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Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens

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Abstract

Appropriate antimicrobial treatment of community-acquired pneumonia (CAP) should be based on the distribution of aetiological pathogens, antimicrobial resistance of major pathogens, clinical characteristics and outcomes. We performed a prospective observational study of 955 cases of adult CAP in 14 hospitals in eight Asian countries. Microbiological evaluation to determine etiological pathogens as well as clinical evaluation was performed. Bronchopulmonary disease (29.9%) was the most frequent underlying disease, followed by cardiovascular diseases

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(19.9%), malignancy (11.7%) and neurological disorder (8.2%). *Streptococcus pneumoniae* (29.2%) was the most common isolate, followed by *Klebsiella pneumoniae* (15.4%) and *Haemophilus influenzae* (15.1%). Serological tests were positive for *Mycoplasma pneumoniae* (11.0%) and *Chlamydia pneumoniae* (13.4%). Only 1.1% was positive for *Legionella pneumophila* by urinary antigen test. Of the pneumococcal isolates, 56.1% were resistant to erythromycin and 52.6% were not susceptible to penicillin. Seventeen percent of CAP had mixed infection, especially *S. pneumoniae* with *C. pneumoniae*. The overall mortality rate was 7.3%, and nursing home residence, mechanical ventilation, malignancy, cardiovascular diseases, respiratory rate > 30/min and hyponatraemia were significant independent risk factors for mortality by multivariate analysis ($P < 0.05$). The current data provide relevant information about pathogen distribution and antimicrobial resistance of major pathogens of CAP as well as clinical outcomes of illness in Asian countries.

Keywords: Community-acquired pneumonia; Aetiology; Epidemiology; Clinical outcome

1. Introduction

Community-acquired pneumonia (CAP) still remains one of the most important causes of death, especially in older adults and those with co-morbid diseases, despite advances in modern medicine [1,2]. Since CAP is a condition with significant mortality and morbidity, early and effective antimicrobial treatment has been a major focus in clinical practice [1]. Pathogen distribution and antimicrobial resistance in major pathogens in a local setting are very important to select appropriate antibiotics for the treatment of CAP. Major identifiable pathogens of CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae* and atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* spp. [1–3]. However, the distribution of aetiological pathogens of CAP may vary by country. Most of the data on pathogen distribution of CAP have been reported from western countries, whilst only a few data are available in the Asian region [2–6]. The recent emergence of antimicrobial resistance in major respiratory pathogens, especially in *S. pneumoniae*, is another critical point for appropriate treatment of CAP. Previous data by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) showed that Asian countries have very serious problems of increasing prevalence and level of antimicrobial resistance to penicillin and macrolides in pneumococcal isolates [7,8].

Although several treatment guidelines have been proposed by different organisations, such as the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS)(2007), the Canadian Society of Infectious Diseases (2000) and Drug-Resistant *Streptococcus pneumoniae* (DRSP) Therapeutic Working Group (2000), treatment recommendations for CAP in Asian countries should be based on the epidemiological information of pathogen distribution and antimicrobial resistance among major respiratory pathogens in the Asian region.

This multinational surveillance study by ANSORP was performed to investigate the epidemiology of aetiological pathogens of CAP in Asian countries, including usual bacterial pathogens and atypical pathogens, as well as to evaluate the clinical outcomes and risk factors of CAP in Asian countries.

2. Materials and methods

2.1. Participating centres

ANSORP conducted a prospective surveillance study from January 2002 to December 2004 in 14 tertiary care hospitals in eight Asian countries: South Korea (Samsung Medical Center, Gangbuk Samsung Hospital, Seoul Veterans Hospital, Seoul; Kyungpook National University, Daegu; Chungnam National University, Daejeon; and Chonnam National University, Gwangju); China (Chao Yang Hospital, Beijing; and Rui Jin Hospital, Shanghai); Taiwan (Chang Gung Memorial Hospital and National Taiwan University, Taipei); Hong Kong (Princess Margaret Hospital, Hong Kong); India (Christian Medical College, Vellore); Singapore (Singapore General Hospital, Singapore); Vietnam (University of Medicine and Pharmacy, HCMC, Vietnam); and The Philippines (Research Institute of Tropical Medicine, Manila).

2.2. Study population and design

Any adult patient who fulfilled all of the following criteria with clinical and radiological diagnosis of CAP was eligible for the study. CAP was defined as follows: (1) new or progressive infiltrate(s), consolidation or pleural effusion consistent with pneumonia on chest radiography performed within 48 h prior to enrolment; (2) fever or a history of fever (defined as an oral temperature > 38 °C); and (3) at least two respiratory signs and symptoms (new or increased cough; purulent sputum or a change in sputum characteristics; auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation; dyspnoea or tachypnoea; peripheral white blood cell (WBC) count >10 000 cells/mm^3 or >15% immature neutrophils or leukopenia with a total WBC count of <4500 cells/mm^3; hypoxemia with a partial pressure of oxygen in arterial blood (PaO_2) <60 mmHg while the patient is breathing room air). Patients younger than 15 years of age, patients who had been hospitalised for more than 72 h or who had been discharged from an acute care hospital within 10 days, patients who had organ transplantation within 6 months, patients with severe acute respiratory syndrome (SARS) or known human immunodeficiency virus (HIV)-infected patients were excluded from the study.

All enrolled patients were evaluated with regard to clinical, radiological and microbiological findings. All available clinical, laboratory and radiological information was recorded. The presence of the following co-morbid conditions was determined by patient report or chart review: bronchopulmonary disease (i.e. asthma, chronic obstructive pulmonary disease or interstitial lung disease); congestive heart failure; coronary artery disease; malignancy; cerebrovascular disease; renal disease; and immunosuppression. Based on these findings, risk class was determined according to the criteria from the Pneumonia Patient Outcomes Research Team (PPORT) study [9].

For this study, no specific antibiotic regimens were recommended. Use of antimicrobial agents in each centre was recorded, and follow-up evaluation was done for clinical, radiological and microbiological responses to antimicrobial therapy. The clinical outcome was measured by the 30-day mortality rate.

2.3. Microbiological evaluation

At the time of enrolment, sputum cultures, blood cultures (if feasible) and serological tests for atypical pathogens were performed. All microbiological evaluations were performed before initiation of antimicrobial treatment. All sputum specimens and other samples of respiratory secretions were Gram stained and examined microscopically for the presence of WBCs, epithelial cells and bacteria. Purulence was measured by microscopy and was acceptable if there was >25 WBCs and <10 squamous epithelial cells. Results from sputum cultures were only considered significant if the above Gram-stain criteria were satisfied.

Given their practical performance, cost, specificity and sensitivity, three serological kits were chosen for detection of atypical pathogens. To detect *M. pneumoniae* and *C. pneumoniae* in all enrolled patients, PLATELIA® *M. pneumoniae* kit (Bio-Rad, Marnes-la-Coquette, France) and *C. pneumoniae* EIA kit (Thermo Labsystems, Helsinki, Finland) were used according to the manufacturers' instructions, which consist of 96-well microplates using enzyme-linked immunosorbent assay (ELISA). These were kits for detecting immunoglobulin G (IgG) and IgM class antibodies. The presence of IgM antibodies allowed the diagnosis of acute infection directly on the first serum sample. If the result of IgM was negative or equivocal, IgG was tested on the first serum (stored after IgM test) and on the second serum (second blood sampling after 8–15 days) samples. If the second titre of IgG increased more than twice compared with the first titre, acute infection was confirmed. To detect *Legionella pneumophila* in all enrolled patients, NOW® Legionella urinary antigen test (Binax Inc., Scarborough, ME) was used, which is an in vitro rapid immunochromatographic assay for the qualitative detection of *L. pneumophila* serogroup 1 antigen in urine specimens from patients with symptoms of pneumonia.

The aetiology of pneumonia was confirmed if one of the following criteria was met: (1) blood cultures yielding a bacterial or fungal pathogen (in the absence of an apparent extrapulmonary focus); (2) pleural fluid or transthoracic needle aspiration cultures yielding a bacterial pathogen; (3) seroconversion (i.e. a four-fold increase in IgG titres); (4) a single increased IgM titre for *C. pneumoniae* or *M. pneumoniae*; (5) positive urinary antigen for *L. pneumophila* or *S. pneumoniae*; and (6) bacterial growth in cultures of bronchoalveolar lavage (BAL) fluid $\geq 10^4$ colony-forming units/mL. The aetiology was considered presumptive if a valid sputum sample yielded one or more predominant bacterial strains [4,5].

2.4. Antimicrobial susceptibility tests

Bacterial isolates from initial cultures were subjected to in vitro testing in each local microbiology laboratory as usual. All isolates were sent to the Central Laboratory (Samsung Medical Center, Seoul, South Korea) for further in vitro testing with various antimicrobial agents. Antimicrobial susceptibility tests were performed by the broth microdilution method according to the standards of the Clinical and Laboratory Standards Institute. Antimicrobial agents tested were penicillin, amoxicillin/clavulanic acid, cefuroxime, ceftriaxone, imipenem, erythromycin, azithromycin, ciprofloxacin, levofloxacin, teicoplanin and vancomycin.

2.5. Statistical analysis

Student's *t*-test was used to compare continuous variables and χ^2 or Fisher's exact test to compare categorical variables. In identifying the independent risk factors for mortality, a stepwise conditional logistic regression analysis was used to control for the effects of confounding variables. All *P*-values were two-tailed and *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 1031 cases were enrolled in the study from 14 centres from January 2002 to December 2004, but 76 cases were excluded owing to inadequate medical records. Therefore, a total of 955 cases (604 men and 351 women) fulfilling diagnostic criteria of CAP were evaluated; 338 (35.4%) from Korea, 114 (11.9%) from Hong Kong, 111 (11.6%) from China, 104 (10.9%) from India, 96 (10.1%) from Singapore, 72 (7.5%) from Vietnam, 65 (6.8%) from Taiwan and 55 (5.8%) from The Philippines.

Demographic characteristics of the patients are shown in Table 1. The mean age (± standard deviation) of the patients was 57.3 ± 13.7 years (range 16–94 years). Bronchopulmonary disease (29.9%) was the most frequent underlying disease, followed by cardiovascular diseases (19.9%), malignancy (11.7%) and neurological disorders (8.2%) (Table 1).

Table 1
Demographic and clinical characteristics of the study population

Characteristic	No. of patients (%) ($n = 955$)[a]
Age, mean ± S.D. (range) (years)	57.3 ± 13.7 (16–94)
Male	604 (63.2)
Underlying diseases	
Bronchopulmonary disorder	286 (29.9)
Cardiovascular disorder	190 (19.9)
Neoplastic disorder	112 (11.7)
Neurological disorder	78 (8.2)
Liver disorder	42 (4.4)
Renal disorder	39 (4.1)
Asplenia or hyposplenia	7 (0.7)
None	278 (29.1)
Co-morbid conditions	
Neutropenia	33/912 (3.6)
Use of immunosuppressant	25/912 (2.7)
Use of corticosteroid	18/912 (2.0)
Smoking	238/912 (26.1)
High alcohol intake	60/912 (6.6)
Residence in nursing home	29/912 (3.2)
Recent hospitalisation	69/912 (7.6)
Prior use of antimicrobial agent	230/760 (30.3)

S.D., standard deviation.
[a] Exact numbers are given for each variable; information was not available for all patients. Unless otherwise indicated, data represent number of patients (%).

A smoking history was reported in 238 patients (26.1%), and 230 patients (30.3%) had a history of prior antibiotic use.

3.2. Clinical manifestations

The clinical, laboratory and radiological findings of patients at enrolment are summarised in Table 2. Cough (92.8%) was the most common symptom, and 10.7% of patients (86/801) presented with altered mentality. Leukocytosis (WBC > 10 000/mm^3), azotaemia (blood urea nitrogen > 30 mg/dL) and hypoxaemia (PaO_2 < 60 mmHg or arterial oxygen saturation (SaO_2) < 90%) were also observed in 66.7%, 19.4% and 14.7%, respectively (Table 2). Multiple lobes were involved in 35.3% of patients and pleural effusion was found in 15.0%.

The disease severity of pneumonia in 929 patients was classified based on PORT criteria at the time of enrolment. Patients belonged to the following classes: 214 (23.0%) to class I; 281 (30.2%) to class II; 170 (18.3%) to class III; 193 (20.8%) to class IV; and 71 (7.6%) to class V. Overall, 593 patients (62.1%) were admitted to hospital and 56 patients (5.9%) were admitted to the Intensive Care Unit.

3.3. Aetiology of CAP

A microbiological aetiology could be determined in 428 (44.8%) of the 955 patients, which was definitive in 223 (52.1%) of cases and presumptive in 205 (47.9%).

Overall, a total of 390 bacterial pathogens were isolated from 349 patients (36.5%). The most common specimen source was sputum (76.4%), followed by blood (6.4%), pleural fluid (4.4%), BAL (2.8%) and other specimens (10.0%). Of the 390 isolates, *S. pneumoniae* (29.2%) was the most frequent isolate, followed by *Klebsiella pneumoniae* (15.4%), *H. influenzae* (15.1%), *Pseudomonas aeruginosa* (6.7%), *Staphylococcus aureus* (4.9%), *Mycobacterium tuberculosis* (3.3%) and *Moraxella catarrhalis* (3.1%) (Table 3).

For serological tests of *M. pneumoniae* and *C. pneumoniae*, paired sera were obtained from 556 and 411 patients, respectively. Of these, positive serological results were obtained from 61 (11.0%) for *M. pneumoniae* and 55 (13.4%) patients for *C. pneumoniae*. For urinary antigen tests of *L. pneumophila*, urine samples were obtained from 648 patients and only 7 (1.1%) of them were positive for *L. pneumophila*.

Of 349 patients with bacterial pathogens isolated, mixed infections were found in 60 patients (17.2%) as follows: 44 patients with two different pathogens, 8 patients with three different pathogens and 8 patients with four different pathogens (Table 3). The most frequent combination was *S. pneumoniae* with *C. pneumoniae* (9/60; 15.0%). Mixed

Table 2
Clinical manifestations and laboratory findings at initial presentation

Findings	No. of patients (%) ($n = 955$)[a]
Symptoms	
Cough	743/801 (92.8)
Purulent sputum	684/776 (88.1)
Dyspnoea	479/766 (62.5)
Chest pain	264/941 (28.1)
Altered mentality	86/801 (10.7)
Signs	
Respiratory rate >30/min	89/955 (9.3)
Heart rate ≥125/min	66/955 (6.9)
Temperature ≥40 °C or < 35 °C	52/955 (5.4)
SBP <90 mmHg	29/955 (3.0)
Laboratory findings	
WBC ≥10 000/mm^3	588/882 (66.7)
BUN ≥ 30 mg/dL	164/847 (19.4)
PaO_2 <60 mmHg or SaO_2 < 90%	122/831 (14.7)
Haematocrit <30%	97/879 (11.0)
Serum sodium <130 mEq/L	79/856 (9.2)
Glucose ≥250 mg/dL	75/840 (8.9)
Arterial pH <7.35	52/750 (6.9)
Radiological findings	
Lobar pneumonia	380/861 (44.1)
Bronchopneumonia	396/861 (46.0)
Interstitial pneumonia	85/861 (9.9)
Multilobar involvement	303/859 (35.3)
Pleural effusion	137/915 (15.0)
Pneumonia severity index	
I	214/929 (23.0)
II	281/929 (30.2)
III	170/929 (18.3)
IV	193/929 (20.8)
V	71/929 (7.6)

SBP, systolic blood pressure; WBC, white blood cells; BUN, blood urea nitrogen; PaO_2, partial pressure of oxygen in arterial blood; SaO_2, arterial oxygen saturation.
[a] Exact numbers are given for each variable; information was not available for all patients.

Table 3
Aetiological distribution of community-acquired pneumonia in Asian countries

Aetiology	No. of isolates (%)
Pathogens isolated ($n = 390$)	
Streptococcus pneumoniae	114 (29.2)
Klebsiella pneumoniae	60 (15.4)
Haemophilus influenzae	59 (15.1)
Pseudomonas aeruginosa	26 (6.7)
Staphylococcus aureus	19 (4.9)
Mycobacterium tuberculosis	13 (3.3)
Moraxella catarrhalis	12 (3.1)
Other pathogens	77 (19.7)
Mycoplasma pneumoniae	61/556 (11.0)
Chlamydia pneumoniae	55/411 (13.4)
Legionella pneumophila	7/648 (1.1)
Mixed infections ($n = 60$)	
S. pneumoniae + *C. pneumoniae*	9 (15.0)
S. pneumoniae + *M. pneumoniae*	5 (8.3)
S. pneumoniae + *K. pneumoniae*	5 (8.3)
S. pneumoniae + *M. catarrhalis*	4 (6.7)
S. pneumoniae + other pathogen	3 (5.0)
H. influenzae + *K. pneumoniae*	5 (8.3)
H. influenzae + *M. catarrhalis*	3 (5.0)
H. influenzae + *C. pneumoniae*	2 (3.3)
H. influenzae + other pathogen	2 (3.3)
K. pneumoniae + *C. pneumoniae*	2 (3.3)
K. pneumoniae + other pathogen	2 (3.3)
C. pneumoniae + *M. tuberculosis*	1 (1.7)
M. pneumoniae + *P. aeruginosa*	1 (1.7)
S. pneumoniae + *H. influenzae* + *C. pneumoniae*	1 (1.7)
S. pneumoniae + *C. pneumoniae* + virus	1 (1.7)
S. pneumoniae + other pathogens	1 (1.7)
H. influenzae + *K. pneumoniae* + *P. aeruginosa*	1 (1.7)
Other pathogens	12 (20.0)

infections were found in 25.4% (29/114) of patients with pneumococcal pneumonia.

3.4. Antimicrobial susceptibility testing

The results of antimicrobial susceptibility testing against major pathogens are summarised in Table 4. Of 57 pneumococcal isolates available, 30 (52.6%) isolates were not susceptible to penicillin: 10 (17.5%) were penicillin intermediate (minimum inhibitory concentration (MIC) = 0.12–1 μg/mL) and 20 (35.1%) were penicillin resistant (MIC ≥ 2 μg/mL). Resistance rates to erythromycin, cefuroxime and ceftriaxone were 56.1%, 47.4% and 7.0%, respectively. No pneumococcal isolates were resistant to vancomycin or levofloxacin.

Of 16 *H. influenzae* isolates, 2 isolates (12.5%) were resistant to azithromycin and all isolates were susceptible to amoxicillin/clavulanic acid, ciprofloxacin and imipenem.

Of 36 *K. pneumoniae* isolates, resistance rates to cefuroxime and ceftriaxone were 11.1% and 2.8%, respectively. All *K. pneumoniae* isolates were susceptible to ciprofloxacin and imipenem (Table 4).

3.5. Antimicrobial therapy

In all 955 cases, antimicrobial therapy was initiated within 24 h after enrolment. Five hundred and forty-two patients (56.8%) received combination therapy as an initial empirical antimicrobial therapy. Of these, third-generation cephalosporin + macrolide (41.3%) was the most frequently prescribed combination regimen, followed by penicillin + macrolide (16.2%), third-generation cephalosporin + fluoroquinolone (7.7%) and penicillin + aminoglycoside (6.3%). Four hundred and thirteen patients (43.2%) received monotherapy as the empirical antimicrobial therapy. Of these, penicillin (36.8%) was the most common agent followed by fluoroquinolone (25.7%), third-generation cephalosporin (17.4%), second-generation cephalosporin (4.6%) and macrolide (3.4%).

3.6. Clinical outcomes of CAP

The clinical outcomes were evaluated in 885 cases that had submitted relevant data for outcome analysis. The overall 30-day mortality rate was 7.3% (65/885). Of 882 patients who were evaluated by the PORT classification, mortality rates were 0.5% in class I (1/201), 1.6% in class II (4/253), 5.4% in class III (9/167), 12.6% in class IV (24/190) and 38.0% in class V (27/71).

With regard to the final clinical outcomes, clinical improvement without modification of antibiotics (58.6%), clinical improvement with modification of antibiotics (18.9%) and death due to pneumonia aggravation (5.9%) were observed, whilst clinical outcomes were undetermined in 16.6% of cases.

In the univariate analyses, risk factors for mortality included old age, nursing home residence, malignancy, cardiovascular diseases, renal diseases, prior hospitalisation, altered mentality, respiratory rate >30/min, systolic blood pressure <90 mmHg, pulse rate >125/min, leukocytosis, azotaemia, hypoxaemia, hyponatraemia, high glucose level, low haematocrit, multilobar involvement, pleural effusion and mechanical ventilation (all $P < 0.05$) (Table 5). Multivariate analysis using a logistic regression model, including the variables associated with mortality by univariate analysis ($P < 0.05$), showed that nursing home residence, mechanical ventilation, malignancy, cardiovascular diseases, respiratory rate > 30/min and hyponatraemia were independent risk factors for mortality ($P < 0.05$) (Table 6).

4. Discussion

The current data provided a comprehensive evaluation of causes and outcomes of patients with CAP in Asian countries from a large, prospective, multicentre study. This ANSORP study highlights several characteristics of CAP in Asian countries: the high prevalence of *S. pneumoniae* as an aetiological pathogen; the relatively high prevalence of mixed infections

Table 4
Antimicrobial susceptibility of major pathogens

Major pathogens	No. of isolates (%)			MIC_{90} (μg/mL)
	S	I	R	
Streptococcus pneumoniae (*n* = 57)				
Penicillin[a]	27 (47.4)	10 (17.5)	20 (35.1)	2
Amoxicillin/clavulanic acid	49 (86.0)	6 (10.5)	2 (3.5)	4/2
Erythromycin	25 (43.9)	0	32 (56.1)	>32
Cefuroxime[b]	30 (52.6)	0	27 (47.4)	8
Ceftriaxone[b]	38 (66.7)	15 (26.3)	4 (7.0)	1
Levofloxacin	57 (100.0)	0	0	1
Vancomycin	57 (100.0)	0	0	0.25
Haemophilus influenzae (*n* = 16)				
Amoxicillin/clavulanic acid	16 (100.0)	0	0	0.5/0.25
Cefuroxime	15 (93.8)	0	1 (6.3)	1
Ceftriaxone	15 (93.8)	0	1 (6.3)	1
Azithromycin	14 (87.5)	0	2 (12.5)	2
Ciprofloxacin	16 (100.0)	0	0	1
Imipenem	16 (100.0)	0	0	2
Klebsiella pneumoniae (*n* = 36)				
Amoxicillin/clavulanic acid	27 (75.0)	1 (2.8)	8 (22.2)	64/32
Cefuroxime	32 (88.9)	0	4 (11.1)	64
Ceftriaxone	35 (97.2)	0	1 (2.8)	0.5
Ciprofloxacin	36 (100.0)	0	0	0.25
Imipenem	36 (100.0)	0	0	0.5

S, susceptible; I, intermediate; R, resistant; MIC, minimum inhibitory concentration; MIC_{90}, MIC of 90% of the organisms.
[a] Susceptible, MIC ≤ 0.1 μg/mL; intermediate, MIC = 0.12–1 μg/mL; resistant, MIC ≥ 2 μg/mL.
[b] Susceptible, MIC ≤ 1 μg/mL; intermediate, MIC = 2 μg/mL; resistant, MIC ≥ 4 μg/mL.

by bacteria and atypical pathogens; antimicrobial practice for the treatment of CAP; clinical outcomes; and risk factors for mortality. Demographic characteristics of the patients in this study were similar with those in previous data from other regions [2–6]. Approximately 71% of all enrolled patients had at least one co-morbid condition, including bronchopulmonary disorder, cardiovascular disorder, malignancy and neurological disorder. There were no significant differences in the clinical presentations between CAP caused by typical bacterial pathogens and atypical pathogens (data not shown).

In this study, aetiological pathogens were identified in 44.8% of cases based on microbiological or serological studies. The relatively low percentage of cases with identifiable aetiology might be due to prior antibiotic use before cultures and difficulties in obtaining adequate sputum specimen [3,4]. Approximately 30% of cases had received antimicrobial therapy before enrolment in this study. Among identified aetiologies, *S. pneumoniae* was the most common pathogen, as previously reported from other regions [4,5]. In vitro resistance to penicillin, macrolides and other antimicrobial agents in pneumococcal isolates from this study was consistent with findings from previous ANSORP studies in Asian countries [7,8]. In particular, a high prevalence of erythromycin resistance with a very high MIC level would preclude the use of macrolides as first-line agents for the treatment of CAP in many Asian countries.

Prevalence rates of *M. pneumoniae* and *C. pneumoniae* in Asian countries were comparable with those in other regions [4–6]. Approximately 25% of CAP cases in Asian countries were caused by these atypical pathogens. Interestingly, however, the incidence of CAP caused by *Legionella* spp. was extremely low (1.1%) in this study. Although the incidence of *Legionella* pneumonia was low in this study, it has been reported as one of the most common atypical pathogens of CAP around the world [3,5]. Another important finding from this study was the relatively high incidence of mixed infections by typical bacteria and atypical pathogens. The significance and frequency of mixed infections in CAP, mainly mixed bacterial–viral infections, has been increasingly reported [5]. Although we did not evaluate the viral aetiology in this study, 17% of CAP cases were caused by multiple pathogens such as *S. pneumoniae* and *C. pneumoniae* or *S. pneumoniae* and *M. pneumoniae*. This epidemiological finding is important in clinical practice because this type of mixed infection may result in treatment failure of monotherapy with β-lactam agents. Tuberculosis (TB) was diagnosed in 13 patients, which showed the same clinical presentations as bacterial pneumoniae. TB should be considered the possible cause of CAP, especially in areas where TB is endemic [4,10].

Selection of appropriate antimicrobial agents is essential for the treatment of CAP, which should be based on suspected microorganisms, risk factors and severity of illness [1]. According to the recent IDSA/ATS guidelines, macrolides, doxycycline or fluoroquinolones are recommended as a monotherapy option for treating

Table 5
Factors associated with 30-day mortality in patients with community-acquired pneumonia in the univariate analysis

	Survivors ($n = 820$)[a]	Non-survivors ($n = 65$)[a]	OR (95% CI)	*P*-value
Old age (≥65 years)	160/820 (19.5)	20/65 (30.8)	1.83 (1.05–3.19)	0.037
Residence in nursing home	23/820 (2.8)	6/65 (9.2)	3.52 (1.38–8.99)	0.015
Underlying diseases				
Bronchopulmonary disorder	258/820 (31.5)	20/65 (30.8)	0.97 (0.56–1.67)	0.908
Cardiovascular disorder	165/820 (20.1)	25/65 (38.5)	2.48 (1.46–4.21)	0.001
Malignancy	92/820 (11.2)	16/65 (24.6)	2.58 (1.41–4.73)	0.001
Neurological disorder	69/820 (8.4)	9/65 (13.8)	1.75 (0.83–3.69)	0.137
Liver disorder	37/820 (4.5)	5/65 (7.7)	1.76 (0.67–4.65)	0.22
Renal disorder	32/820 (3.9)	6/65 (9.2)	2.50 (1.01–6.23)	0.053
Co-morbid condition				
Neutropenia	28/820 (3.4)	4/65 (6.2)	1.86 (0.63–5.46)	0.286
Corticosteroid use	17/820 (2.1)	1/65 (1.5)	0.74 (0.10–5.64)	1.000
Immunosuppressant use	23/820 (2.8)	2/65 (3.1)	1.10 (0.25–4.77)	0.705
Smoking	215/820 (26.2)	21/65 (32.3)	1.34 (0.78–2.31)	0.285
Alcoholism	53/820 (6.5)	6/65 (9.2)	1.47 (0.61–3.57)	0.433
Recent hospitalisation	54/820 (6.6)	13/65 (20.0)	3.55 (1.82–6.91)	0.001
ICU admission	35/819 (4.3)	33/65 (50.8)	23.10 (12.77–41.78)	<0.001
Mechanical ventilation	24/729 (3.3)	36/57 (63.2)	50.36 (25.65–98.87)	<0.001
Symptoms and signs				
Dyspnoea	419/698 (60.0)	56/63 (88.9)	5.33 (2.39–11.86)	<0.001
Chest pain	243/687 (35.4)	21/57 (36.8)	1.07 (0.61–1.87)	0.824
Altered mentality	63/731 (8.6)	23/65 (35.4)	5.81 (3.28–10.27)	<0.001
Temperature ≥40 °C or < 35 °C	39/820 (4.8)	4/65 (6.2)	1.31 (0.45–3.80)	0.549
Respiratory rate > 30/min	63/820 (7.7)	25/65 (38.5)	7.51 (4.28–13.17)	<0.001
SBP < 90 mmHg	22/820 (2.7)	7/65 (10.8)	4.38 (1.79–10.67)	0.004
Pulse rate > 125/min	56/820 (6.8)	9/65 (13.8)	2.19 (1.03–4.66)	0.047
Laboratory findings				
WBC ≥ 10 000/mm^3	531/814 (65.2)	54/63 (85.7)	3.19 (1.56–6.57)	0.001
BUN ≥ 30 mg/dL	139/783 (17.8)	24/59 (40.7)	3.18 (1.83–5.51)	<0.001
PaO_2 < 60 mmHg or SaO_2 < 90%	93/764 (12.2)	29/63 (46.0)	6.15 (3.58–10.57)	<0.001
Haematocrit < 30%	81/812 (10.0)	14/62 (22.6)	2.63 (1.39–4.98)	0.002
Serum sodium < 130 mEq/L	62/789 (7.9)	16/62 (25.8)	4.08 (2.18–7.62)	<0.001
Glucose ≥ 250 mg/dL	63/775 (8.1)	12/61 (19.7)	2.77 (1.40–5.47)	0.002
Arterial pH < 7.35	34/690 (4.9)	18/59 (30.5)	8.47 (4.41–16.27)	<0.001
Pneumonia severity index				
I	200/817 (24.5)	1/65 (1.5)	–	<0.001
II	249/817 (30.5)	4/65 (6.2)	–	
III	158/817 (19.3)	9/65 (13.8)	–	
IV	166/817 (20.3)	24/65 (36.9)	–	
V	44/817 (5.4)	27/65 (41.5)	–	
Multilobar involvement	256/755 (33.9)	32/56 (57.1)	2.60 (1.49–4.51)	<0.001
Pleural effusion	116/805 (14.4)	15/62 (24.2)	1.89 (1.03–3.50)	0.038
Streptococcus pneumoniae	100/820 (12.2)	11/65 (16.9)	1.47 (0.74–2.89)	0.268
Atypical pneumonia	89/820 (10.9)	4/65 (6.2)	0.54 (0.19–1.52)	0.234
Combination therapy	455/798 (57.0)	41/65 (63.1)	1.29 (0.76–2.17)	0.342

OR, odds ratio; CI, confidence interval; ICU, Intensive Care Unit; SBP, systolic blood pressure; WBC, white blood cells; BUN, blood urea nitrogen; PaO_2, partial pressure of oxygen in arterial blood; SaO_2, arterial oxygen saturation.

[a] Exact numbers are given for each variable; information was not available for all patients.

outpatients with CAP [1]. However, macrolides or doxycycline may not be appropriate options for treatment of outpatients with CAP in Asian countries where resistance to macrolides and tetracycline is very prevalent [7]. Also, single use of β-lactam agents would result in clinical failure if CAP is caused by multiple agents including atypical pathogens. The current study showed that regardless of microorganisms, risk factors and severity of CAP, a combination regimen, especially third-generation cephalosporin + macrolide, is one of the most common regimens used for treatment of patients with CAP in Asian countries.

The overall mortality rate of CAP was 7.3%, and one-half of cases died of uncontrolled pneumonia. The current study could identify the risk factors for death, which would be similar to those documented in other studies [11–16]. Among independent risk factors identified in this study, hyponatraemia is a common complication present at the time of

Table 6
Multivariate analysis of independent risk factors for mortality in 777 patients with community-acquired pneumonia

Variable	Adjusted OR (95% CI)	*P*-value
Mechanical ventilation	43.75 (20.16–94.97)	<0.001
Nursing home residence	6.78 (2.11–21.85)	0.001
Respiratory rate > 30/min	5.91 (2.53–13.85)	<0.001
Hyponatraemia	4.08 (1.66–10.03)	0.002
Malignancy	2.88 (1.67–7.14)	0.022
Cardiovascular diseases	2.83 (1.33–6.00)	0.007

OR, odds ratio; CI, confidence interval.

admission for CAP that is associated with more severe illness [17].

Our study may have some limitations. First, the number of cases with CAP from each country is relatively small, which may not represent the national status of pathogen distribution and antimicrobial resistance in these pathogens. Second, since we did not evaluate viral aetiology, we could not estimate the true incidence of mixed infections.

In conclusion, data from this study could provide a better understanding of the aetiology, risk factors, clinical characteristics and outcomes of CAP in Asian countries. Given the prevalence of major bacterial pathogens and antimicrobial susceptibility as well as incidence of atypical pathogens and mixed infections, appropriate antimicrobial options could be recommended for Asian countries.

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References

[1] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl. 2):S27–72.

[2] Fass RJ. Aetiology and treatment of community-acquired pneumonia in adults: an historical perspective. J Antimicrob Chemother 1993;32(Suppl. A):S17–27.

[3] Fang GD, Fine M, Orloff JDA, Arisumi D, Yu VL, Kapoor W, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. Medicine (Baltimore) 1990;69:307–16.

[4] Luna CM, Famiglietti A, Absi R, Videla AJ, Nogueira FJ, Fuenzalida AD, et al. Community-acquired pneumonia: etiology, epidemiology, and outcome at a teaching hospital in Argentina. Chest 2000;118:1344–54.

[5] Ruiz M, Ewig S, Marcos MA, Martinez JA, Sanchez M, Mensa J, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 1999;160:397–405.

[6] Almirall J, Bolibar I, Vidal J, Sauca G, Coll P, Niklasson B, et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. Eur Respir J 2000;15:757–63.

[7] Song JH, Jung SI, Ki HK, Shin MH, Ko KS, Son JS, et al. Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries: a study by the Asian Network for Surveillance of Resistant Pathogens. Clin Infect Dis 2004;38:1570–8.

[8] Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, et al. High prevalence of antimicrobial resistance among clinical pathogens of *Streptococcus pneumoniae* in Asian countries: ANSORP study. Antimicrob Agents Chemother 2004;48:2101–7.

[9] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243–50.

[10] Miller LG, Asch SM, Yu EI, Knowles L, Gelberg L, Davidson P. A population-based survey of tuberculosis symptoms: how atypical are atypical presentations? Clin Infect Dis 2000;30:293–9.

[11] Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, Gudiol F. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 2004;164:502–8.

[12] Menendez R, Torres A, Zalacain R, Aspa J, Martin Villaclaras JJ, Borderias L, et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 2004;59:960–5.

[13] Sin DD, Man SF, Marrie TJ. Arterial carbon dioxide tension on admission as a marker of in-hospital mortality in community-acquired pneumonia. Am J Med 2005;118:145–50.

[14] Ruiz M, Ewig S, Torres A, Arancibia F, Marco F, Mensa J, et al. Severe community-acquired pneumonia. Am J Respir Crit Care Med 1999;160:923–9.

[15] Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. JAMA 1996;275:134–41.

[16] Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. Chest 2005;127:1260–70.

[17] Nair V, Niederman MS, Masani N, Fishbane S. Hyponatremia in community-acquired pneumonia. Am J Nephrol 2007;27:184–90.