Journal of Microbiology, Immunology and Infection (2016) 49, 127—130

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BRIEF COMMUNICATION

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

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Received 28 July 2014; received in revised form 23 September 2014; accepted 5 November 2014
Available online 11 November 2014

KEYWORDS
atypical pneumonia;
empyema;
macrolides

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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http://dx.doi.org/10.1016/j.jmii.2014.11.003

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.

Results

During the study period, PCR for MP was carried out for 327 hospitalized children of which 101 (30.9%) were positive. Eight patients were excluded because there was inadequate material for resistance genotype determination ($n = 7$) or incomplete clinical records ($n = 1$). The remaining 93 patients all had clinical findings indicative of community-acquired pneumonia. Molecular testing of the respiratory specimens revealed the presence of the A2063G mutation in 25 patients (MRMP group), whereas the remaining 68 patients had no mutations (MSMP group). Table 1 showed that the total duration of fever and duration of hospitalization were both significantly longer in the MRMP group than the MSMP group. Significantly more children in the MRMP group than the MRSP group required a change of macrolides to alternative therapy [doxycycline or levofloxacin; 31.6% (6/19) vs. 0% (0/48), $p = 0.001$]. In the MRMP group, change to alternative therapy was required in six children (Table S1 in supplementary data). Two patients had single lobe consolidation (Patients 1 and 3) and four patients had interstitial infiltrates (Patients 2 and 4–6) at presentation. Clinical symptoms had persisted and worsened in all six patients despite macrolide therapy for 3–6 days. In five children, subsequent chest radiographs revealed deterioration of the radiological abnormalities. Multi-lobar consolidation developed in three children (Patients 1–3, Fig. 1). One child developed pleural empyema (Patient 1) and respiratory failure requiring admission to the intensive care unit, ventilation support, and surgical decortication. The remaining three children developed alveolar infiltrates of a segmental nature. All children recovered after switching to doxycycline ($n = 3$), levofloxacin ($n = 1$), or combination of doxycycline and levofloxacin ($n = 2$). A systemic steroid (intravenous methylprednisolone) was given to one child (Patient 1, Fig. 1) because of severe lung injury and slow response to antimicrobial treatment.

Discussion

We described the therapeutic failure of macrolides in the treatment of children hospitalized with MRMP pneumonia. In the MRMP group, a rather high proportion (26.3%, 5/19) of children had pneumonia progression after macrolide failure. This is partly because our hospital is a referral center and sicker children would be transferred from other hospitals to us for further management. Delayed presentation to our hospital after failing therapy as outpatients and a long time lag before the institution of effective therapy are other contributing factors (Table S1 in supplementary data). Therefore, caution is required in the interpretation of the proportion.

As in most other institutions, PCR for MP is not a routine diagnostic test in our hospital.[8] Tests are typically requested when there is a lack of response to standard treatment. Therefore, there is often a time lag of several days to 1 week before laboratory confirmation of the etiological diagnosis. Although several studies have described the therapeutic efficacy of tetracyclines and fluroquinolones in MRMP pneumonia,[3,9] the empirical use of these agents for pediatric pneumonia is a dilemma. Firstly, pneumonia caused by MSMP and MRMP is clinically indistinguishable[1] and there is currently no reliable way of predicting the clinical course of MP pneumonia at presentation. Secondly, tetracyclines and fluroquinolones have the potential for

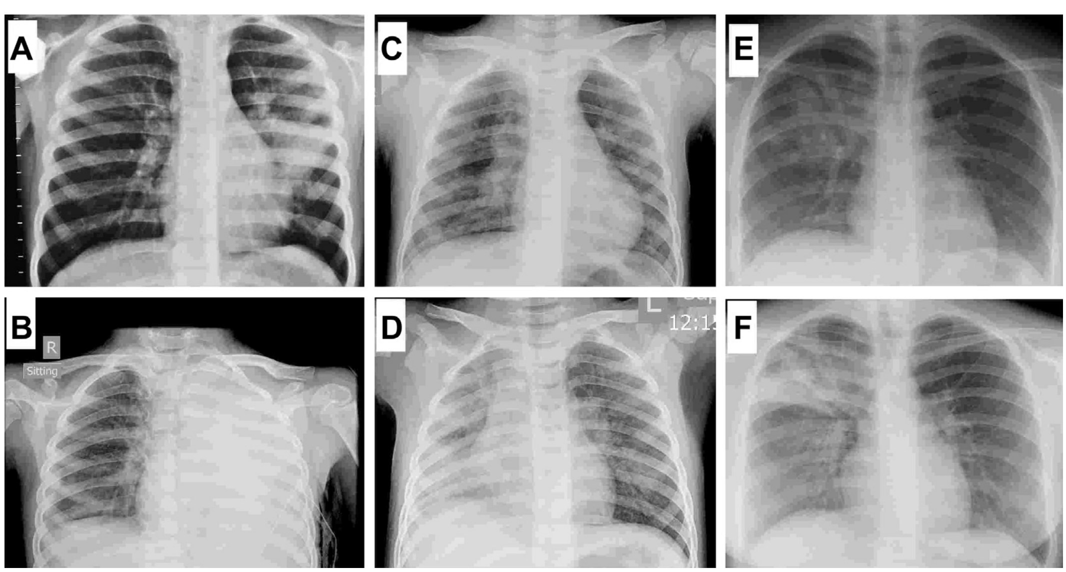

Figure 1. Radiological findings in three hospitalized children with MRMP pneumonia and disease progression after macrolide failure. (A) Patient 1, chest radiograph taken on Day 4 after onset, showing left middle zone consolidation. (B) Patient 1, chest radiograph taken on Day 13 after onset, showing progression of consolidation changes and left side empyema. (C) Patient 2, chest radiograph taken on Day 7 after onset, showing bilateral interstitial infiltrates. (D) Patient 2, chest radiograph taken on Day 12 after onset, showing progression with consolidation changes in right lung and pleural effusion. (E) Patient 3, chest radiograph taken on Day 7 after onset, showing consolidation changes in right upper zone. (F) Patient 3, chest radiograph taken on Day 10 after onset, showing progression of consolidation changes in right lung. MRMP = macrolide-resistant *Mycoplasma pneumoniae* pneumonia.

toxicity in young children. Given the medico-legal implications, the use of these agents for initial treatment of pediatric pneumonia is difficult.[1] Current guidelines on pediatric pneumonia recommend that children with clinical features suspicious of MP be tested to guideline selection, but graded it as a weak recommendation.[8] Recent studies have shown that molecular methods for identifying MP nucleic acid in nasopharyngeal secretions can provide a rapid and reliable diagnosis of MP infection. In our opinion, improving timely access to such rapid tests would definitely help to inform antibiotic selection. However, caution is required in the interpretation of positive MP nucleic acid in the upper respiratory tract because MP may be carried by asymptomatic children and neither serology nor quantitative PCR nor culture differentiated asymptomatic carriage from infection.[10]

In conclusion, this study adds to a better understanding of the consequence of macrolide failure in MRMP pneumonia. Vigilance is required because serious complications can occur in some children within a few days after onset.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

This study has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. This work was supported by grants from the Health and Medical Research Fund (formerly Research Fund for the Control of Infectious Diseases) of the Food and Health Bureau of the Government of the HKSAR; and Consultancy Service for Enhancing Laboratory Surveillance of Emerging Infectious Disease for the HKSAR Department of Health.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2014.11.003.