ETIOLOGIES AND TREATMENT OUTCOMES IN PATIENTS HOSPITALIZED WITH COMMUNITY-ACQUIRED PNEUMONIA (CAP) AT SRINAGARIND HOSPITAL, KHON KAEN, THAILAND

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Abstract. Local epidemiological data on the etiologies of in-patients who are hospitalized with CAP is needed to develop guidelines for clinical practice. This study was conducted to determine the pattern of microorganisms causing community-acquired pneumonia (CAP) in adult patients admitted to Srinagarind Hospital, Khon Kaen, Thailand, between January 2001 and December 2002. Altogether, 254 patients (124 males, 130 females) averaging 56.4 (SD 19.8) years were included. Eighty-six of them (33.8%) presented with severe CAP on initial clinical presentation. The etiologies for the CAP cases were discovered by isolating the organisms from the blood, sputum, pleural fluid, and other sterile sites. Serology for *Chlamydia pneunmoniae* and *Mycoplasma pneumoniae* were performed to diagnose current infection. The causative organisms were identified in 145 patients (57.1%). *Streptococcus pneumoniae* was the commonest pathogen, identified in 11.4% of the cases, followed by *Burkholderia pseudomallei* (11.0%) and *Klebsiella pneumoniae* (10.2%). The atypical pathogens, *C. pneumoniae* and *M. pneumoniae*, accounted for 8.7% and 3.9% of the isolates, respectively. Sixteen patients (6.3%) had dual infections; *C. pneumoniae* was the most frequent co-infecting pathogen. The average length of hospital stay was 12.9 (SD 14.0) days, with 27.9% staying more than 2 weeks. Overall, 83.9% of the patients improved with treatment, 10.2% did not improve and 5.9% died. The most common complications were acute respiratory failure (31.1%) and septic shock (20.9%). We conclude that initial antibiotic use should cover the atypical pathogens, *C. pneumoniae* and *M. pneumoniae*, in hospitalized CAP patients. *B. pseudomallei* is an endemic pathogen in Northeast Thailand, and should be considered in cases of severe CAP.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most common infectious diseases treated in the hospital setting, and is associated with significant morbidity and mortality (Bartlett *et al*, 1995; Ministry of Public Health, 1998). The selection and timing of initial antimicrobial treatment is an important clinical decision (Meehan *et al*, 1997). This decision is usually made before the results of specific microbial tests are available. Antibiotic treatment for CAP is, therefore, initially empirical; relying on epidemiological data of the causative pathogens in a particular geographic area. Although *Streptococcus pneumoniae* remains the most prevalent isolated etiologic agent, other organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis*, as well as atypical pathogens, including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, are now being reported more frequently than in the past (Mandell, 1995). Serological tests for atypical pathogens are often not available, and can not be performed in a routine laboratory. Some specific pathogens, such as *Burkholderia pseudomallei*; are found in endemic areas of the world (Boonsawat *et al*, 1990). Local epidemiological data are needed to develop practice guidelines for each country. We investigated the etiologies of CAP in patients requiring hospitalization, and evaluated treatment outcomes in the hospital setting.

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MATERIALS AND METHODS

This prospective study was carried out between January 2001 and December 2002 at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. Patients, 15 years or older,

who were admitted with CAP were included in this study. The diagnosis of CAP was based on 1) acute onset ≤2 weeks; 2) presenting with three of five of the following signs and symptoms: fever, cough with or without sputum production, dyspnea, pleuritic chest pain, and consolidation or crackles on physical examination; and 3) new infiltration on chest radiographs. We excluded patients who were 1) HIV positive; 2) transferred from another hospital; or 3) hospitalized within 3 weeks before admission.

The demographic data collected for the patients included: age, sex, occupation, and underlying diseases. The clinical symptoms and signs of each patient, and their onset before admission, were also documented. The initial laboratory investigations comprised: a complete blood count (CBC), chest radiograph, sputum Gram's stain and culture, blood culture, and a 5-ml clotted blood sample for serologic testing for *C. pneumoniae* and *M. pneumoniae*. Convalescent serum samples were obtained 2-3 weeks later. All serum samples were separated immediately and stored at -20ºC until the serology tests were done.

The etiology of the pneumonia was achieved by isolation of the organisms from samples of blood, sputum, pleural fluid or other sterile sites. A current infection with *C. pneumoniae* was defined by the detection of IgM antibody or a rising IgG antibody titer in paired sera. A current infection with *M. pneumoniae* was defined as a fourfold rise in the titer of paired sera by the particle agglutination test. The methodologies for the serology tests for *C. pneumoniae* and *M. pneumoniae* are described below.

The management of each patient depended on the individual physician. The results of the serology tests were not used for treatment decisions, because the sera were kept and analyzed at the end of the study. The outcomes of treatment, complications, and length of hospitalizations of all the CAP patients were also evaluated.

Serology for *C. pneumoniae* antibody detection

The Sero CP™-IgM (or IgG) Test is an enzyme immunoassay used for detecting IgM (or IgG) antibodies against *C. pneumoniae* in serum samples. The procedure was performed as described in the manufacturer's instructions. In brief, all the components of the reagent kit and specimens were brought to room temperature, and mixed before use. Fifty microliters of the two negative controls, one positive control and the diluted serum sample (dilute serum 1:105 with diluent for IgM or IgG) each were dispensed into separated wells on the test strip and incubated for 1 hour at 37ºC in a moist chamber. After incubation, the strips were washed with washing buffer 3 times, then tapped dry. Fifty microliters of horseradish peroxidase (HRP) conjugated anti-human IgM (or IgG) at a dilution of 1:300 was added into each well. The strips were further incubated for 1 hour at 37ºC in a moist chamber. After washing with buffer 3 times, 100 μl of tetramethylbenzidine (TMB) substrate was dispended into each well and incubated at room temperature for 15 minutes. The reaction was stopped by adding 100 μl of 1 M H_2SO_4. The absorbance at 450 nm wavelength was determined within 30 minutes.

For the test to be valid, it had to meet the following criteria: 1) the absorbance of the positive control should be ≥0.8; and 2) the average absorbance of the negative control should be >0.1 and ≤0.4.

Calculation of cut-off value (COV) and cut-off index (COI)

The COV and COI were calculated according to the following formula;

COV = NC x 2 ; where NC = the average absorbance for the negative control.

COI = Absorbance of the serum sample/ COV.

Interpretation of results

- If the OD was <COV and the COI was <1.0, the result was negative (*ie* no IgM or IgG antibody was detected). If the COV≤OD≤1.1 x COV, and the COI was between 1 and 1.1, the result was borderline (*ie* a low level of IgM or IgG antibody). If the OD >1.1 x COV and the COI was >1.1, the result was positive (*ie* a relevant levels of IgM or IgG antibody). Then a 'current' *C. pneumoniae* infection was indicated when testing for serum IgM and a 'current or past' infection with *C. pneumoniae* was diagnosed when testing for IgG.

- If the initial and convalescent titers were both borderline the specimen was considered negative.

- To differentiate between a past and current infection when testing for serum IgG, a rise

in COI in the second sample by at least 40% was considered a current infection.

Serology test for *M. pneumoniae* antibody detection

SERODIA-MYCO II is a particle agglutination test kit for the detection of anti-*M. pneumoniae* antibody in human serum. The procedure was performed as described in the instruction manual. The U-shaped microtray was used for a gelatin particle agglutination test as follows. One hundred microliters of the serum diluent was placed into well 1 and 25 μl of diluent into wells 2 through 8 (or more). Twenty-five microliters of specimen was added to well 1 (serum dilution=1:5), mixed; and 25 μl of the mixture was added to well 3. A serial 2-fold dilution was prepared sequentially up to well 8 (or more). Twenty-five microliters of unsensitized particles (tanned gelatin particles) was added to well 2 (final dilution=1:20). Twenty-five microliters of sensitized particles (gelatin particles sensitized with *M. pneumoniae* antigen) was added to wells 3 (final dilution=1:40) through 8 (final dilution=1:1,280) or more. The solution was mixed using a tray mixer, then covered and incubated for 3 hours. For the positive control test, a 1:10 diluted positive control was added to well 2 and then serial 2-fold dilutions were prepared in wells 3 through 8. Twenty-five microliters of unsensitized particles was added to well 2 and 25 μl of sensitized particles was added to wells 3 though 8, mixed and incubated for 3 hours. For the reagent control, a mixture of serum diluent was prepared with both sensitized and unsensitized particles.

Reading the agglutination pattern according to the criteria in the instruction manual confirmed that: 1) the reaction of each specimen and unsensitized particle was negative; 2) the reagent control was negative; and 3) the titer of the positive control was 1:320 on final dilution.

Interpretation of results

- A specimen showing negative with unsensitized particles (1:20 final dilution, well 2) but positive with sensitized particles (1:40 final dilution, well 4 or more) was interpreted as positive. The end antibody titer was determined as the final dilution giving a positive result.

- Regardless of the reading of the reaction pattern with unsensitized particles, a specimen showing negative with sensitized particles (1:40 final dilution, well 4) was interpreted as negative.

- A specimen showing negative with unsensitized particles (1:20 final dilution, well 2) and demonstrating positive and negative with sensitized particles (1:40 final dilution, well 3) was interpreted as indeterminate.

A current infection with *M. pneumoniae* was diagnosed if there was a four-fold rise in titer in the paired sera.

Ethics

The Ethics Committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, approved the research protocol.

Statistical analysis

Descriptive statistics were used. The means and standard deviations were calculated for the continuous data; the numbers and percentages were calculated for the categorical data.

RESULTS

During the 2-year study, 254 patients were diagnosed with CAP and admitted to our hospital. Eighty-six of them (33.8%) presented with severe CAP on initial presentation. A diagnosis of severe CAP, defined by American Thoracic Society (ATS) criteria (Niederman *et al*, 2001), requires one of two major criteria or two of three minor criteria. The major criteria are: 1) need of mechanical ventilation; and 2) septic shock. The minor criteria are: 1) systolic blood pressure <90 mmHg; 2) multilobar involvement; and 3) Pao_2/Fio_2 <250.

The average age, of the 124 male and 130 female patients, was 56.4 (SD 19.8) years. Twenty-four percent were farmers and 14% were in government service. The mean incubation period was 5.6 (SD 4.2) days. Most (87%, 221 of 254) patients had one or more co-morbidities. Underlying diseases included cardiovascular disease (60 cases), diabetes mellitus (48), autoimmune disease (34), renal disease (29), neurological disease (24), hematological disease (21), chronic obstructive lung disease (14), asthma (8), and cirrhosis (6) (Table 1).

The causative organisms were identified in 145 patients (57.1%). *S. pneumoniae* was found in 11.4% of the isolates and was the predomi-

nant pathogen among the hospitalized CAP patients (Table 2). *B. pseudomallei* was the second most frequently observed pathogen (11.0%), followed by *K. pneumoniae* (10.2%). *C. pneumoniae* was found in 8.7% of patients; and *M. pneumoniae*, another atypical pathogen, was found in 3.9%. Other known pathogens were *H. influenzae* (4.3%), *S. aureus* (3.5%), *E. coli* (3.1%), *Streptococcus* spp (3.1%), *P. aeruginosa* (2.4%), *M. catarrhalis* (0.8%), *P. fluorescence* (0.4%), and *P. cepacia* (0.4%).

Dual infections were found in 16 patients (6.3%) (Table 3). *C. pneumoniae* was the most common co-infecting pathogen. The most common dual pathogens were *C. pneumoniae* co-infected with *Streptococcus* spp, found in 4 cases. Other dual infections were: *E. coli* + *K. pneumoniae* (3 cases); *C. pneumoniae* + *K. pneumoniae* (2); *C. pneumoniae* + *B. pseudomallei* (2); *M. pneumoniae* + *Streptococcus* spp (1); *M. catarrhalis* + *S. pneumoniae* (1); *C. pneumoniae* + *M. pneumoniae* (1); *C. pneumoniae* + *H. influenzae* (1); and *C. pneumoniae* + *E. coli* (1).

Hospitalization averaged 12.9 (range, 1-115) days, and 71 patients (27.9%) stayed more than 2 weeks. Overall, 83.9% of patients improved with treatment, 10.2% did not improve and 5.9% died (Table 4). The most common complications were acute respiratory failure (31.1%) and septic shock (20.9%). Other complications prolonging hospital stay were parapneumonic effusions or empyema thoracis (13.0%), hospital acquired pneumonia (8.3%), acute renal failure (6.3%), extrapulmonary infection (3.5%), and pneumothorax (3.1%).

Table 1
Characteristic of patients hospitalized with CAP.

Characteristic	N = 254
Age, year (mean, SD)	56.4 (19.8)
Male:female ratio	0.9 : 1
Incubation, days (mean, SD)	5.6 (4.2)
Occupation (N, %)	
Farmer	61 (24.0)
Government service	36 (14.2)
Business	16 (6.3)
Student	15 (5.6)
Healthy (N, %)	33 (13.0)
Underlying disease[a] (N, %)	221 (87.0)
Cardiovascular disease	60 (23.6)
Diabetes mellitus	48 (17.7)
Autoimmune disease	34 (13.4)
Renal disease	29 (11.4)
Neurological disease	24 (9.4)
Hematologic disease	21 (8.3)
Chronic obstructive lung disease	14 (5.5)
Asthma	8 (3.1)
Cirrhosis	6 (2.4)

[a]Some patients had more than one underlying disease.

Table 2
Etiology of CAP in 254 hospitalized patients.

Etiology[a]	N	%
Unknown	109	42.9
S. pneumoniae	29	11.4
B. pseudomallei	28	11.0
K. pneumoniae	26	10.2
C. pneumoniae	22	8.7
H. influenzae	11	4.3
M. pneumoniae	10	3.9
S. aureus	9	3.5
E. coli	8	3.1
Streptococcus spp	8	3.1
P. aeruginosa	6	2.4
M. catarrhalis	2	0.8
P. fluorescence	1	0.4
P. cepacia	1	0.4

[a]16 patients infected with two organisms.

DISCUSSION

The importance of CAP has led numerous international organizations to publish guidelines to optimize care and improve outcomes. Several changes have occurred during the past decade that have impacted the management of CAP including: the increasing awareness of atypical pathogens (*ie C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*) and the emerging resistance of standard pathogens (most notably *S. pneumoniae*) (File *et al*, 1997; Bartlett *et al*, 1998). Therefore, local epidemiological data are required for developing guidelines for clinical practice.

Our study found pathogens in 57.1% of patients requiring admission to hospital for CAP, despite extensive laboratory investigations. This percentage is similar to that found in previous studies (Bates *et al*, 1992; Bohte *et al*, 1995; Lieberman *et al*, 1996). *S. pneumoniae* remained

Table 3
Organisms and incidence in 16 dual infected patients.

Organisms	N
C. pneumoniae + *Streptococcus* spp	4
E. coli + *K. pneumoniae*	3
C. pneumoniae + *K. pneumoniae*	2
C. pneumoniae + *B. pseudomallei*	2
M. pneumoniae + *Streptococcus* spp	1
M. catarrhalis + *S. pneumoniae*	1
C. pneumoniae + *M. pneumoniae*	1
C. pneumoniae + *H. influenzae*	1
C. pneumoniae + *E. coli*	1

Table 4
Treatment outcomes.

Outcomes	N = 254
Hospital stay, days	
Means (SD)	12.9 (14.0)
Range	1 - 115
Outcome (N, %)	
Improvement	213 (83.9)
No improvement	26 (10.2)
Death	15 (5.9)
Complication (N, %)	
Acute respiratory failure	79 (31.1)
Shock	53 (20.9)
Parapneumonic effusion or empyema thoracis	33 (13.0)
Hospital acquired pneumonia	21 (8.3)
Acute renal failure	16 (6.3)
Extrapulmonary infection	9 (3.5)
Pneumothorax	8 (3.1)

the most frequently isolated etiologic agent, although its incidence appears to be decreasing. Gram-negative pathogens, such as *B. pseudomallei* and *K. pneumoniae*; were found more often in patients hospitalized for CAP. In our study, about 30% of hospitalized CAP patients presented initially with severe CAP and needed intensive care treatment. Among these, *B. pseudomallei* was the most common pathogen isolated in severe CAP, followed by *K. pneumoniae*. A report on the etiology of CAP hospitalized patients in Malaysia found *K. pneumoniae* (10.2%) was the most prevalent, followed by *S. pneumoniae* (5.5%) (Liam *et al*, 2001). For severe CAP, *B. pseudomallei* was the most common pathogen reported in Singapore (Tan *et al*, 1998). These findings differ from western countries (Ewig *et al*, 1999). The reasons for this may be: diabetes mellitus was a common underlying disease and *B. pseudomallei* was endemic in these areas.

C. pneumoniae was the fourth most common isolated pathogen, accounting for 8.7% of CAP patients. This pathogen is now associated in approximately 10% of all cases of pneumonia worldwide (Kauppinen *et al*, 1995). When combined with *M. pneumoniae*, the prevalence of atypical pathogens for hospitalized CAP was 12.6% (8.7% *C. pneumoniae* and 3.9% *M. pneumoniae*). Moreover, *C. pneumoniae* was the most common co-infecting pathogen found in cases of dual infection. These findings are similar to those of Miyashita *et al* (2002) and Wattanathum *et al* (2003). Therefore, empiric coverage of these pathogens with doxycycline, macrolides, or the new fluoroquinolones should be considered (Plouffe, 2000; Salkind *et al*, 2002; File *et al*, 2003), since serologic diagnosis is not available in every hospital, and takes time waiting for the paired sera results.

The morbidity and mortality rates in our hospitalized CAP patients were approximately 16%, with 5.9% dying and 10.2% not improving. These figures are similar to a meta-analysis of CAP outcomes (Fine *et al*, 1995), where the overall mortality for hospital admitted patients was 13.7%; 17.6% for elderly patients and 19.6% for bacteremic patients. The length of hospitalization varied widely, ranging from 1 to 115 days. This may be due to the appropriateness of the initial antibiotic therapy and supportive care. The use of macrolides or new fluoroquinolones, as a part of an initial therapeutic regimen, was associated with lower mortality rates (Gleason *et al*, 1999; Brown *et al*, 2003) and reduced lengths of hospitalization (Stahl *et al*, 1999; Brown *et al*, 2003). Acute respiratory failure and septic shock were the two most common complications, which increased mortality, length of hospitalization, and cost of treatment. When the patients presented with either of these two complications, intensive care therapy was needed (Ewig *et al*, 1998).

In summary, the results of this study showed that *S.pneumoniae* was the most commonly isolated pathogen. Gram-negative bacilli, such as *B. pseudomallei* and *K. pneumoniae*, had a relatively

high prevalence in our region, especially in cases of severe CAP. The occurrence of atypical pathogens such as, *C. pneumoniae* and *M. pneumoniae*, was comparable to other studies. Co-infections were found in 6.3% of cases, and *C. pneumoniae* was the most common co-infecting microorganism. Ultimately, the reduction of pneumonia-related morbidity and mortality will depend on both appropriate initial antibiotic therapy and supportive care. The use of macrolides or new fluoroquinolones as a part of initial therapy for hospitalized CAP patients, and the use of antibiotics to cover *B. pseudomallei* for severe CAP, should be considered in our region.

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