Treatment recommendations of hospital-acquired pneumonia in Asian countries: first consensus report by the Asian HAP Working Group

Jae-Hoon Song, MD, PhD, and the Asian HAP Working Group
Seoul, Korea

Many different treatment options are available for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), which are important causes of morbidity and mortality. Although guidelines for the diagnosis and treatment of HAP and VAP have been published by various American and European societies, these guidelines may not be applicable in all respects to the diagnosis and treatment of HAP and VAP in Asian countries. In addition, clinical practice may vary among Asian countries, due to such factors as availability of specific antibiotics and formulations and their relative cost. In addition, and in particular, different epidemiologic, etiologic, and resistance patterns in Asian countries may affect treatment choices compared with those in Western countries. To address these issues, the Asian-Pacific Research Foundation for Infectious Diseases, together with the Asian Network for Surveillance of Resistant Pathogens, organized the Asian HAP Working Group to discuss current clinical practices and develop consensus treatment recommendations for HAP in Asian countries. The consensus treatment recommendations, summarized herein, represent the findings of an expert panel comprising 30 representatives from 10 Asian countries. (Am J Infect Control 2008;36:S83-92.)

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are serious diseases that are often difficult to treat in clinical practice, resulting in high rates of morbidity and mortality worldwide. Many different treatment options are available. Currently available guidelines for diagnosis and treatment include those prepared by a joint committee of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA)[1] and by the British Thoracic Society.[2]

Although many Asian clinicians follow the general recommendations of the ATS/IDSA guidelines, others follow institutional recommendations or national guidelines when available. Several issues have greater relevance to infectious disease practice in Asian countries compared with other countries; these include, among others, variations in practice due to the epidemiology of HAP, prevalence of multidrug-resistant (MDR) pathogens, practice of antibiotic use, and availability, formulation, and cost of antibiotics. In particular, antimicrobial resistance patterns in Asia may be quite different from those found in the United States and other Western countries, with markedly higher incidences of methicillin-resistant *Staphlyococcus aureus* (MRSA) and MDR pathogens. Some of the most serious pathogens are multidrug- or pandrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* strains, which are resistant to most available treatments. Antimicrobial resistance can lead to inappropriate use of antimicrobial agents, such as overly frequent use or misuse, resulting in more resistance as well as clinical treatment failure. The prevalence of these pathogens has global significance, and this topic is of timely importance for practicing clinicians throughout the Asia-Pacific region.

Recently, the Asian-Pacific Research Foundation for Infectious Diseases (ARFID), in conjunction with the Asian Network for Surveillance of Resistant Pathogens (ANSORP), organized the Asian HAP Working Group to discuss the consensus treatment recommendations for HAP in Asian countries based on the current epidemiologic situation in the region. The first working group meeting, held in Kuala Lumpur, Malaysia on April 22–23, 2006, brought together 30 physicians from 10 Asian countries (Malaysia, Thailand, China, South Korea, India, Taiwan, Hong Kong, Pakistan, Philippines, and Singapore). A list of participants is provided in the

From the Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Asian Network for Surveillance of Resistant Pathogens (ANSORP); and Asian-Pacific Research Foundation for Infectious Diseases (ARFID).

Address correspondence to Jae-Hoon Song, MD, PhD, Division of Infectious Diseases, Samsung Medical Center, 50 IL-won dong, Kangnam-ku, Seoul 135-710, Korea. E-mail: songjh@skku.edu.

Funding: The Asian HAP Working Group meeting was supported by Wyeth Pharmaceuticals and SCS Healthcare.

Conflict of interest: The author has no commercial or other association that might pose a conflict of interest.

0196-6553/$34.00

doi:10.1016/j.ajic.2007.01.015

Appendix. A primary purpose of the meeting was to develop a consensus guideline regarding the best available practices for the treatment of HAP and VAP in these countries. Secondarily, the workshop aimed to further inform the recently published ATS/IDSA guidelines in regard to issues relevant to clinical practice in Asian countries. In this article, we summarize the consensus recommendations generated at this meeting.

METHODOLOGY

Existing governmental and institutional guidelines for the treatment of HAP and VAP in Asian countries, where available, were reviewed on an individual country or individual hospital basis. International guidelines for the treatment of HAP and VAP, including but not limited to the ATS/IDSA guidelines, also were considered, together with international epidemiologic data. Individual physicians representing 10 Asian countries supplemented this with national or local data on epidemiology, etiologic pathogens, diagnostic procedures, antimicrobial resistance, and empirical antimicrobial treatment regimens. Information regarding clinical practice issues in Asian countries was exchanged among the participants and critically analyzed. As the need for further data was identified, insofar as possible, such data were collected and added to the summary draft consensus recommendation.

It was noted that knowledge gaps currently exist regarding evidence or data on the epidemiology, etiology, and antibiotic resistance of pathogens causing HAP and VAP in Asian countries. Evidence-based recommendations specific to clinical practice in Asia can be addressed in only certain areas of clinical practice. This situation is neither surprising nor new. The recent ATS/IDSA guidelines also acknowledge this limitation and emphasize VAP-related treatment issues, because fewer data are available regarding HAP in nonintubated patients. Nonetheless, the evaluation of the current evidence base, and the identification of areas of incomplete knowledge, is considered to be of value in itself to help shape the direction of future research studies.

The expert consensus opinion achieved in the workshop and reported herein is considered an initial step in identifying the best available clinical practices in Asian hospitals. It is understood and expected that in the future, as more relevant data become available, these recommendations will be adapted and modified to reflect a changing evidence base.

NATIONAL AND LOCAL GUIDELINES

Only a few Asian countries have national guidelines for the antibiotic treatment of HAP and VAP (China, the Philippines, Hong Kong, and Taiwan). Two countries, the Philippines and Taiwan, are expected to publish national guidelines for the first time. Earlier guidelines used in Hong Kong (IMPACT guidelines) were updated in 2005.[3] National guidelines used in China are currently under revision.[4] Individual institutional guidelines from Singapore were reviewed; in addition, national guidelines from Singapore for the treatment of HAP have recently been made available.

It was noted that many physicians in Asia are guided by the ATS/IDSA recommendations to greater or lesser degrees, and that some national guidelines (eg, Philippines, Taiwan) also adhere closely to the ATS/IDSA guidelines, with minor modifications. It was agreed that the availability of better surveillance data for HAP and VAP could facilitate the development of national treatment guidelines in many Asian countries.

ANTIBIOTIC TREATMENT OF HAP

Initial approach to empirical therapy

In general, the panel agreed with the initial approach to therapy proposed by previous guidelines (Fig 1).[1] Overall, 2 groups of patients are recognized in the initial treatment algorithm. One group, with early-onset HAP or VAP and no risk for MDR pathogens, has no need for broad-spectrum therapy. (In this context, early-onset HAP or VAP is considered HAP or VAP occurring within the first 4 days of hospitalization; late-onset HAP and VAP, that occurring 5 days or more after hospitalization.) Likely pathogens in early-onset HAP or VAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, MRSA, and antibiotic-susceptible enteric Gram-negative bacilli (ie, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Proteus* species, or *Serratia marcescens*). Recommended treatment for this group is limited-spectrum antimicrobial therapy with either ceftriaxone, fluoroquinolone (levofloxacin, moxifloxacin, or ciprofloxacin), ampicillin-sulbactam, or ertapenem.

The second group, with late-onset HAP or VAP or risk factors for MDR pathogens, requires broad-spectrum therapy. Late-onset HAP and VAP are more likely to be caused by MDR pathogens and are associated with increased morbidity and mortality. Risk factors for MDR pathogens include antimicrobial therapy within the preceding 90 days, current hospitalization of 5 days or longer, high frequency of antibiotic resistance in the community or specific hospital unit, admission from a health care–associated facility, and immunosuppressive disease or immunosuppressant therapy.[1] This group of patients is more likely to be infected by MDR pathogens (*P. aeruginosa*, extended-spectrum beta-lactamase [ESBL]$^+$ *K. pneumoniae*, *Acinetobacter* species, methicillin-resistant *S. aureus*, and *Legionella*

pneumophila). The ATS/IDSA guidelines recommend combination broad-spectrum antibiotic therapy, using either antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbepenem (impipenem or meropenem) or beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam), along with either antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin). If MRSA is suspected, then linezolid or vancomycin is added to the other 2 drugs. If $ESBL^+$ *K. pneumoniae* or an *Acinetobacter* species is suspected, then carbepenem is considered a reliable choice. If *L. pneumophila* is suspected, then the combination regimen should include a macrolide (eg, azithromycin), or fluoroquinolone (ciprofloxacin or levofloxacin) should be used rather than aminoglycoside.

The panel also agreed that the initial empirical antibiotic treatment choice should be guided by such factors as local microbiology and resistance patterns, drug availability and cost, and formulary restrictions on drugs in individual hospitals. These factors are also considered in existing guidelines, but they have greater relevance to practice in Asia, where in particular local microbiology and resistance patterns vary to a greater degree than in Western countries. Cost is also an issue of relatively greater significance for many patients treated by Asian doctors. Clinically, other factors that need to be weighed when selecting initial empirical antibiotic treatment include the results of lower respiratory tract (LRT) Gram stain, disease severity, medication allergies, and underlying comorbidities (eg, renal or hepatic insufficiency), and the impact of such agents on creating further resistance.

LRT cultures may be made from samples obtained by endotracheal aspiration, bronchoalveolar lavage, or protected specimen brush. Although a positive culture cannot always distinguish a pathogen from a colonizing organism, a negative culture has utility in ruling out pneumonia and the presence of MDR pathogens, especially in intubated patients. The inclusion of disease severity in the treatment algorithm was discussed by the Working Group participants. Whereas previous ATS guidelines[5] considered disease severity in selecting treatment, current ATS/IDSA guidelines,[1] as well as national guidelines under development in Taiwan, do not consider this to be a factor. In an individual patient with severe pneumonia, the pneumonia may or may not be related to infection with an MDR pathogen. Although the etiologic agent (eg, methicillin-sensitive *S. aureus*) may be easily treated, the disease may manifest as severe if the host has a weakened immune response due to underlying comorbidities. Nonetheless, it is evident that many Asian physicians continue to regard disease severity as a significant issue in selecting initial empirical antibiotic treatment. In current guidelines, the presence of severe pneumonia is not considered a risk factor for MDR pathogens causing HAP and VAP. As always, clinical judgment is the best guide in the initial empirical selection of treatment. Multiple factors must be weighed, including the individual patient's overall status, timing of disease onset, local microbiologic data, underlying comorbidities, virulence of the suspected etiologic agent, and the presence of risk factors for MDR pathogens (Fig 1).

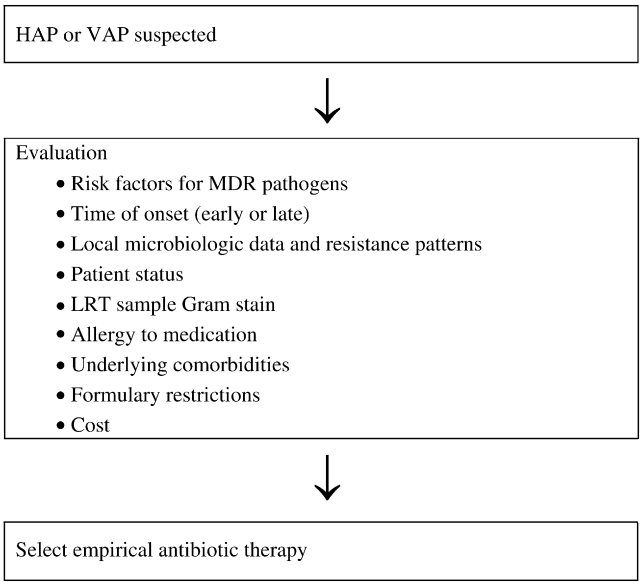

Figure 1. Initial approach to empirical antibiotic therapy in Asian countries.

RECOMMENDED TREATMENT REGIMENS FOR HAP IN ASIA

Early-onset HAP

Many clinicians in Asian countries would choose a single agent to treat early-onset HAP. The consensus recommendation of the panel includes several options and overlaps somewhat with existing guidelines (Table 1).[1] The third-generation cephalosporins (ceftriaxone or cefotaxime), fluoroquinolones (moxifloxacin, levofloxacin, and gatifloxacin), beta-lactam/beta-lactamase inhibitor combinations (amoxicillin/clavulanic acid or ampicillin/sulbactam), and ertapenem are recommended when monotherapy is indicated. Because the current knowledge base on the epidemiology and etiology of HAP in Asian countries is incomplete, the panel did not assign an order of priority in the selection of drug treatment. Rather, each of these options is considered more or less therapeutically equivalent to the others, providing coverage against many of the common potential pathogens causing HAP, including *S.*

Table 1. Initial empirical antibiotic treatment for early-onset HAP: consensus recommendations by the Asian HAP Working Group

Potential pathogen	Recommended regimen*
Streptococcus pneumoniae†	Third-generation cephalosporins (ceftriaxone, cefotaxime)
Haemophilus influenzae	*or*
Methicillin-sensitive *Staphyloccocus aureus*	fluoroquinolones (moxifloxacin, levofloxacin)
Antibiotic-sensitive enteric Gram-negative bacilli:	*or*
Escherichia coli	β-lactam/β-lactamase inhibitor (amoxicillin/clavulanic acid; ampicillin/sulbactam)
Klebsiella pneumoniae	*or*
Enterobacter species	carbepenems (ertapenem)
Proteus species	*or*
Serratia marcescens	third-generation cephalosporins plus macrolide
	or
	monobactam plus clindamycin (for β-lactam– allergic patients)

*Antibiotic options should depend on the local epidemiology of etiologic pathogens.
†The frequency of macrolide-resistant *S. pneumoniae* and MDR *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

Table 2. Initial empirical antibiotic treatment for late-onset HAP: consensus recommendations by the Asian HAP Working Group

Potential pathogen	Recommended antibiotic regimen
Pathogens listed in Table 1 and MDR pathogens	Antipseudomonal cephalosporin (cefepime, ceftazidime)
Pseudomonas aeruginosa	*or*
Klebsiella pneumoniae ($ESBL^+$)*	antipseudomonal carbepene (imipenem or meropenem)
Acinetobacter species*	*or*
	beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam)
MRSA	+/−
	fluoroquinolone (ciprofloxacin or levofloxacin)
	or
	aminoglycoside (amikacin, gentamicin, or tobramycin)
*Legionella pneumophila**	cefoperazone/sulbactam plus fluoroquinolones or aminoglycosides
	plus ampicillin/sulbactam (if sulbactam is not available)
	or
	fluoroquinolone (ciprofloxacin) plus aminoglycoside
	plus
	linezolid or vancomycin†
	plus
	azithromycin or fluoroquinolone

*If an $ESBL^+$ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, then a carbepenem is a reliable choice. If *L. pneumophila* is suspected, then the combination antibiotic regimen should include a macrolide (eg, azithromycin), or a fluoroquinolone (eg, ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.
†If MRSA risk factors are present or there is a high incidence locally.

pneumoniae, *H. influenzae*, MRSA, and antibiotic-sensitive enteric Gram-negative bacilli. To some extent, the choice of agent should incorporate information on local microbiology. Therapy with a monobactam plus clindamycin or fluoroquinolone used alone is recommended for patients who are allergic to beta-lactam agents.

Another consideration for treating early-onset HAP is the use of combination therapy with a third-generation cephalosporin plus a macrolide (eg, azithromycin) or occasionally fluoroquinolone to provide broader initial coverage. The use of combination regimens for empirical therapy may have relevance in specific situations sometimes found in Asian countries. For example, in Pakistan, the etiologic distribution of pathogens causing early-onset HAP is very similar to that of community-acquired pneumonia (CAP), suggesting the need for a regimen providing coverage against atypical pathogens, and thus clarithromycin is often added for this purpose. Given the lack of objective data on the etiologic role of atypical pathogens in early-onset HAP, the panel discussed the need to collect better surveillance data regarding the incidence and prevalence of atypical pathogens in Asian countries and their role in early-onset HAP.

Late-onset HAP

To treat late-onset HAP in Asian countries, the panel primarily recommended using third- or fourth-generation cephalosporins (ceftazidime or cefepime), carbapenems (imipenem or meropenem) or piperacillin/tazobactam in combination with fluoroquinolones or aminoglycosides, plus/minus glycopeptides (vancomycin or teicoplanin) or linezolid (Table 2). Other regimens that may be considered by Asian clinicians include cefoperazone/sulbactam plus fluoroquinolones or aminoglycosides or ampicillin/sulbactam or fluoroquinolones (ciprofloxacin) plus aminoglycosides plus/minus glycopeptides (vancomycin or teicoplanin). The regimen containing antibiotics with sulbactam compound (cefoperazone/sulbactam or ampicillin/sulbactam) was especially recommended for the coverage of MDR *Acinetobacter* spp in some Asian countries.

As with early-onset HAP, the choice of therapy should be guided by local microbiology data. For example, in Korea or Taiwan, where MRSA is a relatively common pathogen found in late-onset HAP, a clinician might choose to add a glycopeptide (vancomycin or teicoplanin) or linezolid as the second drug, rather

than a fluoroquinolone or an aminoglycoside. However, initial therapy with glycopeptides or linezolid is usually not recommended, because in late-onset HAP, up to 20% of etiologic pathogens may be MRSA, and the initial use of drugs directed against this pathogen may increase the likelihood of the emergence of vancomycin resistance in *S. aureus* or enterococci. Alternatively, the clinician might choose to ascertain the presence of Gram-positive cocci by Gram stain before adding vancomycin to therapy with a third-or fourth-generation cephalosporin. In the absence of Gram-positive cocci, vancomycin is not recommended.

Some panel members stated a preference for levofloxacin, moxifloxacin, or gatifloxacin over ciprofloxacin for treating *Acinetobacter*, based on in vitro susceptibility data. Although there is no valid study on this approach, theoretically, aminoglycosides may have decreased bioavailability in the acidic environment of pneumonitis. The panel members agreed that use of ampicillin/sulbactam plus an aminoglycoside does appear to increase the response in some patients. A combination of two drugs containing sulbactam (eg, ampicillin/sulbactam and cefoperazone/sulbactam) may be used to deliver a higher dose of sulbactam. Alternatively, if sulbactam is available as a single agent (as it is in some countries), then the clinician may consider using it together with cefoperazone/sulbactam rather than adding ampicillin/sulbactam. It was noted that in some settings, Gram stain, with appropriate interpretation, can be used to confirm the presence of *Acinetobacter baumannii*. In the case of a confirmed infection, treatment with imipenem plus sulbactam as a single agent (if available) or plus ampicillin/sulbactam is recommended.

Early-onset VAP

In patients with early-onset VAP, the panel recommends, with no order of priority, fourth -generation cephalosporins such as cefepime or carbapenems (imipenem or meropenem) or piperacillin/tazobactam plus/minus fluoroquinolones or aminoglycosides, plus/minus glycopeptides (vancomycin or teicoplanin) or linezolid. Other regimens that may be considered include cefoperazone/sulbactam plus fluoroquinolones or aminoglycosides or ampicillin/sulbactam or fluoroquinolones (ciprofloxacin) plus aminoglycosides plus/minus the glycopeptides vancomycin or teicoplanin (Table 3). As in cases of late-onset HAP, the decision regarding which drug to add, either a fluoroquinolone or an aminoglycoside, and the decision of whether to add a glycopeptide or linezolid, is a matter of clinical judgment.

Table 3. Initial empirical antibiotic treatment for early-onset VAP: consensus recommendations by the Asian HAP Working Group

Potential pathogen	Recommended antibiotic regimen
Pathogens listed in Table 1 and MDR pathogens *Pseudomonas. Aeruginosa* *Klebsiella pneumoniae* (ESBL$^+$) *Acinetobacter* species† MRSA	Antipseudomonal cephalosporin (cefepime) or antipseudomonal carbepenem (imipenem or meropenem) or beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam) +/− fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) +/− linezolid or vancomycin

Cefepime, a fourth-generation cephalosporin, was preferred to ceftazidime (see below) as an initial empirical agent for early-onset VAP. Cefpirome, another fourth-generation cephalosporin available in India, is a possible alternative to cefepime. Cefepime and cefpirome are more resistant to some beta-lactamases (ie, those that are plasmid- or chromosome-mediated) compared with third-generation cephalosporins. Cefepime and cefpirome, like ceftazidime, are active against *P. aeruginosa* and for this reason may be useful in early-onset VAP when there is a low risk for MDR pathogens. As always, the choice of agent should depend on local microbiology and resistance patterns. The panel noted that in some countries, third-generation cephalosporins are not recommended for initial empirical therapy in early-onset VAP. In particular, some organisms, including strains of ESBL$^+$ *E. coli* and *K. pneumoniae* and *Acinetobacter*, display increasing resistance to third-generation cephalosporins. In many Asian countries, there is a high prevalence of one or another of these organisms, all of which are major pathogens of HAP and VAP. For these reasons, ceftazidime is not recommended as initial empirical therapy. Ceftazidime has excellent activity against *Pseudomonas*, however, and its use (always in combination with other drugs) may be considered on a case-by-case basis in patients at low risk for MDR pathogens and early-onset VAP. On the other hand, the panel strongly recommended avoiding ceftazidime in patients at high risk for MDR pathogens and early-onset VAP with fever and leucopenia.

Existing guidelines recommend the use of aminoglycosides rather than fluoroquinolones in a

Table 4. Initial empirical antibiotic treatment for late-onset VAP: consensus recommendations by the Asian HAP Working Group

Potential pathogen	Recommended antibiotic regimen
MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL$^+$) *Acinetobacter* species MRSA	Antipseudomonal carbepenem (imipenem or meropenem) *or* beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam) +/− fluoroquinolone (ciprofloxacin or levofloxacin) *or* aminoglycoside (amikacin, gentamicin, or tobramycin) +/− linezolid or vancomycin cefoperazone/sulbactam + fluoroquinolones or aminoglycosides + ampicillin/sulbactam (if sulbactam is not available) +/− linezolid or vancomycin *or* fluoroquinolone (ciprofloxacin) plus aminoglycoside +/− linezolid or vancomycin

combination regimen with a beta-lactam agent. This recommendation is based on a study demonstrating a trend toward improved survival for patients receiving the aminoglycoside-containing combination but not the fluoroquinolone-containing combination.[6] Among the aminoglycosides, in most Asian clinical settings, amikacin is preferred over gentamicin or tobramycin. Netilmicin, the latest of the aminoglycosides to be marketed, also may be considered. Netilmicin has broad antimicrobial activity against aerobic Gram-negative bacilli and is effective against *Acinetobacter* strains. Many Asian clinicians agree that fluoroquinolones also should be used judiciously. To prevent the emergence of resistant organisms to fluoroquinolones, some institutions have adopted a policy to reserve the use of ciprofloxacin for the treatment of enteric fever and related infections. Restriction of fluoroquinolone use can help maintain the susceptibility of bacterial organisms, which is another reason to select aminoglycosides for combination therapy.

Local microbiology data and the circumstances of the individual patient always should be considered when planning treatment. If there is a high prevalence of a specific organism (eg, *L. pneumophila*), a combination regimen using a fluoroquinolone rather than an aminoglycoside may be preferred. In addition, fluoroquinolones are clearly a better choice in elderly patients and patients with decreased renal function. The panel concurred that ciprofloxacin and levofloxacin are the preferred fluoroquinolones. Ciprofloxacin is more effective than the other fluoroquinolones against *P. aeruginosa*, especially moxifloxacin. If nonfermenter strains other than *Pseudomonas* are suspected, then levofloxacin may be preferred.

Late-onset VAP

In cases of late-onset VAP, the panel recommended the use of carbapenems (imipenem or meropenem) or piperacillin/tazobactam in combination with fluoroquinolones or aminoglycosides plus/minus glycopeptides or linezolid (Table 4). Alternatively, the panel recommended cefoperazone/sulbactam plus fluoroquinolones or aminoglycosides or ampicillin/sulbactam. The use of fluoroquinolones (ciprofloxacin) plus aminoglycosides plus vancomycin or teicoplanin also was recommended. Again, no priorities were assigned among these regimens, due to the lack of objective evidence in Asian countries regarding the comparative clinical efficacy of different regimens. In these recommendations, the carbapenems (imipenem and meropenem) are preferred over third-or fourth-generation cephalosporins because they are more active against ESBL$^+$ Gram-negative bacilli, that is, those expressing plasmid- or chromosome-mediated ESBL. In addition, they are more active against *Pseudomonas* and *Acinetobacter*. Piperacillin/tazobactam is preferred over cefepime because, unlike cefepime, it does not induce ESBL production in Gram-negative bacteria. In addition, piperacillin/tazobactam does not exhibit an inoculum effect, and it proved to be highly active in vitro against *K. pneumoniae* and *E. coli* in a recent Asian study.[7]

Late-onset VAP remains a serious problem with a high mortality rate. The panel agreed that concurrent treatment with 2 or 3 drugs should be considered the norm in late-onset VAP compared with early-onset VAP, in which the clinician may have more latitude in deciding whether to use monotherapy or combination therapy.

SPECIAL CONSIDERATIONS FOR MULTIDRUG-RESISTANT ORGANISMS

The recommended treatments for MDR pathogens are outlined in Table 5.

Methicillin-resistant *Staphylococcus aureus*

The panel recommended vancomycin or teicoplanin as first-line treatment for MRSA Vancomycin therapy requires careful monitoring of blood levels; side effects include nephrotoxicity and ototoxicity. Teicoplanin has fewer serious side effects and does not

require monitoring of serum levels, but it is more expensive. In randomized comparative studies,linezolid demonstrated comparable or superior efficacy to vancomycin for nosocomial pneumonia caused by MRSA.[8,9] Both teicoplanin and linezolid are available in some Asian countries. In addition, panel members concurred that linezolid should be reserved as a second-tier agent (after vancomycin and teicoplanin), to avoid the selection of resistant strains, which would lead to loss of this valuable agent. Tigecycline represents a novel class of agents—glycylcyclines—and is expected to be available in Asia by late 2007.

Pseudomonas aeruginosa

P. aeruginosa has intrinsic resistance to many antimicrobial drugs.[10-12] For the treatment of MDR *P. aeruginosa*, the panel recommended piperacillin/tazobactam or carbapenems plus/minus aminoglycoside or fluoroquinolone (ciprofloxacin). Fluoroquinolones offer the theoretical advantage of improved bioavailability in the respiratory tract, although no study is available comparing fluoroquinolone-based combination therapy with beta-lactam monotherapy.[1] When a fluoroquinolone is used in combination therapy, ciprofloxacin or levofloxacin may be preferred, because they show greater in vitro activity against *P. aeruginosa*. It is important that local susceptibility data support this decision, because some studies have reported a decreased sensitivity of *P. aeruginosa* to fluoroquinolones after widespread use of these drugs in the hospital.[13,14]

If the patient is unresponsive, then some Asian clinicians pursue treatment with polymyxin B or colistin (polymyxin E), possibly with the addition of ciprofloxacin. The use of parenteral colistin[15] and aerosolized colistin[16] for treating MDR *P. aeruginosa* has been described in the literature. Polymyxin B and E are not available in some Asian countries, however.

Acinetobacter species

Although *Acinetobacter* spp are considered generally less virulent than *P. aeruginosa,* they are demonstrating increasing resistance to commonly used antibiotics.[17,18] Cefoperazone/sulbactam, colistin, polymyxin B, tigecycline, or a combination is the recommended treatment. Sulbactam, usually used as an enzyme inhibitor, has direct activity against *Acinetobacter*.[19] Some panel members suggested the use of sulbactam plus moxifloxacin, levofloxacin plus minocycline, chloramphenicol, or imipenem. Although aminoglycosides generally do not appear to be effective against *Acinetobacter* and are not recommended in all patients, the panel noted the successful use of netilmicin, with 50% of strains in a Thai hospital found to be susceptible.

Table 5. Antibiotic regimens against specific antibiotic-resistant pathogens

Pathogen	Rank	Antibiotic regimen
MRSA	1	Vancomycin or teicoplanin
	2	Linezolid or tigecycline
MDR *Pseudomonas aeruginosa*	1	Piperacillin/tazobactam or carbapenems plus/minus aminoglycosides or fluoroquinolones (cipro)
	2	Polymyxin B or colistin plus/minus ciprofloxacin
MDR *Acinetobacter*	1	Cefoperazone/sulbactam and/or tigecycline
	2	Polymyxin B or colistin
ESBL$^+$ *Klebsiella pneumoniae*	1	Carbapenems or tigecycline
	2	Piperacillin/tazobactam
ESBL$^+$ *Eschirichia coli*	1	Carbapenems or tigecycline
	2	Piperacillin/tazobactam

In a patient who is unresponsive to the initial regimen, polymyxin B or colistin, in either parenteral or aerosolized form, are potential alternatives. A study in Singapore reported clinical response rates of 57% against *A. baumannii* and 86% against *P. aeruginosa.*[20] A review of the available literature on this approach has been published recently.[21]

ESBL$^+$ *Escherichia coli* and *Klebsiella pneumoniae*

The panel recommended carbapenems (imipenem or meropenem) or tigecycline as the first-line treatment for ESBL$^+$ *E. coli* and *K. pneumoniae*. Overall, carbapenems have excellent activity against the enterobacteriaceae, including organisms that express plasmid- or chromosome-mediated ESBL. Piperacillin/tazobactam could be an alternative choice in some selected situations. Studies in Asian countries have shown a high degree of in vitro susceptibility of ESBL-producing *E. coli* and *K. pneumoniae* to piperacillin/tazobactam.[22] Susceptibility has been reported to be 77% to 81% in India[7,23] and 88% in China.[24]

DURATION OF ANTIBIOTIC TREATMENT

The duration of antibiotic therapy is a controversial issue in Asian countries. Existing guidelines recommend treatment for 7 days, except for confirmed cases of *P. aeruginosa* infection, in which case treatment should be given for 14 to 21 days.[1] Many Asian clinicians will in practice use antibiotics for a longer period, regardless of the etiologic organism. The panel agreed that initial empirical antibiotic treatment should continue for 7 to 14 days. If an MDR pathogen (eg, MRSA, *P. aeruginosa*, *Acinetobacter* spp, ESBL$^+$ Gram-negative bacilli) is identified, then treatment may be continued for up to 14 days. Current guidelines note that most

patients with VAP who receive appropriate antimicrobial treatment demonstrate a good clinical response within the first 6 days of therapy.[1] Patient response should be evaluated frequently, with consideration given to de-escalating therapy when appropriate. A multicenter, randomized, controlled study[25] that evaluated outcomes in patients with VAP who received antibiotic treatment for either 8 days or 15 days reported similar outcomes for the 2 groups. Except in those patients who were infected with *P. aeruginosa*, the shorter course of treatment was found to be clinically comparable to the longer course. However, in this study the rate of relapse tended to be greater in patients receiving 8 days of treatment when the etiologic agent was *P. aeruginosa* or *Acinetobacter* spp.

ANTIBIOTIC CONTROL AND CYCLING

When an outbreak due to a specific strain of resistant bacteria occurs, restriction of access to specific antibiotics may be an effective measure to curtail the problem. The ATS/IDSA guidelines advocate antibiotic restriction as a potential strategy to reduce the emergence of antimicrobial resistance. Clinical studies evaluating the cycling of gentamicin and amikacin[26] or ceftazidime and ciprofloxacin have shown favorable results, including a reduced incidence of VAP.[27-29] Nonetheless, antibiotic restriction remains controversial. One study has reported that restriction of cephalosporin use led to a 44% reduction in ESBL$^+$ *Klebsiella,* but that during the study period, overuse of imipenem was associated with a 69% increase in the incidence of imipenem-resistant *P. aeruginosa.*[30]

Although the panel members did not report the use of antibiotic cycling programs in their hospitals, many Asian countries practice some form of antibiotic restriction, mainly at the institutional level but sometimes at the national level. In the Philippines, it was noted that the third-generation cephalosporins (except ceftriaxone) have not been used for the past 2 to 3 years in some hospitals, in an effort to curb the emergence of ESBL$^+$ Gram-negative bacilli. In other hospitals, gentamicin and tobramycin have been used alternately over a predetermined period for aminoglycoside therapy. In India, vancomycin and linezolid are alternately placed on reserve for a specific period to treat MRSA. In Pakistan, ceftazidime overuse has given rise to resistant strains of *Pseudomonas* spp, and the drug has fallen out of favor with clinicians. In Taiwan, the use of first-generation cephalosporins, carbapenems, fluoroquinolones, and piperacillin/tazobactam is restricted, which has resulted in the increased use of third-generation cephalosporins. A study that evaluated data from National Taiwan University Hospital from 1994 to 2003 found an increasing use of many antibiotics, with the associated emergence of resistant strains, including ceftazidime-resistant strains of *E. coli* and *S. marcescens*, ciprofloxacin-resistant strains of *E. coli* and *P. aeruginosa*, and carbapenem-resistant strains of *A. baumannii*.[31] Currently, a beta-lactam/beta-lactamase inhibitor combination or fourth-generation cephalosporin is recommended, with a carbapenem agent as a second choice, for the treatment of ICU-acquired infections in Taiwan.

CONCLUSION

Worldwide, various countries and international medical societies have issued guidelines for the treatment of HAP; however, national or even institutional guidelines are not available in many Asian countries. Existing American or European guidelines are best considered in the context of issues relevant to clinical practice in Asia. Such factors as local epidemiology, etiology, antibiotic resistance patterns, the presence of MDR pathogens, antibiotic use, drug availability, and cost are often very significant in determining the best practice in a particular clinical setting, and these factors may vary markedly between Asian and Western hospitals.

To address this need, an expert panel with representatives from 10 Asian countries developed consensus treatment recommendations for the management of HAP in Asian countries. To improve the current knowledge base and fill existing gaps, several areas were identified as topics for further research. There is a need for national and multinational surveillance data to provide better information on the incidence of etiologic pathogens of HAP and VAP (both early- and late-onset cases) and resistance patterns. Of note, *Acinetobacter* appears to be a primary pathogen of HAP in some Asian countries. Consequently, many panel members have emphasized the empirical antibiotic coverage of MDR *Acinetobacter* spp. Nonetheless, further studies are needed to search for optimal therapeutic strategies to treat MDR or PDR *Acinetobacter*. ANSORP could serve as a vehicle to perform international surveillance of antimicrobial resistance and to facilitate implementation of these international efforts. Active communication between physicians and collaborative efforts between different Asian countries are critical to achieving these goals. ARFID, in conjunction with the Asian HAP Working Group, will continuously contribute to making more practical and relevant clinical recommendations for treating HAP and VAP in Asian countries through effective collaboration.

The authors appreciate the support that they received from Yong Rho, Ed Wallace, Mary Michael, and David Wu in Wyeth, as well as Raymond Fortune and Lynn Wills at SCS Healthcare.

References

1. American Thoracic Society, Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Resp Crit Care Med 2005;171:388-416.
2. British Thoracic Society Standards of Care Committee. BTS Guidelines for the management of community-acquired pneumonia in adults. Thorax 2001;56(suppl 4):IV1-64.
3. Interhospital Multidisciplinary Program on Antimicrobial Chemotherapy. Reducing bacterial resistance with IMPACT (3rd ed). Hong Kong: 2005. p. 68. Adapted from Brown EM. Empirical antimicrobial therapy of mechanically ventilated patients with nosocomial pneumonia. J Antimicrob Chemother 1997;40:463-8.
4. Chinese Medical Association, Respiratory Branch. Treatment guidelines for hospital-acquired pneumonia. Chin J Tuber Respir Dis 1999;22:201-2.
5. American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy and preventative strategies. Am J Respir Crit Care Med 1995;153:1711-25.
6. Fowler RA, Flavin KE, Barr J, Weinacker AB, Parsonnet J, Gould MK. Variability in antibiotic prescribing patterns and outcomes in patients with clinically suspected ventilator-associated pneumonia. Chest 2003;123:835-44.
7. Mohanty S, Singhal R, Sood S, Dhawan B, Das BK, Kapil A. Comparative in vitro activity of beta-lactam/beta-lactamase inhibitor combinations against Gram-negative bacteria. Indian J Med Res 2005;122: 425-8.
8. Rubinstein E, Cammarata S, Oliphant T, Wunderlink R. for the Linezolid Nosocomoal Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001;32:402-12.
9. Wunderink RG, Cammarata SK, Oliphant T, Kollef MH. for the Linezolid Nosocomoal Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther 2003;25:980-2.
10. Van Eldere J. Multicenter surveillance of *Pseudomonas aeruginosa* susceptibility patterns in nosocomial infections. J Antimicrob Chemother 2003;51:347-52.
11. Landman D, Quale JM, Mayorga D, Adedeji A, Vangala K, Ravishankar J, et al. Citywide clonal outbreak due to a multiresistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Brooklyn, NY: the preantibiotic era has returned. Arch Intern Med 2002; 162:1515-20.
12. Dubois V, Arpin C, Melon M, Melon B, Andre C, Frigo C, et al. Nosocomial outbreak due to a multiresistant strain of *Pseudomonas aeruginosa* P12: efficacy of cefepime-amikacin therapy and analysis of beta-lactam resistance. J Clin Microbiol 2001;39:2072-8.
13. Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. Emerg Infect Dis 2003;9:1-9.
14. Neuhauser MM, Weinstein R, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among Gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003; 289:885-8.
15. Linden PK, Kusne S, Coley K, Fontes P, Kramer DJ, Paterson D. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2003;37: e154-60.
16. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistnat *Pseudomonas aeruginosa* with aerosolized colistin. Am J Respir Crit Care Med 2000;162:328-30.
17. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. Emerging importance of MDR *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiologic features, and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). Clin Infect Dis 2001;32: S104-13.
18. Nordmann P, Poirel L. Emerging carbapenemases in Gram-negative aerobes. Clin Microbiol Infect 2002;8:321-31.
19. Wood GC, Hanes SD, Croce MA, Fabian TC, Boucher BA. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of *Acinetobacter* ventilator-associated pneumonia. Clin Infect Dis 2002; 34:1425-30.
20. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatmentof pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Clin Infect Dis 2005;41: 754-7.
21. 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.
22. Luzzaro F, Mezzatesta M, Mugnaioli C, Perilli M, Stefani S, Amicosante G, et al. Trends in production of extended-spectrum beta-lactamases among enterobacteria of medical interest: report of the second Italian nationwide survey. J Clin Microbiol 2006;44:1659-64.
23. Jones RN, Rhomberg PR, Varnam DJ, Mathai D. A comparison of the antimicrobial activity of meropenem and selected broad-spectrum antimicrobials tested against multidrug resistant Gram-negative bacilli including bacteraemic *Salmonella* spp: initial studies for the MYSTIC Programme in India. Int J Antimicrob Agents 2002; 20:426-31.
24. Yu Y, Zhou W, Chen Y, Ding Y, Ma Y. Epidemiological and antibiotic-resistant study on extended-spectrum beta-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae* in Zhejiang Province. Chin Med J (Engl) 2002;115:1479-82.
25. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290: 2588-98.
26. Gerding DN, Larson TA, Hughes RA, Weiler M, Shanholtzer C, Peterson LR. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. Antimicrob Agents Chemother 1991;35:1284-90.
27. Kollef MH, Vlasnik J, Sharpless L, Pasque C, Murphy D, Fraser V. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 1997;156:1040-8.
28. Gruson D, Hilbert G, Vargas F, Valentino R, Bebear C, Allery A, et al. Rotation and restricted use of antibiotics in a medical intensive care unit: impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant Gram-negative bacteria. Am J Respir Crit Care Med 2000;162:837-43.
29. Gruson D, Hilbert G, Vargas F, Valentino R, Bui N, Pereyre S, et al. Strategy of antibiotic rotation: long-term effect on incidence and susceptibilities of Gram-negative bacilli responsible for ventilator-associated pneumonia. Crit Care Med 2003;31:1908-14.
30. Rahal JJ, Urban C, Horn D, Freeman K, Segal-Maurer S, Maurer J, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. JAMA 1998;280:1233-7.
31. Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991-2003 at a university hospital in Taiwan. Int J Antimicrob Agents 2005;26:463-72.

APPENDIX: THE ASIAN HAP WORKING GROUP

The meeting was hosted by the Asian Pacific Research Foundation for Infectious Diseases (ARFID). Professor Jae-Hoon Song from the Samsung Medical Center, Sungkyunkwan University, Korea, who is the organizer of ANSORP (Asian Network for Surveillance of Resistant Pathogens) and the Chairman of ARFID, organized the Asian HAP Working Group and its first working group meeting in Kuala Lumpur, Malaysia, in April 22-23, 2006. This meeting was supported by the Korean Society for Chemotherapy; the Taipei Society of Infectious Diseases; the Infectious Disease Association of Thailand; the Society of Infectious Diseases, Singapore; the Malaysia Society of Infectious Diseases and Chemotherapy; the Philippine Society for Microbiology and Infectious Diseases; the Indian Society for Antimicrobial Therapy; and the Infectious Disease Society of Pakistan.

The panel members of Asian HAP Working Group (in alphabetical order) include:

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 the Philippines, Philippine General Hospital, Philippines
Po-Ren Hsueh, MD, National Taiwan University Hospital, Taiwan ROC
Bi Jie Hu, MD, Zhongshan Hospital of Fudan University, People's Republic of China
Yhu-Chering Huang, MD, PhD, Chang Gung Children's Hospital, Taiwan ROC
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 ROC
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 University College of Medicine Severance Hospital, South Korea
Amorn Leelarasamee, MD, Siriraj Hospital, Mahidol University, Thailand
Tzer Pin Raymond Lin, MD, National University Hospital, Singapore
Roslina Abdul Manap, MMED, MRCP, University of Kebangsaa Hospital, 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 Hospital, People's Republic of China
Adisom Wongsa, MD, Siriraj Hospital, Mahidol University, Thailand
Yonghong Xiao, PhD, Institute of Clinical Pharmacology, Peking University, People's Republic of China
Rohani Yasin, MD, Institute of Medical Research, Malaysia