

Clinical characteristics of macrolide-resistant *Mycoplasma pneumoniae* infections among hospitalised children in Singapore

Dear Editor,

Mycoplasma pneumoniae has become the leading cause of paediatric community-acquired pneumonia in countries where pneumococcal vaccination is included in the national immunisation programme, including Singapore.¹ *M. pneumoniae* is intrinsically resistant to beta-lactams due to the absence of cell walls. Macrolides, tetracyclines, and fluoroquinolones are used to treat *M. pneumoniae* infections, and macrolides are recommended in children, due to the potential adverse effects of tetracyclines and fluoroquinolones. Macrolide-resistant *M. pneumoniae* (MRMP) isolates were first observed in 2001.² The prevalence of MRMP worldwide varies from 0.2% in Europe to 90% in East Asia.³ In Singapore, the prevalence of MRMP in hospitalised children was 13% in 2017.⁴ Studies in Asia have reported increased disease severity in persons infected with MRMP,⁵ while others have not detected differences in the clinical course in persons with MRMP versus those with macrolide-susceptible *M. pneumoniae* (MSMP) infections.⁶ We compare differences between hospitalised children with MSMP and those with MRMP infections.

From July 2019 to February 2020, patients younger than 16 years in KK Women's and Children's Hospital, Singapore, who tested positive for *M. pneumoniae* by polymerase chain reaction on nasopharyngeal or throat swab samples, were screened for inclusion. Assessment of genotypic macrolide resistance was done as previously described.⁴ Sequencing was performed retrospectively; thus, the results of genotypic macrolide resistance were not known at the time of treatment. Electronic medical records of patients with *M. pneumoniae* infection were retrospectively reviewed after informed consent was obtained. Demographic and clinical data were collected and matched to the results of genotypic macrolide-resistance testing. Comparisons between binary groups were analysed using chi-square or Fisher's Exact test for categorical variables, and Mann-Whitney U test for continuous variables. All *P* values were two-tailed and differences were considered statistically significant at <0.05.

Between July 2019 and February 2020, 170 patients with *M. pneumoniae* infection consented to participate in this study. Thirty-one patients (18.2%) had

M. pneumoniae strains for which no readable sequence was obtained; they were not included in further analysis. Of the remaining 139 patients, 125 (90%) had *M. pneumoniae* strains that had the wild-type sequence and were presumed to be macrolide-susceptible, and 14 (10%) patients had strains with mutations conferring macrolide resistance. The A2063G point mutation accounted for all 14 *M. pneumoniae* strains with macrolide resistance.

There were no differences in demographics, presenting symptoms, clinical examination or haematological parameters at presentation (Table 1). A higher median C-reactive protein was observed in children with MRMP infections, although this was not statistically significant. Pneumonia constituted the clinical diagnosis in 86 (68.8%) and 11 (78.6%) hospitalised children with MSMP and MRMP infections, respectively (*P*=0.09). Children younger than 5 years were significantly more likely to have *M. pneumoniae* with viral co-infections compared to children older than 5 years (odds ratio [OR] 3.3, confidence interval [CI] 1.5–7.1, *P*=0.002).

All 139 children with MSMP or MRMP infections received treatment with clarithromycin. The median total duration of fever in children with MRMP infection was significantly longer compared to those with MSMP infection (9.0 vs 7.0 days, *P*=0.047). Despite the fact that clinicians were unaware of the presence of macrolide resistance, the odds of antibiotics switched from macrolide to fluoroquinolone or tetracycline in children with MRMP infections was 8.2 that of children with MSMP infections (CI 1.6–41.7, *P*=0.02). Children with MRMP infection who had a switch of antibiotic therapy had a significantly longer median duration of fever during hospitalisation (median 12.0 days, range 6.0–21.0) compared to children with MRMP infection who remained on macrolide therapy (median 1.0 day, range 0–5.0) (*P*=0.005). Eleven (78.5%) children with MRMP infections remained on macrolide therapy, and all defervesced and were discharged.

Pleural effusions were significantly more frequent in children with MRMP infections compared to those with MSMP infections (OR 4.4, CI 1.4–13.9, *P*=0.01), and required more frequent chest drain insertions (*P*=0.048). There were no significant differences between children

Table 1. Demographics, clinical characteristics, treatment and outcomes of children with macrolide-susceptible and macrolide-resistant *Mycoplasma pneumoniae* infections

	MSMP No. (%) (n=125)	MRMP No. (%) (n=14)	P value
Sex			0.78
Male	62 (49.6)	8 (57.1)	
Female	63 (50.4)	6 (42.8)	
Ethnicity			0.81
Chinese	82 (65.5)	10 (71.4)	
Malay	23 (18.4)	2 (14.3)	
Indian	11 (8.8)	2 (14.3)	
Caucasian	2 (1.6)	0	
Others	7	0	
Age, median (range), year	4.4 (0.1–14.6)	4.4 (1.1–11.5)	0.88
Overseas travel in preceding 4 weeks	21 (16.8)	4 (28.6)	0.28
Sick household contacts	64 (51.2)	8 (57.1)	0.78
Underlying conditions			
Asthma	8 (6.4)	3 (21.4)	0.08
Global developmental delay	6 (4.8)	0	1.00
Prior treatment with antibiotic	46 (37.0)	2 (14.0)	0.14
Beta-lactam	41 (89.1)	2 (100)	
Macrolide	2 (4.3)	0	
Unknown	3 (6.5)	0	
Presenting symptoms			
Fever	117 (93.6)	14 (100)	1.00
Maximum temperature, median (range), °C	39.0 (38.0–41.8)	39.8 (38.0–40.6)	0.11
Cough	124 (99.2)	14 (100)	1.00
Rhinorrhoea	30 (24.0)	1 (7.1)	0.19
Shortness of breath	54 (43.2)	7 (50.0)	0.78
Sore throat	122 (97.6)	14 (100)	1.00
Rash	6 (4.8)	0	1.00
Respiratory examination			
Tachypnoea	67 (53.6)	7 (50.0)	1.00
Pulse oximetry reading <95%	28 (22.4)	3 (21.4)	1.00
Crepitations	61 (48.8)	8 (57.1)	0.59
Rhonchi	32 (25.6)	2 (14.3)	0.52
Investigations			
Chest radiograph performed	115 (92)	13 (93)	
Focal consolidation	77 (67.0)	10 (77.0)	0.37

Table 1. Demographics, clinical characteristics, treatment and outcomes of children with macrolide-susceptible and macrolide-resistant *Mycoplasma pneumoniae* infections (Cont'd)

	MSMP No. (%) (n=125)	MRMP No. (%) (n=14)	P value
Multifocal consolidation	17 (14.8)	3 (23.1)	
Peribronchial thickening	15 (13.0)	0	
CRP, mg/L, median (range)	25.4 (1.0–163.8)	69.2 (4.3–282.0)	0.15
Viral co-infection	120 (96)	14 (100)	
<i>Mycoplasma pneumoniae</i> with 1 viral co-infection	32 (26.7)	7 (50.0)	0.21
<i>Mycoplasma pneumoniae</i> with 2 viral co-infections	7 (5.8)	1 (7.1)	
Clinical diagnosis			
Pneumonia	86 (68.8)	11 (78.6)	0.09
Bronchitis	27 (21.6)	0	
Upper respiratory tract infection	12 (9.6)	3 (21.4)	
Total duration of fever, median (range), days	7.0 (0–16)	9.0 (4–28)	0.047
Antibiotic switched from macrolide to fluoroquinolone/tetracycline	4 (3.2)	3 (21.4)	0.02
Pleural effusion	23 (18.4)	7 (50)	0.01
Chest drain inserted	0	2 (28.5)	0.048
Oxygen supplementation	44 (35.2)	6 (42.9)	0.57
Non-invasive ventilation	2 (1.6)	1 (7.1)	0.28
Length of hospitalisation, median (range), days	2.0 (1–15.0)	2.5 (1–22.0)	0.57

CRP: C-reactive protein; MRMP: macrolide-resistant *Mycoplasma pneumoniae*; MSMP: macrolide-susceptible *Mycoplasma pneumoniae*

with MSMP and MRMP infections in terms of the need for oxygen supplementation, non-invasive ventilatory support or length of hospitalisation.

These findings add to the growing literature that reports a prolonged clinical course and more complications in MRMP infections.^{5,7} Delayed effective antimicrobial treatment for *M. pneumoniae* has been postulated to be related to an immune response, which may lead to prolonged or extrapulmonary disease.⁸ It is crucial to note that the majority of children with MRMP infections (78.6%) eventually became afebrile even when receiving macrolide therapy. Clinical response to macrolides in MRMP infections has been described, although the duration of illness tends to be longer.⁹ The usefulness of macrolide treatment in children with MRMP infection is unclear, but there may be anti-inflammatory effects due to the inhibition of cytokine production, including interleukin-8.⁷

The prevalence of MRMP isolates sampled between July 2019 and February 2020 was 10% in our study, which did not differ significantly from the prevalence of

13% in an earlier cohort in Singapore studied between 2013 and 2014.⁴ With relatively low prevalence rates, macrolides remain a suitable first-line antimicrobial for community-acquired pneumonia in children with suspected *M. pneumoniae* infection.

The lack of distinguishing clinical features among children with infections by MRMP and MSMP has also been described in other comparative studies.¹⁰ Until the time when molecular tests for macrolide resistance in *M. pneumoniae* become available on a real-time basis, clinicians will have to rely on the clinical course of the patient and a setting's prevalence of MRMP to guide decisions on switching antimicrobial therapy for children with *M. pneumoniae* infections. Persistent fever despite macrolide therapy and the presence of pleural effusions in children with *M. pneumoniae* infections are factors that may alert clinicians to the presence of macrolide resistance.

Our study involved hospitalised children in a single centre, and macrolide resistance rates may not reflect those of the wider community. The number of children

with MRMP infection was also small, limiting the power of the study.

In conclusion, a longer duration of fever and higher rates of pleural effusions were found in children with MRMP infections compared to those with MSMP infections. The prevalence of MRMP isolates remains low in children in Singapore despite the high rates reported in East Asia, and macrolides remain a suitable first-line antibiotic for children with suspected *M. pneumoniae* infection.

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