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Clinical characteristics of *Mycoplasma pneumoniae* pneumonia in different pediatric age groups

연령에 따른 소아 마이코플라즈마 폐렴의 임상양상의 비교

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한 미 선

ABSTRACT

Clinical characteristics of *Mycoplasma pneumoniae* pneumonia in different pediatric age groups

Mi Seon Han
Department of Clinical Medical Sciences
The Graduate School
Seoul National University

Background: *Mycoplasma pneumoniae* is an important pathogen of childhood community-acquired pneumonia. While *M. pneumoniae* pneumonia generally occurs in school-aged children, recent studies have recognized its burden in young children, yet the difference in clinical feature has not been clarified. The aim of this study is to compare the clinical characteristics of *M. pneumoniae* pneumonia between children of different age groups.

Methods: We reviewed medical records of children with *M. pneumoniae* pneumonia who were treated at the Seoul National University Hospital from January 2010 to December 2015. Patients

were divided into 3 age groups: group 1, <2 years; group 2, 2 to <5 years; group 3, 5 to <18 years. The clinical manifestations and laboratory findings of children in each group were compared.

Results: Of the 411 children with *M. pneumoniae* pneumonia, 39 (9.5%) patients were in group 1, 150 (36.5%) patients in group 2, and 222 (54.0%) patients in group 3. Respiratory viruses were more commonly co-detected in group 1 (51.9%) than group 3 (23.4%, $P = 0.002$). The fever duration of children in group 1 was shorter than that in group 2 (7 days vs. 10 days, $P = 0.021$) and group 3 (7 days vs. 10 days, $P = 0.006$). Group 1 presented with shorter fever duration even though fewer children (56.4%) were treated with macrolide compared to children in group 2 (87.3%) and group 3 (92.8%) ($P < 0.001$). Additionally, the initiation of macrolide from fever onset was late in group 1 when compared to group 2 ($P = 0.016$) and group 3 ($P = 0.004$), and the treatment duration of group 1 was shorter than group 2 ($P = 0.042$). On initial auscultation, wheezing was more frequently heard in group 1 compared to the other two groups ($P < 0.001$). However, when children without respiratory virus co-detection were separately analyzed, there was no significant difference in wheezing among the three age groups. Group 1 children with co-detected respiratory virus tended to have lower rate of rise in antimycoplasma antibody titer than those without

respiratory virus co-detection (57.1% vs. 90.0%, $P = 0.25$).

Conclusions: *M. pneumoniae* pneumonia in young children tended to present with shorter duration of fever, frequent wheezing and co-detection with respiratory viruses. Further studies are needed to elucidate the role of *M. pneumoniae* as a sole pathogen for pneumonia, one of the co-detected pathogens, or asymptomatic colonizer in viral pneumonia in young children.

Keywords: clinical characteristics, *Mycoplasma pneumoniae*, pneumonia, children

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I. INTRODUCTION

Mycoplasma pneumoniae, the smallest self-replicating organism that lacks a cell wall, is an important pathogen causing both upper and lower respiratory tract infections (1, 2). *M. pneumoniae* infection generally occurs more in children than adults, and is a major burden in community-acquired pneumonia (CAP) in children, comprising about 10 to 40% of childhood CAP (3, 4). Approximately 10% of children with *M. pneumoniae* infection are estimated to develop pneumonia (2) and 8 to 34.3% of children with *M. pneumoniae* pneumonia are hospitalized (5, 6). Among 613 children hospitalized for community-acquired lower respiratory tract infection in Italy, 35.8% had *M. pneumoniae* infection while 11% had infection with *Chlamydia pneumoniae* (6). Along with viral pathogens which comprise the top seven etiologies of childhood CAP, *M. pneumoniae* is a common atypical bacterial cause of pneumonia in children (5). The severity of the infection ranges from a mild and self-limiting course to a development of fulminant and severe disease (7).

Co-detection of bacteria and respiratory viruses has been identified in children with *M. pneumoniae* pneumonia (8). Human rhinovirus and adenovirus are commonly co-detected with *M.*

pneumoniae in children with CAP (8, 9). Influenza virus and parainfluenza virus were also reported as common source of infection (10). The contribution of these viruses on the episodes of CAP in pediatric patients with *M. pneumoniae*, however, is not clear (8). In one study no significant impact of virus co-detection on the severity of *M. pneumoniae* pneumonia was found apart from rhinorrhea (9). In contrast, a study in China found that the rate of respiratory virus co-infection was higher in patients with severe *M. pneumoniae* pneumonia than those with mild pneumonia (10).

The epidemics of *M. pneumoniae* infection usually occur at intervals of 3 to 5 years (2, 11). The current general concept of the epidemics is that school-aged children and young adolescents are mainly affected (12-14). The incidence of *M. pneumoniae* infection usually increases along with age and declines after adolescence. Meanwhile, recent studies demonstrate that the infection is also frequent in young children under 5 years of age (15-17) and there is increased attention even in infants (15, 18). The proportion of CAP caused by *M. pneumoniae* in children younger than 5 years is estimated to be from 21 to 48% (16, 19) and 8.8 to 16.2% in infants younger than 1 year (15, 17). When children with community-acquired *M. pneumoniae* pneumonia were evaluated in Taiwan, although *M. pneumoniae* CAP mostly occurred in children over 5

years, the frequency in children aged 5 years or younger was unexpectedly high (16). The percentage of children under 5 years in *M. pneumoniae* pneumonia has also been gradually increasing over the last several years (13). Recent improvements in information quality from laboratories and the recognition of *M. pneumoniae* pneumonia in young children have contributed to increasing report on *M. pneumoniae* pneumonia even in infants (15, 17).

Although the incidence of *M. pneumoniae* pneumonia in children is different on the bases of age and the burden is not minor in young children, only few studies have attempted to compare the clinical characteristics of the disease in children of different age groups. The preceding limited literatures showed age-related difference in clinical symptoms, length of hospitalization, and disease severity (16, 17, 20). Children younger than 5 years had more coryza, tachypnea, vomiting and diarrhea than older children (20), and one study showed that dyspnea is also more common in children under the age of 5 (17). The nationwide study conducted in Taiwan described that children younger than 5 years had a longer hospital stay, higher rate of intensive care unit admission and more oxygen requirement than older children (16). However, these studies are restricted to hospitalized patients and did not specifically take the burden of *M. pneumoniae* pneumonia in infants and toddlers into account.

In this study, we aimed to analyze and compare the clinical manifestations and laboratory findings of *M. pneumoniae* pneumonia in children of different age groups, with young children grouped separately.

II. MATERIALS AND METHODS

1. Study subjects

We retrospectively analyzed children and adolescents under 18 years old who had respiratory symptoms and were tested for *M. pneumoniae* infection (N = 1,156) at the Seoul National University Children's Hospital between January 2010 and December 2015. Cases were defined as *M. pneumoniae* pneumonia by the following criteria: (i) presence of rales on auscultation or infiltration of the lung demonstrated on chest x-ray, and (ii) a fourfold or greater rise in antimycoplasma antibody titer, a single titer greater than or equal to 1:640, a positive PCR for *M. pneumoniae*, or *M. pneumoniae* isolated in culture. Immunocompromised children were not included and children with chronic pulmonary disease or asthma were also excluded as the underlying conditions could affect the auscultation and chest radiograph findings, rendering the exact diagnosis of pneumonia difficult.

Medical records were reviewed and data including the patient's age at diagnosis, sex, location of management (hospitalization or outpatient clinic), clinical signs and symptoms, diagnostic test results for *M. pneumoniae*, use of antibiotics, and respiratory virus co-

detection status were collected. The patients were further divided into three age groups: group 1, <2 years; group 2, 2 to <5 years; group 3, 5 to <18 years, and their clinical characteristics were compared.

2. Diagnostic tests for etiology

The serum specimens were tested for antibodies against *M. pneumoniae* and were titrated using the indirect particle agglutination test kit (SerodiaMycoII, Fujirebio, Tokyo, Japan) according to the manufacturer's instructions. Using the supplied serum diluents, 25 μL of the serum specimens were diluted, and sensitized and unsensitized particle suspensions were further added to give dilutions of 1:40 to 1:20480. The particles in the bottom of the wells were read and buttons, compact, or smooth ring were considered negative. A more extensive ring was read as positive (21). Nasopharyngeal aspirates were obtained using mucus traps and catheters within 1–2 days after visiting the hospital and the specimens were tested by PCR to amplify *P1 adhesin* gene of *M. pneumoniae* as previously described (22). Amplification was performed with 30 cycles using 95℃ for 1 minute, 50℃ for 1 minute, and 72℃ for 1 minute. When at least 2 reproducible results which had no evidence of inhibition were obtained, the results were

accepted. Multiplex PCR was also performed on the nasopharyngeal aspirate specimen to detect respiratory viruses, including respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus, rhinovirus, and coronavirus (Seeplex^{TM} RV12 ACE detection kit, Seegene, Seoul, Korea). For the collected nasopharyngeal aspirate samples, *M. pneumoniae* was isolated in pleuropneumonia-like organism broth and agar media according to previously reported method (23). The broth and agar media were incubated at 37℃ for 6 weeks along with the reference strain M129 (ATCC 29342). When the color of the broth changed from red to orange, the samples were subcultured onto agar plates. Spherical colonies of *M. pneumoniae* were observed under a microscope.

3. Statistical Analysis

In order to compare categorical variables between the age groups, the chi-square test or the Fisher's exact test was used. The Kruskal-Wallis test or the Mann-Whitney U test was used to compare continuous variables. The differences were considered statistically significant when the *P* value was below 0.05. SPSS version 24.0 was used to perform the statistical analysis.

III. RESULTS

1. Diagnosis of *M. pneumoniae* pneumonia

Of the 1,156 patients with respiratory symptoms and tested for *M. pneumoniae* infection, 411 patients met the case definition of *M. pneumoniae* pneumonia. One-hundred-twenty (29.2%) children were diagnosed by the positive antimycoplasma antibody only, where the initial titer was greater or equal to 1:640, or the titers increased fourfold. The diagnosis of *M. pneumoniae* pneumonia was made by PCR or culture only in 73 (17.8%) children. The remaining 218 (53.0%) children had both the positive antibody titer and positive results for PCR or culture of *M. pneumoniae*.

Among the 411 patients with *M. pneumoniae* pneumonia, respiratory virus PCR was performed in 286 (69.6%) patients. Specifically, the test was performed in 69.2% of children in group 1, 70% of group 2, and 69.4% of group 3. Respiratory viruses were simultaneously detected in 84 (29.4%) of the 286 patients. Rhinovirus was the most common virus, followed by respiratory syncytial virus, parainfluenza virus, and adenovirus. Respiratory virus was detected in 14 of 27 children (51.9%) in group 1, 34 of 105 children (32.4%) in group 2, and 36 of 154 children (23.4%) in group

3 (Figure 1). Group 1 had significantly higher rate of respiratory virus co-detection than group 3 (P = 0.002).

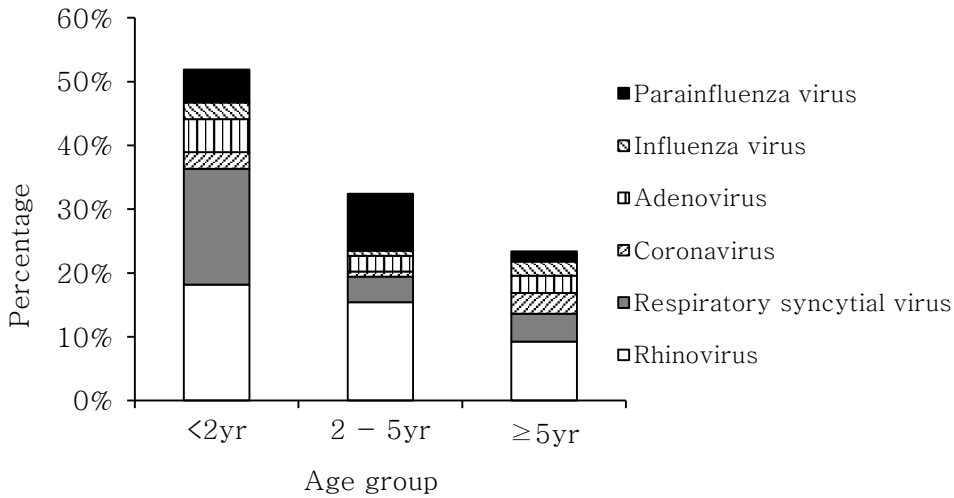

Figure 1. Percentage of co-detected respiratory viruses in *Mycoplasma pneumoniae* pneumonia by age group. The rate of respiratory virus co-detection was significantly higher in children <2 year old than those in children ≥5 years.

2. Clinical characteristics of *M. pneumoniae* pneumonia

Two major outbreaks of *M. pneumoniae* pneumonia occurred in 2011 and 2015, and most of the cases were in between August and October (Figure 2).

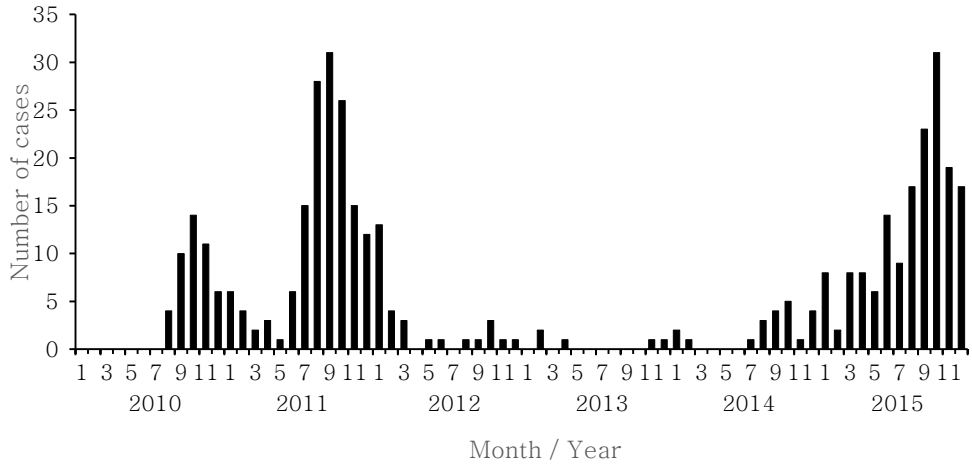

Figure 2. Monthly occurrence of *Mycoplasma pneumoniae* pneumonia between 2010 and 2015. There were major outbreaks of *M. pneumoniae* pneumonia in 2011 and 2015. The occurrence was high from August to October.

The clinical characteristics of patients with *M. pneumoniae* pneumonia are summarized in table 1. The median age of the 411 patients with *M. pneumoniae* pneumonia was 5 years [interquartile range (IQR), 3–7 years]. Two-hundred-thirteen (51.8%) children were male while 198 (48.2%) were female. Of the 411 children, 351 (85.4%) patients were hospitalized and 60 (14.6%) patients were managed as outpatients. Most of the patients (93.4%) presented with fever (≥38.0℃) and the median fever duration was 10 days (IQR, 7–13 days). On initial presentation, wheezing was heard on auscultation in 49 (11.9%) patients, rales was heard in 230 (56.0%) patients, while breath sound was decreased (or tubular breath sound)

in 85 (20.7%) patients. Macrolide was used as initial therapy in 356 (86.6%) children and 3 (0.7%) children received quinolone initially, for a median duration of 13 days (IQR, 9–16 days). Roxithromycin was the most commonly used macrolide (71.7%), followed by clarithromycin (18.5%), azithromycin (9.3%) and erythromycin (0.6%). The median time interval from fever onset to treatment initiation was 5 days (IQR, 3–7 days). Of the 356 children who received treatment with macrolides, 45 (12.6%) patients received second-line treatment with fluoroquinolone as there was no clinical improvement by macrolide alone and resistance to macrolide was suspected. Other antibiotics were co-administered in 157 (43.7%) patients, ampicillin-sulbactam being the most common, as empirical therapeutic agents for coverage of other potential pathogens of community-acquired pneumonia in children.

Table 1. Clinical characteristics of the 411 patients with *Mycoplasma pneumoniae* pneumonia

Characteristics	n
Median age (IQR) (y)	5 (3–7)
Male	213 (51.8)
Location	
Admission	351 (85.4)
Outpatient clinic	60 (14.6)
Clinical signs	
Fever (≥38.0℃)	384 (93.4)
Fever duration, median (IQR) (d)	10 (7–13)
Wheezing	49 (11.9)
Rales	230 (56.0)
Decreased breath sound	85 (20.7)
Treatment	
Macrolide	356 (86.6)
2nd line fluoroquinolone	45 (12.6)
Initiation of macrolide from fever onset, median (IQR) (d)	5 (3–7)
Duration, median (IQR) (d)	13 (9–16)
Combined antibiotics	157 (43.7)

Values are n (%) unless otherwise stated.

IQR denotes interquartile range.

3. Comparison of the clinical manifestations in different age groups

The clinical manifestations of *M. pneumoniae* pneumonia in group 1, 2, and 3 were compared as shown in table 2. There was no difference in hospitalization rate between the three groups. Most of the children in each group equally presented with fever (≥38.0℃), however, the fever duration was significantly different. Children in group 1 presented fever for a median duration of 7 days (IQR, 3–12

days), while group 2 (median 10 days [IQR, 7−13 days]; P = 0.021) and group 3 (median 10 days [IQR, 7−13 days]; P = 0.006) had longer fever duration. Children in group 1 had shorter fever duration even though treatment was initiated significantly later (median 8 days; IQR, 7−11.75 days) than children in group 2 (median 5 days [IQR, 3−7 days]; P = 0.016) and group 3 (median 5 days [IQR, 3−7 days]; P = 0.004) (Table 3). Moreover, while 131 (87.3%) patients in group 2 and 206 (92.8%) children in group 3 received treatment with macrolide, only 22 (56.4%) children under 2 years received treatment (P < 0.001). The median duration of treatment was also significantly shorter in group 1 when compared to group 2 (median 9.5 days [IQR 6.75−14.75 days] vs. median 13 days [IQR, 10−16 days]; P = 0.042). On initial auscultation, wheezing was heard in 33.3% of children in group 1, and this proportion was higher than both group 2 (P < 0.001) and group 3 (P < 0.001). Meanwhile, decreased breath sound was more often heard on auscultation in group 3 (22.5%) when compared to group 1 (7.7%) and this difference was statistically significant (P = 0.034). The proportion of patients with rales showed no difference among the three age groups. A second−line therapy with quinolones was used in 13 (9.9%) children in group 2 and 32 (15.8%) children in group 3. However, none of the patients younger than 2 years received quinolones (P = 0.029).

Table 2. Clinical findings of *Mycoplasma pneumoniae* pneumonia in different age groups

Clinical Variables	Group 1 (n = 39)	Group 2 (n = 150)	Group 3 (n = 222)
Location			
Admission	35(89.7)	128(85.3)	188(84.7)
Outpatient clinic	4(10.3)	22(14.7)	34(15.3)
Clinical signs			
Fever (≥38.0℃)	37(94.9)	137(91.3)	210(94.6)
Fever duration, median (IQR) (d)	7(3-12)	10(7-13)*	10(7-13)†
Wheezing	13(33.3)	14(9.3)*	22(9.9)†
Rales	24(61.5)	89(59.4)	117(52.7)
Decreased breath sound	3(7.7)	32(21.3)	50(22.5)†

Values are n (%) unless otherwise stated.

IQR denotes interquartile range.

*p <0.05, group 1 versus group 2.

†p <0.05, group 1 versus group 3.

Table 3. Treatment of *Mycoplasma pneumoniae* pneumonia in different age groups

Treatment	Group 1 (n = 39)	Group 2 (n = 150)	Group 3 (n = 222)
Macrolide	22 (56.4)	131 (87.3)*	206 (92.8)†
2nd line fluoroquinolone	0 (0.0)	13 (9.9)	32 (15.8)†
Initiation of macrolide from fever onset, median (IQR) (d)	8 (7–11.75)	5 (3–7)*	5 (3–7)†
Duration, median (IQR) (d)	9.5 (6.75–14.75)	13 (10–16)*	13 (10–16)
Combined antibiotics	18 (46.2)	70 (46.7)	90 (40.5)

Values are n (%) unless otherwise stated.

IQR denotes interquartile range.

*p <0.05, group 1 versus group 2.

†p <0.05, group 1 versus group 3.

4. Comparison of *M. pneumoniae* pneumonia in children of different age groups according to the presence of respiratory virus co-detection

When the clinical characteristics were compared depending on the respiratory virus co-detection status, there was no difference in fever duration and auscultation findings in children with co-detected respiratory virus and children without. In group 1, the median fever duration was 6.5 days (IQR, 2.75–15 days) in children with co-

detected respiratory virus and 8 days (IQR, 3–7.5 days) in children without. In children with and without co-detected respiratory virus, wheezing was heard in 35.7% and 15.4%, respectively (P = 0.385).

Of the patients who had co-detected respiratory virus, 82 (97.6%) patients were hospitalized and the median duration of fever was 9.5 days (IQR, 7–13 days). Children in group 1 tended to have shorter fever duration (median 6.5 days [IQR, 2.75–15 days]) than group 2 and 3 (median 9 days [IQR, 7.75–13 days] and 10 days [IQR, 8.25–12 days], respectively), although this difference was not statistically significant (P = 0.702). Patients in group 1 tended to present with wheezing more frequently on initial physical examination compared to group 2 and 3 (35.7% vs. 11.8% and 13.9% respectively, P = 0.108) while decreased breath sound was heard less commonly (7.1% vs. 20.6% and 33.3%, P = 0.126).

Considering the high rate of co-detected respiratory virus in group 1, the characteristics of the 202 children with *M. pneumoniae* pneumonia who did not have respiratory virus co-detection were further analyzed (Table 4). Children in group 1 presented shorter fever duration (median 8 days; [IQR, 3–10 days]) than group 2 (median 11 days [IQR 8–13]; P = 0.016) and group 3 (median 11 days [IQR 7–13]; P = 0.036). The fever duration was shorter in group 1 despite delayed initiation of macrolide from fever onset than

group 2 (9 days vs. 6 days, P = 0.016) and group 3 (9 days vs. 4 days, P = 0.01). On initial auscultation, there was no significant difference in wheezing among the three groups. Decreased breath sound was more heard on initial auscultation in group 2 (40.8%) than group 1 (7.7%, P = 0.027).

Table 4. Clinical findings and treatment of *Mycoplasma pneumoniae* pneumonia without respiratory virus co-detection in children of different age groups

	Group 1 (n = 13)	Group 2 (n = 71)	Group 3 (n = 118)
Clinical signs			
Fever (≥38.0℃)	13(100)	69(97.2)	117(99.2)
Fever duration, median (IQR) (d)	8(3-10)	11(8-13)*	11(7-13)†
Wheezing	2(15.4)	5(7.0)	12(10.2)
Rales	7(53.8)	35(49.3)	62(52.5)
Decreased breath sound	1(7.7)	29(40.8)*	41(34.7)
Treatment			
Macrolide	7(53.8)	65(91.5)*	113(95.8)†
2nd line fluoroquinolone	0(0.0)	10(15.4)	25(22.1)
Initiation of macrolide from fever onset, median (IQR) (d)	9(8-14)	6(4-7)*	4(3-6)†
Duration, median (IQR) (d)	12(9-16)	14(11-16)	14(11-17)
Combined antibiotics	7(53.8)	38(53.5)	64(54.2)

Values are n (%) unless otherwise stated.

IQR denotes interquartile range.

*p <0.05, group 1 versus group 2.

†p<0.05, group 1 versus group 3.

Of the 84 patients who had co-detected respiratory virus, 71 children had their antimycoplasma antibody titer checked, and 55 (77.5%) children had a single titer greater or equal to 1:640, or a fourfold or greater rise in titer (Table 5). In comparison to children in group 2 (79.3%) and group 3 (80%), only 57.1% of children in group 1 had a rise in antimycoplasma antibody titer. This positive rate of antimycoplasma antibody titer in group 1 children with respiratory virus co-detection tended to be lower than that in group 1 children who did not have respiratory virus co-detection (90%, P = 0.25). Among the 62 children with co-detected respiratory virus who were tested for *M. pneumoniae* pneumonia by PCR, 44 (71.0%) children were positive. All of the group 1 children had positive PCR, while 60% of group 2 and 71.4% of group 3 were positive by PCR.

Table 5. Positivity of antimycoplasma antibody titer and PCR in *Mycoplasma pneumoniae* pneumonia with or without respiratory virus co-detection

	Number of patients (%)		
	With respiratory virus co-detection	Without respiratory virus co-detection	*P*
Antibody*	55(77.5)	172(89.1)	0.016
Group 1	4(57.1)	9(90.0)	0.250
Group 2	23(79.3)	64(92.8)	0.078
Group 3	28(80.0)	98(86.0)	0.393
PCR	44(71.0)	110(64.7)	0.372
Group 1	9(100)	5(71.4)	0.175
Group 2	15(60.0)	33(57.9)	0.859
Group 3	20(71.4)	72(67.9)	0.722

*Positive anitimycoplasma antibody titer signifies a single titer equal to 1:640 or greater or a fourfold or greater rise in titer.

IV. DISCUSSION

In the present study conducted at a single tertiary care center, 411 patients were diagnosed with *M. pneumoniae* pneumonia, and the incidence was highest in children ≥5 years of age (54.0%), followed by those from 2 years to <5 years (36.5%) and <2 years (9.5%). Respiratory viruses were more frequently co-detected in young children than older children ≥5 years of age. The fever duration of children under 2 years was significantly shorter than that of children ≥2 years, even though the treatment rate was lower, the initiation of macrolide from symptom onset was more delayed and the treatment duration was shorter. Additionally, children <2 years presented with wheezing significantly more, while the lung sound was decreased in children ≥5 years. However, when children without respiratory virus co-detection were separately analyzed, there was no significant difference in wheezing among the three age groups.

M. pneumoniae pneumonia has the highest prevalence in school-age children and it is more common in children ≥5 years of age than in younger children (2, 5). The prevalence of *M. pneumoniae* pneumonia is also not negligible in children younger than 5 years as the incidence is estimated to be from 21 to 48% (16, 17, 19), and

approximately 15 to 41% are children younger than 2 years (24, 25). The results of our study similarly show that children under 5 years comprise 46% of cases with *M. pneumoniae* pneumonia. About 9.5% of the cases was in children under 2 years, which is lower than in previously reported literatures. This difference in incidence among literatures is attributed to different case definitions of *M. pneumoniae* pneumonia. Moreover, the age at which children attend child care centers or kindergarten in different regions might also affect the incidence in young children, as the environment may contribute to higher risk of *M. pneumoniae* infection (16).

The difference in the incidence of *M. pneumoniae* pneumonia among children of different age groups raises a simple question of whether each age group has distinct clinical features. However, only few literatures have attempted to thoroughly describe and compare the clinical manifestations of *M. pneumoniae* pneumonia in children of different ages. Tachypnea, coryza, diarrhea and vomiting are generally more common in children under 5 years of age (17, 20). According to a nationwide surveillance in Taiwan which analyzed hospitalized children with segmental or lobar pneumonia due to *M. pneumoniae*, the duration of hospitalization was longer and the need for intensive care unit admission as well as oxygen supplement was higher in children ≤5 years when compared to children >5 years

(16). On the contrary, one literature described that older children have a more severe clinical course manifested by longer fever duration and severe pneumonia pattern (25). Different study design to enroll patients and inconsistent diagnostic criteria to define *M. pneumoniae* infection are attributable to these differences in results.

In our study, it is important to note that young children had shorter fever duration and had fewer need for treatment. This difference in clinical features among different age groups could be explained by the immune response induced by *M. pneumoniae*. The pathogenesis of *M. pneumoniae* infection is assumed to be not only by direct injury to the airway epithelium, but also by indirectly induced immune mechanism (26). In *M. pneumoniae* infection, cell-mediated immune response is thought to play an important role in the development of clinical manifestations (27). The percentage of $CD4^+$ T lymphocyte increases and the production of cytokines including IL-2, IL-4, IL-8, IL-10, and IL-18 are increased (28, 29). Meanwhile, the innate response by IL-8 and IL-18 is significantly reduced in young children compared to adolescent as the capacity of alveolar macrophage to stimulate T lymphocytes is decreased in young children (30, 31). IL-8 and IL-18 are significantly increased in patients with severe *M. pneumoniae* pneumonia (29, 32, 33), which explains the more severe manifestations in older children when

compared to children younger than 2 years in our study. Likewise, the severity of clinical features among infants is also age-related (18).

Many children with *M. pneumoniae* infection present with abnormal chest radiograph, and unilateral consolidation is the most common finding (17). The pattern of pneumonia is also distinct in different age groups. In older children, segmental or lobar pneumonia is frequently observed whereas preschool-aged children present with interstitial infiltrations more frequently (17, 25). This could partially explain the more frequent decreased breath sound in older children compared to children younger than 2 years in our study. Repeated infections with *M. pneumoniae* induce mild infiltration of lymphocytes and macrophage in the lung whereas a single infection with the pathogen does not induce pathological damage (28). As the immunity is more mature in older children and the production of cytokines, including IL-18, in response to *M. pneumoniae* increases, there is a higher chance of severe pneumonia such as pleural effusion and fibrotic change in the lungs of older children (29, 32).

An interesting finding feature of *M. pneumoniae* pneumonia in young children under 2 years in this study was that respiratory virus was co-detected in 51.9%. The percentage of the co-detection of respiratory virus was highest in children younger than 2 years,

followed by children from 2 to <5 years, and children ≥5 years. Rhinovirus was the most frequently identified pathogen as in other literature (16). Co-detection of respiratory viruses in bacterial CAP is 7 to 23% (5, 34) and that in *M. pneumoniae* pneumonia is reported to be 7.6% (8). The high rate of co-detection with respiratory virus in young children with *M. pneumoniae* pneumonia poses a question about the role of *M. pneumoniae* in this age group. *M. pneumoniae* could be the true and sole pathogen of pneumonia as it is reported to be the most common bacterial etiology of childhood CAP (5). However, the same study showed that in children <2 years, *M. pneumoniae* comprises only 2% of the detected pathogens and most of the causes of CAP were viruses. It is also possible to assume that *M. pneumoniae* is simply one of the pathogens co-infecting the respiratory tract. In early childhood, the function of alveolar macrophage to stimulate the T lymphocytes as well as the airway epithelium itself is decreased (31). Viral infection on this delicate respiratory tract can stimulate bacterial load increase and subsequently allow co-infections (35). *M. pneumoniae* in young children could act as an aggravating factor on viral upper respiratory tract infection, resulting in the progression to pneumonia.

A recent study, however, has demonstrated that *M. pneumoniae* is carried at a high rate in asymptomatic children (36). This study of

children from 3 months to 16 years of age showed that the prevalence of *M. pneumoniae* by PCR or culture did not differ between asymptomatic children and children with respiratory symptoms (21.2% vs. 16.2%). In children <2 years co-detected with respiratory virus in our study, *M. pneumoniae* PCR performed on nasopharyngeal aspirate was positive in all children while only 57.1% showed a rise in antimycoplasma antibody titer compatible with *M. pneumoniae* infection. This compares with a 90% positivity rate of antimycoplasma antibody titer in those who did not have respiratory virus co-detection. These findings could imply that a large percentage of the positive PCR result for *M. pneumoniae* could have merely represented *M. pneumoniae* colonization in the upper respiratory tract. Additionally, although children <2 years with *M. pneumoniae* pneumonia had wheezing more frequently than older children, there was no difference when children without respiratory virus co-detection were separately analyzed. From these data, we could conjecture that *M. pneumoniae* is an innocent bystander (37) in children <2 years with pneumonia, while respiratory viruses have a greater role in the clinical manifestation of pneumonia.

This study is limited by the retrospective nature of the chart review. The diagnostics tests for *M. pneumoniae* infection were not performed uniformly in all patients with pneumonia so the study

population did not represent the whole. The multiplex PCR for respiratory viruses was also not done in all patients with *M. pneumoniae* pneumonia. Additionally, this study was performed at a tertiary hospital where most of the patients are referred from local clinics. Therefore, our results regarding various aspects of *M. pneumoniae* pneumonia could not be generalized.

In conclusion, we comprehensively analyzed the clinical manifestations of *M. pneumoniae* pneumonia in pediatric patients and compared them in different age groups. We found that young children under 2 years with *M. pneumoniae* pneumonia have shorter fever duration and present more with wheezing than older children. Young children do not need anti-mycoplasma therapy as much as the older, and require shorter treatment duration. Moreover, co-detection with respiratory virus is more common in young children. Additional studies are needed to confirm this age related difference in clinical manifestations and further elucidate the role of *M. pneumoniae* as a sole etiology, cofactor, or asymptomatic colonizer in young children with pneumonia.

V. REFERENCES

1. Cherry JD, Quanquin NM. Mycoplasma and Ureaplasma infections.

In: Cherry J, Harrison G, editors. Textbook of pediatric infectious diseases. 7th ed. Pennsylvania: W.B. Saunders; 2014. p. 2668-2700.

2. Meyer Sauteur PM, Unger WWJ, Nadal D, Berger C, Vink C, Van Rossum AMC. Infection with and carriage of Mycoplasma pneumoniae in children. *Front Microbiol*. 2016;7:1-12.

3. Principi N, Esposito S. Emerging role of Mycoplasma pneumoniae and Chlamydia pneumoniae in paediatric respiratory-tract infections. *Lancet Infect Dis*. 2001;1:334-344.

4. Waites KB. New concepts of Mycoplasma pneumoniae infections in children. *Pediatr Pulmonol*. 2003;36:267-278.

5. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372:835-845.

6. Principi N, Esposito S, Blasi F, Allegra L. Role of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community acquired lower respiratory tract infections. *Clin Infect Dis*. 2001;32:1281-1289.

7. Kannan TR, Hardy RD, Coalson JJ, Cavuoti DC, Siegel JD, Cagle M, et al. Fatal outcomes in family transmission of Mycoplasma pneumoniae. *Clin Infect Dis*. 2012;54:225-231.

8. Diaz MH, Cross KE, Benitez AJ, Hicks LA, Kutty P, Bramley AM, et al. Identification of bacterial and viral codetections with

Mycoplasma pneumoniae using the TaqMan array card in patients hospitalized with community-acquired pneumonia. *Open Forum Infect Dis*. 2016;3:ofw071.

9. Chiu CY, Chen CJ, Wong KS, Tsai MH, Chiu CH, Huang YC. Impact of viral coinfection on mycoplasmal pneumonia in childhood community-acquired pneumonia. *J Microbiol Immunol Infect.* 2015;48(1):51-56.

10. Song Q, Xu BP, Shen KL. Effects of bacterial and viral co-infections of mycoplasma pneumoniae pneumonia in children: analysis report from Beijing Children's Hospital between 2010 and 2014. *Int J Clin Exp Med*. 2015;8:15666-15674.

11. Eun BW, Kim NH, Choi EH, Lee HJ. Mycoplasma pneumoniae in Korean children: the epidemiology of pneumonia over an 18-year period. *J Infect*. 2008;56:326-331.

12. CDC. Outbreak of community-acquired pneumonia caused by Mycoplasma pneumoniae-Colorado, 2000. *JAMA*. 2001;285:2073-2074.

13. Eibach D, Casalegno JS, Escuret V, Billaud G, Mekki Y, Frobert E. Increased detection of Mycoplasma pneumoniae infection in children, Lyon, France, 2010 to 2011. *Euro Surveill*. 2012;17:pii=20094.

14. Chalker V, Stocki T, Litt D, Bermingham A, Watson J, Fleming D,

et al. Increased detection of Mycoplasma pneumoniae infection in children in England and Wales, October 2011 to January 2012. *Euro Surveill*. 2012;17:pii=20081.

15. Gadsby NJ, Reynolds AJ, McMenamin J, Gunson RN, McDonagh S, Molyneaux PJ, et al. Increased reports of Mycoplasma pneumoniae from laboratories in Scotland in 2010 and 2011 – impact of the epidemic in infants. *Euro Surveill*. 2012;17:pii=20110.

16. Ma YJ, Wang SM, Cho YH, Shen CF, Liu CC, Chi H, et al. Clinical and epidemiological characteristics in children with community-acquired mycoplasma pneumonia in Taiwan: A nationwide surveillance. *J Microbiol Immunol Infect*. 2015;48:632-638.

17. Defilippi A, Silvestri M, Tacchella A, Giacchino R, Melioli G, Di Marco E, et al. Epidemiology and clinical features of Mycoplasma pneumoniae infection in children. *Respir Med*. 2008;102:1762-1768.

18. Sun H, Chen Z, Yan Y, Huang L, Wang M, Ji W. Epidemiology and clinical profiles of Mycoplasma pneumoniae infection in hospitalized infants younger than one year. *Respir Med*. 2015;109:751-757.

19. Waris ME, Toikka P, Saarinen T, Nikkari S, Meurman O, Vainionpää R, et al. Diagnosis of Mycoplasma pneumoniae pneumonia in children. *J Clin Microbiol*. 1998;36:3155-3159.

20. Othman N, Issacs D, Kesson A. Mycoplasma pneumoniae infections in Australian children. *J Pediatr Child Health*.

2005;41:671-676.

21. Barker CE, Sillis M, Wreghitt TG. Evaluation of Serodia Myco II particle agglutination test for detecting Mycoplasma pneumoniae antibody: comparison with mu-capture ELISA and indirect immunofluorescence. *J Clin Pathol*. 1990;43:163-165.

22. Kim NH, Lee J a, Eun BW, Shin SH, Chung EH, Park KW, et al. Comparison of polymerase chain reaction and the indirect particle agglutination antibody test for the diagnosis of Mycoplasma pneumoniae pneumonia in children during two outbreaks. *Pediatr Infect Dis J*. 2007;26:897-903.

23. Hong KB, Choi EH, Lee HJ, Lee SY, Cho EY, Choi JH, et al. Macrolide resistance of mycoplasma pneumoniae, South Korea, 2000-2011. *Emerg Infect Dis*. 2013;19:1281-1284.

24. Touati A, Pereyre S, Bouziri A, Achour W, Khaldi A, Jaballah N Ben, et al. Prevalence of Mycoplasma pneumoniae-associated respiratory tract infections in hospitalized children: Results of a 4-year prospective study in Tunis. *Diagn Microbiol Infect Dis*. 2010;68:103-109.

25. Youn YS, Lee KY, Hwang JY, Rhim JW, Kang JH, Lee JS, et al. Difference of clinical features in childhood Mycoplasma pneumoniae pneumonia. *BMC Pediatr*. 2010;10:48.

26. Meyer Sauteur PM, van Rossum AMC, Vink C. Mycoplasma

pneumoniae in children: carriage, pathogenesis, and antibiotic resistance. *Curr Opin Infect Dis*. 2014;27:220-227.

27. Tanaka H, Honma SI, Abe S, Tamura H. Effects of interleukin-2 and cyclosporin A on pathologic features in Mycoplasma pneumonia. *Am J Respir Crit Care Med*. 1996;154:1908-1912.

28. Hayakawa M, Taguchi H, Kamiya S, Fujioka Y, Watanabe H, Kawai S, et al. Animal model of Mycoplasma pneumoniae infection using germfree mice. *Clin Diagn Lab Immunol*. 2002;9:669-676.

29. Ding S, Wang X, Chen W, Fang Y, Liu B, Liu Y, et al. Decreased interleukin-10 responses in children with severe Mycoplasma pneumoniae pneumonia. *PLoS One*. 2016;11:e0146397.

30. Maniar-Hew K, Clay CC, Postlethwait EM, Evans MJ, Fontaine JH, Miller LA. Innate immune response to LPS in airway epithelium is dependent on chronological age and antecedent exposures. *Am J Respir Cell Mol Biol*. 2013;49:710-720.

31. Grigg J, Riedler J, Robertson CF, Boyle W, Uren S. Alveolar macrophage immaturity in infants and young children. *Eur Respir J*. 1999;14:1198-1205.

32. Narita M, Tanaka H, Abe S, Yamada S, Kubota M, Narita M, et al. Close association between pulmonary disease manifestation in Mycoplasma pneumoniae infection and enhanced local production of interleukin-18 in the lung, independent of gamma interferon. *Clin*

Diagn Lab Immunol. 2000;7:909-914.

33. Narita M, Tanaka H, Yamada S, Abe S, Ariga T, Sakiyama Y. Significant role of interleukin-8 in pathogenesis of pulmonary disease due to Mycoplasma pneumoniae infection. *Clin Diagn Lab Immunol*. 2001;8:1028-1230.

34. Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics*. 2004;113:701-707.

35. Brealey JC, Sly PD, Young PR, Chappell KJ. Viral bacterial co-infection of the respiratory tract during early childhood. *FEMS Microbiol Lett.* 2015;362.

36. Spuesens EB, Fraaij PL, Visser EG, et al. Carriage of Mycoplasma pneumoniae in the upper respiratory tract of symptomatic and asymptomatic children: an observational study. *PLoS Med.* 2013;10:e1001444.

37. Meyer Sauteur PM, van Rossum AM, Vink C. Mycoplasma pneumoniae in children: carriage, pathogenesis, and antibiotics resistance. *Curr Opin Infect Dis.* 2014;27:220-227.

국문초록

연령에 따른 소아 마이코플라즈마 폐렴의 임상양상의 비교

한미선

임상의과학과

서울대학교 대학원

배경: *Mycoplasma pneumoniae*는 소아 지역사회획득 폐렴의 주요 원인균으로 *M. pneumoniae* 폐렴은 주로 학동기 소아에서 발생한다. 최근 연구에서 *M. pneumoniae* 폐렴은 어린 연령의 소아에서도 드물지 않게 보고되고 있는데 이들의 임상양상의 차이에 대해서는 아직 뚜렷하게 밝혀진 바가 없다. 본 연구는 *M. pneumoniae* 폐렴의 연령에 따른 임상양상의 차이를 비교하고자 하였다.

연구방법: 2010년 1월부터 2015년 12월까지 서울대학교병원을 방문하여 *M. pneumoniae* 폐렴이 확인된 소아청소년에 대하여 의무기록을 후향적으로 분석하였다. 환자들은 연령에 따라 세 그룹으로 나뉘어졌다: 그룹1, 2세 미만; 그룹2, 2세 이상 5세 미만; 그룹3, 5세 이상 18세 미만. 각 그룹의 임상양상과 검사소견을 비교하여 분석하였다.

결과: *M. pneumoniae* 폐렴이 확인된 411명의 소아청소년 중에서 39명 (9.5%)은그룹1에 해당되었고, 150명 (36.5%)는 그룹2, 222명 (54.0%)

은 그룹3에 해당되었다. 그룹1은 그룹3에 비해 호흡기바이러스 중복검출이 유의미하게 많았다 (P = 0.002). 그룹1의 발열기간은 그룹2 (7일 대 10일, P = 0.021)와 그룹3 (7일 대 10일, P = 0.006)보다 짧았다. 대부분의 그룹2와 그룹3의 소아들은 *M. pneumoniae* 폐렴에 대한 치료가 필요했으나, 그룹1 소아의 56.4%만이 치료를 받았다 (P < 0.001). 발열 시부터 마크로라이드 투약하기까지의 기간은 그룹1이 그룹2 (P = 0.016)와 그룹3 (P = 0.004)에 비해 길었고, 치료기간은 그룹1이 그룹2보다 짧았다 (P = 0.042). 초기 진찰 시 천명음은 그룹1에서 다른 두 그룹에 비해 더 많이 청진되었다 (P < 0.001). 그러나 호흡기바이러스 중복검출이 없었던 소아를 따로 분석했을 때에는 세 그룹에서 천명음의 빈도에는 유의한 차이가 없었다. 호흡기바이러스 중복검출이 있는 그룹1 소아는 호흡기바이러스 중복검출이 없는 소아에 비해 항마이코플라즈마 항체 역가의 증가가 적었다 (57.1% 대 90.0%, P = 0.25).

결론: *Mycoplasma pneumoniae* 폐렴으로 진단된 어린 연령의 소아는 발열 기간이 짧고 초기 진찰 시 천명음이 많이 들리며 호흡기 바이러스 중복검출이 더 흔하다. 향후 *M. pneumoniae*가 어린 연령에서 폐렴의 단일 원인균인지, 다른 병원체와 동시에 검출되는 균인지, 아니면 바이러스 폐렴에서 무증상으로 보균 상태로 있는지에 대한 추가적인 연구가 필요하다.

주요어: 임상양상, 마이코플라즈마, 폐렴, 소아

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