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ORIGINAL ARTICLE

Impact of bacterial and viral coinfection on mycoplasmal pneumonia in childhood community-acquired pneumonia

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Mycoplasma pneumoniae;
Outcomes

Background/Purpose: Coinfection of *Mycoplasma pneumoniae* is not uncommon in children with respiratory syndromes. The purpose of this study was to investigate the impact of bacterial and viral coinfection on mycoplasmal pneumonia in hospitalized children with community-acquired pneumonia (CAP).
Methods: Children coinfected with *M. pneumoniae* in a prospective study of the etiology of CAP at a tertiary pediatric facility Children's Hospital were enrolled and retrospectively reviewed. The data of clinical characteristics, complications, and outcomes of these children were collected and analyzed.
Results: A total of 59 children were enrolled and stratified into three groups: *M. pneumoniae* infection alone ($n = 31$), *M. pneumoniae* with *Streptococcus pneumoniae* coinfection ($n = 9$), and *M. pneumoniae* with virus coinfection ($n = 19$). As compared with children infected with *M. pneumoniae* alone, coinfection of children with *S. pneumoniae* was more likely to occur under the age of 5 years with a longer duration of fever and hospital stay. Furthermore, total leukocyte count and serum C-reactive protein level were also significantly higher in these children ($p < 0.01$). However, no significant difference in clinical characteristics, complications, and outcomes was observed between the patients infected with either *M. pneumoniae* alone or with virus coinfection.

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Conclusion: In children with CAP, the influence on the clinical outcomes of *M. pneumoniae* infection may be heavily dependent on the coinfected pathogen. A potential coexistence of *M. pneumoniae* infection should be considered in children with features suggesting typical bacterial pneumonia.
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Introduction

Mycoplasma pneumoniae is recognized as an important and frequent cause of community-acquired respiratory illness in children.[1,2] *M. pneumoniae* causes up to 40% of community-acquired pneumonia (CAP) in children and as many as 18% of cases require hospitalization.[3] Recent studies showed that 7—30% of the hospitalized children with CAP had evidence of mixed viral—bacterial infections.[1,4—8] Coinfection of *M. pneumoniae* is not uncommon in children with respiratory syndromes. In Taiwan, a prospective study on the etiology of hospitalized children with CAP demonstrated a high incidence (41%) of mixed infections and 37% with *M. pneumoniae* infection.[9] Furthermore, concurrent viral—bacterial infection was identified in approximately 60% of children with *M. pneumoniae* infection. Although most *M. pneumoniae* respiratory infections are mild and self-limited, the clinical features of coinfection of *M. pneumoniae* are not well described. The aim of this study was to investigate the impact of bacterial and viral coinfection on mycoplasmal pneumonia in hospitalized children with CAP. The manifestations and clinical outcomes in such instances are also defined and discussed.

Materials and methods

Study population and design

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (No. 102-0401B). Between August 1, 2001 and July 31, 2002 children coinfected with *M. pneumoniae* in a prospective study of the etiology of CAP at a tertiary pediatric facility Children's Hospital were enrolled and retrospectively reviewed. Pneumonia was defined as the combination of acute respiratory symptoms and infiltrates on chest radiographic images, which were interpreted by attending physicians and radiologists. Children with *M. pneumoniae* pneumonia were stratified into three groups: *M. pneumoniae* alone, *M. pneumoniae* coinfected with *Streptococcus pneumoniae*, and *M. pneumoniae* coinfected with virus. The clinical, laboratory, and radiographic data on admission, as well as complications and outcomes of these patients, were collected, analyzed, and compared.

Microbiological diagnostic method

For *M. pneumoniae*, both acute and convalescent serum were obtained and measured for antibody response (IgM and IgG) to *M. pneumoniae* by enzyme-linked immunosorbent assay methods (Savyon, Ashdod, Israel).[10] Criteria for acute mycoplasmal infection were either a single serum showing positive *M. pneumoniae*-specific IgM or a seroconversion of IgG.[11] *S. pneumoniae* infection was defined by a positive result in blood or pleural fluid culture or the detection of antigens in the pleural fluid by latex agglutination testing. Acute pneumococcal infection was also included for patients who had necrotic lung parenchyma with a positive urine test for *S. pneumoniae* (Binax, Portland, ME, USA).

For viral etiology, viral direct immunofluorescent assay and cultures were performed using sputum or oropharyngeal swabs. A positive result for respiratory syncytial virus (RSV), adenovirus, parainfluenza 1, 2, and 3, and influenza A and B was considered significant. Serum specimens were also examined for these seven respiratory viruses by the complement fixation method (BioWhittaker, Walkersville, MD, USA). A $\geq$4-fold rise in titer, a titer of at least 1:16, or a single titer of at least 1:64 (initial titer 1:2) was considered positive and indicative of acute infection.

Statistical analysis

Statistical analysis was performed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant. Parametric data were compared using analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. When the data were not normally distributed, or were nonparametric data, the Kruskal—Wallis test was used as appropriate. Categorical data were analyzed using contingency table analysis and the Chi-square or Fisher's exact test.

Results

Patients and microbiological diagnosis

Seventy-seven children had evidence of acute *M. pneumoniae* infection (Table 1). In children with paired serum samples for *M. pneumoniae* infection, specific IgM was positive for both occasions in 31 patients and for one occasion in 25 patients. Another 20 patients were positive for specific IgM with a single serum sample obtained at the acute stage. Seroconversion to specific IgG was identified in only one patient who was negative for IgM. For *S. pneumoniae* infection, two of these 77 patients were positive for *S. pneumonia* by blood culture. Of the cases with complicated pleural effusion available for study, eight cases were positive for *S. pneumoniae* by latex agglutination test and eight cases were diagnosed with *S. pneumoniae* infection

Table 1 Etiologic agents of 77 hospitalized children with mycoplasmal community-acquired pneumonia (CAP)

Etiologic agent	Proportion (%)
Mycoplasma pneumoniae alone	31/77 (40)
Mixed infection	46/77 (60)
Bacteria	
Streptococcus pneumoniae	9
Chlamydia sp.	5
S. pneumoniae + *Chlamydia* sp.	3
Virus	
Adenovirus	5
Influenza A	4
Respiratory syncytial virus (RSV)	3
Parainfluenza-1	2
Parainfluenza-2	1
Parainfluenza-3	1
Adenovirus + influenza A	1
Adenovirus + parainfluenza-2	1
RSV + influenza A	1
Bacteria and virus	
Chlamydia sp. + adenovirus	2
Chlamydia sp. + adenovirus + RSV	1
S. pneumoniae + adenovirus	2
S. pneumoniae + RSV	1
S. pneumoniae + influenza A	1
S. pneumoniae + influenza B	1
S. pneumoniae + influenza B + adenovirus + parainflenza-3	1
M.ycobacterium tuberculosis + adenovirus	1

only by urine pneumococcal antigen. Eighteen patients coinfected with two other bacterial pathogens or mixed viral–other bacterial infections were excluded. A total of 59 children were included in this study and stratified into three groups: *M. pneumoniae* alone ($n = 31$), *M. pneumoniae* coinfected with *S. pneumoniae* ($n = 9$), and *M. pneumoniae* coinfected with virus ($n = 19$).

Demographic and clinical characteristics

The mean age of 59 children (19 boys, 40 girls) was 4.8 ± 0.9 years. All of the patients with *S. pneumoniae* coinfection were aged <5 years and most patients with virus coinfection were female (89%). Fever (100%), cough (100%), and rhinorrhea (54%) were the three most common symptoms. The duration of fever before admission was similar in the different groups of children. However, the duration of fever was significantly longer ($p < 0.05$) in patients coinfected with *S. pneumoniae*. The most common findings on physical examination were crackles on auscultation. Tachypnea and decreased breath sounds due to parapneumonic effusions were significantly more common in patients with *S. pneumoniae* coinfection ($p < 0.05$). In contrast, rhinorrhea was significantly higher ($p < 0.01$) in patients with virus coinfection. The demographic data and the clinical characteristics of children enrolled are summarized in Table 2.

Laboratory and radiographic findings

No significant difference was noted in terms of differential white blood cell count, hemoglobin level, or platelet count between the patients with *M. pneumoniae* infection alone and those with mixed *S. pneumoniae* or virus infection. However, total leukocyte count and serum C-reactive protein levels on admission ($p < 0.01$) were significantly higher in patients with *S. pneumoniae* coinfection. Focal reticulonodular patterns (64%) and parahilar peribronchial infiltrates (32%) were the two most common chest radiographic findings. Moreover, lobar consolidation and pleural effusions were significantly more common in children with *S. pneumoniae* coinfection ($p < 0.05$).

Complications and outcomes

No significant difference was observed between the patients infected with *M. pneumoniae* alone and those coinfected with virus. Of the nine patients with *S. pneumoniae* coinfection, three with complications (respiratory failure in 2, thoracostomy in 1) required intensive care. All of these children with *M. pneumoniae* pneumonia were treated with azithromycin manufactured by Pfizer (10 mg/kg of body weight/day for 3 days). In children coinfected with *S. pneumoniae*, the earlier prescribed empirical antibiotics for *S. pneumoniae* were continued until the fever had subsided. The duration of hospitalization was significantly longer ($p < 0.01$) in patients with *M. pneumoniae* and *S. pneumoniae* coinfection than in those with *M. pneumoniae* infection alone. All children recovered uneventfully. Comparisons of laboratory findings, radiographic manifestations, complications, and outcomes in various groups of children with *M. pneumoniae* infection are shown in Table 3.

Discussion

Mycoplasma pneumoniae plays a significant role as a cause of CAP in children.[1–3] The occurrence of *M. pneumonia* CAP throughout the year and seasonal peaks have been reported in varying periods ranging from the end of summer to winter.[12–14] In the present study, infection with *M. pneumoniae* occurred year-round and was similarly common in autumn. The incidence of mycoplasmal pneumonia was greatest among children aged 3–7 years, as reported previously.[15] Coinfection with *S. pneumonia*, however, mostly occurred in children aged <5 years, which may be explained partly by a relatively high rate of nasopharyngeal carriage of *S. pneumoniae* in preschool-aged children.[16]

In children, several previous studies indicate that patients with coinfection accounted for 30–52% of cases of *M. pneumoniae* infection.[6,17,18] Results from the present study however showed that the occurrence of coinfection of *M. pneumoniae* with other pathogens, either viruses or other bacteria, was common, at up to 60%. The trend towards high rates of coinfection with *M. pneumoniae* infection may be attributed to the higher number of laboratory methods used for pathogens in this study.

Presenting symptoms and radiographic findings in children with mycoplasmal pneumonia are nonspecific and often similar to what is also seen with other various

Table 2 Comparisons of demographic and clinical characteristics of children at enrollment in various etiological groups

Characteristics	*Mycoplasma pneumoniae* monoinfection ($n = 31$)	*M. pneumoniae* with *Streptococcus pneumoniae* coinfection ($n = 9$)	*p*	*M. pneumoniae* with virus coinfection ($n = 19$)	*p*
Age (y)	5.6 ± 1.0	3.8 ± 0.7	0.11	4.9 ± 1.0	0.59
<5	12 (39)	9 (100)	<0.01	10 (53)	0.39
≥5	19 (61)	0 (0)		9 (47)	
Sex					
Male	14 (45)	3 (33)	0.71	2 (11)	<0.05
Female	17 (55)	6 (67)		17 (89)	
Season					
Summer	9 (29)	1 (11)	0.60	1 (5)	0.18
Autumn	15 (48)	5 (56)		10 (53)	
Winter	4 (13)	1 (11)		4 (21)	
Spring	3 (10)	2 (22)		4 (21)	
Symptoms and signs					
Fever	31 (100)	9 (100)	N/A	19 (100)	N/A
Days before admission	5.7 ± 1.0	5.0 ± 1.0	0.76	4.5 ± 0.8	0.25
Days of total	7.6 ± 1.3	11.3 ± 3.5	<0.05	5.6 ± 0.9	0.17
Cough	31 (100)	9 (100)	N/A	19 (100)	N/A
Rhinorrhea	13 (42)	3 (33)	0.72	16 (84)	<0.01
Abdominal pain	5 (16)	4 (44)	0.17	5 (26)	0.47
Tachypnea	1 (3)	4 (44)	<0.01	0 (0)	>0.99
Chest pain	1 (3)	1 (11)	0.40	0 (0)	>0.99
Rales	15 (48)	3 (33)	0.48	11 (58)	0.57
Wheezes	3 (10)	0 (0)	>0.99	2 (11)	>0.99
Decreased breath sounds	4 (13)	5 (56)	<0.05	3 (16)	>0.99

Data are no. (%) of patients or mean ± standard deviation (SD). The *p* value is for comparison of patients with *M. pneumoniae* monoinfection at baseline.
N/A = Not available.

respiratory viruses, or bacteria.[19] In the present study, the clinical characteristics of tachypnea, and elevated leukocyte count and C-reactive protein level were commonly seen in children coinfected with *S. pneumoniae* and *M. pneumoniae*. Radiographic findings of lobar consolidation and parapneumonic effusions were also significantly common in such instances. However, the association between these abnormalities and bacterial pneumonia caused by *S. pneumoniae* has been well described in children with CAP.[20] Apparently, the clinical and radiographic characteristics may overlap in children with pneumonia either caused by *S. pneumoniae* alone or by coinfection with *M. pneumoniae* and *S. pneumoniae*. It is important for clinicians to realize that a potential coexistence of *M. pneumoniae* infection should be considered in children with features suggesting typical bacterial pneumonia.

Mixed infections with *M. pneumoniae* are common in hospitalized children with respiratory syndromes; however, the clinical implications have not been well described.[6,17,18] In the present study, children coinfected with virus presented with similar clinical symptoms, laboratory findings, radiologic findings, and clinical outcomes in comparison with children infected with *M. pneumoniae* alone. In contrast, the clinical presentations of children coinfected with *S. pneumoniae* were more likely to be severe, and they were likely to have a longer hospital stay. These findings support literature reports indicating that severe bacterial infection may have either followed or coincided with *M. pneumoniae* respiratory infection by facilitating alterations in local respiratory immunity or structure and function.[21,22] In this study, 20% of children with pneumonia had three or more microorganisms found by virus culture or serology methods. Although virus alone plays a minor role in severe childhood pneumonia that requires hospitalization, viral infection is believed to have a substantial role of predisposing children to typical bacterial infections.[9] However, it must be emphasized that *M. pneumoniae* infection may also precede viral or other bacterial respiratory infections.[22]

Pneumonia caused by *S. pneumoniae* usually accompanies intense inflammation followed by parapneumonic effusion and empyema.[20,23,24] In the present study, *M. pneumoniae* infection complicated by pleural effusion resulting in the need for intensive care was significantly found in children coinfected with *S. pneumoniae*. The influence on the clinical outcomes of *M. pneumoniae* coinfection may be heavily dependent on the coinfected pathogen other than *M. pneumoniae* itself. A potentially unfavorable outcome such as necrotizing pneumonitis, lung abscess, and acute respiratory distress syndrome caused by *M. pneumoniae* is, however, occasionally encountered, attributed to the increase of macrolide-resistant *M.*

Table 3 Comparisons of laboratory findings, radiographic manifestations, complications, and outcomes in various etiological groups

Characteristics	*Mycoplasma pneumoniae* monoinfection ($n = 31$)	*M. pneumoniae* with *Streptococcus pneumoniae* coinfection ($n = 9$)	p	*M. pneumoniae* with virus coinfection ($n = 19$)	p
Laboratory findings					
Leukocyte count ($\times 10^9$/L)	9.122 ± 1.797	15.422 ± 3.707	<0.01	10.605 ± 2.559	0.60
Neutrophils, %	68.7 ± 5.0	77.2 ± 6.3	0.25	69.3 ± 7.2	0.99
Lymphocytes, %	21.0 ± 4.0	12.4 ± 6.8	0.14	21.5 ± 6.0	0.99
Hemoglobin (g/L)	112 ± 4	103 ± 8	0.06	113 ± 4	0.86
Platelet count ($\times 10^{12}$/L)	26.26 ± 3.74	28.71 ± 10.42	0.82	28.35 ± 3.87	0.78
C-reactive protein (mg/L)	66.5 ± 24.0	296.1 ± 114.3	<0.01	96.7 ± 56.5	0.96
Radiographic findings					
Focal reticulonodular pattern	20 (65)	4 (44)	0.44	14 (74)	0.55
Parahilar peribronchial infiltrates	12 (39)	2 (22)	0.45	5 (26)	0.54
Lobar consolidation	8 (26)	6 (67)	<0.05	0 (0)	<0.05
Pleural effusions	3 (10)	4 (44)	<0.05	1 (5)	>0.99
Complications and outcomes					
Parapneumonic effusions	3 (10)	4 (44)	<0.05	1 (5)	>0.99
Chest tube placement	0 (0)	1 (11)	0.23	0 (0)	N/A
Oxygen hood	13 (42)	4 (44)	>0.99	9 (47)	0.78
Intensive management	0 (0)	3 (33)	<0.01	0 (0)	N/A
Respiratory failure requiring ventilation	0 (0)	2 (22)	<0.05	0 (0)	N/A
Uneventful recovery	31 (100)	6 (67)	<0.05	19 (100)	N/A
Hospital stay (d)	5.1 ± 1.1	11.2 ± 4.2	<0.01	4.3 ± 0.7	0.42

Data are no. (%) of patients or mean ± SD. The p value is for comparison of patients with *M. pneumoniae* monoinfection at baseline. N/A = Not available.

pneumoniae in recent years.[25–28] Although the respiratory symptoms caused by *M. pneumoniae* are usually self-limiting, therapeutic agents active against mycoplasma could be a critical component of managing severe cases of *S. pneumoniae* and *M. pneumoniae* coinfection.[21,22]

In conclusion, a coinfection of *M. pneumoniae* with other bacteria or virus is frequently seen in children with CAP. The influence on the clinical outcomes of *M. pneumoniae* infection may be heavily dependent on the coinfected pathogen. In preschool-aged children with CAP who present with tachypnea and a chest radiograph showing lobar consolidation, either with or without parapneumonic effusions, a typical bacterial pathogen, either alone or coinfected with *M. pneumoniae*, should be considered.

Conflicts of interest

The authors have no conflicts of interest to declare.

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