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ORIGINAL ARTICLE

Clinical and epidemiological characteristics in children with community-acquired mycoplasma pneumonia in Taiwan: A nationwide surveillance



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KEYWORDS

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Background: Community-acquired pneumonia (CAP) is the leading cause of hospitalization of children. *Mycoplasma pneumoniae* is one of the most common pathogens. The disease severity is diverse, and the diagnosis remains a challenge to clinical pediatricians. The aims of this study are to provide a nationwide surveillance of the epidemiology and clinical manifestations of community-acquired mycoplasma pneumonia (CAMP) in children in Taiwan.

Methods: The medical records of children enrolled by the Taiwan Pediatric Infectious Disease Alliance (TPIDA) project during 2010–2011 were reviewed. Hospitalized children with segmental or lobar pneumonia were included. The demographic, clinical, laboratory and radiographic data were analyzed. Nasopharyngeal swabs, pleural effusion, and serum were collected for multiplex viral and bacterial polymerase chain reaction (PCR), mycoplasma immunoglobulin M (IgM), or paired immunoglobulin G (IgG) titer.

Results: There were overall 127 children with CAMP. Among them, 16 (12.6%) children had PCR and IgM positivity, 74 (58.3%) children had a positive serologic study, 34 (27.8%) children had positive PCR detection, and three (2.4%) children had paired IgG above a four-fold increase. Enrolled patients were divided into two groups before and after the age of 5 years. Children younger than 5 years or younger had a significantly longer hospitalization, higher intensive care unit (ICU) admission rates, and more complications. They were more frequent to receive oxygen supplementation and even surgical intervention. The white blood cell counts and C-reactive protein levels were higher in children 5 years old or younger.

Conclusion: *Mycoplasma pneumoniae* is an important etiology of CAP in children 5 years or younger. They had a longer length of hospitalization, higher inflammatory responses, and more complications, compared to children older than 5 years.

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Introduction

Pneumonia is a common complication of respiratory tract infection. For younger children, elders, and immunocompromised individuals, pneumonia can lead to death. According to World Health Organization (WHO), pneumonia was a major cause of mortality among children in 2010.¹ Pneumonia accounts for 21% of mortality in children younger than 5 years in African and Eastern Mediterranean regions and 12% of mortality in the Americas and in European regions.² In Taiwan, pneumonia was the fifth cause of death in children 1–14 years old in 2012.³ Community-acquired pneumonia (CAP) is also a common cause of hospitalization of children. Community-acquired pneumonia is usually clinically classified as “typical” or “atypical” pneumonia. Typical pneumonia is caused by bacteria and atypical pneumonia is caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or viruses. In previous reports, *M. pneumoniae* has an important role in pediatric CAP.

M. pneumoniae is a small fastidious bacterium that lacks a cell wall. This unique feature makes it invisible on Gram stain, difficult to culture, and even insensitive to general antibiotics such as the beta-lactams used to treat CAP. As a causative pathogen of atypical pneumonia, *M. pneumoniae* infection can occur at any age. School-aged children and adolescents have the highest attack rates. Children younger than 3 years tend to develop upper air way infection, whereas children 5–20 years tend to develop acute bronchitis and pneumonia.^{4–6} Fever and cough are the most common symptoms,⁷ but extrapulmonary manifestations occur occasionally. The severity of *M. pneumoniae* infection varies from self-limited upper respiratory tract

infection to complicated pneumonia to even mortality.⁸ The prevalence of macrolide-resistant *M. pneumoniae* is rising in Japan⁹ and China,¹⁰ although recent studies show that the recent resistance rate is 12.3–23% in Taiwan.^{11,12} Macrolide remains the first-line drug to treat *M. pneumoniae* infection.

The “gold standard” for the diagnosis of *M. pneumoniae* infection is still lacking. Single positivity of serum immunoglobulin M (IgM) and a four-fold or greater titer increase in serum immunoglobulin G (IgG) are the most common laboratory diagnostic tools. Polymerase chain reaction (PCR) is a sensitive but time-consuming method. The cost and technique-dependent procedure limits the use of PCR. Prompt diagnosis of *M. pneumoniae* infection remains challenging in the current era. By using radiographic findings, the aims of this study are to provide nationwide surveillance of the epidemiology and clinical manifestations of community-acquired mycoplasma pneumonia (CAMP) in hospitalized children in Taiwan.

Methods**Taiwan Pediatric Infectious Disease Alliance**

Taiwan Pediatric Infectious Disease Alliance (TPIDA) is a collaborative consortium established by nine pediatric infectious disease departments of tertiary medical centers, which include the National Taiwan University Hospital (Taipei City, Taiwan), Mackay Memorial Hospital (Taipei City, Taiwan), Chang Gung Memorial Hospital at Linkou (Linkou, Taiwan), China Medical University Hospital (Taichung City, Taiwan), National Cheng Kung University

Hospital (Tainan City, Taiwan), Kaohsiung Chang Gung Memorial Hospital (Kaohsiung City, Taiwan), Buddhist Tzu Chi General Hospital (Hualien, Taiwan). In 2010, nationwide surveillance of childhood CAP began. The study was approved by the Institutional Review Board in each hospital. Informed consent was obtained from each participating patient or the patient's parents or guardian. This study was approved by the Institutional Review Boards of the aforementioned institutions.

Enrollment criteria

Hospitalized children under 18 years who were diagnosed from 2010 to 2011 as having CAP with radiographic evidence in participant hospitals were prospectively enrolled. The demographic data, clinical features, laboratory findings and radiographic evidence were analyzed. The enrolled children were further divided into two groups before and after the age of 5 years.

Radiographic definitions

Chest radiographs of the enrolled patients were interpreted by two pediatricians without knowledge of the patients' clinical information. Based on the consensus of interpretation,¹³ the area and distribution of the lung parenchyma and the abnormality of the pleura were evaluated. Patients with segmental or lobar pneumonia and complete clinical information were included.

Case definitions

All nasopharyngeal swabs were submitted for the detection of viral pathogens: direct fluorescent antibody testing, viral culture, and nucleic acid tests. Multiplex PCR of the pleural effusion was performed to identify other respiratory bacterial pathogens. The nucleic acid tests to detect *M. pneumoniae* from nasopharyngeal samples were executed. Serum samples were tested for the presence of antibodies to *M. pneumoniae* by using the IgM-specific Mycoplasma

Immuno-Card, an enzyme immunoassay by Meridian Bioscience (Cincinnati, OH), and the *Mycoplasma pneumoniae* IgG/IgM Antibody Test System (FTI-SERODIA-myc II test; Fujirebio Inc., Taipei, Taiwan) under the manufacturers' instructions.

M. pneumoniae infection was defined by one of the following criteria: (1) positivity of mycoplasma IgM in acute stage, (2) positive detection of *M. pneumoniae* in nasopharyngeal swab by PCR, (3) four-fold or greater increase in the mycoplasma IgG titer in the acute stage and convalescent stage. Patients with complicated pneumonia were defined as patients who had pleural effusions, pneumatoceles, or respiratory failure with intubation.

Statistical analysis

All statistical analysis was performed using PASW Statistic software, version 18.0 for Windows (18.0; SPSS Inc., Chicago, Illinois, USA). Parametric data were compared using analysis of variance (ANOVA). Categorical data were analyzed using contingency table analysis and Pearson's Chi-square test. Statistical significance was defined as $p < 0.05$ in the tests.

Results

Clinical and radiographic findings

Between 2010 and 2011, 492 children in the TPIDA project with segmental or lobar pneumonia were enrolled. There were overall 128 (26.0%) children with CAMP. One patient who was not hospitalized was excluded. Most children with CAP were 3–10 years old. The mean age was 6.11 ± 3.13 years and the male-to-female ratio was 1:1.2. There were 61 children 5 years or younger and 66 children older than 5 years (Table 1). However, *M. pneumoniae* had highest the attribution to CAP in children over 5 years old (Fig. 1). The seasonal distribution of patients with CAP showed that the number of cases decreased in May, June, and July (Fig. 2). In 2010, the number of CAMP cases

Table 1 Demographic data and clinical characteristics of children with CAMP in the 2010–2011 TPIDA project

	≤5 y/o <i>n</i> = 61 (%)	> 5 y/o <i>n</i> = 66 (%)	Total <i>N</i> = 127 (%)	<i>p</i>
Age (y)	3.88 ± 0.91	8.17 ± 3.03	6.11 ± 3.13	< 0.001*
Sex (male)	26 (42.6)	32 (48.5)	58 (45.7)	0.593
School attendance	41 (67.2)	63 (95.5)	104 (81.9)	< 0.001
Underlying disease	3 (4.9)	1 (1.5)	4 (3.1)	0.350
Symptoms				
Fever	60 (98.4)	66 (100)	126 (99.2)	0.480
Cough	59 (96.7)	64 (97.0)	123 (96.9)	> 0.99
Tachypnea	21 (34.4)	8 (12.1)	29 (22.8)	0.003
Vomiting	17 (27.9)	9 (13.6)	26 (20.5)	0.005
Abdominal pain	9 (14.8)	11 (16.7)	20 (15.7)	0.799
Diarrhea	7 (11.5)	8 (12.1)	15 (11.8)	0.781

* The *p* values in bold font indicate statistical significance.

CAMP = community-acquired mycoplasma pneumonia; TPIDA = Taiwan Pediatric Infectious Disease Alliance; y/o = years old.

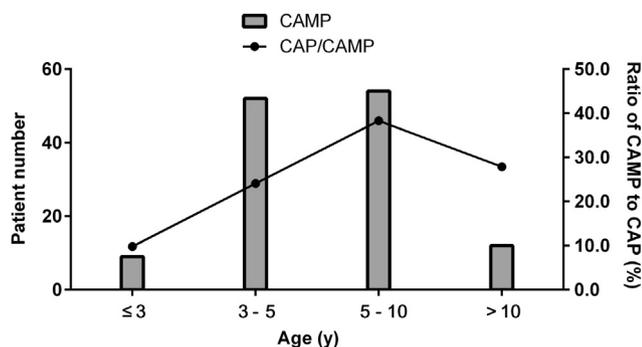


Figure 1. Age distribution of patients with CAMP and the ratio of CAMP to CAP in the 2010–2011 TPIDA project. CAMP = community-acquired mycoplasma pneumonia; CAP = community-acquired pneumonia; TPIDA = Taiwan Pediatric Infectious Disease Alliance.

peaked in January and June. In 2011, the percentage of *M. pneumoniae* infection was approximately 20–40% of CAP cases. Among them, 16 (12.6%) patients had both PCR and IgM positivity, 74 (58.3%) patients had positive serologic study, 34 (27.8%) patients had positive PCR detection, and 3 (2.4%) patients had paired IgG titer with a four-fold or greater increase.

Among the patients, 81.9% of them attended school (95.5% of the children were older than 5 years and 67.2% of the children were 5 years or younger, $p < 0.001$). Four children had underlying disease, which included two children 5 years or younger with neurologic diseases, one child with asthma, and one child older than 5 years with atrial septal defect status post operation. The most common symptoms in all children were fever (99.2%) and cough (96.9%). Tachypnea and vomiting were significantly higher in children 5 years or younger ($p < 0.05$). The right and left lower lungs were overall the most common involved areas (Fig. 3). The location of the major lesion of pneumonia was not statistically different in both age groups. One-half of the children had lobar pneumonia in both groups.

Clinical course and laboratory findings

M. pneumoniae was the single pathogen identified in 75.4% of children 5 years or younger and in 83.3% of children older than 5 years. Codetection of bacteria and virus were observed in both groups (Table 2). Seven children 5 years or younger and one child older than 5 years had bacteria codetection, which were all *Streptococcus pneumoniae*. Adenovirus and rhinovirus were the most common code-detected viruses in both groups. The mean duration of fever was 8.34 ± 4.50 days and there was no statistical difference in either age group (Table 3). The duration of hospitalization was significantly longer in children 5 years or younger ($p < 0.001$), and the need for intensive care unit (ICU) admission and oxygen supplement were also significantly higher ($p < 0.05$). In total, 6 (9.8%) children 5 years or younger received ventilator support and 9 (14.8%) children received video-assisted thoracoscopic surgery (VATS). Among children who underwent surgery, 5 of them had *S. pneumoniae* in the pleural effusion (4 infections were serotype 19A, 1 infection was serotype 3). None of the children older than 5 years received surgery, and only one child was intubated. In total, 60.6% patients received macrolide, which included 52.5% of children 5 years or younger and 68.2% of children older than 5 years. No significant difference in macrolide prescription was observed. The highest white blood cell counts ($10,649 \pm 5342/\text{mm}^3$ vs. $16,387 \pm 10,840/\text{mm}^3$, $p < 0.05$) and the C-reactive protein levels (8.68 ± 9.19 mg/dL vs. 14.00 ± 12.10 mg/dL, $p < 0.05$) were significantly higher in children 5 years or younger.

In total, 33 children had complicated pneumonia, which included 24 children 5 years or younger and nine children older than 5 years. Children 5 years or younger had a significantly higher rate of complicated pneumonia (39.3% vs. 13.6%, $p < 0.05$). Most children with complicated pneumonia presented with pleural effusion (30/33, 90.9%); 21.2% of children had respiratory failure, and 6.1% of children had pneumatoceles. Only 14 (42.4%) of them received macrolide. Compared to children without complications,

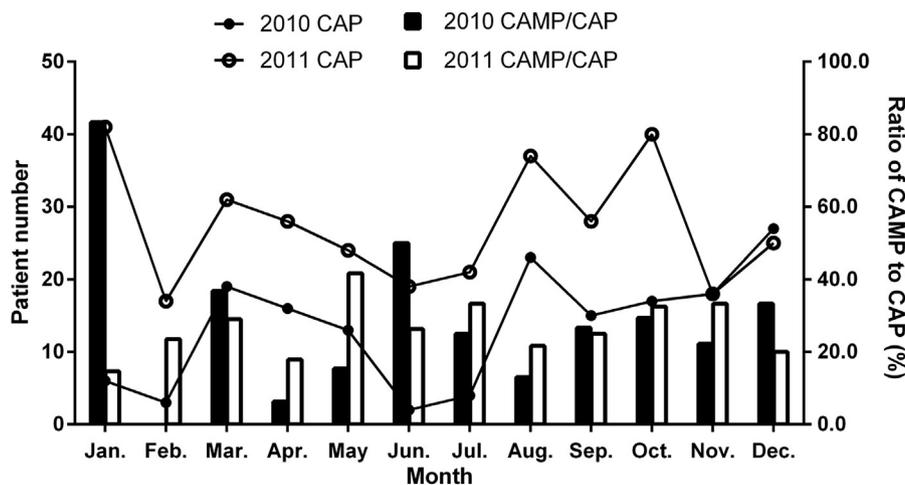


Figure 2. The number of patients with CAP and the ratio of CAMP to CAP, according to the month of the year. CAMP = community-acquired mycoplasma pneumonia; CAP = community-acquired pneumonia.

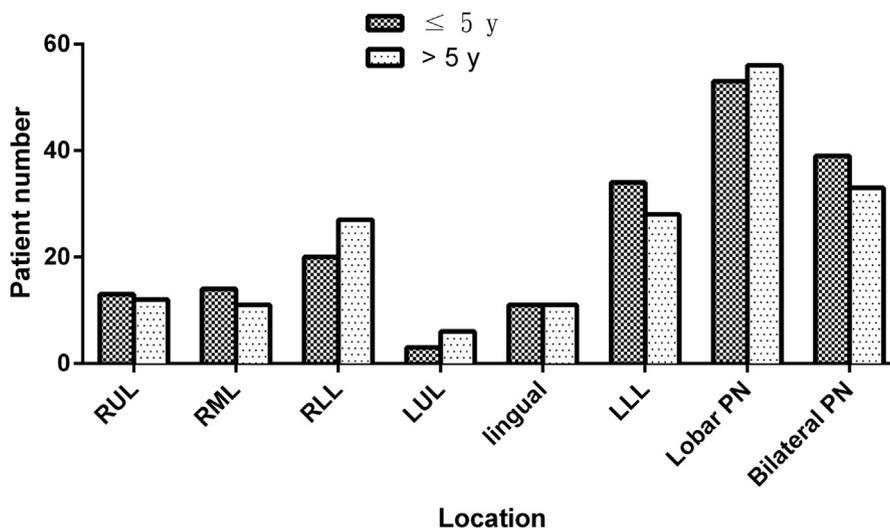


Figure 3. The chest radiographic presentation of children with community-acquired mycoplasma pneumoniae. LLL = left lower lobe; LUL = left upper lobe; PN = pneumonia; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

these children had a significantly lower rate of macrolide treatment ($p < 0.05$).

Discussion

Community-acquired pneumonia is a common pediatric disease worldwide. The disease severity varies by etiology, age and host immunity. Thus, pediatric CAP shows a diversity in epidemiology and clinical manifestations in different countries. Among the hospitalized children with CAP, 79–85.6% had at least one identified pathogen.^{14–16} The incidence of *M. pneumoniae* infection ranged 7–37%.^{14,15} Prospective, single-hospital based studies demonstrate that at least one pathogen was detected in 79% of hospitalized children with CAP, which includes 26% of *M. pneumoniae*, 11% of *C. pneumoniae*, and 19% of viruses.^{15,16} An analysis study in Singapore identified pathogens in 38.4% of children, which include typical bacteria in 10.3% of infections, *M. pneumoniae* in 20.3% of infections, and viruses in 5.5% of infections.¹⁷ A local surveillance study can provide more useful information for clinicians. In

northern Taiwan, a prospective study demonstrated that *S. pneumoniae*, *M. pneumoniae*, and viruses accounted for 42%, 37%, and 41%, respectively, of hospitalized children with CAP.¹⁴ Codetection was common in the current study.

Table 2 Codetection of pathogens in children with CAMP

	≤ 5 y/o n = 61 (%)	> 5 y/o n = 66 (%)
<i>M. pneumoniae</i>	46 (75.4)	55 (83.3)
<i>M. pneumoniae</i> + bacteria	7 (11.5) ^a	1 (2.3) ^c
<i>M. pneumoniae</i> + virus	9 (14.8) ^b	10 (15.2) ^d

^a All infections were *Streptococcus pneumoniae*.

^b Four infections were adenovirus, and three infections were rhinovirus.

^c The infections were *Streptococcus pneumoniae*.

^d Five infections were adenovirus and two infections were rhinovirus.

CAMP = community-acquired mycoplasma pneumoniae; *M. pneumoniae* = *Mycoplasma pneumoniae*; y/o = years old.

Table 3 The clinical course and laboratory data of children with CAMP

	≤ 5 y/o n = 61 (%)	> 5 y/o n = 66 (%)	p
Clinical course			
Duration of fever (d)	8.77 ± 5.14	7.94 ± 3.81	0.549
Hospitalization (d)	10.87 ± 9.20	6.29 ± 4.56	< 0.001*
ICU admission	20 (32.8)	8 (12.1)	0.006
O ₂ requirement	29 (47.5)	19 (28.8)	0.016
Ventilation use	6 (9.8)	1 (1.5)	0.053
VATS	9 (14.8) ^a	0 (0)	0.001
Macrolide use	32 (52.5)	45 (68.2)	0.202
Laboratory data			
Highest WBC (/mm ³)	16387 ± 10840	10649 ± 5342	0.001
Highest CRP (mg/dL)	14.00 ± 12.10	8.68 ± 9.19	0.018
Complications			
Pleural effusion	24 (39.3)	9 (13.6)	0.001
Pneumatocele	2 (3.3)	0	0.229
Respiratory failure	6 (9.8)	1 (1.5)	0.642

^a Five of the patients had *S. pneumoniae* in the pleural effusion.

* The p values in bold font indicate statistical significance.

CAMP = community-acquired mycoplasma pneumoniae; CRP = C-reactive protein; ICU = intensive care unit; O₂ = oxygen; VATS = video-assisted thoracoscopic surgery; WBC = white blood cell; y/o = years old.

The prevalence of CAMP was 26.0% in hospitalized children, which was similar to the findings in previous reports. However, children 5 years or younger accounted for nearly one-half (48%) of children with CAMP, and they had a more complicated clinical course and outcome. Some studies report that the prevalence of children 5 years or younger with CAMP was approximately 46.5–61.5%.^{18,19} Korppi et al²⁰ also observed that children younger than 4 years had a higher hospitalization rate with CAMP in comparison to children older than 5 years (67% vs. 4%, respectively). However, the studies had some inconsistencies because of the heterogeneity in case definition. Most studies only enrolled hospitalized children, and thus other children having CAMP with mild symptoms may be missed. Another limitation of meta-analysis is the variability of diagnostic tools in each study. Methods that were used to detect *M. pneumoniae* infection included culture, complement fixation, serologic testing, and molecular-based detection assays.^{21,22} There is still no single “gold standard” for diagnosis. The most convenient diagnostic method are commercial serologic testing kits such as enzyme immunoassay and indirect immunofluorescence.^{21,22} However, the serologic testing depends on the change between two consecutive serum IgG titers, which can only provide evidence of recent infection retrospectively. Single serum IgM positivity can be used to prove acute *M. pneumoniae* infection, but IgM can only be detected 1–2 weeks after infection. The development of PCR may overcome the limitation of serologic tests and provide sensitive evidence in acute infection.²³ During the community outbreaks of CAMP, Thurman et al²¹ found decreased sensitivity of PCR with increased interval between symptom onset and specimen collection; however, the serologic assays have an opposite trend. Many studies have been conducted to compare serologic testing and PCR for the diagnosis of *M. pneumoniae* infection, and a great discrepancy between these two methods has been observed.^{24,25} A large retrospective study, which investigated more than 10,000 hospitalized children with *M. pneumoniae* infection, found a higher discrepancy rate in the results between PCR and IgM tests in children younger than 3 years. They suggest that PCR is the preferred method for *M. pneumoniae* diagnosis in younger children because of their immature immune response to *M. pneumoniae* infection.²⁵ Although the advantage of PCR is its high sensitivity, the result of PCR cannot be used to differentiate the asymptomatic carriage of *M. pneumoniae* in upper respiratory tract from true infection.²⁶ A combination of *M. pneumoniae* molecular and serologic methods may be the most suitable way to diagnose *M. pneumoniae* infection. A single positive result may not be a strong indicator for diagnosis.

Our study showed two-thirds of children 5 years or younger attended kindergarten. The school attendance rate may be variable in different socioeconomic cultures. One hypothesis is that the younger age of school attendance may contribute to a higher carriage rate of *M. pneumoniae* and lead to higher risk of *M. pneumoniae* infection. Therefore, general surveillance of the carriage rate of *M. pneumoniae* in the general population is needed. In this study, children with complicated pneumonia had a lower rate of a prescription for macrolide. *M. pneumoniae* infection may be a self-limited disease in most condition,

although prompt treatment can decrease the rate of complications.

The current study represented the presentations of hospitalized children with CAMP in Taiwan from 2010 to 2011 by the TPIDA project.

This study has some limitations. First, selection bias is unpreventable, especially in a multicenter study. In addition, younger children with CAP had greater tendency for hospitalization, compared to school-aged children. Second, only our own inclusion criteria was defined and failed to establish the consistency of *M. pneumoniae* infection. This limitation also exists in other studies of *M. pneumoniae* infection, which results in a difficulty in comparing the results. Third, each hospital may have different tools to diagnose *M. pneumoniae* infection. The PCR of *M. pneumoniae* was performed in a central laboratory, whereas the serology tests were performed in each hospital. The differences in sensitivity and specificity may cause selection bias. Fourth, codetection, coinfection, or contamination of coexisting pathogens was not well defined, which is also a common limitation in other studies of pneumonia in children.

In conclusion, *M. pneumoniae* remains an important pathogen in pediatric CAP. *M. pneumoniae* had a higher attribution in children older than 5 years with CAP, although children younger than 5 years with CAMP had a more complicated clinical course and higher inflammatory responses. Definite diagnosis may depend on the application of the molecular and serologic techniques. Further surveillance studies are needed to explore the carriage rate of *M. pneumoniae* in the general population in the community.

Conflicts of interest

None to declare.

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