Efficacy and safety of azithromycin combined with glucocorticoid on refractory Mycoplasma pneumoniae pneumonia in children

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Introduction: The aim of this study was to evaluate the efficacy and safety of azithromycin (AZI) combined with glucocorticoid (GC) in the treatment of children with refractory Mycoplasma pneumoniae.

Methods: Computer search for PubMed, EMBase, Cochrane Library, China Biomedical Literature Database (CBMdisc), China Knowledge Network (CNKI), Wanfang, VIP (VIP), and a randomized controlled trial (RCT) of AZI combined with GC in the treatment of children with refractory Mycoplasma pneumoniae pneumonia test (RCT), the search time limit is built until March 20, 2019. Two researchers independently performed literature screening, data extraction, and literature risk bias, and meta-analysis was performed using RevMan 5.3 software.

Results: A total of 12 RCTs were included, including 1130 patients. Meta-analysis showed that AZI combined with GC therapy significantly improved the total effective rate of the disease compared with the conventional treatment group (odds ratio [OR] = 6.37, 95% confidence interval [CI] = 4.03, 10.07; \(P < .00001\); \(I^2 = 0\)%), effectively shortened the antipyretic time (SMD = -2.29; 95% CI = -2.70, -1.88; \(P < .0001\)); promoted lung inflammation absorption (SMD = -1.89; 95% CI = -2.38, -1.40; \(P < .0001\)), reduced cough time (SMD = -2.39; 95% CI = -2.80, -1.99; \(P < .0001\)); shortened hospital stay (SMD = -2.19; 95% CI = -3.21, -1.17; \(P < .0001\)); improved imaging findings (OR = 5.38; 95% CI = 1.09, 26.51, \(P = .04\)); reduced inflammation index (SMD = -3.15; 95% CI = -4.93, -1.36; \(P = .004\)); improved immune function (SMD = 1.29; 95% CI = -0.02, 2.60; \(P < .0001\)); had no significant adverse reactions (OR = 1.18; 95% CI = 0.71, 1.98; \(P = .53\)).

Conclusions: According to the current limited research evidence, the addition of GCs to the conventional treatment of refractory Mycoplasma pneumoniae pneumonia in children can improve the clinical efficacy to a certain extent, and the safety is better. However, due to the quality and quantity of the included literature, the conclusions of this study need to be confirmed by more high-quality studies.

Abbreviations: AZI = azithromycin, CBM-disc = Chinese Biomedical Literature Database on Disc, CI = confidence interval, CNKI = China National Knowledge Infrastructure, GC = glucocorticoid, MD = Mean difference, OR = odds ratio, RCT = randomized controlled trial, RMPP = Refractory mycoplasma pneumoniae pneumonia, RR = relative risk, SD = standard deviation, UDCA = ursodeoxycholic acid, VIP = Vendor Information Pages.

Keywords: azithromycin, children, glucocorticoid, meta-analysis, refractory mycoplasma pneumoniae pneumonia.
1. Introduction

Refractory Mycoplasma pneumoniae (RMPP) mainly refers to the Mycoplasma pneumoniae pneumonia characterized by persistent fever and progressive exacerbations of clinical symptoms, signs, and related imaging manifestations after standard treatment with macrolide drugs for ≥1 week, which is one of the community-acquired pneumonias with unclear clinical etiology. The condition of this disease changes relatively rapidly, and extensive pulmonary inflammation can occur in a relatively short time, which is often accompanied by other complications such as massive pleural effusion, pleural thickening, pulmonary abscess, pneumothorax, and so on. In more severe cases, children may have bronchiolitis obliterans, atelectasis, and systemic inflammatory response syndrome, which seriously threaten their health. At present, RMPP is mainly treated by antimicrobial, suppressing the overactive immune response and bronchoalveolar lavage, but the clinical efficacy is still poor. In recent years, many clinicians have used azithromycin (AZI) combined with glucocorticoid (GC) to treat the disease, but there is no evaluation on the efficacy and safety of the combined treatment scheme at home or abroad. Therefore, this study will systematically evaluate the efficacy and safety of AZI combined with GC in the treatment of RMPP, so as to provide an optimal plan for clinical treatment of this disease.

2. Methods

2.1. Ethical review

All the clinical trials included in the present study were approved by the Institutional Review Board.

2.2. Selection of studies

We included all randomized controlled trials (RCTs) of AZI combined with GC therapy for RMPP in children. The control group was routinely given symptomatic treatment such as low-flow oxygen inhalation, correcting the imbalance of water electrolyte and acid-base disorders, and AZI to fight infection, whereas AZI combined with GC was given to the treatment group on the basis of the control group. And there was no restriction on drug dose and administration in both groups. Studies were excluded if they were with no valid data, unable to obtain the full text through multiple channels, and about animal experiments and review articles. For different researches on the same research object, the latest research results or the research with the largest sample size were adopted, whereas articles with duplicate publications of the same research results were excluded.

The primary outcome index was the total effective rate of treatment. And the secondary outcome index included clinical symptoms (such as antipyretic time, rale vanishing time, cough recovery time), imaging manifestations, inflammation marker (such as blood routine, CRP, inflammatory cytokines, T cell subsets, among others), average hospital stay, and adverse reaction rate, and so on.

2.3. Search method for identification of studies

We searched for RCTs of AZI combined with GC therapy for RMPP in children using the databases of PubMed, Embase, Cochrane Library, CBMdisc, CNKI, Wanfang Data, VIP data by the computer from the first available date to March 20, 2019. Meanwhile manual retrievals of references that met the inclusion criteria of relevant included studies were combined to achieve the literature recall rate. The Chinese search terms were as follows: AZI, methylprednisolone, prednisone, dexamethasone, hydrocortisone, children, refractory pneumonia mycoplasma pneumonia; whereas the English search terms were AZI, methylprednisolone, prednisone, dexamethasone, hydrocortisone, children, refractory pneumonia mycoplasma pneumonia. Retrieval of all relevant studies was based on consensus between all authors, and in addition, the reference list of the selected articles was further searched for additional relevant studies.

2.4. Data collection and extraction

This study was independently conducted and cross-checked by 2 main researchers in the studies selection and data extraction process. If there was any disagreement in the data extraction process, it should be resolved through discussion or with the assistance of a trained third party. In the studies selection process, the researchers carefully read the titles to exclude the literatures that were obviously inconsistent with the research topic, and then read the abstracts and the full text to further exclude the irrelevant literature. And the incomplete studies data could be obtained by email or telephone follow-up. The included literature contained: (1) basic information of related literature (title, first author, publication time, and so on); (2) general characteristics of study objects and related interventions; (3) assessing the risk of bias; (4) treatment outcome indicators in the literature.

2.5. Method of assessing the risk of bias

The bias risk assessment of the included literatures was mainly conducted by 2 researchers independently, and then cross-checked with each other’s results. We used the risk of bias evaluation tool as recommended in the Cochrane manual 5.1.0 for randomized controlled trials.

2.6. Data analysis

The statistical analysis of this study was mainly performed by RevMan 5.3 software. Mean difference (MD) was used as effect analysis statistics for quantitative data, while risk ratio (RR) for binary variables. Each effect size provides 95% confidence interval (CI). The heterogeneity among the studies was evaluated by \( \chi^2 \) test (\( \alpha = 0.1 \)), and the different heterogeneities were evaluated by \( I^2 \). If there was no significantly statistical heterogeneity among the results, the fixed-effect model was used for statistical analysis. On the contrary, the main sources of relevant heterogeneity should be further analyzed. After excluding the influencing factors of clinical heterogeneity, the random-effect model should be given for statistical analysis. The test level of meta-analysis was \( \alpha = 0.05 \). If there was significant clinical heterogeneity, subgroup analysis or sensitivity analysis should be used, or only descriptive analysis should be performed.

3. Results

3.1. Studies selection procedures and results

A total of 284 initial related literatures were retrieved and 12 related RCT studies met the inclusion criteria after importing
into EndNote software for duplicate checking and reading titles, abstracts and full texts. A total of 1130 cases of RMPP were included in the included studies, including 566 cases in the control group (conventional treatment plus AZI) and 564 cases in the treatment group (combined with GC group) (Table 1, Table 2). Flowchart depicting the identification and selection of relevant studies is shown in Figure 1).

### 3.2. Quality assessment

We evaluated the quality of each study, random method, allocation concealment, blinding method, data integrity, selective reporting, and other bias (Table 3).

### Table 1

**Design and demographic information of the studies included in the meta-analysis.**

| First author, year | Country | Design | Total | AZI + GC | Control | AZI + GC | Control |
|-------------------|---------|--------|-------|----------|---------|----------|---------|
| Tang et al, 2017²⁶ | China   | RCT    | 102   | 51       | 51      | 7.4 ± 4.9 | 6.9 ± 4.3 |
| Fu, 2017²⁷        | China   | RCT    | 32    | 46       | 46      | 7.45 ± 4.02 | 7.68 ± 4.23 |
| Zheng, 2017²⁸     | China   | RCT    | 68    | 34       | 34      | 5.6 ± 1.5  | 6.1 ± 1.8  |
| Zhou et al, 2018²⁹ | China   | RCT    | 120   | 60       | 60      | 4.8 ± 1.4  | 4.8 ± 1.5  |
| Wu et al, 2018³⁰  | China   | RCT    | 106   | 53       | 53      | 5.2 ± 2.1  | 5.1 ± 2.3  |
| Lan et al, 2019³¹ | China   | RCT    | 60    | 30       | 30      | 5.4 ± 0.4  | 5.0 ± 0.5  |
| Zheng and Sun, 2018³² | China   | RCT    | 200   | 100      | 100     | 6.7 ± 1.5  | 7.0 ± 1.7  |
| Li, 2018³³        | China   | RCT    | 86    | 43       | 43      | 7.1 ± 1.5  | 8.1 ± 1.1  |
| An, 2017³⁴        | China   | RCT    | 60    | 30       | 30      | -         | -        |
| Lin and Li, 2017³⁵ | China   | RCT    | 30    | 45       | 45      | 6.4 ± 3.2  | 6.7 ± 3.3  |
| Zhang and Zia, 2014³⁶ | China   | RCT    | 88    | 44       | 44      | -         | -        |
| Luo et al, 2014³⁷  | China   | RCT    | 58    | 28       | 30      | 7.9 ± 4.1  | 7.6 ± 4.5  |

AZI = azithromycin, GC = glucocorticoid, RCT = randomized controlled trial, SD = standard derivation.

### Table 2

**Treatment regimens and outcome indicators of the studies included in the meta-analysis.**

| First author, year | AZI | GC | Outcome indicators |
|-------------------|-----|----|--------------------|
| Tang et al, 2017²⁶ | IV AZI 10 mg/kg, qd × 5 days; discontinued for 4 days; then oral for 3 days, total for 4 consecutive courses. | IV MP 2 mg/kg, qd × 3 days; 2 mg/kg qd for 2 days | 1 2 3 4 5 6 |
| Fu, 2017²⁷        | IV AZI 10 mg/kg, qd × 5 days; discontinued for 3 days; then continued for 3 days, total for 3 consecutive courses. | IV MP 2 mg/kg, qd × 3 days; taper (3–5 days) to 0.6 mg/kg/day, total consecutive courses within 1 mo. | 1 2 4 |
| Zheng, 2017³⁸     | IV AZI 10 mg/kg, qd × 5 days; then oral for 3 days, discontinued for 4 days; total for 3 consecutive courses. | IV MP 2 mg/kg, qd × 3–5 days | 1 2 3 4 |
| Zhou et al, 2018³⁹ | IV AZI 10 mg/kg, qd × 3 days; discontinued for 4 days; total for 2 consecutive courses. | IV MP 1 mg/kg bid until normothermia, then oral prednisone 1 mg/kg/day until symptoms disappear. | 1 2 3 4 5 6 |
| Wu et al, 2018³⁰  | IV AZI 10 mg/kg, qd × 3 days; discontinued for 4 days; total for 4 consecutive courses. | IV MP 2 mg/kg, qd × 4 days; taper to 1 mg/kg/day until symptoms disappear. | 1 2 3 4 6 |
| Lan et al, 2019³¹ | IV AZI 10 mg/kg, qd × 3 days. | IV MP 2 mg/kg, qd × 3 days | 2 |
| Zheng and Sun, 2018³² | IV AZI 10 mg/kg, qd × 5 days; discontinued for 4 days; then oral for 3 days | IV MP 1 mg/kg bid; taper (3–5 days) to 0.5–1 mg/kg/day, until temperature back to normal for 48 h. | 1 2 4 5 6 |
| Li, 2018³³        | IV AZI 10 mg/kg, qd × 5 days; discontinued for 4 days; total for 3 to 4 consecutive courses. | Oral MP Tablets 2 mg/kg, qd × 5 days, taper to 1 mg/kg, qd × 2 days | 1 6 |
| An, 2017³⁴        | IV AZI 10 mg/kg, qd × 3–5 days; discontinued for 4 days; then oral for 3 days, discontinued for 4 days; total for 3 consecutive courses. | IV DEX 0.3–0.5 mg/kg, bid × 4–5 days; oral prednisone 1–1.5 mg/kg/day (divided in 3 daily doses), taper (3–4 days) to drug discontinuance. | 1 2 6 |
| Lin and Li, 2017³⁵ | Unknown | IV DEX 0.2–0.3 mg/kg, qd × 5 days | 1 2 4 |
| Zhang and Zia, 2014³⁶ | Unknown | IV DEX 0.2–0.3 mg/kg, qd × 5 days | 1 2 4 |
| Luo et al, 2014³⁷  | IV AZI 10 mg/kg, qd × 5 days. | Oral MP tablets 1 mg/kg, bid × 5 days | 3 4 6 |

AZI = azithromycin, bid = twice/day, DEX = dexamethasone, GC = glucocorticoid, IV = intravenous, MP = methylprednisolone, qd = once/day. 1. overall response rate; 2. clinical symptoms (time of fever relieving; time of disappearing of cough, and moist rales); 3. image changes; 4. changes in inflammatory markers; 5. inpatient time; 6. adverse reaction.
not reporting the rale vanishing time\textsuperscript{[13,16]}\textsuperscript{[13–16,18]}. Subgroup analysis showed that meta-analysis results of random effect model in terms of antipyretic time showed that AZI combined with GC group (493 cases) was higher than the control group (493 cases) (MD = 2.60; 95% CI = 3.11, 2.10; \( P < .0001 \)). In terms of the rale vanishing time, meta-analysis results of the random-effect model showed that the AZI combined with GC group (433 cases) was better than the control group (433 cases) (MD = –3.24; 95% CI = –4.24, –2.60; \( P < .0001 \)). Meta-analysis results of random-effect model showed that AZI combined with GC group was superior to the control group in the aspect of cough recovery time (MD = –3.42; 95% CI = –4.05, –2.79; \( P < .0001 \)) (Fig. 3).

**Figure 1.** Flowchart depicting the identification and selection of relevant studies.

**Table 3**

| First author, year | Random method | Allocation concealment | Blinding method | Data integrity | Selective reporting | Other bias |
|--------------------|----------------|------------------------|-----------------|-----------------|---------------------|------------|
| Tang et al, 2017\textsuperscript{[8]} | Random number table | Unclear | Investigator and subject | Unclear | Integrity | None | Unclear |
| Fu, 2017\textsuperscript{[9]} | Random number table | Unclear | Outcome evaluator | Unclear | Integrity | None | Unclear |
| Zheng, 2017\textsuperscript{[10]} | Unclear | Unclear | Data integrity | None | Integrity | None | Unclear |
| Zhou et al, 2018\textsuperscript{[11]} | Random number table | Unclear | None | Unclear | None | Unclear |
| Wu et al, 2018\textsuperscript{[12]} | Random number table | Unclear | None | Unclear | None | Unclear |
| Lan et al, 2015\textsuperscript{[13]} | Simple randomization | Unclear | None | Unclear | None | Unclear |
| Zheng and Sun, 2018\textsuperscript{[14]} | Random number table | Unclear | None | Unclear | None | Unclear |
| Li, 2018\textsuperscript{[15]} | Random number table | Unclear | None | Unclear | None | Unclear |
| An, 2017\textsuperscript{[16]} | Unclear | Unclear | None | Unclear | None | Unclear |
| Lin and Li, 2015\textsuperscript{[17]} | Random number table | Unclear | None | Unclear | None | Unclear |
| Zhang and Zia, 2014\textsuperscript{[18], [19]} | Random number table | Unclear | None | Unclear | None | Unclear |
| Luo et al, 2014\textsuperscript{[19]} | Unclear | Unclear | None | Unclear | None | Unclear |
Figure 2. Meta-analysis of the effect of AZI + GC on total effective rate. AZI = azithromycin, GC = glucocorticoid.

Figure 3. Meta-analysis of the effect of AZI + GC on remission time of clinical symptom. AZI = azithromycin, GC = glucocorticoid.
3.5. Effect of AZI + GC on hospital stay

A total of 5 RCTs reported hospital stay with analysis showing that there were 302 cases in the AZI combined with GC group and 302 cases in the control group.\cite{11,12,14,17,18} And meta-analysis results of random effect model showed that AZI combined with GC group was better than control group ($MD = -4.63; 95\% CI -6.15, -3.17; P < .0001$) (Fig. 4).

3.6. Effect of AZI + GC on image changes

A total of 2 RCTs reported imaging changes.\cite{10,19} The analysis showed that there were 49 cases in the AZI combined with GC group and 48 cases in the control group in terms of inflammatory exudation absorption rate. And Meta-analysis results of random effect model showed that AZI combined with GC group was better than control group (OR = 5.38; 95\% CI 1.09, 26.51; $P = .04$) (Fig. 5).

3.7. Effect of AZI + GC on changes of inflammatory markers

A total of 7 RCTs reported changes in inflammatory index CRP.\cite{8,9,11,12,14,17,18} and the analysis showed 399 cases in the AZI combined with GC group and 399 cases in the control group. And meta-analysis results of random effect model showed that AZI combined with GC group was superior to the control group ($MD = -7.17; 95\% CI -12.06, -2.28; P = .004$). A total of 4 RCTs reported the changes of CD4/CD8 with 249 cases in the AZI combined with GC group and 249 cases in the control group.\cite{11,14,17,18} And meta-analysis results of the random-effect model showed that the AZI combined with GC group was superior to the control group ($MD = 0.22; 95\% CI 0.12, 0.32; P < .0001$) (Fig. 6).

3.8. Effect of AZI + GC on adverse reactions

A total of 7 RCTs reported adverse reactions with 371 cases of adverse reaction rates in the AZI combined with GC group and 371 cases in the control group.\cite{8,10,11,12,14,15,16} And meta-analysis results of the random-effect model showed that there was no difference in adverse reactions between the AZI combined with GC group and the control group (RR = 1.15; 95\% CI 0.73, 1.81; $P = .56$) (Fig. 7).

4. Discussion

Mycoplasma is the main pathogen of pneumonia. The cure rate of this disease has been improved obviously with the application of macrolide antibiotics. GC has been widely used in the treatment of adult refractory Mycoplasma pneumoniae. But for the treatment of pediatric refractory Mycoplasma pneumoniae, the application of GC still lacks evidence-based medical evidence. In this study, a meta-analysis of 12 randomized controlled clinical trials showed that GC combined with AZI could effectively improve the cure rate of RMPP in children. Therefore, subgroup analysis suggested that combined medication could significantly shorten the duration of fever, improve cough symptoms, promote the absorption of pulmonary inflammation, shorten hospital stay, reduce the level of inflammatory factors, and regulate the immune system of the body in children, so as to achieve the purpose of enhancing the curative effect. The main mechanism may be due to the strong anti-inflammatory effect of GCs, and the relatively high concentration of GCs in lung tissues, and that the short-term application was not significantly correlated with water and sodium retention. This study also showed that the combined medication had clear efficacy and no obvious adverse reactions compared with the simple application of macrolide antibiotics.
In this study, there were 10 RCTs studied the effective rate for statistical analysis. The results of fixed-effect model meta-analysis showed no significant heterogeneity. Meta-analysis results showed that the total effective rate of AZI combined with GC group was higher than that of control group. However, compared with AZI therapy alone, the results of analysis on the effect of combination medication on clinical symptom relief showed that there was significant heterogeneity in the meta-analysis on antipyretic time, resorption of pulmonary rales, cough relief time. After the sensitivity analysis was used to remove the relevant studies one by one, there was no significant change in heterogeneity, suggesting that the results of system evaluation were relatively stable. After the meta-analysis using the random-effect model, it showed that the combination medication was significantly better than the control group. Similarly, the meta-analysis also showed significant statistical heterogeneity in the imaging effects, inflammatory factors and hospital stay for children treated with combination medication, but no significant change in heterogeneity was observed after sensitivity analysis. After the meta-analysis using the random effect model, it showed that combination medication had significant advantages over the control group. However, the analysis results of adverse reactions showed that in the 7 included RCT studies with adverse reactions recorded, the meta-analysis results showed no significant heterogeneity, and there was no significant statistical difference between the combination medication and the single medication, suggesting that the combination medication did not increase the adverse reactions in children and was relatively safe. Studies on GC therapy for RMPP have also demonstrated its effectiveness. According to Lee et al., when treating severe MPP in children, children who received 1 mg/kg/day of oral prednisone and gradually reduced the dose within a week benefited a lot. The research results of Tamura et al. showed that intravenous drip of 30 mg/kg/day methylprednisolone for three consecutive days could effectively treat refractory mycoplasma pneumoniae. These results are consistent with the
conclusions of this study. Therefore, AZI combined with GCs can effectively treat RMPP, which is worthy of clinical promotion and application.

The limitations of this study are: the overall qualities of the included research literatures were relatively low, for example, the unclear random method and a large risk of bias, which could make the conclusions less credible; the sample sizes of relevant studies were small, and there was no high-quality multicenter research, resulting in low statistical efficiency; different studies had different treatment regimens, such as the dose, course of treatment and reduction methods of therapeutic drugs, leading to clinical heterogeneity. This requires that we should try our best to conduct multicenter randomized controlled studies in the follow-up studies, so as to improve the quality of the studies and provide standardized treatment strategies for the clinical practice.

5. Conclusion

Based on our current evidence, the addition of GCs to conventional AZI therapy can effectively improve the clinical efficacy with relatively good safety. But GCs should be used for a short time because of the side effect of inhibiting the growth and development of children. In addition, GCs should be avoided in children with severe active peptic ulcer, fungal infection and hematological diseases. Finally, more high-quality studies are needed to confirm the conclusions of this study due to the limitations of the quality and quantity of the included literatures.

Author contributions

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