*Original Article*

# Impact of infectious etiology on the outcome of Taiwanese patients hospitalized with community acquired pneumonia

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## Abstract

Introduction: This study aimed to assess the relationships between infectious etiology, empiric treatment, and outcomes in Taiwanese patients with community acquired pneumonia (CAP).

Methodology: A retrospective analysis of the data of 208 adult patients from a single medical center was performed with patients classified as having low or high disease severity based on the Pneumonia Severity Index (PSI). Patients with PSI ≤ 90 (n=120) were classified as low severity and patients with PSI > 90 (n=88) were classified as high severity.

Results: The low-risk group had significantly higher rates of infection with *Chlamydia pneumoniae* (*C. pneumoniae*) and *Mycoplasma pneumoniae* (*M. pneumoniae*), whereas the high-risk group had significantly higher rates of infection with *Klebsiella pneumoniae* (*K. pneumoniae*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) ($p < 0.05$). Empiric treatment in both groups was in accordance with the 2007 guidelines issued by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS). Twenty-nine of 208 patients (13.9%) died, one in the low-risk group and 28 in the high-risk group. The highest rates of mortality were in patients infected with *P. aeruginosa* or *K. pneumoniae*.

Conclusions: In the present study, we demonstrated that the patients with different severity had different microbiologic etiology. In general, *P. aeruginosa* and *K. pneumoniae* were the most commonly isolated organisms in high-risk patients who died from CAP. We showed that use of the IIDSA/ATS guidelines for treatment of CAP in Taiwan resulted in a better outcome in the low PSI group.

**Key words:** community-acquired pneumonia; epidemiology; pathogen; Pneumonia Severity Index; Taiwan; guidelines

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## Introduction

Community-acquired pneumonia (CAP) remains a common but potentially life-threatening infectious disease. The mortality rates of severe CAP (6.6%-16.7%) remain high [1] and CAP is the sixth leading cause of death in Taiwan. In 2006, 5396 deaths in Taiwan (23.6 persons per 100,000) were attributed to pneumonia [2]. The causative pathogens of CAP may be associated with geographic area and the presence of underlying diseases [3]. Early appropriate empirical antimicrobial therapy has been shown to be crucial to the outcome of severe CAP [3]. The importance of the microbiological etiology of CAP has been recognized; however, there is little information about the microbiological etiology of CAP on clinical outcome [3,4].

The effectiveness of an antibiotic regimen depends on several factors including causative pathogen, susceptibility to antibiotics, and geographical distribution. Acute pneumonia may be caused by a variety of microorganisms. However, for critically ill patients, antibiotic therapy is generally started empirically until the causative pathogens are identified and susceptibility testing is accomplished. One of the most critical and difficult decisions facing the clinician who treats patients with severe CAP is the choice of empiric antibiotic therapy and the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) has proposed guidelines to facilitate this [5]. Although these guidelines are useful in most common etiologies of CAP, whether these guidelines are also suitable for severe CAP caused by other pathogens is still unknown.

Numerous studies have documented the relationship between specific pathogenic bacteria and the severity of CAP. A prospective study of adult patients with CAP on the Mediterranean coast of Spain indicated that *Streptococcus pneumoniae* (*S. pneumoniae*) was the most prevalent species, either alone or co-infected with other organisms [6]. Similarly, other studies indicated that *S. pneumoniae* was the most common pathogen responsible for CAP among hospitalized patients in Thailand and Taiwan [7,8]. However, Taiwan and South Africa have reported uniquely relatively high incidence of *Klebsiella pneumoniae* (*K. pneumoniae*) infection in CAP, and *K. pneumonia* was responsible for 54% (31/57) of the mortalities of bacteremic pneumonia among severe patients in Taiwan [9].

Assessment of disease severity is a critical step in the management of CAP. Many studies have attempted to stratify patients by CAP severity and identify patients at highest risk for death. Risk factors for CAP-associated mortality include age greater than 65 years, male sex, and the presence of certain comorbidities [6]. Scoring systems such as the Pneumonia Severity Index (PSI) have been developed to assess disease severity and predict mortality [10,11]. However, the general consensus showed that such scores should be used with caution and only in connection with clinical judgment.

In this study, we aimed to characterize the etiology of CAP in Taiwanese patients with different severities of disease. We also investigated the relationship of etiological agents, treatment, and severity score of patients who were admitted to our hospital for CAP.

## Methodology

*Patients and diagnostic criteria*

Data were retrospectively collected from patients who were at least 15 years old and admitted for treatment of CAP by the Emergency or Outpatient Departments of the Chung Shan Medical University Hospital (Taichung City, Taiwan), a tertiary-care hospital, between 1 January 2007 and 31 December 2008. A total of 250 consecutively presenting patients were initially enrolled, and 42 patients were excluded due to incomplete microbiology data (n = 11), young age (n = 2), loss of follow up after discharge (n = 8), missing major laboratory data (n = 10), previous hospitalization, referral from another hospital, recent antibiotic use before admission (n = 9), HIV infection (n = 1), or neutropenia (n = 1). This study was approved by the hospital's Institution Review Board (permit number CSH05124).

Demographic characteristics, comorbidities, symptoms and signs of pneumonia, laboratory results, and previous antibiotic treatment were recorded upon admission. The diagnostic criteria for CAP, based on the guidelines of the IDSA/ATS [5], were as follows: typical infiltration changes on chest X-ray films within one day of symptom onset, as indicated in the radiology report; at least one clinical manifestation, such as cough, yellow and thick sputum, or fever (> 37.8°C); or at least two minor criteria, such as tachypnea, dyspnea, pleural pain, chest pain, confusion or disorientation, lung consolidation, or white cell count (WBC) greater than 12,000 cells/μL. Exclusion criteria were as follows: outpatient status; transfer from another hospital or hospital admission within the previous three weeks; presence of other acute conditions, such as pulmonary edema, pulmonary embolism, or malignancy that appeared during follow-up; severe immunocompromised status, including severe neutropenia (WBC < $1.0 \times 10^9$ cells/L); organ or bone marrow transplant; and HIV infection. The severity of pneumonia was assessed with the PSI [12], Acute Physiology and Chronic Health Evaluation II (APACHE II) [13], and CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older) [14] scores.

*Study design and methodology*

A preliminary multivariate analysis of our data indicated that a PSI greater than 90 was an independent risk factor for mortality. Thus we stratified patients into two groups: low risk (PSI ≤ 90) and high risk (PSI > 90). Disease outcome was categorized as follows: survival (the patient was

discharged after treatment or recovered during hospitalization); the patient did not recover (experienced respiratory failure or septic shock, or required mechanical ventilation for more than 21 days during hospitalization); and all causes of mortality within 30 days during hospitalization.

Microbiologic evaluation was performed as described previously [15]. One set of sputum smears was examined by Gram staining, and two sets of blood cultures or pleural fluid cultures were examined before administration of antibiotics. A positive sputum smear was defined as one that had more than 25 polymorphonuclear cells and fewer than 10 epithelial cells per low-power field. BinaxNow *S. pneumoniae* kits (Inverness Medical Professional Diagnostics, Princeton, NJ, USA) were used to test for *S. pneumoniae* antigens in urine, BinaxNow *Legionella pneumophila* (*L. pneumophila*) kits (Inverness Medical Professional Diagnostics, Princeton, NJ, USA) were used to test for *L. pneumophila* antigens in urine and enzyme-linked immunosorbent assays (ELISAs; Inverness Medical Professional Diagnostics)) were used to detect this organism in serum. *M. pneumoniae* was identified with a serum complement fixation test. *Chlamydophila pneumoniae* (*C. pneumoniae*) was identified with a serum ELISA that detected antibodies (IgM, IgA, or IgG) against *C. pneumonia*, while *K. pneumoniae* and *Pseudomonas aeruginosa* (*P. aeruginosa*) were identified by culture of sputum and blood specimens. Antimicrobial susceptibility testing was performed using Kirby-Bauer disk diffusion method and Etest method according to the criteria of the National Committee on Clinical Laboratory Standards (NCCLS; 2004).

Species identification was categorized as definite, presumptive, mixed infection, or unknown [15]. A definite diagnosis was made if i) a single species (bacterial or mycoplasmal) was isolated from blood cultures or pleural fluid cultures; ii) the urine antigen tests were positive for *S. pneumoniae*; iii) there was a four-fold elevation in serum antibody titers for *M. pneumoniae* (≥ 1:160) or *C. pneumoniae* (IgM, IgA, or IgG); iv) there was an increase in *C. pneumoniae* (IgM ≥ 1:32 titer). However, it is important to note that the lack of specificity makes it a challenge to use this method as a confirmatory test for *C. pneumoniae*; or v) the urine antigen tests were positive for *L. pneumophila*. A presumptive diagnosis was made if the following criteria were met: i) a single predominant strain of bacteria was detected in sputum culture that agreed with the results of Gram staining of the sputum smear; ii) an antibody titer against *M. pneumoniae* (≥ 1:160) was detected in serum specimens obtained during the acute or recovery stages [7]; or iii) a positive titer of *C. pneumoniae* IgA or IgG ( ≥ 1:512) was present [7]. A mixed infection diagnosis was made according to the above diagnostic criteria when more than one pathogen was present. A diagnosis of unknown etiology was made when no pathogen could be isolated.

The empiric antibiotics prescribed during the first 24 hours of hospitalization were defined to be the initial empiric antibiotics. All initial empiric antimicrobial therapies, whether or not they adhered to the IDSA/ATS guidelines, were recorded. Although all patients were treated before the release of these guidelines, for the purpose of this retrospective analysis, records were stratified according to whether they would have adhered to these guidelines.

*Statistical analysis*

Statistical analyses were performed with SPSS 15.0 (IBM, SPSS Inc., Chicago, IL, USA). Data was expressed as medians with first and third quartiles for continuous variables, and *n* with percentage for categorical variables. For comparisons, the Mann-Whitney *U* test was performed for continuous variables that did have not parametric distributions, and a Pearson's chi-square or Fisher's exact test was performed for categorical variables. The kappa agreement test was used to check for concordance between CURB-65 and APACHE II scores and PSI scores. The binary logistic regression was applied to indicate the mortality of patients regarding to the prognostic factors. The level of significance was set at $\alpha = 0.05$.

## Results

*Demography, clinical characteristics, diagnoses, treatments, and outcomes*

A total of 208 patients were included in the final analysis. Table 1 shows the demographic and clinical characteristics of the 120 patients (57.7%) in the low-risk group and the 88 patients (42.3%) in the high-risk group. The median age was 63 years (range 43 to77 years) and 55.8% of these patients were male. Age and proportion of males were significantly greater in the high-risk group and all measured clinical characteristics were significantly different for the two groups except for proportion of liver disease and platelet count.

The most common comorbidities were cerebrovascular diseases (29.3%), congestive heart failure (15.9%), neoplastic diseases (10.1%), and liver

**Table 1.** Demographic and clinical characteristics of patients with community-acquired pneumonia stratified by risk group

| Variable | Total (n = 208) | Low risk (n = 120) | High risk (n = 88) | P value |
|---|---|---|---|---|
| Age[a], years | 63.0 (43.0 , 77.0) | 45.5 (33.0 , 64.5) | 77.0 (66.5 , 82.5) | < .001* |
| Sex[b], n (%) | | | | 0.017* |
| Males | 116 (55.8) | 58 (48.3) | 58 (65.9) | |
| Females | 84 (44.2) | 62 (51.7) | 30 (34.1) | |
| Nursing home resident[b] | 3 (1.4) | 1 (0.8) | 2 (2.3) | 0.575 |
| Cerebrovascular diseases[b] | 61 (29.3) | 14 (11.7) | 47 (53.4) | < .001* |
| Congestive heart failure[b] | 33 (15.9) | 9 (7.5) | 24 (27.3) | < .001* |
| Neoplastic diseases[b] | 21 (10.1) | 5 (4.2) | 16 (18.2) | 0.001* |
| Liver diseases[b] | 20 (9.6) | 8 (6.7) | 12 (13.6) | 0.092 |
| Smoker[b] | 63 (30.3) | 30 (25.0) | 33 (37.5) | 0.053 |
| Drinker[b] | 41 (19.7) | 21 (17.5) | 20 (22.7) | 0.349 |
| Systemic steroids before hospitalization[b] | 20 (9.6) | 13 (10.8) | 7 (8.0) | 0.475 |
| WBC[a], count/μL | 10,500 (7255, 14,295) | 9625 (6905, 13,160) | 11,810 (8400, 14,815) | 0.029* |
| Platelet[a], count $\times 10^3$/μL | 197 (153, 262) | 195 (160, 252.5) | 205 (136.5, 275.5) | 0.809 |
| Serum BUN[a],mg/dL | 15.7 (10.5, 25.9) | 11.9 (9.5, 16.7) | 25.8 (16.8, 42.8) | < .001* |
| Serum creatinine[a],mg/dL | 1.0 (0.8, 1.3) | 0.9 (0.7, 1.0) | 1.3 (0.9, 2.1) | < .001* |
| Serum glucose[a] ,mg/dL | 127.5 (104.0, 164.0) | 116.0 (99.0, 138.0) | 155.0 (118.0, 209.5) | < .001* |
| ALT (GPT)[a], IU/l | 22 (14 , 32.5) | 21.5 (13.5 , 32.5) | 22 (14 , 33.5) | 0.686 |
| AST (GOT)[a], IU/l | 23 (17 , 34) | 22.5 (17 , 33) | 23 (17 , 40) | 0.801 |
| Albumin[a], g/dl | 3.1 (2.6 , 3.5) | 3.5 (3.1 , 4) | 2.7 (2.4 , 3.2) | 0.002* |
| Na[a], mmol/dl | 138 (134 , 140) | 138 (136 , 140) | 137 (132 , 140) | 0.044 |
| PSI score[a] | 81 (46 , 115) | 51 (30 , 73.5) | 121 (103.5 , 145) | < .001 |
| CURB-65 score[a,b] | 1 (0 , 2.0) | 0 (0 , 1.0) | 2 (1.0 , 2.0) | < .001*,† |
| ≤ 2 | 139 (66.8) | 108 (90.0) | 31 (35.2) | |
| > 2 | 69 (33.2) | 12 (10.0) | 57 (64.8) | |
| APACHE II score[a,b] | 8 (5.0 , 13.0) | 5 (3.0 , 8.0) | 13 (10.0 , 18.0) | < .001*,‡ |
| ≤ 15 | 178 (85.6) | 120 (100.0) | 58 (65.9) | |
| > 15 | 30 (14.4) | 0 (0) | 30 (34.1) | |
| Hospitalization stay[a], day | 6 (4 , 11) | 5 (4 , 7) | 11 (5.5 , 18) | <.001* |

Abbreviations: CAP = community-acquired pneumonia; PSI = Pneumonia Severity Index; low risk (PSI ≤ 90) and high risk (PSI > 90); APACHE II = Acute Physiology and Chronic Health Evaluation II; WBC = white blood cell; ALT = alanine aminotransferase; GPT = glutamic pyruvic transaminase; AST = aspartate aminotransferase; GOT = glutamic oxaloacetic transaminase; BUN = blood urea nitrogen.
Data are expressed as [a]median (first and third quartiles) for continuous variables, and [b]*n* (%) for categorical variables and were tested with [a]Mann-Whitney *U* test, and [b]Chi-square or Fishers' exact test.
†,‡ The concordance between CURB-65 and PSI scores was moderate, and that between APACHE II and PSI scores was fair (†kappa = 0.56 for CURB-65 and ‡0.37 for APACHE II).
*$P < 0.05$ indicated the significance of the comparison of variables between low and high risk groups.

diseases (9.6%). The potential risk factors related to CAP were smoking (30.3%), drinking (19.7%) and systemic use of steroids before hospitalization (9.6%). The median PSI score was 81 (range 46-115) and significantly higher in the high-risk group compared to the low-risk group (121[103.5-145] vs.51 [46-115]; P < .001). The median APACHE II score was 8 (range 5-13) and it was significantly higher in the high-risk group compared to the low-risk group (5[3-8] vs.13 [10-18]; P < .001). The CURB-65 was significantly higher in the high-risk group compared to the low-risk group (0[0-1] vs.2 [1-2]; P < .001). The median hospitalization stay was 6 days (range 4 to 11 days), and patients in the high-risk group had significantly longer hospital stays compared to those in the low-risk group (11 days [5.5-18] vs.5 days [4-7]; P < .001).

Table 2 summarizes the diagnoses, treatments, and outcomes for all patients. A definitive diagnosis was made for 99 patients (47.6%), a presumptive diagnosis for 24 patients (11.5%), an unknown etiology for 52 patients (25.0%), and mixed infection (definite with mixed or presumptive with mixed) for 33 patients (15.8%). Twenty-seven patients (13%) had positive blood cultures and a significantly greater number of pathogens were isolated from blood specimens of the high-risk group (20.5% vs. 7.5%; P = 0.018). Eighty-eight patients (42.3%) had cultures positive from respiratory secretions. A total of 33 out of 156 patients (15.9%) were serologically positive for *M.*

**Table 2**. Diagnosis, treatment, and outcomes of patients with community-acquired pneumonia stratified by risk group

| Variable | Total (n = 208) | Low (n = 120) | High (n = 88) | P value |
|---|---|---|---|---|
| **Diagnosis** | | | | 0.099 |
| Definite | 99 (47.6) | 59 (49.2) | 40 (45.5) | |
| Presumptive | 24 (11.5) | 18 (15.0) | 6 (6.8) | |
| Unknown | 52 (25.0) | 30 (25.0) | 22 (25.0) | |
| Definite and Mixed with more than two pathogens | 24 (11.5) | 10 (8.3) | 14 (15.9) | |
| Presumptive and Mixed with more than two pathogens | 9 (4.3) | 3 (2.5) | 6 (6.8) | |
| Source of pathogens isolated [b] | | | | 0.018* |
| Blood | 27 (13.0) | 9 (7.5) | 18 (20.5) | |
| Other[1] | 181 (87.0) | 111 (92.5) | 70 (79.5) | |
| **Treatment** | | | | |
| Adherence IDSA/ATS guidelines[b], n (%) | 148 (71.2) | 90 (75.0) | 58 (65.9) | 0.153 |
| Time to first antibiotic injection [a], hour | 4.7 (2.5, 8.0) | 5.0 (2.5, 7.9) | 4.5 (2.5, 8.2) | 0.478 |
| Fluoroquinolone treatment[2,b], n (%) | 84 (40.4) | 56 (46.7) | 28 (31.8) | 0.031* |
| **Outcome[b]**, n (%) | | | | < .001* |
| Survival | 179 (86.1) | 119 (99.2) | 60 (68.2) | |
| 30 day Mortality | 29 (13.9) | 1 (0.8) | 28 (31.8) | |

Abbreviations: CAP = community-acquired pneumonia; PSI = Pneumonia Severity Index; low risk (PSI ≤ 90) and high risk (PSI > 90); adherence IDSA/ATS guidelines indicated the patient numbers of the initial empirical treatment with antibiotics was determined by the 2007 Infectious Diseases Society of America/American Thoracic Society consensus guidelines; Survival indicates that the patient was discharged after the treatment or recovered during this hospitalization; mortality indicates that the patient died within 30 days in this hospitalization.
Data are expressed as [a]median (first and third quartiles) for continuous variables and [b]*n* (%) for categorical variables and tested by [a]Mann-Whitney *U* test and [b]Chi-square or Fisher's exact test.
[1] 88 patients (42.3%) had cultures positive from respiratory secretions. Serology testing were positive in *M. pneumoniae* 13.1%(33 patients), *C. pneumoniae* 11.9% (30 patients in 156 patients).The positive *S. pneumoniae* antigens in urine was eight patients(3.84%) and urine *L. pneumophila* antigen was positive only two patients.
[2]Patients were treated initially with fluoroquinolones (levofloxacin and moxifloxacin).

*pneumoniae,* while 30 of 156 patients (11.9%) were positive for *C. pneumoniae*. Eight patients were positive for *S. pneumoniae* antigen and urine specimens from two patients were positive for *L. pneumophila* antigen.

Initial empiric antibiotic treatment was analyzed based on the 2007 IDSA/ATS guidelines, or non-IIDSA/ATS guidelines. One hundred and forty eight patients (71.2%) were treated in accordance with the 2007 IIDSA/ATS guidelines; 75.0% were in the low-risk group and 58 patients (65.9%) were in the high-risk group (P = 0.153). There was no significant difference between the two groups. The use of fluoroquinolones as initial empiric antibiotic treatment was significantly greater in the low-risk group compared to the high-risk group (46.7% vs. 31.8%; P = 0.031).

*Microbiologic findings relative to mortality*

A total of 251 species of bacteria were isolated from the 208 patients (data not shown). Table 3 lists distributions of the most frequently isolated species and all additional species listed in the Table notes.

There were significant differences between the two groups in the rates of infection by the five most frequently isolated species (Table 3). For instance, in the low-risk group, the most frequently isolates were *C. pneumoniae* (P = 0.014) and *M. pneumoniae* (P = 0.013), whereas in the high-risk group, there were more isolates of *K. pneumoniae* (P = 0.001) and *P. aeruginosa* (P = 0.017). In contrast, there was no significant difference between the two groups with respect to isolate rates of *S. pneumoniae* or other less frequently isolated species.

Twenty-nine out of 208 (13.9%) patients died. A total of 28 patients were in the high-risk group; the mortality was significantly greater in the high-risk group (31.8% vs. 0.8%; P < .001) and only one patient was in the low-risk group (Tables 2 and 4). The highest rates of mortality were in patients infected with *K. pneumoniae*, *P. aeruginosa*, and *S. pneumoniae*, and these were also the pathogens most frequently isolated from patients who died. The only patient who died in the low-risk group was infected with *K. pneumoniae* and *S. pneumoniae* (Table 4).

*Analysis of predictive factors relative to mortality*

Significant variables obtained from univariate analysis shown in Tables 1, 2 and 3 were subjected to multivariate analysis to evaluate the association between mortality and PSI level, age, gender, location,

**Table 3.** Distribution of causative pathogens in community-acquired pneumonia patients stratified by risk group

| Pathogen | Total (n = 156 ) | Low risk (n = 90) | High risk (n = 66) | P value |
|---|---|---|---|---|
| Total number of definite and presumptive infections[b] | 199 (79.3) | 105 (78.8) | 94 (81.0) | |
| *Mycoplasma pneumoniae* | 33 (13.1) | 26 (19.3) | 7 (6.0) | 0.013* |
| *Chlamydia pneumoniae* | 30 (11.9) | 22 (16.3) | 8 (6.9) | 0.014* |
| *Streptococcus pneumoniae* | 28 (11.2) | 17 (12.6) | 11 (9.5) | 0.363 |
| *Klebsiella pneumoniae* | 28 (11.2) | 11 (8.1) | 17 (14.7) | 0.001* |
| *Pseudomonas aeruginosa* | 15 (6.0) | 3 (2.2) | 12 (10.3) | 0.017* |
| Other infectious etiologies | 65 (25.9) | 26 (19.3) | 39 (33.6) | 0.065 |
| Unknown etiologies | 52 (20.7) | 30 (22.2) | 22 (19.0) | - |

n: the number of patients. Data are expressed as number of infections caused by the pathogen (%).
PSI = Pneumonia Severity Index; low risk (PSI ≤ 90) and high risk (PSI > 90)
*$P < 0.05$ indicated the frequency of pathogens for infection type was significantly different between two groups.
[a] In all cases, the causative pathogens included definitely or presumptively identified microorganism. Only major pathogens (>10 isolations) were listed. Other infectious agents (number of isolates) were: Gram positive pathogens: *Gemella haemolysans* (1), *Gemella morbillorum* (1), *Staphylococcus aureus* (4), *Streptoccuus constellatus* (1), *Streptococcus mitis* (3), *Streptococcus pneumoniae* (27), *Streptococcus sanguinis* (1); Gram negative pathogens*: Acinetobacter baumannii* (1), *Escherichia coli* (8), *Haemophilus influenza* non type b (4), *Klebsiella oxytoca* (2), *Klebsiella pneumoniae* (28), *Morganella morganii* (2), *Pseudomonas aeruginosa* (15), *Serratia marcescens* (1); Atypical*: Legionaella pneumophila* (2); *Mycoplasma pneumoniae (33), Chlamydia pneumoniae (30);* Fungi*: Aspergillus flavus* (1), *Cryptococcus neoformans* (1)*;* Viruses: Influenza virus A (1), Influenzae virus B (1)*;* Others*: Mycobacterium tuberculosis* (9), *Mycobacterium intracellular* type 1 (1), *Nocardia asteroides* (1)
Unknown etiologies: not related to infectious pathogens.
[b]Some patients were infected with multiple microorganisms; therefore, the total frequencies were greater than the numbers of patients.

and serum BUN in all patients (Table 5). Our data shows that the risk of mortality was 59.2 times higher with PSI values > 90 compared to PSI values ≦ 90 (95% CI, [7.00-501.83]; P < .001). Based on the low mortality in the PSI ≦ 90 group (only one patient died in this group), the odds ratio may only be considered as a reference value for further study.

## Discussion

In this study, approximately 60% of the patients were male with a median age of 63 years. All of them had at least one underlying condition including cerebrovascular diseases, congestive heart failure, neoplastic diseases, liver diseases, smoking, drinking and systemic use of steroids before hospitalization. Hence host factors are believed to be important for *K. pneumoniae* or *P. aeruginosa* CAP in the patients. Nonetheless, our analysis showed that *M. pneumoniae* was the most common species when a definite or presumptive identification was possible. Comparison of the rates of infection of our patients based on PSI score indicated that patients in the high-risk group had significantly higher incidence of infection with *K. pneumoniae* or *P. aeruginosa* compared to patients in the low-risk group. In contrast, patients in the low-risk group were more likely to be infected with *C. pneumoniae* or *M. pneumoniae* than those in the high-risk group. The mortality rate was higher for patients with high PSI scores, as expected. However, because only one patient within the low-risk group died, these data should be interpreted with caution. The most common pathogens in patients who died were *K. pneumoniae*, *P. aeruginosa*, and *S. pneumoniae*. The results of our study are similar to those of previous reports in Taiwan and different from those reported previously in Western countries. For example, Lauderdale *et al*. [8] examined data for patients with CAP from 13 hospitals in Taiwan and reported that the most common etiologic agents were *S. pneumoniae* (23.8%), *M. pneumoniae* (14.3%), *C. pneumoniae* (7.1%), and *K. pneumoniae* (4.8%). Similar results were reported from a study of hospitalized patients in Thailand, in which *S. pneumoniae* (22.4%) and *C. pneumoniae* (16.3%) were the most common species [7]. In the present study, *M. pneumoniae* was the most commonly isolated pathogen (13.1% of all patients) and *K. pneumoniae* was the most commonly isolated pathogen from patients with high PSI scores (14.7%). The high incidence of *K. pneumoniae* that we observed in severely ill patients was consistent with that of a previous study [16]. *K. pneumoniae* was the most common species isolated from patients with

**Table 4.** The association between mortality and specific microorganisms in patients with community-acquired pneumonia stratified by risk group

| Definite microorganism | Total (n = 29) | Low risk (n = 1) | High risk (n = 28) |
|---|---|---|---|
| *Streptococcus pneumoniae* | 3 | | 3 |
| *Staphylococcus aureus* | 2 | | 2 |
| *Klebsiella pneumoniae* | 4 | | 4 |
| *Pseudomonas aeruginosa* | 2 | | 2 |
| *Klebsiella pneumoniae* and *Streptococcus pneumoniae* | 1 | 1 | |
| *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* | 3 | | 3 |
| *Mycobacterium tuberculosis* | 3 | | 3 |
| *Escherichia coli* | 1 | | 1 |
| *Acinetobacter baumannii* | 1 | | 1 |
| Others | 2 | | 2 |
| Unknown etiologies | 7 | | 7 |
| Total | 29 | 1 | 28 |

n: the number of patients. Data are expressed as number of infections caused by the pathogen (%).
PSI = Pneumonia Severity Index; low risk (PSI ≤ 90) and high risk (PSI > 90).

**Table 5.** Odds ratio and 95% confidence intervals in multivariate logistic regression analysis to evaluate the association between mortality and related factors in patients with community-acquired pneumonia

| Variables | OR [95% CI. for OR] | P value |
|---|---|---|
| Age | | |
| ≧65 years | 0.76 [0.26-2.18] | 0.603 |
| < 65 years | 1 | - |
| Sex | | |
| Male | 1.91 [0.71-5.15] | 0.200 |
| Female | 1 | - |
| Source of pathogens isolated | | |
| Blood | 2.66 [0.91-7.76] | 0.073 |
| Others | 1 | - |
| PSI level | | |
| > 90 | 59.2 [7.00-501.83] | < .001* |
| ≦90 | 1 | - |
| Serum BUN | 1.00 [0.98-1.02] | 0.819 |

OR (95% CI.) with P-value was the estimated odds ratio (OR) with 95% confidence interval of OR from multivariate logistic regression analysis.
* P < 0.05. P-value was the significance of the estimated OR.

severe CAP who required mechanical ventilation at an intensive care unit in Taiwan. Ko *et al*. (2002) also reported geographic differences in the pattern of community-acquired bacteremia caused by *K. pneumoniae*, and that *K. pneumoniae*-mediated CAP was especially common in Taiwan and South Africa [9]. These results highlight the importance of identifying the prevalence of different pathogen species.

One of our most important findings was that the IIDSA/ATS international guidelines for treatment of CAP must be used with caution for treatment of severe CAP in Taiwan. These guidelines were developed only based on studies of CAP in patients who were not in the ICU and who were not infected with other common pathogens, such as *S. pneumoniae*, *M. pneumoniae, C. pneumoniae*, *Haemophilus influenzae* and *Legionella* spp. [5]. In the low-risk group, empiric treatment for this category of patients is with a respiratory fluoroquinolone or a beta-lactam plus a macrolide. In our study, the result was concordant with IDSA/ATS guidelines. However, in the high-risk (PSI > 90) group, our results revealed that patients with CAP were treated inconsistently with IDSA/ATS guidelines and had a higher risk of in-patient mortality and had significantly longer length of hospital stay. Our data revealed that adherence to treatment guidelines results in better outcomes, especially in the low-risk group. In addition, *Legionella* spp., which is commonly associated with CAP in western countries [18], was only a minor etiology in our study. Hence the study shows that use of the IIDSA/ATS guidelines for treatment of CAP in Taiwan had a better outcome in the low-PSI group. The association of empiric treatment with outcome in the high-PSI group should be confirmed in future studies.

Although a positive correlation between PSI score and mortality was observed, the utility of such scoring systems remains a matter of debate. Recent reviews have compared the accuracy of the PSI score, CURB-65 score, CRB-65score, and other indices of disease severity [10,11]. The general consensus shows that such systems were useful tools for clinical decision-making. The results of the present study extend these previous findings by demonstrating a significant effect of an etiologic agent on the PSI score. If these results are applied in other geographic regions in which the prevalence of causative organisms differs, the PSI might provide additional useful information for the management of CAP.

There are some potential limitations of the present study. We enrolled only hospitalized patients at a single hospital. Hospitalized patients generally have higher PSI scores, so this may have led to selection bias. A second limitation is that among our hospitalized patients, we did not have species identification in 52 patients (25%), and identification of the etiologic agents in 33 patients (15.8%) was based on inference. In our study, our hospital used urine *L. pneumophila* antigen as a diagnostic tool; however, this underestimates the *L. pneumophila* because it only detects *L. pneumophila* serum type1. One major confounding factor of this study is the lack of specificity of the serum ELISA to detect antibodies (IgM, IgA, or IgG) against *C. pneumoniae*; it is, therefore, a challenge to use this method as a confirmatory test for *C. pneumoniae*.

Finally, we used the PSI, CURB65, and APACHE II scores as severity assessment tools and predicted patients with an increased risk of death among CAP cases in the univariate analysis. This method could not be very accurate because of the retrospective design of our study.

In conclusion, *M. pneumoniae* was the most common organism isolated from our patients with CAP. However, patients with more severe illness (PSI > 90) had significantly higher incidence of infection with *K. pneumoniae* and *P. aeruginosa*. The relationship between infection with *K. pneumoniae* and severe CAP is especially important in Taiwan and other parts of Asia, where it continues to be a significant cause of CAP. Our results provide valuable epidemiologic information on CAP in central Taiwan and may offer the epidemiologic information for revising guidelines for treatment of CAP in Taiwan and Asia in the future [20,21]. Finally, the study shows that use of the IIDSA/ATS guidelines for empiric treatment of CAP in Taiwan has a better outcome in a low-PSI group.

## References

1. Ewig S, Woodhead M, Torres A (2011) Towards a sensible comprehension of severe community-acquired pneumonia. Intensive Care Medicine 37: 214-223.
2. Lee YT, Chen SC, Shyu LY, Lee MC, Wu TC, Tsao SM, Yang SF (2012) Significant elevation of plasma cathepsin B and cystatin C in patients with community-acquired pneumonia. Clinica Chimica Acta 413: 630-635.
3. Cilloniz C, Ewig S, Ferrer M, Polverino E, Gabarrus A, Puig de la Bellacasa J, Mensa J, Torres A (2011) Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. Critical Care 15: R 209.
4. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F (2009) Epidemiology of community-acquired pneumonia in older adults: A population-based study. Respiratory Medicine 103:309-316.

5. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr. Musher DM, Niederman MS, Torres A, Whitney CG (2007) Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 44: S 27-72.
6. Gutiérrez F, Masiá M, Rodríguez JC, Mirete C, Soldan B, Padilla S, Henandez I, De Ory F, Royo G, Hidalgo AM (2005) Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain. Clin Microbiol Infect 11: 788-800.
7. Wattanathum A, Chaoprasong C, Nunthapisud P, Chantaratchada S, Limpairojn N, Jatakanon A, Chantadisai N (2003) Community-acquired pneumonia in Southeast Asia: the microbial differences between ambulatory and hospitalized patients. Chest 123: 1512-1519.
8. Lauderdale TL, Chang FY, Ben RJ, Yin HC, Ni YH, Tsai JW, Cheng SH, Wang JT, Liu YC, Cheng YW, Chen ST, Fung CP, Chuang YC, Cheng HP, Lu DC, Liu CJ, Huang IW, Hung CL, Hsiao CF, Ho M (2005) Etiology of community acquired pneumonia among adult patients requiring hospitalization in Taiwan. Respir Med 99: 1079-1086.
9. Ko WC, Paterson DL, Sagnimeni AJ, Hansen DS, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, Mulazimoglu L, Trenholme G, Klugman KP, McCormack JG, Yu VL (2002). Community-acquired *Klebsiella pneumoniae* bacteremia: global differences in clinical patterns. Emerg Infect Dis 8: 160-166.
10. Niederman MS (2009) Making sense of scoring systems in community acquired pneumonia. Respirology 14: 327-335.
11. Singanayagam A, Chalmers JD, Hill AT (2009) Severity assessment in community-acquired pneumonia: a review. QJM 102: 379-388.
12. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 336: 243-250.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13: 818-829.
14. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT (2003) Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58:377-382.
15. Feldman C, Alanee S, Yu VL, Richards GA, Ortqvist A, Rello J, Chiou CC, Chedid MB, Wagener MM, Klugman KP (2009) Severity of illness scoring systems in patients with bacteraemic pneumococcal pneumonia: implications for the intensive care unit care. Clin Microbiol Infect 15: 850-857.
16. Hu HC, Huang CC, Tsai YH, Lee CH, Hsieh MJ (2005) Outcome analysis of patients requiring mechanical ventilation with severe community-acquired pneumonia and identified bacterial pathogens. Chang Gung Med J 28: 229-236.
17. Man SY, Lee N, Ip M, Antonio GE, Chau SS, Mak P, Graham CA, Zhang M, Lui G, Chan PK, Ahuja AT, Hui DS, Sung JJ, Rainer TH (2007) Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. Thorax 62: 348-353.
18. Jespersen S, Sogaard O, Schonheyder H, Fine MJ, Ostergaard L (2010) Clinical features and predictors of mortality in admitted patients with community- and hospital-acquired legionellosis: A Danish historical cohort study. BMC Infect Dis 10: 124.
19. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, Nusbaumer C, Tamm M, Christ-Crain M (2007) Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 7: 10.
20. Guidelines on antimicrobial therapy of pneumonia in adults in Taiwan, revised 2006 (2007) J Microbiol Immunol Infect 40:279-283.
21. Hsueh PR (2002) Guidelines for the Management of Lower Respiratory Tract Infections in Asia. Infect Dis Clin Pract 11: S12-19.

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