The JRS Guidelines for the Management of Community-acquired Pneumonia in Adults: An Update and New Recommendations

Naoyuki Miyashita¹, Toshiharu Matsushima² and Mikio Oka¹

Abstract

Community-acquired pneumonia (CAP) continues to be a major medical problem. Since CAP is a potentially fatal disease, early appropriate antibiotic treatment is vital. Epidemiologic studies have shown that in the combined cause-of-death category, pneumonia ranks fourth as the leading cause of death in Japan. Therefore, the Japanese Respiratory Society (JRS) provided guidelines for the management of CAP in adults in 2000. Because of evolving resistance to antimicrobials and advances in diagnosis, treatment and prevention of CAP, it is felt that an update should be provided every three years so that important developments can be highlighted and pressing questions can be answered. Thus, the guidelines committee updated its guidelines in 2005. The basic policy and main purposes of the JRS guidelines include; 1) prevention of bacterial resistance and 2) effective and long-term use of medical resources. The JRS guidelines have recommended the exclusion of potential and broad spectrum antibiotics, fluoroquinolones and carbapenems, from the list of first-choice drugs for empirical treatment. In addition, the JRS guidelines have recommended short-term usage of antibiotics of an appropriate dose and pathogen-specific treatment using rapid diagnostic methods if possible.

Key words: community-acquired pneumonia, guideline, antimicrobial resistance, rapid diagnostic test, severity, pathogen-specific treatment

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CAP guidelines in several countries

Community-acquired pneumonia (CAP) is a common, but serious respiratory disease. Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death worldwide (fourth as the leading cause of death in Japan), and there continue to be major controversies concerning the antimicrobial management of this infection. Recognizing the clinical importance of CAP, over the past several years, different medical societies, health organizations and individual authors in different countries have proposed specific guidelines for the management of CAP to help physicians make decisions about the management of the individual patient (1-10). Each set of guidelines has its own strengths and weaknesses, but individually they have helped in the organization and codification of our approach to the patient with CAP. More recently, some guidelines have updated their recommendations because of evolving resistance to antimicrobials and advances in diagnosis, treatment and prevention of CAP (11-18). In addition, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) will be publishing joint guidelines for the treatment of CAP.

The JRS guidelines

The Japanese Respiratory Society (JRS) began developing its guidelines in 1998 and provided CAP guidelines in March 2000 (19). After publishing guidelines, the guideline committee performed a nationwide survey of 1,258 patients to assess the treatment of CAP in Japan (20). The results suggested that the JRS guidelines are useful and appropriate and that antimicrobial agents were generally being selected

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Table 1. Summary of Updated and New Recommendations for JRS Guidelines 2005

<table>
<thead>
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<th>Update</th>
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<tr>
<td>Clinical severity assessment</td>
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<td>Initial site of treatment decision</td>
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<td>Clinical differentiation of atypical pneumonia</td>
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<td>Microbiological investigation</td>
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<td>Selection of antimicrobial agents</td>
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<th>New addition</th>
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<tr>
<td>Urinary antigen test (Streptococcus pneumonia &amp; Legionella)</td>
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<tr>
<td>Viral pneumonia (SARS, Influenza, Avian influenza)</td>
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<td>Legionella pneumonia</td>
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<td>Theory of pharmacokinetics/pharmacodynamics</td>
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<td>Pneumonia in elderly persons</td>
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<tr>
<td>Adjuvant and general therapy in addition to antibiotics</td>
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<tr>
<td>(steroid, immunoglobulin, G-CSF, etc.)</td>
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<tr>
<td>Performance indicators</td>
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<tr>
<td>(initial administration time of antibiotics, discharge criteria,</td>
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<td>switching criteria from i.v. to p.o., etc.)</td>
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<tr>
<td>Prevention of pneumonia (Vaccine)</td>
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<td>Aspiration pneumonia</td>
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<td>Advantages and disadvantages of antimicrobial agents</td>
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in accordance with the guidelines. However, the committee identified a number of issues to be addressed in guideline updates including criteria for physiological assessment, the handling of cases in which physical findings and laboratory test results are not in agreement, age-related issues (especially the treatment of patients over the age of 65), the differentiation between bacterial pneumonia and atypical pneumonia, the weighing of underlying diseases and complications, and guidelines regarding the use of adjuvant therapy (20). The committee decided that an update should be provided every three years so that important developments can be highlighted and pressing questions can be answered. Therefore, it has been revising them since December 2003 and updated them in October 2005 (21). The major and important changes have been in the recommendations for severity assessment, the initial site of treatment decision, microbiological investigation including the urinary antigen test, clinical differentiation of atypical pneumonia and antibiotics selection including newer drugs. A summary of the updated and new recommendations in the JRS guidelines is given in Table 1.

Etiology and antimicrobial resistance

During the past five years, many researchers have been carrying out studies on CAP etiologies and antimicrobial resistance in Japan and the number of findings is growing every year. As for epidemiological studies, a multi-center CAP surveillance has been performed in seven medical schools and their affiliate hospitals (Saito A, in preparation). The results of this study together with other prospective studies have demonstrated that Streptococcus pneumoniae and atypical pathogens including the Mycoplasma pneumoniae and Chlamydia pneumoniae are common pathogens (Table 2) (22-25). In addition, a prospective study of CAP etiology has been performed in an ambulatory setting for the first time in Japan (Fig. 1) (25). The results indicated that the incidence of infection caused by two atypical pathogens, M. pneumoniae and C. pneumoniae, was higher among outpatients than among hospitalized patients. A lower incidence of bacteria, especially S. pneumoniae, may be related to the younger age of the patients, a low incidence of comorbidities and the limitations of the tests performed. A multicenter study in an ambulatory setting is necessary.

The etiologic agent which is most clearly differentiated between Japan and Western countries is the frequency of drug-resistant S. pneumoniae (26-28). A recent study found that the frequency of penicillin-resistant and macrolide-resistant S. pneumoniae has been increasing gradually in Japan (26). Furthermore, approximately half of S. pneumoniae cases show strong resistance to macrolides with minimum inhibitory concentrations (MICs) greater than or equal to 256 μg/mL (26, 27). More than 50% of the isolates of macrolide-resistance gene in Japan have been erm B, which generally occurs with higher MIC values than mef A-positive isolates (27). Marked geographical differences in the prevalence of both penicillin- and macrolide-resistance have been observed and the highest rates have been found in Asia (27-31). It has been suggested that the clinical outcome was not associated with macrolide susceptibility because macrolides have other effects in addition to their antimicrobial effect, such as an anti-inflammatory effect, good penetration to sites of infection and concentration of drug in phagocytes. However, clinical failure of initial treat-
Figure 1. Etiology of community-acquired pneumonia in 106 outpatients and 400 hospitalized patients.

Table 2. Etiology of Community-acquired Pneumonia in Three Prospective Studies in Japan

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<tr>
<td><em>S. pneumoniae</em> (%)</td>
<td>26.3</td>
<td>26.0</td>
<td>24.5</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>13.0</td>
<td>7.5</td>
<td>18.5</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>9.3</td>
<td>6.6</td>
<td>5.2</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>6.8</td>
<td>5.8</td>
<td>6.5</td>
</tr>
<tr>
<td><em>Anaerobes</em></td>
<td>5.5</td>
<td>2.8</td>
<td>3.9</td>
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<tr>
<td><em>Moraxella catarrhais</em></td>
<td>3.8</td>
<td>2.2</td>
<td>2.2</td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3.3</td>
<td>2.1</td>
<td>3.4</td>
</tr>
<tr>
<td><em>Virus</em></td>
<td>3.0</td>
<td>1.7</td>
<td>15.9</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>2.0</td>
<td>2.4</td>
<td>1.3</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2.0</td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td><em>Streptococcus milleri group</em></td>
<td>1.8</td>
<td>3.2</td>
<td>2.2</td>
</tr>
<tr>
<td><em>Legionella</em> spp.</td>
<td>1.5</td>
<td>0.6</td>
<td>3.9</td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
<td>1.3</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>0.5</td>
<td>Not done</td>
<td>2.6</td>
</tr>
<tr>
<td>Others</td>
<td>0.8</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>34.5</td>
<td>36.1</td>
<td>26.7</td>
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*Miyanishi et al., references 24 and 25; Ishida et al., references 22 and 23; Saito et al., reference 21.

Physicians often use models of prognosis to quantify the severity of illness and guide the initial site of treatment decision for patients with CAP. The Pneumonia Severity Index (PSI) is based on the findings of the Pneumonia Patient
Outcomes Research Team (PORT) cohort study by Fine et al. (34). They stratified patients into five risk classes according to 20 clinical and laboratory variables, and found a clear correlation between mortality and risk class. The PSI appears to be an excellent predictor of mortality in patients with CAP. Utilization of the PSI for initial risk assessment has been widely endorsed by organizations such as the IDSA and others (12-14). The findings of the Japanese study also support previous results that risk correlates well with the medical outcome (35, 36). Unfortunately, the PSI may not be practical for routine application in busy hospital emergency departments or primary care settings because of its complicated requirement for computation of a score based on 20 variables. Moreover, it is designed for assessing patients with lower risk rather than those with severe CAP.

An alternative severity assessment tool is the “CURB score” proposed by the British Thoracic Society (BTS) and modified by Neill et al (37). This relies on four easily measurable clinical features (confusion, urea, respiratory rate and blood pressure) and was developed mainly as a means of identifying patients with severe CAP at high risk of mortality. This simple severity scoring system correlates well with mortality (38, 39) but it does not identify patients at low risk of mortality who might be suitable for early hospital discharge or home management. Subsequently, Lim et al modified the CURB score and derived from it a new severity assessment tool, the “CURB-65 score”, which includes age ≥ 65 years as a fifth prognostic variable based on the largest cohort study (40). The advantage of the CURB-65 score is that it provides a bigger range of sensitivities for specificity, thus enabling patients to be stratified as possibly suitable for three different management options in low, intermediate and high mortality risk groups. The 2004 update of the BTS CAP guidelines states that patients with a CURB-65 score < 2 may be suitable for outpatient treatment (16). Recently, these three validated prognostic rules (PSI, CURB and CURB-65) were compared in predicting 30-day mortality in a large cohort study (41). The results showed that the more complex PSI has a higher discriminatory power for short-term mortality, defines a greater proportion of patients at low risk, and is slightly more accurate in identifying patients at low risk than either CURB score.

For the assessment of CAP severity, the JRS guidelines recommend the use of two criteria, physiological and radiological examinations which include five clinical features (radiological spread, temperature, pulse rate, respiratory rate and dehydration) and laboratory data which include three clinical features (WBC count, C-reactive protein value and PaO₂ or SpO₂ value) (19). In addition, the guidelines recommend that prediction be determined to be more severe for patients who are <65 years old or have serious underlying diseases and that patients with a serious condition (cyanosis, shock, systolic pressure > 90 mmHg or diastolic pressure > 60 mmHg) are to be judged as severe CAP. Some studies have found a clear correlation between mortality and CAP severity, but many studies have identified a number of issues, including the criteria for physiological assessment, handling of cases in which physiological and radiological findings and laboratory test results are not in agreement,
Update on differential diagnosis between atypical pneumonia and bacterial pneumonia

One feature of the Japanese CAP guidelines is a trial to be carried out to differentiate between atypical pneumonia and bacterial pneumonia. In Japan, *M. pneumoniae* has been the third leading pathogen of CAP, but it is becoming the second leading pathogen, and its incidence is gradually increasing. We have been diagnosing and treating *M. pneumoniae* pneumonia based on many clinical features (44). The clinical presentation of *C. pneumoniae* pneumonia as a single etiologic agent also resembles that of patients with *M. pneumoniae* pneumonia (44, 45). In addition, the JRS recommends the restriction of quinolone usage as the empirical first-choice drug, with the exclusion of selected patients, 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 has proposed a differential diagnosis for bacterial pneumonia and atypical pneumonia (*M. pneumoniae* and *C. pneumoniae*) for the selection of an appropriate antibiotic for the management of mild-to-moderate pneumonia (19). The guidelines have set up nine parameters and criteria based on clinical symptoms, physical signs and laboratory data. Using this differential table, we were able to distinguish approximately 85% of *M. pneumoniae* and more than 90% of bacterial pneumonia (46).

The guidelines are for general practitioners and non-specialized doctors, and were selected to allow easy differentiation of CAP in an outpatient setting without special examinations. The data obtained from three prospective studies of CAP (total of 1,880 patients) (23, 46-48) were analyzed and we extracted six items from frequently observed background factors, clinical symptoms and laboratory findings of patients with atypical pneumonia, as shown in Table 3 (21). Multiple regression analysis showed all items of the criteria to be valid except for “age” in patients with *C. pneumoniae* pneumonia. The sensitivity and specificity rates for atypical pneumonia were 77.0% and 93.0%, respectively, based on four or more items of the criteria (21). Fig. 3 shows the accordance rate with each parameter in the present patients with CAP.

This differentiation is necessary to identify cases of classical atypical pneumonia which should be treated with macrolides or tetracyclines. The remainder should receive β-lactams as often as possible. It is our intention, in other words, to treat *S. pneumoniae* with β-lactams. Our reasons for doing so are based on the fact that 1) *S. pneumoniae* is highly and frequently resistant to macrolides and tetracyclines in Japan, and 2) *S. pneumoniae* has a tendency to...
cause severe or fatal pneumonia. However, in the elderly and in patients with underlying diseases, the differential diagnosis may be difficult, or a mixed infection may be latent. Therefore, in this patient group, it is necessary to consider administering, from the beginning, a β-lactam drug plus a macrolide or tetracycline, or only fluoroquinolone to cover bacterial and atypical pneumonia.

**Update on microbiological investigations**

The JRS guidelines recommend pathogen-oriented treatment as the initial appropriate therapy in cases in which an etiologic diagnosis is established or strongly suspected. Therefore, the use of rapid diagnostic tests, such as sputum Gram staining, before antibiotic treatment is recommended. From our experience, we consider sputum Gram staining to be a highly specific test and a useful tool in the early presumptive diagnosis of CAP caused by some pathogens, and especially S. pneumoniae. However, the usefulness of the sputum Gram stain and culture is controversial (11, 49-51) for the following reasons: 1) a good-quality sputum sample cannot be obtained from >50% of patients with CAP, 2) sensitivity and specificity vary substantially with different observers and settings (interpretation is observer-dependent), 3) a positive result for pneumococcus is poorly predictive of the ability to recover the organism from sputum or a blood culture, 4) their use is of no value in the management of non-severe CAP and in primary-care hospitals without microbiologic laboratory facilities. Therefore, the guidelines recommend the expectorated sputum Gram stain and culture only for inpatients. In 2005, the pneumococcal urinary antigen test (Binax NOW, Binax, Portland, ME, USA) became available as a rapid diagnostic method for adults in Japan. This assay is an immunochromatographic membrane test used to detect cell wall polysaccharide and the results are unaffected by the previous use of antibiotics. It has the potential advantages of rapidity (within 15 min) and simplicity compared to those for sputum Gram stain. Several studies have shown that the urinary antigen test is a highly sensitive and specific tool for the early diagnosis of pneumococcal pneumonia, particularly for patients for whom the results of sputum Gram staining are unavailable and for those with high-risk pneumonia (52-58). Japanese studies also have demonstrated that the urinary antigen test has a high sensitivity ranging from 72% to 76% and a high specificity of 94% for the diagnosis of pneumococcal pneumonia (47, 59-61). Thus, the JRS guidelines recommend the use of this assay for both inpatients and outpatients. Another urinary antigen test which detects the Legionella spp. is also available and is described below.

The overall sensitivity of blood culture in CAP is particularly low for patients with non-severe CAP and no comorbid diseases and for those who have received antibiotic treatment before admission (49, 62-64). The blood culture is recommended for severe pneumonia. A rapid antigen detection assay for influenza virus is also recommended for rapid detection of this pathogen for epidemiologic purposes and/or treatment (65-67). This assay can provide a diagnosis in 15-20 min, but test performance varies with the specific test used, sample type, duration of illness and patient age. Sensitivity is approximately 50%-70% in adults, therefore negative results do not completely exclude the diagnosis.

**Advances and new additions**

There have been many important developments in the past five years. The most important topics worldwide and especially in Asia area have been the emergence of the severe acute respiratory syndrome (SARS) coronavirus and the avian influenza A (H5N1) epidemics (68-74). Fortunately, there has been no occurrence of human infections in Japan and no epidemic period of SARS (Phase 0) was observed worldwide after the end of outbreaks in July 2003. However, an epidemic of avian influenza A (H5N1) was observed in early 2004 in Japan. At that time, avian influenza A (H5N1) virus infections in humans occurred in Southeast Asia, such as in Viet Nam and Thailand, and its geographic distribution is expanding to Cambodia, Indonesia, China, Turkey and Iraq. It has led to the deaths of more than 50 people in these areas and poses an increasing fresh human influenza pandemic threat. Local and nationwide recommendations for the prevention and clinical management of these new pathogens are being made and updated (75, 76).

Legionella pneumophila, which ranks as a first or second pathogen, is sufficiently severe to require admission to an ICU (77). The epidemiologic risk factors include recent travel with an overnight stay outside of the home, recent changes in domestic plumbing, renal or hepatic failure, diabetes and systemic malignancy. In Japan, hot spring bathing and bathing in a circulating bath are considered the most important environmental risk factors (78, 79) and many outbreaks of Legionnaires’ disease at hot springs have been reported (80-82). However, the importance of Legionnaires’ disease has not been recognized in Japan because of the lack of rapid and sensitive laboratory diagnostic tests. Currently, there are two commercially available tests in Japan, the Biotest Legionella urine antigen EIA (Biotest AG, Dreich, Germany, available from 2003) and the Binax NOW Legionella urinary antigen immunochromatographic test (Binax, Portland, ME, USA, available from 2004), for the detection of the L. pneumophila antigen in urine (83-88). This assay is now an established and valuable tool for the diagnosis of Legionnaires’ disease, particularly in regions where L. pneumophila serogroup 1 is the most common cause of the disease. The most important feature of this assay appears to be its > 99% specificity, which is a requirement when testing for a relatively rare disease (88). Furthermore, a moderate-to-high sensitivity for L. pneumophila infections has been demonstrated, ranging from 56 to 99% (88). The severity appears to be associated with the clinical severity of the disease, with high sensitivity in severe disease and low sensitivity in mild disease (89-91). This assay provides for...
an early diagnosis and the initiation of appropriate antibiotic therapy resulting in improved outcomes in both mortality and satisfying the need for intensive care. Therefore, the Legionella urinary antigen test is recommended for hospitalized CAP patients. Other new additions have been made in the separate sections listed in Table 1.

### Treatment algorithm and recommendations for antimicrobial therapy

The JRS guidelines seek to address the management of CAP according to disease severity; Fig. 4 illustrates the classification.

As mentioned above, the JRS guidelines propose a differential diagnosis for bacterial pneumonia and atypical pneumonia using a scoring system in the empirical antibacterial selection for CAP. Penicillins with or without a beta-lactamase inhibitor, or cephalosporins, are consider appropriate empirical therapy for suspected bacterial pneumonia. If atypical pneumonia is suspected, then the guidelines recommend the use of macrolides or tetracyclines. The basic selection of these antibiotics is acceptable for patients who have no co-morbid diseases or are younger. Therefore, we also added options for the selection of other antibiotics when patients have co-morbid diseases, are more than 65 years old or have used antibiotics recently.

In severe CAP patients who need ICU admission, the JRS guidelines propose combination therapy with new quinolones, tetracyclines or macrolides plus carbapenems, 3rd or 4th generation cephems plus clindamycin, monobactam plus clindamycin or glycopeptide plus aminoglycoside.

In addition to empiric therapy, the guidelines include pathogen-specific therapy with recommendations for antimicrobial selection when S. pneumoniae, Haemophilus influenzae, klebsiella spp., Staphylococcus aureus, Moraxella catarrhalis, Streptococcus spp., Pseudomonas aeruginosa, An aerobe and Legionella are detected by microbiological laboratory tests. Furthermore, the guidelines include nine special conditions and environments such as exposure to birds, resulting in psittacosis, and hot spring or circulating bath facility use, resulting in Legionnaire’s disease. Information about the selection of newer antibiotics such as telithromycin, moxifloxacin and doripenem is also included.

### Conclusions

The JRS updated the CAP guidelines in 2005 based on new evidence. The basic policy and main purposes of the JRS guidelines are the prevention of bacterial resistance and effective and long-term use of medical resources. The JRS guidelines recommend the exclusion of potential and broad spectrum antibiotics, fluoroquinolones and carbapenems, from among first-choice drugs for empirical treatment. The JRS guidelines also recommend the short-term usage of antibiotics of an appropriate dose and pathogen-specific treatment using rapid diagnostic methods when possible.

The JRS CAP Guideline Committee gratefully acknowledges Professor Lionel A. Mandell (McMaster University, Canada) for his excellent advice in preparing the update of the guidelines. The meeting of CAP guidelines with JRS guideline members and Professor Mandell was held in Washington D.C. on October 31, 2004.

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