Original Article

Effects of minocycline on macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia in children: a single-center retrospective study

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Background: Macrolide-resistant *Mycoplasma pneumoniae* (*Mp*) has become widespread in the world. We sought to determine the independently associated risk factors for refractory *Mp* pneumonia among macrolide-unresponsive *Mp* pneumonia children treated with minocycline and to investigate the effects of minocycline against macrolide-unresponsive *Mp* pneumonia.

Methods: In our center, we retrospectively analyzed the data of hospitalized macrolide-unresponsive *Mp* pneumonia patients aged ≤18 years old who changed macrolide therapies to minocycline treatments between March 2013 and September 2018. Patient characteristics and defervescence after minocycline treatment were compared between refractory *Mp* pneumonia and non-refractory *Mp* pneumonia groups. Multivariable logistic regression analysis was performed among these macrolide-unresponsive *Mp* pneumonia patients.

Results: Among 150 included macrolide-unresponsive *Mp* pneumonia children treated with minocycline; 30 cases (20.0%) were refractory *Mp* pneumonia. Duration of macrolide treatment before administration of minocycline (odds ratio =2.87, 95% CI: 1.79–4.61, P<0.001) and serum procalcitonin levels (odds ratio =13.50, 95% CI: 1.22–149.57, P=0.034) were independently associated with refractory *Mp* pneumonia. Defervescence after minocycline treatment was significantly longer among the refractory *Mp* pneumonia group than in the non-refractory *Mp* pneumonia group (median 2 *vs.* 1 day, P<0.001). Only one case (0.7%) suspected of a side effect of minocycline therapy was observed.

Conclusions: Two risk factors independently associated with refractory *Mp* pneumonia were determined. Early use of minocycline might safely prevent macrolide-unresponsive *Mp* pneumonia from progressing to refractory *Mp* pneumonia.

Keywords: *Mycoplasma pneumoniae* (*Mp*); macrolide; minocycline; defervescence

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Introduction

Mycoplasma pneumoniae (*Mp*) is a common causative pathogen of community-acquired pneumonia (CAP) in children. Macrolides are the first line antimicrobials against *Mp* infections in the clinical practice. However, macrolide-resistant *Mp* has become widespread in the world (1-4). A large variance has been identified in the macrolide-resistant *Mp* rates (54.5–100%) across different regions of China (5). In Shanghai, the macrolide-resistant *Mp* rate has been estimated to be 90% (6). The clinical and bacteriological

efficacy of macrolides for treating macrolide-resistant *Mp* infection was lower than that for children of macrolide-sensitive *Mp* infection (7,8). Besides an increasing bacterial load, an excessive host immune response among patients with macrolide-unresponsive *Mp* might be the pathogenesis of the lung injury (9,10). Without properly treating these patients, refractory *Mycoplasma pneumoniae* pneumonia (RMPP) may occur.

It's well known that minocycline (tetracycline) is effective in the treatment of children with macrolide-resistant *Mp* infection (7,8,11). In the Japanese guidelines for the management of respiratory infectious diseases in children, changing treatment to a tetracycline antibiotic has been recommended in possible macrolide-resistant *Mp* infection (12). The purpose of this study was to determine the independently associated risk factors for RMPP among macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia (MUMPP) children treated with minocycline and to investigate the effects of minocycline against MUMPP. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tp-21-356).

Methods

Subjects and study design

We retrospectively analyzed the medical records of patients with MUMPP aged ≤18 years old who changed macrolide therapies to minocycline treatments and were hospitalized at Shanghai Children's Medical Center between March 2013 and September 2018.

The diagnosis of *Mycoplasma pneumoniae* pneumonia (MPP) was defined as: (I) CAP was confirmed: the presence of fever, acute respiratory symptoms (cough, tachypnoea, difficult breathing), or both, plus presence of new infiltrate on chest radiography or consolidation (13); (II) *Mp* infection was confirmed: positive detection of *Mp* RNA in throat swab samples or/and *Mp* DNA in sputum samples.

Among MPP patients, MUMPP was defined as persistent fever ≥38.0 ℃ at ≥72 hours after macrolide treatment (14). The MUMPP cases were divided into two groups, RMPP and non-refractory *Mycoplasma pneumoniae* pneumonia (NRMPP).

RMPP was defined as cases showing persistent fever and clinical as well as radiological deterioration despite macrolide therapy for 7 days or more (15).

Patients whose minocycline were: (I) used due to macrolide allergy; (II) misused; (III) used in macrolide-responsive MPP; (IV) used to treat non-Mp infection; or (V) used before MUMPP was confirmed were excluded.

According to the requirements of our center, informed consent was obtained from their guardians before minocycline therapy. Minocycline was administered orally twice daily at a dose of 1–2 mg/kg/time for 7–10 days. Because of side effects such as tooth discoloration, minocycline was mainly chosen for patients ≥8 years old.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical committee of Shanghai Children's Medical Center approved the study (No. SCMCIRB-W2021035) and individual consent for this retrospective analysis was waived.

Data collection

The collected data from the medical records included clinical features, laboratory data, chest X-ray findings, treatments, hospital stays, time to defervescence after initial minocycline treatment, and side effects associated with minocycline one week after discharge. Extrapulmonary symptoms included pericarditis or myocarditis, skin rash, hepatitis, arthralgia, anemia or thrombocytopenia, and neurologic symptoms. Coinfection with other respiratory pathogens was defined as having documented bacterial (obtained by culture of respiratory secretions), viral (identified through MultiResPathogen Nucleic Acid Assay (16) for respiratory syncytial virus, adenovirus, parainfluenza virus, and influenza virus A and B), or fungal infection (determined by metagenomic analysis of bronchoalveolar lavage fluid) and *Mp* infection concurrently within the same disease event. The chest X-ray findings were from the records read by two radiologists and classified as interstitial pneumonia, lobar pneumonia, or bronchopneumonia. Interstitial pneumonia was characterized by reticular and irregular opacities with increased perivascular makings presenting in interstitial infiltrate. Lobar pneumonia and bronchopneumonia were defined as the presence of a homogeneous airspace consolidation and an inhomogeneous airspace consolidation, respectively (17).

Mp RNA detection

Throat swabs were obtained within 24 h of admission. A qualitative diagnostic kit (Wuhan Zhongzhi Biotechnologies Inc., Hubei, China) for *Mp* RNA was used to determine

Mp infection according to methods published before (16). In brief, pathogen nucleic acids were reverse transcribed to cDNA. Amplified RNA products were acquired from cDNA using T7 RNA polymerase. Fluorescence signals generated from the chemiluminescence mixture of RNA amplification products were then detected.

Mp DNA detection

The qualitative determination of *Mp* DNA that may be present in a sputum sample was detected using Mycoplasma Pneumoniae Real Time PCR Kit (Liferiver Bio-Tech Corp., Shanghai, China). Briefly, DNA was extracted from a sputum sample. Mp DNA was specifically amplified by the master containing reagents and enzymes. The amplified Mp DNA fragment was detected by fluorimeter channel FAM with the fluorescent quencher BHQ1.

Statistical analysis

Data were presented as medians and interquartile range for continuous variables and frequencies and percentages for categorical variables. Continuous variable comparisons between the groups were performed using Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test. For investigating the independent risk factors of RMPP among MUMPP patients treated with minocycline, the significance of each variable in *Table 1* was assessed by univariable logistic regression analysis. Variables with a P value <0.05 were included in the multivariable logistic regression analysis. Statistical significance was determined as a 2-sided P value <0.05. Statistical analyses were performed using SPSS software 25.0 (IBM SPSS Statistics, Armonk, NY, USA).

Results

Patient characteristics

A total of 163 CAP patients treated with minocycline were screened; of those, 150 children with MUMPP whose macrolide therapies were changed to minocycline treatments were included in this study (*Figure 1*). Among these included patients, 30 cases (20.0%) were in the RMPP group, and 120 (80.0%) were in the NRMPP group. Patient characteristics were summarized in *Table 1*. Among the RMPP group, two patients were coinfected with bacteria (including *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*), three patients were coinfected with viruses (including respiratory syncytial virus, adenovirus, and influenza virus B), and one patient was coinfected with fungus (*Candida albicans*). Among the NRMPP group, three patients were coinfected with bacteria (including *Klebsiella pneumonia*, *enterobacter cloacae*, and *Acinetobacter baumannii*), four patients were coinfected with viruses (including respiratory syncytial virus, adenovirus, parainfluenza virus, and influenza virus A), and no patient was coinfected with fungus. Among the MUMPP patients treated with minocycline, the state of illness was more serious in the RMPP group than in the NRMPP group (*Table 2*).

Risk factors for RMPP among MUMPP patients treated with minocycline

Multivariable logistic regression analysis was performed to determine the independently associated risk factors for RMPP among MUMPP patients treated with minocycline. As *Table 3* shows, duration of macrolide treatment before administration of minocycline (odds ratio =2.87, 95% CI: 1.79–4.61, P<0.001) and serum procalcitonin levels (odds ratio =13.50, 95% CI: 1.22–149.57, P=0.034) were independently associated with increased odds of RMPP.

Defervescence after minocycline treatment

After the change to minocycline treatments among those MUMPP patients, time to defervescence ranged from 1 to 16 days with a median of 1 day (interquartile range 1–2). After stratifying, time to defervescence after minocycline treatment was significantly longer among the RMPP group than in the NRMPP group (median 2 *vs.* 1 day, P<0.001).

Safety

One week after discharge, only one case (0.7%) with increased serum levels of alanine aminotransferase (ALT), which quickly returned to normal value after discontinuation of medication, was suspected to be caused by minocycline treatment.

Discussion

To our knowledge, this is the first study to determine the independently associated risk factors for RMPP among MUMPP children treated with minocycline. Then, we

Table 1 Patient characteristics

Characteristic	MUMPP (n=150)	RMPP (n=30)	NRMPP (n=120)	Odds ratio (95% CI)	P
Age (years), median (IQR)	9 (8.0–10.0)	9 (7.0–11.0)	9 (8.0–10.0)	0.99 (0.98–1.01)	0.363
Male/female	74/76	15/15	59/61	1.03 (0.46–2.30)	0.935
Weight (kg), median (IQR)	30.3 (24.0–39.3)	29.3 (20.4–36.6)	30.9 (24.3–39.6)	0.98 (0.95–1.02)	0.304
Duration of fever before admission (days), median (IQR)	7 (6.0–9.0)	13 (8.0–14.0)	7 (6.0–8.0)	1.45 (1.24–1.69)	<0.001
Coinfection with other respiratory pathogens, n (%)	13 (8.7)	6 (20.0)	7 (5.8)	4.04 (1.25–13.08)	0.020
Erythrocyte sedimentation rate (mm/h), median (IQR)	42 (28.0–58.0)	51 (39.0–71.0)	38 (27.0–56.0)	1.03 (1.01–1.05)	0.004
C-reactive protein (mg/L), median (IQR)	14 (7.0–29.0)	14 (7.0–37.0)	14 (8.0–28.0)	1.01 (0.99–1.02)	0.314
Leukocyte count ($\times 10^9$/L), median (IQR)	7.9 (6.4–9.9)	9.2 (7.3–11.4)	7.8 (6.3–9.7)	1.16 (1.04–1.30)	0.010
Neutrophil proportion (%), median (IQR)	68.0 (60.5–75.7)	69.7 (59.6–78.3)	68.0 (60.9–74.0)	1.02 (0.99–1.06)	0.225
Serum procalcitonin (ng/mL), median (IQR)	0.1 (0.1–0.3)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	4.25 (1.21–14.95)	0.024
Lactate dehydrogenase (IU/L), median (IQR)	782 (634.0–1,023.0)	938 (690.0–1,518.0)	754 (624.0–960.0)	1.00 (1.00–1.00)	0.129
Ferritin (ng/mL), median (IQR)	128.6 (93.2–223.4)	217.2 (128.6–477.9)	117.9 (91.2–189.0)	1.00 (1.00–1.00)	0.202
Interleukin-6 (pg/mL), median (IQR)	11.3 (5.1–19.6)	6.7 (3.9–15.5)	12.3 (5.4–19.7)	1.00 (0.98–1.02)	0.671
Chest X-ray findings, n (%)					
Interstitial pneumonia	33 (22.0)	9 (30.0)	24 (20.0)	Reference	
Lobar pneumonia	44 (29.3)	12 (40.0)	32 (26.7)	1.00 (0.36–2.76)	1.00
Bronchopneumonia	73 (48.7)	9 (30.0)	64 (53.3)	0.38 (0.13–1.06)	0.064
Duration of macrolide treatment before administration of minocycline (days), median (IQR)	5 (3.0–7.0)	8 (7.0–11.0)	4 (3.0–6.0)	2.95 (1.95–4.44)	<0.001
Use of penicillins or/and cephalosporins, n (%)	150 (100.0)	30 (100.0)	120 (100.0)	1.00 (1.00–1.00)	1.000

IQR, interquartile range; MUMPP, macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia; RMPP, refractory *Mycoplasma pneumoniae* pneumonia; NRMPP, non-refractory *Mycoplasma pneumoniae* pneumonia; CI, confidence interval.

investigated the effects of minocycline against MUMPP.

The progression of MUMPP to RMPP led to serious clinical adverse consequences. When compared with NRMPP patents, RMPP ones required more frequent use of corticosteroid and bronohoalveolarlavage, were more likely to be admitted to ICU, had a longer length of hospital stay, and might be associated with more extrapulmonary complications (*Table 2*). Preventing MUMPP from progressing to RMPP may reduce the severity of illness.

Besides the occurrence of resistant strains, excessive inflammatory responses play a vital role in the pathogenesis of RMPP (9). Inflammatory regulatory factors such as high-mobility group box protein 1 (9) and microRNA-146a-5p (18) have been proved to be actively involved in regulating inflammation of RMPP and serve as molecular markers for RMPP. Coinfections (19) and corticosteroid resistance (20) may also contribute to the development of RMPP. Identifying the risk factors of RMPP will be of great significance for preventing the occurrence of RMPP.

Duration of macrolide treatment before administration of minocycline was independently associated with increased odds of RMPP. This indicates that early use of minocycline might prevent MUMPP from progressing to RMPP. In

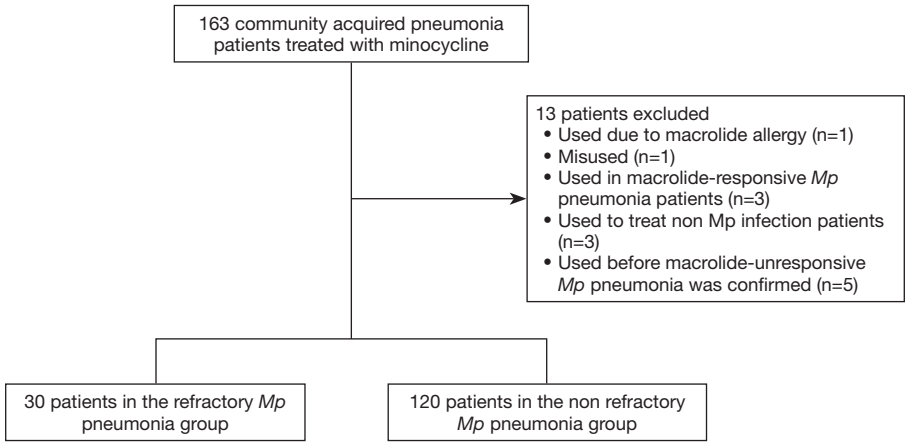

Figure 1 Flowchart of included patients.

Table 2 Severity of MUMPP treated with minocycline

Characteristic	MUMPP (n=150)	RMPP (n=30)	NRMPP (n=120)	P
Patients requiring corticosteroid, n (%)	118 (78.7)	30 (100.0)	88 (73.3)	0.001
Patients requiring bronohoalveolarlavage, n (%)	44 (29.3)	21 (70.0)	23 (19.2)	<0.001
Patients requiring ICU admission, n (%)	4 (2.7)	4 (13.3)	0 (0.0)	0.001
Duration of hospital stay, median days (IQR)	7 (5.0–9.0)	12 (9.0–17.0)	6 (5.0–8.0)	<0.001
Extrapulmonary symptoms, n (%)	17 (11.3)	8 (26.7)	9 (7.5)	0.007

IQR, interquartile range; MUMPP, macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia; RMPP, refractory *Mycoplasma pneumoniae* pneumonia; NRMPP, non-refractory *Mycoplasma pneumoniae* pneumonia; ICU, intensive care unit.

Table 3 Variables associated with RMPP among MUMPP children treated with minocycline in multivariable logistic regression analysis

Variable	OR (95% CI)	P value
Duration of fever before admission	1.21 (0.98–1.50)	0.080
Coinfection with other respiratory pathogens	1.66 (0.14–19.35)	0.686
Erythrocyte sedimentation rate	0.99 (0.95–1.03)	0.535
Leukocyte count	1.18 (0.96–1.46)	0.121
Serum procalcitonin	13.50 (1.22–149.57)	0.034
Duration of macrolide treatment before administration of minocycline	2.87 (1.79–4.61)	<0.001

MUMPP, macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia; RMPP, refractory *Mycoplasma pneumoniae* pneumonia; OR, odds ratio; CI, confidence interval.

the Japanese guidelines for the management of respiratory infectious diseases in children, changing treatment to a tetracycline antibiotic has been recommended in a lack of defervescence within 48 h after the initiation of macrolide therapy (12). We recommend changing the antibiotic treatment to minocycline at 72 h when MUMPP is suspected, especially in settings without possibility of testing mutations in the 23S ribosomal RNA gene.

Minocycline has excellent bactericidal activity against macrolide-unresponsive Mp and macrolide-susceptible Mp (7,21). In China, high macrolide resistance (54.5–100%) has been observed across different regions (5,6,22).

Early application of minocycline may effectively reduce the macrolide-unresponsive Mp burden. In addition, minocycline has been considered beneficial for diseases with an inflammatory basis (23). Therefore, minocycline may exert anti-inflammatory activities that are independent of its bactericidal activity among MUMPP patients.

Increased PCT levels (24) are common in RMPP patients. In our study, serum procalcitonin levels were independently associated with increased odds of RMPP among MUMPP patients treated with minocycline. While patients with normal value of procalcitonin might be considered to be a low-risk subgroup of RMPP, the incidence of RMPP would increase as the serum procalcitonin levels increased. Increased levels of serum procalcitonin might be an indicator of early initiation of minocycline therapy.

Consistent with other studies (7,8,11,25,26), minocycline showed good clinical efficacy in our study. Defervescence with a median of 1 day (interquartile range 1–2) was observed in all MUMPP patients after minocycline therapy. However, when MUMPP progressed to RMPP, time to defervescence after minocycline treatment became longer (median 2 *vs.* 1 day, P<0.001). This further indicates the necessity of early application of minocycline in MUMPP patients.

When used in pediatric patients, minocycline rarely may cause side effects (8,27). In our study, only one case (0.7%) with increased serum levels of ALT was suspected to be caused by minocycline. Minocycline might be very safe in treating pediatric patients with MUMPP.

One limitation is that our study was not a prospective study. Therefore, selective bias could not be avoided. Randomized therapeutic trials are necessary to further support our findings. Because drug resistance gene detection is not a routine test item in our center, no performance in detecting mutations in the 23S ribosomal RNA gene which is associated with macrolide-resistant Mp is another limitation. However, if MUMPP can be effectively treated without drug resistance gene test results, this minocycline therapy might have better economic and clinical benefits.

Conclusions

Duration of macrolide treatment before administration of minocycline and serum PCT levels are independent risk factors for RMPP among MUMPP pediatric patients treated with minocycline. Early use of minocycline might safely prevent MUMPP from progressing to RMPP.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethical committee of Shanghai Children's Medical Center (No. SCMCIRB-W2021035) and individual consent for this retrospective analysis was waived.

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