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ORIGINAL RESEARCH

Efficacy and Influencing Factors of Sangju Cough Mixture in the Adjuvant Treatment of Adult Patients with *Mycoplasma pneumoniae* Infection: A Retrospective Study

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Purpose: Sangju-Yin, supplemented with some drugs, has frequently demonstrated therapeutic efficacy against colds, albeit its effect on *Mycoplasma pneumoniae* (MP) infection remains unknown. Therefore, we aimed to elucidate the treatment efficacy and influencing factors of a Sangju cough mixture on MP infection in adults.

Patients and Methods: Between January 2021 and December 2022, 150 adult patients with MP infection at the Lishui Hospital of Traditional Chinese Medicine Affiliated with Zhejiang University of Traditional Chinese Medicine were assigned to the treatment (administered Sangju cough mixture and moxifloxacin tablets) or the control (administered moxifloxacin tablets) groups.

Results: When compared with the control group, the treatment group exhibited significantly improved traditional Chinese medicine syndrome scores, increased $CD4^+$ T cell levels, and decreased $CD8^+$ T cell levels (all $P < 0.05$). After 7 days of treatment, the negative conversion rate of the MP-specific immunoglobulin M (MP-IgM) antibody of the treatment group was not significantly different from that of the control group ($P > 0.05$); however, after 14 days of treatment, the rate was significantly higher in the treatment group ($P < 0.05$). The univariate regression analysis revealed that combined chronic respiratory disease, failure to take Sangju cough mixture, combined pneumonia, Nutritional Risk Screening 2002 (NRS 2002) score of at least 3 points, and age were associated with the negative conversion of the MP-IgM antibody (all $P < 0.05$). Nevertheless, the multivariate regression model revealed that the NRS 2002 score of at least 3 points was not an independent risk factor ($P > 0.05$).

Conclusion: Sangju cough mixture can improve symptoms, accelerate the negative conversion time of MP-IgM antibody, and promote rehabilitation of the patients.

Keywords: *Mycoplasma pneumoniae* infection, Sangju cough mixture, moxifloxacin, negative conversion time, influencing factors

Introduction

Various virulence factors, including membrane lipoproteins, polysaccharides, and invasive nucleases, are responsible for causing *Mycoplasma pneumoniae* (MP) infection.[1] MP is an important causative agent of respiratory tract infections in children and adults; furthermore, it can lead to community outbreaks, with clinical manifestations ranging from self-limiting to life-threatening and from the lung to the extrapulmonary regions.[2] Studies in China and other Asian countries have reported that MP is the most common atypical pathogen in patients with community-acquired pneumonia and acute respiratory tract infection, second only to *Streptococcus pneumoniae*.[3,4] MP lacks a cell wall and is sensitive to beta-lactams, glycopeptides, and fosfomycin.[5,6] Owing to the small size of MP, it can spread via droplets and lead to an epidemic.[7]

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The medications for MP infection primarily include quinolones, macrolides, and tetracyclines. However, their optimal doses and treatment durations remain unclear; as such, in clinical settings, a treatment period of 10–14 days is generally recommended.[8] Recent studies have reported an increasing rate of macrolide resistance, possibly because it is extensively used empirically to treat respiratory infections.[9,10] Furthermore, fluoroquinolones can result in skeletal dysplasia, QT interval prolongation, rashes, and gastrointestinal discomfort.[11] In addition, tetracyclines can induce tooth yellowing and enamel dysplasia;[12] these challenges limit the use of these drugs in some specific populations. Therefore, exploring new and effective methods to overcome the harm caused by MP infection to humans and social stability is urgently warranted. Studies have reported that traditional Chinese medicine (TCM) can inhibit MP activity, relieve its clinical symptoms, and regulate patients' immune function, without significant adverse drug reactions.[13,14]

Sangju-Yin, derived from the Detailed Analysis of Epidemic Warm Diseases,[15] is a pungent and naturally cooling agent that can clear away heat to inhibit wind, diffuse lung qi, and suppress cough. However, it exhibits slightly inferior effectiveness in relieving cough and resolving phlegm.[16] Therefore, drugs such as Baibu, Baiqian, and Aster are frequently added to strengthen the therapeutic effects of Sangju-Yin. Sangju cough mixture comprises Sangju-Yin plus Baiqian, *Fritillaria thunbergii, Xanthium sibiricum, Scutellaria baicalensis*, reed root, mulberry leaves, and chrysanthemum, which disperse wind-heat and relieve cough; almonds, *Cynanchum glaucescens*, and *Platycodon grandiflorum*, which lower lung qi and relieve cough; *Fritillaria thunbergii* and *Scutellaria baicalensis*, which disperse lung heat; and *Forsythia suspensa* and reed root, with heat-clearing, detoxifying, and thirst-quenching properties. A previous study has reported the effects of this mixture on the treatment of the common cold, coronavirus, Hand, Foot and Mouth Disease.[16–18] The Chinese scholars revealed that Sangju zhike granules had significant clinical efficacy and high safety in the treatment of adults with MP infection.[19] Nevertheless, no studies have reported its effect on MP infection.

Therefore, in the present study, we investigated the curative effect of Sangju cough mixture combined with moxifloxacin tablets on MP infection in adults and determined the factors influencing the negative conversion time of the MP-specific immunoglobulin M (MP-IgM) antibody.

Materials and Methods

Study Participants

In this retrospective study, 231 adult patients with MP infection who were diagnosed and treated at the outpatient clinic of the Lishui Hospital of Traditional Chinese Medicine Affiliated with Zhejiang University of Traditional Chinese Medicine from January 2021 to December 2022 were included. Patients who were allergic to moxifloxacin (n = 3), those who received moxifloxacin tablets for <7 days (n = 21) or TCM for <7 days (n = 19), and those who did not undergo follow-up after the treatment (n = 38) were excluded. Finally, 150 patients were included (Figure 1). MP infection diagnosis was based on the Expert Consensus on the Diagnosis and Treatment of *Mycoplasma pneumoniae* Pneumonia in Adults, as issued by the Infection Group of the Chinese Thoracic Society.[20] Patients with a history of epidemiological exposure, respiratory symptoms such as cough and sore throat, and positive laboratory results for MP infection (the MP-IgM titer increased by at least fourfold in double serum samples from the acute and convalescent phases or decreased but was at least 1:160 in the particle agglutination test and 1:64 in the complement fixation test or positive for the MP-IgM antibody) were diagnosed with MP infection. Based on the Guidelines for the Diagnosis and Treatment of Common Diseases in Internal Medicine of Traditional Chinese Medicine issued by the Chinese Society of Traditional Chinese Medicine, patients with MP infection conformed to wind-heat attacking the lung syndrome of the TCM theory.[21]

This study was approved by the ethics committee of Lishui Hospital of Traditional Chinese Medicine (Approval No.: LW-048/2023) and was conducted in accordance with the Declaration of Helsinki. Moreover, as the clinical data did not involve names, addresses, or other personal information and considering the retrospective nature of the investigation, the need for obtaining informed consent from the participants was waived off.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: patients aged 18–70 years who met the diagnostic standards for MP infection. The exclusion criteria were as follows: (1) adults with severe or refractory MP infection or other serious clinical conditions requiring

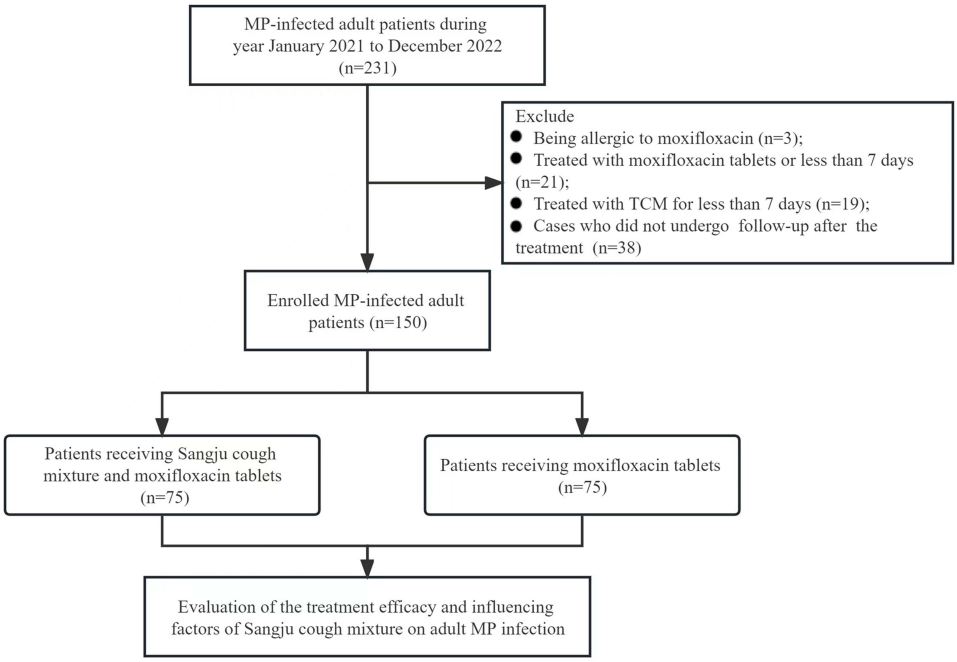

Figure 1 Flow chart depicting the patient inclusion process in this study.
Abbreviation: MP-IgM, *Mycoplasma pneumoniae*-specific immunoglobulin M.

treatment monitoring; (2) pregnant women, women preparing for pregnancy, or lactating women; (3) patients with combined cardiovascular, cerebrovascular, liver, kidney, hematopoietic, and mental health diseases; (4) those with long-term use of immunosuppressants; (5) those who were allergic to the Western medicine or TCM used in this study; (5) those with gastrointestinal bleeding and other diseases and who cannot tolerate TCM; and (6) those who were receiving other oral TCM within 14 days before receiving Sangju cough mixture.

Grouping

The patients were divided into two groups based on whether they received Sangju cough mixture for cough relief: treatment and control groups, with 75 participants in each group. The treatment group was administered 0.4 g of moxifloxacin tablets once daily and 20 mL of Sangju cough mixture three times for 7–14 days. On the other hand, the control group only received 0.4 g of moxifloxacin tablets once daily for 7–14 days.

Data Collection

Quantitative Detection of Serum MP-IgM Antibody Levels

Before and after the treatment, 5 mL of peripheral venous blood was collected from each patient. The blood samples were centrifuged at 3000 rpm for 5 min to separate the serum. The serum samples were stored at −80°C. Passive agglutination with an MP antibody detection kit (Yahuilong Biotechnology Co., Ltd., Shenzhen, China) was used to quantitatively detect the serum MP-IgM antibody levels. An MP-IgM titer of at least 1:80 was considered positive.

T-Lymphocyte Subset Testing

Before and after the treatment, venous blood sample was collected from the patients to isolate the serum. The immunofluorescence method was used to identify the changes in the T-lymphocyte count. The T-lymphocyte subset detection kit (Beckman Coulter, USA) was used in accordance with the manufacturer's instructions.

Indicators

TCM Syndrome Score

No, mild, moderate, and severe symptoms were rated 0, 1, 2, and 3 points, respectively. The symptoms included fever, aversion to colds, sore throat, cough, nasal congestion, thirst, chest tightness, chest pain, and dyspnea.

Negative Conversion Rate of the MP-IgM Antibody

Before and 7 and 14 days after the treatment, the serum samples were prepared to determine the negative conversion rate of the MP-IgM antibody, which was calculated using the following equation: Negative conversion rate (%) = number of negative cases/total positive cases × 100%.

Statistical Analysis

SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. The χ^2 test was performed to compare the categorical variables. The measurement data that were normally distributed were represented as the mean ±standard deviation. The independent samples *t*-test was performed to compare the groups. The measurement data that were not normally distributed were presented as the median and interquartile range. The Mann–Whitney *U*-test was performed to compare the groups. Univariate analysis with the χ^2 or Fisher's exact test was performed to identify the factors influencing the treatment outcomes. In addition, multivariate analysis was performed using a binomial logistic regression model to calculate the odds ratio (OR) and 95% confidence interval (CI). $P < 0.05$ indicated statistical significance.

Results

Comparison of TCM Syndrome Scores and T-Lymphocyte Subset Levels

After treatment, the TCM symptom scores and $CD4^+$ T-cell counts were significantly improved in the treatment group when compared with that in the control group (both $P < 0.05$). In contrast, $CD8^+$ T-cell counts significantly decreased in the treatment group when compared with that in the control group ($P < 0.05$; Table 1).

Comparison of the Negative Conversion Rate of the MP-IgM Antibody

After 7 days of treatment, the treatment group showed a negative conversion rate of 68.00% (51/75), with no significant difference between both the groups ($P > 0.05$). After 14 days of treatment, the treatment group showed a negative conversion rate of 89.33% (67/75); this was significantly higher than that of the control group (76.00% [57/75], $P < 0.05$; Table 2).

Univariate Analysis Result

Univariate analysis was conducted based on the negative conversion of the MP-IgM antibody after 14 days of treatment. Combined chronic respiratory disease, failure to take Sangju cough mixture, combined pneumonia, Nutritional Risk

Table 1 Comparison of the TCM Syndrome Scores and T-Lymphocyte Subsets Levels Between the Two Groups

Group	CD4+ T-Cell		CD8+ T-Cell		TCM Syndrome Score	
	Before Treatment ($\bar{x} \pm SD$)	After Treatment ($\bar{x} \pm SD$)	Before Treatment ($\bar{x} \pm SD$)	After Treatment ($\bar{x} \pm SD$)	Before Treatment ($\bar{x} \pm SD$)	After Treatment ($\bar{x} \pm SD$)
Treatment group	36.71 ±3.92	45.34 ±3.29	30.67 ±3.57	23.29 ±3.20	17.80 ±4.52	4.96 ±2.38
Control group	37.69 ±3.66	42.84 ±3.62	29.83 ±3.14	24.81 ±2.44	17.31 ±4.42	6.01 ±2.86
t	1.580	4.436	1.516	3.277	0.676	2.454
P	0.116	< 0.001	0.132	0.001	0.500	0.015

Abbreviations: TCM, traditional Chinese medicine; $\bar{x} \pm SD$, mean ±standard deviation.

Table 2 Comparison of the Negative Conversion Rates of MP-IgM Antibody Between the Two Groups After Treatment

Group	Number of Cases	Turning Negative After 7 Days of Treatment (n, %)	Remaining Positive After 7 Days of Treatment (n, %)	Turn Negative After 14 Days of Treatment (n, %)	Remaining Positive After 14 Days of Treatment (n, %)
Treatment group	75	51 (68.00)	24 (32.00)	67 (89.33)	8 (10.67)
Control group	75	40 (53.33)	35 (46.67)	57 (76.00)	18 (24.00)
χ^2		3.381		4.653	
P		0.066		0.031	

Abbreviation: MP-IgM, *Mycoplasma pneumoniae*-specific immunoglobulin M.

Screening 2002 (NRS 2002) score of at least 3 points, and age were associated with the negative conversion of the MP-IgM antibody (all $P < 0.05$). In contrast, sex, disease course of <1 week, hypertension, diabetes, body mass index, white blood cell count, and C-reactive protein level were not influencing factors (all $P > 0.05$; Table 3).

Multivariate Analysis Result

Binary logistic regression analysis was performed using the treatment outcomes as the dependent variable (0 for no conversion and 1 for conversion) and combined with pneumonia, the administration of Sangju cough mixture, NRS 2002 score of at least 3 points, and chronic respiratory diseases (0 for no and 1 yes for 1). Age, combined pneumonia, combined chronic respiratory diseases, and failure to take the Sangju cough mixture were independent risk factors for the negative conversion rate of the MP-IgM antibody in adult patients (all $P < 0.05$). However, an NRS 2002 score of at least 3 points was not identified as a risk factor ($P > 0.05$; Table 4).

Table 3 Univariate Analysis of the Factors Affecting the Negative Conversion Rate of MP-IgM Antibody in Adult Patients with MP Infection

Factor		Turning Negative (n)	Remaining Positive (n)	χ^2/t	*P*
Gender	Male	40	12	1.832	0.176
	Female	84	14		
Suffering from chronic respiratory diseases[a]	Yes	20	9	4.710	0.030
	No	104	17		
Disease duration <1 week	Yes	50	10	0.031	0.860
	No	74	16		
Hypertension	Yes	36	10	0.899	0.343
	No	88	16		
Diabetes	Yes	23	9	3.306	0.069
	No	101	17		
Failure to take Sangju cough mixture	Yes	67	8	4.653	0.031
	No	57	18		
Combined pneumonia	Yes	8	13	33.855	<0.001
	No	116	13		
NRS 2002 score ≥3	Yes	5	9	23.757	<0.001
	No	119	17		
BMI (kg/m^2)	<18.5	12	1	2.008	0.349
	18.5–24	104	25		
	>24	8	0		
White blood cell (g/L)		5.70 (4.73, 7.68)	5.65 (4.87, 6.63)	0.502	0.494
CRP (mg/L)		7.55 (4.80, 15.55)	10.10 (4.13, 15.68)	0.616	0.621
Age (years)	18–44	80	3	51.868	<0.001
	45–59	33	5		
	60–70	11	18		

Abbreviations: MP-IgM, *Mycoplasma pneumoniae*-specific immunoglobulin M; NRS, Nutritional Risk Screening; BMI, body mass index, CRP, C-reactive protein; [a]Chronic obstructive pulmonary disease and asthma (after remission).

Table 4 Multivariate Analysis of the Factors Affecting the Negative Conversion Rate of MP-IgM Antibody in Adult Patients with MP Infection

Variables		B	P	OR	95% CI
Age (years)	18–44	–	–	1	–
	45–59	3.543	<0.001	34.563	5.704–209.448
	60–70	2.490	0.004	12.063	2.232–65.183
Combined pneumonia	Yes	−3.553	<0.001	0.029	0.004–0.190
	NO	–	–	1	–
Failure to take Sangju cough mixture	Yes	1.689	0.042	5.414	1.062–27.594
	NO	–	–	1	–
NRS 2002 score ≥3	Yes	− 1.245	0.155	0.288	0.052–1.602
	NO	–	–	1	–
Suffering from chronic respiratory diseases	Yes	2.048	0.030	7.750	1.220–49.250
	NO	–	–	1	–

Abbreviations: MP-IgM, *Mycoplasma pneumoniae*-specific immunoglobulin M; OR, odds ratio; CI, confidence interval; NRS, Nutritional Risk Screening.

Discussion

Previous studies have reported that MP infection is similar to the febrile disease in the TCM theory; both are infectious, epidemic, and seasonal and exhibit wind-heat-attacking lung syndrome.[22] Another study has reported that MP infection is closely associated with the pathogenesis of damp pathogens[23] and that there are two types of pathogens in the early stage of MP infection: cool dryness caused by dryness pathogens similar to wind-cold and warm dryness caused by damp pathogens similar to wind-heat.[23] The Zhejiang Province has a subtropical monsoon climate, with MP infection commonly occurring in the winter and spring seasons; it is most prone to form wind-heat pathogens. Therefore, it is common to observe wind-heat attacking the lung syndrome in the early stage of MP infection. In the present study, we enrolled 150 patients with MP infection and observed that the TCM syndrome score of the treatment group (received additional Sangju cough mixture) was significantly lower than that of the control group, indicating that Sangju cough mixture could significantly disperse wind, clear heat, promote lung qi, and relieve cough and phlegm.

The primary pathogenesis of MP-induced intrapulmonary infection is adhesion damage, nutrient depletion, invasion, cytokine-induced inflammatory damage, and immune evasion. On the other hand, the primary pathogenesis of extra-pulmonary infection is invasion-mediated direct damage and indirect damage caused by host immune responses.[24] MP infection is closely associated with host immune disorders, with an increasingly compromised host immune function with MP infection progression.[25] Some studies have reported that $CD3^+$ and $CD4^+$ T-cell counts are significantly decreased and $CD8^+$ T-cell counts are increased in the acute phase of MP infection.[26,27] Therefore, it is important to monitor T-lymphocyte subsets to elucidate the efficacy and prognosis of MP infection. In the present study, we identified that, in the two patient groups with MP infection, $CD4^+$ T-cell counts significantly increased after treatment compared with those before treatment; on the other hand, $CD8^+$ T-cell counts significantly decreased, with more pronounced effects in the treatment group than in the control group, implying that Sangju cough mixture improved the immune system of patients with MP infection. Moreover, a previous study has reported that Sangju-Yin, a component of Sangju cough mixture, could reverse the inhibitory activity of some P450 enzymes, including CYP1A2 and CYP2C6, caused by the oral administration of monarch drugs, which delayed drug metabolism, improved their plasma concentrations and therapeutic effects, and decreased adverse events, suggesting that Sangju-Yin can act as an adjuvant drug to combine with different compounds,[28] which is consistent with our findings. In addition, a prior investigation revealed that Sangju-Yin reduced the cough frequency in the mouse model by downregulating the expression of TRPV1, which is expressed throughout the entire respiratory system, and the activation of the TRPV1 channel induced cough reflex along the nerve-conduction pathway.[29,30] Another study has reported that Sangju-Yin can be a potential anticancer agent for human oral squamous cell carcinoma by inducing apoptosis and suppressing cancer-related signaling pathways.[31]

In the present study, we observed that older age resulted in a longer negative conversion time of the MP-IgM antibody. However, Yu et al reported that age does not affect MP-IgM antibody titers,[32] possibly because the study participants were children of age ≤15 years; in contrast, the participants in the present study were adults. Furthermore, we observed that patients complicated with pneumonia had more severe symptoms and complications, with a longer negative conversion time of the MP-IgM antibody, which may be attributed to the difficulty in the clearance of MP and impaired immune functions.[33] Williams et al reported that patients with chronic obstructive pulmonary disease experience complex interactions between innate and adaptive immune systems, possibly inducing lung parenchymal destruction and remodeling, increasing the effector function of $CD8^+$ T-cells, and leading to the onset of other lung diseases.[34] Furthermore, Hanhan et al reported that children with MP infection are more likely to develop acute asthma, particularly those with pulmonary inflammatory lesions on chest X-rays.[35] Another study has reported that patients with asthma have decreased mucosal-associated variant T-cell counts, possibly leading to increased body inflammation in response to allergens and other stimuli.[36] In the present study, we observed that the Sangju cough mixture can accelerate the negative conversion time of the MP-IgM antibody, possibly because it exhibits an improved effect on the symptoms and immune functions of the infected patients.

This study had some limitations. First, it was a non-randomized, retrospective study, which introduced some bias in our findings. Second, the study results were obtained from small samples. Therefore, a large sample group with a longer follow-up period is warranted to confirm the safety and efficacy of the Sangju cough mixture.

Conclusion

In conclusion, we employed a treatment regimen based on the Sangju cough mixture for patients with MP infection. This treatment regimen improved the symptoms and immune functions of patients, accelerated the negative conversion time of the MP-IgM antibody, and promoted recovery of the patients. Nevertheless, the abovementioned findings should be comprehensively validated and explored in the future.

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Disclosure

The author report no conflicts of interest in this work.

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