

# Low-dose versus high-dose methylprednisolone for children with severe *Mycoplasma pneumoniae* pneumonia (MCMP): Study protocol for a randomized controlled trial

Baoping Xu<sup>1\*</sup> | Xiaoxia Peng<sup>2\*</sup> | Yao Yao<sup>1</sup> | Ju Yin<sup>1</sup> | Lanqin Chen<sup>1</sup> | Jun Liu<sup>1</sup> | Hao Wang<sup>1</sup> | Liwei Gao<sup>1</sup>  
Adong Shen<sup>3</sup> | Kunling Shen<sup>1</sup>

<sup>1</sup>China National Clinical Research Center for Respiratory Diseases, Department of Respiratory Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

<sup>2</sup>Center for Clinical Epidemiology & Evidence-based Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

<sup>3</sup>Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

## Correspondence

Kunling Shen, China National Clinical Research Center for Respiratory Diseases, Department of Respiratory Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China.  
E-mail: kunlingsheng1717@163.com

\*These authors contributed equally to this work.

## Funding source

This study is supported by National Key Technology Research and Development Program of the Ministry of Science & Technology of China (2013BAI09B11), Capital Health Research and Development of Special (2014-1-2094 and 2016-1-2092) and Beijing Municipal Science & Technology Commission (Z171100001017081).

Received: 25 January, 2018

Accepted: 25 May, 2018

## ABSTRACT

**Background:** Severe *Mycoplasma pneumoniae* pneumonia (MPP) may develop with long-term pulmonary outcomes despite treatment with macrolides. Combined treatment with glucocorticoids can improve this outcome, though the optimal dosage is unknown. The aim of this study was to investigate the effects of low- and high-dose methylprednisolone in reducing the percentage of long-term pulmonary outcomes for children with severe MPP.

**Methods:** A randomized, single-blind, parallel-controlled, multicenter clinical trial, methylprednisolone for children with severe *M. pneumoniae* pneumonia (MCMP), is being conducted in China. Pediatric patients ( $\leq 18$  years of age, expected number = 402) admitted to the hospital with a clinical diagnosis of severe MPP and fulfilling inclusion and exclusion criteria are randomized (ratio of 1:1) to either a low-dose (2 mg/kg/d) or high-dose (10 mg/kg/d) methylprednisolone treatment group for 3 days followed by tapering of methylprednisolone over 12 days and combined with azithromycin. The primary composite outcome will be incidence of atelectasis, bronchiectasis, or bronchiolitis obliterans at 6-months after treatment. Secondary outcomes include recovery time of patient temperature, proportion of pulmonary lesions absorbed, changes of mucosa identified by bronchoscopy, length of hospital stay, pulmonary function and number of participant(s) needing intensive care. Assessments will be made at baseline, post-treatment and at 1-month, 3-month and 6-month follow-ups.

**Discussion:** This is the first randomized clinical trial designed to evaluate the safety and efficacy of low- versus high-dose methylprednisolone for reducing long-term pulmonary outcomes in pediatric patients with severe MPP. The results of this study will provide scientific evidence to guide clinical practice for the treatment of severe MPP. Trial registration: This study is registered at ClinicalTrials.gov (NCT02303587).

## KEYWORDS

Glucocorticoids, Severe *Mycoplasma pneumoniae* pneumonia, Children

DOI: 10.1002/ped4.12041

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

©2018 Chinese Medical Association. *Pediatric Investigation* published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development.

## INTRODUCTION

*Mycoplasma pneumoniae* is one of the major pathogens causing community-acquired pneumonia (CAP) in Chinese children, accounting for 47.8% of CAP in children of all ages. In children 5 years or older, *M. pneumoniae* accounts for over 70% of CAPS cases, which is higher than in the U.S. (19% in children over 5 years old).<sup>1,2</sup> The prognosis for patients with *M. pneumoniae* pneumonia (MPP) is usually good. However, cases of severe MPP are often complicated by multi-organ damage (e.g. hepatitis, myocarditis, encephalitis) or serious long-term pulmonary outcomes such as bronchiolitis obliterans, bronchiectasis, or atelectasis.<sup>3</sup> It has been reported that the incidence of severe MPP in Chinese children has been increasing over the past ten years, reaching approximately 40% of all MPP cases.<sup>4-7</sup> The pathogenesis of severe MPP is unclear, though there is some evidence implicating excessive cytokine release and activation of cell-mediated immune responses to the pathogen as well as development of macrolide resistance.<sup>8</sup>

Optimal treatment of children with severe MPP is unclear. Recent studies have suggested that azithromycin combined with glucocorticoids may improve the prognosis of children with severe MPP.<sup>9-12</sup> Lee et al reported that when prednisolone (1 mg/kg/d for 3–7 days) was added to the treatment of children with severe or refractory MPP, the clinical status and radiographic findings were better than for children treated with azithromycin alone.<sup>13, 14</sup> You et al<sup>15</sup> and Tamura et al<sup>16</sup> showed methylprednisolone (30 mg/kg/d) pulse therapy in patients with severe or refractory MPP quickly improved the radiological and laboratory abnormalities of these patients. Youn et al<sup>17</sup> and You et al<sup>15</sup> reported that high-dose glucocorticoids (10 or 30 mg/kg/d) for patients with no response to low-dose glucocorticoids (1 mg/kg/d) could induce clinical and radiographical improvement within 3 days. Other studies have shown that glucocorticoids dramatically benefit patients with severe MPP, this benefit is attributed to the anti-inflammatory effects of glucocorticoids during *M. pneumoniae* infection.<sup>18</sup>

Considering the side effects of glucocorticoids on the pituitary body and adrenal cortex, low-dose glucocorticoids (1–2 mg/kg) are used more widely in clinical practice for children with severe MPP. However, prospective studies to investigate superiority between low- and high-dose glucocorticoid treatment are lacking. Appropriate methods and optimal dosage of glucocorticoids have not been fully clarified. Additionally, most reported studies used recent curative effect index rather than long-term outcomes as the primary end point to evaluate the role of glucocorticoids.

We have conducted a pilot study of 32 pediatric patients with severe MPP, among them, 18 patients received low-dose methylprednisolone (2 mg/kg/d) and 14 patients

received high-dose methylprednisolone (10 mg/kg/d). After completion of the 6-month follow-up, the experimental results showed the incidence of long-term pulmonary outcomes in the low-dose group (50.0%, 9/18) was higher than in the high-dose group (35.7%, 5/14). Patients in both groups had no adverse effects though this may be because of the low number of cases in our study. To further validate the use of methylprednisolone in patients with severe MPP, we are conducting the first large, randomized control trial (RCT) to assess the safety and efficacy of treatment with low- versus high-dose methylprednisolone for reducing long-term pulmonary outcomes in patients with severe MPP.

## METHODS

### Objectives

The first aim of our proposed multicenter, single-blind, RCT is to evaluate low- versus high-dose methylprednisolone for reducing long-term pulmonary outcomes of pediatric patients with severe MPP. We plan to evaluate whether high-dose methylprednisolone treatment is superior to low-dose methylprednisolone treatment for improving long-term pulmonary outcomes in children with severe MPP. The second aim of our study is to demonstrate the safety of low- and high-dose methylprednisolone treatment in children with severe MPP.

### Study Design

Methylprednisolone for children with severe *M. pneumoniae* pneumonia (MCMP) is a randomized, single-blind, parallel-controlled, multicenter clinical trial. The overall design is shown in Figure 1. MCMP is registered at ClinicalTrials.gov (NCT02303587). Participants will be enrolled from six study centers in China from November 2014 to December 2018. Table 1 details the geographic region, sites and predicted numbers of hospitalized children with severe MPP for this study.

**TABLE 1** Study centers and predicted numbers of hospitalized children with severe *M. pneumoniae* pneumonia.

Centers	Hospitals	Number of patients
North China	Beijing Children's Hospital, Capital Medical University	150
	Capital Institute of Pediatrics	140
	Shanxi Children's Hospital	30
Northeast China	Shengjing Hospital of China Medical University	70
	Children's Hospital of Changchun	30
Northwest China	Women and Children's Health Hospital of yinchuan City	30

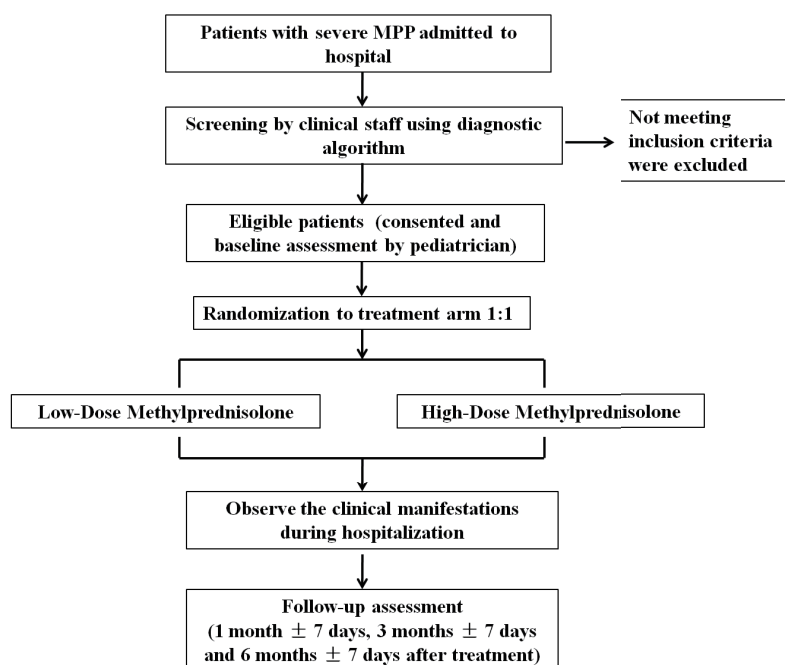


FIGURE 1 Study design flow diagram.

### Ethics statement

Studies have shown that severe MPP patients are at a high risk to develop outcomes and may benefit from glucocorticoid therapy. Patients will be subject to continued follow-up until they recover. Before randomization code allocation, the guardians of eligible patients will be asked to sign the informed consent, if the child is older than 10 years of age, he or she will be asked to sign the informed consent as well. The study protocol has been approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University, China (No: 2017-k-1).

### Participants and recruitment procedure

All hospitalized patients less than 18 years old with severe MPP will be enrolled in this study. Diagnosis of severe MPP is based on clinical manifestations (fever, cough, wheezing), physical examination, serologic test (*M. pneumoniae* antibody detection using the passive agglutination [PA] method [Serodia-Myco II, Fujirebio, Japan]), *M. pneumoniae* PCR test of nasopharyngeal secretions and imaging.<sup>19,20</sup> *M. pneumoniae* infection is defined as single titers of serum *M. pneumoniae* antibody  $\geq 1:320$ , or single titers of serum *M. pneumoniae* antibody  $\geq 1:160$  with positive PCR of *M. pneumoniae* or seroconversion (antibody titer increase of  $\geq 4$  fold between paired sera). Sputum smear and culture of bacteria and fungi, tuberculin skin test and interferon-gamma release assay (when necessary) are performed before using antibiotics to exclude other pathogen specific pneumonia. Indirect immunofluorescence assays (Diagnostic Hybrids,

Ohio, USA) to detect respiratory syncytial viruses (RSV), influenza viruses (A and B), parainfluenza viruses (1, 2, 3) and adenoviruses (ADV) antigens are performed using nasopharyngeal swabs. Detailed inclusion and exclusion criteria are shown in Table 2.

### Interventions and follow-up

Eligible patients are centrally randomized into two groups. Patients in the low-dose group receive 2 mg/kg/d ( $\leq 60$  mg/d) intravenous methylprednisolone for 3 days followed by tapering over 12 days (Table 3). If the patient's temperature is more than 38°C 12 to 24 h after treatment is initiated, methylprednisolone is adjusted to 4 mg/kg/d at day 2 for 3 days, followed by tapering over 12 days. Patients in the high-dose group receive 10 mg/kg/d ( $\leq 300$  mg/d) intravenous methylprednisolone for 3 days followed by tapering over 12 days (Table 3). When methylprednisolone is reduced to 10–20 mg/d, patients can change to an oral formula and be discharged if necessary. Basic treatment with azithromycin is used in both groups following previously published guidelines.<sup>19,20</sup>

After discharge, patients in both groups are followed-up at 1-month, 3-months and 6-months. Items to be monitored at follow-up include clinical manifestations and adverse events such as hyperglycemia, hypertension and intraocular pressure. Assessment of pulmonary lesions, including atelectasis, bronchiectasis and bronchiolitis obliterans will be evaluated at the 6-month follow-up. If the patients do not recover after 6 months, follow-up will be continued until the patient completely recovers or 1 year after treatment.

**TABLE 2** Inclusion and exclusion criteria

Inclusion criteria: fulfill all of the followings	
1.	Less than 18 years old
2.	Severe pneumonia that is defined as pneumonia with one of the followings: <ul style="list-style-type: none"> <li>◇ poor general condition</li> <li>◇ increased respiratory rate( infant&gt;70/min, older children&gt;50/min)</li> <li>◇ dyspnea</li> <li>◇ cyanosis</li> <li>◇ multilobe involvement or ≥ 2/3 lung involvement</li> <li>◇ extrapulmonary complication</li> <li>◇ pleural effusion</li> <li>◇ Transcutaneous oxygen saturation in room air ≤92%</li> </ul>
3.	Serum <i>M. pneumoniae</i> antibody ≥ 1:320, or serum <i>M. pneumoniae</i> antibody ≥ 1:160 with positive PCR of <i>M. pneumoniae</i> or seroconversion (increased antibody titers ≥4 folds)
Exclusion criteria: if fulfilling any of the followings will be excluded	
◇	Evidence of other pathogen specific (bacterial, viral, fungal, tuberculosis) pneumonia
◇	Respiratory failure requiring mechanical ventilation
◇	Liver failure or renal insufficiency or heart failure
◇	Other system diseases: congenital heart disease, kidney disease, connective tissue disease, immunodeficiency, tumor, hypertension, diabetes mellitus or hemophagocytic syndrome
◇	Recurrent respiratory tract infection
◇	Congenital bronchopulmonary dysplasia
◇	Increased intraocular pressure
◇	History of continuous use of glucocorticosteroid ≥1 week in previous 3 months
◇	Having contraindications to glucocorticosteroids or azithromycin
◇	Using of immunosuppressant before randomization
◇	Undergoing trial for other medications or instruments in the last 3 months.

**TABLE 3** Randomized assigned interventions of methylprednisolone

Time of treatment	Group	
	Low-dose group (mg/kg/d)	High-dose group (mg/kg/d)
Day 1	2	10
Day 2	2	10
Day 3	2	10
Day 4	1	1
Day 5	1	1
Day 6	1	1
Day 7	0.5	0.5
Day 8	0.5	0.5
Day 9	0.5	0.5
Day 10	0.25	0.25
Day 11	0.25	0.25
Day 12	0.25	0.25

**Randomization and blinding**

The randomization code list is generated centrally by the Center for Clinical Epidemiology and Evidence-based Medicine, Beijing Children’s Hospital. Patients who meet criteria for enrollment are randomized (1:1) into two treatment groups. The procedure for randomized allocation includes: identification of participant by

name, identification number and center series number, allocation of a random number to a medical center using an interactive voice response system, specification of a drug administration procedure for each participant. After consent and prior to randomization, site staff register each recruit on a web-based electronic data capture system. Each recruit is assigned a unique study patient identification number by the system. After assignment of the randomization code, researchers are un-blinded to the treatment dosage of methylprednisolone while the patients and data analyst are blinded to treatment groups.

**Study outcomes**

The primary composite outcome is the incidence of atelectasis, bronchiectasis or bronchiolitis obliterans at the 6-month follow-up. The outcome is measured independently by two radiologists. Atelectasis is defined as collapse of alveolar spaces with segmental or lobe volume decrease. Radiologic manifestations might show consolidation of the alveolar cavity and compensating emphysema of other lung tissues. Bronchiectasis is a structural abnormality characterized by abnormal dilation and distortion of the bronchial tree. Chest computerized axial tomography (CT) scan shows dilated and thickened airways, including tram or parallel lines and ring shadows on cross section. Bronchiolitis obliterans is a disease that results in obstruction of the smallest airways of the lungs due to inflammation. It is defined as expiratory air trapping (mosaic or diffuse) and bronchial wall thickening on high-

resolution CT and obstructive changes with air trapping, but without reversibility following inhaled bronchodilator of pulmonary function test.

Secondary outcomes include recovery time of the patient's temperature, proportion of pulmonary lesions absorbed, changes of mucosa identified by bronchoscopy, length of hospital stay, number of participant(s) needing intensive care, number of participant(s) with acute respiratory distress syndrome, hemophagocytic syndrome, death, or any adverse event/severe adverse event (eg. hyperglycemia, hypertension) during the trial and pulmonary function at the 6-month follow-up.

### Study Data

Demographic information is recorded on standardized case report forms (CRF) at baseline. Clinical and laboratory

data are obtained at baseline and every planned time point after initiation of treatment. During follow-up, the physical status and imaging examination data are recorded on CRFs. The details of data collection for the study are described in Table 4. All laboratories of the participating centers are internationally validated and standardized. In different phases of the trial, specific lab tests will be done as appropriate for disease condition, which will be determined the pediatrician and noted on the CRF. Using double data entry with an adjudication process, completed forms are reviewed and data are entered into electronic CRFs (eCRFs). Trial monitoring (including trial safety, protocol adherence and data quality) and reporting of adverse events are conducted under the supervision of the trial's medical monitor. All subjects are to be questioned regarding adverse events during treatment at each visit. All reported adverse events will be analyzed regardless of the investigators assessments of causality.

**TABLE 4** Study schedule of clinical trial (6 months).

Items	Study visit/trial phases								
	Baseline assessment	Treatment				Follow-up			
	Day 0	Day 1	Day 2	Day 3-12	Discharged day	1 month ± 7 days	3 months ± 7 days	6 months ± 7 days	Post-final visit
Consent	X								
Demographic information	X								
Medical history	X					X	X	X	X
Manifestation and physical examination	X	X	X	X	X	X	X	X	X
X-ray				X					
Chest CT	X							X	
Laboratory test <sup>†</sup>	X				X	X	X	X	X
Pathogen test <sup>‡</sup>	X								
Blood pressure	X	X	X	X	X	X	X	X	X
Blood glucose	X	X	X	X	X			X	
Tuberculin test	X								
Fundus and intraocular pressure exam	X				X	X	X	X	X
Bone Density Measurement	X				X	X	X	X	X
Lung function test	X					X	X	X	X
ECG	X				X				
Bronchoscope <sup>§</sup>			X						
Methylprednisolone		X	X	X					
Modify the dose in the low-dose group <sup>¶</sup>			X						
Adverse event/Severe adverse event		X	X	X	X	X	X	X	X

Notes: <sup>†</sup> Laboratory tests include blood gas analysis, blood biochemical indexes (including electrolytes, liver, renal and cardiac function), whole blood cell analysis, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), coagulation function (including D-Dimer), serum ferritin (SF), immune function test; whether or not to check is according to the patient's condition in different visit time. During the follow up, if the results are normal, no further laboratory tests will be necessary. <sup>‡</sup> Pathogen tests include *Mycoplasma pneumoniae* antibody, PCR of *Mycoplasma pneumoniae* of nasopharyngeal swab, smear and culture of bacteria and fungi of sputum, tuberculin skin test, interferon-gamma release assay (when necessary) and nasopharyngeal swab for virus antigen. <sup>§</sup> Bronchoscope will be done according to the patient's condition. <sup>¶</sup> Modify the dose in the low-dose group means, if the temperature is more than 38°C after 12 hours to 24 hours of initiated treatment, the participants will receive methylprednisolone 4 mg/kg/d at day 2 for 3 days followed by tapering over 14 days.



### Sample size and statistical analysis

The sample size for this two-arm trial was calculated on the basis of the comparison of low- versus high-dose methylprednisolone treatment. Using the data from our previous pilot study, we assumed a rate of pulmonary outcomes of 50% in the low-dose methylprednisolone group and 35% in the high-dose methylprednisolone group. To achieve a statistical power of 80% (two-sided type 1 error of 5%), the calculated sample size of each treatment group was 167 patients per treatment group (334 in total). Considering an expected loss to follow-up of at least 20%, 201 patients per treatment group (402 in total) were required.

The primary composite outcomes of the low- and high-dose methylprednisolone groups at the 6-month follow-up will be compared by Chi-square test with two-sided tests at the 5% level of significance. Efficacy of the two groups will be assessed using the relative risk, number needed to treat and 95% CI (confidence interval). The occurrence of long-term pulmonary outcomes during follow-up will be described using a Kaplan-Meier curve. Using this description, a COX proportional hazards model will be established.

### DISCUSSION

MPP is mild or benign in most children worldwide. However, nearly 40% of children in China progress to severe MPP despite appropriate antibiotic treatment.<sup>4</sup> Pediatric patients can present with complications such as pleural effusion, multi-organ damage and long-term pulmonary outcomes (bronchiolitis obliterans, bronchiectasis or atelectasis).<sup>7</sup> Previous studies<sup>11,12</sup> have shown that adjuvant treatment with glucocorticoids was beneficial for alleviating respiratory symptoms and reducing levels of inflammatory factors in patients with severe or refractory MPP. However, the optimal dosage of glucocorticoids is not clear and has never been mentioned in clinical guidelines. In the clinic, routine dosage of methylprednisolone is usually 1–2 mg/kg/d for severe MPP, although outcomes still remain in some cases, especially in severe patients. A retrospective study<sup>21</sup> with small case numbers showed that methylprednisolone pulse therapy was superior to low-dose methylprednisolone in recovery time of patient temperature and proportion of pulmonary lesion absorption. To date, prospective RCTs to compare the benefits and safety of low- and high-dose glucocorticoid treatment for children with severe MPP have not been conducted. Previous studies<sup>13–16</sup> often used recent curative effect index, including length of stay, recovery time of patient temperature or inflammatory marker(s) to evaluate the benefits of glucocorticoids. These studies did not use a long-term outcome index. Our MCMP trial is the first study designed to evaluate the benefits and safety of low- and high-dose glucocorticoid

treatment for reducing long-term pulmonary outcomes in patients with severe MPP. We chose the percentage of atelectasis, bronchiectasis or bronchiolitis obliterans at the 6-month follow-up as primary outcome measures to assess the long-term effect of methylprednisolone treatment. Patients are only enrolled if they meet our stringent inclusion criteria for severe MPP, this ensures the rate of pulmonary outcomes will be high in our study.

There are many available glucocorticoids, including hydrocortisone, dexamethasone, methylprednisolone, prednisolone and prednisone; currently, the appropriate choice of glucocorticoid for treatment is debatable. Previous studies reported that methylprednisolone, a median-effect drug, had a powerful anti-inflammatory function and was often used in patients with severe pneumonia.<sup>22–25</sup> Taking this into account, we decided to use methylprednisolone for treatment in our study. Hydrocortisone is a natural glucocorticoid with a short-term effect, often used in critically ill patients in combination with a mineral corticoid.<sup>26</sup> There is little research to support the use of dexamethasone in patients with severe MPP, aside from a report in 2011,<sup>27</sup> likely because of its strong side effects on the pituitary body and adrenal cortex. Prednisone is only available as an oral formula and cannot be used in patients with severe liver insufficiency, making methylprednisolone preferred.

A previous study<sup>28</sup> showed that high-dose and long-term use of glucocorticoids in the treatment of severe sepsis and septic shock can cause co- and re-infections, hyperglycemia or even excess mortality in adults. Accordingly, our RCT evaluates the adverse effects of both low- and high-dose methylprednisolone by monitoring blood glucose, blood pressure and intraocular pressure both when the patients are in the hospital and after discharge, with follow-up at 1-, 3-, and 6-months after completion of treatment. Bone et al<sup>28</sup> recommended tapering of the glucocorticoid dosing to avoid a rebound of inflammatory markers. Thus, we included tapering of methylprednisolone dosing in our study. Another study<sup>29</sup> showed that if glucocorticoids were given for more than seven days in a row, the risk of side effects would increase, while a shorter course of glucocorticoids may not improve the primary outcome. Therefore, we have limited the use of methylprednisolone to 12 days in our study.

The macrolide-resistance rate of *M. pneumoniae* was reported to be higher in China than in other countries, with a resistance rate of over 90%.<sup>30,31</sup> However, our previous study<sup>31</sup> showed there was no significant difference in treatment response to azithromycin between the macrolide-resistant and macrolide-sensitive groups other than duration of fever, which is in line with the results of a study by Suzuki et al.<sup>32</sup> This may contribute to the difference between in vitro and in vivo studies. Although tetracyclines and quinolones are effective antibiotics for

treatment of macrolide-resistant *M. pneumoniae*, they are not recommended for children under 8 or 12 years old, respectively, because of potential dental enamel damage and bone toxicity. Azithromycin is the first line antibiotic choice for MPP. In our study, azithromycin is used as the basic treatment in both study groups.

In conclusion, this large and adequately powered randomized trial is expected to determine the efficacy and safety of low- and high-dose methylprednisolone treatment combined with azithromycin for reducing long-term pulmonary outcomes in pediatric patients with severe MPP. This RCT addresses a large knowledge gap in an under-researched area. The results of this trial will provide scientific evidence to guide clinical practice in the treatment of severe MPP in pediatric patients.

Our study has several limitations. First, we are only studying hospitalized children with severe MPP, so the benefit of methylprednisolone in CAP caused by other pathogens is not evaluated. Second, methylprednisolone is the only glucocorticoid used to treat severe MPP in our study, and effects of other glucocorticoids are not evaluated. Finally, our study data are from Chinese pediatric patients, limiting the generalizability to non-Chinese populations. Additional studies will be needed to verify the results of our study.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## REFERENCES

- Ma H, Sun L, Wu X, et al. The etiology of community-acquired pneumonia in hospitalized children of single center in Beijing. *Chin J Evid Based Pediatr.* 2015;10:361-365. (In Chinese)
- Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med.* 2015;372:835-845.
- Yu Z, Liu X, Jiang Z. Analysis of relevant factors of severe *Mycoplasma pneumoniae* pneumonia in acute phase in children. *Chin J Appl Clin Pediatr.* 2011;4:246-249. (In Chinese)
- Jin J, Wang L, Wang M.Z, Zhang. Clinical features and bronchoscopy treatment for 378 patients of *Mycoplasma pneumoniae* pneumonia in children. *Chongqing Medicine.* 2015;44:4815-4817. (In Chinese)
- Wang L, Duan J. Clinical report on 68 cases of refractory *Mycoplasma pneumoniae* pneumonia (RMPP). *Chinese Journal of Experimental and Clinical Virology.* 2011;25:224-226. (In Chinese)
- Eun BW, Kim NH, Choi EH, Lee HJ. *Mycoplasma pneumoniae* in Korean children: the epidemiology of pneumonia over an 18-year period. *J Infect.* 2008;56:326-331.
- Diaz MH, Benitez AJ, Winchell JM. Investigations of *Mycoplasma pneumoniae* infections in the United States: trends in molecular typing and macrolide resistance from 2006 to 2013. *J Clin Microbiol.* 2015;53:124-130.
- Takiguchi Y, Shikama N, Aotsuka N, et al. Fulminant *Mycoplasma pneumoniae* pneumonia. *Intern Med.* 2001;40:345-348.
- Youn YS, Lee SC, Rhim JW, et al. Early additional immunomodulators for *Mycoplasma pneumoniae* pneumonia in children: An observation study. *Infect Chemother.* 2014;46:239-247.
- Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;53:e25-76.
- Uehara S, Sunakawa K, Eguchi H, et al. Japanese guidelines for the management of respiratory infectious diseases in children 2007 with focus on pneumonia. *Pediatr Int.* 2011;53:264-276.
- Respiratory Branch of Chinese Pediatric Society of Editorial Board of Chinese Journal of Applied Clin. Expert consensus on diagnosis and treatment of *Mycoplasma pneumoniae* pneumonia in children (2015). *Chin J Appl Clin Pediatr.* 2015;30:1304-1308. (In Chinese)
- Luo Z, Luo J, Liu E, et al. Effects of prednisolone on refractory *Mycoplasma pneumoniae* pneumonia in children. *Pediatr Pulmonol.* 2014;49:377-380.
- Lee KY, Lee HS, Hong JH, et al. Role of prednisolone treatment in severe *Mycoplasma pneumoniae* pneumonia in children. *Pediatr Pulmonol.* 2006;41:263-268.
- You SY, Jwa HJ, Yang EA, et al. Effects of methylprednisolone pulse therapy on refractory *Mycoplasma pneumoniae* pneumonia in Children. *Allergy Asthma Immunol Res.* 2014;6:22-26.
- Tamura A, Matsubara K, Tanaka T, et al. Methylprednisolone pulse therapy for refractory *Mycoplasma pneumoniae* pneumonia in children. *J Infect.* 2008;57:223-228.
- Youn YS, Lee KY. *Mycoplasma pneumoniae* pneumonia in children. *Korean J Pediatr.* 2012;55:42-47.
- Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med.* 2005;353:1711-1723.
- Hu YM, Jiang ZF, editors. *Zhu Futang's Practical Pediatrics (7th ed).* 2002:1175-1180.
- Subspecialty Group of Respiratory Diseases, The Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Guidelines of management of community acquired pneumonia in children (the revised edition of 2013). *Chin J Pediatr.* 2013;51:745-752. (In Chinese)
- Chen L, Liu J, Zhao S, Yang Y, Wu J. Clinical features and treatment of refractory *Mycoplasma pneumoniae* pneumonia unresponsive to conventional dose methylprednisolone in children. *Chin J Pediatr.* 2014;52:172-176. (In Chinese)
- Mikami K, Suzuki M, Kitagawa H, et al. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. *Lung.* 2007;185:249-255.
- Wan YD, Sun TW, Liu ZQ, et al. Efficacy and safety of corticosteroids for community-acquired pneumonia: A systematic review and meta-analysis. *Chest.* 2016;149:209-219.

24. Nagy B, Gaspar I, Papp A, et al. Efficacy of methylprednisolone in children with severe community acquired pneumonia. *Pediatr Pulmonol.* 2013;48:168-175.
25. Lan Y, Yang D, Chen Z, et al. Effectiveness of methylprednisolone in treatment of children with refractory *Mycoplasma pneumoniae* pneumonia and its relationship with bronchoalveolar lavage cytokine levels. *Chin J Pediatr.* 2015;53:779-783. (In Chinese)
26. Steigbigel NH. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *Curr Infect Dis Rep.* 2003;5:363-364.
27. Hirao S, Wada H, Nakagaki K, et al. Inflammation provoked by *Mycoplasma pneumoniae* extract: implications for combination treatment with clarithromycin and dexamethasone. *FEMS Immunol Med Microbiol.* 2011;62:182-189.
28. Bone RC, Fisher CJ Jr, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med.* 1987;317:653-658.
29. Polverino E, Cilloniz C, Dambava P, et al. Systemic corticosteroids for community-acquired pneumonia: reasons for use and lack of benefit on outcome. *Respirology.* 2013;18:263-271.
30. Liu Y, Ye X, Zhang H, et al. Characterization of macrolide resistance in *Mycoplasma pneumoniae* isolated from children in Shanghai, China. *Diagn Microbiol Infect Dis.* 2010;67:355-358.
31. Feng X, Li Q, Sun L, et al. The clinical characteristics of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in Children: a case-control study. *Chin J Evid Based Pediatr.* 2016;11:357-360. (In Chinese)
32. Suzuki S, Yamazaki T, Narita M, et al. Clinical evaluation of macrolide-resistant *Mycoplasma pneumoniae*. *Antimicrob Agents Chemother.* 2006;50:709-712.

**How to cite this article:** Xu B, Peng X, Yao Y, et al. Low-dose versus high-dose methylprednisolone for children with severe *Mycoplasma pneumoniae* pneumonia (MCMP): Study protocol for a randomized controlled trial. *Pediatr Invest.* 2018;2:176-183. <https://doi.org/10.1002/ped4.12041>