

Comparative efficacy and safety of traditional Chinese patent medicine in the treatment of *Mycoplasma pneumoniae* pneumonia in children

A protocol for systematic review and meta-analysis

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Abstract

Background: *Mycoplasma pneumoniae* pneumonia (MPP) is a common respiratory disease in children. Its incidence rate is increasing year by year. The drug resistance rate of macrolide antibiotics and other conventional treatment methods is higher, and there are limitations in clinical application. Traditional Chinese patent medicine (TCPM) is a powerful weapon to treat this disease. At present, there is no comparison of the safety and effectiveness of multiple TCPMs in the treatment of MPP in children. Therefore, we take the method of network meta-analysis to systematically compare the efficacy of various TCPMs in the treatment of this disease.

Methods: We will conduct comprehensive searches of Cochrane Library, PubMed, Web of Science, Clinical Trials, China National Knowledge Infrastructure, Chinese Scientific Journals Database, Chinese BioMedical Literature, Wanfang Database, and other electronic databases. The time frame is set from the establishment of the database to October 2020. All randomized controlled trials that meet the inclusion criteria will be included in this study. The 2 researchers will independently screen the literature according to the inclusion criteria, extract the data, and assess the bias risk of the included study. We will evaluate all the obtained data and evidence through Bayesian network meta-analysis, and use Stata 15.0 to process and analyze the data.

Results: Through this study, we will evaluate the efficacy and safety of a variety of TCPMs for the treatment of MPP in children.

Conclusion: The purpose of this study is to provide a strong reference for clinical application of TCPMs in the treatment of MPP in children, and to provide an important basis for clinicians to make correct judgments and put forward accurate treatment plans.

Ethics and dissemination: This review does not involve any human or animal experiments and therefore does not require ethical approval.

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Abbreviations: CAP = community-acquired pneumonia, MP = *Mycoplasma pneumoniae*, MPP = *Mycoplasma pneumoniae* pneumonia, RCTs = randomized controlled trials, RMPP = refractory *Mycoplasma pneumoniae* pneumonia, SMPP = severe *Mycoplasma pneumoniae* pneumonia, TCPMs = traditional Chinese patent medicines.

Keywords: *Mycoplasma pneumoniae* pneumonia in children, network meta-analysis, protocol, traditional Chinese patent medicine

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Mycoplasma pneumoniae (MP) is a common pathogen of community-acquired pneumonia (CAP) in children. In addition to causing primary atypical pneumonia, we can also see bronchitis and other respiratory tract infectious diseases, clinical symptoms of digestive system, cardiovascular system and nervous system.^[1–3] The main clinical manifestations of *M. pneumoniae* pneumonia (MPP) are fever, persistent dry cough, and less sputum. The course of the disease can last for 2 weeks or even longer. It is more common in school-age children, accounting for about 10% to 40% of CAP. It is easily spread in communities and institutions. During the epidemic of MP, the infection rate can reach 30% to 50%.^[4–7] At present, macrolide antibiotics are the first-line drugs for the treatment of MP infection. However, long-term use of these drugs will easily change the morphology, structure, metabolism, and other aspects of MP, increasing of clinical drug resistance rate, which makes the treatment of MP infection more difficult.^[8] At the same time, due

to MP resistance, mixed infection, and immune damage, there are more and more clinical cases of refractory *M. pneumoniae* pneumonia (RMPP) and severe *M. pneumoniae* pneumonia (SMPP). The disease progresses rapidly, and severe cases may have pulmonary complications such as pleural effusion, pulmonary necrosis, and extrapulmonary manifestations such as myocarditis, encephalitis, hepatitis, and even cause multiple organ failure. Some cases can also develop into acute respiratory distress syndrome, necrotizing pneumonia, etc, which seriously endanger children's life and health.^[9,10]

This disease is mainly caused by MP infection, and its pathogenesis is complex. Previously, the disease was considered as a self-limited disease with mild symptoms. With many experimental and clinical research findings, MP adheres to the surface of epithelial cells of the respiratory tract of the host and produces toxins such as hydrogen peroxide and respiratory distress syndrome, which results in epithelial cell injury, weakening ciliary movement, and inducing cell apoptosis.^[11,12] Also, the host immune response may be involved in the pathogenesis of MPP, and there is a certain degree of immune dysfunction during the pathogenesis of MPP.^[13,14] The levels of IgG, IgM, and IgA were high in the acute and convalescent stages of MPP. Moreover, the imbalance of Th1 and Th2 cells existed in MPP children, and the dynamic balance of the cytokine network in the body was destroyed, thereby mediating the immune response. At the same time, due to MP antigen has the same antigen structure as the brain, heart, liver, kidney, and smooth muscle of the human body, resulting in MP cannot be effectively immune cleared by host cells. Instead, it can stimulate the body to produce the corresponding antibody, cause cross immune reaction, appear RMPP, SMPP, even encephalitis, myocarditis, hepatitis, glomerulonephritis, autoimmune hemolytic anemia, and other extrapulmonary manifestations.^[15,16]

There are various treatment methods for MPP in children, and corresponding treatment measures will be taken according to different symptoms, severity of disease, and complications. It mainly includes drug therapy, fiberoptic bronchoscopy intervention, and the combination of drugs and interventional therapy.^[17] The therapeutic drugs include macrolides, fluoroquinolones, tetracyclines, and glucocorticoids.^[18] Drug therapy mainly plays a therapeutic role by inhibiting the synthesis of MP protein and DNA. However, tetracycline antibiotics can cause yellowing of teeth, enamel hypoplasia, gastrointestinal irritation, hepatotoxicity, and other side effects, which are forbidden to children under 8 years old; quinolones can cause cartilage and joint damage and affect children's bone development;^[19,20] macrolides have a resistance rate of up to 90% in some epidemic years,^[21] the patients with macrolide resistant MP infection had longer fever duration, hospitalization time, and antibiotic treatment course, which increased the difficulty and cost of treatment.^[22] Immunosuppressive agents such as glucocorticoid or immunoglobulin are needed to effectively curb the disease progression. However, there is no consensus on the exact starting time, dosage or duration of immunomodulators.^[23,24]

Traditional Chinese patent medicine (TCPM) is a kind of traditional Chinese medicine product which is made of Chinese medicine as raw material, in order to prevent and treat diseases according to the prescribed prescription and preparation technology. It has the characteristics of stable property, easy to carry and store. It plays an important role in improving clinical symptoms, preventing disease progression, and reducing adverse reactions. Clinical use of TCPM in the treatment of children with

MPP has a good effect, many studies have confirmed this point. The commonly used TCPMs include Xiao'er Xiaoji Zhike Oral Liquid, Pudilan Xiaoyan Oral Liquid, Lianhuaqingwen Granules, Xiaoer Feire Kechuan oral Liquid, etc. Because there are many varieties of TCPMs in the treatment of MPP in children, the comprehensive comparison of different varieties cannot be reflected by traditional meta-analysis. This network meta-analysis protocol will provide clinicians with comprehensive and reliable summary evidence by comparing the efficacy and safety of different TCPMs in the treatment of MPP in children.

2. Materials and methods

We will conduct this study in strict accordance with PRISMA-P^[25] specification.

2.1. Study registration

The network meta-analysis is registered with the International Registration System Review and Meta-analysis Research Platform (INPLASY) under the registration number of INPLASY 20201001008.

2.2. Inclusion criteria

2.2.1. Type of study. We will include all randomized controlled trials (RCTs) studies published in Chinese or English on the use of TCPMs in the treatment of MPP in children. Still, we need to exclude studies that are not RCT, including meta-analysis, non-clinical studies, lack of data, or poorly designed studies.

2.2.2. Participants. The diagnosis of MPP in children will follow the guidelines for CAP in children.^[26] Children aged 1 to 15 years who have been diagnosed with MPP will be included. There are no restrictions on the child's race, gender, or disease severity and course of the disease.

2.2.3. Interventions. The experimental group was treated with TCPMs combined with conventional Western medicine, TCPMs including Xiao'er Xiaoji Zhike Oral Liquid, Pudilan Xiaoyan Oral Liquid, Lianhuaqingwen Granules, Xiaoer Feire Kechuan oral Liquid, etc. The control group was treated with Western medicine conventional treatment, including symptomatic treatment or oral macrolide drugs or intravenous infusion of macrolide drugs. We exclude RCT studies using 2 or more TCPMs or combined acupoint application and cupping therapy.

2.2.4. Outcomes. The main outcome measures were fever abatement time, cough relief, or disappearance time, pulmonary rales disappearance time; secondary outcome indicators were hospitalization days, lung X-ray showed inflammatory infiltration subsided time, total effective rate, etc. The included literature all covered 1 or more of the above main indicators.

2.3. Database and search strategy

We will search PubMed, Web of Science, the Cochrane Library, China National Knowledge Infrastructure, Chinese BioMedical Literature, Chinese Scientific Journals Database, Embase, Clinical Trials, and Wan Fang data databases through computer to collect the RCT study of TCPMs in the treatment of children with MPP. The basic search strategy will be adjusted according to different databases.

Table 1
Detail of the search strategy for PubMed.

NO.	Search item
1#	"Pneumonia, <i>Mycoplasma</i> " [MeSH]
2#	((((((((((((Pneumonia, primary atypical[title/abstract]) or (atypical pneumonia, primary [title/abstract]) or (atypical pneumonias, primary [title/abstract]) or (pneumonias, primary atypical[title/abstract]) or (primary atypical pneumonia[title/abstract]) or (primary atypical pneumonias [title/abstract]) or (<i>Mycoplasma</i> Pneumonia [title/abstract]) or (<i>Mycoplasma</i> pneumonias [title/abstract]) or (pneumonias, <i>Mycoplasma</i> [title/abstract]) or (<i>Mycoplasma ovipneumoniae</i> infection [title/abstract]) or (<i>Mycoplasma ovipneumoniae</i> infections [title/abstract]) or (<i>Mycoplasma pneumoniae</i> infection [title/abstract]) or (<i>Mycoplasma pneumoniae</i> infections [title/abstract]) or (<i>Mycoplasma</i> dispar infection [title/abstract]) or (<i>Mycoplasma</i> dispar infections[title/abstract]))))))))))))
3#	1# or 2#
4#	"child" [MeSH]
5#	children[title/abstract]
6#	4# or 5#
7#	"Complementary therapies" [MeSH]
8#	((((((((((((TCPM [Title/Abstract] OR (traditional Chinese medicine [title/abstract]) or (therapies, complementary [title/abstract]) or (therapy, complementary [title/abstract]) or (complementary medicine [title/abstract]) or (medicine, complementary [title/abstract]) or (alternative medicine [title/abstract]) or (medicine, alternative [title/abstract]) or (alternative therapies [title/abstract]) or (therapies, alternative [title/abstract]) or (therapy, alternative [title/abstract]) or (herbal therapy [title/abstract]) or (herb therapy [title/abstract]) or (Chinese patent medicine [title/abstract]) or (Chinese proprietary medicine [title/abstract]) or (Chinese herbal drugs [title/abstract]) or (herbal [title/abstract]))))))))))))
9#	7# or 8#
10#	((((Randomly [title/abstract] or (random allocation [title/abstract]) or (randomized [title/abstract]) or (controlled clinical trial [Title/Abstract]) or (randomized controlled trial [title/abstract]))
11#	3# and 6# and 9#and 10#

TCPM = traditional Chinese patent medicine.

We will search for RCTs of TCPMs in the treatment of MPP in children from the establishment of the database to October 2020 by using the combination of Medical Subject Headings words and free words. The main search terms include "Traditional Chinese patent medicine or TCPM, MPP in children, MP infection in children, MP in children, and randomized controlled trials or RCT", etc. The detailed search strategy based on the PubMed database is shown in Table 1.

2.4. Study selection and data extraction

According to the retrieval strategy formulated in advance, articles retrieved from the above database are imported into Endnote X9 document (Stanford, Connecticut, USA) management software for classified management. The 2 researchers screened the literature according to the inclusion and exclusion criteria, and cross-checked them. If there is any dispute, they will discuss it with the third researcher and solve it through negotiation. The recorded data included necessary information (title, author, journal, publication date, age, sample size, course of the disease, treatment process), specific intervention measures, detailed results.

2.5. Risk of bias assessment

In this study, 2 reviewers independently read the title and abstract of the literature, and further read the full text of the literature that may meet the inclusion criteria to determine whether they really meet the inclusion criteria. According to the quality evaluation standard of Cochran Library evaluation manual, the quality of methodology was evaluated from the aspects of random distribution, allocation concealment, blind method, integrity of result data, selective report, and other bias.^[27] The quality of the included articles is classified as "low", "High" and "unclear". In the evaluation process, if 2 researchers disagree, they will be resolved through mutual discussion or the third researcher will decide.

2.6. Statistical analysis

We will use Stata 15.0 software (LLC 4905 Lakeway drive College Station TX 77845 USA) for statistical analysis. The odds ratio is used for counting data, and the mean difference is used for measurement data. The above effect quantities are all expressed by 95% confidence interval. The results were presented in tabular form.

The inconsistency test is mainly used to evaluate the degree of inconsistency between the direct comparison results and the indirect comparison results. When there is a closed loop between various intervention measures, the inconsistency test is needed. Using Stata software for Z test, the result $P > .05$ indicates that the consistency is good, otherwise, there is inconsistency. The bias analysis of outcome indicators will carry out, and the existence of publication bias was judged according to the P value. If $P > .05$, there is no significant publication bias.

2.7. Evaluation of heterogeneity

Our meta-analysis collected the same kind of research from different countries and regions. The research design is diverse, so there are some differences. If heterogeneity exists, we will perform subgroup analysis and sensitivity analysis.

2.8. Subgroup analysis and sensitivity analysis

We will make a comprehensive analysis of the causes of heterogeneity. If the evidence is sufficient, we will conduct subgroup analysis to determine the source of heterogeneity. If the data is sufficient, we will consider the subgroup analysis, and conduct sensitivity analysis combined with the improvement of clinical symptoms, and further evaluate the clinical similarity and methodology included in this study to ensure the reliability of the results of this study.

2.9. Evaluation of publication bias

The total effective rate, the duration of fever relief, the cough relief or disappearance time, and the disappearance time of

pulmonary rales after treatment were taken as the indicators. The inverted funnel plot was drawn with the standard effect amount's standard error as the ordinate and each effect quantity as the abscissa. If the inverted funnel plot is basically symmetrical, it indicates that there is a small sample effect or publication bias in this study.

2.10. Grading the quality of evidence

We will assess the quality of evidence regarding bias risk, indirectness, inconsistency, imprecision, and publication bias.^[28]

3. Discussion

MP has become one of the most important pathogens of bronchitis and pneumonia in school-age children. The autoimmune system of school-age children is not yet perfect, the immune system is weak, and they are susceptible to MP and cross infection in school district institutions. The course of disease after MP infection is relatively long, if not timely intervention. It is easy to cause myocardial damage, liver dysfunction and other extrapulmonary manifestations, and even develop into RMPP, SMPP, which seriously damages children's health. Whether macrolide drugs, glucocorticoids, immunoglobulin, there are obvious limitations in clinical application.

TCPMs are guided by the theory of traditional Chinese medicine. The selection of prescription is rigorous and the compatibility is appropriate. After long-term clinical application, it is an effective, simple, and cheap prescription. It is processed by scientific preparation technology, with good therapeutic effect and few side effects. The dosage forms of children's medicine are mostly granules and liquid preparations, with good taste and easy to take.

In this study, we will introduce Medical Subject Headings mate analysis based on existing studies to evaluate the advantages and disadvantages of various TCPMs for the treatment of MPP in children to provide a more powerful basis for clinical rational drug use. The quality of the underlying data may bias the quality of our analysis. Therefore, in the follow-up study, we will include more high-quality, multicenter clinical, data rich studies, and evidence to evaluate the efficacy and safety of TCPMs in the treatment of MPP in children.

Author contributions

Conceptualization: Hongan He, Baoqing Zhang.

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