Macrolide-Resistant *Mycoplasma pneumoniae* Pneumonia in Adolescents and Adults: Clinical Findings, Drug Susceptibility, and Therapeutic Efficacy

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We investigated differences in the clinical findings between 30 patients with macrolide-resistant *Mycoplasma pneumoniae* pneumonia and 43 patients with macrolide-sensitive *M. pneumoniae* pneumonia in adolescents and adults. No differences in clinical presentation were observed between the two groups. Among patients with macrolide-resistant *Mycoplasma pneumoniae* pneumonia, treatment was more effective in the groups that received quinolones and minocycline than in the group that received macrolides ($P = 0.0361$ and $P = 0.0237$, respectively).

Mycoplasma pneumoniae is a major cause of community-acquired pneumonia (CAP) in school-age children and young adults (1, 2). A specific diagnosis of *M. pneumoniae* infection is important because treatment with routinely used β -lactam antibiotics is ineffective against these organisms because they lack a cell wall. Thus, the Japanese Respiratory Society (JRS) CAP guidelines have been recommended as a rapid and simple scoring system based on clinical and laboratory findings for the presumptive diagnosis of *M. pneumoniae* pneumonia (1, 3, 4). Our recent study demonstrated that the JRS scoring system was the most useful tool for initiating the administration of adequate antibiotic therapy for probable *M. pneumoniae* pneumonia among the rapid diagnostic methods tested (5).

Although *M. pneumoniae* pneumonia is usually mild in severity, macrolide-resistant (MR) *M. pneumoniae* with mutations in the 23S rRNA gene has emerged in pediatric patients with CAP (6, 7). More than 60% of *M. pneumoniae* strains in pediatric patients showed high resistance to 14- and 15-membered ring macrolides with a MIC of ≥ 64 mg/liter (8–10). The clinical and bacteriological efficacy of macrolides for treating cases of MR *M. pneumoniae* pneumonia was lower than that in cases of macrolide-sensitive (MS) *M. pneumoniae* pneumonia in pediatric patients (9–13). In contrast to pediatric patients, the available data on MR *M. pneumoniae* infection in adolescent and adult patients are limited (8, 14). The purpose of the present study was to identify a means of rapidly distinguishing MR *M. pneumoniae* pneumonia from MS *M. pneumoniae* pneumonia in daily clinical practice without waiting for genetic analysis results. We compared the underlying conditions, pneumonia severity, clinical symptoms, laboratory data, prognostic factors, and radiographic findings between patients with MR *M. pneumoniae* pneumonia and those with MS *M. pneumoniae* pneumonia (MR patients and MS patients, respectively) in adolescents and adults. Based on the clinical presentation, we evaluated the usefulness of rapid and simple clinical diagnostic methods (5), the JRS scoring system (1, 3, 4), and high-resolution computed tomography (HRCT) (15, 16) for the early presumptive diagnosis of *M. pneumoniae* pneumonia. An additional purpose of this study was to investigate the drug susceptibility of MR isolates and differences in therapeutic efficacy against MR *M. pneumoniae* among macrolides, quinolones, and minocycline.

Adolescent and adult patients with CAP who visited 12 insti-

tutions participating in the Atypical Pathogen Study Group from January 2008 to September 2012 were enrolled in this study. 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 caused by preexisting or other known causes. Exclusion criteria included the following: immunosuppressive illness (i.e., HIV positivity, neutropenia secondary to chemotherapy, use of >20 mg/day prednisone or other immunosuppressive agents, and history of organ transplant), hospitalization in the preceding 30 days, residence in a nursing home or extended care facility, and active tuberculosis. All cases of pneumonia occurring more than 3 days after hospitalization were considered nosocomial and were excluded. During the study period, 844 CAP cases were assessed using culture and PCR for *M. pneumoniae*. Finally, we enrolled and analyzed 73 cases of *M. pneumoniae* infection who were positive for *M. pneumoniae* in culture and/or by the PCR method. Of these, all cases were PCR positive and 29 cases were culture positive. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee at Kawasaki Medical School.

We used a standardized questionnaire for collecting clinical information. Information on patient background and clinical signs and symptoms collected included cough, sputum production, sore throat, dyspnea, chest pain, headache, nausea, and vomiting. Blood tests for peripheral white blood cell count, C-reactive protein, and oxygen partial pressure of arterial blood and chest X-ray were performed at the first visit. The severity of pneumonia was assessed by the use of a clinical severity scale, the Pneumonia Severity Index (PSI), published by the Infectious Diseases Society of America, which was calculated from data regarding age, com-

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plications, physical examination findings, and laboratory data (17).

Microbiological tests, culture, real-time PCR, and serological tests were performed as described previously (2, 4, 5). Cultivation of *M. pneumoniae* was carried out with pleuropneumonia-like organism (PPLO) broth (Difco, Detroit, MI, USA). Sputum samples or nasopharyngeal swab specimens were cultured using 2 ml of PPLO broth for 4 weeks at 37°C. In PPLO broth where the color had changed from red to yellow with glucose consumption, *M. pneumoniae* colonies were purified using a PPLO agar plate. *M. pneumoniae* finally was identified by hemadsorption of colonies with a 5% suspension of guinea pig erythrocytes. DNA then was extracted by using a QIAamp DNA minikit (Qiagen K. K., Tokyo, Japan) in accordance with the manufacturer's instructions. *M. pneumoniae* DNA was detected by real-time PCR targeting a conserved part of the gene coding for the P1 adhesin. Antibodies to *M. pneumoniae* were measured using a particle agglutination test (Serodia-Myco II kit; Fujirebio, Tokyo, Japan). The microbial etiology was classified as definitive, presumptive, or unknown as reported previously (5).

A search for mutations at positions 2063, 2064, and 2617 in the *M. pneumoniae* 23S rRNA domain V gene region was performed using a direct sequencing method in samples with a positive culture or PCR result, as reported previously (7–9). The MICs of 11 antimicrobial agents for the *M. pneumoniae* isolates were determined by microdilution methods (18). Reference strain FH was used as a drug-susceptible control. The antimicrobial agents used for MIC determination were as follows: erythromycin, clarithromycin, azithromycin, rokitamycin, clindamycin, minocycline, tetracycline, tosufloxacin, garenoxacin, levofloxacin, and moxifloxacin. The MICs against *M. pneumoniae* isolates collected in this study were compared with those against MR isolates from pediatric patients that were collected in another study (9).

HRCT examinations were performed as reported previously (15). Three chest radiologists (18, 14, and 12 years of experience, respectively), who were blinded to the diagnoses, retrospectively and independently assessed the presence of consolidation, ground-glass attenuation, centrilobular nodules, thickening of the bronchial wall, reticular or linear opacity, pleural effusion, and lymphadenopathy (15). The final decisions for the presence of each finding and the opacity pattern for each case were reached by consensus among the three radiologists. We analyzed the patients whose CT images were obtained before treatment with antibiotics because antibiotics could influence CT findings. Finally, we analyzed chest HRCT findings in 36 MS patients and 25 MR patients.

The therapeutic efficacy of antibiotics against MS and MR *M. pneumoniae* pneumonia was evaluated among macrolides (clarithromycin and azithromycin), minocycline, and quinolones (garenoxacin, levofloxacin, tosufloxacin, and moxifloxacin). The primary antibiotic selection was made by the attending physician. All 20 admitted patients were administered minocycline at 200 mg/day intravenously. One patient with severe CAP was administered β -lactam plus minocycline, and the remaining 53 patients were administered macrolides or quinolones orally. The dosages of azithromycin, garenoxacin, levofloxacin, and moxifloxacin were 500 mg, 400 mg, 500 mg, and 400 mg once daily, respectively, and clarithromycin and tosufloxacin were administered twice daily at doses of 400 mg and 600 mg, respectively, in accordance with the package insert accompanying each drug. If clinical symptoms and signs had not improved by the second visit, antibiotic

TABLE 1 Underlying conditions and clinical findings in patients with MS and MR *M. pneumoniae* pneumonia at the first examination

Variable	MS patients	MR patients	P value
No. of patients	43	30	
Mean age (range), yr	23.1 (16–45)	21.9 (16–42)	0.1011
No. of males/females	23/20	15/15	0.8150
No. (%) of patients with comorbid illnesses	7 (16)	5 (16)	>0.9999
No. (%) of patients in Pneumonia Severity Index risk classes			
I to III	32 (74)	25 (83)	0.4053
IV	10 (23)	5 (17)	>0.9999
V	1 (2)	0	>0.9999
No. (%) of patients hospitalized	13 (30)	7 (23)	0.5997
No. (%) of patients with clinical symptoms			
Cough	43 (100)	29 (96)	0.4110
Sputum production	25 (58)	15 (50)	0.6332
Sore throat	12 (28)	6 (20)	0.5830
Dyspnea	6 (14)	2 (6)	0.4577
Chest pain	5 (11)	1 (3)	0.3903
Headache	12 (28)	6 (20)	0.5830
Nausea and/or vomiting	3 (7)	1 (3)	0.6391
Laboratory findings			
White blood cell count, mean (no./ μ l)	6,650	6,840	0.2111
C-reactive protein, mean (mg/dl)	3.5	3.2	0.3298
No. (%) of PaO ₂ values of <60 torr	5 (11)	1 (3)	0.3903
No. (%) of patients requiring respiratory support	1 (2)	0	>0.9999
No. (%) of patients requiring ICU admission	1 (2)	0	>0.9999
No. (%) of deaths, <30 days	0	0	>0.9999

treatment was changed by the attending pediatrician to minocycline or quinolones.

One of the criteria for evaluating the clinical outcome in CAP patients is defervescence (1). In this study, we assessed the clinical outcome using fever because previous studies also assessed only febrile days to evaluate the clinical outcome in MR patients (9–13). In addition, we evaluated the therapeutic efficacy of antibiotic treatment at 48 h because previous reports demonstrated that the mean numbers of febrile days in MS patients during macrolide administration were 1.4 and 1.5 days (11, 12).

Statistical analysis was performed using Stat View version 5.0 (SAS Institute Inc., Cary, NC, USA). The incidences of underlying conditions, clinical findings, and radiographic findings were analyzed using Fisher's exact test. Mean age of patients and laboratory data were compared using Student's *t* test. For each radiological finding, kappa values were calculated between the readers.

Thirty of 73 patients (41%) with *M. pneumoniae* pneumonia were found to be infected with MR *M. pneumoniae*. Among these 30 MR patients, 27 had an A-to-G transition at position 2063 in domain V on the 23S rRNA gene (A2063G) and three had an A-to-G transition at position 2064 (A2064G). No mutations at site 2617 in domain V of the 23S rRNA gene were observed.

Underlying conditions, pneumonia severity, clinical symptoms, laboratory data, and prognostic factors of MR patients and MS patients are presented in Table 1. No significant differences were observed between MR patients and MS patients. Using the JRS scoring system, which is a rapid clinical diagnostic method for presumptive diagnosis of *M. pneumoniae* pneumonia, the diagnostic sensitivity was 80% in MR patients and 81% in MS patients.

TABLE 2 Chest CT findings of patients with MS and MR *M. pneumoniae* pneumonia at the first examination

Finding	No. (%) of patients with finding		P value
	MS patients (n = 36)	MR patients (n = 25)	
Consolidation	22 (61)	13 (52)	0.6001
Ground-glass attenuation	25 (69)	15 (60)	0.5847
Centrilobular nodules	28 (78)	21 (84)	0.7454
Bronchial wall thickening	28 (78)	21 (84)	0.7454
Reticular or linear opacity	9 (25)	4 (16)	0.5300
Pleural effusion	5 (14)	2 (8)	0.6895
Lymphadenopathy	7 (19)	3 (12)	0.5047

Chest HRCT findings for MS patients and MR patients are listed in Table 2. The kappa value between the readers was 0.624 for consolidation, 0.581 for ground-glass attenuation, 0.771 for centrilobular nodules, 0.572 for thickening of the bronchial wall, 0.591 for reticular or linear opacity, 0.8901 for pleural effusion, and 0.632 for lymphadenopathy. Of the 25 MR patients, bronchial wall thickening and centrilobular nodules were observed most frequently (84% each), followed by ground-glass attenuation (60%), and air-space consolidation (52%). Reticular or linear opacities, pleural effusion, and lymphadenopathy were also observed, but at low frequencies. No significant differences were observed between MS patients and MR patients. When we judged *M. pneumoniae* pneumonia as showing radiographic features with the combination of bronchial wall thickening and centrilobular nodules and/or ground-glass attenuation with lobular distribution (15, 16), the diagnostically significant findings for suspecting *M. pneumoniae* pneumonia were found in 69% of MS patients and 70% of MR patients.

Among the 13 isolates of MR *M. pneumoniae*, the MIC₉₀ values for 14- and 15-membered macrolides, such as erythromycin, clarithromycin, and azithromycin, were >128 µg/ml, >128 µg/ml, and 128 µg/ml, respectively; MIC values in the MS reference strain were 0.0039 µg/ml, 0.002 µg/ml, and 0.00025 µg/ml, respectively (Table 3). Conversely, tetracycline, minocycline, and all four quinolones showed good antimycoplasmal activity, with MIC₉₀ values of 0.5 µg/ml, 2.0 µg/ml, and 0.5 to 0.0625 µg/ml, respec-

tively, against MR *M. pneumoniae* isolates, which were equal to those for the MS reference strain. No differences in the drug susceptibilities of MR *M. pneumoniae* isolates were observed between pediatric patients and adolescent and adult patients.

The therapeutic efficacy of anti-*M. pneumoniae* antibiotics against MS and MR *M. pneumoniae* is shown in Table 4. All enrolled patients had fever higher than 38°C at baseline. Among MS patients, macrolides (8 patients on azithromycin and 6 patients on clarithromycin), quinolones (7 patients on garenoxacin, 3 patients on levofloxacin, 4 patients on tosufloxacin, and 2 patients on moxifloxacin), and minocycline showed good clinical efficacy, with defervescence within 48 h after initiation of antibiotics observed in 71%, 81%, and 91% of patients, respectively (no statistically significant difference between the three groups). Among MR patients, defervescence within 48 h after initiation of antibiotics was observed in 28% of patients in the macrolide group (7 patients on azithromycin and 7 patients on clarithromycin), 77% of the quinolone group (3 patients on garenoxacin, 3 patients on tosufloxacin, and 3 patients on levofloxacin), and 85% of the minocycline group. Treatment was more effective in the quinolone and minocycline groups than in the macrolide groups ($P = 0.0361$ and $P = 0.0237$, respectively). Among 14 MR patients who received macrolide antibiotics (7 patients on azithromycin and 7 patients on clarithromycin), treatment was changed to other antimycoplasmal antibiotics in 10 patients (6 patients to minocycline, 3 patients to garenoxacin, and 1 patient to moxifloxacin), but no antibiotic changes were recorded for patients in the quinolone and minocycline groups.

The clinical presentation, such as underlying conditions, pneumonia severity, clinical symptoms, laboratory data, prognostic factors, and radiographic findings, of *M. pneumoniae* pneumonia is clearly differentiated from that of nonatypical pneumonia (1–5, 15, 16). Thus, the JRS guidelines are on trial to differentiate between *M. pneumoniae* pneumonia and nonatypical pneumonia using a unique and simple scoring system (1). In this study, we investigated whether we could rapidly distinguish MR *M. pneumoniae* pneumonia from MS *M. pneumoniae* pneumonia without waiting for genetic analysis results. No differences in clinical presentation were observed between MS patients and MR patients. The same clinical features demonstrated that diagnostic sensitiv-

TABLE 3 *In vitro* antimycoplasmal activity against reference strain and clinical isolates of MR *M. pneumoniae*

Antimicrobial agent	Reference strain FH	MIC (µg/ml) for:					
		Isolates from adolescent and adult patients (n = 13)			Isolates from pediatric patients (n = 125)		
		Range	50%	90%	Range	50%	90%
Erythromycin	0.0039	128–>128	>128	>128	128–>128	>128	>128
Clarithromycin	0.002	128–>128	>128	>128	128–>128	>128	>128
Azithromycin	0.00025	16–>128	64	128	16–>128	64	128
Rokitamycin	0.0156	0.0156–0.25	0.0625	0.25	0.0625–1	0.25	0.5
Clindamycin	2	64–>128	128	>128	32–>128	128	>128
Minocycline	1	0.25–2	1	2	0.25–4	1	2
Tetracycline	0.5	0.25–1	0.5	0.5	0.25–1	0.5	0.5
Tosufloxacin	0.25	0.125–0.5	0.25	0.5	0.125–0.5	0.25	0.5
Garenoxacin	0.0313	0.0156–0.0625	0.0313	0.0625	0.0156–0.125	0.0313	0.0625
Levofloxacin	0.5	0.5–1	0.5	0.5	0.25–1	0.5	0.5
Moxifloxacin	0.0625	0.0625–0.125	0.125	0.125	0.0313–0.125	0.0625	0.125

TABLE 4 Clinical efficacies of macrolides, quinolones, and minocycline against MS and MR *M. pneumoniae* pneumonia

Variable	MS patients			MR patients		
	Macrolides	Quinolones	Minocycline	Macrolides	Quinolones	Minocycline
No. of patients	14	16	12	14	9	7
Mean age, yr	19.6	26.2	24.3	19.1	25.5	23.1
No. of males/females	7/7	9/7	6/6	7/7	5/4	3/4
No. (%) of patients with defervescence within 48 h after antibiotic administration	10 (71)	13 (81)	11 (91)	4 (28)	7 (77)	6 (85)
No. (%) of patients with antibiotic change at second visit	6 (42) ^a	0	0	10 (71) ^b	0	0

^a Antibiotic changed to minocycline for 3 patients and to quinolones for 3 patients.

^b Antibiotic changed to minocycline for 6 patients and to quinolones for 4 patients.

ities of the JRS scoring system and chest HRCT were identical between MS patients and MR patients.

A2063G in domain V of the 23S rRNA is the most frequent mutation associated with MR *M. pneumoniae* in pediatric patients, followed by A2063T, A2064G, and A2063C (9). In this study, MR isolates in adolescent and adult patients were shown to have the same prevalence of mutations as that in pediatric patients, with 90% of isolates having the A2063G mutation. The MIC₉₀ values of 11 antimicrobial agents against *M. pneumoniae* isolates from these adolescent and adult patients were very similar to those of isolates from pediatric patients. The MIC values were well correlated with clinical improvement, in which defervescence within 48 h after initiation of antibiotics was observed in 28% of patients in the macrolide group, 77% of patients in the quinolone group, and 85% of patients in the minocycline group.

Our study had several limitations. First, the number of patients in each treatment group was low and the type of quinolone used varied. Another limitation was that the present study was not a randomized trial to compare the efficacies of several antibiotics against MR strains. Large-scale, randomized therapeutic trials are necessary to establish clinical guidelines with regard to the most appropriate antimicrobial agents to use against these MR strains.

In conclusion, patients with MR *M. pneumoniae* pneumonia could not be differentiated clinically from patients with MS *M. pneumoniae* pneumonia. The clinical efficacy of macrolides for treating cases of MR *M. pneumoniae* was low. Physicians might use minocycline instead of macrolides when MR *M. pneumoniae* pneumonia is suspected and lack of defervescence within 48 h after initiation of macrolide treatment is observed.

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