Original Article

The efficacy and safety of azithromycin in chronic respiratory diseases related cough

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Background: Azithromycin is potential for preventing exacerbations in chronic respiratory diseases. However, rare attention was paid to the cough symptom of such airway diseases by azithromycin intervention. We summarized the efficacy and safety of azithromycin in chronic respiratory diseases related cough.

Methods: We searched 4 electronic databases (PubMed, EMBASE, Cochrane, and Web of Science) to identify randomized controlled trials (RCTs) comparing the change of Leicester Cough Questionnaire (LCQ) score, cough visual analogue scale (VAS) and side effects of azithromycin in patients of chronic respiratory diseases with cough.

Results: We identified 5 RCTs (n=879 patients) in pooled analyses. Compared to placebo, azithromycin intervention had no effect in reducing cough [mean difference (MD) 0.73; 95% CI: −0.78 to 2.24; P=0.34] with significant heterogeneity (P=0.03, I^2=71%). However, heterogeneity is caused by one study. After removal of this study, azithromycin administration had shown clinically important improvement in LCQ score (MD 1.30; 95% CI: 1.15–1.46; P<0.00001; I^2=0%). In addition, no significant difference was detected in adverse events and azithromycin administration probably had less central nervous system side effects for chronic respiratory diseases with cough.

Conclusions: The addition of oral azithromycin may result in significant benefit for chronic respiratory diseases related cough. Azithromycin was safe for those patients with cough.

Keywords: Azithromycin; cough, efficacy; adverse events; systematic review

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Introduction

Cough is one of the most common respiratory symptom, which affects 8–10% of the adult population, leading to seek medical care in western countries as well as in China (1-3). Chronic respiratory diseases causing cough include asthma, eosinophilic bronchitis, postnasal drip syndrome or rhinosinusitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, etc. (1,4,5). The management of these patients should be aimed at pathogeny cure. Several treatments for chronic respiratory diseases with cough have been identified over the past decades, including inhaled corticosteroids (ICS), neuromodulatory therapies, non-pharmacologic therapies and other therapies (6-8).

Generally, ICS, β2 adrenergic receptor agonist and muscarinic receptor antagonist have been proposed to be the basic treatments for chronic respiratory diseases, including asthma and COPD (9,10). After inhalers, advanced therapies are also available, including phosphodiesterase inhibitors, leukotriene receptor antagonist, N-acetylcysteine, even immunotherapy (monoclonal antibodies) (9,10). However, their treatment response often limited in case of refractory cough (8,11,12). Therefore, better approaches to chronic respiratory diseases with cough are needed.

Besides antibacterial effects, azithromycin, as a kind of macrolide antibiotics, has been reported to have anti-inflammatory and immunomodulatory effects in chronic airway inflammatory diseases, including bronchiectasis, COPD, asthma (13-16). A recently meta-analysis assessed the efficacy and safety of long-term add-on treatment of azithromycin in asthma (17). They mainly focused on the therapeutic effect of azithromycin in lung function [forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF)], symptom control, quality of life [Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ)] and airway inflammation (16,17). However, rare attention was paid to the cough symptom of such airway diseases, which had greater impact on quality of life for some patients than other symptoms (18,19). Therefore, we did a systematic review aiming to provide a summary of the efficacy and safety of azithromycin in patients of chronic respiratory diseases with cough. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-119).

Methods

Inclusion and exclusion criteria

We included prospective randomized controlled trials (RCTs) involving patients of chronic respiratory diseases with cough. Azithromycin should be administrated as compared with placebo or in combination with other treatments as compared with other treatments alone. We limited publications to the English language. We excluded crossover trials, abstract publications, before-after studies, conference presentations, editorials and case reports. No statement on medical ethics is required for the systematic review and meta-analysis.

Search strategy

To increase the sensitivity of the search strategy, we combined the terms "azithromycin" with "cough" as key words or Medical Subject Headings (MeSH) terms. Four databases, including PubMed, EMBASE, Cochrane, and Web of Science, were searched from electronic databases inception to October, 1st, 2019. We systematically screened abstracts and full text articles for studies that met our eligibility criteria. The process was performed by two researchers (J Zhou and F Yi) independently.

Outcome assessment

The primary outcome of this review was the improvement of cough, assessed by Leicester Cough Questionnaire (LCQ), the Cough Quality-of-Life Questionnaire (CQLQ) and the cough visual analogue scale (VAS). The secondary outcome was the incidence of adverse effects by azithromycin for the treatment of cough.

Data abstraction

Two investigators (J Zhou and F Yi) reviewed and abstracted data from each retrieved article and supplement independently. Discrepancies were resolved by discussion and consensus.

Quality assessment

The quality of all included trials was reviewing by the details in their method sections and their supplemental materials. The trial quality was appraised by using the Cochrane collaboration tool for assessing risk of bias (RoB) (20), including assessment of random sequence generation, allocation concealment, blinding (of interventions, outcome measurement or assessment), selective reporting bias and incomplete outcome data. For each criterion, we appraised the RoB to be either of low, high, or unclear risk. Two researchers (J Zhou and F Yi) assessed the trial quality independently and disagreements were resolved by discussion.

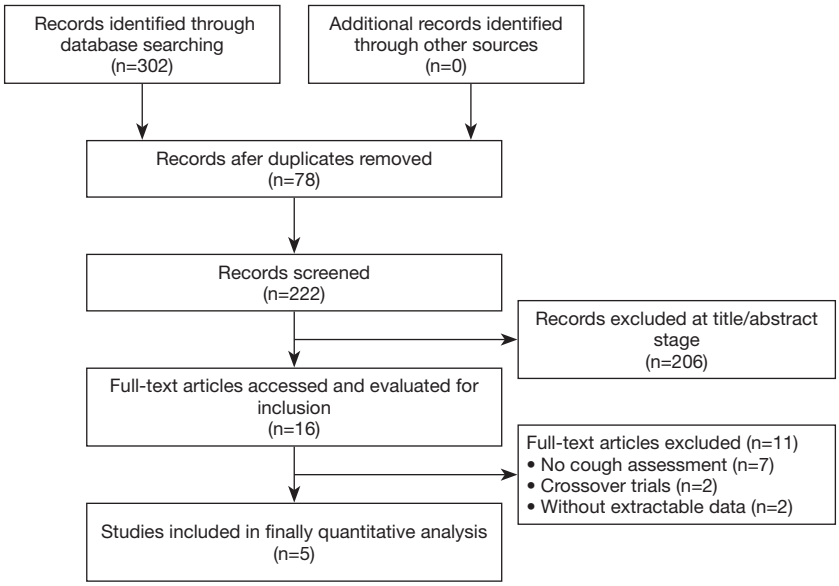

Figure 1 Search strategy of meta-analysis on selecting patients for inclusion.

Assessment of heterogeneity

We used the I^2 statistic to evaluate the heterogeneity on pooled data. If an I^2 value was greater than 50%, then a substantial heterogeneity was indicated (20). Fixed-effects model was used to pool data when heterogeneity was insignificant. When significant heterogeneity was found, then the random effects models would be used to pool data.

Statistical analysis

The changes in LCQ score and adverse events rates were analysed in this meta-analysis. Continuous data and categorical data were pooled by using the mean difference (MD) and risk ratio (RR), with the 95% confidence intervals (CIs). The comparison of the outcome between the azithromycin and placebo was conducted with Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and two-sided P values less than 0.05 were considered to be statistically significant.

Results

Characteristics of included trials

We identified 302 potentially eligible studies. After exclusion of duplicate and irrelevant articles, 16 studies were retrieved to be reviewed in greater detail. Of these, we excluded 11 studies that did not meet our eligibility criteria and thus included 5 trials in our review (*Figure 1*). All of the included studies were designed as randomised, double-blind, placebo-controlled clinical trials. Of the 5 RCTs, two studies were conducted in patients with asthma (15,21), one study was conducted in patients with COPD (22). Hodgson *et al.* conducted a study in patients with bronchial hyperresponsiveness (23). Saiman *et al.* conducted a study in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa (24). The characteristics of the studies are shown in *Table 1*.

RoB of included studies

All included trials were reported to be low risk of performance bias and four studies were assessed to be at low RoB with respect to selection bias except for one study for which selection bias was deemed unclear (21). Two trials assessed to be at low RoB with regard to completeness of outcomes data, selective outcomes reporting, and other potential sources of bias (15,24). But the other three trials were considered to be at unclear risk with respect to the above bias (21-23) (*Figure 2*).

Azithromycin in cough

Cough can be assessed by many ways and the LCQ has been well validated with internal consistency, repeatability and

Table 1 Characteristics and designs of the included studies

NO.	Author	Journal, years	Study design	Population	Therapy	Study size	Follow-up (weeks)	Outcomes
1	Berkhof, *et al.*	Respiratory Research, 2013	Single-centre randomised double-blind placebo-controlled trial	Patients diagnosed of COPD GOLD stage ≥2 suffering from chronic productive cough ≥12 weeks	Azithromycin 250 mg three times a week for 12 weeks *vs.* placebo	84	12–18	Primary endpoints: LCQ total and domain scores at 12 weeks Secondary endpoints: SGRQ total score, SF-36 score, spirometry
2	Hodgson, *et al.*	Chest, 2016	Randomized, double-blind, placebo-controlled parallel group trial	Patients with treatment-resistant cough	Azithromycin 500 mg daily for 3 days followed by 250 mg 3 times a week for 8 weeks *vs.* placebo	44	4, 8, 12	Primary outcome: change from baseline of LCQ score at week 8 Secondary outcome: cough severity score and FeNO
3	Cameron, *et al.*	eur respir j. 2013	Randomised double-blind parallel-group trial	Current smokers with chronic asthma	Azithromycin 250 mg per day for 12 weeks *vs.* placebo	71	4, 8, 12	Primary outcome: PC20, FeNO, induced sputum, ACQ, LCQ, AQLQ
4	Saiman, *et al.*	JAMA, 2010	Multicenter, randomized, double-blind placebo-controlled trial	Patients with cystic fibrosis uninfected with Pseudomonas aeruginosa	250 or 500 mg of azithromycin 3 days per week for 168 days	260	24	Primary outcome: change in FEV1. Secondary outcomes: spirometry, exacerbations, changes in microbiology and adverse events
5	Gibson, *et al.*	Lancet, 2017	Multicentre randomised, double-blind, placebo-controlled trial	Patients with persistent uncontrolled asthma	Azithromycin 500 mg or placebo 3 times per week for 48 weeks	420	48	Primary outcome: the rate of asthma exacerbations and asthma quality of life

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease; LCQ, Leicester Cough Questionnaire; SGRQ, St. George's Respiratory Questionnaire; FeNO, fractional exhaled nitric oxide; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in one second.

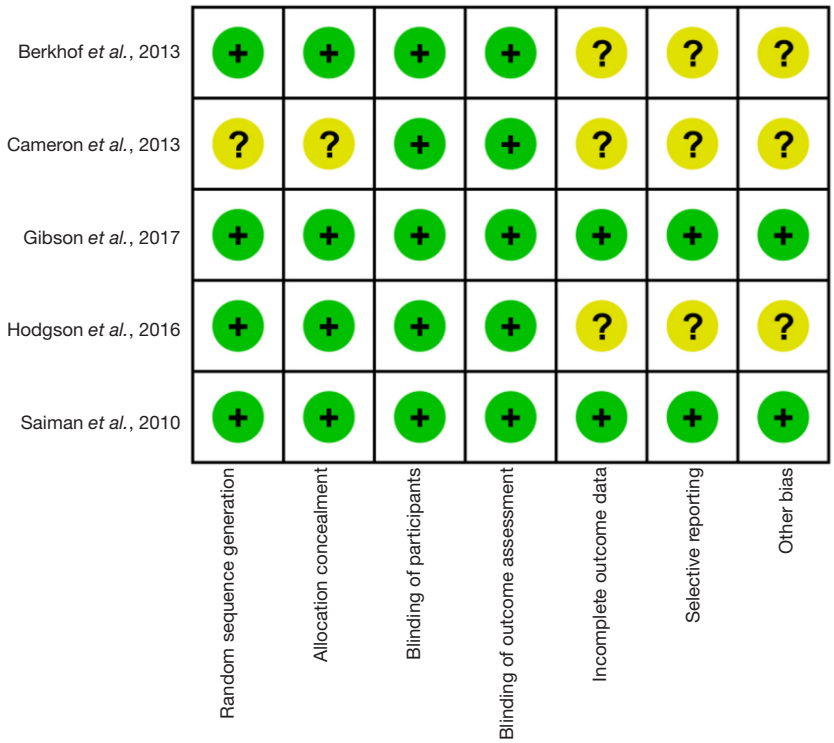

Figure 2 Risk of bias for each study. Green represents low risk of bias, yellow represents unclear risk of bias.

responsiveness (25,26). However, only three of the included trials have reported the change of LCQ (21-23). Compared to placebo, azithromycin intervention had no effect in reducing cough (n=198, MD 0.73; 95% CI: −0.78 to 2.24; P=0.34; I^2=71%). Further analysis showed that the trial from Cameron *et al.* (21) was main source of heterogeneity. When excluding the above trial, the left two trials (22,23) had shown clinically important improvement in LCQ score by azithromycin administration (n=121, MD 1.30; 95% CI: 1.15–1.46; P<0.00001; I^2=0%) (*Figure 3*).

There other two studies did not assessed cough by LCQ. The study from Saiman *et al.* showed that azithromycin intervention significantly reduced the frequency of cough (−23% treatment difference; 95% CI: −33 to −11; P<0.001) and productive cough (−11% treatment difference; 95% CI: −19 to −3; P=0.01) than those in placebo group (24). Another study from Gibson *et al.* measured cough by using cough VAS. They found that there was a significant reduction in cough and sputum production VAS in patients using azithromycin (15). No included study measured cough by using CQLQ.

Adverse events

There were four trials report the adverse events during azithromycin intervention (15,22-24). A pooled analysis applied in a random effect model revealed that there was no significant difference in upper respiratory (n=808, RR 1.11; 95% CI: 0.68–1.79; P=0.68), gastrointestinal (n=808, RR 0.95; 95% CI: 0.26–3.50; P=0.94) and other adverse events (n=808, RR 0.91; 95% CI: 0.49–1.70; P=0.77) between the two groups. However, pooled data showed that azithromycin intervention had less central nervous system than the placebo in a fixed effect model (heterogeneity I^2=7%, P=0.03) (*Figure 4*).

Discussion

Our systematic review pooled the data of 879 patients of chronic respiratory diseases with cough from five randomised, placebo controlled clinical trials to evaluate the efficacy of azithromycin on cough. It showed that the addition of oral azithromycin to standard care for the

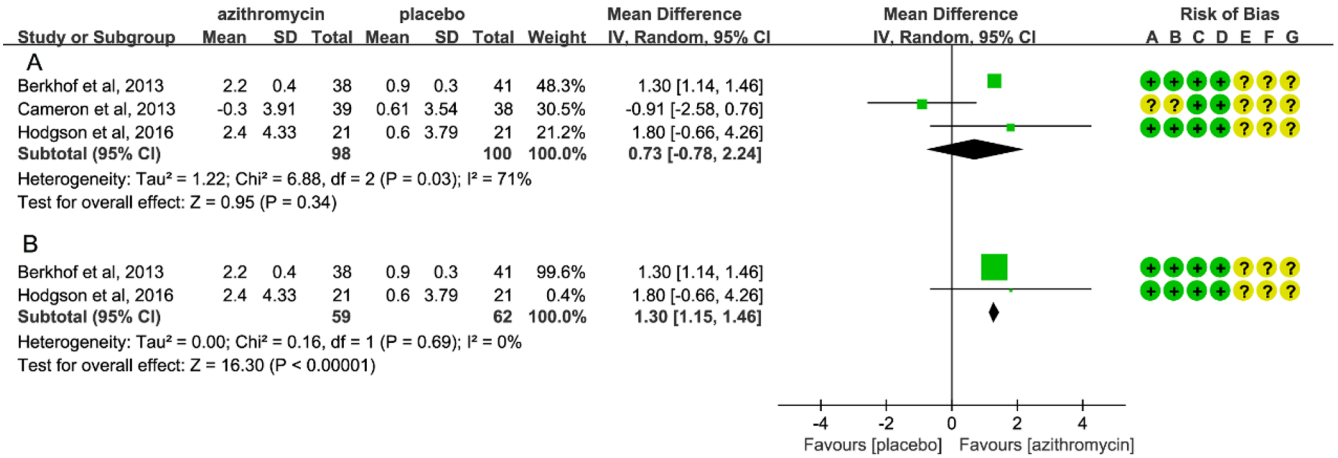

Figure 3 Azithromycin in chronic respiratory diseases with cough. Green represents low risk of bias, yellow represents unclear risk of bias. A: Random sequence generation; B: allocation concealment; C: blinding of participants and personnel; D: blinding of outcome assessment; E: incomplete outcome data; F: selective reporting; G: other bias.

associated respiratory diseases resulted in no statistically significant benefit for reducing cough in three eligible trials but with significant heterogeneity. After excluding the substantial heterogeneity trial, we found that addition of oral azithromycin could improve LCQ score and cough VAS score, reduce the incidence of cough. In addition, the treatment was well-tolerated. No significant side effect of azithromycin treatment was found. And pooled data showed that azithromycin intervention had less central nervous system than the placebo.

Azithromycin, a macrolide antibiotic with a broader microbial spectrum and fewer side effects was recommended in many indications. However, azithromycin was reported to play an important role in anti-inflammatory and immunomodulatory activities independent of their antimicrobial activity in chronic respiratory diseases, including bronchiectasis, COPD, asthma etc. (13-15). More importantly, azithromycin was demonstrated to prevent exacerbations in chronic respiratory diseases (27). A significant decrease in the exacerbation rate of cystic fibrosis patients with chronic Pseudomonas infection was reported after using azithromycin (28,29). Maintenance treatment with azithromycin significantly decreased the frequency of exacerbations and improved quality of life of COPD patients (14,30). Azithromycin also succeeded in reducing the exacerbation rate of persistent uncontrolled asthma (15). Azithromycin was considered to be the holy grail to prevent exacerbations in chronic respiratory diseases (27).

Cough, as one of the most common symptoms in chronic respiratory diseases, was usual to be overlooked. Cough could be difficult to treat and contributed to poor quality of life, with a significant impact on physical, psychological, and social activities (19,23). Based on a clinical founding of a dramatic improvement in patients with chronic respiratory diseases treated with azithromycin, we mainly focused on the efficacy and safety of azithromycin in symptoms of cough. Therefore, we conducted a systematic review of the literatures and the pooled data had shown that azithromycin had no statistically significant benefit for reducing cough but with significant heterogeneity. The trial from Cameron *et al.* (21) might be the main source of heterogeneity. There were unclear risks of selection bias (including assessment of random sequence generation, allocation concealment), selective reporting bias and attrition bias due to lack of such information in the manuscript. However, the other two trials (22,23) had shown low risk of selection bias, performance bias and detection bias. And the pooled data of the two trials showed a clinically important improvement in LCQ score by azithromycin administration. Similarly, another two eligible trials with low risks of bias also showed that azithromycin intervention significant reduced both the incidence of cough (24) and the cough VAS score (15). Therefore, additional azithromycin administration maybe benefits for patients of chronic respiratory diseases with cough in a well-designed and high-quality trial.

Eosinophilic inflammation is an important cause of cough symptom (31,32). The possible mechanism of azithromycin in relieving cough may be an anti-inflammatory effect both

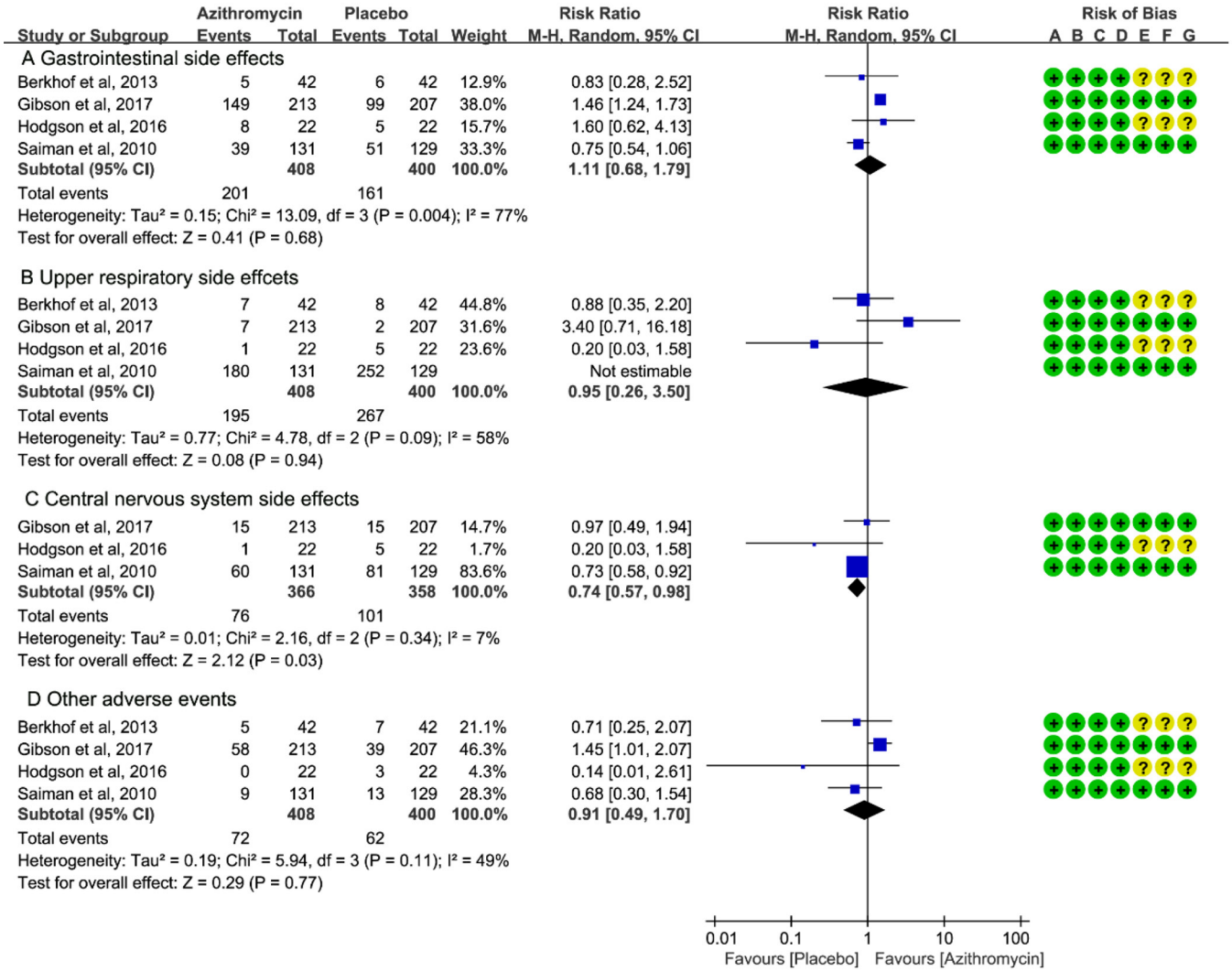

Figure 4 Side effects of azithromycin. Green represents low risk of bias, yellow represents unclear risk of bias. A: Random sequence generation; B: allocation concealment; C: blinding of participants and personnel; D: blinding of outcome assessment; E: incomplete outcome data; F: selective reporting; G: other bias.

systemically and locally within the airway. Azithromycin has complex immunomodulatory effects on eosinophilic airway inflammation and inhibition of cytokine production (33,34). Moreover, azithromycin could suppress $CD4^+$ T-cell activation by direct modulation of mTOR activity, which inhibited eosinophil differentiation and allergic inflammation (35,36). Therefore, additional azithromycin administration maybe benefits for patients of chronic respiratory diseases with cough.

For the safety analysis, we classified nasal congestion, pharyngolaryngeal pain, rhinorrhea, common cold, cough into upper respiratory side effects. Vomiting, upper abdominal pain, nausea, diarrhea, ulcus ventriculi, abnormal liver function tests were classified into gastrointestinal side effects. Pyrexia, fatigue, vertigo, tinnitus, hearing loss headache were classified into central nervous system side effects. Other adverse events included rash, allergy, oral thrush, QTc prolongation, back pain, rib pain, myocardial infarction, supraventricular tachycardia, heart failure, hyperhidrosis, malaise etc. We found that there was no significant difference in upper respiratory, gastrointestinal and other adverse events of azithromycin treatment in patients of chronic respiratory diseases with cough. Moreover, azithromycin intervention had less central

nervous system than the placebo. Therefore, additional azithromycin administration may be safety for patients of chronic respiratory diseases with cough.

There were several limitations in this meta-analysis. Firstly, the eligible trial was limited and the sample size was relatively small, the conclusion of our analysis might be carefully made before transferring to a large cough population. Secondly, potential publication bias may not be ignored and we failed to identify potential unpublished negative studies that may alter the outcome. In addition, the heterogeneity derived from the design of an RCT, causes of cough, baseline treatment, the dosage and period of azithromycin treatment among studies, which might contribute to the inconsistency. Finally, for the safety analysis, side effects were classified into certain scale such as upper respiratory and gastrointestinal adverse events rather than one side effect by one comparison, which may cover certain significant side effects.

Conclusions

Our systematic review and meta-analysis found that the addition of oral azithromycin to standard care for the associated respiratory diseases resulted in statistically significant benefit for patients with cough. Azithromycin administration was safety and probably showed less central nervous system side effects for patients with cough. However, more RCTs with large sample size should be conducted to establish the precise role of azithromycin in the chronic respiratory diseases related cough treatment.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting Checklist. Available at http://dx.doi.org/10.21037/apm-20-119

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-119). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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