Guiding principles for treating *Mycoplasma pneumoniae* pneumonia

the Japanese Society of Mycoplasmology

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* The following recommendations are based on experts' opinions, and therefore, designated as 'Guiding principles' instead of 'Guidelines'.

Recommendations for the diagnosis and treatment of *Mycoplasma pneumoniae* pneumonia in children (≤ 15 years of age)

These recommendations are based on the Guidelines for the Diagnosis and Treatment of *Mycoplasma pneumoniae* Pneumonia in Children: A Supplement to the Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2011 (February 19, 2013) by Japan Pediatric Society (http://www.jpeds.or.jp/uploads/files/saisin_130219_2.pdf).

Executive Summary

1. It is preferable to use gene amplification methods to detect mycoplasmal DNA such as the loop-mediate isothermal amplification (LAMP) assay or the quenching probe polymerase chain reaction (Q-probe PCR) test or immunochromatography tests to detect mycoplasmal antigens to confirm the acute phase diagnosis of *M. pneumoniae* pneumonia.
2. Macrolides are recommended as the first-line drug of choice for the treatment of *M. pneumoniae* pneumonia.
3. The efficacy of macrolides may be assessed with a relatively high accuracy by the presence or absence of defervescence within 48-72 hours after initiation of macrolide treatment.
4. The use of tosufloxacin or tetracyclines may be considered for patients with pneumonia who do not respond to macrolides, when necessary. However, tetracyclines are a relative contraindication for use in children younger than 8 years of age.
5. The duration of antimicrobial treatment should be the length recommended for each drug.
6. Systemic administration of corticosteroids may be considered for patients with serious pneumonia, although it should be reserved for patients who do not respond to appropriate antimicrobial treatment.

Descriptions

#1. Since it is often difficult to make a diagnosis of *M. pneumoniae* pneumonia infection during the acute phase only on the basis of antibody titers in a single serum sample collected at onset of illness, it is preferable to use gene amplification methods to detect mycoplasmal DNA such as the loop-mediate isothermal amplification (LAMP) assay or the quenching probe polymerase chain reaction (Q-probe PCR) test or immunochromatography tests to detect mycoplasmal antigens to confirm the acute phase diagnosis of *M. pneumoniae* pneumonia.

A confirmatory diagnosis of *M. pneumoniae* pneumonia may be made by antibody titer analysis and detection of causative organisms (e.g., isolation and culture or DNA amplification). The most accurate and practical method of making a diagnosis of acute phase *M. pneumoniae* infection in the clinical setting is the LAMP test which is performed to detect mycoplasmal DNA [1)]. The LAMP test is performed using either throat swabs (including nasopharyngeal swabs) or sputum samples. In addition, the Q-probe PCR test is currently available in Japan, being covered by the national health insurance. In serological examinations using particle agglutination and complement fixation methods, a single positive antibody titer in an acute phase serum sample does not always indicate acute *M. pneumoniae* infection. A confirmatory diagnosis of *M. pneumoniae* pneumonia should be made on the basis of the difference in titer between paired samples obtained during the acute and convalescent phases. A positive IgM test in the acute phase serum sample is important because IgM develops early after primary infection. The ImmunoCard Mycoplasma, a rapid enzyme immunoassay for the detection of IgM to *M. pneumoniae*, is useful in the diagnosis of *M pneumoniae* infection, but physicians should be aware of the fact that the test may be positive for a relatively long period of time after infection and patients with a history of *M. pneumoniae* infection may show positive results.

#2. Macrolides are recommended as the first-line drug of choice for the treatment of *M. pneumoniae* pneumonia.

The minimal inhibitory concentrations (MICs) of macrolides against macrolide-sensitive *M. pneumoniae* are quite low [2-4], and the pathogen is completely eradicated from the airways at the end of treatment [5, 6]. On the other hand, the MICs of tosufloxacin and tetracyclines against *M. pneumoniae* are relatively high, and in some patients infection may persist in the airways, and be disseminated after treatment [7]. Accordingly, macrolides should be used as the first-line treatment for macrolide-sensitive *M. pneumoniae* infection (Table 1). The prevalence of macrolide resistance of *M. pneumoniae* varies at different areas and times. The prevalence of macrolide-resistant *M. pneumoniae* is more than 90% among patients who have been treated with macrolides and do not show symptomatic improvement, and is 50% or less among patients with no history of macrolide treatment. Macrolide treatment is recommended for patients who have not received macrolides. The use of tosufloxacin or tetracyclines as the first-line treatment should be avoided whenever possible.

Table 1. Recommended treatments for pediatric patients of *M. pneumoniae* pneumonia

Drug	Route of administration	Drug dose (mg/kg/day)	Divided dose/day	Treatment period (days)
Erythromycin	Oral	25–50	4–6	14
Clarithromycin	Oral	10–15	2–3	10
Azithromycin	Oral	10	1	3
Tosufloxacin	Oral	12	2	7 –14
Minocycline	Oral or intravenous drip infusion	2 - 4	2	7 –14

#3. The efficacy of macrolides may be assessed with a relatively high accuracy by the presence or absence of defervescence within 48-72 hours after initiation of macrolide treatment.

Within the first 48 hours of macrolide treatment, fever disappears in more than 80% patients with pneumonia due to macrolide-sensitive *M. pneumoniae*, while it remains in about 70% of patients with pneumonia due to macrolide-resistant *M. pneumoniae* [8]. Accordingly, the efficacy of macrolide treatment may be assessed by the presence or absence of defervescence within the first few days after initiation of macrolide treatment. However, since *M. pneumoniae* infection tends to disappear spontaneously, defervescence may be noted in some patients with pneumonia due to macrolide-resistant *M. pneumoniae* within the first few days of treatment with macrolides that are not effective against the causative organism [8]. On the other hand, some patients with pneumonia due to macrolide-sensitive *M. pneumoniae* have persistent fever for several days after initiation of treatment with macrolides that are effective against the causative organism. In order to clarify whether the causative organism is sensitive or resistant to macrolides in such patients, the causative organism should be obtained through isolation and culture, and tested for drug susceptibility or for a point mutation in 23S ribosomal RNA domain V. When fever persists, physicians should also look for other causes of pneumonia such as *Streptococcus pneumoniae* and viruses.

#4. The use of tosufloxacin* or tetracyclines may be considered for patients with pneumonia who do not respond to macrolides, when necessary. However, tetracyclines are a relative contraindication for use in children younger than 8 years of age.

Among the currently available antimicrobial agents indicated for children, those likely to be effective in the treatment of pneumonia due to macrolide-resistant *M pneumoniae* are tosufloxacin and tetracyclines (e.g. minocycline, Table 1). Tosufloxacin fine granules for pediatric use are the only fluoroquinolone that is indicated for the treatment of pneumonia in children in Japan.

Tetracyclines are a relative contraindication for use in children younger than 8 years of age since they may cause adverse drug reactions such as transient bone development retardation, tooth discoloration and enamel hypoplasia [9]. When the use of antimicrobial agents other than macrolides is considered necessary for the treatment of *M. pneumoniae* pneumonia in this age group, tosufloxacin should be used*. Physicians should use fluoroquinolones in the treatment of *M. pneumoniae* infection in children appropriately on the basis of the recommendations for the treatment of pneumonia in the Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2011 in order to prevent the development of quinolone-resistant strains.

There is insufficient evidence that clindamycin is effective in the treatment of *M. pneumoniae* infection, and the use of clindamycin is not recommended in Japan and other countries. Since macrolide-resistant *M. pneumoniae* is highly resistant to clindamycin [4], this drug should not be used for the treatment of macrolide-resistant *M. pneumoniae* infection.

* Tosufloxacin and other fluoroquinolone agents should not be used routinely for the treatment of *M. pneumoniae* pneumonia. *M. pneumoniae* infections in children often disappear spontaneously [10], and children do not always need antimicrobial treatment. *M. pneumoniae* readily becomes resistant to fluoroquinolones through a single point mutation. Since fluoroquinolones have a broad antimicrobial spectrum, they may promote drug resistance of Gram-negative rods and other nontarget organisms in normal flora of the human body. Quinolone-resistant strains have become a big problem [11], and appropriate use of quinolones especially in children is recommended throughout the world. As fluoroquinolones are inferior to minocycline in terms of reducing macrolide-resistant mycoplasma [12], the use of fluoroquinolones should be limited to patients who need the treatment.

#5. The duration of antimicrobial treatment should be the length recommended for each drug.

The recommended duration of macrolide treatment for patients with pneumonia due to macrolide-sensitive *M. pneumoniae* is 14 days for erythromycin, 10 days for clarithromycin, and 3 days for azithromycin (5 days in Western countries) [5, 6, 9]. It is believed that tosufloxacin and tetracyclines (minocycline) should be given for at least 7-14 days [7, 13-15]. The antimicrobial activities of tosufloxacin and tetracyclines (minocycline) against macrolide-resistant *M. pneumoniae* are similar to those against macrolide-sensitive strains [4]. Children may return to school and kindergarten when major symptoms such as fever and coughing disappear [9].

#6. Systemic administration of corticosteroids may be considered for patients with serious pneumonia, although it should be reserved for patients who do not respond to appropriate antimicrobial treatment.

The pathophysiology of *M. pneumoniae* pneumonia is mainly associated with the host immune reaction. Host immune function may become excessive and lead to serious conditions despite treatment using effective antimicrobial agents. Systemic administration of corticosteroids may be effective in such patients. Systemic administration of corticosteroids is expected to be effective in patients with severe pneumonia with fever lasting for ≥7 days and a lactase dehydrogenase of >480 IU/L [16]. However, further studies should be conducted to establish criteria for systemic corticosteroid treatment and optimal methods of administering corticosteroids. At present, corticosteroids should be given only to patients with serious pneumonia who do not respond to treatment with antimicrobial agents that are effective against the causative organism, and should not be prescribed to patients with no clear diagnosis or those who do not receive appropriate antimicrobial treatment.

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Recommendations for the diagnosis and treatment of *Mycoplasma pneumoniae* pneumonia in adolescents and adults (≥ 16 years of age)

The following recommendations are presented as clinical questions and their answers.

Executive Summary

1. It is preferable to use gene amplification methods to detect mycoplasmal DNA such as the loop-mediate isothermal amplification (LAMP) assay or the quenching probe polymerase chain reaction (Q-probe PCR) test or immunochromatography tests to detect mycoplasmal antigens to confirm the acute phase diagnosis of *M. pneumoniae* pneumonia.
2. Macrolides are recommended as the first-line drug of choice for the treatment of *M. pneumoniae* pneumonia and the recommended treatment period is from 7 to 10 days (except for azithromycin).
3. The efficacy of macrolides can be assessed by the presence or absence of defervescence within 48-72 hours after initiation of the macrolide treatment.
4. Seven-ten days of administration of tetracyclines or fluoroquinolones is recommended for patients with pneumonia who do not respond to macrolides, when necessary.
5. Systemic administration of corticosteroids concomitantly with an appropriate anti-microbial drug may be considered for patients with respiratory failure.

Clinical Questions

#1 What methods are useful for diagnosing *M. pneumoniae* pneumonia in adults?

#2 What is the first-line drug of choice and how long should it be used to treat *M. pneumoniae* pneumonia in adults?

#3 What are the signs of macrolide resistance in *M. pneumoniae* pneumonia?

#4 What is the first-line drug of choice and how long should it be used to treat pneumonia due to macrolide-resistant *M. pneumoniae*?

#5 What is the treatment for patients with serious *M. pneumoniae* pneumonia complicated by respiratory failure?

Descriptions

#1 What methods are useful for diagnosing *M. pneumoniae* pneumonia in adults?

It is preferable to use gene amplification methods to detect mycoplasmal DNA such as the loop-mediate isothermal amplification (LAMP) assay or the quenching probe polymerase chain reaction (Q-probe PCR) test or immunochromatography tests to detect mycoplasmal antigens to confirm the acute phase diagnosis of *M. pneumoniae* pneumonia.

The diagnosis and therapeutic strategy for *M. pneumoniae* pneumonia in adults can fundamentally be made according to the scoring system of the Japanese Respiratory Society guidelines for the management of community-acquired pneumonia (JRS CAP GL) in adults to differentiate between atypical pneumonia and bacterial pneumonia [1)], as well as according to serological and molecular detection methods. Nevertheless, a Cochrane review on 7 clinical investigations has revealed that an accurate diagnosis of *M. pneumoniae* pneumonia is difficult to obtain solely based on signs and symptoms such as coughing, wheezing, fever, and auscultatory findings [2)].

M. pneumoniae pneumonia is usually diagnosed by isolation and culture, titer analysis of specific antibodies, and molecular amplification methods. While isolation of the organism from the respiratory samples can be a definitive diagnosis, this methodology has not been used in a routine clinical practice because it takes a few weeks to obtain a result. Titer analysis of specific antibodies and molecular amplification are acute phase diagnostic methods. Among them, the loop-mediated isothermal amplification (LAMP) is a rapid and simple method that does not require specific devices like PCR. In the clinical setting, the overall agreement between the LAMP method and a culture method has been reported to be as high as 95.6% using oropharyngeal swabs and 98.5% using sputum samples, respectively, and that between the LAMP method and PCR as high as 97.8%. In addition, the Q-probe PCR test is currently approved by the Japanese Ministry of Health, Labour and Welfare and covered by the national health insurance. Accumulation of evidence in adults is warranted.

In addition to those methods, the immunochromatography method (ImmunoCard Mycoplasma) has been used widely as a rapid diagnostic method. This method utilizes serum samples and detects *M. pneumoniae*-specific IgM antibodies, which has disadvantages of false negatives due to the facts that it takes 3-4 days from the formation of pathological features of pneumonia to the development of specific IgM antibodies in blood, and that a sufficient amount of IgM may not be developed in reinfections in adults. The utility of this method as a rapid diagnostic test is also limited due to the fact that a test result may remain positive for a long period of time after infection [3-5)]. Since June 2013, rapid antigen detection kits have been marketed in Japan, which utilize immunochromatographical methodology using an oropharyngeal swab as a sample. While their test sensitivity has been reported as 60-75%, the specificity may reach nearly 100%. Accumulation of evidence in adults is expected.

#2 What is the first-line drug of choice and how long should it be used to treat *M. pneumoniae* pneumonia in adults?

Macrolides are recommended as the first-line drug of choice for the treatment of *M. pneumoniae* pneumonia in adults, and the recommended treatment period is from 7 to 10 days (except for azithromycin).

The frequency of *M. pneumoniae* pneumonia is high in adult CAP; most of the patients are under 40 years of age, and it is seldom seen in elderly patients. While the JRS CAP GL recommends macrolides, tetracyclines, and fluoroquinolones as the treatment modality, the order in which they should be used is not stated.

In vitro drug susceptibility studies of *M. pneumoniae* have shown that the MICs of macrolides against macrolide-sensitive *M. pneumoniae* are quite low, and those of fluoroquinolones and tetracyclines are relatively high when compared with macrolides. The use of macrolides fits the purpose of reducing coughing promptly and thereby preventing the extension of droplet infection. Accordingly, macrolides should be used as the first-line treatment for adult outpatients with macrolide-sensitive *M. pneumoniae* infection, and tetracyclines and fluoroquinolones as the second-line treatment (Table 2).

There has been no clinical investigation to compare the efficacy of tetracyclines with that of fluoroquinolones. On this point, the JRS CAP GL indicates that fluoroquinolones should be avoided for the initial treatment in young patients suspected of having *M. pneumoniae* pneumonia because of the concern surrounding the emergence of quinolone resistance in *Streptococcus pneumoniae* and other respiratory pathogenic bacteria for CAP. Indeed, an *in vitro* experiment proved that fluoroquinolones are capable of inducing resistance against *M. pneumoniae* [6]. Tetracyclines are superior to other antimycoplasmal drugs in view of drug resistance because they have been known not to induce resistance in *M. pneumoniae*. However, there are too few primary physicians who have experience of using tetracyclines and an insufficient number of clinical investigations to support evidence of the efficacy of tetracyclines against *M. pneumoniae*. Respiratory quinolones should be prescribed for a high risk group of elderly patients with pneumonia, because it is postulated that the frequency of *M. pneumoniae* pneumonia is extremely low in the elderly.

Intravenous injection of tetracyclines is recommended as the first-line treatment for hospitalized patients in view of regulation of resistance as mentioned above (Table 3). There is insufficient evidence concerning the appropriate duration of treatment for adults with *M. pneumoniae* pneumonia, and there is no description in the JRS CAP GL concerning the duration of treatment for *M. pneumoniae* infection of adults. On this point, according to the clinical investigation by Miyashita et al. [7], antimycoplasmal drugs were most frequently used for 7 days with a mean of 8 days in adults. Accordingly, it is concluded as the experts' opinion that 7-10 days of administration of antimycoplasmal drugs is recommended.

Table 2. Recommended treatments for adult outpatients of *M. pneumoniae* pneumonia

	Drug	Route of administration	mg/dose	Dose/day
First-line drug	Clarithromycin	Oral	200	2
	Azithromycin (Slow-release formulation)	Oral	2000	1 (1 day)
	Azithromycin	Oral	500	1 (3 days)
	Erythromycin	Oral	200	4 –6
Second-line drug	Minocycline	Oral	100	2
	Levofloxacin	Oral	500	1
	Garenoxacin	Oral	400	1
	Moxifloxacin	Oral	400	1
	Sitafloxacin	Oral	100	2
		Oral	200	1
	Tosufloxacin	Oral	150	2–3

Table 3. Recommended treatments for adult inpatients of *M. pneumoniae* pneumonia

	Drug	Route of administration	mg/dose	Dose/day
First-line drug	Minocycline	Intravenous (drip infusion)	100	2
	Azithromycin	Intravenous (drip infusion)	500	1
	Erythromycin	Intravenous (drip infusion)	300–500	2–3
Second-line drug	Levofloxacin	Intravenous (drip infusion)	500	1
	Ciprofloxacin	Intravenous (drip infusion)	300	2

#3 What are the signs of macrolide resistance in *M. pneumoniae* pneumonia?

> The efficacy of macrolides can be assessed by the presence or absence of defervescence within 48-72 hours after initiation of the macrolide treatment.

Fever in children disappears in more than 80% of patients with pneumonia due to macrolide-sensitive *M. pneumoniae* within the first 48 hours of macrolide treatment, while it remains in about 55-70% of patients with pneumonia due to macrolide-resistant *M. pneumoniae* [8-10]. According to a comparative analysis by Miyashita et al. involving adult patients with macrolide-sensitive and macrolide-resistant *M. pneumoniae* [7], while fever disappears in 71% of patients with pneumonia due to macrolide-sensitive *M. pneumoniae* within the first 48 hours of macrolide treatment, defervescence was observed in only 28% of patients with pneumonia due to macrolide-resistant *M. pneumoniae*. Accordingly, also in adults, the efficacy of macrolide treatment may be assessed by the presence or absence of defervescence within 48-72 hours after initiation of the macrolide treatment because defervescence cannot be achieved, similarly to in children, in 70% of adult patients with macrolide-resistant *M. pneumoniae*.

#4 What is the first-line drug of choice and how long should it be used to treat pneumonia due to macrolide-resistant *M. pneumoniae*?

Seven-ten days of administration of tetracyclines or fluoroquinolones is recommended for patients with pneumonia who do not respond to macrolides, when necessary.

Antimycoplasmal activities of fluoroquinolones and tetracyclines are well retained against macrolide-resistant *M. pneumoniae* according to the previous reports [7, 11-13], of which, the data exclusively on adults are available in only the report by Miyashita et al. [7]. Based on that report, although a simple comparison between adults and children is hampered by the limited number of cases, the drug susceptibility patterns of resistant strains obtained from adults can be considered similar to those of children.

Epidemiological data on children have revealed that the prevalence of macrolide-resistant *M. pneumoniae* is more than 90% among patients who have been treated with macrolides and do not show symptomatic improvement, and it is 50% or less among patients with no history of macrolide treatment. While the epidemiological data of Japan on the drug susceptibility of *M. pneumoniae* against antimycoplasmal drugs suggest an increase in the resistance rate of *M. pneumoniae*, the exact frequency of resistance or risk factors for resistance remain uncertain in adults. It is less likely that the resistance rate in adults is much different from that in children owing to the fact that *M. pneumoniae* infects humans fundamentally by droplet infection through intimate contact. Nevertheless, there have been few reports on adult cases of macrolide-resistant *M. pneumoniae* infection to date when compared with those on pediatric cases [7, 14]. It might be more difficult for macrolide-resistant *M. pneumoniae*, that is more fastidious in growth than sensitive strains, to grow in adults who have superior immunity to children.

Tetracyclines are the first-line, alternative drug of choice for patients with pneumonia due to macrolide-resistant *M. pneumoniae* in terms of both oral and intravenous administration. Studies in children have demonstrated that tetracyclines eradicate macrolide-resistant *M. pneumoniae* faster than fluoroquinolones with a higher rate and fever subsides faster upon treatment with tetracyclines than with fluoroquinolones [9, 10]. Moreover, since tetracyclines do not induce resistance as mentioned before, they are a reasonable alternative in the treatment of macrolide-resistant *M. pneumoniae* infection. On the other hand, since they may induce liver dysfunction in some cases, careful attention must be paid during treatment.

The frequent use of fluoroquinolones may lead to the development of quinolone-resistance in the near future, and in case an epidemic occurs involving dual macrolide- and quinolone-resistant *M. pneumoniae*, no treatment modality is possible for children. It is important to pay special attention to avoid producing quinolone-resistance during the treatment of *M. pneumoniae* pneumonia in adults.

Although no practical studies have explored the appropriate duration of antimicrobial treatment for macrolide-resistant *M. pneumoniae* pneumonia in adults, 7-10 days of administration of antimycoplasmal drugs is recommended as the experts' opinion.

Table 4. Recommended treatments for adult outpatients of macrolide-resistant *M. pneumoniae* pneumonia

	Drug	Route of administration	mg/dose	Dose/day
First-line drug	Minocycline	Oral	100	2
Second-line drug	Levofloxacin	Oral	500	1
	Garenoxacin	Oral	400	1
	Moxifloxacin	Oral	400	1
	Sitafloxacin	Oral	100	2
			200	1
	Tosufloxacin	Oral	150	2–3

Table 5. Recommended treatments for adult inpatients of macrolide-resistant *M. pneumoniae* pneumonia

	Drug	Route of administration	mg/dose	Dose/day
First-line drug	Minocycline	Intravenous (drip infusion)	100	2
Second-line drug	Levofloxacin	Intravenous (drip infusion)	500	1
	Ciprofloxacin	Intravenous (drip infusion)	300	2

#5 What is the treatment for patients with serious *M. pneumoniae* pneumonia complicated by respiratory failure?

Systemic administration of corticosteroids concomitantly with an appropriate anti-microbial drug may be considered for patients with respiratory failure. As a representative regimen, methylprednisolone is administered at 500-1000 mg/day for 3-5 days concomitantly with an appropriate anti-microbial drug.

While the prognosis of *M. pneumoniae* pneumonia in adults is generally favorable, a few patients may develop respiratory failure. Since excessive immune response against *M. pneumoniae* is considered as the main cause of respiratory failure, systemic administration of corticosteroids as anti-inflammatory agents is reasonable for severe cases [15, 16]. Miyashita et al. [15] pointed out, in an analysis of 227 cases of *M. pneumoniae* pneumonia including 13 patients who required mechanical ventilation, that the delay in commencement of appropriate antimycoplasmal drugs was a factor responsible for developing respiratory failure when the patients with respiratory failure were compared with those without respiratory failure, although there has been no prospective study addressing risk factors for devastation. In addition to that, a retrospective review by Izumikawa et al. [16] revealed that the appropriate initial treatment is important in preventing respiratory failure because of the fact that 41 patients out of the 52 patients investigated who had respiratory failure were initially prescribed antimicrobials that are not appropriate for treating *M. pneumoniae* pneumonia. Apart from this, since there have been no studies to explore the relation between macrolide-resistance and devastation such as respiratory failure, investigations on this point are highly expected.

Concerning treatment, Miyashita et al. [15] reported that of the 13 patients with severe or refractory *M. pneumoniae* pneumonia who required mechanical ventilation, nine were successfully treated by high dose corticosteroids combined with anti-mycoplasmal agents. Izumikawa et al. [16] reported that a relatively high dose of methylprednisolone (> 500 mg/day) was effective in 7 out of the 18 adult *M pneumoniae* pneumonia cases with respiratory failure within 5 days of treatment. As the experts' opinion, the combined administration of methylprednisolone (500-1000 mg/day) for 3-5 days with an appropriate use of anti-mycoplasmal drugs is recommended for *M. pneumoniae* pneumonia cases with respiratory failure in adults.

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Conflicts of Interest

Conflicts of interest for each member (at the time of publication of the Japanese version) can be obtained on demand from the Japanese Society of Mycoplasmology (JSM) office.

Addendum

Recent evidence has shown that the macrolide-resistance rate of *M. pneumoniae* has gradually and steadily been decreasing in Japan; from 90% in 2011 to 71% (54% when limited to primary institutes) in 2015 (a nationwide survey, by the courtesy of Drs. Miyuki Morozumi and Satoshi Iwata of Keio University), from 82% in 2012 to 67% in 2013, 60% in 2014 and 42% in 2015 (a nationwide survey, by the courtesy of Dr. Kazunobu Ouchi of Kawasaki Medical School), from 88% in 2012 to 60% in 2013, 56% in 2014 and 54% in 2015 (Kanagawa Prefecture, by the courtesy of Dr. Hitomi Ohya of Kanagawa Prefectural Institute of Public Health), from 67% in 2013 to 73% in 2014 and 42% (13% for primary institutes and 54% for secondary institutes) in 2015 (Osaka Prefecture, by the courtesy of Dr. Chihiro Katsukawa of Osaka Prefectural Institute of Public Health).

These figures were presented in domestic meetings of Japan, and each has not been, and may be, published elsewhere in the English literature. To avoid affecting future publication from each institute, comments on these figures are withheld here.