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# Independent predictors for longer radiographic resolution in patients with refractory *Mycoplasma pneumoniae* pneumonia: a prospective cohort study

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## ABSTRACT

**Objectives** To examine prospectively the radiographic clearance of refractory *Mycoplasma pneumoniae* pneumonia (RMPP) in immunocompetent children, and to identify independent predictors of time to complete radiographic resolution in patients with RMPP.

**Design** A prospective cohort study.

**Setting** Children's Hospital of Soochow University, China.

**Participants** A total of 187 patients with RMPP treated with bronchoscopy were prospectively enrolled in the study between January 2012 and December 2015.

**Methods** Serial chest radiographs were obtained after discharge every 4 weeks up to a maximum of 24 weeks after diagnosis or until large infiltration on chest radiographs had resolved. Multivariate logistic regression was performed to identify independent predictors of time to complete radiographic resolution.

**Results** Of the 187 patients with RMPP, bronchial mucus plug formation was detected in 73 (39.0%). C reactive protein (CRP) ≥50 mg/L, lactate dehydrogenase (LDH) ≥480 U/L, total fever duration ≥10 days and presence of mucus plugs were associated with longer time to radiographic clearance (all p<0.01). Compared with children without mucus plugs, those with mucus plugs were significantly more likely to have longer time to radiographic clearance (adjusted OR: 11.5; 95% CI 2.5 to 45.7; p<0.01).

**Conclusion** Clinicians might use duration of fever, CRP, LDH and presence of mucus plugs as parameters to identify children at a longer time to radiographic clearance in patients with RMPP.

## Strengths and limitations of this study

- This is the first study to analyse prospectively the risk factors associated with longer time to radiographic clearance in patients with refractory *Mycoplasma pneumoniae* pneumonia in China.
- A prospective follow-up of chest radiographs was obtained after discharge every 4 weeks up to a maximum of 24 weeks after diagnosis or until large infiltration on chest radiographs had resolved.
- Our study was a single-centre-based study, which might have introduced a selection bias.
- There might be some patients who had coinfection with other pathogens which could not be detected and might therefore lead to longer radiographic clearance.
- The serum and nasopharyngeal samples were not collected on the same day after disease onset, which might produce measurement bias.

## INTRODUCTION

*Mycoplasma pneumoniae* is a common aetiology of childhood community-acquired pneumonia (CAP).[1 2] *M. pneumoniae* infections are usually mild, while in recent decades paediatricians are facing increasing numbers of patients with refractory *Mycoplasma pneumoniae* pneumonia (RMPP). RMPP often shows no improvement in clinical and radiological findings despite appropriated macrolides treatment. Corticosteroids have been proven to be effective in treating RMPP.[3 4] However, despite the use of corticosteroids, some patients with RMPP still have persisting fever and radiological deterioration. They required investigation using bronchoscopy.[5 6]

We encountered several cases of RMPP who had mucus plug formation under bronchoscopy. RMPP, especially those with mucus plug, may have a longer radiographic resolution time. Some patients may have long-standing pulmonary sequelae such as bronchiectasis.[7 8] No investigations have been reported with careful statistical consideration given to the prognostic significance of factors in the radiographic resolution of RMPP. We sought to examine prospectively the radiographic clearance of RMPP in immunocompetent children. The risk factors associated with longer time to radiographic clearance in patients with RMPP were analysed.

## METHODS

### Cohort description

Patients with CAP who were hospitalised in the Department of Respiratory Medicine

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in the Children's Hospital of Soochow University from 1 January 2012 to 31 December 2015 were evaluated prospectively to identify those who met the criteria for RMPP. RMPP was considered when there is (1) cough, fever or auscultatory findings, together with pulmonary infiltrates on chest radiograph; (2) a significant rise in *M. pneumoniae* IgG or seroconversion in paired sera, together with *M. pneumoniae* DNA detected in nasopharyngeal aspirates; and (3) persisting fever (>38.5°C) and radiological deterioration after macrolide therapy for 7 days or more. Bronchoscopy was indicated when lobar consolidation or atelectasis persisted on chest X-ray film after corticosteroid therapy for 1 week. Chest X-ray films were followed up after discharge every 4 weeks up to a maximum of 24 weeks after diagnosis or until large infiltration on chest radiographs had resolved.

### Patient and public involvement

From 1 January 2012 to 31 December 2015, the following patients were included in our study: (1) patients with cough, fever or auscultatory findings, together with pulmonary infiltrates on chest radiograph; and (2) age of 1 month to 14 years. The following patients were excluded from the study: (1) patients with bronchopulmonary dysplasia, congenital heart diseases, immunodeficiency and heredity neurological disorders; and (2) those who had evidence of coinfection with other pathogens.

### Diagnostic tests for *M. pneumoniae*

Nasopharyngeal aspirates were obtained within 1 day after patients were admitted. As described previously, specimens were tested to amplify fragment of P1 adhesin gene using PCR analysis.[6] A quantitative *M. pneumoniae* DNA diagnostic kit (DaAn Gene, Guangzhou, China) was used. The target specific for *M. pneumoniae* genome is 16S rRNA gene.

Paired serum samples were taken on admission and at least 2 weeks after the first serum sampling. The serum samples were tested for IgM and IgG antibodies against *M. pneumoniae* using an ELISA kit (Serion ELISA MP IgG/IgM, Institut Virion\Serion, Germany). The cut-off value was 0.5 × mean optical density (OD) of the control serum of the kit. As described previously, a significant rise in IgG titre was defined as a doubling of the OD value above the cut-off. A seroconversion was defined as the first serum that was negative and the second serum with an OD at least twice the cut-off.[6]

### Data collection and interpretation of radiographs

Serial posteroanterior and lateral chest radiographs were obtained after discharge every 4 weeks up to a maximum of 24 weeks after diagnosis or until large infiltration on chest radiographs had resolved. All radiographs were evaluated independently by two radiologists (PP and WLG), who did not know patients' clinical condition. Chest radiographs were reviewed by the two radiologists in sequence with the prior films for comparison. If differences in interpretation of radiographs occurred, it would be resolved by joint consensus between the two radiologists. The radiographs were reviewed for the presence of consolidation, atelectasis and pleural disease (effusion or thickening). Consolidation, atelectasis and pleural disease were defined by standard radiographic criteria.[9]

Clinical and laboratory data on gender, age, total fever duration, length of hospital stay, white blood cell (WBC) count, percentage of neutrophils (% neutrophils), platelet count, lactate dehydrogenase (LDH) and C reactive protein (CRP) were collected.

### Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 22.0). For continuous variables, comparison of means was conducted using t-test. For ordinally scaled data, Wilcoxon rank-sum test was used. For categorical variables, $\chi^2$ or Fisher's exact test was used. A univariate analysis of eight influence factors (age, sex, WBC, CRP, LDH, number of involved lobes [unilobar vs multilobar involvement], presence of pleural effusion and presence of mucus plug) was performed. Multiple regression analysis was performed to select the variables associated with time to complete radiographic resolution. Probabilities of 0.05 or less were considered significant. A sample size estimation was calculated using the Power Analysis and Sample Size (PASS) software. Based on a likely sample proportion of interest variable having the tested trait (p) of 45%,[5] with 95% confidence (α=0.05) and a 10% margin of error of the estimate, the minimum required sample size was n=132.

**Table 1** Descriptive analysis of demographic, laboratory, radiographic and bronchoscopic findings of the study population

| Variables | |
|---|---|
| Male to female ratio | 102:85 |
| Age in years, mean±SD | 6.1±2.2 |
| Unilobar disease, n (%) | 99 (52.9) |
| Multilobar disease, n (%) | 88 (47.1) |
| Pleural effusion, n (%) | 46 (24.6) |
| White cell count, median (quartile), $\times 10^9$/L | 7.8 (6.1, 11.0) |
| % Neutrophils, median (quartile) | 75.5 (61.1, 82.4) |
| C reactive protein, median (quartile), mg/L | 32.9 (12.4, 59.7) |
| Lactic dehydrogenase, median (quartile), U/L | 669.5 (486.5, 789.1) |
| Bronchial mucus plug formation, n (%) | 73 (39.0) |
| Total fever duration, median (quartile), days | 10 (7, 13) |
| Length of hospital stay, median (quartile), days | 11 (9, 17) |

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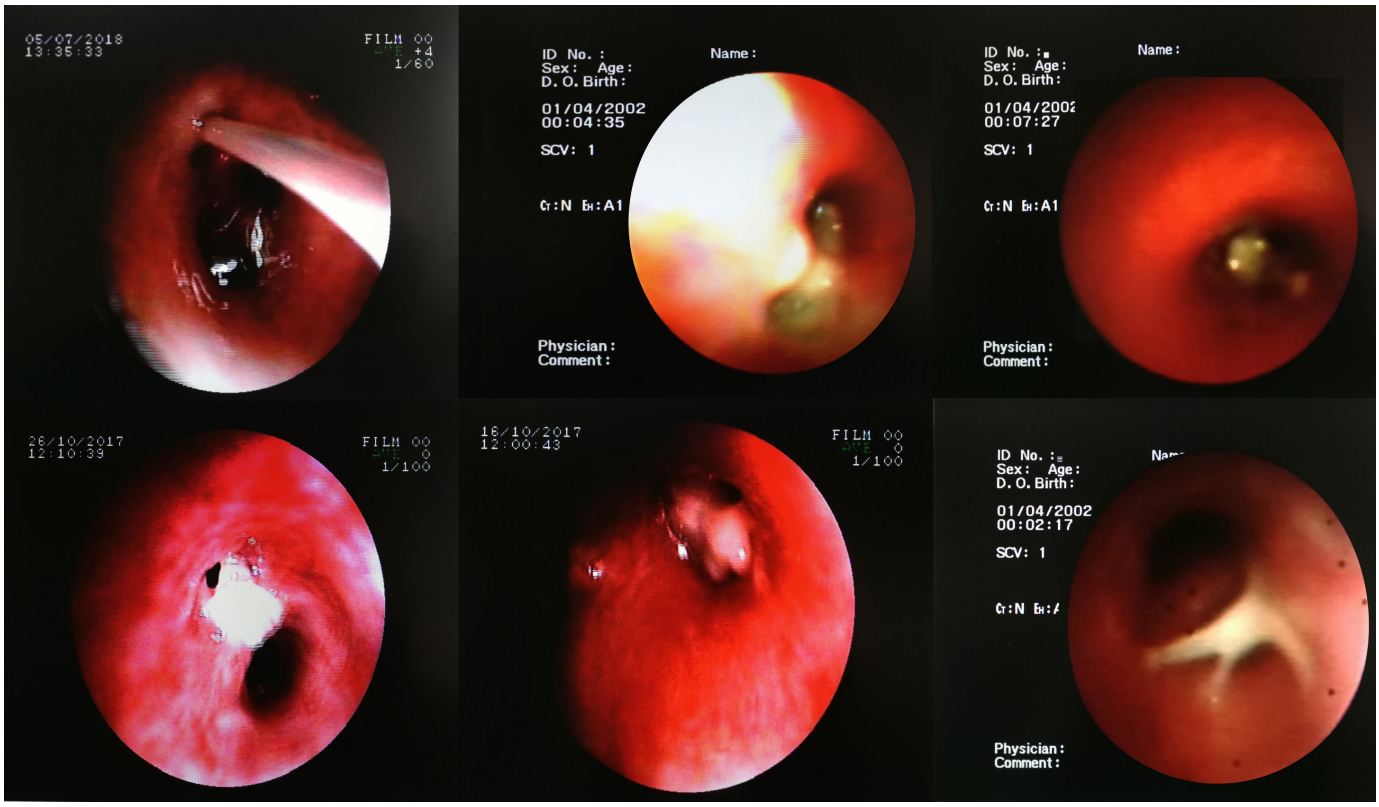


**Figure 1** Bronchoscopic findings of patients with refractory *Mycoplasma pneumoniae* pneumonia with mucus plug.

## RESULTS

In total there were 8482 patients included during the 4-year period. Among these 8482 patients, 2124 (25.0%) were positive by PCR and 2374 (27.9%) had a significant antibody response. *M. pneumoniae* infection was finally diagnosed in 1721 (20.3%) patients. Of the patients with *M. pneumoniae* infection, 223 with RMPP qualified for enrolment in the study. Twenty-one (9.4%) refused to participate, and 15 (6.7%) agreed to participate but did not return for their follow-up chest radiographs. Finally, 187 patients were recruited and received follow-up chest radiographs. These patients were referred to as the study group. The patients who were eligible but excluded (n=36) demonstrated no statistically significant difference in age and sex compared with the studied patients (n=187, both p>0.05). There was also no significant difference in the presence of mucus plug in the study group and unenrolled group (p=0.44).

**Table 2** Radiographic resolution pattern in refractory *Mycoplasma pneumoniae* pneumonia

| Period (week) | Remaining patients* (n=187) | Mucus plug group (n=73) | Non-mucus plug group (n=114) |
|---|---|---|---|
| 0 | 187 | 73 | 114 |
| 4 | 91 | 48 | 43 |
| 8 | 53 | 28 | 25 |
| 12 | 18 | 13 | 5 |
| 16 | 6 | 5 | 1 |
| 20 | 4 | 4 | 0 |
| 24 | 4 | 4 | 0 |

*Patients remaining with abnormal radiographic findings.

The 187 patients with RMPP (86 girls and 101 boys) had a mean age of 6.1±2.2 years. Descriptive statistics are shown in table 1. Ninety-nine (52.9%) had unilobar involvement, while 88 (47.1%) had multilobar involvement. Forty-six (24.6%) had pleural effusion. Bronchial mucus plug formation was detected in 73 (39.0%) patients (figure 1). The median total fever duration was 10 (7, 13) days and the median length of hospital stay was 11 (9, 17) days.

Approximately half of the patients had complete radiographic clearance by 4 weeks, and 72.7% demonstrated radiographic resolution by 8 weeks. One hundred and eighty-three (97.9%) had complete clearance at the end of the study period, and four (0.5%) had persistent abnormalities at 24 weeks (table 2). The median time to radiographic clearance of all participants was 4 weeks (IQR: 4–8 weeks). Twenty-seven per cent of the subjects had a time to radiographic clearance for >8 weeks. In unadjusted analysis, time to radiographic clearance for >8 weeks was associated with % neutrophils, CRP, LDH, pleural effusion, mucus plug and total fever duration when compared with those with time to radiographic clearance ≤8 weeks (all p<0.01; table 3). Other variables (sex, age, lobar involvement and WBC) showed no difference.



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Table 3 Demographic, laboratory, radiographic and bronchoscopic findings of children with refractory *Mycoplasma pneumoniae* pneumonia, according to time to radiographic clearance

| Characteristics | Time to radiographic clearance ≤8 weeks (n=134) | Time to radiographic clearance >8 weeks (n=53) | P value |
|---|---|---|---|
| Male/female | 73/61 | 30/23 | 0.79 |
| Age in years, mean±SD | 5.7±2.5 | 6.3±2.9 | 0.47 |
| White cell count, median (quartile), $\times 10^9$/L | 8.4 (6.3, 11.2) | 8.54 (6, 11.8) | 0.91 |
| % Neutrophils, median (quartile) | 60.3 (21.5, 66.4) | 67.4 (22.1, 72.5) | <0.01 |
| C reactive protein, median (quartile), mg/L | 11.8 (4.9, 28.7) | 22.9 (9.7, 66.4) | <0.01 |
| Lactic dehydrogenase, median (quartile), U/L | 396 (326.6, 506.2) | 515.9 (329.5, 688.9) | <0.01 |
| Multilobar disease, n (%) | 11 (8.2) | 6 (11.3) | 0.51 |
| Pleural effusion, n (%) | 24 (17.9) | 17 (32.0) | <0.01 |
| Bronchial mucus plug formation, n (%) | 13 (9.7) | 21 (39.6) | <0.01 |
| Total fever duration ≥10 days, n (%) | 26 (19.4) | 23 (43.4) | <0.01 |

The multivariable logistic regression model for time to radiographic clearance for >8 weeks is shown in table 4. Controlling for six clinical characteristics, the significant predictors of longer time to radiographic clearance were CRP ≥50 mg/L, LDH ≥480 U/L, total fever duration ≥10 days and presence of mucus plugs (all p<0.01). Compared with children without mucus plugs, those with mucus plugs were significantly more likely to have longer time to radiographic clearance (adjusted OR: 11.5; 95% CI 2.5 to 45.7; p<0.01).

## DISCUSSION

This is the first study, to our knowledge, that focused on the follow-up chest radiographic clearance in patients with RMPP. CRP, LDH, total fever duration and presence of mucus plugs were independently associated with longer time to radiographic clearance.

*M. pneumoniae* infection is a common respiratory disease in children.[10] In recent years, an increasing number of patients with RMPP are being reported, especially in Asian countries.[4 11–14] The role of mucus plug in RMPP has been extensively studied recently.[5 6 15] Xu *et al*[5] identified age, total fever duration, LDH and CRP as independent risk factors for mucus plug formation. Wang *et al*[15] found that on bronchoscopic imaging, the mucus plug served as a promising predictor of early RMPP diagnosis for paediatric patients with large pulmonary lesions. Our previous study also found that patients with RMPP with mucus plug were prone to being corticosteroid-resistant and had a longer total fever duration and hospital stay.[6] Our study further highlighted the role of mucus plugs in the time to radiographic clearance in patients with RMPP.

Table 4 Multivariable predictors of time to radiographic clearance >8 weeks among children with refractory *Mycoplasma pneumoniae* pneumonia

| Characteristics | OR (95% CI) | P value |
|---|---|---|
| C reactive protein ≥50 mg/L | 3.1 (1.7 to 5.2) | <0.01 |
| Lactic dehydrogenase ≥480 U/L | 2.8 (1.5 to 4.5) | <0.01 |
| Total fever duration ≥10 days | 13.5 (7.8 to 41.4) | <0.01 |
| Bronchial mucus plug formation | 11.5 (2.5 to 45.7) | <0.01 |

In our study, we found that the presence of mucus plugs was associated with longer time to radiographic clearance in patients with RMPP. Liang and her colleagues[8] found that *M. pneumoniae* pneumonia with severe cilia abnormalities was associated with longer time to radiographic clearance, but they did not focus on analysis of the mucus plugs in the bronchoscopic findings. Mucus plug formation was actually a manifestation of severe cilia abnormalities. Severe cilia abnormalities disrupt the mucociliary clearance, causing mucus plug which is responsible for the development of atelectasis and delayed radiographic resolution.[10 16] The persistent presence of atelectasis led to a longer radiographic resolution time and long-standing pulmonary sequelae, such as bronchiectasis or bronchiolitis obliterans.[17–19] Thus, careful management and follow-up are needed for patients with mucus plugs.

Currently, bronchoscopy is an important tool for therapeutic interventions in patients with lobar atelectasis.[7 20 21] Zhang *et al*[7] investigated 35 paediatric subjects with RMPP and found that bronchoscopy was efficacious and well tolerated. Abu-Hasan *et al*[20] suggested that bronchoscopy could be safe and effective in treating acute lung collapse and atelectasis that was refractory to conventional therapy. Kreider and Lipson[21] also found that bronchoscopy was safe and effective in treating critically ill patients. Our study also highlighted the importance of bronchoscopy, especially for patients with mucus plug.

To investigate the risk factors for longer time to radiographic clearance, we also chose variables that are commonly examined in our hospital. Three independent factors, namely total fever duration, CRP and LDH, were identified. LDH and CRP were variables that are elevated in many pulmonary diseases and were reported to be associated with RMPP in several studies.[13–15 22] Recently, serum LDH 4 plus 5 were found to be better biomarkers



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than the total LDH for RMPP in children.[23] The precise mechanisms of RMPP remain unknown. Pathogen-related substances or other host factors during hyperactive immune reactions may be responsible for lung injury.[24] Therefore, it may be logical to propose that patients with severe RMPP have severe lung injury and higher clinical parameter values such as CRP and LDH, requiring long-term recovery time. LDH level may be associated with true lung injury and subsequent prolonged recovery period of tissue repair. Therefore, it is reasonable to recommend that the early use of immune modulators, without waiting for the antibiotic's effect, contributes to the effective reduction of immune-mediated lung injury in *M. pneumoniae* infection.[25]

The study has some limitations. First, our study was a single-centre-based study, which might have introduced a selection bias. The results reported in our Soochow area cannot be extrapolated to other areas in China. Thus, a multicentre study is needed in the future. Second, there might be some patients who had coinfection with other pathogens which could not be detected and might therefore lead to longer radiographic clearance. Third, the serum and nasopharyngeal samples were not collected on the same day after disease onset, which might produce measurement bias.

In conclusion, clinicians might use duration of fever, CRP, LDH and presence of mucus plugs as parameters to identify children at a longer time to radiographic clearance in patients with RMPP.

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**Contributors** YY conceived and designed the study. RZ and WJ conducted the study. LH and XH analysed the data and interpreted the data. LH provided guidance on the data analysis. All authors drafted the manuscript, and read, edited and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Competing interests** None declared.

**Patient consent for publication** Parental/guardian consent obtained.

**Ethics approval** This research project was reviewed and approved by the Institutional Review Board of Suzhou University.

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**Data sharing statement** No additional unpublished data are available.

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