Is it possible to distinguish between atypical pneumonia and bacterial pneumonia?: evaluation of the guidelines for community-acquired pneumonia in Japan

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Summary The Japanese Respiratory Society (JRS) published the guidelines for the management of community-acquired pneumonia in 2000. The guidelines set up nine parameters and criteria for the differential diagnosis of atypical pneumonia and bacterial pneumonia based on clinical symptoms, physical signs and laboratory data. To evaluate the performance of these guideline criteria, 91 cases of *Chlamydia pneumoniae* (53 cases were pure-*C. pneumoniae* and 38 cases were mixed-*C. pneumoniae* pneumonia), 103 cases of *Mycoplasma pneumoniae* (86 cases were pure-*M. pneumoniae* and 17 cases were mixed-*M. pneumoniae* pneumonia) and 144 cases of bacterial (*Streptococcus pneumoniae* and/or *Haemophilus influenzae*) pneumonia were analyzed. The accordance rate for a suspected atypical pneumonia with the guideline criteria was 84.8% for pure-*M. pneumoniae* pneumonia and 60.3% for pure-*C. pneumoniae* pneumonia, but only 9.0% for bacterial pneumonia, 12.1% for mixed-*C. pneumoniae* pneumonia and 16.6% for mixed-*M. pneumoniae* pneumonia. Overall, the sensitivity and specificity of the criteria in the JRS guidelines were 75.5% and 90.9%, respectively. Our results indicated that the differentiation of pneumonia in the JRS guidelines is useful for the diagnosis of *M. pneumoniae* pneumonia, but difficult to apply to the diagnosis of *C. pneumoniae* pneumonia.

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Introduction

Community-acquired pneumonia (CAP) continues to be a major medical problem. Since CAP also is a potentially fatal disease, even in previously healthy persons, early appropriate antibiotic treatment is vital. Epidemiologic studies show that in the combined cause-of-death category, pneumonia ranks sixth as the leading cause of death in the United States and fourth in Japan. Because of this high morbidity, guidelines for CAP management have been promoted throughout the world during the past decade. In 1993, the American Thoracic Society (ATS) established guidelines to assist primary care physicians in antibiotic selection for the initial empiric treatment of CAP in adults.1
Subsequently, in 1998, the Infectious Diseases Society of America (IDSA) published guidelines for the treatment of CAP. These guidelines were revised in 2001 and 2003, respectively. The recommendations for initial antimicrobial therapy are based on pathogen probabilities, modifying factors and the severity of CAP. In Western countries, there have been many prospective studies on the etiology of CAP. These studies demonstrated that Streptococcus pneumoniae including drug-resistant S. pneumoniae (DRSP) and atypical pathogens including the Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella species, are the common pathogens. Therefore, macrolides, doxycycline and fluoroquinolones are recommended for primary empiric monotherapy or combined-therapy with \( \beta \)-lactams in both ATS and IDSA, since each has activity against common bacterial pathogens and atypical pathogens.

The Japanese Respiratory Society (JRS) has been developing its guidelines since 1998 and published CAP guidelines in March 2000. In Japan, there have been three reports on the etiology of CAP among the Japanese population. Ishida et al. were the first to investigate CAP's etiology. Subsequently, we and Saito et al., respectively, reported newer data obtained from 200 and 238 patients with CAP using the same microbiological methods. All these studies demonstrated that the most common pathogen was S. pneumoniae, followed by Haemophilus influenzae, with the third or fourth leading pathogens being atypical pathogens; i.e., C. pneumoniae or M. pneumoniae. Thus, in general, the etiology of CAP in Japan does not differ significantly from that in Western countries except for the low incidence of Legionella species. The etiologic agent which most clearly differentiates Japan from Western countries is the frequency of DRSP. A recent study found that the frequency of penicillin-intermediate resistance S. pneumoniae and penicillin-resistant S. pneumoniae combined has been increasing gradually in Japan. Furthermore, about half of S. pneumoniae cases show strong resistance to erythromycin with minimum inhibitory concentrations (MICs) greater than or equal to 256 \( \mu g/ml \). Additionally, these erythromycin-resistant S. pneumoniae cases also show strong resistance to tetracycline and new macrolides such as clarithromycin and azithromycin. Marked geographical differences in the prevalence of both penicillin and macrolide resistance have been observed and the highest rates have been found in Asia. Clinical failure of initial treatment using macrolides against S. pneumoniae pneumonia has also been reported in Japan. On the other hand, fluoroquinolone-resistant S. pneumoniae (defined as levofloxacin MIC greater than or equal to 8 \( \mu g/ml \)) has been detected, but with low prevalence. However, prevalence is greater in Asia than in Western countries. Therefore, the JRS recommends the restriction of quinolone usage to prevent an increase in the frequency of quinolone-resistant strains to the high frequency of macrolide or tetracycline-resistant strains. Based on these facts, the JRS proposed a differential diagnosis between bacterial pneumonia and atypical pneumonia for the selection of an appropriate antibiotic for the management of mild-to-moderate pneumonia. The guidelines set up nine parameters and criteria for the differential diagnosis, and JRS members demonstrated that these guideline criteria were a useful tool for distinguishing between mycoplasmal and bacterial pneumonia on preliminary reports. However, the parameters and criteria were made based on the clinical features of M. pneumoniae pneumonia and there have been no studies to evaluate patients with another common atypical pathogen, C. pneumoniae.

In this study, we assessed the Japanese CAP guidelines with regard to whether we could distinguish pneumonia with atypical pathogens including C. pneumoniae and M. pneumoniae from pneumonia with common bacteria including S. pneumoniae and H. influenzae.

Subjects and methods

Study population

Adult patients with CAP who visited an outpatient clinic or were admitted to Kawasaki Medical School Hospital, Kawasaki Medical School Kawasaki Hospital or Kurashiki Daiichi Hospital, Okayama, Japan, between April 1998 and July 2003 were enrolled in this study. We also included adult patients with CAP enrolled in a multicenter CAP surveillance study performed in seven medical schools and their affiliate hospitals in Japan. None of our patients were immunocompromised; that is, there were no patients with HIV infection, patients with neutropenia secondary to chemotherapy or patients on immunosuppressants, patients from nursing homes or patients with recent (<30 days) admission to hospital. The diagnosis was based on clinical signs and symptoms (cough, fever, productive sputum, dyspnea, chest pain or abnormal breath sounds), and radiographic pulmonary abnormalities that were at least segmental and were not due to preexisting or other known causes. Concerning the hospitalized patients, all cases of pneumonia...
occurring more than 3 days after hospitalization were considered nosocomial and were excluded.

**Microbiologic laboratory tests**

Blood cultures and nasopharyngeal swab specimens were obtained from all patients and, if pleural fluid and sputum were available, a Gram’s stain test and a quantitative culture were obtained. Sputum data were only evaluated when the Gram’s stain test revealed numerous leukocytes (>25 in a x 100 microscopic field) and few squamous epithelial cells (<10 in a x 100 microscopic field). Certain invasive methods such as bronchoscopic examination were employed to obtain specimens in some patients after full explanation of the procedures. These specimens were also used for culturing of *M. pneumoniae* and *Legionella* species on pleuropneumonia-like organism base (Becton Dickinson Microbiology Systems, MD, USA), 20% horse serum, 10% fresh yeast extract, thallium acetate (final concentration 0.5 mg/ml) and sterile penicillin G (final concentration 1000 U/ml) and buffered charcoal-yeast extract alpha agar, respectively. Cultures for *C. pneumoniae* and *Chlamydia psittaci* were performed in cycloheximide-treated HEp-2 cells. The specimens were placed in a sucrose-phosphate-glutamate (SPG) transport medium. Each specimen in the SPG medium was sonicated and briefly centrifuged (900 x g for 10 min) and then the supernatant was overlayed on confluent monolayers of HEp-2 cells grown on round coverslips (14 mm in diameter) set in 24-well cell culture plastic plates. The plates were centrifuged at 1200 x g for 60 min at room temperature. Next, 1 ml of a culture medium consisting of Eagle’s minimal essential medium (Nissui Pharmaceuticals Co, Tokyo, Japan), 10% heat-inactivated fetal calf serum (Gibco BRL Life Technologies Inc, Grand Island, NY, USA) and cycloheximide (Nakarai Tesque Inc, Tokyo, Japan) at a final concentration of 1 μg/ml was applied. Then the plates were incubated in 5% CO2 at 35°C for 72 h and all specimens were passaged twice. Following incubation, a genus-specific fluorescein isothiocyanate-conjugated monoclonal antibody (Chlamydia FA Seiken; Denka Seiken, Tokyo, Japan) and *C. pneumoniae* species-specific monoclonal antibodies were used to stain inclusions. Inclusion bodies formed in the cells were observed with a Nikon epifluorescence microscope at x 200 or x 400 magnification.

Paired serum samples were collected at intervals of at least 4 weeks (range, 4 to 12 weeks; average, 5 weeks) after onset. Complement fixation tests were done in all patients for antibodies to influenza A and B viruses, adenovirus, respiratory syncytial virus, cytomegalovirus, parainfluenza virus types 1, 2 and 3 and *M. pneumoniae*. Antibody to the *Legionella* species was measured by the microagglutination test (detection of *L. pneumophila* serogroups 1–6, *L. bozemanii*, *L. dumoffii*, *L. gormanii* and *L. micdadei*) and *Coxiella burnetii* was measured by the indirect immunofluorescence test. The microimmunofluorescence (MIF) test was employed for titration of IgG and IgM antibodies against chlamydial species, using formalinized elementary bodies of *C. pneumoniae* KKpn-15 and TW-183, *C. trachomatis* L2/434/Bu and *C. psittaci* 6BC strains as antigens. Rheumatoid factors were absorbed with Gullsorb (Gull Laboratories, Salt Lake City, UT, USA) before IgM titrations. In addition to serology and/or culturing, the urinary antigen test (Binax NOW, Portland, MN, USA) was used for detection of *S. pneumoniae* and *L. pneumophila*.

**Criteria for determination of microbial etiology**

The microbial etiology was classified as “definitive”, “presumptive” or “unknown”. Bacteria were considered to be definitive causative agents when isolated from blood or pleural fluid cultures. We considered the results of sputum cultures in combination with Gram’s stain findings. An organism showing heavy (≥10^7 cfu/ml) or moderate (10^5 cfu/ml) growth of a predominant bacterium on a sputum culture was considered to be a presumptive pathogen. Any microorganism isolated from bronchoalveolar lavage fluid was considered to be a presumptive pathogen when its concentration reached >10^5 cfu/ml in quantitative culture. If *M. pneumoniae* or the *Legionella* species were isolated from a specimen, that specimen was considered to be a definitive pathogen even if the culture showed little growth. *L. pneumophila* and *S. pneumoniae* were considered to be a presumptive agent when the urinary antigen test was positive.

For serologic tests, a four-fold rise in the antibody titer level between paired sera was considered definitive. *C. pneumoniae* and *C. psittaci* infection was defined as IgM ≥1:32 or a four-fold rise in IgG or IgM.

**Differential diagnosis**

The Japanese guidelines propose a scoring system to differentiate between bacterial and atypical
pneumonia.\textsuperscript{9} The guidelines set up nine parameters based on clinical symptoms, physical signs and laboratory data. Six of these parameters are concerned with clinical and physical examination; (1) under 60 years old, (2) no underlying disease, (3) an outbreak of pneumonia is currently in the family or community, (4) the patient has paroxysmal cough, (5) the patient has a relatively slow pulse rate in relation to the fever and (6) the patient has absence of abnormal physical examination of the chest. Three parameters are related to biological and radiological examination; (7) a normal WBC count ($<10,000$/mm\(^3\)), (8) a chest radiograph showing a ground glass opacity (pattern) and (9) detection of no organisms in the sputum by Gram’s stain. When there is a correlation of items of more than three parameters among the clinical symptoms and physical signs or of items of more than five parameters among clinical symptoms, physical signs and laboratory data, then the guidelines recommend the use of macrolides or tetracyclines for a suspected atypical pneumonia. If these criteria are not met, the guidelines recommend the use of $\beta$-lactams for a suspected bacterial pneumonia.

### Statistical analysis

Statistical analysis was done by Fisher’s exact test. A mean age comparison was done by Student’s $t$-test.

### Results

The patients who fulfilled the diagnostic criteria for pneumonia caused by $S$. pneumoniae, $H$. influenzae, $C$. pneumoniae or $M$. pneumoniae, which are the top four leading causes of CAP in Japan,\textsuperscript{10-13} formed the groups for comparison of the guidelines. Five hundred ninety-eight CAP patients were enrolled in this study. Among all CAP cases, there were 144 cases where a bacterium, $S$. pneumoniae and/or $H$. influenzae (10 cases were blood culture positive), was the pathogen identified by the panel of diagnostic tests used, 91 cases where $C$. pneumoniae was identified and 103 cases where $M$. pneumoniae was identified. Of the 91 cases of $C$. pneumoniae, 71 demonstrated four-fold or greater rises in IgG antibody titers, while 41 cases demonstrated four-fold or greater rises in IgM antibody titers (21 cases met both criteria). All cases of $M$. pneumoniae demonstrated four-fold antibody seroconversion (31 cases were culture positive).

Among the 91 cases of $C$. pneumoniae, $C$. pneumoniae was the only pathogen identified in 53 cases (58.2%), while one or more additional etiological factors were found in 38 cases (41.8%). Table 1 shows the distribution of etiologies among the 38 cases of mixed-$C$. pneumoniae pneumonia. As for $M$. pneumoniae cases, $M$. pneumoniae was the only pathogen identified in 86 cases (83.5%), while one or more additional etiological factors were found in 17 cases (16.5%). Table 2 shows the distribution of etiologies among the 17 cases of mixed-$M$. pneumoniae pneumonia. Recently, we reviewed 62 cases of community-acquired $C$. pneumoniae pneumonia and noted that the clinical presentation of CAP cases with multiple pathogens and cases in whom $C$. pneumoniae was the only pathogen identified differed.\textsuperscript{16} These findings were also confirmed in another study.\textsuperscript{17} In this study, therefore, we divided the $C$. pneumoniae or $M$. pneumoniae pneumonia cases into two groups: those in whom $C$. pneumoniae or $M$. pneumoniae was the only pathogen identified (pure-$C$. pneumoniae or pure-$M$. pneumoniae pneumonia) and those with mixed-$C$. pneumoniae or mixed-$M$. pneumoniae pneumonia with other bacteria (excluding five cases of concomitant infection with $M$. pneumoniae or $C$. pneumoniae) in order to analyze the differential diagnosis of the Japanese CAP guidelines.

**Fig. 1** shows the age distribution and Table 3 shows the backgrounds of the patients with the three etiological agents of CAP, bacteria ($S$. pneumoniae and/or $H$. influenzae), $C$. pneumoniae

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
Pathogens & Cases no. \\
\hline
$Streptococcus pneumoniae$ & 11 \\
$Haemophilus influenzae$ & 5 \\
$Mycoplasma pneumoniae$ & 5 \\
$Moraxella catarrhalis$ & 2 \\
$Legionella pneumophila$ & 2 \\
$Klebsiella pneumoniae$ & 1 \\
$Staphylococcus aureus$ & 1 \\
$S$. $Pneumoniae + H$. $influenzae$ & 4 \\
$S$. $Pneumoniae + S$. $aureus$ & 2 \\
$S$. $Pneumoniae + M$. $pneumoniae$ & 1 \\
$S$. $Pneumoniae + M$. $catarrhalis$ & 1 \\
$H$. $influenzae + S$. $aureus$ & 1 \\
$M$. $Pneumoniae + S$. $aureus$ & 1 \\
$S$. $aureus + M$. $catarrhalis$ & 1 \\
Single agent* & 53 \\
\hline
\end{tabular}
\caption{Frequency distribution of additional etiologies of community-acquired pneumonia in 91 patients infected with $C$. pneumoniae.}
\end{table}

* $C$. pneumoniae was the only pathogen identified.
and *M. pneumoniae*. Analysis of the age distribution of the CAP patients in our study showed that while CAP affects adults of all ages, the mean age of the patients with bacterial pneumonia and mixed-*C. pneumoniae* pneumonia (65.1 and 64.8 years) was significantly higher than that of those with pure-*C. pneumoniae* pneumonia (54.7 years; \( P = 0.001 \)), pure-*M. pneumoniae* (35.1 years; \( P = 0.0001 \)) and mixed-*M. pneumoniae* pneumonia (45.5 years; \( P = 0.001 \)).

The mean age of the patients with pure-*C. pneumoniae* pneumonia was also significantly higher than that of those with pure-*M. pneumoniae* pneumonia \( (P = 0.0001) \) pneumonia. There were no statistically significant differences in terms of gender or smoking history between the patients with mixed-*C. pneumoniae* and those with bacterial pneumonia, but the frequencies of a smoking history with pure-*C. pneumoniae* and *M. pneumoniae* pneumonia were significantly lower than those of mixed-*C. pneumoniae* and bacterial pneumonia. Regarding prognostic factors, no patients required respiratory support and/or admission to an intensive care unit (ICU) and no patients died among the patients with pure-*C. pneumoniae* or *M. pneumoniae* pneumonia.

Table 4 shows the accordance rate with each parameter of the guideline criteria in patients with atypical pneumonia and bacterial pneumonia. In both atypical pneumonia, high prevalence rates were observed in the first (under 60 years old), second (no underlying disease), fourth (the patient has paroxysmal cough), sixth (the patient has absence of abnormal physical examination of the chest), seventh (WBC count <10,000/mm\(^3\)) and ninth (no organisms have been detected in the sputum by Gram’s stain or there is no sputum production) criteria parameters. The accordance rates of the other three parameters were almost identical in both atypical pathogens but were low.

The accordance rate for a suspected atypical pneumonia with the guideline criteria was 84.8% in pure-*M. pneumoniae* pneumonia and 60.3% in pure-*C. pneumoniae* pneumonia, but only 9.0% in bacterial pneumonia, 12.1% in mixed-*C. pneumoniae* pneumonia and 16.6% in mixed-*M. pneumoniae* pneumonia (Table 5). The sensitivity, specificity and likelihood ratio of the guideline criteria for a diagnosis of *M. pneumoniae* pneumonia were 84.8%, 90.9% and 9.318, respectively. The area under the Receiver Operating Characteristic (ROC) curve of the guideline criteria for a diagnosis of *M. pneumoniae* pneumonia was 0.852. The sensitivity, specificity and likelihood ratio of the guideline criteria for a diagnosis of *C. pneumoniae* pneumonia were lower than that of *M. pneumoniae* pneumonia, being 60.3%, 90.9% and 6.626, respectively. The area under the ROC curve of the
Differential diagnosis of atypical pneumonia and bacterial pneumonia

Table 3  Backgrounds of the patients with the three etiological agents of community-acquired pneumonia.

<table>
<thead>
<tr>
<th></th>
<th>C. pneumoniae</th>
<th>M. pneumoniae</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pure (n = 53)</td>
<td>Mixed (n = 33)</td>
<td>Pure (n = 86)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>54.7</td>
<td>64.8</td>
<td>35.1</td>
</tr>
<tr>
<td>Smoking history</td>
<td>30 (56.6)</td>
<td>22 (66.6)</td>
<td>30 (34.8)</td>
</tr>
<tr>
<td>Respirator support (%)</td>
<td>0</td>
<td>3 (9.0)</td>
<td>0</td>
</tr>
<tr>
<td>ICU admission (%)</td>
<td>0</td>
<td>3 (9.0)</td>
<td>0</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>0</td>
<td>1 (3.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4  Accordance rate (%) with each item of the guideline criteria in patients with the three etiological agents of community-acquired pneumonia.

<table>
<thead>
<tr>
<th></th>
<th>C. pneumoniae</th>
<th>M. pneumoniae</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pure (n = 53)</td>
<td>Mixed (n = 33)</td>
<td>Pure (n = 86)</td>
</tr>
<tr>
<td>1. Age &lt; 60 years</td>
<td>60.3</td>
<td>27.2</td>
<td>83.7</td>
</tr>
<tr>
<td>2. No underlying disease</td>
<td>64.1</td>
<td>45.4</td>
<td>84.8</td>
</tr>
<tr>
<td>3. Pneumonia outbreaks in the family or community</td>
<td>11.3</td>
<td>0</td>
<td>12.7</td>
</tr>
<tr>
<td>4. Paroxysmal cough</td>
<td>64.1</td>
<td>30.3</td>
<td>75.5</td>
</tr>
<tr>
<td>5. Relatively slow pulse rate in relation to the fever</td>
<td>9.4</td>
<td>6.0</td>
<td>19.7</td>
</tr>
<tr>
<td>6. Absence of abnormal chest examination</td>
<td>79.2</td>
<td>12.1</td>
<td>79.0</td>
</tr>
<tr>
<td>7. WBC count &lt; 10,000/mm³</td>
<td>84.9</td>
<td>39.3</td>
<td>84.8</td>
</tr>
<tr>
<td>8. Ground glass pattern on chest radiograph</td>
<td>39.6</td>
<td>36.3</td>
<td>37.2</td>
</tr>
<tr>
<td>9. No pathogens in Gram's stain or no sputum</td>
<td>86.7</td>
<td>12.1</td>
<td>90.6</td>
</tr>
</tbody>
</table>

Discussion

The JRS started to develop its guidelines in 1998 and published the guidelines for CAP in March 2000. The Japanese guidelines seek to address the management of CAP according to disease severity. Pneumonia is divided at first into three categories: mild to moderately severe pneumonia, severe pneumonia, and pneumonia under special conditions and environments. The special circumstances include eight conditions such as exposure to birds, resulting in psittacosis, and hot spring or circulating bath facility use, resulting in Legionnaire’s disease. Mild to moderately severe pneumonia is further divided under bacterial or atypical causative pathogens using a differential table. The reason for this differentiation is to identify classical atypical pneumonia to treat it with macrolides or tetracyclines and to treat the remainder with β-lactams. In other words, it is our intention to treat S. pneumoniae with β-lactams as much as possible. Our reasons for doing so are based on the fact that S. pneumoniae is highly and frequently resistant to macrolides and tetracyclines in Japan, and that it has a tendency to cause severe or fatal
pneumonia. In cases suspected to be of bacterial origin, the JRS recommends the sputum Gram’s stain or other rapid diagnostic tests such as the urine antigen test. The clinical presentation of community-acquired C. pneumoniae pneumonia has been investigated in several countries. In those studies, the diagnostic criteria for pneumonia caused by C. pneumoniae were a four-fold or greater increase in the titer for any Ig class of antibodies to C. pneumoniae between paired serum samples or an IgG titer of ≥1:512, or the presence of IgM (≥1:16) antibodies for any serum sample examined by the MIF test. In addition, some studies included a high IgA titer as one of the diagnostic criterion of acute C. pneumoniae pneumonia. However, the employment of criteria using the single serum antibody, IgG ≥1:512, is a controversial issue because a high incidence of IgG ≥1:512 has been seen among healthy asymptomatic subjects. Further, the criteria for the definition of IgA levels as indicative of acute infection have not been established. Based on these facts, the Centers for Disease Control and Prevention (CDC, USA) and the Laboratory Centre for Disease Control (LCDC, Canada) made a recommendation for the standardization of C. pneumoniae assays. They recommended that the MIF test remain the only currently acceptable approach and discouraged the use of a single elevated IgG titer for determining acute infection. In this study, therefore, we excluded the IgG titer ≥1:512 and any IgA titer from our diagnostic criteria in accordance with the CDC and LCDC recommendation.

In addition, atypical pathogens have been reported to cause pneumonia frequently in association with other respiratory pathogens, mainly S. pneumoniae. However, it has been suggested that C. pneumoniae may not be the primary cause of the pneumonia but it might disrupt the normal clearance mechanisms, enabling other pathogens to invade. C. pneumoniae has been shown to have a ciliastatic effect on ciliated bronchial epithelial cells in vivo. M. pneumoniae also exerts a toxic effect on the ciliated human epithelium. Further, we observed that the clinical presentation of CAP cases with multiple pathogens and cases in whom C. pneumoniae was the only pathogen identified differed. Therefore, we also believe that mixed cases of mild or asymptomatic upper respiratory tract infections are probably induced by atypical pathogens and are followed by secondary bacterial pneumonia due to another proven etiology. In this study, in order to analyze the clinical picture of pneumonia cases, we divided the C. pneumoniae or M. pneumoniae pneumonia cases into two groups: those in whom C. pneumoniae or M. pneumoniae was the only pathogen identified and those with mixed-C. pneumoniae or pure-M. pneumoniae pneumonia. Our results indicated that C. pneumoniae pneumonia as a single etiological agent is mild to moderate and that the clinical pictures, with the exception of underlying conditions, closely resembled those of M. pneumoniae pneumonia. Our results differed from those of previous reports and we suspected that it might be possible to distinguish between C. pneumoniae or M. pneumoniae and bacterial pneumonia.

<table>
<thead>
<tr>
<th>Clinical symptoms and physical signs</th>
<th>C. pneumoniae Pure</th>
<th>Mixed</th>
<th>M. pneumoniae Pure</th>
<th>Mixed</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 53</td>
<td>32 (60.3)</td>
<td>4 (12.1)</td>
<td>73 (84.8)</td>
<td>2 (16.6)</td>
<td>13 (9.0)</td>
</tr>
<tr>
<td>n = 33</td>
<td>30 (56.6)</td>
<td>3 (9.0)</td>
<td>69 (80.2)</td>
<td>1 (8.3)</td>
<td>4 (2.7)</td>
</tr>
</tbody>
</table>

*Excluding five pneumonia patients with M. pneumoniae.
†Excluding five pneumonia patients with C. pneumoniae.
§S. pneumoniae and/or H. influenzae.
It is well known that differentiation between atypical and bacterial pneumonia is not always possible in the initial diagnosis.\textsuperscript{3,5,23–25} However, the JRS demonstrated that it would be possible to distinguish between \textit{M. pneumoniae} and bacterial pneumonia in preliminary studies using the guideline criteria.\textsuperscript{9} Recently, Ishida et al. evaluated the JRS scoring system to differentiate atypical pneumonia from bacterial pneumonia and they demonstrated that about 81\% of \textit{M. pneumoniae} and 92\% of bacterial pneumonia could be distinguished using the guideline criteria.\textsuperscript{11} In this study, we also assessed the JRS guidelines with regard to whether we could distinguish between atypical pneumonia and bacterial pneumonia and confirmed that about 85\% of pure-\textit{M. pneumoniae} and more than 90\% of bacterial pneumonia could be distinguished using the guideline criteria. Our results were quite consistent with former these results. On the other hand, the accordance rate in patients with pure-\textit{C. pneumoniae} pneumonia was 60\% and lower than that of pure-\textit{M. pneumoniae} pneumonia. The different accordance rates between \textit{C. pneumoniae} and \textit{M. pneumoniae} were based on underlying conditions such as age and underlying diseases (Tables 3, 4). Therefore, we also assessed the guidelines when the patients were under 60 years old and high accordance rates were observed in patients with both atypical pneumonia. However, for 30\% of patients under 60 years old, the guidelines could lead to an inappropriate initial empirical antimicrobial therapy since the suspected atypical pneumonia was, in fact, a bacterial pneumonia. That findings indicated that the guideline criteria should not be used for the differential diagnosis of CAP in patients under 60 years old because of the low specificity.

In both atypical pneumonia, high accordance rates were observed in the fourth (the patient has paroxysmal cough), sixth (the patient has absence of abnormal physical examination of the chest), seventh (WBC count <10,000/mm\textsuperscript{3}), and ninth (no organisms have been detected in the sputum by Gram’s stain or there is no sputum production) criteria parameters. However, regarding the third guideline criteria parameter (an outbreak of pneumonia is currently in the family or community), there have been many reports of outbreaks of \textit{C. pneumoniae} infection in families, schools, military barracks and nursing homes worldwide.\textsuperscript{18} We have also encountered outbreaks of \textit{C. pneumoniae} infection in some schools and families, and have also encountered outbreaks of \textit{M. pneumoniae} infection in families.\textsuperscript{33} But the incidence of pneumonia outbreaks has not been very high. We believe, however, that the occurrence of outbreaks in families or groups is a very important feature of both \textit{C. pneumoniae} and \textit{M. pneumoniae} infection and should be included as a reference. Furthermore, the prevalence rates for a relatively slow pulse rate in relation to the fever reported in association with other intracellular infections such as legionellosis and psittacosis were low in both \textit{C. pneumoniae} and \textit{M. pneumoniae} pneumonia. In addition, the sixth (the patient has absence of abnormal physical examination of the chest) and eighth (chest radiograph shows a ground glass pattern) criteria parameters were subjective factors. Individual medical doctors may differ in their judgment concerning them. It seems, therefore, that some items in the criteria should be excluded or changed to objective factors. However, we did not evaluate other atypical pathogens, such as \textit{Chlamydia psittaci}, \textit{Coxiella burnetti} and \textit{Legionella} species, in this study because their incidence is low and they are not common pathogens in Japan.\textsuperscript{10–13} In the future, we will have to accumulate pneumonia cases caused by these atypical pathogens and analyze the clinical presentation to assess whether some items in the criteria of the JRS guidelines should be excluded or words should be changed.

In conclusion, our results indicated that the differentiation of pneumonia in the JRS guidelines is useful for the diagnosis of \textit{M. pneumoniae} pneumonia as a single etiological agent, but difficult for the diagnosis of \textit{C. pneumoniae} pneumonia. However, JRS scoring system to differentiate atypical pneumonia from bacterial pneumonia may hardly be transferrable to the situation in Western countries.

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References


