Phil J Microbiol Infect Dis 2005;34:53-7.
16. Rajaduraipandi K, Mani KR, Panneerselvam K, Mani M, Bhaskar M, Manikandan P. Prevalence and antimicrobial susceptibility pattern of methicillin-resistant *Staphylococcus aureus*: a multicentre study. Indian J Med Microbiol 2006;24:34-8.
17. Hafiz S, Hafiz AN, Ali L, Chughtai AS, Memon B, Ahmed A, et al. Methicillin-resistant *Staphylococcus aureus*: a multicenter study. J Pak Med Assoc 2002;52:312-5.
18. Linares J. The VISA/GISA problem: therapeutic implications. Clin Microbiol Infect 2001;7(Suppl 4):8-15.
19. Trakulsomboon S, Danchaivijtr S, Rongrungruang Y, Dhiraputra C, Susaemgrat W, Ito T, et al. First report of methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin in Thailand. J Clin Microbiol 2001;39:591-5.
20. Lulitanond A, Chanawong A, Sribenjalux P, Kaewkes W, Charoensri N, Leumsai D, et al. Occurrence of methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin in Srinagarind Hospital. J Infect Dis Antimicrob Agents 2005;22:9-14.
21. Phongsamart W, Sriefungfung S, Tiensasitorn C, Vanprapar N, Chearskul S, Chokephaibulkit K. The first pediatric case of *Staphylococcus aureus* with heterogenous resistant to vancomycin endocarditis in Thailand. J Med Assoc Thai 2005;88(Suppl 8):S264-8.
22. Song JH, Hirmatsu K, Suh JY, Ko KS, Ito T, Kapi M, et alAsian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group. Emergence in Asian countries of *Staphylococcus aureus* with reduced susceptibility to vancomycin. Antimicrob Agents Chemother 2004;48:4926-8.
23. Kim HB, Lee YS, Kim BS, Cha JO, Kwon SU, Lee HJ, et al. Prevalence and clinical implications of *Staphylococcus aureus* with a vancomycin MIC of 4 mcg/mL in Korea. Microb Drug Resist 2006;12:33-8.
24. Petdachai W. Nosocomial pneumonia in a newborn intensive care unit. J Med Assoc Thai 2000;83:392-7.
25. Suri A, Mahapatra AK, Kapil A. Acinetobacter infection in neurosurgical intensive care patients. Natl Med J India 2000;13:296-300.
26. Singh AK, Sen MR, Anapurba S, Bhattacharya P. Antibiotic sensitivity pattern of the bacteria isolated from nosocomial infections in ICU. J Commun Dis 2002;34:257-63.
27. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-Wittell M, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111-8.
28. Falagas ME, Kasiakou SK, Tsiodras S, Michalopoulos A. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. Clin Med Res 2006;4:138-46.
29. Lee K, Ha GY, Shin BM, Kim JJ, Kang JO, Jang SJ, et al. Metallo-β-lactamase-producing gram-negative bacilli in Korean Nationwide Surveillance of Antimicrobial Resistance group hospitals in 2003: continued prevalence of VIM-producing *Pseudomonas* spp. and increase of IMP-producing *Acinetobacter* spp. Diagn Microbiol Infect Dis 2004;50:51-8.
30. Yu YS, Yang Q, Xu XW, Hs Kong, Xu GY, Zhong BY. Typing and characterization of carbapenem-resistant *Acinetobacter calcoaceticus-baumannii* complex in a Chinese hospital. J Med Microbiol 2004;53: 653-6.
31. Johnson DM, Biedenbach DJ, Jones RN. In vitro evaluation of broad-spectrum β-lactams in the Philippines medical centers: role of fourth-generation cephalosporins. The Philippines Antimicrobial Resistance Study Group. Diagn Microbiol Infect Dis 1999;35:291-7.
32. Grover SS, Sharma M, Pasha ST, Singh G, Lal S. Antimicrobial susceptibility pattern and prevalence of extended spectrum β-lactamase (ESBLs) producing strains of *Klebsiella pneumoniae* from a major hospital in New Delhi. J Commun Dis 2004;36:17-26.
33. Jain A, Roy I, Gupta MK, Kumar M, Agarwal SK. Prevalence of extended-spectrum β-lactamase-producing gram-negative bacteria in septicaemic neonates in a tertiary carehospital. J Med Microbiol 2003;52:421-5.
34. Jitsurong S, Yodsawat J. Prevalence of extended-spectrum β-lactamases (ESBLs) produced in blood isolates of gram-negative bacteria in a teaching hospital in southern Thailand. Southeast Asian J Trop Med Public Health 2006;37:131-5.

35. Chayakulkeeree M, Junsriwong P, Keerasuntonpong A, Tribuddharat C, Thamlikitkul V. Epidemiology of extended-spectrum β-lactamase producing gram-negative bacilli in Siriraj Hyospital, Thailand, 2003. Southeast Asian J Trop Med Public Health 2005;36:1503-9.
36. Chen MJ, Wang H, China Nosocomial Pathogens Resistance Surveillance Study Group. Continuous surveillance of antimicrobial resistance among nosocomial gram-negative bacilli from intensive care units in China (article in Chinese). Zhonghua Yi Xue Za Zhi 2003;10:375-81.
37. Ho PL, Tsang DN, Que TL, Ho M, Yuen KY. Comparison of screening methods for detection of extended-spectrum β-lactamases and their prevalence among *Escherichia coli* and *Klebsiella* species in Hong Kong. APMIS 2000;108:237-40.
38. Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, Kawakami S, Miyazawa Y, et al. Regional variation in the prevalence of extended-spectrum β-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998-2002). Diagn Microbiol Infect Dis 2005;52:323-9.
39. Jabeen K, Zafar A, Hasan R. Frequency and sensitivity pattern of extended spectrum β-lactamase-producing isolates in a tertiary care hospital laboratory of Pakistan. J Pak Med Asoc 2005;55:436-9.
40. Jones RN, Rhomberg PR, Varnam DJ, Mathai D. A comparison of the antimicrobial activity of meropenem and selected broad-spectrum antimicrobials tested against multi-drug resistant gram-negative bacilli including bacteraemic *Salmonella* spp.: initial studies for the MYSTIC programme in India. Int J Antimicrob Agents 2002;20:426-31.
41. Liao CH, Sheng WH, Want JT, Sun HY, Wang HK, Hsueh PR, et al. In vitro activities of 16 antimicrobial agents against clinical isolates of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in two regional hospitals in Taiwan. J Microbiol Immunol Infect 2006;39:59-66.
42. Wang H, Chen M, China Nosocomial Pathogens Resistance Surveillance Group. Surveillance for antimicrobial resistance among clinical isolates of gram-negative bacteria from intensive care unit patients in China, 1996 to 2002. Diagn Microbiol Infect Dis 2005;51:201-8.
43. Girlich D, Naas T, Leelaporn A, Poirel L, Fennewald M, Nordmann P. Nosocomial spread of the integron-located veb-1-like cassette encoding an extended-spectrum β-lactamase in *Pseudomonas aeruginosa* in Thailand. Clin Infect Dis 2002;34:603-11.

APPENDIX

Panel members of Asian HAP Working Group were (in alphabetical order) the folowing: Jae-Hoon Song, MD, PhD (organizer) Samsung Medical Center, Korea; Altaf Ahmed, MD, Liaquat National Hospital, Pakistan; Nor Liza Ariffin, MD, University Malaya, Malaysia; Rajesh Chawla, MD, Indraprastha Apollo Hospital, India; Manolito Chua, MD, Research Institute for Tropical Medicine, Philippines; Tulsi Chugh, MD, SGR Hospital, India; Renato Dantes, MD, University of Philippines, Philippine General Hospital, Philippines; Po-Ren Hsueh, MD, National Taiwan University Hospital, Taiwan, R. O. C.; Bi Jie Hu, MD, Zhongshan Hospital of Fudan University, Shanghai, China; Yhu-Chering Huang, MD, PhD, Chang Gung Children's Hospital, Taiwan R. O. C.; Muhammad Jawed, MB, BS, Liaquat National Hospital, Pakistan; Ki-Suck Jung, MD, PhD, Hallym University Sacred Heart Hospital, South Korea; Lalitha Kesavan, MD, Christian Medical College, India; Wen-Chien Ko, MD, National Cheng Kung University Hospital, Taiwan R. O. C.; KiTae Kwon, MD, Samsung Medical Center, Korea; Raymond Wai Man Lai, MB, ChB, FRCPA, FHKAM, Prince of Wales Hospital, Hong Kong; Kyungwon Lee, MD, PhD, Yonsei Univ College of Medicine Severance Hospital, South Korea; Amorn Leelarasamee, MD, Siriraj Hospital, Mahidol University, Thailand; Tzer Pin Raymond Lin, MD; Roslina Abdul Manap, MMED, MRCP, Hospital University Kebangsaa Malaysia, Malaysia; Naseem Salahuddin, ABMI, FACP, Liaquat National Hospital, Pakistan; Raman Sardana, MD, Indraprastha Apollo Hospital, India; Thomas So, FRCP, FHKAM, Princess Margaret Hospital, Hong Kong; Chusana Suankratay, MD, PhD, Chulalangkorn University, Thailand; Paul Tambyah, MD, National University of Singapore, Singapore; Hui Wang, PhD, Peking Union Medical College, China; Adisom Wongsa, MD, Yonghong Xiao, PhD, Institute of Clinical Pharmacology, Peking University, China; Rohani Yasin, MD, Institute of Medical Research, Malaysia.