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ORIGINAL RESEARCH

Clinical Efficacy of Qingke Mixture in Treating Mycoplasma Pneumonia in Children: A Randomized Controlled Trial

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Background: Mycoplasma pneumoniae pneumonia (MPP) is a common respiratory infection in children, current treatments are limited by resistance and side effects. This study aims to evaluate the clinical efficacy and safety of combining Qingke Mixture with azithromycin for treating MPP in children.

Methods: This prospective, randomized, double-blind, controlled trial included 92 children diagnosed with MPP. The treatment group received Qingke Mixture and azithromycin, while the control group received azithromycin alone. Outcomes assessed included clinical symptoms, inflammatory markers, immune response, pulmonary function, and adverse events.

Results: The treatment group showed significantly higher clinical efficacy (95.65% vs 80.43%, $P < 0.05$). The treatment group showed faster resolution of pulmonary symptoms, shorter hospital stays, and greater improvements in pulmonary function and TCM symptom scores ($P < 0.05$). Inflammatory markers (WBC, CRP, IL-6, IL-8) were significantly lower, while immunoglobulin levels (IgA, IgG, IgM) and T lymphocyte subsets (CD3+, CD4+/CD8+ ratio) were higher in the treatment group compared to the control group ($P < 0.05$). The incidence of adverse events was low in both groups, with no statistically significant difference.

Conclusion: Qingke Mixture combined with azithromycin significantly improves clinical outcomes in children with MPP, enhancing efficacy while maintaining safety.

Keywords: mycoplasma pneumoniae pneumonia, Qingke mixture, azithromycin, pediatric pneumonia, clinical efficacy and safety

Introduction

MPP is a common respiratory infection in children, primarily caused by *Mycoplasma pneumoniae*. It is one of the significant causes of community-acquired pneumonia (CAP) in children, with 10% to 40% of pediatric CAP cases being attributed to *Mycoplasma pneumoniae* infection.[1] In recent years, there has been a rise in *Mycoplasma pneumoniae* infections, contributing to increased morbidity, healthcare burden, and complications such as wheezing, asthma, and, in severe cases, extrapulmonary manifestations like myocarditis or encephalitis.[2] *Mycoplasma pneumoniae* is sized between bacteria and viruses and can pass through bacterial filters. It is primarily transmitted via the respiratory tract, and its path ogenic mechanisms are still not entirely understood.[3]

Mycoplasma pneumoniae lacks a cell wall, which is a major factor in its pathogenicity and drug resistance profile. The absence of a cell wall renders beta-lactam antibiotics ineffective, leaving macrolides, tetracyclines, and fluoroquinolones as the primary treatment options.[4] Among these, macrolides are the most commonly prescribed in children due to their lower toxicity profile compared to tetracyclines and fluoroquinolones, which are contra-indicated in pediatric populations.[5] However, the prolonged use of macrolides often leads to side effects such as nausea, vomiting, and diarrhea, and the increasing prevalence of resistant strains further limits the application of macrolide antibiotics.[6] The rising prevalence of Macrolide resistant mycoplasma pneumoniae (MRMP) has made the

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management of MPP more complex, often necessitating longer courses of treatment or combination therapies, which may lead to increased adverse drug reactions and greater healthcare costs.[7] Furthermore, current pharmacological treatments focus primarily on eliminating the pathogen and controlling symptoms but do not address the immune dysregulation or inflammation often observed in severe cases of MPP.[8] This underscores the necessity for novel therapeutic agents that can target both the infection and the host's immune response while minimizing adverse effects.

Traditional Chinese Medicine (TCM) has distinct advantages in the treatment of MPP. Its therapeutic approaches are diverse and flexible, ranging from internal herbal decoctions and external treatments to integrated Chinese and Western medicine therapies, all of which have shown good clinical efficacy.[9] TCM not only effectively alleviates symptoms and shortens the duration of illness, but also has fewer side effects and a lower risk of drug resistance.[10] Given the limitations of current treatments for MPP, particularly in the context of macrolide resistance, exploring alternative therapeutic options is of paramount importance. The Qingke Mixture used in this study is a novel combination of several traditional Chinese medicinal herbs, formulated based on classical prescriptions and modern clinical experience in treating respiratory diseases. Its main components include Fructus Perillae, Herba Ephedrae, Baical Skullcap Root, Radix Peucedani, Radix Bupleuri, Almond, Densefruit Pittany Root-Bark, Fritillariae Cirrhosae Bulbus, Lobed Kudzuvine Root, Houttuynia Herb, and Glycyrrhiza Uralensis Fisch, prepared as a decoction suitable for pediatric use. Although this combination has not been previously evaluated in clinical trials, individual components such as Baical Skullcap Root and Glycyrrhiza Uralensis Fisch have demonstrated anti-inflammatory, antitussive, expectorant, antimicrobial, and immune-regulatory properties. Baical Skullcap Root primarily exerted anti-inflammatory and antimicrobial effects by inhibiting pro-inflammatory cytokines and modulating immune pathways,[11] while Glycyrrhiza Uralensis Fisch showed anti-inflammatory, antitussive, and immune-modulatory effects through active components such as glycyrrhizin.[12] Given that azithromycin remains the standard first-line treatment for MPP in children, and considering the rising prevalence of macrolide-resistant *Mycoplasma pneumoniae*, we chose to evaluate Qingke Mixture as an adjunctive therapy. This combination approach reflects clinical practice patterns in traditional Chinese medicine hospitals, aiming to enhance therapeutic efficacy, modulate immune responses, and potentially reduce the course and dosage of antibiotics.

Therefore, this study aims to evaluate the clinical efficacy and safety of Qingke Mixture combined with azithromycin in children with MPP.

Methods

Trial Design

This study was a prospective, randomized, double-blind, controlled trial designed to evaluate the efficacy and safety of the traditional Chinese medicine Qingke Mixture combined with azithromycin in the treatment of MPP in children. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Changchun University of Chinese Medicine (approval number: CCZYFYKYLL2024-005). The trial was registered on the International Traditional Medicine Clinical Trial Registration Platform (http://itmctr.ccebtcm.org.cn/) with the registration number: ITMCTR2024000355. Before the start of the study, the parents or guardians of the patients were fully informed about the purpose, methods, and potential risks of the study, and written informed consent was obtained after their agreement.

Patients Recruitment

This study included children diagnosed with MPP at the Affiliated Hospital of Changchun University of Chinese Medicine between January 2024 and September 2024. To confirm single-pathogen infection by *Mycoplasma pneumoniae*, all enrolled children underwent routine pathogen screening, including nasopharyngeal swab or sputum cultures, respiratory pathogen nucleic acid tests (including influenza virus, respiratory syncytial virus, adenovirus), and *Mycoplasma pneumoniae*-specific IgM/IgG serological tests.

Patients

Inclusion Criteria

(1) 1≤ age ≤14 years old;
(2) Meet the diagnostic criteria for MPP in children as outlined in the Expert Consensus on the Diagnosis and Treatment of Mycoplasma pneumoniae Pneumonia in Children (2023 edition);[13]
(3) There were obvious clinical symptoms of irritating cough and chest imaging examination supported the diagnosis;
(4) Serum Mycoplasma pneumoniae specific antibody IgM or IgG test was positive;
(5) The child can actively cooperate with the completion of treatment and the child's family members sign a written informed consent.

Exclusion Criteria

(1) Concurrent with other respiratory infections;
(2) Damage of liver and kidney function;
(3) Unable to cooperate with medical staff in related diagnosis and treatment during treatment;
(4) Test patients with drug allergy;
(5) Patients with severe digestive or blood system abnormalities;
(6) Recent treatment with immunosuppressants and other antibiotics.
(7) Children with congenital or acquired immunodeficiency disorders.

Sample Size Calculation

The primary outcome used for sample size estimation was the total clinical effective rate. Based on clinical observations and reference data from previous studies, where the combination of TCM and azithromycin achieved a total effective rate of 95.08% compared to 82.76% with azithromycin alone,[14] we conservatively estimated the effective rate of the control group to be 75% and that of the treatment group to be 95%. This conservative estimation was made considering differences in treatment duration, TCM formulations, and evaluation criteria between our study and the referenced literature, which may lead to variation in actual clinical efficacy.

Assuming a one-sided significance level of $\alpha = 0.05$ and a statistical power of $1-\beta = 0.80$, with an allocation ratio of 1:1 between the treatment and control groups, the required sample size was calculated using the TrialSize package in R. The result indicated that 46 participants were needed in each group, yielding a total sample size of 92 to ensure adequate statistical power for the study.

Randomization and Blinding

Eligible patients were randomly assigned to the treatment group and the control group in a 1:1 ratio. The random numbers were generated by a statistician unfamiliar with the study using SPSS 26.0 software and placed in sealed, opaque envelopes labeled with numbers. These envelopes were randomly distributed to the children's family members, and the random allocation was completed based on the random numbers. To minimize potential bias, a double-blind method was adopted, ensuring that throughout the study, the children, their family members, and the primary investigators were unaware of the group assignments. The final statistical analysis of the study data was performed by a statistician who was not involved in the randomization process.

Intervention Measures

All patients received symptomatic and supportive treatment after admission, such as clearing heat, relieving cough, eliminating phlegm, etc., according to the following treatment plan. The drug will be dispensed by an unwitting nurse to a patient with a corresponding drug number based on the drug number. The control group of children with routine intravenous azithromycin injection, 10 mg/ (kg/d) for 5 consecutive days. The treatment group was given a Qingke mixture based on the control group. Formula composition (the following were all used in the pharmacy of whole-component granules of our hospital): Fructus perillae 10g, herba ephedrae 4g, baical skullcap root 10g, radix peucedani 10g, radix bupleuri 10g, almond 5g, densefruit pittany root-bark 10g, fritillariae chrrhosae bulbus 4g, lobed kudzuvine

root 10g, houttuynia herb 10g, glycyrrhiza uralensis fisch 5g (water extract juice 120mL). Dosage: For children under 3 years old, 20mL each time; For children aged 3 to 5 years, 30mL each time; For Children 6 years and older, 40mL each time; Oral treatment 3 times daily for 5 days. The pharmacological effects of the components of the Qingke mixture were detailed in Table S1.

Outcome Measurements

Treatment response was evaluated at two time points: at baseline (prior to treatment) and on day 6 following completion of the 5-day treatment course. Clinical symptoms (eg, cough, fever, pulmonary rales) were assessed daily by attending physicians using a standardized clinical evaluation checklist to ensure consistency across participants. Pulmonary imaging (chest X-ray) was conducted on admission and repeated after treatment to evaluate changes in lung lesions. Traditional Chinese Medicine (TCM) symptom scores were recorded at baseline and post-treatment using a standardized scoring system (Table S2), and were interpreted in conjunction with the therapeutic response criteria described in the Efficacy Evaluation section.

Laboratory inflammatory and immune indicators—including C-reactive protein (CRP), white blood cell count (WBC), interleukin-6 (IL-6), interleukin-8 (IL-8), immunoglobulin levels (IgA, IgG, IgM), and T lymphocyte subsets (CD3+, CD4+, CD8+, CD4+/CD8+ ratio)—were measured before treatment and on day 6 after treatment completion. Pulmonary function indicators (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], FEV1/FVC) were also assessed pre- and post-treatment to evaluate respiratory recovery.

Baseline characteristics included gender, age, disease duration, body mass index (BMI), and TCM symptom score. Clinical outcomes measured included length of hospital stay, time to cough resolution, fever clearance time, disappearance time of pulmonary rales, body temperature, heart rate, and respiratory rate.

Adverse events—including nausea and vomiting, diarrhea, and rash—were monitored daily during hospitalization. Additionally, to evaluate drug-related safety, liver and kidney function indicators were assessed before and after treatment. Liver function was evaluated using alanine aminotransferase (ALT) and aspartate aminotransferase (AST), while renal function was assessed using blood urea nitrogen (BUN) and serum creatinine (Scr). These biochemical tests were conducted on Day 0 (baseline) and Day 6 (after treatment completion). No post-discharge follow-up was conducted, as the study focused on in-hospital responses based on predefined clinical, laboratory, and safety indicators.

Efficacy Evaluation

The evaluation is based on the efficacy standards for "pneumonia asthma" as outlined by the National Administration of Traditional Chinese Medicine's "Standards for Diagnosis and Efficacy of Traditional Chinese Medicine Diseases and Syndromes":[15]

(1) Markedly effective: Chest X-ray shows the patient's lungs have returned to normal, body temperature and blood routine have normalized, and associated clinical symptoms and signs have disappeared.
(2) Effective: Chest X-ray shows reduced lung shadows but still visible, and blood routine tests still show signs of infection. Clinical symptoms and signs have improved but are not fully resolved.
(3) Ineffective: The above symptoms remain unchanged or worsen.

Total effective rate = [(number of markedly effective cases + number of effective cases)/total cases] ×100%.

This three-level classification system served as the standardized criterion for evaluating treatment response across all enrolled patients.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. Measurement data following a normal distribution were described as mean ± standard deviation ($\bar{x} \pm S$), and comparisons were made using the *t*-test. Data not following a normal distribution were expressed as the median M (P25, P75), and comparisons were conducted using the rank-sum

test. Categorical data were presented as n(%), and comparisons were made using the χ^2-test or Fisher's exact test. A P-value of < 0.05 was considered statistically significant.

Results

Participants

Between January 2024 and September 2024, a total of 117 children diagnosed with MPP were recruited. Among them, 25 children were excluded due to not meeting the inclusion criteria (n=22) or declining to participate (n=3) (Figure 1). Ultimately, 46 patients were enrolled in the control group and 46 patients in the treatment group. No participants withdrew from the trial, and data collection was completed for all included patients.

Baseline Characteristics

There were no statistically significant differences between the control and treatment groups in terms of gender, age, BMI, course of disease, or TCM symptom scores (Table 1), indicating that the two groups were comparable.

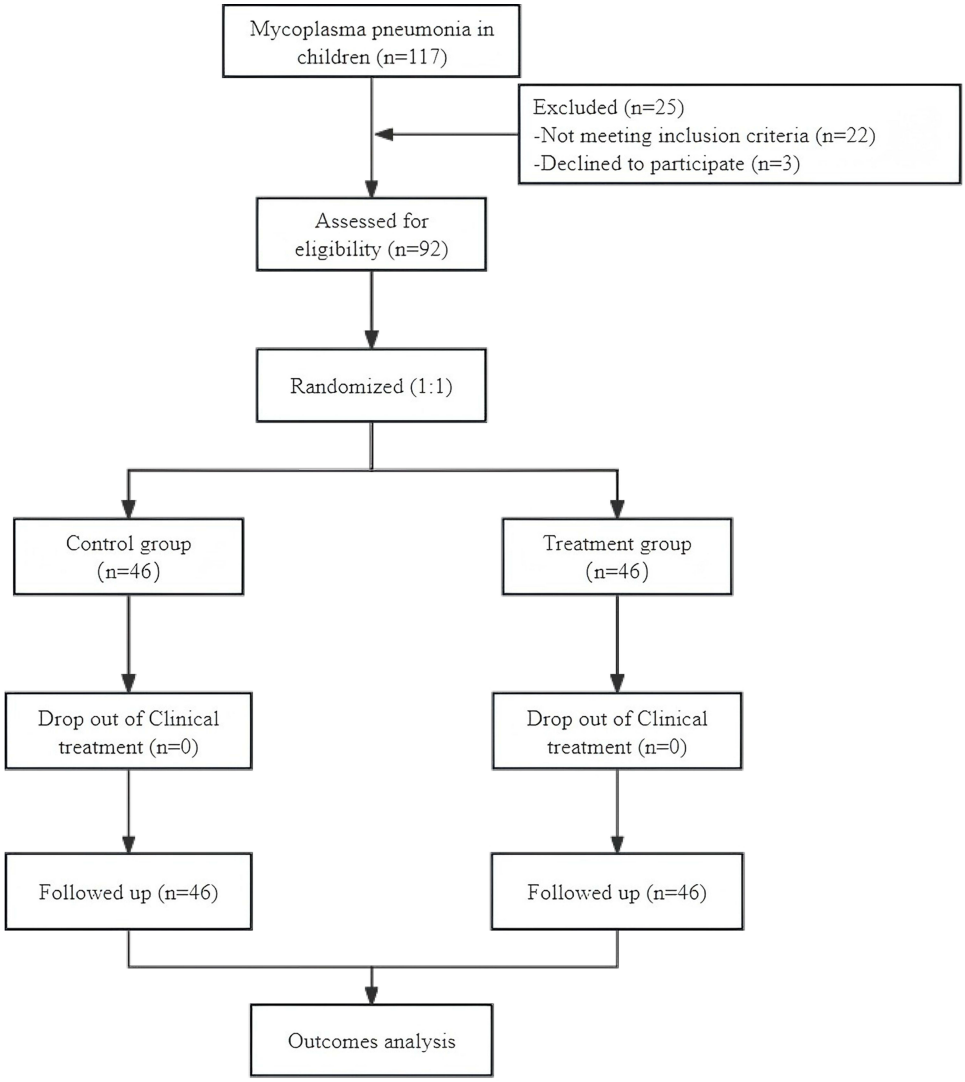

Figure 1 Study flowchart.

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Table 1 Comparison of Baseline Characteristics Between the Two Groups of Patients

Variable	Category	All (n=92)	Control Group (n=46)	Treatment Group (n=46)	P	Methods
Gender, n(%)	Female	54(58.70)	29(63.04)	25(54.35)	0.397	Chi-square test
	Male	38(41.30)	17(36.96)	21(45.65)		
Age, median[IQR]	-	8.00[6.00, 10.00]	8.00[5.00, 10.00]	8.00[6.00, 10.00]	0.715	Mannwhitney-U
BMI, median[IQR]	-	16.60[14.48, 18.58]	16.53[14.57, 19.47]	16.41[14.46, 18.38]	0.758	Mannwhitney-U
Course of disease, median[IQR]	-	6.00[5.00, 7.00]	6.00[5.00, 7.00]	6.00[5.00, 7.00]	0.691	Mannwhitney-U
TCM symptom score, median[IQR]	-	13.00[12.00, 15.00]	13.00[11.00, 15.00]	13.00[12.00, 14.00]	0.645	Mannwhitney-U

Note: Units: Course of disease: day.

Clinical Efficacy

After treatment, clinical symptoms improved in both groups. The clinical efficacy rate was 80.43% in the control group and 95.65% in the treatment group (Table 2). The combination of azithromycin and Qingke Mixture significantly enhanced the overall clinical efficacy compared to azithromycin alone, with a statistically significant difference ($P < 0.05$).

Comparison of Clinical Symptoms and Pulmonary Function

Before treatment, there were no statistically significant differences in clinical symptoms and pulmonary function between the two groups. However, after treatment, the treatment group had significantly shorter times for the disappearance of pulmonary rales, fever clearance, cough resolution, and hospital stay compared to the control group. The treatment group also exhibited significantly lower body temperature, heart rate, and respiratory rate. In addition, pulmonary function, as measured by FEV1, was significantly higher in the treatment group, and the TCM symptom scores were lower ($P < 0.05$) (Table 3).

Table 2 Comparison of Clinical Efficacy Between the Two Groups of Patients

Group	N (92)	Markedly Effective, n(%)	Effective, n (%)	Ineffective, n(%)	Total Effective Rate, n(%)
Control group	46	13(28.26)	24(52.17)	9(19.57)	37(80.43)
Treatment group	46	21(45.65)	23(50.00)	2(4.35)	44(95.65)
X^2					5.06
P					0.025

Table 3 Comparison of Clinical Symptoms and Lung Function Between the Two Groups of Patients

Variable	All (n=92)	Control Group (n=46)	Treatment Group (n=46)	P	Methods
TCM symptom score after, median[IQR]	6.00[6.00, 7.00]	7.00[7.00, 7.00]	6.00[6.00, 6.00]	<0.001	Mannwhitney-U
Length of stay, median[IQR]	8.00[7.00, 11.00]	8.00[7.00, 11.00]	8.00[7.00, 9.00]	0.030	Mannwhitney-U
Disappearance time of cough, median[IQR]	5.20[4.10, 6.10]	6.10[5.80, 6.40]	4.10[3.90, 4.20]	<0.001	Mannwhitney-U
Fever clearance time, mean(±SD)	3.09±1.13	3.55±1.02	2.63±1.05	<0.001	*t*-test
Disappearance time of pulmonary rales, median[IQR]	5.30[4.30, 6.30]	6.20[5.80, 7.00]	4.30[3.50, 4.90]	<0.001	Mannwhitney-U
Body temperature before, median[IQR]	38.89[38.40, 39.71]	38.89[38.50, 39.70]	38.80[37.70, 39.90]	0.870	Mannwhitney-U
Body temperature after, median[IQR]	36.50[36.20, 36.50]	36.50[36.40, 36.50]	36.30[36.20, 36.50]	0.016	Mannwhitney-U
Heart rate before, mean(±SD)	96.27±6.57	97.35±7.63	95.20±5.07	0.119	*t*-test
Heart rate after, median[IQR]	86.00[82.00, 90.00]	90.00[82.00, 96.00]	83.00[82.00, 86.00]	<0.001	Mannwhitney-U
Respiratory rate before, mean(±SD)	29.03±1.96	29.35±1.74	28.72±2.12	0.126	*t*-test
Respiratory rate after, median[IQR]	24.00[23.00, 26.00]	26.00[24.00, 27.00]	23.00[23.00, 25.00]	<0.001	Mannwhitney-U
FEV1 before, mean(±SD)	1.24±0.11	1.23±0.09	1.26±0.12	0.186	*t*-test
FEV1 after, mean(±SD)	1.44±0.30	1.32±0.30	1.57±0.25	<0.001	*t*-test
FVC before, mean(±SD)	1.64±0.14	1.66±0.15	1.63±0.12	0.316	*t*-test
FVC after, mean(±SD)	1.70±0.27	1.66±0.29	1.74±0.23	0.153	*t*-test
FEV1/FVC before, mean(±SD)	0.76±0.09	0.75±0.09	0.78±0.09	0.132	*t*-test
FEV1/FVC after, median[IQR]	0.89[0.75, 0.98]	0.86[0.63, 1.00]	0.89[0.80, 0.98]	0.101	Mannwhitney-U

Notes: Units: Length of stay, disappearance time of cough, fever clearance time, disappearance time of pulmonary rales: day. Body temperature: °C. Heart rate, respiratory rate: beats/min. FEV1, FVC: L; FEV1/FVC: %.

Comparison of Inflammatory and Immune Markers

Before treatment, there were no statistically significant differences between the two groups in terms of serum inflammatory factors or immune levels. However, after treatment, the treatment group showed significantly lower levels of WBC, CRP, IL-6, and IL-8 compared to the control group ($P < 0.05$). In terms of immunoglobulin levels, both groups showed significant improvements post-treatment, but the treatment group had significantly higher levels of serum IgA, IgG, and IgM than the control group ($P < 0.05$). Similarly, T lymphocyte subsets increased significantly in both groups after treatment, with the treatment group showing significantly higher levels of CD3+, CD4+, and CD4+/CD8+ ratio, and significantly lower CD8+ levels compared to the control group (Table 4).

Adverse Events in the Two Groups

Detailed records were kept of the adverse reactions in both groups during the treatment process. The results showed that the main adverse events were nausea, vomiting, diarrhea, and rash, all of which were mild and did not affect the continuation of treatment. In the control group, there were 3 cases of nausea and vomiting, 1 case of diarrhea, and 1 case of rash, with no other significant adverse reactions observed. The incidence of adverse events in the control group was 10.87%. In the treatment group, there were 2 cases of nausea and vomiting and 1 case of diarrhea, with no other significant adverse reactions observed. The incidence of adverse events in the treatment group was 6.52%. There was no statistically significant difference in the incidence of adverse events between the two groups ($P > 0.05$) (Table 5).

In addition, there were no statistically significant differences between the two groups in baseline liver and renal function indicators. After treatment, levels of ALT, AST, BUN, and Scr remained within the normal clinical range in both groups, and no significant differences were observed between the treatment and control groups ($P > 0.05$). These results suggest that the addition of Qingke Mixture did not impose additional hepatic or renal burden (Table 6). These findings support the safety of Qingke Mixture as an adjunct therapy in pediatric MPP.

Table 4 Comparison of Inflammatory and Immune Markers Between the Two Groups of Patients

Variable	All (n=92)	Control Group (n=46)	Treatment Group (n=46)	P	Methods
WBC before, median[IQR]	11.24[9.86, 12.30]	11.24[9.95, 12.15]	11.08[9.71, 12.64]	0.728	Mannwhitney-U
WBC after, median[IQR]	8.39[6.35, 12.42]	9.30[6.77, 14.06]	7.89[5.64, 10.93]	0.074	Mannwhitney-U
CRP before, mean(±SD)	13.60±2.92	13.68±3.02	13.52±2.80	0.796	*t*-test
CRP after, mean(±SD)	6.54±2.90	8.75±1.81	4.33±1.94	<0.001	*t*-test
IgA before, median[IQR]	0.70[0.58, 0.78]	0.63[0.57, 0.78]	0.70[0.63, 0.80]	0.211	Mannwhitney-U
IgA after, mean(±SD)	1.48±0.32	1.37±0.23	1.59±0.36	<0.001	*t*-test
IgG before, mean(±SD)	7.34±1.21	7.27±1.29	7.42±1.11	0.556	*t*-test
IgG after, mean(±SD)	12.05±2.39	10.87±2.11	13.24±2.03	<0.001	*t*-test
IgM before, mean(±SD)	1.11±0.11	1.10±0.12	1.13±0.09	0.309	*t*-test
IgM after, median[IQR]	1.40[1.19, 1.53]	1.29[1.08, 1.49]	1.52[1.36, 1.62]	<0.001	Mannwhitney-U
CD3 before, mean(±SD)	51.37±4.26	52.06±4.33	50.68±4.08	0.123	*t*-test
CD3 after, mean(±SD)	66.08±6.74	62.44±5.55	69.73±5.78	<0.001	*t*-test
CD4 before, mean(±SD)	30.96±2.73	31.25±2.99	30.68±2.41	0.322	*t*-test
CD4 after, mean(±SD)	37.75±3.31	36.84±3.28	38.67±3.08	0.008	*t*-test
CD8 before, mean(±SD)	30.06±2.16	29.87±2.12	30.26±2.18	0.392	*t*-test
CD8 after, mean(±SD)	25.82±2.53	27.62±1.73	24.03±1.83	<0.001	*t*-test
CD4/CD8 before, mean(±SD)	1.04±0.12	1.05±0.14	1.02±0.10	0.178	*t*-test
CD4/CD8 after, mean(±SD)	1.48±0.21	1.34±0.15	1.62±0.17	<0.001	*t*-test
IL6 before, mean(±SD)	17.48±2.06	17.34±2.08	17.63±2.03	0.506	*t*-test
IL6 after, mean(±SD)	10.95±3.11	13.62±1.66	8.28±1.52	<0.001	*t*-test
IL8 before, mean(±SD)	26.63±1.57	26.90±1.59	26.36±1.50	0.101	*t*-test
IL8 after, median[IQR]	10.83[9.11, 12.31]	12.09[11.03, 14.59]	9.10[6.93, 10.31]	<0.001	Mannwhitney-U

Notes: Units: IgA, IgG, IgM: g/L. CD4, CD8+, CD3+: %. WBC: $\times 10^9$/L; CRP: mg/L; L6, IL8: pg/mL.

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Table 5 Comparison of Adverse Events Between the Two Groups

Group	N (92)	Nausea and Vomiting, n(%)	Diarrhea, n(%)	Rash, n(%)	Adverse Event Rate, n(%)
Control group	46	3(6.52)	1(2.17)	1(2.17)	5(10.87)
Treatment group	46	2(4.35)	1(2.17)	0(0.00)	3(6.52)
X^2					0.14
P					0.71

Table 6 Comparison of Liver and Renal Function Before and After Treatment

Variable, Mean(±SD)	All (n=92)	Control Group (n=46)	Treatment Group (n=46)	P	Methods
ALT before	21.66 (4.19)	21.78 (4.13)	21.54 (4.29)	0.786	*t*-test
ALT after	21.95 (4.39)	21.89 (4.24)	22.00 (4.58)	0.906	*t*-test
AST before	26.21 (5.81)	25.98 (6.03)	26.44 (5.64)	0.709	*t*-test
AST after	26.65 (5.43)	26.46 (5.61)	26.85 (5.31)	0.732	*t*-test
BUN before	4.20 (0.92)	4.18 (0.89)	4.21 (0.95)	0.848	*t*-test
BUN after	4.25 (0.94)	4.24 (0.90)	4.26 (0.98)	0.886	*t*-test
Scr before	38.93 (5.43)	39.12 (5.28)	38.75 (5.64)	0.746	*t*-test
Scr after	39.11 (5.44)	39.25 (5.10)	38.97 (5.82)	0.807	*t*-test

Notes: Units: ALT, AST: U/L. BUN: mmol/L. Scr: μmol/L.

Discussion

Azithromycin is a widely used macrolide antibiotic in the treatment of MPP, especially in pediatric populations.[16] Its effectiveness primarily lies in its ability to inhibit bacterial protein synthesis and reduce inflammation. However, its clinical application is often limited by the development of drug resistance, as well as its inability to fully address the complex pathophysiological processes associated with MPP, such as immune dysregulation and persistent inflammation.[17] These limitations underscore the need for adjunctive therapeutic strategies that can enhance treatment efficacy and reduce adverse outcomes. In this study, azithromycin was used as standard therapy in both groups, and the treatment group received additional Qingke Mixture. This design was intended to evaluate the clinical efficacy and safety of combining Qingke Mixture with azithromycin. Azithromycin remains the first-line treatment for MPP due to its long half-life, high tissue penetration, and relatively low hepatic and renal toxicity.[18] However, the increasing prevalence of macrolide resistance and the potential for gastrointestinal side effects and vascular irritation with prolonged use necessitate the exploration of combination therapies.

The primary findings of this study indicate that the combination of azithromycin with Qingke Mixture significantly enhances clinical efficacy (95.65% vs 80.43%, $P < 0.05$), reduces inflammatory markers, and improves pulmonary function in children with MPP compared to azithromycin alone. Importantly, our study highlights that the combination therapy reduced the time required for the disappearance of pulmonary rales, fever, and cough, and shortened hospital stays ($P < 0.05$). These results are consistent with the growing body of evidence supporting the use of integrative medicine in MPP. For example, studies have shown that Jiedu Pingsu Decoction combined with azithromycin can improve T cell subset levels, immune function, and inflammatory factors in children with MPP, resulting in increased clinical effectiveness (94.12% vs 82.35%).[19] In our study, the clinical efficacy rate of azithromycin combined with traditional Chinese medicine in treating pediatric MPP exceeded the outcomes reported in previous studies, suggesting that Qingke Mixture may exert complementary or synergistic effects when used alongside azithromycin. Compared to other integrative treatment approaches, our findings indicate that Qingke Mixture may offer additional benefits in modulating immune responses and alleviating clinical symptoms. This is evidenced by the increased levels of T lymphocyte subsets and the decreased levels of pro-inflammatory cytokines such as IL-6 and IL-8, indicating a better-regulated immune response. These improvements in immune modulation and inflammation control likely contribute to the better clinical outcomes observed. For example, Qingfei Huayu Decoction combined with conventional Western medicine has been shown to enhance clinical efficacy, hasten symptom relief, and improve inflammatory states (eg, reducing IL-6 and IL-8 levels) in pediatric MPP. Animal studies on Qingfei Huayu Decoction suggest that its mechanism may involve the Notch signaling pathway.[20]

The innovative aspect of this research lies in the use of Qingke Mixture, which has not been previously studied as a treatment for MPP in children, as this specific combination of herbal ingredients is being used for the first time in treating pediatric MPP. In TCM, MPP is often classified under the categories of "lung-heat" or "phlegm-heat obstructing the lung", where the pathogenesis involves internal heat, phlegm accumulation, and qi stagnation, impairing the lung's normal dispersing and descending functions.[21] In TCM, treatment of MPP involves regulating internal imbalances, such as addressing cold and heat within the body, promoting the expulsion of phlegm from the lungs, and improving the flow of energy (qi) and blood.[22] This holistic approach aims to strengthen the body's immune system and ultimately eliminate pathogens, leading to better overall health. Qingke Mixture, the TCM formulation used in this study, is composed of several herbal ingredients with pharmacological actions that align with these treatment principles. For example, herbs such as herba ephedrae is commonly used in TCM to clear lung heat and resolve phlegm.[23] Baical skullcap root is well-documented for their anti-inflammatory and antibacterial properties, which may directly address the underlying pathophysiology of MPP.[24] Modern pharmacological studies have demonstrated that Herba Ephedrae stimulates adrenergic receptors, promoting the release of norepinephrine and adrenaline, which relaxes bronchial smooth muscles and reduces airway remodeling, thus helping to relieve asthma and cough symptoms.[25] Additionally, Fructus Perillae plays a role in restoring immune balance by regulating the Th1/Th2 imbalance and suppressing eosinophilic inflammation in the airways. This helps to mitigate bronchial hypersensitivity and reduce the severity of asthma-like symptoms, offering anti-inflammatory and immunomodulatory benefits in the treatment of respiratory conditions.[26] Several studies have demonstrated that these herbs have potent immunomodulatory and anti-inflammatory effects, which likely contribute to the observed improvements in clinical outcomes.

Modern medicine has shown that regulating immune response and controlling inflammation play an important role in MPP treatment.[27] The immune response in MPP involves both innate and adaptive immunity, with key roles played by T lymphocyte subsets and inflammatory cytokines.[28] In our study, we observed significant improvements in immune function markers, including increased CD3+, CD4+, and the CD4+/CD8+ ratio, along with reduced CD8+ levels. These findings suggest that the combination of Qingke Mixture and azithromycin may enhance the immune system's ability to combat *Mycoplasma pneumoniae* infection, potentially by promoting T helper cell function while modulating cytotoxic T cell activity. The reduction in pro-inflammatory cytokines such as IL-6 and IL-8 further indicates that this combination therapy may mitigate excessive inflammatory responses, which are often responsible for tissue damage and prolonged recovery in MPP.[29] In addition to the observed improvements in T lymphocyte subsets, our study also demonstrated significant changes in immunoglobulin levels, specifically IgM, IgG, and IgA. Immunoglobulins play a vital role in the body's defense against infections, with IgM being the first antibody produced in response to infection, followed by IgG, which provides longer-term immunity, and IgA, which protects mucosal surfaces.[30] The treatment group exhibited increased levels of IgM and IgG, suggesting an enhanced ability to mount an effective immune response against *Mycoplasma pneumoniae*. The rise in IgA levels indicates improved mucosal immunity, which is particularly important in respiratory infections like MPP, as it helps protect the lungs from further pathogen invasion and supports the clearance of residual pathogens from the respiratory tract.[31] These immunomodulatory effects align with the current understanding of MPP treatment in modern medicine, where the regulation of immune responses is considered crucial for reducing complications and improving patient outcomes.[32] By enhancing both immune function and reducing inflammation, the combination of Qingke Mixture and azithromycin appears to offer a more comprehensive treatment approach for MPP than azithromycin alone, with Qingke Mixture possibly contributing additional immunoregulatory benefits.

This study has several limitations. First, the trial was conducted with a small sample size, although none withdrew from the trial. Second, the treatment and follow-up period was relatively short, and some patients had not fully recovered by the end of the study. Third, the selected inflammatory biomarkers are not specific to MPP and may reflect responses to infections other than MPP. Although patients with confirmed co-infections were excluded, the overlapping inflammatory responses cannot be entirely ruled out. Fourth, age-dependent dosing of the Qingke Mixture may have introduced variability in treatment response among different age groups. Although dosing was determined according to standard pediatric practices, this heterogeneity should be acknowledged when interpreting the therapeutic efficacy. Fifth, this study did not include macrolide resistance testing. Although patients with recent antibiotic use were excluded and randomization helped minimize potential bias, the absence of resistance profiling may influence the interpretation of azithromycin efficacy. Lastly, this was a single-center study, and the geographic characteristics of the enrolled population may have influenced the results. Therefore, future multicenter randomized controlled trials with larger sample sizes are needed to validate the conclusions of this study.

Conclusions

Qingke Mixture combined with azithromycin significantly improves clinical outcomes in children with MPP. The combination therapy enhances symptom resolution, reduces inflammatory markers, boosts immune function, and improves pulmonary function without increasing adverse events. Qingke Mixture offers a safe and effective adjunctive treatment for pediatric MPP.

Data Sharing Statement

The original contributions presented in the study are included in the article and Supplementary files of the present research article.

Ethical Statement

The study was approved by the Ethics Committee of the Affiliated Hospital of Changchun University of Chinese Medicine (approval number: CCZYFYKYLL2024-005). The trial was registered on the International Traditional Medicine Clinical Trial Registration Platform (http://itmctr.ccebtcm.org.cn/) with the registration number: ITMCTR2024000355. The patients and their guardians signed the informed consent and participated this study voluntarily.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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