Clinical features of *Mycoplasma pneumoniae* coinfection and need for its testing in influenza pneumonia patients

Jung Heon Kim[1#], Jae Hyun Kwon[2#], Jeong-Yong Lee[3], Jong Seung Lee[1], Jeong-Min Ryu[1], Sung-Han Kim[4], Kyoung Soo Lim[1], Won Young Kim[1]

[1]Department of Emergency Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [2]Department of Emergency Medicine, National Medical Center, Seoul, Korea; [3]Department of Pediatrics, [4]Department of Infectious Diseases, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Contributions: (I) Conception and design: JH Kwon, JH Kim, SH Kim, WY Kim; (II) Administrative support: JH Kwon, JH Kim, JMR, KS Lim, WY Kim; (III) Provision of study materials or patients: JH Kwon, JH Kim, WY Kim; (IV) Collection and assembly of data: JH Kwon, JH Kim, JY Lee; (V) Data analysis and interpretation: JH Kwon, JH Kim, JY Lee, JS Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

Correspondence to: Won Young Kim. Department of Emergency Medicine, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. Email: wonpia73@naver.com.

Background: To investigate the clinical features of coinfection due to *Mycoplasma pneumoniae* (*M. pneumoniae*), a common copathogen in influenza, in influenza pneumonia patients.

Methods: We reviewed 4,465 patients with influenza who visited a tertiary care hospital emergency department in Seoul (Korea) from 2010 through 2016, and underwent immunoglobulin M (IgM) serology or polymerase chain reaction (PCR) for *M. pneumoniae*. Influenza pneumonia was defined as laboratory-confirmed influenza plus radiographic pneumonia. Patients with healthcare-associated pneumonia or non-mycoplasma bacterial coinfection were excluded. Clinical, laboratory, and radiographic findings and outcomes of the influenza pneumonia patients with and without *M. pneumoniae* coinfection were compared. Multivariable logistic regression analysis was performed to identify factors associated with the coinfection.

Results: Of 244 influenza pneumonia patients, 41 (16.8%) had *M. pneumoniae* coinfection. These patients were younger with a higher frequency of age of 5–10 years, and had higher white blood cell (WBC) and lymphocyte counts; lower concentration of C-reactive protein (CRP). The coinfection had no association with specific radiographic findings and poor outcome. Multivariable analysis showed the age of 5–10 years (adjusted odds ratio, 18.83; 95% confidence interval, 5.899–60.08; P<0.001) as the factor associated with the coinfection.

Conclusions: *M. pneumoniae* coinfection in influenza pneumonia may be associated with the age of 5–10 years, and otherwise clinically indistinct from influenza pneumonia without the coinfection. This finding suggests the need for *M. pneumoniae* testing in patients aged 5–10 years with influenza pneumonia.

Keywords: Child; coinfection; influenza, human; pneumonia, bacterial; pneumonia, mycoplasma

Introduction

Following the influenza A (H1N1) pandemic in 2009, seasonal influenza remains a critical public health issue (1). Besides neuraminidase inhibitor treatment, influenza pneumonia often requires hospitalization and antibiotic therapy for a possible bacterial coinfection (2). It is difficult to distinguish between influenza pneumonia with and without bacterial coinfection because of the overlapped manifestations (3). *Mycoplasma pneumoniae* (*M. pneumoniae*) is a common bacterial pathogen associated with community-acquired pneumonia (CAP) (4,5). Recently, this bacterium has been suggested as a potential cofactor for influenza pneumonia (6). *M. pneumoniae* is not susceptible to beta-lactam antibiotics recommended by the current guidelines for pediatric CAP (7). Conversely, in young adults with CAP, indiscriminate use of macrolides may lead to the development of macrolide-resistant *M. pneumoniae* (8). Thus, early detection of *M. pneumoniae* coinfection in children and young adults with influenza pneumonia could help optimize the antibiotic therapy.

We aimed to investigate the clinical features of *M. pneumoniae* coinfection in influenza pneumonia patients. Clinical, laboratory and radiographic findings, and outcomes of influenza pneumonia patients with and without the coinfection were compared.

Methods

Study design and setting

This retrospective study was conducted at a tertiary care hospital emergency department (ED) in Seoul, Korea. The ED staffs care for approximately 70,000 adults and 35,000 children annually. We reviewed all patients with influenza pneumonia as a primary diagnosis who had visited the ED, and subsequently underwent *M. pneumoniae* testing from January 2010 through December 2016. This period comprised 6 whole and 2 partial (2009–2010 and 2016–2017) influenza seasons in Korea.

At our institution, patients with influenza-like illness suggestive of CAP frequently underwent testing for *M. pneumoniae* and respiratory viruses as part of the initial workup. Further, for microbiological diagnosis, the blood and sputum (if present) of all patients suspected of CAP were analyzed by culture. In some cases, cultures from the pleural fluid or endotracheal aspirates were analyzed. During the study period, the coverage rate of influenza vaccines among Korean children and adults ranged from 45.2% to 49.7%, and from 29.6% to 34.9%, respectively (9). The institutional review board approved this study with a waiver for informed consent (IRB No. S2017-0232-0001).

Study population and definitions

All consecutive influenza pneumonia patients who underwent *M. pneumoniae* testing were included in the current study. We excluded patients with healthcare-associated pneumonia (confirmed >48 h after ED presentation or <2 weeks after discharge from a hospital), and those with non-mycoplasma bacterial coinfection. Patients with viral coinfection were included due to the little impact on outcome among critically ill patients with influenza A (10).

Influenza pneumonia was defined as laboratory-confirmed influenza *plus* radiographic pneumonia (peribronchial infiltration, consolidation or pleural effusion) reported by an attending radiologist. *M. pneumoniae* coinfection was defined as a case having positive results of *M. pneumoniae* testing including immunoglobulin M (IgM) serology and polymerase chain reaction (PCR).

Influenza and M. pneumoniae testing

For influenza testing, PCR (CFX96, BIORAD, Hercules, CA) or immunofluorescence assay (Sofia Fluorescent Immunoassay Analyzer, Quidel, San Diego, CA, USA) of the nasopharyngeal secretion was performed. The PCR assay was set up to detect the presence of influenza A and B (without subtype information), adenovirus, coronavirus, parainfluenza, rhinovirus, respiratory syncytial virus, human bocavirus, human metapneumovirus, and enterovirus. The sensitivities of the immunofluorescence assay for influenza A and B were 82.2% and 77.9%, respectively (11).

For *M. pneumoniae* testing, IgM chemiluminescence immunoassay (LIAISON *M. pneumoniae* IgM, DiaSorin S.p.A., Saluggia, Italy), a qualitative test without a specific titer, was performed using the blood. The turnaround time was less than 3 days. A PCR assay (AmpliSens *M. pneumoniae/Chlamydophila pneumoniae*-FEP, Ecoli s.r.o., Bratislava, Slovak Republic) was occasionally performed using the nasopharyngeal secretion or sputum.

Data collection

Clinical findings included age (years), gender, ED visits during the influenza seasons, respiratory distress [age-

adjusted tachypnea (7), chest retraction, and oxyhemoglobin saturation <90%], temperature, abnormal breathing sounds (crackle and wheezing), and comorbidity (pulmonary, hemato-oncologic, cardiac, renal, neurologic, hepatic, and immunosuppressive diseases) (12). Besides the chronological age, age of 5–15 years was collected as a categorical variable to assess the association of the coinfection and the age group with the highest incidence *M. pneumoniae* infection (13).

Laboratory findings included white blood cell (WBC), absolute neutrophil, lymphocyte, and platelet counts; concentrations of hemoglobin, creatinine, and C-reactive protein (CRP); the results of influenza and *M. pneumoniae* testing; and the results of cultures. Radiographic findings included consolidation and pleural effusion on a chest radiograph. By definition of the radiographic pneumonia, all influenza pneumonia patients without the aforementioned radiographic findings had at least peribronchial infiltration.

Outcome variables included the use of neuraminidase inhibitors and macrolides, time-to-neuraminidase inhibitor (time from ED arrival to initiation of neuraminidase inhibitor therapy), time-to-macrolide (time from ED arrival to initiation of macrolide therapy), viral coinfection, severe CAP [defined as per the Infectious Disease Society of America criteria for severe CAP in children and adults (7,14)], hospitalization (overall and at intensive care units), the length of hospital stay (days), and in-hospital mortality.

Statistical analysis

Data are presented as the mean with standard deviation or median with the interquartile range for continuous variables; and as a number and absolute or relative frequency for categorical variables. Student's *t*-tests or Mann-Whitney *U* tests were used to compare continuous variables, and chi-square tests or Fisher's exact tests were for categorical variables.

Multivariable logistic regression analysis was performed to identify factors associated with *M. pneumoniae* coinfection. The value of P<0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

Study population

Among a total of 4,465 patients with laboratory-confirmed influenza who visited the ED during the study period,

244 influenza pneumonia patients met all the inclusion criteria (*Figure 1*). Generally, the influenza pneumonia occurred during the influenza seasons (91.4%), and was due to influenza A (80.7%). The overall rate of bacterial coinfection was 33.4% (102 of the 305 patients). *M. pneumoniae* coinfection was detected in 41 patients (16.8%; 95% confidence interval, 12.6–22.0%) whose IgMs or PCRs were positive. Of these, 14 patients underwent PCR: 5 were positive for both IgM and PCR, 2 were negative for IgM and positive for PCR, and 7 were positive for IgM and negative for PCR (mutually exclusive). Sixty-one patients with non-mycoplasma bacterial coinfection were excluded (the interested reader can find them in *Table S1*). Viral coinfections were detected in 29 patients (the interested reader can find them in *Table S2*).

Temporal and age distribution of M. pneumoniae coinfection

The temporal distribution of influenza pneumonia was consistent with the influenza seasons (*Figure 2*). The proportion of influenza A in each season generally mirrored the epidemic patterns in Korea (The interested reader can find them in *Table S3*). Hence, despite the absence of strain information, we speculated that the study population followed the major strain patterns in Korea. *M. pneumoniae* coinfection was most frequent in the patients aged 10 years or younger (*Figure 3*).

Distinction between influenza pneumonia with and without M. pneumoniae coinfection

Tables 1 and *2* outline the clinical, laboratory, and radiographic findings, and outcomes. The patients with *M. pneumoniae* coinfection were younger (usually 10 years or younger), with a higher frequency of age of 5–14 years. This variable was regarded as the age of 5–10 years due to the absence of patients aged 11–14 years in this population (*Figure 3*). The patients with the coinfection had lower frequency of comorbidity. These patients had higher WBC, lymphocyte, and platelet counts, and lower concentrations of creatinine and CRP, than those without the coinfection. Radiographic findings showed no differences between the two groups.

Factors associated with M. pneumoniae coinfection

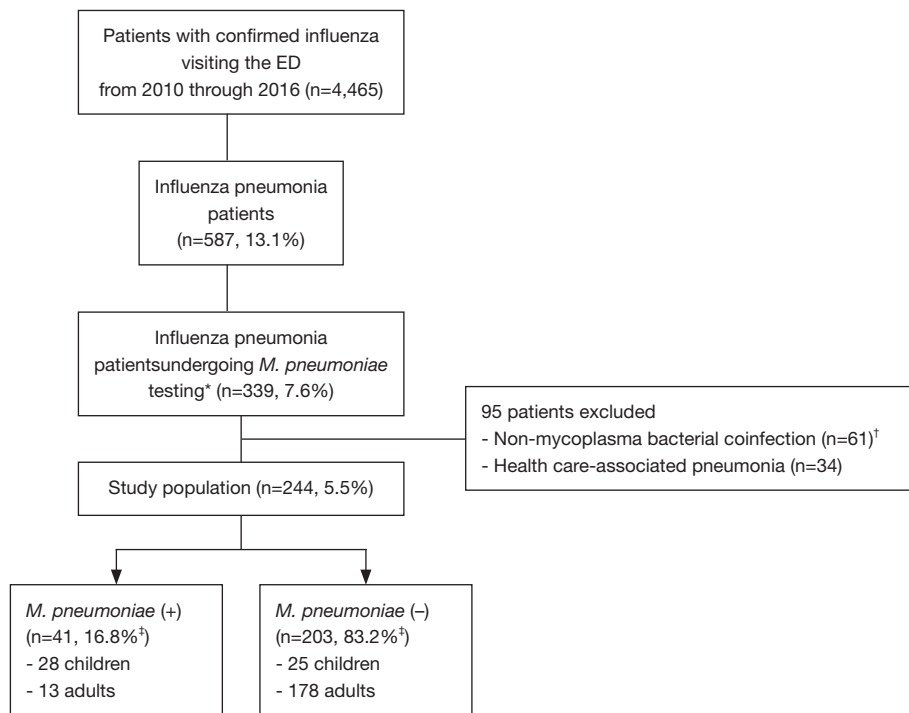Multivariable logistic regression analysis showed the age

Figure 1 Flowchart for the selection of patients. *Mycoplasma pneumoniae* testing was performed with immunoglobulin M serology or polymerase chain reaction; [†]The interested reader can find them in *Table S1*; [‡]The denominator is 244.
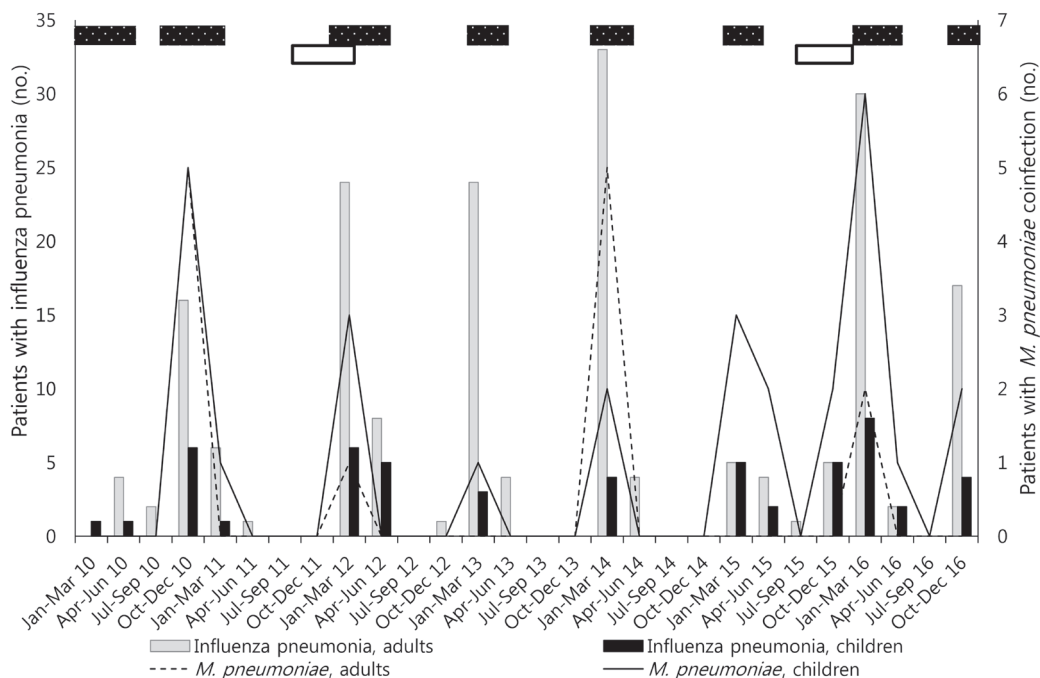

Figure 2 The quarterly trend of influenza pneumonia patients with *Mycoplasma pneumoniae* coinfection from 2010 through 2016. The temporal distribution of influenza pneumonia mirrored the influenza seasons in Korea (horizontal, stippled bars). By contrast, endemic *M. pneumoniae* infections occurred outside the 2 recent epidemics in Korea (horizontal, white bars).
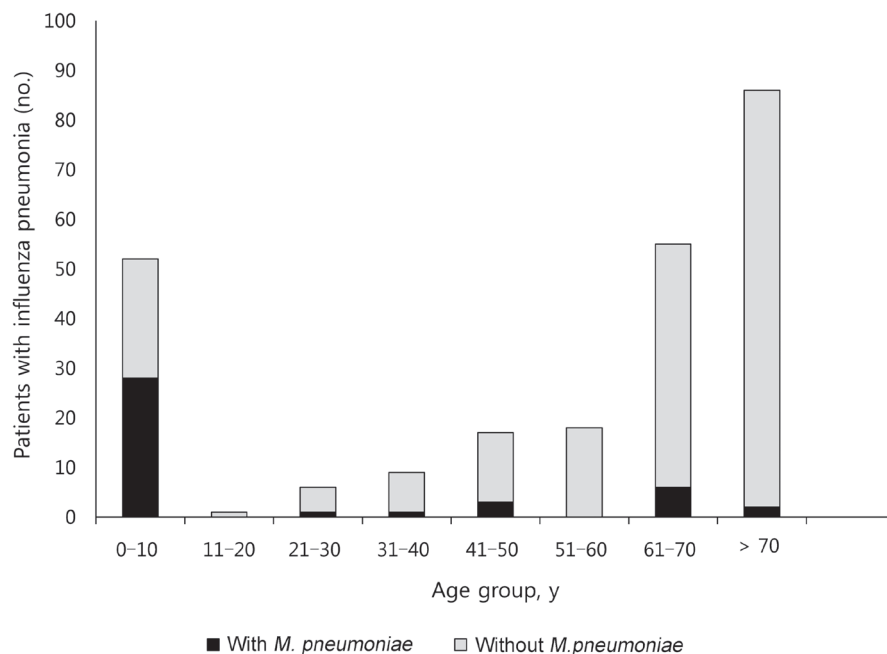
Figure 3 The age distribution of influenza pneumonia patients with and without *Mycoplasma pneumoniae* coinfection. The coinfection was most frequent in the patients aged 10 years or younger.

of 5–10 years (adjusted odds ratio, 18.83; 95% confidence interval, 5.899–60.08; P<0.001) as the factor associated with *M. pneumoniae* coinfection. Lymphocyte count did not reach the statistical significance (for 10^3 cells/mm^3 increment of the count; adjusted odds ratio, 1.001; 95% confidence interval, 1.00–1.001; P<0.001).

Outcomes

Neuraminidase inhibitors were more frequently administered to treat the patients without *M. pneumoniae* coinfection than those with the coinfection (*Table 3*). Macrolides were more frequently administered to the patients with the coinfection (68.3% *vs*. 36.0%, P<0.001). However, this antibiotic therapy showed no association with the better outcome (The interested reader can find them in *Table S4*). No differences between the two groups were found with respect to the time-to-neuraminidase inhibitor and time-to-macrolide. The patients with the coinfection had more frequent viral coinfections. No other differences for the outcome variables were found between the two groups.

Subanalysis performed to the children

Because 28 of the 41 patients with *M. pneumoniae* coinfection

were children, we performed a subanalysis to assess the association of the age of 5–10 years and the coinfection in the children (n=53) (*Tables 4,5*). The children with the coinfection tended to belong to the age group more frequently, but did not reach the statistical significance. Due to the small sample size, we could not perform a multivariable analysis. Like the entire study population, macrolides were more frequently administered to the children with the coinfection (82.1% *vs*. 48.0%, P=0.009) (*Table 6*). No other differences for the outcome variables were found.

Discussion

We found that *M. pneumoniae* coinfection in influenza pneumonia patients was associated with the age of 5–10 years, and otherwise clinically indistinguishable from influenza pneumonia without the coinfection in a hospital-based population. The age group is slightly older than the age younger than 2–5 years that is at high risk for influenza pneumonia (12). Thus, *M. pneumoniae* testing may be useful in early detection of the bacterium in influenza pneumonia patients aged 5–10 years who are at relatively low risk for influenza pneumonia.

Previous reports support the clinical indistinguishability between influenza pneumonia with and without *M.*

Table 1 Clinical findings of the influenza pneumonia patients with and without *Mycoplasma pneumoniae* coinfection

Variable	Total (n=244)	With *M. pneumoniae* (n=41)	Without *M. pneumoniae* (n=203)	P
Age, y	64.0 (31.3–73.8)	5.0 (2.0–8.3)	67.0 (50.0–75.0)	<0.001
Age 5–10 y	17 (7.0)	12 (29.3)	5 (2.5)	<0.001
Women	107 (43.9)	16 (39.0)	91 (44.8)	0.495
Influenza season	223 (91.4)	38 (92.7)	185 (91.1)	>0.999
Respiratory distress	65 (26.6)	9 (22.0)	56 (27.6)	0.457
Temp, ℃	37.8 (36.8–38.6)	37.9 (37.1–38.6)	37.6 (36.7–38.6)	0.461
Crackle	140 (57.4)	24 (58.5)	116 (57.1)	0.869
Wheezing	48 (19.7)	9 (22.0)	39 (19.2)	0.687
Any comorbidity	154 (63.1)	17 (41.5)	137 (67.5)	0.002
Pulmonary	67 (27.5)	11 (26.8)	56 (27.6)	0.921
Hemato-oncologic	49 (20.1)	6 (14.6)	43 (21.2)	0.340
Cardiac	42 (17.2)	2 (4.9)	40 (19.7)	0.022
Renal	24 (9.8)	0 (0)	24 (11.8)	0.018
Neurologic	16 (6.6)	2 (4.9)	14 (6.9)	>0.999
Hepatic	8 (3.3)	1 (2.4)	7 (3.4)	>0.999
Immunosuppressive	7 (2.9)	0 (0)	7 (3.4)	0.605

The values are expressed as the median (interquartile range) or number (%).

Table 2 Laboratory and radiographic findings

Variable	Total (n=244)	With *M. pneumoniae* (n=41)	Without *M. pneumoniae* (n=203)	P
WBCs, $10^3/mm^3$	9.1 (6.7–13.7)	11.2 (7.8–15.5)	8.8 (6.5–13.1)	0.040
ANC, $10^3/mm^3$	7.1 (4.9–10.4)	8.2 (4.9–11.7)	7.1 (4.9–10.3)	0.489
Lymphocytes, $10^3/mm^3$	1.1 (0.8–1.7)	1.6 (1.1–3.0)	1.0 (0.7–1.5)	<0.001
Hemoglobin, g/dL	12.4±2.0	12.7±1.8	12.4±2.1	0.297
Platelets, $10^3/mm^3$	194.0 (143.0–280.8)	250.0 (185.0–356.0)	186.0 (137.0–250.0)	<0.001
Creatinine, mg/dL	0.8 (0.5–1.1)	0.5 (0.4–0.8)	0.8 (0.6–1.2)	<0.001
CRP, mg/dL	6.9 (2.9–14.0)	3.6 (2.0–7.0)	7.6 (3.4–14.9)	0.004
Influenza A	197 (80.7)	31 (75.6)	166 (81.8)	0.361
Consolidation	106 (43.4)	16 (39.0)	90 (44.3)	0.531
Pleural effusion	39 (16.0)	6 (14.6)	33 (16.3)	0.796

The values are expressed as the mean ± standard deviation, median (interquartile range) or number (%). WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein.

Table 3 Outcomes

Variable	Total (n=244)	With *M. pneumoniae* (n=41)	Without *M. pneumoniae* (n=203)	P
NMIs	191 (78.3)*	26 (63.4)	165 (81.3)	0.011
Any antibiotics	237 (97.1)	39 (95.1)	198 (97.5)	0.334
Macrolides	101 (41.4)	28 (68.3)	73 (36.0)	<0.001
Time-to-NMI, d	2.1±1.6	1.7±0.9	2.1±1.6	0.268
Time-to-macrolide, d	1.1±0.4	1.2±0.7	1.1±0.3	0.331
Viral coinfection[†]	29 (11.9)	11 (26.8)	18 (8.9)	0.003
Severe CAP[‡]	83 (34.0)	16 (39.0)	67 (33.0)	0.458
Hospitalization, overall	193 (79.1)	33 (80.5)	160 (78.8)	0.810
Hospitalization, ICU	29 (11.9)	1 (2.4)	28 (13.8)	0.059
Length of hospital stay, d	6.0 (3.0–10.0)	5.0 (3.0–7.0)	6.0 (3.0–11.0)	0.064
In-hospital mortality	6 (2.5)	1 (2.4)	5 (2.5)	>0.999

The values are expressed as the mean ± standard deviation, median (interquartile range) or number (%). *, of these, 142 and 49 patients received oseltamivir and peramivir, respectively; [†], the interested reader can find them in *Table S2*; [‡], defined as per the Infectious Disease Society of America criteria for severe CAP in children and adults (7,14). NMI, neuraminidase inhibitor; CAP, community-acquired pneumonia; ICU, intensive care unit.

Table 4 Clinical findings of the children (n=53)

Variable	Total (n=53)	With *M. pneumoniae* (n=28)	Without *M. pneumoniae* (n=25)	P
Age, y	2.0 (1.0–5.5)	3.5 (1.3–6.0)	1.0 (1.0–3.0)	0.050
Age 5–10 y	17 (32.1)	12 (42.9)	5 (20.0)	0.075
Women	21 (39.6)	13 (46.4)	8 (32.0)	0.284
Influenza season	46 (86.8)	25 (89.3)	21 (84.0)	0.694
Respiratory distress	12 (22.6)	6 (21.4)	6 (24.0)	0.823
Respiratory rate	28.0 (24.0–32.0)	28.0 (24.0–30.0)	30.0 (24.0–42.6)	0.400
Temp, ℃	38.1 (37.3–38.8)	38.0 (37.2–38.7)	38.4 (37.4–38.9)	0.556
Crackle	29 (54.7)	15 (53.6)	14 (56.0)	0.859
Wheezing	16 (30.2)	8 (28.6)	8 (32.0)	0.786
Any comorbidity	14 (26.4)	6 (21.4)	8 (32.0)	0.384
Pulmonary	4 (7.5)	2 (7.1)	2 (8.0)	>0.999
Hemato-oncologic	4 (7.5)	3 (10.7)	1 (4.0)	0.613
Cardiac	6 (11.3)	0 (0)	6 (24.0)	0.008
Renal	0 (0)	0 (0)	0 (0)	NA
Neurologic	1 (1.9)	1 (3.6)	0 (0)	>0.999
Hepatic	1 (1.9)	0 (0)	1 (4.0)	0.472
Immunosuppressive	2 (3.8)	0 (0)	2 (8.0)	0.218

The values are expressed as the median (interquartile range) or number (%).

Table 5 Laboratory and radiographic findings of the children (n=53)

Variable	Total (n=53)	With *M. pneumoniae* (n=28)	Without *M. pneumoniae* (n=25)	P
WBCs, 10^3/mm^3	10.4 (6.9–14.4)	11.0 (7.9–14.1)	9.5 (5.7–15.7)	0.327
ANC, 10^3/mm^3	6.3 (3.8–9.2)	6.5 (4.6–9.5)	5.4 (2.1–8.8)	0.119
Lymphocytes, 10^3/mm^3	2.1 (1.3–3.9)	2.5 (1.2–3.6)	1.9 (1.3–4.9)	0.581
Hemoglobin, g/dL	12.0±1.5	12.4±1.4	11.6±1.4	0.054
Platelets, 10^3/mm^3	290.0 (214.5–377.0)	298.5 (214.3–418.8)	250.0 (205.0–336.5)	0.173
Creatinine, mg/dL	0.4 (0.3–0.4)	0.4 (0.3–0.5)	0.4 (0.3–0.4)	0.402
CRP, mg/dL	3.2 (1.6–6.6)	3.0 (1.8–4.9)	3.4 (1.5–7.1)	0.742
Influenza A	36 (67.9)	19 (67.9)	17 (68.0)	0.991
Consolidation	17 (32.1)	11 (39.3)	6 (24.0)	0.234
Pleural effusion	7 (13.2)	4 (14.3)	3 (12.0)	>0.999

The values are expressed as the mean ± standard deviation, median (interquartile range) or number (%). WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein.

Table 6 Outcomes of the children (n=53)

Variable	Total (n=53)	With *M. pneumoniae* (n=28)	Without *M. pneumoniae* (n=25)	P
NMIs	29 (54.7)	15 (53.6)	14 (56.0)	0.859
Any antibiotics	46 (86.8)	26 (92.9)	20 (80.0)	0.234
Macrolides	35 (66.0)	23 (82.1)	12 (48.0)	0.009
Time-to-NMI, d	1.7±0.9	1.5±0.8	1.8±1.0	0.459
Time-to-macrolide, d	1.3±0.7	1.3±0.8	1.3±0.5	0.765
Viral coinfection	18 (34.0)	9 (32.1)	9 (36.0)	0.767
Severe CAP	28 (52.8)	13 (46.4)	15 (60.0)	0.323
Hospitalization, overall	37 (69.8)	21 (75.0)	16 (64.0)	0.384
Hospitalization, ICU	0 (0)	0 (0)	0 (0)	NA
Length of hospital stay, d	5.0 (2.0–6.0)	5.0 (1.3–6.0)	6.0 (2.0–6.5)	0.187
In-hospital mortality	0 (0)	0 (0)	0 (0)	NA

The values are expressed as the mean ± standard deviation, median (interquartile range) or number (%). NMI, neuraminidase inhibitor; CAP, community-acquired pneumonia; ICU, intensive care unit.

pneumoniae coinfection. Clinical assessment of *M. pneumoniae* pneumonia alone is inaccurate (15). In addition, low WBC count and CRP concentration in influenza pneumonia (16) may hinder distinguishing between influenza pneumonia with and without the coinfection. The radiographic findings of *M. pneumoniae* pneumonia vary from centrilobular nodule to consolidation (17,18). Despite the unproven impact on the outcome in the current study, the coinfection has a potential for aggravating the disease

course. Fischer *et al*. (19) found a fever of longer duration in *M. pneumoniae* CAP than in other CAPs.

The implications of *M. pneumoniae* coinfection in influenza pneumonia should be investigated further because the bacterium is an emerging pathogen in both CAP and influenza pneumonia. A recent population-based study in the United States reported that *M. pneumoniae* was the most common bacterial pathogen in pediatric CAP (20). Dhanoa *et al*. (21) reported that *M. pneumoniae* was the

most common bacterial copathogen during the 2009 H1N1 pandemic. In the current study, the bacterium was the most common bacterial copathogen in influenza pneumonia. Conversely, a recent study on the coinfection in *M. pneumoniae* pneumonia shows that influenza was the most common viral copathogen (22).

M. pneumoniae testing should be performed to optimize the antibiotic therapy in the setting of the coinfection. In this setting, the current guidelines for pediatric CAP, which recommend macrolides as empirical antibiotics only in cases of presumed atypical pneumonia (7), can lead to omission of macrolide therapy. It is hard to clinically presume *M. pneumoniae* coinfection due to the nonspecific manifestations (15). During influenza seasons, awareness of positive influenza test results could reduce potentially necessary antibiotic therapy (23). This reduction is possibly more harmful to patients aged 5–10 years who have a high incidence of *M. pneumoniae* infection.

In the current study, macrolides were given more frequently to the patients with *M. pneumoniae* coinfection without a delay. This finding, along with the clinical indistinguishability, may support the utility of *M. pneumoniae* testing performed at the ED. This speculation is less likely to be refuted by unproven benefit of macrolide therapy (24) because our topic regarding the coinfection is a matter of the diagnostic plan, rather than a therapeutic modality. The implications of the testing might be less important for adults given the recommendation of macrolides as empirical antibiotics in CAP (14) and lower frequency of *M. pneumoniae* CAP (25).

The current study has some limitations. First, serology may lead to false negativity, particularly within 1 week of infection or reinfection, or false positivity, such as remote infections or carrier states (26,27). For instance, in the current study, the 7 patients who were positive for IgM and negative for PCR may correspond to false positivities. However, the coinfection rate of 16.8% was less likely to be overestimated. This rate approximates to the rate of PCR-proven *M. pneumoniae* of 16% that was reported in the 408 patients aged 5–9 years with CAP requiring hospitalization (20). Second, we were unable to know strains of influenza, and yet the strains might affect the clinical features. Third, the coinfection itself does not necessarily mean a secondary bacterial pneumonia because this entity needs the evidence of superinfection (28), and a mere 3–10% of *M. pneumoniae* infections manifest as CAP (29).

Briefly, *M. pneumoniae* coinfection in influenza pneumonia may be associated with the age of 5–10 years, and otherwise clinically indistinguishable from influenza pneumonia without the coinfection. Thus, prompt *M. pneumoniae* testing could contribute to early detection of the coinfection in influenza pneumonia, especially in patients aged 5–10 years who are infrequently contract influenza pneumonia.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The institutional review board approved this study with a waiver for informed consent (IRB No. S2017-0232-0001).

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Table S1 Non-mycoplasma bacterial copathogens detected in the excluded patients (n=61)

Bacterium	No. (%)
Staphylococcus aureus	12 (19.7)
NTM	11 (18.0)
Klebsiella spp.	10 (16.4)
Pseudomonas aeruginosa	8 (13.1)
Streptococcus pneumoniae	6 (9.8)
Other*	14 (23.0)

*, *Moraxella catarrhalis* (n=3), *Haemophilus influenzae* (n=2), *Enterobacter* spp. (n=2), *Acinetobacter baumannii* (n=2), *Mycobacterium tuberculosis* (n=1), *Serratia marcescens* (n=1), *S. pyogenes* (n=1), *Enterococcus* spp. (n=1), and *Escherichia coli* (n=1). NTM, nontuberculous mycobacteria.

Table S2 Viral copathogens (n=29)

Virus	No.
Rhinovirus	10
Adenovirus	7
RSV	5
Parainfluenza	4
Bocavirus	4
Coronavirus	3
HMPV	2

RSV, respiratory syncytial virus; HMPV, human metapneumovirus.

Table S3 The predominant strains of influenza A in the United States and Korea from 2009 through 2017

Influenza season	Predominant strain, the US	Predominant strain, Korea				
		Detection of influenza	H1N1	pH1N1	H3N2	B*
2016–2017	H3N2	1,173[†]	0	4 (0.4)	866 (73.8)	303 (25.8)
2015–2016	pH1N1	1,320[‡]	0 (0)	582 (44.1)	62 (4.7)	675 (51.1)
2014–2015	H3N2	1,609	0 (0)	176 (10.9)	836 (52.0)	597 (37.1)
2013–2014	pH1N1	2,094	0 (0)	346 (16.5)	640 (30.6)	1,108 (52.9)
2012–2013	H3N2	1,704	0 (0)	332 (19.5)	1,276 (74.9)	96 (5.6)
2011–2012	H3N2	3,785	0 (0)	1 (0.0)	1,950 (51.5)	1,834 (48.5)
2010–2011	H3N2	1,976	0 (0)	1,651 (83.5)	308 (15.6)	17 (0.9)
2009–2010	pH1N1	6,466	0 (0)	4,748 (73.4)	8 (0.1)	1,710 (26.5)

*, no strains of influenza B have been reported by the Korea Centers for Disease Control and Prevention; [†], preliminary data; [‡], one patient had nontypeable influenza A during the 2015–2016 season.

Table S4 Outcomes of the *Mycoplasma pneumoniae* coinfection patients with and without macrolide therapy

Variable	Total (n=41)	Macrolides (n=28)	No macrolides (n=13)	P
Severe CAP	16 (39.0)	12 (42.9)	4 (30.8)	0.466
Hospitalization, overall	33 (80.5)	21 (75.0)	12 (92.3)	0.199
Hospitalization, ICU	1 (2.4)	0 (0)	1 (7.7)	0.142
Length of hospital stay, d	5.0 (3.0–7.0)	5.0 (3.5–6.0)	6.0 (3.0–18.0)	0.159
In-hospital mortality	1 (2.4)	0 (0)	1 (7.7)	0.142

The values are expressed as the median (interquartile range) or number (%). CAP, community-acquired pneumonia; ICU, intensive care unit.