Comparison of efficacy of antimicrobial agents among hospitalized patients with *Mycoplasma pneumoniae* pneumonia in Japan during large epidemics of macrolide-resistant *M. pneumoniae* infections: A nationwide observational study

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Summary: Compared to patients who started treatment for *M. pneumoniae* pneumonia with quinolones, those who began treatment with macrolides and tetracyclines had greater odds of being switched to alternatives. Thirty-day mortality, however, did not differ between these groups.

Abstract

Background. *Mycoplasma pneumoniae* strains with resistance to macrolides have been spreading worldwide. This study aimed to clarify which antimicrobial agent is a better treatment for patients with *M. pneumoniae* pneumonia in a setting with large epidemics of macrolide-resistance.

Methods. Adult patients hospitalized with laboratory-confirmed *M. pneumoniae* pneumonia from 2010 to 2013 were identified from the Diagnosis Procedure Combination database, a national database in Japan. Drug switching, length of stay (LOS), 30-day mortality, and total costs of patients who underwent macrolide, quinolone, and tetracycline therapy were compared using propensity score analyses.

Results. Eligible patients (N = 1650) from 602 hospitals, were divided into the macrolide-group (n = 508), quinolone-group (n = 569), and tetracycline-group (n = 573). We found that 52.8%, 21.8%, and 38.6% of patients in the macrolide, quinolone, and tetracycline groups, respectively, had to switch drugs ($p < 0.0001$). There was no significant difference in the LOS and the 30-day mortality rates among these three groups. Cost was highest in the quinolone group ($p = 0.0062$). The propensity score-matched pairs (n = 487×2) generated from the quinolone and tetracycline groups also showed a lower proportion of patients requiring switches in the quinolone group than in the tetracycline group (21.2% versus 39.6%, $p < 0.0001$), but not in the LOS, mortality and cost.

Conclusion. There were no significant differences in the LOS and mortality among any anti-mycoplasmal drugs as initial treatment for hospitalized *M. pneumoniae* pneumonia patients despite the lower switching rate in the quinolone group.

Introduction

Antimicrobial agents for the treatment of *Mycoplasma pneumoniae* infections include macrolides, quinolones, and tetracyclines. Macrolides are usually selected as the first-line treatment because of they have a low minimum inhibitory concentration against *M. pneumoniae*, low toxicity and because they are not contraindicated in children [1]. However, macrolide resistance has been increasing worldwide, with its prevalence being 13% in the USA, 26% in Italy, 30% in Israel, approximately 80% in Japan, and over 90% in China [2-6].

Clinical evidence evaluating which antimicrobial agent is appropriate in areas with epidemics of macrolide-resistant *M. pneumoniae* infections is required. In Japan, there were epidemics of *M. pneumoniae* pneumonia between 2010 and 2013, during which the prevalence of macrolide-resistant strains was reported to be as high as 80% [5, 7, 8]. The aim of this study was to ascertain which antimicrobial agent would be the most appropriate treatment during such epidemics using a nationally available database.

Materials and Methods

Data source

We used a large, nationwide database available from the Japanese Diagnosis Procedure Combination (DPC) system. This dataset was collected from our survey of hospitals that use the DPC system and voluntarily participate with non-disclosure agreements. Public access to the DPC database is not permitted; the database was, however, open for confidential use by our research team [9]. The database contains claims information and discharge abstract data of patients from more than 1,000 participating hospitals, including 92% (244/266) of all tertiary hospitals in Japan [10]. Baseline patient information includes age, sex, primary

diagnosis, and comorbidities at admission, coded using the International Classification of Diseases, 10th Revision (ICD-10) codes [11]. The database also includes the dosages and dates of administration of all drugs including anti-mycoplasmal agents and other antibiotics, and blood products administered during admission. All interventional procedures were decoded from the original Japanese codes. Dates of admission and discharge, bedside procedures, drugs administered, and status at discharge (dead or alive) were recorded using a uniform data submission format. The DPC is an administrative database with information of inpatients inputted at discharge. Thus, for this study, patient follow-up began from the day of admission and ended on the day of discharge from the hospital, transfer to other hospitals, or death. It was impossible to investigate an outpatient treatment before admission and follow up patients after discharge since this was beyond the scope of the database.

Data were anonymized by stripping all personally identifiable information during extraction and analyzed within the protected environment of the Nagasaki University Hospital. The need for informed consent was waived by the institutional review board of the Nagasaki University Hospital (Nagasaki, Japan), which also approved the study design (Institutional Review Board No. 16092620).

Patient selection

We identified hospitalized patients with laboratory-confirmed *M. pneumoniae* pneumonia from January 2010 to December 2013. During this period, there were multiple large epidemics of *M. pneumoniae* infections, and the prevalence of macrolide-resistant *M. pneumoniae* in Japan was reported to be more than 80% [5, 7, 8, 12]. We included patients who were aged ≥18 years and who had undergone diagnostic testing (paired antibody titers, polymerase chain reaction, and antigen detection) to confirm *M. pneumoniae* infection. In

many cases, antibodies to *M. pneumoniae* were measured by the passive agglutination test, which is a more advanced alternative to the complement fixation test [13]. Single measurements of antibody titer and cold agglutinin tests were not included as diagnostic tests in this study because those are not specific tests for *M. pneumoniae* infection. We restricted the analysis to adults because of limitations in the use of quinolones and tetracycline in children [1].

Exclusion criteria were as follows: 1) discharge within 2 days of admission; 2) use of multiple antimicrobial agents within 2 days of admission; 3) no use of any antimicrobial agent within 2 days of admission, and 4) use of antimicrobial agents for <3 days. We eventually recruited patients who were started on single antimicrobial agents within 2 days of admission and treated for more than 3 days.

Variables and endpoints

Comorbidities were evaluated using the Charlson comorbidity index (CCI), a method of predicting mortality by classifying or weighting comorbidities [11]. The CCI has been widely used by health researchers to measure the case mix and burden of disease. The CCI includes 17 conditions with major impact on survival. A higher CCI score reflects the presence of severe comorbidities. The Japan Coma Scale (JCS) was used to assess the level of consciousness for all patients at admission. This score is categorized into 4 groups: 0 (alert), 1–3 (delirium), 10–30 (somnolence), and 100–300 (coma). A JCS score of 100 is equivalent to a Glasgow Coma score of 6–9 [14]. We assessed all medications administered and interventions performed within 30 days of admission.

The endpoints measured were switching to another anti-mycoplasmal agent, the length of

stay (LOS), all-cause 30-day mortality, and total costs of all drugs used including anti-mycoplasmal agents and all other prescribed drugs, given in the Japanese Yen and US dollar (1.00 JPY = 0.009017 USD). We defined switching to another anti-mycoplasmal agent as the administration of an agent that was different from the first-line agent upon cessation of the initial one after 5 days of admission.

Statistical analysis

Fisher's exact or Pearson's chi-square test was used to compare discrete variables; analysis of variance was used to compare the means of continuous variables in several groups simultaneously, and the t-test was used to compare the difference between the mean of two groups. To compare the efficacies of quinolone and tetracycline therapy, we performed a one-to-one matching between the group that started treatment with quinolones and those who started treatment with tetracycline based on the estimated propensity scores for each patient in order to minimize the bias due to confounding variables [15]. We performed a comparison between the quinolone and tetracycline groups, but not the macrolide group because we assumed that most study patients had macrolide-resistant *M. pneumoniae* infections.

To estimate the propensity score, we fitted a logistic regression model for starting treatment with quinolone as a function of patient demographics that included age, sex, CCI, and each of the comorbidities included in the CCI (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, renal disease, any malignancy, moderate or severe liver disease, metastatic solid tumor). Other parameters used included the JCS score, the use of other supportive drugs (catecholamines, immunoglobulin, sivelestat sodium),

blood-product transfusion (red blood cells, platelets, fresh frozen plasma), interventions (hemodialysis, invasive ventilation, non-invasive ventilation), and admission to the intensive care unit [14]. Catecholamines used included dopamine, dobutamine, and noradrenaline (norepinephrine). A one-to-one matched analysis using nearest-neighbor matching was performed based on the patients' estimated propensity scores. A match was said to have occurred when a patient in the quinolone group had an estimated score within 0.2 standard deviations (SD) of a patient in the tetracycline group [16]. We examined the balance in baseline variables using standardized differences, where >10% was regarded as imbalanced [17].

To identify factors that influenced the switching of anti-mycoplasmal agents, we performed multivariable logistic regression analyses for all patients, macrolide-treated patients, quinolone-treated patients, and tetracycline-treated patients, who needed a change of agents, adjusting for selected characteristics with statistically significant differences. Odds ratios (ORs) and their 95% confidence intervals (CIs) were then calculated. All statistical analyses were performed using JMP 12.0 software (SAS Institute, Cary, NC, USA). All tests were two-tailed, and a p-value < 0.05 was considered to be statistically significant.

Results

Patients

A total of 2,718 patients were admitted with *M. pneumoniae* pneumonia to 690 hospitals during the 4-year study period. Among them, 2,390 patients were diagnosed by paired antibody titers, 213 by polymerase chain reaction, and 153 by antigen detection (Fig 1). Overall, 1,068 patients were excluded based on the various exclusion criteria previously mentioned. No patients died within 2 days of admission. The remaining 1,650 patients from

602 hospitals, were divided into 3 groups – those that started treatment with a macrolide (n = 508), with a quinolone (n = 569), and with a tetracycline (n = 573). A breakdown of the drugs used within each group is shown in Supplementary Table 1. Descriptive statistics for all patients are presented in Table 1. When the three groups were simultaneously compared, patients who were treated with quinolone had more complex comorbidities; the number of patients with altered sensorium was highest in the tetracycline group; patients within the quinolone group tended to require more supportive drugs, more blood-product transfusion, more mechanical ventilation, and more admissions to the intensive care unit. The total duration of antimicrobial treatment including switched agents was 7.8 ± 4.8 days for patients in the macrolide group, 9.1 ± 4.7 days for patients in the quinolone group, and 8.7 ± 4.2 days for patients in the tetracycline group, which showed a statistically significant difference ($p < 0.0001$).

Outcomes

The proportion of patients who were switched to other anti-mycoplasmal agents was significantly different among the three groups ($p < 0.0001$) (Table 2). The switches occurred as follows: macrolide to quinolone (42.5%), quinolone to macrolide (15.5%), and tetracycline to quinolone (25.1%). The duration of first-line treatment until the switch was 3.1 ± 3.0 days for patients in the macrolide group, 8.0 ± 4.7 days for patients in the quinolone group, and 6.9 ± 3.3 days for patients in the tetracycline group, which showed a statistically significant difference ($p < 0.0001$). LOS was longest in the macrolide group (18.5 ± 22.8 days) and shortest in the tetracycline group (15.9 ± 20.07 days) though this difference was not significant ($p = 0.0995$). There was no difference in the 30-day mortality among the three groups ($p = 0.5472$). The total cost of all drugs used during hospitalization was highest in the quinolone group and lowest in the tetracycline group ($p = 0.0062$).

From the quinolone and tetracycline groups, 487 propensity score-matched pairs were generated (Fig 1). After propensity score matching, the baseline patient characteristics were well balanced between the quinolone and tetracycline groups since all standardized differences were <10%. The total duration of anti-mycoplasmal treatment was almost equal in both quinolone (8.9 ± 4.6 days) and tetracycline groups (8.6 ± 4.0 days) ($p = 0.2736$). The proportion of patients who were switched to other anti-mycoplasmal agents was lower in the quinolone group than in the tetracycline group (21.2% versus 39.6%, $p < 0.0001$) (Table 3). There were no significant differences in the LOS, 30-day mortality, and total cost of all drugs between the two groups ($p = 0.7963$, $p = 1.0000$, and $p = 0.3519$, respectively).

Characteristics of patients who needed to be switched to other anti-mycoplasmal agents

A logistic regression analysis adjusting for parameters showed statistically significant differences in all characteristics of all patients (Supplementary Table 2), and revealed that the selection of a macrolide as first-line therapy was a major factor necessitating a change to other anti-mycoplasmal agents when compared to quinolone group (OR: 4.2, 95% CI: 3.2–5.5, $p < 0.0001$) (Table 4). Treatment with tetracycline also showed a high OR against quinolone treatment (OR: 2.4, 95% CI: 1.8–3.1, $p < 0.0001$). For patients treated with macrolides, only males showed a statistical difference between those who were switched to another anti-mycoplasmal agent and those who were maintained on macrolides. For patients treated with a quinolone, congestive heart failure, diabetes with chronic complications, solid metastatic tumor, or hemodialysis were factors associated with switching of anti-mycoplasmal agents. Interestingly, for diabetic patients within the tetracycline group, those who had chronic complications had higher odds (OR = 6.8) of being switched to another anti-mycoplasmal agent compared to those without chronic complications (OR = 0.4) (Table 4).

Discussion

Our study assessed the efficacy of macrolide, quinolone, and tetracycline therapies in hospitalized adult patients with *M. pneumoniae* pneumonia in an area with large epidemics of macrolide-resistant *M. pneumoniae* infections. In the case of macrolide-resistant *M. pneumoniae* strains, another choice of antimicrobial treatment may be required, including quinolones and tetracyclines. Quinolone and tetracycline regimens have been reported to be more effective than macrolide regimens in patients infected with macrolide-resistant *M. pneumoniae* [8, 18, 19]. However, macrolides appear to be clinically effective in some patients infected with macrolide-resistant strains [20-22]. This observation can be explained by the fact that *M. pneumoniae* infections are often self-limiting and that the anti-inflammatory effects of macrolides may contribute to the improvement in clinical symptoms [1]. These conflicting results made it more challenging to determine the most suitable regimen for *M. pneumoniae* infections in an area with large epidemics of macrolide-resistant *M. pneumoniae* infections. Therefore, clinical studies including a large number of patients were required to clarify this. We resolved this by using a large nationwide administrative database spanning several years.

Our study revealed that over half of the patients treated with macrolides needed to be switched to other anti-mycoplasmal agents and required a slightly longer period of admission than patients treated with quinolones and tetracycline. The existence of macrolide-resistant *M. pneumoniae* infections may affect the results of this study though no anti-mycoplasmal susceptibility tests were performed in this study. However, we did not note an increase in mortality rates, which might indicate that a delay in selecting a suitable anti-mycoplasmal

treatment could be recovered by switching to suitable agents within an average of 3.1 days after first macrolide administration despite prolongation of hospitalization, which can be a favorable result for children for whom there is a limitation in the use of quinolones and tetracycline.

It is important to determine whether quinolone or tetracycline is better against *M. pneumoniae* pneumonia if macrolides cannot be used for some reason. Okada et al. reported that tetracycline might be superior to quinolones in decreasing numbers of *M. pneumoniae* DNA copies in nasopharyngeal samples more quickly [8]. This result seems to indicate that the use of a tetracycline regimen could shorten the LOS compared to the use of a quinolone regimen. However, our study revealed that the LOS of patients in both the tetracycline and quinolone groups did not differ. Additionally, the odds of switching to other agents were surprisingly higher in the tetracycline group than in the quinolone group. Although we could not analyze reasons for switching agents in this study, it may have been due to some reasons such as no clinical improvement or adverse effects of the initial regimen. Moreover, no studies have compared the adverse effects of tetracycline and quinolone therapy in adult hospitalized patients with *M. pneumoniae* pneumonia. It has however been reported that tetracycline use results in digestive and skin disorders and headaches, which often necessitate switching of medication [23]. If tetracycline has a better anti-mycoplasmal effect than a quinolone, the reason for a more frequent switching in the tetracycline group may have been the poor tolerance compared to that noted in those using quinolones.

Cost benefit analysis was also conducted, which is an important factor to consider in selecting a more appropriate agent for the treatment of *M. pneumoniae* infection. We considered the total cost of all drugs used, including anti-mycoplasmal agents and all other

prescribed drugs because treatment failure would generate additional costs. Among the three groups, the quinolone group showed the highest cost, which might be attributable to the severity of their infection because patients of this group had required invasive ventilation more frequently and stayed in the ICU longer than patients of the two other groups. If quinolone treatment is more expensive than macrolide or tetracycline treatment, physicians could select a non-quinolone agent as an initial treatment since other variables such as LOS and 30-day mortality showed no significant difference between these medications despite the possibility that the outcome of drug switching was different.

This study has some limitations. First, the diagnosis of *M. pneumoniae* pneumonia for most patients depended on paired antibody titers in this study. Therefore, there might have been a selection bias to select patients who need longer hospitalization. It may be a disadvantage in this analysis for the macrolide-treated group because azithromycin-treated and those who were discharged earlier than those treated with other agents due to its shorter duration of treatment, were excluded from this analysis. If those patients were included in the study, the proportion of patients requiring switching to other antimicrobial agents from macrolides might have been smaller than the value in the current study. Second, we could not determine the prevalence of macrolide-resistant *M. pneumoniae* in this study. On the other hand, there was no geographical bias in this study because study patients were selected from various parts of Japan because we used a nationwide database. The larger proportion of patients who needed switching from macrolides to other anti-mycoplasmal agents might also indicate that many patients had macrolide-resistant *M. pneumoniae* in this study. Last, although we used a nationwide database, it was retrospective and observational, without randomization. Although we used the propensity score matching to adjust for differences in baseline characteristics and disease severity, bias arising from unmeasured confounders, such as complications of other

causes of bacterial pneumonia, clinical variables, laboratory values, and pneumonia severity index, may have been present. Large randomized trials are warranted to confirm these, but it may not be easy to perform such trials, considering that this is a rare condition. Thus, the present study may provide the best attainable level of evidence on this issue.

In conclusion, this study revealed that macrolide-treated patients more frequently needed to switch agents than patients treated with quinolones and tetracyclines despite the absence of an increase in mortality for hospitalized patients with *M. pneumoniae* pneumonia in large epidemics of macrolide-resistant *M. pneumoniae* infections. In addition, patients treated with quinolones had a lower possibility of a switch to other medications than those treated with a tetracycline. However, we have to note the risk of increasing resistance to quinolones if this antibiotic is used inappropriately.

Abbreviations

CCI: Charlson comorbidity index; CI: confidence interval; DPC: Japanese Diagnosis Procedure Combination; ICD-10: International Classification of Diseases, tenth revision codes; JCS: Japan Coma Scale; LOS: length of stay; OR: odds ratio; SD, standard deviation

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Author's contributions

Study concept, design, data analysis, and manuscript drafting: M. Tashiro. Data acquisition: K. Fushimi. Study supervision and critical revision of the manuscript for important intellectual content: all authors. Final approval for submission has been provided by all authors.

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References

1. Pereyre S, Goret J, Bebear C. *Mycoplasma pneumoniae*: Current Knowledge on Macrolide Resistance and Treatment. Front Microbiol **2016**; 7: 974.
2. Zheng X, Lee S, Selvarangan R, et al. Macrolide-Resistant *Mycoplasma pneumoniae*, United States. Emerg Infect Dis **2015**; 21(8): 1470-2.
3. Chironna M, Sallustio A, Esposito S, et al. Emergence of macrolide-resistant strains during an outbreak of *Mycoplasma pneumoniae* infections in children. J Antimicrob Chemother **2011**; 66(4): 734-7.
4. Averbuch D, Hidalgo-Grass C, Moses AE, Engelhard D, Nir-Paz R. Macrolide resistance in *Mycoplasma pneumoniae*, Israel, 2010. Emerg Infect Dis **2011**; 17(6): 1079-82.
5. Kawai Y, Miyashita N, Kubo M, et al. Nationwide surveillance of macrolide-resistant *Mycoplasma pneumoniae* infection in pediatric patients. Antimicrob Agents Chemother **2013**; 57(8): 4046-9.
6. Zhao F, Liu G, Wu J, et al. Surveillance of macrolide-resistant *Mycoplasma pneumoniae* in Beijing, China, from 2008 to 2012. Antimicrob Agents Chemother **2013**; 57(3): 1521-3.
7. Matsuda K, Narita M, Sera N, et al. Gene and cytokine profile analysis of macrolide-resistant *Mycoplasma pneumoniae* infection in Fukuoka, Japan. BMC Infect Dis **2013**; 13: 591.
8. Okada T, Morozumi M, Tajima T, et al. Rapid effectiveness of minocycline or doxycycline

against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. Clin Infect Dis **2012**; 55(12): 1642-9.

9. Tashiro M, Fushimi K, Takazono T, et al. A mortality prediction rule for non-elderly patients with community-acquired pneumonia. BMC Pulm Med **2016**; 16: 39.

10. Tagami T, Matsui H, Fushimi K, Yasunaga H. Intravenous immunoglobulin and mortality in pneumonia patients with septic shock: an observational nationwide study. Clin Infect Dis **2015**; 61(3): 385-92.

11. Sundararajan V, Quan H, Halfon P, et al. Cross-national comparative performance of three versions of the ICD-10 Charlson index. Med Care **2007**; 45(12): 1210-5.

12. Yamazaki T, Kenri T. Epidemiology of *Mycoplasma pneumoniae* Infections in Japan and Therapeutic Strategies for Macrolide-Resistant *M. pneumoniae*. Front Microbiol **2016**; 7: 693.

13. Daxboeck F, Krause R, Wenisch C. Laboratory diagnosis of Mycoplasma pneumoniae infection. Clin Microbiol Infect **2003**; 9(4): 263-73.

14. Tagami T, Matsui H, Horiguchi H, Fushimi K, Yasunaga H. Low-dose corticosteroid use and mortality in severe community-acquired pneumonia patients. Eur Respir J **2015**; 45(2): 463-72.

15. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive

cardiac management on AMI survival using propensity score and instrumental variable methods. JAMA **2007**; 297(3): 278-85.

16. Tagami T, Matsui H, Fushimi K, Yasunaga H. Prophylactic Antibiotics May Improve Outcome in Patients With Severe Burns Requiring Mechanical Ventilation: Propensity Score Analysis of a Japanese Nationwide Database. Clin Infect Dis **2016**; 62(1): 60-6.

17. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med **2014**; 33(7): 1242-58.

18. Kawai Y, Miyashita N, Kubo M, et al. Therapeutic efficacy of macrolides, minocycline, and tosufloxacin against macrolide-resistant *Mycoplasma pneumoniae* pneumonia in pediatric patients. Antimicrob Agents Chemother **2013**; 57(5): 2252-8.

19. Miyashita N, Akaike H, Teranishi H, Ouchi K, Okimoto N. Macrolide-resistant *Mycoplasma pneumoniae* pneumonia in adolescents and adults: clinical findings, drug susceptibility, and therapeutic efficacy. Antimicrob Agents Chemother **2013**; 57(10): 5181-5.

20. Suzuki S, Yamazaki T, Narita M, et al. Clinical evaluation of macrolide-resistant *Mycoplasma pneumoniae*. Antimicrob Agents Chemother **2006**; 50(2): 709-12.

21. Matsubara K, Morozumi M, Okada T, et al. A comparative clinical study of macrolide-sensitive and macrolide-resistant *Mycoplasma pneumoniae* infections in

pediatric patients. J Infect Chemother **2009**; 15(6): 380-3.

22. Cardinale F, Chironna M, Chinellato I, Principi N, Esposito S. Clinical relevance of *Mycoplasma pneumoniae* macrolide resistance in children. J Clin Microbiol **2013**; 51(2): 723-4.

23. Gaillard T, Madamet M, Pradines B. Tetracyclines in malaria. Malar J **2015**; 14: 445.

Figure legends

Figure 1. Patient selection

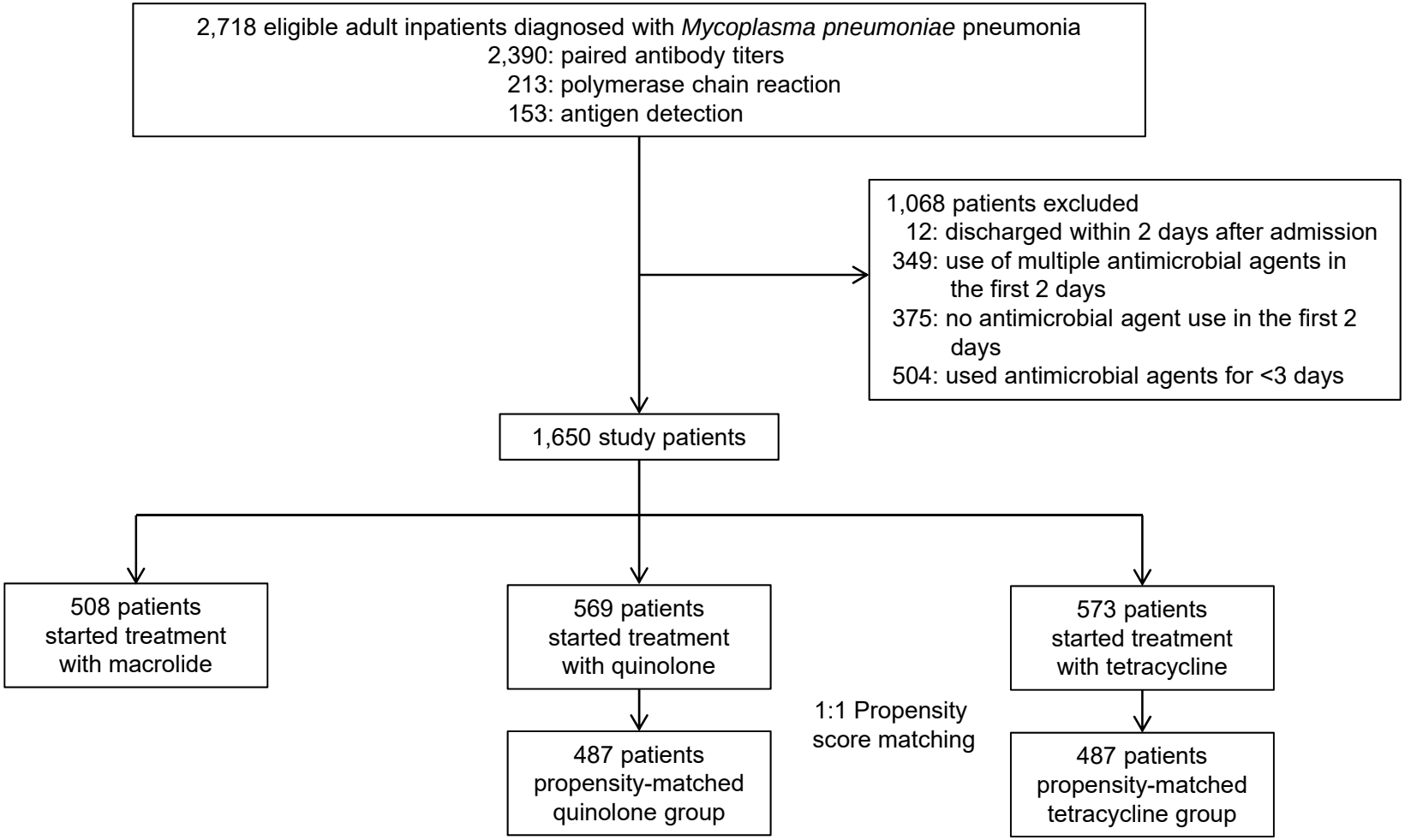

Figure 1. Tashiro et al.

Table 1. Baseline patient characteristics

Characteristic	Macrolide (n = 508)	Quinolone (n = 569)	Tetracycline (n = 573)	*p value*
Age, years	49.7 ±22.4	50.5 ±20.7	50.6 ±24.0	0.7575
Male	232 (45.7)	283 (49.7)	259 (45.2)	0.2452
Preexisting comorbid conditions				
Charlson comorbidity index	0.6 ±1.0	0.8 ±1.1	0.7 ±1.0	0.0046
Myocardial infarction	2 (0.4)	2 (0.4)	2 (0.3)	0.9909
Congestive heart failure	32 (6.3)	37 (6.5)	49 (8.6)	0.2715
Peripheral vascular disease	2 (0.4)	1 (0.2)	2 (0.3)	0.7852
Cerebrovascular diseases	8 (1.6)	16 (2.8)	21 (3.7)	0.1077
Dementia	8 (1.6)	6 (1.1)	17 (3.0)	0.0490
Chronic pulmonary disease	86 (16.9)	106 (18.6)	76 (13.3)	0.0429
Rheumatic disease	9 (1.8)	19 (3.3)	10 (1.7)	0.1259
Peptic ulcer disease	21 (4.1)	31 (5.4)	22 (3.8)	0.3799
Mild liver disease	15 (3.0)	26 (4.6)	24 (4.2)	0.3683
Diabetes without chronic complications	36 (7.1)	51 (9.0)	53 (9.3)	0.3910
Diabetes with chronic complications	7 (1.4)	11 (1.9)	9 (1.6)	0.7643
Hemiplegia or paraplegia	0 (0.0)	0 (0.0)	4 (0.7)	0.0231
Renal disease	12 (2.4)	17 (3.0)	8 (1.4)	0.1876
Any malignancy	28 (5.5)	43 (7.6)	35 (6.1)	0.3654
Moderate or severe liver disease	0 (0.0)	3 (0.5)	1 (0.2)	0.1967
Metastatic solid tumor	1 (0.2)	4 (0.7)	1 (0.2)	0.2511
Consciousness level (Japan Coma Scale)				
0	472 (92.9)	537 (94.4)	513 (89.5)	0.0468
1-3	25 (4.9)	22 (3.9)	42 (7.3)	
10-30	6 (1.2)	4 (0.7)	13 (2.3)	
100-300	5 (1.0)	6 (1.1)	5 (0.9)	

(Continued)

Table 1. Continued

Characteristic	Macrolide (n = 508)	Quinolone (n = 569)	Tetracycline (n = 573)	*p value*
Other supportive drug use				
Catecholamine	14 (2.8)	26 (4.6)	13 (2.3)	0.0688
Immunoglobulin	12 (2.4)	17 (3.0)	10 (1.7)	0.3848
Sivelestat sodium	10 (2.0)	28 (4.9)	6 (1.0)	0.0001
Blood transfusion				
Red blood cells	18 (3.5)	17 (3.0)	11 (1.9)	0.2532
Platelets	1 (0.2)	6 (1.1)	1 (0.2)	0.0538
Fresh frozen plasma	3 (0.6)	4 (0.7)	2 (0.3)	0.7093
Interventions				
Hemodialysis	7 (1.4)	11 (1.9)	6 (1.0)	0.4507
Invasive ventilation	17 (3.3)	34 (6.0)	12 (2.1)	0.0023
Non-invasive ventilation	5 (1.0)	3 (0.5)	1 (0.2)	0.1959
Intensive care unit admission	14 (2.8)	21 (3.7)	7 (1.2)	0.0281

Data are shown as n (%) or mean ± SD (standard deviation).
Catecholamines include dopamine, dobutamine, and noradrenaline.
Acquired immune deficiency syndrome which was evaluated using Charlson comorbidity index, was excluded from this table because there were no patients

Table 2. Comparisons of outcomes among the three groups

Characteristic	Macrolide (n = 508)	Quinolone (n = 569)	Tetracycline (n = 573)	*p value*
Switch to other antimicrobial agents	268 (52.8)	124 (21.8)	221 (38.6)	<0.0001
to macrolide	- -	88 (15.5)	105 (18.3)	-
to quinolone	216 (42.5)	- -	144 (25.1)	-
to tetracycline	83 (16.3)	48 (8.4)	- -	-
Length of stay, days±SD	18.5 ±22.8	17.2 ±18.2	15.9 ±20.0	0.0995
30-day mortality	7 (1.4)	12 (2.1)	8 (1.4)	0.5472
Total cost of all drugs used in hospitalization				
Japanese Yen	109,913 ±324,402	130,612 ±352,871	70,538 ±287,267	0.0062
US Dollar	991 ±2925	1178 ±3182	636 ±2590	

Data are shown as n (%) or mean ± SD (standard deviation).
1.00 Japanese Yen = 0.009017 US Dollar

Table 3. Comparisons of outcomes between the propensity-matched groups

Characteristic	Quinolone	Tetracycline	Risk difference (95% CIs)	*p value*
Switch to other antimicrobial agents	21.2% (103/487)	39.6% (193/487)	-18.5% (-24.1 to -12.8)	<0.0001
to macrolide	15.4% (75/487)	18.3% (89/487)	-2.9% (-7.6 to 1.8)	0.2656
to quinolone	- -	25.9% (126/487)	- - -	-
to tetracycline	7.8% (38/487)	- -	- - -	-
Length of stay, days±SD	15.5 ±14.6	15.2 ±19.8	0.3 (-1.9 to 2.5)	0.7963
30-day mortality	1.6% (8/487)	1.6% (8/487)	0.0% (-1.7 to 1.7)	1.0000
Total cost of all drugs used in hospitalization				
Japanese Yen	89,664 ±233,120	73,306 ±309,638	16,358 (-18,108 to 50,824)	0.3519
US Dollar	809 ±2102	661 ±2792	148 (-163 to 458)	

Definition of abbreviations: SD, standard deviation; CIs, confidential intervals
1.00 Japanese Yen = 0.009017 US Dollar

Table 4. Logistic regression for patients who needed change of antimicrobial agents

Factor	ORs (95% CIs)	*p value*
All patients		
Start with macrolide	4.2 (3.2 to 5.5)	<0.0001
Start with tetracycline	2.4 (1.8 to 3.1)	<0.0001
Male	1.4 (1.1 to 1.7)	0.0014
Diabetes without chronic complications	0.6 (0.4 to 0.9)	0.0112
Diabetes with chronic complications	2.6 (1.1 to 6.3)	0.0232
Hemodialysis	3.4 (1.4 to 8.8)	0.0077
Macrolide treated patients		
Male	1.8 (1.2 to 2.5)	0.0016
Quinolone treated patients		
Congestive heart failure	2.3 (1.1 to 5.0)	0.0369
Diabetes with chronic complications	4.3 (1.2 to 16.3)	0.0277
Metastatic solid tumor	13.6 (1.2 to 337.4)	0.0344
Hemodialysis	4.0 (1.1 to 15.1)	0.0381
Tetracycline treated patients		
Diabetes without chronic complications	0.4 (0.2 to 0.8)	0.0057
Diabetes with chronic complications	6.8 (1.0 to 132.3)	0.0439
Invasive ventilation	4.2 (1.2 to 19.9)	0.0280

Definition of abbreviations: ORs, odds ratios; CIs, confidence intervals
The ORs were adjusted for parameters which showed statistically significant differences from all characteristics of patients.
References of start with macrolide and tetracycline were quinolone.

Table 4. Tashiro et al.

Supplementary Table 1.
Breakdown of each drug group

Macrolide group (n = 508)		
Azithromycin	322	(63.4)
Clarithromycin	142	(28.0)
Erythromycin	44	(8.7)
Quinolone group (n = 569)		
Levofloxacin	306	(53.8)
Ciprofloxacin	123	(21.6)
Pazufloxacin	101	(17.8)
Garenoxacin	32	(5.6)
Moxifloxacin	4	(0.7)
Sitafloxacin	2	(0.4)
Tosufloxacin	1	(0.2)
Tetracycline group (n = 573)		
Minocycline	572	(99.8)
Doxycycline	1	(0.2)

Data are shown as n (%).
Pazufloxacin, sitafloxacin, and tosufloxacin are only available in Japan.

Supplementary Table 2.
Comparisons of patient characteristics between those who needed a switch and those who did not need a switch to other antibacterial drugs

Characteristic	Switch to other antibacterial drugs	No switch to other antibacterial drugs	*p value*
All patients (n = 1650)			
Number of patient	613 (100.0)	1037 (100.0)	
Starting agent			
macrolide	268 (43.7)	240 (23.1)	<0.0001
quinolone	124 (20.2)	445 (42.9)	
tetracycline	221 (36.1)	352 (33.9)	
Male	315 (51.4)	459 (44.3)	0.0058
Diabetes without chronic complications	38 (6.2)	102 (9.8)	0.0104
Diabetes with chronic complications	17 (2.8)	10 (1.0)	0.0079
Hemodialysis	16 (2.6)	8 (0.8)	0.0045
Macrolide treated patients (n = 508)			
Number of patient	268 (100.0)	240 (100.0)	
Male	140 (52.7)	92 (38.3)	0.0018
Quinolone treated patients (n = 569)			
Number of patient	124 (100.0)	445 (100.0)	
Congestive heart failure	14 (11.3)	23 (5.2)	0.0220
Diabetes with chronic complications	6 (4.8)	5 (1.1)	0.0168
Metastatic solid tumor	3 (2.4)	1 (0.2)	0.0341
Hemodialysis	6 (4.8)	5 (1.1)	0.0168
Tetracycline treated patients (n = 573)			
Number of patient	221 (100.0)	352 (100.0)	
Diabetes without chronic complications	11 (5.0)	42 (11.9)	0.0048
Diabetes with chronic complications	8 (3.6)	1 (0.3)	0.0027
Invasive ventilation	9 (4.1)	3 (0.9)	0.0136

Data are shown as n (%).
Definition of abbreviations: SD, standard deviation; CIs, confidential intervals
This table includes only characteristics that showed statistically significant differences.