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

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Abstract. Most patients with community-acquired pneumonia are treated as out-patients with empirical therapy, since initially the etiologic agent is unknown. We prospectively assessed the etiologies and treatment outcomes of pneumonia from February 2003 to 2004 at ambulatory clinics. Forty-four patients were included with a mean age of 49.2 (SD 18.2) years. The male to female ratio was 1:1.4. The incubation period was 6.9 (SD 4.4) days. Half of the patients were healthy. Asthma and COPD were common in patients with underlying diseases. The etiologic diagnosis was determined by a sputum culture and a serology test of paired serum samples. Hemo-culture produced no growth in any patients. Atypical pathogens and *H. influenzae* were the most common finding, each occurring in 31.8% of the patients followed by *S. pneumoniae* and *H. parainfluenzae* (27.3% each). Twenty-two patients were infected with multiple pathogens. *C. pneumoniae* was the most common co-infecting pathogen. Two of 12 *S. pneumoniae* isolates were penicillin resistant. Nine of 14 *H. influenzae* isolates were cotrimoxazole resistant and 8 of 14 were not sensitive to erythromycin. For *H. parainfluenzae*, 11 of 12 isolates were not sensitive to erythromycin, and 7 of 12 were not sensitive to cotrimoxazole. Oral antibiotics were prescribed as out-patient treatment. Forty patients (90.9%) improved, with symptoms-score improvement averaging 6.4 days. Four patients got worse and needed a change of antibiotics, the symptoms usually worsen within 3-5 days. We conclude that, antibiotics for CAP out-patients should cover atypical pathogens, *H. influenzae*, *S. pneumoniae* and *H. parainfluenzae*. If the clinical symptoms do not respond after 3-5 days of out-patient treatment, resistance or an unusual organism (*eg B. pseudomallei*) should be considered.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common illness with about 4 million cases occurring in the United States each year (Garibaldi, 1985). Fifty to eighty percent of patients with CAP are treated on an ambulatory basis (Coley *et al*, 1996). However, most of our knowledge about the clinical manifestations and outcomes of CAP comes from studies among patients requiring admission to the hospital.

Nowadays, reports of increasing resistance of pathogens associated with CAP, increasing frequency of atypical pathogens, and the availability of an increasing number of antimicrobials have made treatment decision more involved (Lieberman, 1999; Heffelfinger *et al*, 2000). The choice of antimicrobial therapy is usually empirical because the etiologic agent is unknown at initial diagnosis (Niederman *et al*, 2001; Mandell *et al*, 2003). There are no specific clinical or radiological features which suggest with confidence the etiological agent of CAP (Macfarlane *et al*, 1984; Fang *et al*, 1990; Pomilla and Brown, 1994). Therefore, local epidemiological data regarding the causative pathogens in a particular geographic area are important in developing practical guidelines for physicians to carry out these CAP out-patients. The aim of this study was to determine the specific pathogens causing out-patient CAP and clinical outcome of these patients in northeast Thailand.

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MATERIALS AND METHODS

This prospective study was carried out between February 2003 and February 2004 at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. Patients, 18 years or older presenting with acute CAP not needing parenteral antibiotics or admission, were included. The criteria for diagnosis of acute CAP were based on: 1) fever (>37.5°C) *vs* WBC >10,000/mm^3 or band >15%; 2) new, sudden onset of at least two of the following signs or symptoms including cough, dyspnea or tachypnea, chills, pleuritic chest pain, purulent sputum or change in sputum character, sign of consolidation or rales on physical examination; and 3) new infiltration shown on chest radiograph. Patients with severe CAP requiring hospitalization were not included. Severe CAP was indicated by the presence of: a chest X ray showing multilobar involvement, shock, altered mental status, total peripheral white blood cell count <4,000/mm^3, need for mechanical ventilation or vasopressors, acute renal failure, or hypothermia (temperature <35°C). We also excluded patients discharged from another hospital within 10 days or who had a special condition (aspirated pneumonia, tuberculosis, bronchiectasis, bronchogenic CA and HIV positive).

Each patient gave written informed consent. The history of illness and physical examination was performed by the physician. Pneumonia-related symptoms and signs (temperature, cough, dyspnea, tachypnea, pleuritic chest pain, chills, sputum production and characteristics, and chest auscultation) were recorded at visit 1 (day 1), visit 2 (day 8-11), and visit 3 (day 17-21). Complete blood counts and chest radiographs were performed at visit 1. The following laboratory tests were done to identify the causative organisms: 1) sputum Gram's stain and culture, 2) two specimens for blood culture, 3) *S. pneumoniae* urinary antigen test, and 4) serology test for *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila* with paired sera (visit 1 and 3). The methodology of the cultures and serologic studies are described below.

Oral antibiotics were prescribed for outpatient CAP, an advance macrolide, new fluoroquinolone, or ketolide. Between days 3 and 5 of treatment, every patient was contacted by telephone to ascertain, if the patient's symptoms had worsened, which would indicated clinical treatment failure.

A daily diary card was used by each patient to record treatment in order to verify the patient's symptoms (score) and compliance. Five CAP symptoms scores were measured daily: cough, shortness of breath, fatigue, fever, and bodyache. The severity of symptoms were graded by visual analogue scales between 0 and 5.

Culture identification and susceptibility test

The sputum samples were examined after Gram's staining. A qualifying sputum sample yielded <10 squamous epithelial cells and ≥25 polymorphonuclear leukocytes per low-power field (100x). If adequate sputum was collected, all of the sputum samples were plated on chocolate, blood and MacConkey's agars. The culture plates were incubated overnight at 37°C with a 3-5% carbon dioxide atmosphere for the chocolate agar. After incubation, the numbers and types of colonies were recorded. Each colony type was identified using Gram's staining and conventional biochemical tests, such as the X and V factor requirement for identification of *Haemophilus* and the optochin test for *Streptococcus pneumoniae*. Blood samples were cultured in bottles of the BacT/Alert continuous monitoring system (Organon Tenika, Durham, NC). Gram stains, plated culture and further identification were performed. Antimicrobial susceptibility testing was performed by the standard disk diffusion method in accordance with the National Committee for Clinical Laboratory Standard (NCCLS) guidelines. *S. aureus* ATCC® 25923, *S. pneumoniae* ATCC® 49619 and *H. influenzae* ATCC® 49247 (American Type Culture Collection, Rockville, Maryland, USA) were used as controls. The isolates of *H. influenzae*, *H. parainfluenzae*, *S. aureus* and *M. catarrhalis* were tested for β-lactamase production. Identification sticks of β-lactamase (Nitrocefin) (Oxoid, Basingstoke, Hampshire, England) were used according to the manufacturer's instructions.

Serologic studies

Serum samples were collected during acute and convalescent periods. The samples were

tested for antibodies to *M. pneumoniae* using gel particle agglutination (SERODIA-MYCO II, Fujirebio, Japan). Indirect immunofluorescence techniques were used to detect antibodies to Legionella and IgM, IgG and IgA to *C. pneumoniae* (Focus Technologies, USA). For *M. pneumoniae*, the four-fold increase in the antibody titer level between the paired sera or an elevated single titer of ≥1:40 was considered as positive. For Legionella, a 4-fold rise in the titer of the paired serum samples indicated a recent exposured to *L. pneumophila*. In the case of *C. pneumoniae*, a non-reactive sample (IgG <1:16 or IgA <1:16 or IgM <1:10) suggested that the patient had no current infection. A single specimen IgG endpoint titer ≥512 or IgM ≥1:10 indicated a possible acute infection while a single specimen IgA endpoint titer ≥1:16 in the absence of IgM titer might indicate a re-infection or chronic infection. When the paired serum samples were tested, a 4-fold rise in the titer of IgG or IgA or IgM indicated a recent exposure to *C. pneumoniae*.

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 number and percentages for the categorical data.

RESULTS

During the one-year study, 44 patients were diagnosed with CAP and treated as out-patients. Eighteen were male and twenty-six female. The age averaged 49.5 (SD 18.2) years, minimum 18 and maximum 81 years. The mean duration of symptoms was 6.9 (SD 4.4) days. Twenty-seven percent of them were farmers. Over half had no underlying disease. In cases who had underlying diseases, asthma (13.6%), COPD (9.1%), DM (9.1%) and old TB (9.1%) were the most common (Table 1).

The mean white blood cell count on the first day was 12,190.9 cells/mm^3, with a range of 3,000 to 26,200 cells/mm^3. The mean percentage of polymorphonuclear leukocytes was 70.2%, with a range of 34.2% to 92.6% (Table 2). The most common pattern seen on initial chest radiograph was bilateral interstitial infiltration (43.2%). Localized patchy alveolar infiltra-

Table 1
Characteristics of out-patients with CAP.

Characteristic	N = 44
Age, year (mean, SD)	49.5 (18.2)
Male:female ratio	1 : 1.4
Incubation, days (mean, SD)	6.9 (4.4)
Occupation (N, %)	
Farmer	12 (27.3%)
Government service	6 (13.6%)
Healthy (N, %)	23 (52.3%)
Underlying disease[a] (N, %)	21 (47.7%)
Asthma	6 (13.6%)
Chronic obstructive pulmonary disease	4 (9.1%)
Diabetes mellitus	4 (9.1%)
Old pulmonary tuberculosis	4 (9.1%)
Alcoholism	3 (6.8%)
Other	5 (11.4%)

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

Table 2
Initial laboratory findings (N=44).

Lab test	Results
Complete blood count (CBC)	
White blood cell count (mm^3)	
Mean (SD)	12,190.9 (4,958)
Min	3,000
Max	26,200
Polymorphonuclear leukocytes (%)	
Mean (SD)	70.2 (14.8)
Min	34.2
Max	92.6
Chest radiograph N (%)	
Localized alveolar lesion	14 (31.8%)
Multiple patchy alveolar lesion	2 (4.5%)
Localized interstitial lesion	3 (6.8%)
Bilateral interstitial lesion	19 (43.2%)
Localized alveolar + bilateral interstitial lesion	5 (11.4%)
Multiple patchy alveolar + bilateral interstitial	1 (2.3%)

Table 3
Etiology of CAP in 44 out patients.

Etiology[a]	N = 44	%
H. influenzae	14	31.8
S. pneumoniae	12	27.3
H. parainfluenzae	12	27.3
C. pneumoniae	10	22.7
K. pneumoniae	4	9.1
L. pneumophila	3	6.8
M. pneumoniae	1	2.3
B. pseudomallei	1	2.3
S. aureus	1	2.3
M. catarrhalis	1	2.3
β-streptococci not group A, B	1	2.3
Pseudomonas sp	1	2.3
A. baumanii	2	4.5
β-streptococci group A	1	2.3
Pasteurella multocida	1	2.3
P. aeruginosa	1	2.3
M. lacunata	1	2.3
Unknown	4	9.1

[a]22 patients infected with more than one pathogen

Table 4
Dual infection in 18 patients.

Organisms	N
C. pneumoniae + *H. influenzae*	3
S. pneumoniae + *H. parainfluenzae*	3
C. pneumoniae + *S. pneumoniae*	2
L. pneumophila + *H. parainfluenzae*	2
K. pneumoniae + *H. influenzae*	1
S. pneumoniae + *K. pneumoniae*	1
H. influenzae + *H. parainfluenzae*	1
H. influenzae + *L. pneumophila*	1
C. pneumoniae + *B. pseudomallei*	1
C. pneumoniae + *Pasteurella multocida*	1
S. pneumoniae + *P. aeruginosa*	1
S. pneumoniae + *M. catarrhalis*	1

Table 5
Tripple infection in 4 patients.

Organisms	N
H. influenzae+*S. pneumoniae*+*C. pneumoniae*	1
H. influenzae+*S. pneumoniae*+*K. pneumoniae*	1
β-streptococci group A+*S. pneumoniae*+ *C. pneumoniae*	1
H. influenzae + *C. pneumoniae* + *S. aureus*	1

tion was detected in 31.8%. Other patterns of lesions are described in Table 2.

The causative organism(s) were identified in 40 patients (90.9%), most by sputum culture, pneumococcal urinary antigen, or a serologic test of paired sera. The hemocultures revealed no growth in any patients. *H. influenzae* was found in 31.8% of isolates and was the predominant pathogen among CAP out-patients (Table 3). *S. pneumoniae* and *H. parainfluenzae* were the second and third most frequent pathogens, each found in 27.3%. *C. pneumoniae* was the most common atypical pathogen found in 22.7% of patients. *L. pneumophila* and *M. pneumoniae*, were other atypical pathogens, found in 6.8% and 2.3%, respectively. Other pathogens were *K. pneumoniae* (9.1%), *A. baumanii* (4.5%), *B. pseudomallei* (2.3%), *M. catarhralis* (2.3%), *M. lacunata* (2.3%), β-streptococci group A (2.3%), β-streptococci not group A, B (2.3%), *S. aureus* (2.3%), *Pseudomonas* sp (2.3%), *P. aeruginosa* (2.3%), and *Pasteurella multocida* (2.3%).

Half of our patients (22) were infected with more than one pathogen (Tables 4 and 5). *C. pneumoniae* was the most common co-infecting pathogen found in 10 of these 22 patients (45.4%). The most common co-infecting pathogens were *C. pneumoniae* and *H. influenzae* (3/22) and *S. pneumoniae* and *H. parainfluenzae* (3/22). Other co-infecting pathogens were *S. pneumoniae* and *C. pneumoniae* (2/22) and *L. pneumophila* and *H. parainfluenzae* (2/22).

Antimicrobial susceptibility results of the common pathogens are as follows. Two of the twelve *S. pneumoniae* isolation were penicillin resistant. Nine of the fourteen *H. influenzae* isolates were resistant to cotrimoxazole; while seven isolates had intermediate susceptibilities and one was resistant to erythromycin. Of the twelve *H. parainfluenzae* isolates; six had intermediate susceptibilities and five were resistant to erythromycin, while one isolate was intermediately susceptible and six resistant to Cotrimoxazole.

Table 6
Treatment outcomes.

Outcome	N = 44
Outcome N (%)	
Improved	40 (90.9)
Not improved	4 (9.1)
Date of symptom score (days to improvement)	
Mean (SD)	6.4 (2.2)
Min	2
Max	10

The antibiotics prescribed were ketolide (52.3%), advance macrolide (45.4%), or a new fluoroquinolone (2.3%). Forty patients (90.9%) had clinical and radiologic improvement (Table 6). Symptoms-score improvement on diary cards averaged 6.4 days, range 2 to 10 days. Four patients (9.1%) showed no improvement or were clinically worse by days 3-5 of treatment (according to a telephone visit). One patient needed to be admitted because of a high fever and progress of the chest radiograph after on oral advance macrolide. In this case, sputum grew out *B. pseudomallei* and diabetes mellitus was detected after hospitalization. The fever came down and clinical improvement was observed after 3 days of intravenous ceftazidime plus cotrimoxazole. The patient was then treated with oral doxycycline plus cotrimoxazole for a further twenty weeks. In the other three cases that did not improve, the oral antibiotics were changed according to the culture and susceptibility tests. Two cases were on advanced macrolides, sputum cultures persistently grew *K. pneumoniae*, so the antibiotic was changed to a new fluoroquinolone. One case was on ketolide, the sputum culture grew *H. influenzae*, so the antibiotic was changed to an advanced macrolide.

DISCUSSION

Most patients with CAP are managed as out-patients, and this trend is likely to continue. The number of potential pathogens has expanded with the recent identification of *C. pneumoniae* and *L. pneumophila* (Bochud *et al*, 2001) as common causes of CAP. Successful management requires the clinician make an accurate diagnosis, carefully select those that can be safely be treated as out-patients, provide close follow-up, and treat appropriately based on local epidemiology (Pomilla and Brown, 1994). Because an exact causative agent of CAP is difficult to determine at the time of presentation, treatment is based empirically on prevalence studies.

Over half of CAP out-patients were previously healthy. In cases with underlying diseases, asthma and COPD were common. A chest radiograph was recommended in all guidelines for the diagnosis of CAP in patients with signs and symptoms of respiratory tract infection (Niederman *et al*, 2001; Mandell *et al*, 2003). In our study, the common radiographic findings were interstitial infiltration, followed by localized patchy alveolar infiltration.

Pneumococcal urinary antigen is a rapid bedside laboratory diagnostic test (Pesola, 2001). The etiologies were determined mostly by culture of the sputum and a serology test of paired sera, but this is time consuming. According to the literature, blood cultures yield positive results in only 0.69% of outpatients (Campbell *et al*, 2003), so the test has little utility in the ambulatory management of CAP. Indeed, in our study, the blood culture showed no growth in any patients. Although we extensively investigated the causative agents, known pathogens were detected in 90.9% of patients.

The atypical pathogens, *C. pneumoniae*, *L. pneumophila* and *M. pneumoniae*, accounted for 31.8% of the causative organisms in our CAP out-patients. This high prevalence of atypical pathogens in ambulatory patients is similar to many studies done in other out-patient settings (Berntsson *et al*, 1986; Marrie *et al*, 1996; Wattanathum *et al*, 2003). Furthermore, *C. pneumoniae* was the most common co-infecting pathogen found in our study and other reports (Kauppinen and Saikku, 1995; Lieberman *et al*, 1996). Antibiotics needed to cover these organisms included doxycycline, macrolides, new fluoroquinolones, or ketolides.

Other important organisms which were relevant in our CAP out-patients included *H. influenzae*, *S. pneumoniae*, and *H. parainfluenzae*.

These bacterial pathogens were identified with varying frequencies across positive culture studies in CAP out-patients. Anderson *et al* (1991) reported a majority of cases being positive for *H. influenzae*, with *S. pneumoniae* ranking second. Chien *et al* (1993) Found *S. pneumoniae* the predominant causative organism, while *H. influenzae* ranked second. *H. parainfluenzae* was the most commonly identified pathogen in a study by Ramirez *et al* (1999), with *H. influenzae* ranking second.

Penicillin resistant *S. pneumoniae* (PRSP) is increasing in incidence worldwide (Doern *et al*, 1996; Campbell and Silberman, 1998), in our study it was not a great problem. Penicillin resistant *S. pneumoniae* should be carefully monitored; our findings may be due to our small sample size. In previous report of PRSP pneumonia in Thailand, most (37%) had intermediate resistance, and only 4.3% had high resistance (Sangthawan *et al*, 2003). It is evident that ongoing studies are necessary to determine the impact of changing bacterial antimicrobial susceptibilities on the therapy of out-patient pneumonia.

As with other bacterial pathogens, resistance to antimicrobial agents in *H. influenzae* is a concern. Canadian surveillance studies conducted between 1997 and 1999, found that 14% to 22% of *H. influenzae* strains were resistant to cotrimoxazole, and up to 33% were no longer fully susceptible to clarithromycin (Zhanel *et al*, 2000). *H. parainfluenzae* is assumed to have low pathogenicity. It is possible that *H. parainfluenzae* may have been a secondary pathogen following pneumonia initiated by another etiologic agent (Pillai *et al*, 2000). The data show that *H. parainfluenzae* isolates often display reduced susceptibility to amoxycillin, erythromycin, and cotrimoxazole (Munday *et al*, 1997).

The treatment failure rate in our study, with advanced macrolides, new fluoroquinolones and ketolides, was low (9.1%). Fantin *et al* (2001) noted that 7.6% (9/117) treated on an ambulatory basis subsequently required admission to the hospital. Therefore, follow-up is important in order to confirm whether the patient is responding to the empiric treatment. Based on our findings; patients should be re-evaluated if they do not improve in 3-5 days of treatment. Those failing to improve may need hospitalization or to be switched to a different antibiotic. Drug resistant organisms or unusual organisms (*B. pseudomallei*) should be considered.

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