Effects of Bronchoalveolar Lavage on Refractory *Mycoplasma pneumoniae* Pneumonia

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INTRODUCTION: This study prospectively evaluated the effect of early bronchoalveolar lavage (BAL) on refractory *Mycoplasma pneumoniae* pneumonia with radiologically proven large pulmonary lesions in children. METHODS: A total of 35 children diagnosed as having refractory *M. pneumoniae* pneumonia with radiologically proven large pulmonary lesions completed the study. According to the time point of BAL, they were divided into 2 groups. In the early BAL group, BAL was performed within 3 d after admission ($n = 22$); in the late BAL group, BAL was performed 3 d later after admission ($n = 13$). Clinical effects were compared between these 2 groups. RESULTS: After BAL therapy, improvement in clinical symptoms and laboratory findings as well as resolution of pulmonary lesions on radiography were obtained in all subjects. The median fever duration after admission was 4 (2–7) d and 5 (2–10) d ($P < .05$), and the median hospitalization duration was 7 (5–10) d and 10 (5–14) d ($P < .05$), respectively, in the early BAL group and the late BAL group. Approximately 7 d after admission, 67% of subjects in the early BAL group showed resolution of atelectasis on x-ray image versus a corresponding rate of 14% in the late BAL group ($P < .05$). Furthermore, laboratory indices recovered quicker in the early BAL group than in the late BAL group ($P < .01$). CONCLUSIONS: BAL appeared to be efficacious and well-tolerated treatment for refractory *M. pneumoniae* pneumonia with radiologically proven large pulmonary lesions, and early application of BAL may be more beneficial. *Key words: bronchoalveolar lavage; children; mycoplasma pneumonia; pneumonia; refractory; flexible bronchoscopy.* [Respir Care 2014;59(9):1433–1439.

Introduction

Mycoplasma pneumoniae is a common causative organism of respiratory infections in children.[1,2] Although *M. pneumoniae* pneumonia is usually a benign self-limited disease, it may sometimes cause various extrapulmonary complications such as encephalitis,[3] arthritis,[4] pericarditis,[5] and anemia,[6] and can progress to a severe life-threatening pneumonia, such as necrotizing pneumonitis,[7] ARDS,[8] and fulminant pneumonia.[9]

For children, macrolides are the first choice agents for *M. pneumoniae* infections. However, there still are chances for aggravation of *M. pneumoniae* infection despite appropriate antibiotic therapy. These cases are usually defined as refractory *M. pneumoniae* pneumonia showing clinical and radiological deterioration despite macrolide antibiotic therapy for 7 d or longer.[10,11] Although the underlying mechanisms are still uncertain, the macrolide-resistant *M. pneumoniae* infection and excessive immunological in-

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flammation are most commonly proposed.[12,13] Based on the latter mechanism, corticosteroids have been used with satisfactory therapeutic effect for children with refractory *M. pneumoniae* pneumonia.[11,14,15] However, due to the potential risk of causing side effects and blurring diagnosis when using corticosteroids early in medication, it is advisable for physician to make decisions prudently.

Flexible fiberoptic bronchoscopy (FOB) was first reported to be performed in children 23 y ago,[16] and since then it has been widely accepted and applied.[17-19] The main advantages of the FOB include 3 aspects. First, endobronchial abnormalities up to the fifth generation can be visualized directly. Second, samples from the lower airway can be obtained for bacteriologic, cytologic, and histologic detection with minimal damage. Third, FOB can offer additional therapeutic interventions, such as removing mucous plug or foreign body.[20,21] Therefore, FOB with bronchoalveolar lavage (BAL) has now become an important means of diagnosis and therapy for respiratory diseases, including refractory pneumonia. However, until now there has been a paucity of data about BAL for the diagnosis and therapy of pediatric refractory *M. pneumoniae* pneumonia.

In this report, we prospectively studied 35 pediatric subjects with refractory *M. pneumoniae* pneumonia, who showed large lesions on their chest radiograph. Therapeutic BAL was adopted, and its clinical, laboratory, and radiological effects were analyzed.

QUICK LOOK

Current knowledge

Mycoplasma pneumonia is a common cause of respiratory infections in children. Refractory *Mycoplasma pneumoniae* pneumonia is defined as clinical and radiological deterioration despite macrolide antibiotic therapy for 7 d. Refractory *M. pneumoniae* pneumonia is associated with systemic complications.

What this paper contributes to our knowledge

Therapeutic bronchoalveolar lavage (BAL) in children with refractory *M. pneumoniae* pneumonia with radiologic evidence of large pulmonary lesions reduced fever, corrected laboratory indices, and provided symptomatic relief. Early BAL in refractory *M. pneumoniae* pneumonia should be considered.

Methods

Subjects

We conducted the study at Children's Hospital, Zhejiang University School of Medicine (Hangzhou, People's Republic of China). All the refractory *M. pneumoniae* pneumonia patients who were admitted to the hospital between January 1, 2013 and June 30, 2013 were eligible for the study. All the subjects had signs and symptoms indicative of pneumonia on admission, including fever, cough, abnormal lung auscultation, and a new infiltrate on chest radiograph.[22] The diagnosis of *M. pneumoniae* infection was based on positive results for serologic test (*M. pneumoniae* immunoglobulin M-positive and antibody titer $\geq$ 1:160) and/or positive results for *M. pneumoniae* polymerase-chain-reaction tests of nasopharyngeal secretions or BAL. The diagnosis of refractory *M. pneumoniae* pneumonia was based on the presence of persistent fever and clinical as well as radiological deterioration after azithromycin treatment for 7 d or longer.[10,11] In addition, to be eligible for recruitment, subjects were required to have large pulmonary lesions on radiological findings. Large lesion means that the extent of infiltration on chest radiography was more than one third of the lung.[23] We excluded patients with other respiratory tract infections and tuberculosis by the following tests: purified protein derivative, blood cultures, nasopharyngeal aspirate/swab cultures, nasopharyngeal aspirate/swab for virus antigens detection (respiratory syncytial viruses, influenza viruses, adenovirus, and parainfluenza virus), and serology for *Chlamydia pneumoniae* and *Legionella pneumophila*. Patients who received corticosteroids before admission or had underlying diseases such as chronic cardiac and pulmonary disease and immunodeficiency were also excluded.

Study Design

This was an observational prospective study. All of the enrolled subjects had indications for FOB and BAL because of radiologically proven large pulmonary lesions and unresponsiveness to routine antibiotic therapy. Once parental consent was obtained and preoperative preparations were completed, the BAL was performed. According to the time point of BAL, they were divided into 2 groups. The early BAL group subjects received BAL within 3 d after admission (including the third day of hospitalization), whereas the late BAL group had this procedure $>$ 3 d after admission. Both groups received similar supportive and symptomatic treatments, including sputum aspiration, nebulization, and fluid therapy. Subjects were discontinued from the study if they met exclusion criteria during the hospitalization, if their parents were unwilling for them to remain as study subjects, or if they were discharged before the end of study.

The study was approved by the ethics committee of the Children's Hospital, Zhejiang University School of Medicine. All parents or legal guardians provided written in-

formed consent before conducting the study and any study-related procedures.

BAL Under Flexible Bronchoscopy

According to the age and body weight of the subjects, 3 kinds of FOB were used as follows: Olympus (Japan) BFXP40 (2.8 mm external diameter and 1.2 mm working channel), BF-3C30 (3.6 mm, 1.2 mm), and BF-P40 (4.9 mm, 2.2 mm). After fasting for > 6 h, the subjects were sedated with intravenous midazolam (0.1–0.15 mg/kg), and topical anesthesia with 1% lidocaine to the nose, vocal cords, and trachea was added. The flexible bronchoscope was wedged in the orifice of lobar bronchi where the large pulmonary lesion was localized on chest radiograph. BAL with normal saline (weight < 20 kg: 1 mL/kg/time, 3 times; weight > 20 kg: 20 mL/time, 3 times) was conducted with −25 to approximately −100 mm Hg suction. We also collected BAL fluid from subjects for microbiological determinations, as we previously reported.[24,25] During the procedure, we monitored the heart rate, breathing frequency, and pulse oxygen saturation (S_{pO_2}). Once hypoxia (cyanosis, low S_{pO_2}, and/or high heart rate) occurred, oxygen of appropriate concentration was given at once, and the procedure was stopped temporarily when necessary.

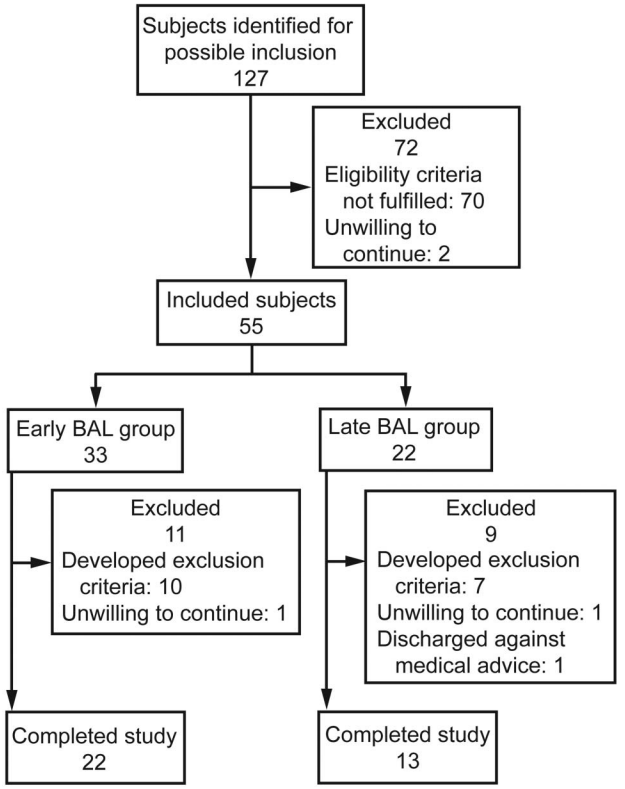

Fig. 1. Study flow chart. BAL = bronchoalveolar lavage.

Data Collection

The following data before and during hospitalization were recorded: demographics; fever duration before admission; duration of macrolide therapy before admission; the incidence of severe *M. pneumoniae* pneumonia and extrapulmonary complications; the presence of lobar atelectasis and pleural effusion; and the results of blood tests including white blood cell (WBC) count, the differential of neutrophils as well as lymphocytes, C-reactive protein, procalcitonin, and lactate dehydrogenase. All subjects were followed until discharge from hospital. Body temperature and respiratory tract signs and symptoms of subjects were examined at study entry and every 8 h thereafter. A febrile day was defined as a day during which the body temperature exceeded 38.0°C at least once.[26] Febrile days after admission and hospitalized days were also assessed. The WBC count and C-reactive protein were detected at study entry and every 2–3 d thereafter. All subjects underwent chest x-rays before admission and again approximately 7 d after admission. The severity of pneumonia was evaluated according to the diagnostic standard of pneumonia advocated by British Thoracic Society.[27] During the hospitalization, we also evaluated the extrapulmonary complications (eg, liver function abnormalities, myocarditis, encephalitis, and rash) of subjects.[28] The safety of subjects was also evaluated by recording adverse events during hospitalization.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 software (SPSS, Chicago, Illinois). Normally distributed data were expressed as mean ± SD. An independent-sample *t* test was used to compare these data. Data with a skewed distribution were expressed as median values (range from minimum to maximum). The comparisons were made by Mann-Whitney U test. Chi-square tests were used to compare categorical data. Statistical significance was defined as $P < .05$.

Results

General Information and Clinical Data

One hundred and twenty-seven subjects were identified as suffering from refractory *M. pneumoniae* pneumonia and therefore potentially eligible for the study. We excluded 70 of those subjects because they did not fulfill the inclusion criteria, and 2 subjects were not willing to continue. Twenty subjects did not complete the study because they developed exclusion criteria, were unwilling to con-

Table 1. Clinical Information of Refractory *Mycoplasma pneumoniae* Pneumonia Subjects Before BAL Therapy

Clinical information	Total Subjects (n = 35)	Early BAL Group (n = 22)	Late BAL Group (n = 13)	P
Age (y)	7.3 ± 2.8	7.6 ± 2.7	6.8 ± 3.0	.41
Male/female	20/15	12/10	8/5	.69
Fever duration prior to admission (d)*	8 (7–21)	8 (7–21)	8 (7–13)	.78
Duration of macrolide therapy before admission (d)*	7 (7–13)	7 (7–13)	7 (7–9)	.43
WBC ($\times 10^9$/L)*	6.91 (1.98–21.30)	6.48 (3.59–21.30)	7.77 (1.98–14.68)	.89
N (%)*	73.0 (24.7–86.5)	70.9 (28.9–82.2)	77.5 (24.7–86.5)	.35
L (%)*	18.9 (8.1–72.3)	20.0 (10.5–63.8)	15.3 (8.1–72.3)	.15
C-reactive protein (mg/dL)*	37 (2–160)	45 (4–160)	28 (2–160)	.05
Procalcitonin (ng/mL)*	0.20 (0.06–5.46)	0.17 (0.06–3.21)	0.45 (0.09–5.46)	.65
LDH (IU/L)*	494 (110–2159)	461 (165–893)	503 (110–2159)	.28
Subjects with lobar atelectasis on chest x-ray (%)†	46 (16/35)	41 (9/22)	54 (7/13)	.46
Subjects with pleural effusion on chest x-ray (%)†	51 (18/35)	50 (11/22)	54 (7/13)	.83
Subjects with severe *M. pneumoniae* pneumonia (%)†	29 (10/35)	32 (7/22)	23 (3/13)	.58
Subjects presenting with extrapulmonary complications (%)†	54 (19/35)	50 (11/22)	62 (8/13)	.51
Digestive system (liver function abnormalities)†	53 (10/19)	55 (6/11)	50 (4/8)	
Cardiovascular system (myocarditis)†	16 (3/19)	18 (2/11)	13 (1/8)	
Rash†	26 (5/19)	27 (3/11)	25 (2/8)	
Nervous system (encephalitis)†	5 (1/19)	0 (0/11)	13 (1/8)	

LDH normal range: 120–300 IU/L. *P*, group 1 vs group 2.
* Data are shown as median (range).
† Data are shown as percentage (n).
BAL = bronchoalveolar lavage
WBC = white blood cells
N = neutrophils
L = lymphocytes
LDH = lactate dehydrogenase

tinue, or left the hospital against medical advice. The remaining 35 subjects completed the study (Fig. 1).

Clinical information of enrolled subjects before admission is shown in Table 1. The mean age of the 35 subjects was 7.3 ± 2.8 y (range, 1–13 y). Twenty subjects were male. The median prior-to-admission duration of fever was 8 (7–21) d. The median WBC count on admission was 6.91 (1.98–21.30) × 10^9/L with 73.0% (24.7–86.5%) neutrophils and 18.9% (8.1–72.3%) lymphocytes. The median value of C-reactive protein was 37 (2–160) mg/dL, which was severalfold higher than normal reference. The median levels of procalcitonin and lactate dehydrogenase on admission were 0.20 (0.06–5.46) ng/mL and 494 (110–2,159) IU/L, respectively. Of the 35 subjects, extrapulmonary complications were found in 19 cases (54%), including liver function abnormalities in 10, myocarditis in 3, rash in 5, and encephalitis in 1. We also evaluated the severity of *M. pneumoniae* pneumonia and found the incidence of severe *M. pneumoniae* pneumonia was 29% in all subjects. However, none of these subjects was transferred to the ICU or given mechanical ventilation during hospitalization. The median hospitalization duration was 7 (5–14) d. In addition to clinical symptoms, radiological findings were also evaluated. We found that 46% of the subjects showed lobar atelectasis and 51% of the subjects showed pleural effusion on their chest x-rays.

Among the 35 subjects, 34 yielded positive results for both *M. pneumoniae* immunoglobulin M in serum and polymerase-chain-reaction test in nasopharyngeal secretions and/or BAL. One subject had positive *M. pneumoniae* immunoglobulin M only. *M. pneumoniae* polymerase chain reaction was positive in 31 subjects (89%) using BAL specimens, and in 22 subjects (63%) using nasopharyngeal secretions (P = .01).

Baseline characteristics of the early BAL group and the late BAL group were compared in Table 1. Twenty-two subjects were enrolled in the early BAL group (12 males, 10 females), with a mean age of 7.6 ± 2.7 y (range, 1–13 y). Thirteen subjects were enrolled in the late BAL group (8 males, 5 females), with a mean age of 6.8 ± 3.0 y (range, 2–11 y). The median time lag from admission to BAL procedure was 2.5 (1–3) d in the early BAL group and 5 (4–12) d in the late BAL group. Between these 2 groups, there were no significant differences in these baseline data, including fever duration before admission, duration of macrolide treatment before admission, laboratory

Table 2. Clinical Information of Refractory *Mycoplasma pneumoniae* Pneumonia Subjects After BAL Therapy

Information	Total Subjects ($N = 35$)	Early BAL Group ($n = 22$)	Late BAL Group ($n = 13$)	*P*
Fever duration after admission (d)*	4 (2–10)	4 (2–7)	5 (2–10)	.03
Median hospitalization duration (d)*	7 (5–14)	7 (5–10)	10 (5–14)	.02
Median time for WBC count recovered (d)*	6 (1–13)	6 (1–7)	8 (1–13)	.003
Median time for C-reactive protein recovered (d)*	7 (1–13)	6 (1–7)	8 (1–13)	.001
Atelectasis resolution rate (%)†	44 (7/16)	67 (6/9)	14 (1/7)	.04
Pleural effusion disappearance rate (%)†	39 (7/18)	55 (6/11)	14 (1/7)	.09
Subjects with mucus plugs under bronchoscope (%)†	20 (7/35)	14 (3/22)	31 (4/13)	.22
Subjects with positive result for *M. pneumoniae* polymerase chain reaction of BAL (%)†	89 (31/35)	96 (21/22)	77 (10/13)	.10

P, group 1 vs group 2. We evaluated the atelectasis resolution rate and pleural effusion disappearance rate ~7 d after admission (if the hospitalization duration was < 7 d, we evaluated on the day of discharge).
* Data are shown as median (range).
† Data are shown as percentage (*n*).
BAL = bronchoalveolar lavage
WBC = white blood cells

abnormalities, severity of radiographic findings, incidence of extrapulmonary complications, and incidence of severe *M. pneumoniae* pneumonia, as shown in Table 1.

Clinical, Laboratory, and Radiological Effectiveness

Among 35 subjects who received bronchoscopy, bronchial membrane inflammation was noted in all subjects, whereas mucus plug was noted only in 7 subjects. As shown in Table 2, we found that there were no significant differences between the 2 groups in the incidence of mucus plug (14% vs 31%, $P = .22$). We also compared the positive rate for *M. pneumoniae* of BAL in all subjects, and found that the positive rate for *M. pneumoniae* was 96% in the early BAL group and 77% in the late BAL group, with no significant difference ($P = .10$).

After BAL therapy, symptom relief was obtained in all subjects. Peak body temperature decreased significantly within 24 h in all subjects, and body temperature returned to normal in 28 (out of 35) subjects within 2 d. The median duration of fever after BAL therapy was 1 (0–6) d. Moreover, rapid resolution of atelectasis in pulmonary lobes was documented on radiography (Fig. 2).

Comparing data between the 2 groups, we found that the median duration of fever after admission was shorter in the early BAL group (4 [2–7] d) than that in the late BAL group (5 [2–10] d) ($P = .03$). The early BAL group's median hospitalization duration was 7 (5–10) d versus the late BAL group's 10 (5–14) d ($P = .02$). As shown in Table 2, we also found that WBC count and C-reactive protein recovered more quickly in the early BAL group than those in the late BAL group ($P = .003$, $P = .001$, respectively). In addition to clinical symptoms, we found improved radiological manifestations in the early BAL group compared to the late BAL group. Approximately 7 d after admission, 67% of subjects in the early BAL group showed atelectasis resolution versus 14% in the late BAL group ($P = .04$). A higher rate of pleural effusion disappearance was also seen in the early BAL group when compared with the late BAL group (55% vs 14%), but the difference did not reach statistical significance ($P = .09$).

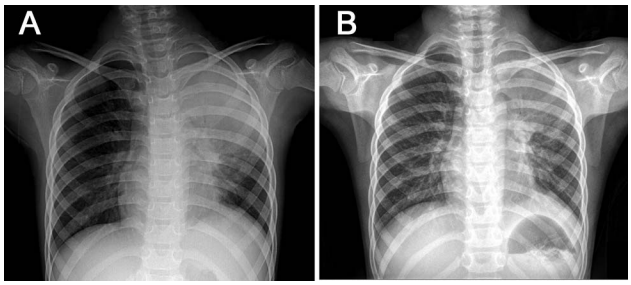

Fig. 2. Chest radiographies of case 1 (8-y-old female). A: on admission; B: 7 d after bronchoalveolar lavage therapy.

Adverse Events

There were no obvious adverse events in any subjects during the BAL procedure. After performing BAL, no deterioration in clinical manifestations, radiographic findings, or laboratory results was observed in any subjects from either group. All subjects were discharged without morbidity.

Discussion

Although *M. pneumoniae* infection was traditionally thought to be a self-limited process, increasing numbers of severe and even fatal cases of *M. pneumoniae* infections

have been reported.[3-9] Reports of cases of refractory *M. pneumoniae* pneumonia, which displays clinical and radiological progression after macrolide therapy for 7 d or longer, are increasing as well.[11,14,15]

The reasons why refractory *M. pneumoniae* pneumonia occurs remain unclear, but it is widely accepted that immunological response mediated by T cells seems to play an important role in the progress of refractory *M. pneumoniae* pneumonia. Animal studies showed that the peribronchiolar and perivascular regions were initially infiltrated by a large number of lymphocytes, mainly CD_4 T cells when the animals were infected with *M. pneumoniae*.[29] It was also demonstrated that the levels of serum interleukin-18, which promoted Th1 responses, were higher in severe *M. pneumoniae* infection than those in mild cases.[30] Thus, stronger immunological reactions may underlie more severe pathological infiltration in the lung. In our study, the elevated C-reactive protein may have indicated severe systemic inflammatory response to *M. pneumoniae* infection.

Given that the *M. pneumoniae* infection was an immunity-mediated disease, clinicians could adopt immunosuppressive therapy to treat it. There have been some reports demonstrating that corticosteroids were used for refractory *M. pneumoniae* pneumonia in children with satisfactory results. Tamura et al[11] reported that it was apparently an efficacious and well-tolerated treatment to administer methylprednisolone intravenously with a dosage of 30 mg/kg/d for 3 consecutive days for refractory *M. pneumoniae*. Luo et al[14] demonstrated that oral prednisolone of 2 mg/kg/d combined with intravenously azithromycin was helpful for children with refractory *M. pneumoniae* pneumonia.

However, tuberculosis is still a heavy burden in China, and it should be taken into account when differential diagnosis is made for refractory pneumonia. Some patients may be simultaneously infected with *M. pneumoniae* and tuberculosis, and sometimes transient tuberculin anergy may occur in *M. pneumoniae* infection. Therefore, clinicians should rule out tuberculosis as a potential cause of pulmonary infiltrates, especially in refractory pneumonia, and prescribe corticosteroid administration with caution. Because it will take several days to exclude tuberculosis, delayed use of corticosteroids might result in longer fever duration and more severe pulmonary inflammation. Therefore, we should find a new way to help control local inflammation in refractory *M. pneumoniae* pneumonia.

Currently, FOB with BAL is an important and indispensable tool to assess the structure and function of lower airways and to diagnose pulmonary infiltrative lesions in pediatric patients. Lacroix et al[31] have demonstrated that BAL was safe and more efficient than blood culture to detect pathogens in patients presenting with pneumonia. In our results, we found that BAL was a more effective method to identify pathogens than nasopharyngeal secretion detection (89% vs 63%, $P = .01$). Furthermore, endobronchial tuberculosis could be excluded earlier. Additionally, FOB could also perform therapeutic interventions. Several studies have shown that FOB with BAL was the preferred treatment for lobar atelectasis.[32,33] Abu-Hasan et al[32] suggested that BAL could be safe and effective in treating acute lung collapse and atelectasis that was refractory to conventional therapy. To our knowledge, this is the first study to focus on the effect of BAL in patients with refractory *M. pneumoniae* pneumonia in a prospective fashion. In our study, we evaluated the effect of BAL on refractory *M. pneumoniae* pneumonia with large infiltrative lesions in 35 subjects, and analyzed the impact of application time on the curative effect. Interestingly, we found that after BAL therapy peak body temperature in all subjects decreased significantly within 24 h, and radiological as well as laboratory abnormalities recovered rapidly. Furthermore, our study showed that early application of BAL could ameliorate clinical symptoms faster, and improve radiographic and laboratory findings earlier than late application. After starting the therapy, body temperature for subjects in the early BAL group returned to normal within 4 (2–7) d versus 5 (2–10) d in the late BAL group ($P < .05$). Hospitalization duration was shortened and more subjects obtained atelectasis resolution in the early BAL group than in the late BAL group ($P < .05$). Peripheral WBC count and C-reactive protein recovered more quickly in the early BAL group ($P < .01$). However, our study involved only a small number of subjects, and a larger prospective study is needed to confirm the role of BAL therapy in refractory *M. pneumoniae* pneumonia.

Conclusions

We performed an observational prospective study evaluating the effect of BAL in children with refractory *M. pneumoniae* pneumonia and radiologically proven large pulmonary lesions. The BAL intervention demonstrated a positive outcome with rapid improvement in clinical, radiographic, and laboratory results. Early application of BAL may render greater benefit in curing children with refractory *M. pneumoniae* pneumonia and large pulmonary lesions.

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