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BRIEF COMMUNICATION

Severe macrolide-resistant *Mycoplasma pneumoniae* pneumonia associated with macrolide failure

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We investigated differences in outcomes between 68 children hospitalized with macrolide-sensitive *Mycoplasma pneumoniae* pneumonia (MSMP group) and 25 children hospitalized with macrolide-resistant *M. pneumoniae* pneumonia (MRMP group). In the MRMP group, 19 children received macrolides and clinical failure occurred in six of which five had pneumonia progression during therapy.

Introduction

Mycoplasma pneumoniae (MP) is a common cause of respiratory tract infections in school-aged children. Although mild cases may resolve spontaneously without specific treatment, targeted antibiotic therapy is required for more serious infections, especially those with pneumonia.[1] Macrolides, fluoroquinolones, and tetracyclines are therapeutic options for MP infection, but only the macrolides have been approved for use in young children.[1,2] In the past decade, macrolide-resistant *M. pneumoniae* (MRMP) have been increasingly prevalent worldwide and rates of >50% have been found in Japan and China.[1,3] MRMP occurs because of point mutation in the 23S rRNA with substitutions at the 2063 and 2064 positions associated with high-level resistance.[4] MRMP infections have been associated with persistence of symptoms (fever and cough), slower reduction in bacterial load, longer length of hospitalization, and more

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frequent requirement for alternative therapy.[1,5] Nonetheless, information on the relationship between macrolide failure and disease progression remains limited.[2,5] Here, we studied this issue by a retrospective review of all pediatric MP pneumonia in our hospital where the incidence of MRMP was estimated to be approximately 30%.[4]

Materials and methods

This study was conducted in a University-affiliated hospital with 1650 beds. Pediatric patients (1−17 years) hospitalized with pneumonia (according to clinical symptoms, chest examination, and radiological abnormalities) were included if their respiratory tract specimens were positive for MP by PCR from January 2011 to March 2013. Microbiological investigations including blood culture and nasopharyngeal aspirate (NPA) for common respiratory viruses (influenza A and B, parainfluenza virus, adenovirus, and respiratory syncytial virus) were routinely carried out.[6] For older children, sputum specimens were collected with standard procedures. Additional investigations including tests for pneumococcal antigen (urine or pleural fluid) and PCR assays for *Streptococcus pneumoniae* DNA (pleural fluid) were conducted upon request.[4,7] Request for MP nucleic acid detection was initiated by the frontline clinicians.[2,4] Melting curve analysis was used to identify MRMP mutations retrospectively for this study, as described previously.[2,4] Patients were categorized on the basis of the presence or absence of 23S rRNA gene mutations as MRMP and macrolide-sensitive *M. pneumoniae* (MSMP), respectively. Clinical information was retrospectively obtained from the patient's record. Antibiotics were administered according to standard dosages including macrolides (azithromycin, 10 mg/kg/d, once daily; clarithromycin, 15 mg/kg/d, twice daily), tetracycline (doxycycline, 4 mg/kg/d, twice daily), fluoroquinolones (levofloxacin, 8 mg/kg/d, once daily) and β-lactams (amoxicillin-clavulante, 45−90 mg/kg/d, twice or thrice daily, ceftriaxone, 50−80 mg/kg/d, once or twice daily). The patient demographics, disease course (oxygen requirement and intensive care admission), antibiotic treatment, and outcome were compared between MSMP and MRMP patients. Pneumonia progression was defined by the worsening of respiratory symptoms and increased radiological abnormalities. Macrolide failure was defined by pneumonia progression after at least 2 days of macrolide treatment. The Chi-square or the Fisher's exact test (2-tailed) was used for categorical variables. Continuous variables were tested by using the Student *t* test. The GraphPad software (San Diego, CA, USA) was used for all statistical analyses.

Table 1 Patient characteristics

Characteristics	MSMP group	MRMP group	*p*
No. of patients	68	25	
Age (y)	8.10 ± 3.9	8.96 ± 3.2	0.736
Female	35 (51)	16 (64)	0.350
Days from onset before hospitalization	7.0 ± 2.3	7.5 ± 2.4	0.912
Chronic underlying disease			
Asthma	8 (12)	1 (4)	0.436
Other diseases[a]	3 (4)	1 (4)[b]	> 0.99
Other respiratory pathogen[b]	3 (4)	1 (4)	> 0.99
Antibiotics given			
β-lactam	32 (47)	16 (64)	0.167
Macrolides[c]	48 (70.5)	19 (76)	0.795
Tetracyclines	1 (1.4)	3 (12)	0.058
Quinolones	0 (0)	3 (12)	0.018
Required oxygen	3 (4.4)	4 (16)	0.081
ICU admission	1 (1.5)	2 (8)	0.175
Radiological progression during macrolide	0 (0)	5 (26.3)	0.003
Outcome			
Total fever (d)	8.1 ± 2.8	9.8 ± 3.7	0.039
Length of stay in hospital (d)	3.3 ± 2.3	5.8 ± 4.8	0.001
Change of macrolides to alternative therapy[d]	0	6 (31.6%)	0.001
30-d mortality	0 (0)	0 (0)	NA

[a] Including cardiovascular diseases ($n = 2$) and Down's syndrome ($n = 1$) in the MSMP group and liver transplantation ($n = 1$) in the MRMP group.
[b] Three MSMP patients each with parainfluenza virus, respiratory syncytial virus, and adenovirus respectively, and one MRMP patient with sputum culture positive for *Haemophilus influenzae*. No patient had pneumococcal coinfection.
[c] Three patients in the MSMP group received azithromycin. The remaining 45 patients in the MSMP group and all 19 patients in the MRMP group received clarithromycin.
[d] Percentages among children treated with macrolide.
Data are presented as *n* (%) or mean ± SD.
MRMP = macrolide-resistant *Mycoplasma pneumoniae* pneumonia; MSMP = macrolide-sensitive *M. pneumoniae* pneumonia; NA = not applicable.