

Chlamydial pneumonia in children requiring hospitalization: effect of mixed infection on clinical outcome

Ming-Han Tsai¹, Yhu-Chering Huang¹, Chih-Jung Chen¹, Pen-Yi Lin¹, Luan-Yin Chang²,
Cheng-Hsun Chiu¹, Kuo-Chien Tsao³, Chung-Guei Huang³, Tzou-Yien Lin¹

¹Division of Pediatric Infectious Diseases, Chang Gung Children's Hospital, Taoyuan; ²Department of Pediatrics, National Taiwan University Hospital, Taipei; and ³Department of Clinical Pathology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

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The etiology of community-acquired pneumonia (CAP) in a children's hospital was studied among 209 previously healthy children treated from August 1, 2001 to July 31, 2002. A total of 26 children (12.4%) with a diagnosis of chlamydial infection were included in this study. The diagnosis of chlamydial infection was based on either a positive immunofluorescent assay result for chlamydial antigen in sputum, or positive serologic results for immunoglobulin M (IgM), an IgG titer $\geq 1:640$ or a 4-fold rise in IgG titer by microimmunofluorescence test. Fourteen patients (53.8%) were female and 20 (76.9%) were less than 5 years of age. The onset of infection occurred between August and January in 21 cases (80.7%). Twenty one patients (80.8%) had other pathogens identified. Fever and cough were the most common presenting symptoms. The signs and symptoms were similar for the children with and without coinfection except for tachypnea and wheezing sound, which were significantly more common in patients with mixed infection. None of the laboratory parameters seemed to be specific for chlamydial infection; however, serum C-reactive protein level was significantly higher in cases with mixed infection. Among the 26 children, 12 (46.2%) needed respiratory therapy, and most of them (91.7%, 11/12) had coinfection. Two patients (7.7%) with mixed infection were admitted to the pediatric intensive care unit. One had lobar pneumonia with pleural effusion and the other had necrotizing pneumonia requiring surgical intervention. None of the patients died. In conclusion, *Chlamydia* sp. was identified in 12.4% of children with CAP in this series, and mixed infections were common (80.8%) among these patients. The clinical course of chlamydial pneumonia was not serious in most patients, but alertness is needed to the possibility of developing severe pneumonia in cases with bacterial coinfection.

Key words: Bacterial pneumonia, *Chlamydia*, community-acquired infection, hospitalization, risk factors

Chlamydia pneumoniae, 1 of 3 species of the genus *Chlamydia*, is an important cause of acute respiratory tract infections (RTIs) as well as pneumonia. Previous studies have suggested that approximately 50% of adults worldwide have antibody to *C. pneumoniae* and 10% of cases of community-acquired pneumonia (CAP) in adults are associated with *C. pneumoniae* infection [1]. However, few data are available with regard to *C. pneumoniae* in pediatric age groups [2,3].

Recent studies have shown that *C. pneumoniae* seems to play a more significant role as a cause of lower RTIs in children [4-6]. In previous studies, the incidence of pneumonia due to *C. pneumoniae* among

children ranged from 1-10%, and seroepidemiologic investigations have shown that *C. pneumoniae* is a common cause of RTIs in children between 5 and 15 years of age [1,7]. This pathogen also seems to be related to wheezing and may play a role in the exacerbation of childhood asthma [5,6,8,9]. Therefore, it is important to clarify the clinical presentations of children with CAP due to *C. pneumoniae*.

Recently, the etiology of CAP in 209 hospitalized children was prospectively investigated in our hospital and revealed that *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and viruses were equally common etiologic agents [10]. Coinfections (40.7%, 85/209) were frequently seen. Detailed etiologic agents of CAP in these 209 children will be discussed elsewhere. The aim of this study was to delineate the role of chlamydial infection in children with CAP

Corresponding author: Dr. Yhu-Chering Huang, Department of Pediatrics, Chang Gung Children's Hospital, 5 Fu-Hsin Street, Kweishan 333, Taoyuan, Taiwan.
E-mail: ychuang@adm.cgmh.org.tw

using both serologic tests and direct antigen detection methods. In this investigation, mixed infection was extraordinarily common in children with chlamydial pneumonia and significantly associated with the clinical outcomes. However, few studies [11,12] related to this subject have been reported before and it is thus interesting to delineate and compare the manifestations of patients with and without mixed infection.

Materials and Methods

Study population and diagnostic methods

The etiology of previously healthy children aged between 3 months and 18 years who were admitted to Chang Gung Children's Hospital due to CAP from August 1, 2001 to July 31, 2002 was investigated. Pneumonia was defined as the combination of acute respiratory symptoms and infiltrates on chest radiographs which were interpreted by attending physicians and radiologists. A total of 209 patients, 102 males and 107 females, were included. The median age of the patients was 4 years 3 months (range, 7 months to 16 years 7 months). Table 1 shows the methods used for etiologic investigations [7,13-16].

Chlamydial etiology of pneumonia was determined by antigen detection and serologic methods. Chlamydial antigen detection in sputum was performed by immunofluorescent assay (IFA), and antibody response to *C. pneumoniae* in serum was measured by microimmunofluorescence (MIF; Virion, Switzerland) [7,15]. The criteria for acute chlamydial infection were either positive sputum antigen, a 4-fold or higher rise in immunoglobulin G (IgG) titers, a single positive IgM result in serum, or an IgG titer $\geq 1:640$. Sputum antigen detection was done in 166 patients (79.4%) and the results were positive in 14 cases. For serum antibody response measurements, paired sera were collected in

122 cases (58.4%) and a single serum sample in 82 cases (39.2%). The results were positive in 13 patients, including 1 patient whose sputum antigen was also positive. Based on the data obtained from all tests, a total of 26 children fulfilled the diagnostic criteria for chlamydial infection.

Statistical analysis

Data were analyzed with statistical package SPSS system (version 10.0). Student's *t* test was used for continuous variables analysis. A *p* value ≤ 0.05 was considered statistically significant.

Results

Demographic characteristics

Of the 26 patients with chlamydial infection, 14 (53.8%) were male and 12 were female. Their ages ranged from 12 months to 14 years 4 months, with a median of 3 years 6 months. Twenty patients (76.9%) were aged between 1 and 5 years. The onset of infections occurred between August and January in 21 patients (80.7%).

Twenty one patients (80.8%) had other pathogens identified, including: *M. pneumoniae* in 6 patients; *S. pneumoniae* in 4; virus in 3; and 2 or more pathogens in 8 patients. The etiology of infections in the patients is shown in Table 2.

Clinical manifestations

Table 3 summarizes the clinical signs and symptoms of the study population at admission. Fever (100%) and cough (100%) were the most common clinical manifestations. The duration of fever before admission ranged from 1 to 14 days, with a mean of 6.04 days (median, 5 days). Excluding tachypnea and wheezing sound, the signs and symptoms at enrollment were

Table 1. Diagnostic tests used in 209 children with community-acquired pneumonia

Organism	Assay	Reference(s)
Bacteria	Cultures (blood, pleural effusion)	
<i>S. pneumoniae</i>	Urine <i>S. pneumoniae</i> antigen detection (Binax NOW test)	[13]
<i>M. pneumoniae</i>	ELISA	[14]
<i>C. pneumoniae</i>	Sputum antigen detection (DFA)	
	Serum antibody response (MIF)	[7,15]
Virus		
Respiratory syncytial virus, parainfluenza virus-1, -2, -3, adenovirus and influenza viruses A and B	Sputum antigen detection (DFA)	
	Serum antibody response (CF)	[16]
	Virus isolation	

Abbreviations: ELISA = enzyme-linked immunosorbent assay; DFA = direct immunofluorescent assay; MIF = microimmunofluorescence; CF = complement fixation

Table 2. Etiology of community-acquired pneumonia due to chlamydial infection in 26 children

Etiology	No. (%)
<i>Chlamydia</i> sp. alone	5 (19)
Mixed infection	21 (81)
<i>M. pneumoniae</i> + <i>Chlamydia</i> sp.	6
<i>S. pneumoniae</i> + <i>Chlamydia</i> sp.	4
Virus + <i>Chlamydia</i> sp.	3
Influenza A + <i>Chlamydia</i> sp.	2
Adenovirus + <i>Chlamydia</i> sp.	1
≥3 infectious agents, <i>Chlamydia</i> sp. +	8
<i>S. pneumoniae</i> + <i>M. pneumoniae</i>	2
<i>S. pneumoniae</i> + parainfluenza-1	1
<i>M. pneumoniae</i> + adenovirus	1
<i>M. pneumoniae</i> + adenovirus + RSV	1
MRSA + parainfluenza-1	1
RSV + parainfluenza-2	1
RSV + adenovirus	1

Abbreviations: RSV = respiratory syncytial virus; MRSA = methicillin-resistant *Staphylococcus aureus*

similar for children with and without other pathogen coinfection. The duration of the illness and hospitalization were somewhat longer for the children with mixed infection but this difference was not significant.

Laboratory findings

Leukocytosis (white blood cell count >15,000/mm³) was noted in 8 children (30.8%), with a mean leukocyte count of 11,053/mm³. Thrombocytopenia (platelet <100,000/mm³) was only found in 1 child (3.8%), with a mean platelet count of 282,000/mm³. Serum C-reactive

protein (CRP) concentration [normal, <10 mg/L] was elevated in 18 (88.5 %) cases. There was no significant difference in total white blood cell counts, hemoglobin, and platelet count between children with and without coinfection. However, serum CRP concentration was significantly higher in patients with mixed infection (mean, 113.8 mg/L vs 46.9 mg/L; $p=0.030$). The most common radiographic finding was a localized segmental infiltrate (17 patients [65.4%]). The laboratory data of the patients are shown in Table 4.

Treatment and outcome

Antimicrobial treatment was given according to the judgment of the attending physicians in the absence of serologic results. Eighteen children (69.2%) received a macrolide (erythromycin, 17 children; azithromycin, 1 child) and 16 of them also received other antibiotics. The other 8 children were treated with cefuroxime (in 2 children), penicillin (in 2), ampicillin (in 2), amoxicillin-clavulanate (in 1), and combination antibiotic treatment with vancomycin and ceftriaxone (in 1), respectively. The mean duration of antibiotic therapy was 12.3 days, including erythromycin treatment, which had a mean duration of 7.7 days. No significant difference was noted in the duration of erythromycin or total antibiotic treatment in children with and without mixed infection.

Twelve patients (46.2%) needed respiratory therapy such as oxygen hood or ventilator support, and most of them (91.7%, 11/12) had other pathogen coinfection. Two patients (7.7%) coinfecting with *M. pneumoniae*

Table 3. Clinical signs and symptoms at admission in 26 children with chlamydial pneumonia

Characteristic	Total (n = 26)	Mixed infection (n = 21)	Isolated infection (n = 5)
	No. (%)	No. (%)	No. (%)
Fever	26 (100)	21 (100)	5 (100)
<5 days	8 (31)	8 (38)	0
≥5 days	18 (69)	13 (62)	5 (100)
Cough	26 (100)	21 (100)	5 (100)
Rhinorrhea	16 (62)	13 (62)	3 (60)
Tachypnea	4 (15)	4 (19)	0
Wheeze	2 (8)	2 (10)	0
Rales	15 (58)	12 (57)	3 (60)
Rhonchi	7 (27)	6 (29)	1 (20)
Diarrhea	1 (4)	0	0
Vomiting	4 (15)	3 (14)	1 (20)
Abdominal pain	1 (4)	1 (5)	0
Duration of illness (days) [mean ± SD] ^a	9.15 ± 4.49	9.43 ± 4.78	8.00 ± 3.08
Duration of hospitalization (days) [mean ± SD] ^a	7.31 ± 4.91	7.76 ± 5.20	5.40 ± 3.05

^a $p<0.05$ was considered to be significant. No significant difference in duration of either the illness or hospitalization was found between the 2 groups.

Table 4. Laboratory findings at admission in children with chlamydial pneumonia

Test	Total (n = 26) No. (%)	Mixed infection (n = 21) No. (%)	Isolated infection (n = 5) No. (%)	<i>p</i> ^a
Leukocyte count (/mm ³)				
Mean ± SD	11,053 ± 5749	11,600 ± 5868	8760 ± 5,169	0.317
Range	2,300-24,400	2300-24,400	2600-16,100	
Median	10,145	10,700	7000	
<5000	4 (15)	3 (14)	1 (20)	
5000-15,000	14 (54)	11 (52)	3 (60)	
>15,000	8 (31)	7 (33)	1 (20)	
Hemoglobin (g/dL)				
Mean ± SD	11.0 ± 1.3	10.9 ± 1.3	11.3 ± 1.4	0.616
Range	8.6-13.8	8.6-13.8	9.9-13.4	
Platelet count (10 ³ /mm ³)				
Mean ± SD	282 ± 120	269 ± 129	336 ± 48	0.077
Range	84-676	84-676	290-403	
<100	1	1	0	
≥100	25	20	5	
C-reactive protein (mg/L)				
Mean ± SD	100.9 ± 89.7	113.8 ± 93.8	46.9 ± 42.2	0.030
Range	2.0-351.7	2.0-351.7	2.0-92.8	
<10	3 (12)	1 (5)	2 (40)	
10-40	5 (19)	5 (24)	0	
>40	18 (69)	15 (71)	3 (60)	

Abbreviation: SD = standard deviation

^a*p*<0.05 was considered to be significant.

and methicillin-resistant *S. aureus* (MRSA) respectively, were admitted to the pediatric intensive care unit (PICU). The patient coinfecting with *M. pneumoniae* had lobar pneumonia with pleural effusion, and the other patient coinfecting with MRSA had necrotizing pneumonia requiring surgical intervention. None of the patients died.

Discussion

This study found that most children (76.9%, 20/26) with chlamydial pneumonia were between 1 and 5 years old, which is not in agreement with previous investigations [1,2,8,17]. A seroepidemiologic study from the United States by Kuo et al found that antibodies to *C. pneumoniae* were frequently (78.4%) present in children 5 to 14 years old [17]. The cause of this discrepancy in age distribution is not clear. Previous studies found that most children younger than 5 years of age had not developed antibodies detectable by MIF test [8,18], and some *C. pneumoniae* infections, especially in young children, were missed if MIF test alone was used for the diagnosis of chlamydial pneumonia. In this study, most *C. pneumoniae* infections were diagnosed by a positive result of chlamydial antigen in patients

younger than 5 years of age (14/20, 70%) and may cause this discrepancy.

The importance of mixed infections in chlamydial pneumonia has not previously been emphasized. In a review of 8 studies of CAP by Kauppinen and Saikku [11], a total of 176 cases of *C. pneumoniae* were analyzed, of which 68 (39%) represented pneumonia with more than 1 apparent etiology, and the most common associated organism was *S. pneumoniae*. Most of our patients (80.8%, 21/26) had coinfection with pathogens other than *Chlamydia* sp. and the most common were *M. pneumoniae* and *S. pneumoniae*. Upper RTI caused by *C. pneumoniae* may pave the way for invasion by other bacteria, such as *M. pneumoniae* or *S. pneumoniae* [11]. Therefore, the symptoms and signs of patients with *C. pneumoniae* pneumonia should be evaluated more carefully since the clinical pictures may just reflect the manifestations due to the associated pathogen rather than *C. pneumoniae* itself.

No sign or symptom appears to be unique for pneumonia caused by *C. pneumoniae*. File et al analyzed the characteristics of 26 patients with pneumonia due to isolated *C. pneumoniae* and found that the illness was mild, associated with limited temperature elevation, and nonspecific [19]. In addition, they found that

non-productive cough was common and fever was usually low grade. In contrast, pneumonia in patients with mixed infections is relatively severe. The cough is productive (with purulent sputum), the onset is acute and severe, usually requiring hospitalization, and leukocytosis is common [11]. In the present study, only increased rate of occurrence of tachypnea and higher level of serum CRP were significantly noted in patients with mixed infection. Thus, diagnosis of *C. pneumoniae* pneumonia on the basis of clinical parameters alone is difficult in patients with mixed infection.

Laboratory diagnosis of *C. pneumoniae* infection is based on isolation of the agent in cell culture, direct antigen detection, or the detection of a specific serum antibody response by the MIF test, which can differentiate *C. pneumoniae* from another 2 species (*C. trachomatis*, *C. psittaci*). To date, use of MIF serology with *C. pneumoniae* antigen has provided the most sensitive and specific method for diagnosis of acute *C. pneumoniae* infection [7,15]. In contrast to the MIF test, the complement fixation test, which detects antibodies against chlamydial lipopolysaccharide, is also widely available but is unable to distinguish the 3 chlamydial species [17]. Antigen detection by enzyme-linked immunosorbent assay (ELISA) method, using genus-specific antibody that is commonly used for *C. trachomatis*, shows poor sensitivity and is not widely used for diagnosis of *C. pneumoniae* infection [17]. In this study, we also used antigen detection test by IFA as a diagnostic tool. Although the antigen detection test cannot differentiate the 3 species of the genus *Chlamydia*, all 14 patients in this study who had a positive result of antigen detection were considered to have *C. pneumoniae* infection since *C. trachomatis* infection is rare among patients with their age distribution, which was between 12 months and 14 years 4 months.

Very little data on the effectiveness of different therapies for *C. pneumoniae* pneumonia are available [20]. The infections have a remarkable tendency to recur [21], and this pathogen may pave the way for invasion by other bacteria, leading to a severe bacterial pneumonia [11]. Recent studies have also shown that *C. pneumoniae* is associated with the initiation and promotion of asthma [5,6,9]. A complete course of effective antibiotic treatment therefore seems to be indicated. *C. pneumoniae* is susceptible to macrolides and the recommended regimen is erythromycin or clarithromycin administered for 10 days to 2 weeks [2, 22]. Several studies also showed that in the case of

C. pneumoniae infections, the use of a macrolide is associated with better clinical outcomes compared with the use of other antibiotics [23,24].

In this series, most (69.2%) of the patients were treated with macrolides, but the mean duration of erythromycin treatment was less than the recommended treatment course (7.7 vs 10-14 days). Although there was no significant difference in the extent of clinical improvement between children receiving macrolides and those not receiving macrolides, whether there was no difference in long-term clinical outcomes and rates of recurrence between these 2 groups remains unclear. Further long-term follow-up studies are needed. All of the patients treated with antibiotics but not with macrolides had other pathogen coinfection and a satisfactory outcome. Most (91.7%) of the patients treated with respiratory therapy such as oxygen hood or ventilator support also had other pathogen coinfection, and both of the patients admitted to PICU for intensive care had mixed infection. These findings suggest that the clinical outcomes may have been more closely related to the presence of mixed infections, or to having received appropriate treatment.

In conclusion, *C. pneumoniae* is not infrequent and plays an important role in acute lower RTIs in children. Mixed infection is very common in patients with *C. pneumoniae* pneumonia. It is difficult to differentiate *C. pneumoniae* pneumonia from pneumonia of other etiologies on the basis of clinical parameters alone, and the diagnosis must be based on laboratory tests. Patients with other pathogen coinfection may have a more severe illness and thus a worse clinical outcome.

References

1. Jantos CA, Wienpahl B, Schiefer HG, Wagner F, Hegemann JH. Infection with *Chlamydia pneumoniae* in infants and children with acute lower respiratory tract disease. *Pediatr Infect Dis J* 1995;14:117-22.
2. Grayston JT. *Chlamydia pneumoniae* (TWAR) infections in children. *Pediatr Infect Dis J* 1994;13:675-85.
3. Hammerschlag MR. Atypical pneumonias in children. *Adv Pediatr Infect Dis* 1995;10:1-39.
4. Block S, Hedrick J, Hammerschlag MR, Cassel GH, Craft JC. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. *Pediatr Infect Dis J* 1995;14:471-7.
5. Hahn DL, Dodge RW, Gougliatnikov R. Association of *Chlamydia pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *JAMA*

- 1991;266:225-30.
6. Kraft M, Cassell GH, Henson JE. Detection of *Mycoplasma pneumoniae* in the airways of adult with chronic asthma. *Am J Respir Crit Care Med* 1998;158:998-1001.
 7. Wang SP. The microimmunofluorescence test for *Chlamydia pneumoniae* infection: technique and interpretation. *J Infect Dis* 2000;181(Suppl 3):S421-5.
 8. Normann E, Gnarpe J, Gnarpe H. *Chlamydia pneumoniae* in children with acute respiratory tract infections. *Acta Paediatr* 1998;87:23-7.
 9. Emre U, Roblin PM, Gelling M. The association of *Chlamydia pneumoniae* infection and reactive airway disease in children. *Arch Pediatr Adolesc Med* 1994;148:727-32.
 10. Tsai MH, Huang YC, Chiu CH, Lin PY, Chen CJ, Wong KS. Etiology of community-acquired pneumonia in hospitalized children in Taiwan. The 176th Scientific Meeting of the Taiwan Pediatric Association, Taipei, Nov, 2003.
 11. Kauppinen M, Saikku P. Pneumonia due to *Chlamydia pneumoniae*: prevalence, clinical features, diagnosis, and treatment. *Clin Infect Dis* 1995;21(Suppl 3):S244-51.
 12. Normann E, Gnarpe J, Gnarpe H, Wettergren B. *Chlamydia pneumoniae* in children attending day-care centers in Gavle, Sweden. *Pediatr Infect Dis J* 1998;17:474-8.
 13. Faden H, Heimerl M, Varma C, Goodman G, Winkelstein P. Urinary excretion of pneumococcal cell wall polysaccharide in children. *Pediatr Infect Dis J* 2002;21:791-3.
 14. Hirschberg L, Krook A, Pettersson CA, Vikerfors T. Enzyme-linked immunosorbent assay for detection of *Mycoplasma pneumoniae* specific immunoglobulin M. *Eur J Clin Microbiol Infect Dis* 1998;7:420-3.
 15. Peeling RW, Wang SP, Grayston JT, Blasi F, JensBoman, Clad A, et al. *Chlamydia pneumoniae* serology: interlaboratory variation in microimmunofluorescence assay results. *J Infect Dis* 2000;181(Suppl 3):S426-9.
 16. Hsiung GD. Complement fixation test. In: Hsiung GD, ed. *Diagnostic virology*. New Haven, CT: Yale University Press; 1982:42-9.
 17. Kuo CC, Jackson LA, Campbell LA, Grayston JT. *Chlamydia pneumoniae* (TWAR). *Clin Microbiol Rev* 1995;8:451-61.
 18. Falck G, Gnarpe J, Gnarpe H. Prevalence of *Chlamydia pneumoniae* in healthy children and in children with respiratory tract infections. *Pediatr Infect Dis J* 1997;16:549-54.
 19. File TM, Plouffe JF, Breiman RF, Skelton SK. Clinical characteristics of *Chlamydia pneumoniae* infection as the sole cause of community-acquired pneumonia. *Clin Infect Dis* 1999; 29:426-8.
 20. Lipsky BA, Tack KJ, Kuo CC, Wang SP, Grayston JT. Ofloxacin treatment of *Chlamydia pneumoniae* (strain TWAR) lower respiratory tract infections. *Am J Med* 1990;89:722-4.
 21. Grayston JT, Kuo CC, Wang SP, Altman J. A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. *N Engl J Med* 1986;315:161-8.
 22. Hammerschlag MR. Antimicrobial susceptibility and therapy of infections caused by *Chlamydia pneumoniae*. *Antimicrob Agents Chemother* 1994;38:1873-8.
 23. Gendrel D, Raymond J, Moulin F. Etiology and response to antibiotic therapy of community-acquired pneumonia in French children. *Eur J Clin Microbiol Infect Dis* 1997;16:46-7.
 24. Gleason PP, Kapoor WN, Stone RA. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *JAMA* 1997;278:32-9.