Risk Factor Analysis of Acute Respiratory Distress Syndrome Among Hospitalized Patients with *Chlamydophila pneumoniae* Pneumonia

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Background: *Chlamydophila pneumoniae* (*C. pneumoniae*) pneumonia-associated acute respiratory distress syndrome (ARDS) is rare and has been seldom reported, but the outcome is usually fatal. This study was designed to identify the risk factors for hospitalized *C. pneumoniae* patients developing ARDS and to describe the outcomes.

Methods: A retrospective study was performed to evaluate hospitalized patients over 18 years old diagnosed with *C. pneumoniae* pneumonia in a tertiary medical center.

Results: Eleven patients who fulfilled the diagnostic criteria were included in this study. ARDS developed in 6 of 11 patients and mostly within 7 days of admission. Five of 6 patients needed to be transferred to the intensive care unit, and all of these patients died. The patients who developed ARDS had higher initial Acute Physiology and Chronic Health Evaluation II scores and CURB-65 (confusion, urea, respiratory rate, blood pressure, age) scores. The risk factors for developing ARDS included age ≥ 75 years, comorbid disease such as congestive heart failure, diabetes or liver cirrhosis, APACHE II score ≥ 12, CURB-65 score ≥ 2, white blood cell count > 12,000/mm^3 or < 4,000/mm^3, serum creatinine ≥ 1.4 mg/dL, and bilateral or multilobar involvement.

Conclusion: *C. pneumoniae* associated with ARDS has a higher mortality, and several risk factors, such as older age, underlying comorbidity and bilateral or multilobar involvement, should be identified earlier. [*J Chin Med Assoc* 2007; 70(8):318–323]

Key Words: acute respiratory distress syndrome, *Chlamydophila pneumoniae*, mortality, pneumonia, risk factors

Introduction

Chlamydia is now recognized as a common source of respiratory infection; most humans will have an infection at least once during their lifetime,[1] and the infection is often subclinical or mildly self-limited. The genus *Chlamydophila* includes *Chlamydophila pneumoniae* (*C. pneumoniae*), *Chlamydophila psittaci* and *Chlamydophila trachomatis*; *C. pneumoniae* has been identified as an important cause of pneumonia since the 1980s. Several studies have reported *C. pneumoniae* involvement in 6–20% of community-acquired pneumonia;[2,3] the clinical picture of *Chlamydia* pneumonia is usually mild and prolonged. However, the course of illness, even in the elderly, is not essentially different from the course of other bacterial pneumonia infections, and severe life-threatening disease with respiratory failure requiring intensive care unit (ICU) support has seldom been reported.[4,5] Although most severe *Chlamydia* pneumonia patients are elderly or have comorbid disease, several case reports of healthy adults with acute hypoxemic respiratory failure due to infection with *C. pneumoniae* can be found.[6–9] Studies have shown that 35–47% of *C. pneumoniae* pneumonia is mixed with other pathogens, the most common being *Streptococcus pneumoniae*.[10–12] Thus, the clinical presentation may be severe and sometimes resemble bacterial pneumonia. *C. pneumoniae* pneumonia-associated

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acute respiratory distress syndrome (ARDS) is rare, but the outcome is usually fatal. An early recognition of the risk of developing ARDS could reduce this high mortality. Therefore, this study was designed to identify the risk factors for hospitalized *C. pneumoniae* pneumonia patients developing ARDS, and to describe the outcomes.

Methods

Patients

Between January 1995 and January 2005, patients over 18 years of age who were diagnosed with *C. pneumoniae* pneumonia while hospitalized in Taipei Veterans General Hospital, a tertiary medical center, were retrospectively analyzed. The diagnosis of *C. pneumoniae* pneumonia was based on clinical symptoms and signs (cough, fever, dyspnea, abnormal breathing sounds), radiographic findings showing new pulmonary infiltration, and microimmunofluorescence (MIF) test criteria suggested by the Centers for Disease Control and Prevention (CDC)[13] and evaluated by a College of American Pathologists-accredited laboratory. Using these criteria, 21 patients with a discharge diagnosis of *C. pneumoniae* pneumonia were re-evaluated, and only 5 patients who fulfilled the criteria of acute infection (IgM ≥ 1:16 or a 4-fold increase in IgG) and 6 patients who fulfilled the criteria of possible acute infection (IgG ≥ 1:512) were included in this study. The study was approved by the institutional review board of Taipei Veterans General Hospital.

Patient evaluation

In addition to the MIF test for *C. pneumoniae*, all patients underwent clinical and radiographic evaluation. The following variables were recorded: age, sex and underlying disease. Within 24 hours after admission, vital signs, such as systolic blood pressure, body temperature, pulse rate and respiratory rate, laboratory findings, chest radiographic features (unilateral or bilateral), and numbers of lobes involved (involvement of more than 2 lobes was defined as multilobar involvement) were recorded, as well as blood culture and sputum culture data collected within 2 days after admission, serologic tests for *Mycoplasma* and *Legionella* pneumonia, initial empiric antibiotics used, hospital days and survival status. The severity of illness was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and CURB-65 score (a 6-point score, 1 point each for confusion, urea > 7 mmol/L, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, age ≥ 65 years)[14] within 24 hours after admission. Patients developing acute respiratory failure with ARDS, defined by the ATS/ERS criteria,[15] comprised the ARDS group, and the others, the non-ARDS group. Arterial blood gas data, time to progression, and ICU admission data were also collected. The clinical characteristics of the ARDS group and the non-ARDS group were analyzed and compared.

Serologic test

C. pneumoniae-specific serum IgG and IgM levels were determined by the MIF method using a commercial kit (SeroFIA-Chlamydia; Savyon Diagnostics, Ashdod, Israel). Sera were tested for IgG in serial 2-fold dilutions from 1:8 to the endpoint, and in a single dilution of 1:20 for IgM. Primary infection with *Chlamydia pneumoniae* was defined as IgM ≥ 1:16, and re-infection was defined as IgG ≥ 1:512, or a 4-fold increase in IgG without elevation of IgM.[16] Also, all patients had negative serologic tests for *Mycoplasma* and *Legionella* pneumonia.

Statistical analysis

We compared categorical data using χ^2 statistics or Fisher's exact test, and continuous data using the Mann–Whitney *U* test. We assumed statistical significance for $p < 0.05$.

Results

Eleven patients met the CDC diagnostic criteria for acute or possibly acute *C. pneumoniae* infection, and ARDS developed in 6 of 11 patients, usually within 7 days of admission; only 1 patient developed ARDS on the 14th day. Five of 6 patients needed to be transferred to the ICU, and all of these patients died (Table 1). All ARDS patients had higher initial APACHE II (Figure 1) and CURB-65 scores (Table 1). Mixed infection with other pathogens was found in 3 of 11 patients, and they all developed ARDS within 7 days (Table 1) and died, although there was no statistical significance when compared to the others ($p = 0.121$). When analyzing the clinical data gathered within 24 hours of admission in relation to ARDS, the APACHE II score, CURB-65 score, systolic blood pressure, serum creatine, and lactate dehydrogenase all showed significant differences between the ARDS and non-ARDS groups (Table 2). In a further exploration of the risk factors between the 2 groups, we discovered that those aged ≥ 75 years, with underlying disease (including congestive heart failure, diabetes or liver cirrhosis), an APACHE II score ≥ 12,

Table 1. Characteristics of 11 hospitalized *Chlamydia* pneumonia patients

Patient number	Age (yr)/sex	Admission APACHE II score	Admission CURB-65 score	Comorbidity	Mixed infection*	Infection status†	ICU admission	ARDS	Time to ARDS (d)	Mortality
1	82/M	30	3	CVA, COPD	N	Re-infection	Y	Y	0	Y
2	61/F	26	2	DM	ORSA, *P. aeruginosa*	Re-infection	Y	Y	0	Y
3	44/M	22	1	Liver cirrhosis, DM, COPD	N	Re-infection	N	Y	14	N
4	90/F	14	2	CHF	GNB	Primary	Y	Y	6	Y
5	85/M	12	2	CHF	ORSA	Primary	Y	Y	7	Y
6	82/M	12	2	Malignancy	N	Re-infection	Y	Y	3	Y
7	43/F	11	0	AS	N	Re-infection	N	N	–	N
8	75/M	6	1	N	N	Re-infection	N	N	–	N
9	71/M	5	1	N	N	Re-infection	N	N	–	N
10	48/M	4	0	N	N	Primary	N	N	–	N
11	62/M	3	0	N	N	Re-infection	N	N	–	N

**Blood culture or sputum culture collected within 2 days after admission was defined as mixed infection pathogen; †primary infection of Chlamydophila pneumoniae was defined as having an IgM antibody ≥ 1:16, and re-infection was defined as having an IgG antibody ≥ 1:512 or a 4-fold increase in IgG without elevation of IgM. APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; ARDS = acute respiratory distress syndrome; CVA = cardiovascular accident; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; CHF = congestive heart failure; AS = ankylosing spondylitis; ORSA = oxacillin-resistant Staphylococcus aureus; P. aeruginosa = Pseudomonas aeruginosa; GNB = Gram-negative bacillus; N = no; Y = yes.*

Figure 1. Acute Physiology and Chronic Health Evaluation (APACHE) II scores in the acute respiratory distress syndrome (ARDS) and non-ARDS groups of hospitalized *Chlamydophila pneumoniae* pneumonia patients ($p < 0.01$).

a CURB-65 score ≥ 2, abnormal white blood cell count (WBC > 12,000/mm^3 or < 4,000/mm^3), serum creatine > 1.4 mg/dL, and bilateral or multilobar radiologic involvement showed a statistically significant difference in the development of ARDS, while no difference could be found in sex, smoking history, C-reactive protein, primary infection or re-infection with *C. pneumoniae*, and initial treatment with appropriate antibiotics, including macrolide or quinolone (Table 3), within 24 hours.

Discussion

C. pneumoniae pneumonia is generally considered to be a mildly infectious disease; however, severe manifestations evolving into ARDS, with high mortality, especially in the elderly, have been reported occasionally.[17] In another community-acquired pneumonia study, 6 of 25 *C. pneumoniae* pneumonia patients had respiratory failure; 5 were > 60 years old and had other underlying diseases.[5] In our study, 6 of 11 *C. pneumoniae* pneumonia patients developed ARDS, with 5 deaths; 5 of 11 *C. pneumoniae* pneumonia patients without ARDS all survived. The higher mortality may be attributed to the high prevalence of ARDS (6/11) and the relatively older population compared with other studies,[4,10] with a mean age of 68 years in our study. Since the MIF test had some false-negative results, and tissue culture or polymerase chain reaction assay of respiratory secretions could not be performed in this retrospective study, and given the fact that our hospital is a tertiary referral center, many mild but

Table 2. Clinical data within 24 hours of admission of the acute respiratory distress syndrome (ARDS) group and the non-ARDS group*

	ARDS ($n=6$)	Non-ARDS ($n=5$)	Total ($n=11$)	p
Age (yr)	74.00 ± 17.74	59.25 ± 16.09	67.55 ± 17.05	0.18
CURB-65 score	2.00 ± 0.63	0.40 ± 0.55	1.27 ± 1.01	< 0.01†
APACHE II score	19.33 ± 7.76	5.80 ± 3.11	13.18 ± 9.16	< 0.01†
Physical examination				
SBP (mmHg)	96.17 ± 17.20	134.25 ± 15.20	111.40 ± 25.06	< 0.01†
Temperature (°C)	37.93 ± 1.15	37.85 ± 0.62	37.90 ± 0.93	0.79
RR (/min)	22.33 ± 5.61	21.75 ± 2.06	22.10 ± 4.36	0.93
Pulse (/min)	127.17 ± 21.32	112.25 ± 8.85	121.20 ± 18.38	0.13
Laboratory data				
WBC (/mm^3)	12,733.33 ± 7,033.54	8,625.00 ± 2,786.13	11,090 ± 5,879.80	0.33
Hemoglobin (mg/dL)	11.00 ± 1.49	12.63 ± 2.13	11.65 ± 1.86	0.08
Platelets (/mm)	188,500 ± 86,586	189,250 ± 151,033	188,800 ± 108,484	1.00
CRP (mg/dL)	13.23 ± 10.09	6.60 ± 4.90	10.58 ± 8.73	0.33
Creatine (mg/dL)	2.15 ± 1.08	0.85 ± 0.17	1.63 ± 1.05	0.02†
Total bilirubin (mg/dL)	1.57 ± 1.19	0.85 ± 0.45	1.28 ± 0.99	0.35
Albumin (g/dL)	2.83 ± 0.55	3.60 ± 0.37	3.14 ± 0.61	0.07
CK (U/L)	179.00 ± 146.00	53.25 ± 34.30	128.70 ± 128.27	0.07
LDH (U/L)	539.33 ± 201.28	215.25 ± 89.71	409.70 ± 230.65	0.02†

**Data are presented as mean ± standard deviation; †$p < 0.05$. APACHE = Acute Physiology and Chronic Health Evaluation; SBP = systolic blood pressure; RR = respiratory rate; WBC = white blood cell count; CRP = C-reactive protein; CK = creatine kinase; LDH = lactate dehydrogenase.*

serologically negative suspicious cases may have been treated as atypical pneumonia and underestimated in this study, causing a higher prevalence of ARDS.

C. pneumoniae has been reported to cause pneumonia frequently in association with other respiratory pathogens, and mixed infection was noted in 35–47% of cases.[10,18] Three of 11 (27%) patients in this study had mixed infection with other pathogens found by sputum cultures collected within 2 days of admission, and all of these patients died. Gram-negative bacilli and oxacillin-resistant *Staphylococcus* were the main pathogens, and all of the patients had been admitted to other hospitals in the 3 months prior to this episode. In a previous study,[10] *C. pneumoniae* as a single etiology often manifested mild illness, however, mixed infection might have been the predisposing factor for ARDS and mortality. Our study found mixed infection in 50% of the ARDS group of patients, and none in the non-ARDS group, although there was no statistical significance.

The CURB-65 score is a simple tool for risk assessment of community-acquired pneumonia and has significant correlation with 30-day mortality, need for mechanical ventilation, and patients' rate of hospital admission for community-acquired pneumonia.[19] All non-ARDS group patients in this study had lower CURB-65 scores (< 2); in addition, the risk of developing ARDS was significant when CURB-65 score ≥ 2. It seemed that the CURB-65 score also predicted the outcome of *C. pneumoniae* pneumonia.

In primary *C. pneumoniae* infection, the MIF IgM antibody is first detectable about 3 weeks after disease onset, then the IgG antibody appears 6–8 weeks later. However, in re-infection, the IgM antibody may not appear, and the IgG antibody titer quickly rises within 2 weeks.[16] Pneumonia due to *Chlamydia* re-infection can be more or less severe than that due to primary infection.[18] In this study, we found that primary or re-infection was not related to the development of ARDS.

Cigarette smoking has been considered to be a risk factor for *C. pneumoniae* infection; however, this was not seen in our study, as in others.[5] A specific finding is that the initiation of appropriate antibiotics with quinolone or macrolide did not prevent further ARDS development.

The limitations of this study include the small sample size from a single tertiary medical center, and being a retrospective review, some important factors worthy of exploration could not be explored. We did find that ARDS was a strong poor prognostic factor for *Chlamydia* pneumonia, and that if precipitating factors could be recognized earlier, the higher mortality of *C. pneumoniae* associated with ARDS might be diminished. However, these clinical significances require exploration in further prospective studies.

Table 3. Risk factor analysis and mortality between the acute respiratory distress syndrome (ARDS) group and the non-ARDS group

	ARDS ($n=6$)	Non-ARDS ($n=5$)	p
Demographic factors			
Age > 75 yr	4 (66%)	0 (0%)	0.045*
Sex (male/female)	4/2	4/1	0.576
Smoking	2 (33%)	1 (20%)	0.576
COPD	2 (33%)	0 (0%)	0.273
Underlying comorbidity†	6 (100%)	1 (20%)	0.015*
Physical examination			
SBP < 90 mmHg	2 (33%)	0 (0%)	0.273
Temperature > 38°C	2 (33%)	2 (40%)	0.652
RR > 24/min	2 (33%)	0 (0%)	0.273
Pulse > 109/min	5 (83%)	2 (40%)	0.197
Serum laboratory findings			
WBC > 12,000 or < 4,000/mm^3	4 (66%)	0 (0%)	0.045*
CRP > 8 mg/dL	5 (83%)	2 (40%)	0.197
Creatine > 1.4 mg/dL	4 (66%)	0 (0%)	0.045*
Na < 130 mmol/L	1 (17%)	1 (20%)	0.727
K > 5.5 or < 3.5 mmol/L	3 (50%)	1 (20%)	0.348
Radiographic involvement			
Bilateral involvement	6 (100%)	1 (20%)	0.03*
Multilobar involvement‡	5 (83%)	0 (0%)	0.017*
Other characteristics			
APACHE II score ≥ 12	6 (100%)	0 (0%)	< 0.01*
CURB-25 score ≥ 2	5 (83%)	0 (0%)	< 0.01*
Primary infection§	2 (33%)	1 (20%)	0.576
Mixed infection‖	3 (50%)	0 (0%)	0.121
Initial appropriate antibiotics¶	2 (33%)	3 (60%)	0.392
ICU admission	5 (83%)	0 (0%)	0.013*
Mortality	5 (83%)	0 (0%)	0.013*

**p < 0.05; †includes malignancy, congestive heart failure, liver cirrhosis, diabetes, cardiovascular accident and ankylosing spondylitis; ‡chest radiography > 2-lobe involvement; §primary infection of Chlamydophila pneumoniae defined as IgM antibody ≥ 1:16; ‖mixed infection with other respiratory pathogen(s); ¶antibiotics included macrolide or quinolone. COPD = chronic obstructive pulmonary disease; SBP = systolic blood pressure; RR = respiratory rate; WBC = white blood cell count; CRP = C-reactive protein; APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.*

In conclusion, *C. pneumoniae* patients associated with ARDS have higher mortality and ICU admission rates. The risk factors for developing ARDS when a patient is hospitalized may include an older age and higher initial APACHE II and CURB-65 scores, underlying comorbid disease, severe leukocytosis or leukopenia, impaired renal function and bilateral or multilobar involvement.

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