Levels of Interleukin-2, Interferon-γ, and Interleukin-4 in Bronchoalveolar Lavage Fluid From Patients With *Mycoplasma* Pneumonia: Implication of Tendency Toward Increased Immunoglobulin E Production

Young Yull Koh, MD*; Yang Park, MD*; Hoan Jong Lee, MD*; and Chang Keun Kim, MD‡

**ABSTRACT.** *Objective.* In connection with the possible relationship between *Mycoplasma* infection and the onset of asthma, several studies have shown not only a high level of serum total immunoglobulin E (IgE) but also the production of IgE specific to *Mycoplasma* or common allergens during the course of *Mycoplasma* infection. It has been suggested that the balance of T helper type 1 (TH1)/T helper type 2 (TH2) immune response may regulate the synthesis of IgE. The objective of this study was to investigate the pattern of cytokine response (TH1 or TH2) during an episode of acute lower respiratory tract infection caused by *Mycoplasma pneumoniae.*

**Study Design.** Using a bronchoalveolar lavage (BAL) with flexible bronchoscopy procedure, this study determined the levels of interleukin (IL)-2, interferon (IFN)-γ (TH1), and IL-4 (TH2) in the supernatant of BAL fluid as well as the BAL cellular profiles of patients with *Mycoplasma pneumonia* (n = 14). These results were compared with those of patients with pneumococcal pneumonia (n = 12) or those of children with no identifiable airway infections (control group: n = 8).

**Results.** The BAL cellular profile in the *Mycoplasma pneumonia* group was characterized by a high percentage of neutrophils and lymphocytes. A significantly increased level of IL-2 was found in both pneumonia groups, compared with the control group. In contrast, the IFN-γ level was not different for the 3 groups. The level of IL-4 and ratio of IL-4/IFN-γ were significantly elevated in the *Mycoplasma pneumonia* group, but not in the pneumococcal pneumonia group, compared with the controls.

**Conclusions.** IL-4 levels and IL-4/IFN-γ ratios in BAL fluid are significantly higher in patients with *Mycoplasma pneumonia* than in patients with pneumococcal pneumonia or control participants. The BAL cytokine data suggest a predominant TH2-like cytokine response in *Mycoplasma pneumonia*, thus representing a favorable condition for IgE production. *Pediatrics* 2001;107(3). URL: http://www.pediatrics.org/cgi/content/full/107/3/e39; interleukin-2, interferon-γ, interleukin-4, bronchoalveolar lavage, *Mycoplasma, pneumococcus, pneumonia.*

**ABBREVIATIONS.** IgE, immunoglobulin E; TH1, T helper type 1; TH2, T helper type 2; IFN, interferon; IL, interleukin; BAL, bronchoalveolar lavage; FB, fiber-optic bronchoscopy; SD, standard deviation.

Results of several studies over the past decade have provided evidence linking *Mycoplasma* infection with asthma exacerbation and have raised the possibility that *Mycoplasma* infection is a factor in the pathogenesis of asthma. An acute exacerbation of wheezing in asthmatic participants in association with *Mycoplasma* infection has been well-documented. In addition, *Mycoplasma pneumoniae* has been found in the lower airways of chronic, stable asthmatics with a greater frequency than in control participants, suggesting a pathogenic mechanism in chronic asthma. It has even been suggested that *Mycoplasma* infection may be responsible for the subsequent development of asthma. In a follow-up study of 50 children with *Mycoplasma* respiratory illness, developed clinical signs of asthma for the first time. There is also a report that describes a previously healthy participant who had an initial asthmatic attack after recovering from *Mycoplasma pneumonia.*

Several studies support the theory of a possible relationship between *Mycoplasma* infection and the onset of asthma. It has been reported that *Mycoplasma* infections could induce transient or persistent airway hyperresponsiveness. The level of serum total immunoglobulin E (IgE) has been shown to increase in the acute phase of *Mycoplasma* infection. As has been reported for virus infection, wheezing during *Mycoplasma* infection may be related to higher serum IgE levels. *Mycoplasma*-specific IgE and IgE specific to common allergens unrelated to the infectious agent have been detected during the course of *Mycoplasma* infection. Although the baseline IgE levels have not been presented to be certain that the increase in IgE is caused by *Mycoplasma* infections, these observations raise the possibility that *Mycoplasma* infections may stimulate an inflammatory response that promotes IgE production.

The development of cellular or humoral immune responses will depend on a repertoire of cytokines produced by numerous cells, including CD4+ helper T cells. These lymphocytes can be subdivided into 2 subsets, T helper type 1 (TH1) and T helper type 2.

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(TH2), based on their cytokine profiles. TH1 cells are characterized by the secretion of interferon (IFN)-γ and interleukin (IL)-2 and promote cell-mediated immunity. TH2 cells selectively produce IL-4 and IL-5, and they are involved in the development of humoral immunity. It has been suggested that the balance of TH1/TH2 immune response may regulate the synthesis of IgE, because IL-4 is the critical stimulus that induces the isotype switch to IgE antibody production, whereas IFN-γ inhibits the switch.12

The aim of this study was to investigate the pattern of cytokine response (TH1 or TH2) during an episode of acute lower respiratory infection caused by M pneumoniae. To perform the study, we determined the levels of IL-2, IFN-γ (TH1), and IL-4 (TH2) in the supernatant of bronchoalveolar lavage (BAL) fluid as well as the BAL cellular profiles in patients with Mycoplasma pneumonia. These results were compared with those of patients with pneumococcal pneumonia or those of children with no identifiable airway infections (control group).

METHODS

Study Population

The study participants included 14 patients with Mycoplasma pneumonia, 12 patients with pneumococcal pneumonia, and 8 controls who underwent fiber-optic bronchoscopy (FB) with BAL between January and July of 1999 as part of an approved study protocol or for clinical indications. Complete history taking, physical examination, and routine laboratory testing were performed on all participants. Serum total IgE was measured on the day of FB with BAL. None of them had previously suffered from allergic disease or experienced asthma-like syndrome.

The Mycoplasma pneumonia group consisted of 8 boys and 6 girls (mean: 7.1 years old; range: 3.2–12.9 years) who had a clinical condition that necessitated hospitalization. The diagnosis of Mycoplasma pneumonia was based on clinical (fever, cough, dyspnea, rales, etc.) and radiologic (chest infiltrates) criteria, and on the antibody titer determined by the microparticle agglutination method with a commercial kit13 (Sorodi-Myco II, Fujirebio, Japan). Using this method, the first titer was checked at the onset of pneumonia symptoms, and M pneumoniae was identified as the cause if 2 conditions were met: 1) a fourfold or greater increase in the antibody titer between the 2 consecutive sera, which were sampled with an interval of 3 to 7 days, and 2) an antibody titer of at least 1:160 for 1 of the 2 sera. Two patients with Mycoplasma pneumonia who underwent FB with BAL were excluded from the analysis because of a positive viral culture (n = 1) and an insufficient lavage return (n = 1).

The pneumococcal pneumonia group consisted of 8 boys and 4 girls (mean: 5.6 years old; range: 3.2–10.9 years). All of these needed hospitalization for their primary lung infection; 5 of these patients were treated in the intensive care unit. The diagnostic criteria for pneumococcal pneumonia were an acute clinical pneumonia and the presence of opacities on the chest radiograph, together with the growth of Streptococcus pneumoniae in blood or BAL cultures. Three patients with pneumococcal pneumonia were excluded from the analysis because of a positive viral culture (n = 1) and an insufficient lavage return (n = 2).

Eight children who were admitted with indications for flexible bronchoscopy (eg, lung mass, stridor, localized emphysema) served as controls (mean age: 6.2 years; range: 3.4–10.6 years). They had no identifiable airway infections for a 4-week period before the study.

The parents or legal guardians of the participants enrolled in this study gave informed consent, and the study was approved by the hospital ethics committee.

FB With BAL

FB with BAL was performed, between 2 and 5 days postadmission, following the previously described guidelines14 with a 3.6-mm pediatric flexible bronchoscope (Olympus BF-3C3O; Olympus, New Hyde Park, NY) for children <8 years old and a 4.8-mm flexible bronchoscope (Olympus BF-TIT10) for older children. Premedication consisted of intramuscular atropine sulfate (0.01–0.02 mg/kg and <1 mg) and intravenous midazolam (0.1–0.2 mg/kg). During bronchoscopy, oxygen and epinephrine were readily available, and patients had an intravenous infusion to provide venous access. Heart rate and transcutaneous oxygen saturation were monitored throughout the procedure and continued for 1 hour. Topical anesthesia of the upper and lower airways used 2% lidocaine. BAL was performed either in an area most prominently affected on the chest radiographs (pneumonia groups) or in the right middle lobe (control group) by gently wedging the tip of the bronchoscope in a segmental or subsegmental bronchus. Three 1-mL/kg aliquots of sterile, nonbacterial-stable saline at room temperature were instilled through the instrumentation channel. Each aliquot was immediately aspirated into a sterile specimen container using a wall suction pressure of 100 to 150 mm Hg. BAL fluid aspirated after each instillation was pooled together into a single specimen and immediately placed on ice.

Processing and Analysis of the BAL Fluid

The total amount of recovered fluid was measured and the recovery was calculated as a percentage of the volume instilled. Pooled BAL fluid was placed into 2 aliquots. One aliquot of the pooled BAL fluid was submitted for viral (respiratory syncytial virus, adenovirus, influenza A and B, para-influenza 1 and 3, and cytomegalovirus) and bacterial cultures to the hospital microbiology department. The remainder of the pooled BAL fluid was taken to the laboratory for analysis of the cellular and fluid fractions. The fluid was centrifuged at 400 g for 10 minutes at 4°C to separate fluid from cells. Total cell count was measured using a hemocytometer (Weber, Teddington, United Kingdom). Differentials were obtained from cytopsin (Shandon, Pittsburgh, PA) slide preparations, using a May-Grunwald-Giemsa stain and by figuring a percentage of 400 cells. The cell-free fluid was frozen at −70°C until required for cytokine assay.

Concentration of the BAL Fluid

Because of the large dilution effect of the instilled fluid and the expected low concentration of cytokines in the BAL samples, it was necessary to concentrate the BAL fluid before analysis to obtain measurable quantities of various cytokines. Therefore, BAL fluid was concentrated using Centricon-10 concentrators (Amicon Co, Beverly, MA) with a molecular weight cutoff of 10 KD according to the manufacturer’s recommendations. Briefly, two 4-mL aliquots of BAL fluid per patient were centrifuged at 4900 g using Sorvall ultracentrifuge (DuPont Co, Wilmington, DE). Several centrifuge cycles were performed. Two hundred-microliter and 100-μL volumes were retained, which corresponded to 20- and 40-fold concentrations, respectively.

Cytokine Assays

IL-2 and IFN-γ levels were measured in 20-fold concentrated BAL fluid, and IL-4 was measured in 40-fold concentrated BAL fluid using a commercial enzyme-linked immunosorbent assay kit from Endogen (Woburn, MA). The kits were able to detect concentrations as low as 6 pg/mL of IL-2 and 2 pg/mL of IFN-γ and IL-4. All assays were run in duplicate and the mean value was used for statistical analysis. When cytokines were undetectable, the minimum detectable level was used in the analysis.

Statistical Analysis

Cytokine levels were expressed per milliliter in concentrated BAL fluid and were presented as mean ± standard deviation (SD). Cellularity data were expressed as the number per milliliter in unconcentrated BAL fluid (total cell count) or as a percentage of the total cell count (cell differential) and were presented as median with interquartile range (25th–75th). Because the majority of the data were not normally distributed, nonparametric analysis was used. Screening of data for differences in cytokine and cell profiles among groups was performed using the Kruskall-Wallis test. When significant differences were identified, individual groups were compared by using the Mann-Whitney U test. A P value of <.05 was considered statistically significant.
RESULTS

The characteristics of the participants studied are shown in Table 1. There were no significant differences in age, sex, and blood eosinophil counts. Mycoplasma and pneumococcal pneumonia groups had significantly higher blood leukocyte counts than did the control group, whereas the Mycoplasma pneumonia group had a significantly higher serum IgE than did the other 2 groups.

FB with BAL was relatively well-tolerated by all participants. Minor procedure-associated complications occurred on 6 occasions, including transient hypoxia (n = 3), transient bradycardia (n = 2), and minor epistaxis (n = 1). These complications did not preclude the completion of the procedure. Two children had a transitory hoarse cough and 2 others had a low grade fever of up to 38°C, which occurred within 12 hours of the procedure. These adverse events resolved spontaneously within 24 hours.

The recovery of BAL fluid, the absolute number of total cells per milliliter in the returned fluid, and the percentages for each cell type are shown in Table 2. The recovery ranged from 30.6% to 60.8% of the fluid introduced. It was less in the 2 pneumonia groups than in the control group, but the difference did not reach statistical significance. The total cell number was significantly higher in the pneumococcal pneumonia group than in the Mycoplasma pneumonia or control groups. There were significant differences in the percentages of macrophages, neutrophils, and lymphocytes among the 3 groups. The neutrophil percentages in both pneumonia groups were significantly higher than in the control group. The lymphocyte percentage of the Mycoplasma pneumonia group was also higher than that of the control group, but was similar for the pneumococcal pneumonia and for the control groups. The percentage of macrophages was lower in both pneumonia groups in conjunction with a marked increase in the percentage of neutrophils and/or lymphocytes.

The levels of IL-2 and IFN-γ in the concentrated BAL fluid of the 3 studied groups are shown in Fig 1. IL-2 levels in the Mycoplasma and pneumococcal pneumonia groups were 22.6 ± 7.8 pg/mL (mean ± SD) and 26.2 ± 9.2 pg/mL, respectively, which were significantly higher than that (12.4 ± 2.4 pg/mL) in the normal control group. In contrast, IFN-γ levels were not increased in the Mycoplasma (7.9 ± 2.5 pg/mL) or pneumococcal pneumonia group (9.3 ± 3.0 pg/mL), compared with the control group (7.7 ± 1.8 pg/mL). The levels of IL-4 and the ratio of IL-4/IFN-γ are shown in Fig 2. The samples from 3 participants (pneumococcal pneumonia: n = 2; normal control: n = 1) had no detectable amount of IL-4, and, therefore, the censored value (2 pg/mL) was used. A significantly higher level of IL-4 (6.4 ± 3.6 pg/mL) was found in the Mycoplasma pneumonia group than in the pneumococcal pneumonia group (3.5 ± 1.5 pg/mL) or in the control group (3.0 ± 1.1 pg/mL). The difference in IL-4 between the pneumococcal pneumonia and the control groups was not significant. Similarly, the ratio of IL-4/IFN-γ was significantly increased in the Mycoplasma pneumonia group (0.85 ± 0.50) but not in the pneumococcal pneumonia group (0.41 ± 0.22), compared with the control group (0.40 ± 0.17). When patients in the Mycoplasma pneumonia group were divided according to family history of atopy (Fig 3), we found higher IL-4 levels in patients with a family history of atopy (8.7 ± 3.2 pg/mL) than those without (5.4 ± 3.4 pg/mL), although this was not statistically significant (P = .076). No difference in IFN-γ levels was found between the 2 subgroups (data not shown). The ratio of IL-4/IFN-γ was similarly different (P = .054) between patients with (1.18 ± 0.41) and without a family history of atopy (0.72 ± 0.49). The trend to increased IL-4 and IL-4/IFN-γ ratio with a family history of atopy did not exist in pneumococcal pneumonia patients (3 with positive family history and 9 with negative family history) or control participants (3 with positive family history and 5 with negative family history; data not shown).

DISCUSSION

Our results have shown that levels of IL-2 and IL-4 and IL-4/IFN-γ ratios in BAL fluid were significantly higher in patients with Mycoplasma pneumonia than in control participants, whereas only the IL-2 level was increased in patients with pneumococcal pneumonia. The BAL cytokine data in Mycoplasma pneumonia suggest a predominant TH2-type cytokine response, representing an inflammatory process that promotes IgE production.

Data on the cytokine profile in terms of TH1 or TH2 type in M pneumoniae infection are scarce and controversial. Kita et al15 could not identify the production of IL-4 in response to M pneumoniae in human peripheral blood mononuclear cells, while Schaffner et al16 reported that the lymphoblastoid cell line showed mRNA expression for IL-4 after stimulation with M pneumoniae. In a study to determine whether M pneumoniae infection leads to the production of IFN-γ, Arai et al17 observed what seemed to be increased levels of this cytokine. Nakayama et al,18 in contrast, observed the suppression of IFN-γ production during the acute stage of M pneumoniae infection. M pneumoniae-induced production of IL-2 is also controversial: one study shows such induction,15 whereas another reported a negative finding.19 Most of the above studies have determined cytokine levels in cell culture in vitro; there-

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**TABLE 1.** Clinical Characteristics of the Three Groups

<table>
<thead>
<tr>
<th></th>
<th><em>Mycoplasma</em> Pneumonia (n = 14)</th>
<th><em>Pneumococcal Pneumonia</em> (n = 12)</th>
<th><em>Control Participants</em> (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>7.1 ± 2.7</td>
<td>5.6 ± 2.3</td>
<td>6.2 ± 2.5</td>
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<tr>
<td>Sex (M:F)</td>
<td>8:6</td>
<td>8:4</td>
<td>5:3</td>
</tr>
<tr>
<td>Blood eosinophils* (*/mm³)</td>
<td>184.0 ± 113.4</td>
<td>170.8 ± 90.7</td>
<td>148.5 ± 96.1</td>
</tr>
<tr>
<td>Blood leukocytes* (*/mm³)</td>
<td>12.930 ± 3785‡</td>
<td>14.835 ± 4450‡</td>
<td>5995 ± 1324†</td>
</tr>
<tr>
<td>Serum IgE+ (IU/mL)</td>
<td>182.0§</td>
<td>93.3</td>
<td>109.7</td>
</tr>
<tr>
<td>(97.7–338.8)</td>
<td>(47.9–182.0)</td>
<td>(74.1–162.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD.
† Geometric mean (range of 1 SD).
‡ P < .01 compared with control participants.
§ P < .05 compared with pneumococcal pneumonia or control participants.
Therefore, these results may not adequately reflect local immune response within the respiratory tract.

BAL is a valuable research tool for the assessment of cellular and noncellular factors associated with inflammations of the lower respiratory tract.20 With the introduction of smaller fiber-optic bronchoscopes in recent years, a growing number of studies have investigated BAL constituents in children.21 We adjusted BAL volume to body weight, which has been shown to yield a constant fraction of epithelial lining fluid in children.22 The recovery of BAL fluid in our study was similar to that previously reported in children with chronic bronchial disease23 (2 pneumonia groups) or in healthy children24 (control group). The region of lung sampled by FB with BAL depends on the sizes of children for anatomic and technical reasons.24 The effects of sampling bronchi in different orders were not likely to influence our results, because the age was not different among the studied groups.

Our findings in BAL fluid indicated that IL-2 and IL-4 levels were significantly higher but that the IFN-γ level was similar in the Mycoplasma pneumonia group compared with controls. It was not possible to attribute the cytokine levels specifically to this pathogen in the absence of pneumonia attributable to another pathogen for comparison. Therefore, the present study included patients with pneumococcal pneumonia, which is the most common form of bacterial pneumonia. BAL cytokine analysis in these patients revealed a significantly increased level of IL-2, with normal concentrations of IL-4 and IFN-γ.

IL-4 has been measured in serum,25 and it is possible that the elevated IL-4 level in Mycoplasma pneumonia may have resulted from increased plasma leakage. However, we believe this unlikely, because IL-4 was not increased in pneumococcal pneumonia in light of a well-documented increased plasma leakage attributable to lung inflammation caused by this disease.26 The timing for BAL was mostly within 24 hours of the antibiotic administration for the pneumococcal pneumonia group and within 24 hours of the serologic documentation in the Mycoplasma pneumonia group. Although it is true that these points in time are different in relation to the appearance of clinical manifestations of infection, patients in both groups were still symptomatic and laboratory signs of infection (elevated erythrocyte sedimentation rate,
C-reactive protein, leukocytosis) were positive. Therefore, we believe that the comparison of cytokine levels in BAL fluid between the 2 groups remains valid.

IL-4 can elicit IgE production by B lymphocytes, whereas IFN-γ is a potent inhibitor of IgE synthesis. Thus, an increase in IL-4 and the IL-4/IFN-γ ratio in BAL fluid of patients with Mycoplasma pneumonia may be responsible for the elevated serum level of total IgE in these patients (Table 1). Previous studies have shown not only a high level of serum total IgE, but also the production of Mycoplasma-specific IgE and IgE specific to common allergens unrelated to the infectious agent in the acute phase of Mycoplasma pneumonia. Mycoplasma infections lead to the destruction of the respiratory mucosal cells and, thus, may facilitate the penetration of allergens into the mucosa. The cytokine profile in the BAL fluid of patients with Mycoplasma pneumonia, in conjunction with such an increased exposure to the microorganism itself and/or common allergens, seems to represent a favorable condition for an IgE response that may result in the release of chemical mediators leading to bronchospasm, airway inflammation, and airway hyperresponsiveness.

The elevated IL-4 level and IL-4/IFN-γ ratio sug-
gest a TH2-type response in *Mycoplasma* pneumonia. However, IL-2, a cytokine associated with a TH1-type response, was also found to be elevated. Because in vitro T lymphocytes produce mainly IL-2 when first stimulated, this IL-2 increase could be attributable to an initial, possibly nonspecific, TH0-type response. It is also possible that the cytokine profile may be one of various patterns that do not polarize to TH1 or TH2 types. In this regard, it is of interest that in atopic asthma, which is characterized by TH2 immune response, an increase in IL-2 and its mRNA expression was noted in BAL fluid after inhaled allergen challenge.

Although IL-4 and the IL-4/IFN-γ ratio increased in the *Mycoplasma* pneumonia group, it should be noted that a large variation was observed in their distribution. It may, therefore, be questioned whether >1 population was included in our *Mycoplasma* pneumonia group. We considered the possibility that a genetic predisposition to atopy may enhance the imbalance of local IL-4 and IFN-γ secretion. Although the number of patients in the current study was not sufficient to conclude with certainty, we found a trend toward increased IL-4 and IL-4/IFN-γ ratio in BAL fluid of *Mycoplasma* pneumonia patients with a family history of atopy (Fig 3). It is theoretically possible that atopic status per se might have some influence on cytokine profile in BAL fluid. Although none of our studied participants suffered from atopic diseases, we cannot rule out the possibility that some of our participants had been atopic, because of a lack of data from the preinfectious stage. However, we believe that our finding is less likely to be attributable to this factor, because the trend was not shown in pneumococcal pneumonia patients and control participants. An analogous observation was made in respiratory syncytial virus infection by Roman et al, who found significantly more IL-4 production by phytohemagglutinin-stimulated peripheral blood mononuclear cells in infants with a family history of atopy. Our result raises the possibility that there may be synergistic immunologic interaction between *Mycoplasma* infections and a genetic predisposition to atopy, which favors IgE production.

The total cell number in BAL fluid was found to be higher in patients with pneumococcal pneumonia but was similar for the *Mycoplasma* pneumonia and the control groups. This suggests that the inflammatory response of lungs to pneumococcal infection is more potent than their response to *Mycoplasma* infection, in terms of the recruitment of cells into lumen. The percentages of neutrophils and lymphocytes in the *Mycoplasma* pneumonia group were significantly greater than in the control group, whereas in the pneumococcal pneumonia group only neutrophils were increased. This is in line with previous reports of BAL cellularity in *Mycoplasma* and bacterial pneumonia. Hayashi et al reported an increase in activated T cells and the CD4/CD8 ratio of the lymphocyte subpopulation in the BAL fluid of patients with *Mycoplasma* pneumonia. The difference in terms of lymphocyte number and activation in the airway lumen may have implications on the local cytokine response in the 2 forms of pneumonia. Additional studies, including the use of cell separation, RNA polymerase chain reaction, and in situ hybridization techniques, will be required to determine the cellular source of the cytokines.

Importantly, our present study is confined to the acute phase of *Mycoplasma* pneumonia and cannot answer questions about the possible duration of the imbalance in the IL-4/IFN-γ after *Mycoplasma* infection. A prospective study is needed to determine the duration of TH2-like cytokine response, when allergic sensitization might more easily occur. Another point is that the grade of *Mycoplasma* pneumonia in our study may represent a more severe one than that seen in the general community, the natural outcome of selecting the hospitalized patients for the study. Additional study is needed to determine whether our results are generalizable to the majority of patients with *Mycoplasma* pneumonia.

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