Long-Term Macrolide Treatment for Non-Cystic Fibrosis Bronchiectasis in Children: A Meta-Analysis

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Abstract

Recurrent bacterial infection causes frequent exacerbations of Bronchiectasis (BE). The effectiveness and safety of macrolide long-term administration in BE remains controversial, especially in children with little treatment to prevent exacerbation. We conducted this meta-analysis to determine the usefulness of long-term macrolide in pediatric BE. We searched PubMed, Cochrane Library databases, Embase, KoreaMed, Igaku Chuo Zasshi, and Chinese National Knowledge Infrastructure databases. We identified randomized controlled trials (RCTs) on long-term macrolide treatment (≥ 4 weeks) in non-cystic fibrosis BE in children aged < 18 years. The primary outcome was frequency of acute exacerbation; secondary outcomes were changes in pulmonary function, sputum scores, and adverse events including bacterial resistance. We included four RCTs. Long-term macrolide treatment showed a significant decrease in the frequency of exacerbation (odds ratio [OR], 0.30; 95% confidence interval [CI], 0.10 to 0.87), mean number of exacerbations per patient (mean difference, -1.40; 95% CI, -2.26 to -0.54) and sputum purulence score (mean difference, -0.78; 95% CI, -1.32 to -0.24). However, long-term macrolide treatment was accompanied by increased carriage of azithromycin-resistant bacteria (OR, 7.13). Long-term macrolide administration prevents exacerbation of BE in children, but risks increasing antibiotic resistance. Benefits and risks should be weighed and determined on a patient-by-patient basis.

Introduction

Bronchiectasis (BE) is a chronic lung disease characterized by irreversible dilatation and distortion of the small airways including cartilage with hyperconcentrated airway mucus.[1,2] Diverse diseases associated with respiratory infections, can cause non-cystic fibrosis BE in children.[3] With the increasing awareness of disease and accessibility of medical resources, BE is no longer considered an orphan disease as the prevalence of BE is increasing.[4] BE is a troublesome condition because it is accompanied by frequent exacerbation.[3] The quality of life for patients is significantly reduced because hospitalization is repeated due to frequent deterioration, especially in children, the quality of life for the whole family is also reduced. Families with BE pediatric patients may experience school/work losses and are therefore a significant disease in terms of the burden of disease.[5]

Perturbation and alteration of bacteria in the airway of patients with BE is associated with persistent airway inflammation, chronic production of purulent sputum, and recurrent lower respiratory infection.[6] The frequent exacerbations of BE, which is closely linked with deterioration of pulmonary function, poor quality of life, and reduced lifespan, play a critical role in the progression of BE with chronic persistent airway inflammation. Therefore, the prevention of exacerbation in patients with BE is necessary to stabilize the airway inflammation, especially in children, when considering its influence over a lifetime.

Besides the antibiotic effects, macrolides have immunomodulatory effects through the regulation of pro-inflammatory and anti-inflammatory immune responses.[7] Based on this evidence,[7] long-term macrolide treatment has been applied to control the exacerbation of BE. Although several meta-analyses on the effects of long-term macrolide treatment for prevention of exacerbation, improvement of lung function and quality of life have been performed in cystic fibrosis and non-cystic fibrosis BE in adult patients,[8] data on pediatric non-cystic fibrosis BE are lacking. The present meta-analysis was performed to determine the efficacy and safety of long-term macrolide treatment for non-cystic fibrosis BE in children.

Materials And Methods

Literature search

The following databases were searched: PubMed, Cochrane Library databases, Embase, KoreaMed, Igaku Chuo Zasshi (ICHUSHI), Chinese National Knowledge Infrastructure (CNKI) on July 2nd, 2020. There were no language restrictions. Search terms included “Macrolides”, “Azithromycin”, “Clarithromycin”, “Roxithromycin”, “Erythromycin”, “Bronchiectasis”, “Kartagenar syndrome”, and “Ciliary motility disorders”.

Inclusion criteria

Randomized controlled trials (RCTs) of more than 4 weeks of macrolide treatment that compared with placebo or no intervention for long-term management of stable BE in infants, children, and adolescents under the age of 18 years were included in the present meta-analysis. The ciliary motility disorders, including Kartagenar syndrome, were included.

Exclusion criteria

We excluded RCTs that were performed in BE with cystic fibrosis in children and BE in adult patients. Studies performed for insufficient periods were excluded.

Primary and secondary outcomes

The primary outcomes were exacerbations of BE. The exacerbations of BE were assessed as frequency of exacerbations and hospitalization due to exacerbations. The secondary outcomes were changes in pulmonary function, including forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), sputum scores, cytokines in sputum/bronchoalveolar lavage (BAL) and adverse events including bacterial resistance.

Data extraction and analysis

All references were independently extracted by two reviewers. De-duplicated studies were imported into Covidence online software (https://www.covidence.org). Two review authors reviewed the titles and abstracts of de-duplicated studies and chose the relevant studies. Any discrepancies were solved through discussion. Then two reviewers independently reviewed the full text of the selected article once again. We perform data extraction including participants’ data, inclusion/exclusion criteria, intervention details, and outcome measurements. Any differences on data extraction were solved by discussion and, if necessary, consultation to third reviewer.

Assessment of quality and the level of evidence

Quality was assessed by two reviewers independently using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[9] according to the 7 domains: random sequence generation; blinding of patients; allocation concealment; selective reporting; incomplete outcome data; and other biases. Each of these domains was rated as low, high, or unclear risk. The level of evidence was assessed with the GRADE approach (GRADE pro, Version 3.6 for Windows, Grade Working group).[10]

Statistical analysis

The final selected RCTs were combined using Review Manager 5.2.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.). The heterogeneity of RCTs was accessed using Cochrane Q statistic. After checking heterogeneity of RCTs with I^2 statistic, a random effects model was applied. Odds ratio (OR) for

dichotomous variables and mean differences for continuous variables with 95% confidence intervals (95% CI) were calculated. $P < 0.05$ was considered statistically significant.

Results

Literature review and selection

We searched 452 articles, of which 41 were excluded because of duplication. After screening of the titles and abstracts, 387 records were removed due to irrelevant publishing types or studies. Four of the 24 full-text articles were qualified for analysis. Figure 1 describes the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) of this meta-analysis.

Characteristics of the included RCTs

Four eligible RCTs were included in the present meta-analysis. The summarized characteristics of the included RCTs are shown in Table 1. There were a total of four studies administering roxithromycin,[11] erythromycin,[12] azithromycin,[13] and clarithromycin,[14] respectively. The macrolide formulations used in each study were differed in both their composition and dosage. In the roxithromycin study,[11] 13 children aged 10–18 (mean age, 13.3 years) were given 4 mg/kg, twice a day for 12 weeks.[11] In the erythromycin study, 17 children with an mean age of 9.1 took 125 mg (less than 15 kg) or 250 mg (more than 15 kg) once a day for a total of 52 weeks.[12] In the azithromycin study, 45 children aged 1 to 8 years (mean age, 4.0 years) were taken at 30 mg/kg, once a week, for 24 months.[13] The clarithromycin study applied 15 mg/kg of clarithromycin once a day for three months for 17 children, along with the use of mucolytics and chest physiotherapy for 17 children (mean age, 13.1 years).[14]

Table 1
Summary of the randomized control trials on long-term macrolide administration in children with non-cystic fibrosis bronchiectasis

Study	Characteristics				Intervention and study duration		Outcome
	Country	Year	Number of subjects; mean age of experiment group, y	Number of subjects; mean age of control group, y	Experimental group	Control group	
Koh, 1997	South Korea	1995–1996	13; 13.3 ± 2.5	12; 12.9 ± 2.6	Roxithromycin 4mg/kg twice a day for 12 weeks	Placebo for 12 weeks	FEV1, PD20, Exacerbation, Sputum purulence score, sputum leukocyte score
Masekela, 2013	South Africa	2009–2011	17; 8.4 ± 2.4	14; 9.1 ± 2.1	Erythromycin 125 mg (≤ 15kg), 250mg (> 15kg) once a day for 52 weeks	placebo group for 52 weeks	Number of exacerbations, PFT (FEV1, FVC), cytokines
Valery, 2013	Australia	2008–2010	45; 3.99 ± 2.14	44; 4.22 ± 2.3	azithromycin (30 mg/kg) once a week for up to 24 months	placebo once a week for up to 24 months	exacerbation rate (respiratory episodes treated with antibiotics)
Yalcin, 2006	Turkey	1999–2000	17; 13.1 ± 2.7	17; 11.9 ± 2.9	Clarithromycin 15mg/kg, once daily with supportive therapies (mucolytic & expectorant medications, postural drainage) for 3 months	Supportive therapies (mucolytic & expectorant medications, postural drainage) for 3 months	Sputum production, PFT (FEF25-75%), cytokines and culture using BAL fluids

BAL, bronchoalveolar lavage; FEF25-75%, forced expiratory flow at 25–75% of forced vital capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PD20, provocative dose of methacholine causing a 20% fall in FEV1; PFT, pulmonary function test

Outcomes

Primary outcomes: Exacerbations of bronchiectasis

Three trials investigated the effects of macrolide long-term treatment on the frequency of acute exacerbation of BE.[11–13] Although macrolide preparations were different, long-term use of macrolide significantly reduced the frequency of acute exacerbation of BE (OR, 0.30; 95% CI, 0.10 to 0.87) (Fig. 2A). With long-term macrolide treatment, the mean exacerbations of BE per patient was also significantly reduced (mean difference, -1.40; 95% CI, -2.26 to -0.54) (Fig. 2B).[12,13] One study was available to examine the effect of azithromycin long-term treatment on hospitalization due to exacerbation of BE. There was no significant difference in frequency of exacerbation related admission in the azithromycin group compared to the control group (OR, 0.28; 95% CI, 0.07 to 1.11) (Fig. 2C).[13]

Secondary outcome: pulmonary function

There were three studies on the effect of macrolide long-term treatment on FEV1 % predicted at endpoint in children with BE. [11–13] There was no significant difference between FEV1 after treatment of macrolide and control (mean difference, 2.28; 95% CI, -2.39 to 6.95) (Fig. 3A).

Two studies conducted on the effect of macrolide long-term treatment on changes in FEV1 % predicted in patients with BE.[11,12] There was no significant difference in changes of FEV1 % predicted before and after treatment in the macrolide group and controls (mean difference, 2.19; 95% CI, -2.81 to 7.19) (Fig. 3B).

One trial conducted on the effect of erythromycin long-term treatment on FVC at endpoint in children with BE.[8] Macrolide-treated group and the control group, FVC at endpoint had no significant difference (mean difference, 5.00; 95% CI, -5.61 to 15.61) (Fig. 3C). One study has been published on the effects of erythromycin long-term treatment on changes in FVC % predicted in patients with BE.[12] There was no significant difference in FVC changes after treatment of long-term macrolides and controls (mean difference, 1.00; 95% CI, -9.43 to 11.43) (Fig. 3D).

Secondary outcome: Sputum score

Data on the effect of roxithromycin long-term treatment on sputum production were available in one trial.[11] The difference between the macrolide-treated group and the comparator's sputum purulence score was − 0.78 (95% CI, -1.32 to -0.24), meaningfully decreasing in the macrolide-treated group (Fig. 4A). There was no significant decrease in sputum leukocyte score in the macrolide-treated group compared to the control group (Fig. 4B).[7]

Secondary outcome: Cytokines

One trial investigated the effect of long-term macrolide treatment on IL-8 levels in the sputum from the children with non-cystic fibrosis BE. The study showed that IL-8 (endpoint, log) levels in the erythromycin-treated group was − 0.48 (-2.84 to 1.88), no significant difference from the levels in the control group (Fig. 5A).[9] There was another study on the effect of macrolide long-term treatment on IL-8 levels, but the samples were BAL. The study showed that the level of log transformed IL-8 in the BAL after macrolide treatment was − 0.06 (-2.26 to 2.14), which was no significant difference from the control group (Fig. 5B).[10]

There was also one study investigated the effects of erythromycin on the TNF-α level in the sputum.[12] The study showed that the difference in the log-transformed TNF- α levels after macrolide treatment in the macrolide-treated group and the control group was − 0.02 (-0.95 to 0.91), which was not significant (Fig. 5C). There was another study on the effect of long-term macrolide treatment on the TNF-α level in BAL. The study showed no differences in

the log-transformed TNF-α levels in the BAL fluid at the end of the study between macrolide treatment group and control group. (mean difference, -0.01; 95% CI, -2.28 to 2.26) (Fig. 5D).[12]

Secondary outcome: antibiotic resistance

Date on emergence of resistance to antibiotics after long-term macrolide therapy was available in one study.[13] The long-term use of azithromycin significantly increased the incidence of azithromycin-resistant *S. pneumoniae* (OR, 13.20; 95% CI, 1.61 to 108.19) (Fig. 6A). The long-term use of azithromycin significantly increased the incidence of azithromycin-resistant *S. aureus* (OR, 4.16; 95% CI, 1.06 to 16.32) (Fig. 6B). The long-term use of azithromycin significantly increased the incidence of azithromycin-resistant bacteria (OR, 7.13; 95% CI, 2.13 to 23.79) (Fig. 6C).

Secondary outcome: other adverse events

The macrolide long-term treatment did not increase the incidence of serious adverse events (OR, 0.43; 95% CI, 0.17 to 1.05) (Fig. 7A).[11] The macrolide long-term treatment did not increase the incidence of other adverse events (OR, 0.78; 95% CI, 0.33 to 1.83) (Fig. 7B).[6]

Discussion

This meta-analysis shows that long-term macrolide treatment over 3–24 months in cases of pediatric non-cystic fibrosis BE reduces the frequency of exacerbation with a decrease in the mean number of exacerbations per patient during the macrolide treatment period. In addition, we found that long-term macrolide treatment improved the sputum purulence score; however, it did not affect the pulmonary function index and cytokine levels, including IL-8 and TNF-α, in the sputum and BAL. As an adverse effect of long-term macrolide treatment, the rate of azithromycin-resistant bacteria significantly increased (azithromycin-resistant *Streptococcus pneumoniae*, OR, 13.2; azithromycin-resistant *Staphylococcus aureus*, OR: 4.1; azithromycin-resistant any bacteria, OR: 7.13), although no other serious adverse reactions were identified. Our meta-analysis provides an assessment of the advantages and disadvantages of long-term macrolide treatment focused on pediatric non-cystic fibrosis BE.

We meta-analyzed the effects of macrolides for acute exacerbation in pediatric BE with three RCTs, that were performed with roxithromycin for 12 weeks,[11] erythromycin for 52 weeks,[12] and azithromycin for up to 24 months.[13] They showed consistent results on reduction of the number of exacerbation, although the RCTs were performed for different study durations in different study populations, including immunocompromised children due to HIV infection in one RCT.[12] One study on the effects of clarithromycin did not investigate the effect of long-term macrolide on the frequency of exacerbation of bronchiectasis in children but pulmonary functions and sputum cytokines.[14] One study showed a significant decrease in sputum purulence score in group with roxithromycin compared to control group.[11] Although there was heterogeneity in the protocols of the RCTs for macrolides, dosage of macrolides, study duration, age, and characteristics of the study population, we concluded that long-term macrolide treatment has beneficial effects on the reduction of exacerbation and sputum score in children with non-cystic fibrosis BE.

Despite the beneficial effects, it is important to consider the safety of long-term macrolide treatment in children. Among the four RCTs included in the meta-analysis, only one study investigated the adverse reactions.[13] The critical adverse reactions in the long-term macrolide treatment group significantly increased azithromycin–resistant bacteria, including *S. pneumonia* and *S. aureus*, when 30 mg/kg of azithromycin were administered once a week

for up to 24 months.[13] In the era of increasing macrolide resistance,[15,16] the increased risk of macrolide resistance in the long-term macrolide treatment in pediatric non-cystic fibrosis BE arouse attention to the widespread use of long-term macrolide treatment in children. The benefits of long-term macrolide treatment and the risks of bacterial resistance must be weighed.

Although a previous study reported that administering azithromycin for 5 days can increase the risk of cardiovascular diseases in adults[17] and long-term macrolide treatment in adults with non-cystic fibrosis BE showed gastrointestinal complications, including diarrhea, nausea, vomiting or abdominal discomfort,[18] no adverse events were reported in long-term macrolide treatment in cases of pediatric non-cystic fibrosis bronchiectasis compared to the control group.[13] In addition, there was no reported severe adverse events of long-term macrolide treatment in children with non-cystic fibrosis BE. To identify and prevent the adverse reactions of long-term macrolide treatment, regular monitoring on the possible complications, such as cardiovascular diseases, are warranted in future studies. Despite these adverse reactions, long-term macrolide treatment can be one of the options that can decrease the exacerbation of non-cystic fibrosis BE in children, if other treatment strategies are insufficient.

There are some limitations in the present study. The RCTs in the present meta-analysis are differ in terms of characteristics of the study population (age, sex, and severity of bronchiectasis, and immune-state), study duration, and the classes of macrolide. Despite protocols' heterogenicity, this meta-analysis is a study that analyzes limited results so far, and it is clear that long-term macrolide treatment helps prevent pediatric BE from deteriorating. The question is which one to choose between the benefits of preventing deterioration and the risk of increased antibiotic resistance. The findings of this meta-analysis can be one of the alternatives for the long-term management of pediatric non-cystic fibrosis BE in the absence of a definite treatment other than the administration of antibiotics in exacerbation.[1]

In conclusion, long term macrolide treatment prevents exacerbation of BE in children, but increases antibiotic resistance. Long-term macrolide treatment cannot be claimed uniformly in all pediatric BE patients because there are clear risks coexisting with benefits. However, long-term macrolide therapy would be one treatment option, given that there are no other special treatments for BE exacerbation prevention and the poor quality of life for pediatric patients. The decision shall be made in consideration of various factors, such as the condition of individual patients, duration of disease, quality of life, etc. Valuable studies on the treatment of the area of pediatric BE are needed in the future.

Declarations

Authors’ contributions

L.E and J.Y.H wrote this manuscript. L.E, S.I.S, K.J.D, Y.H.J, M.T.K, J.G.C, H.Y.H, C.H.J, S.D.I, K.K.H, K.H.S, K.Y.H, W.S.I, L.Y.J, J.S.S, and J.Y.H did the data collection. L.E, S.I.S, K.J.D, Y.H.J, M.T.K, J.G.C, H.Y.H, J.H.J, S.D.I, K.K.H, K.H.S, K.Y.H, W.S.I, L.Y.J, J.S.S, and J.Y.H searched literatures and did the data interpretation. All authors reviewed and approved the final version of the manuscript.

Conflict of interest: There is no conflict of interest to declare.

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Figures

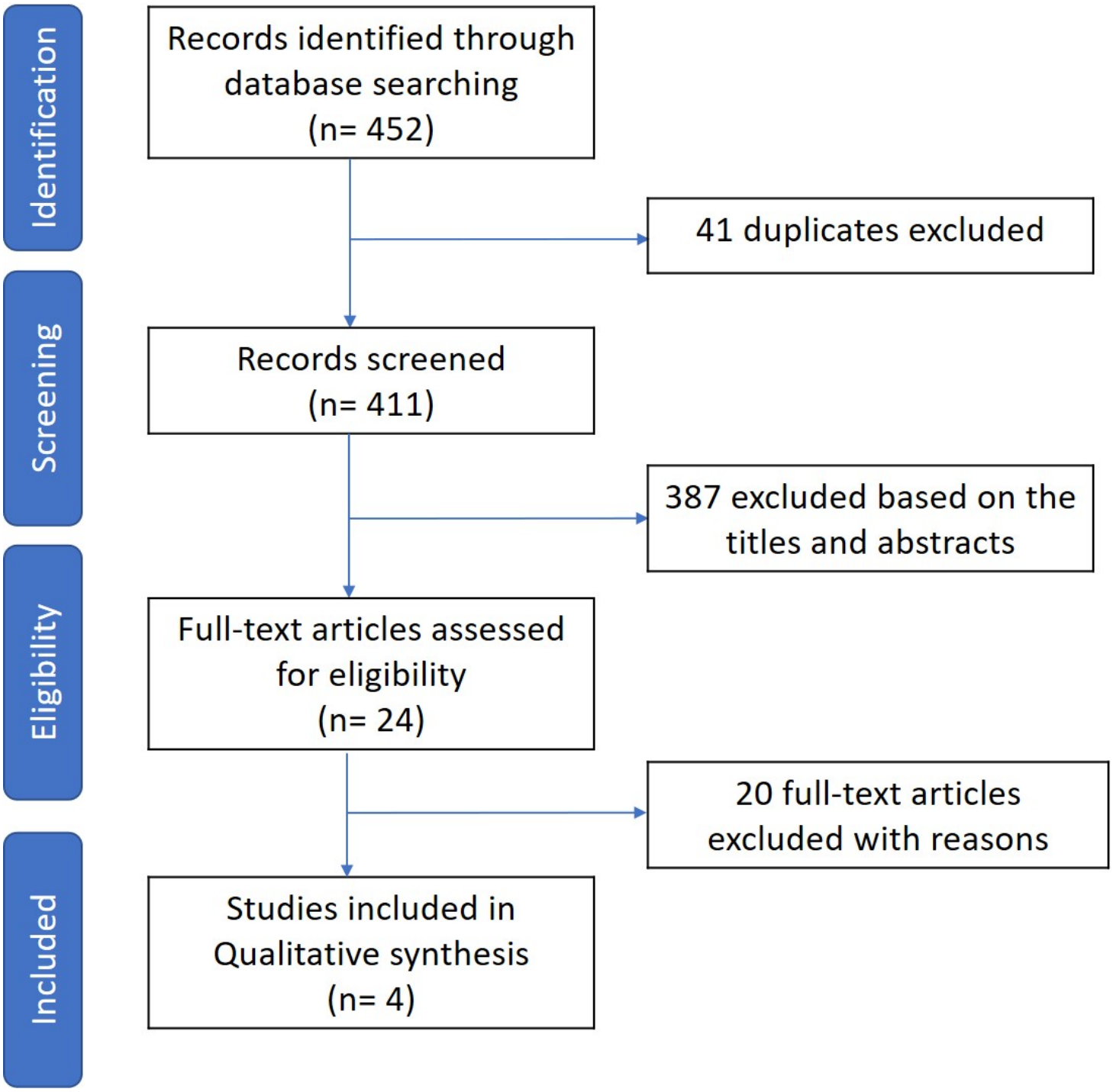

Figure 1

PRISMA flow diagram.

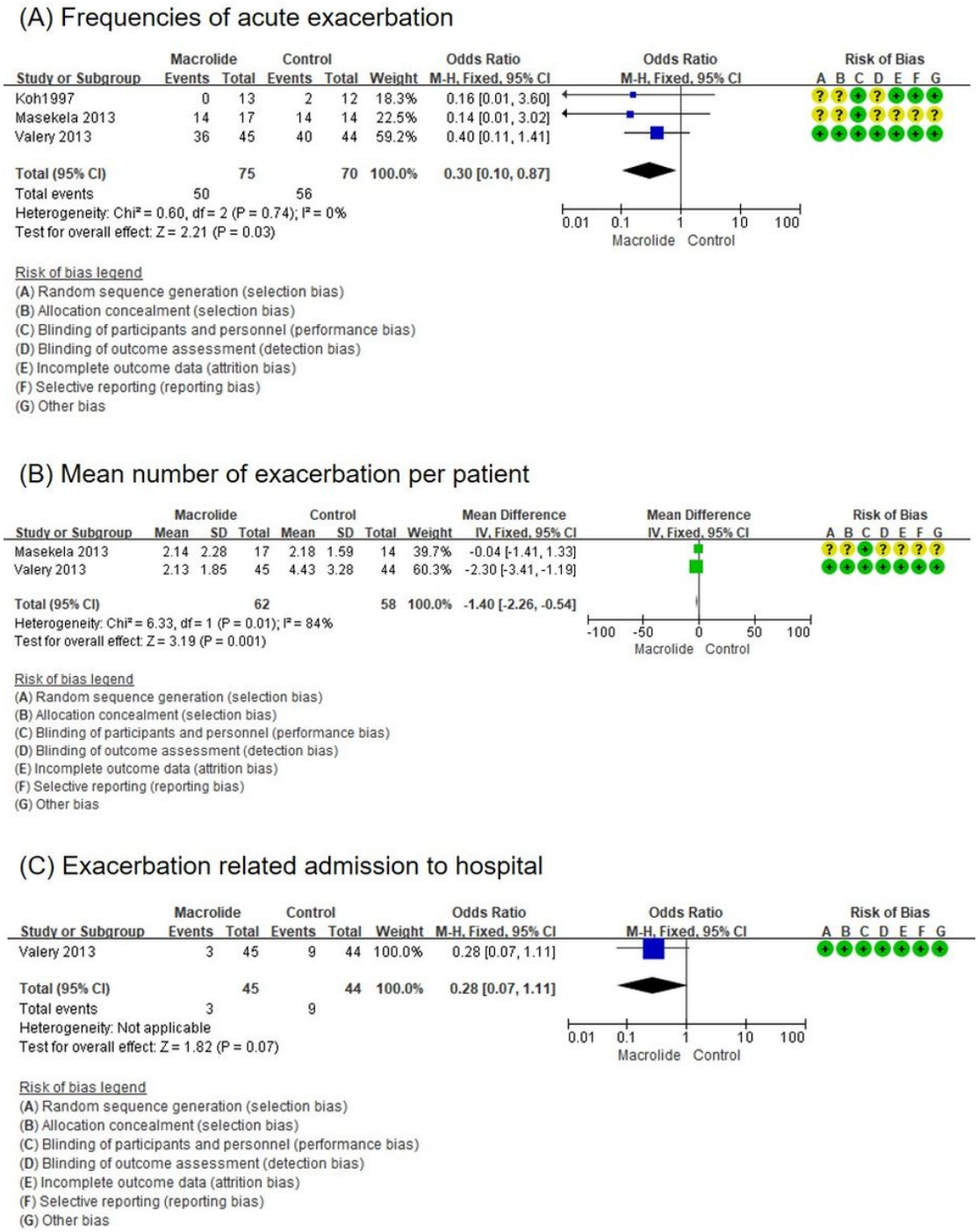

Figure 2

Forest plot of the effects of long-term macrolide treatment on acute exacerbation of bronchiectasis in children with non-cystic fibrosis bronchiectasis. (A) Frequencies of acute exacerbation, (B) mean number of exacerbations of bronchiectasis per patient, and (C) exacerbation related admission to the hospital.

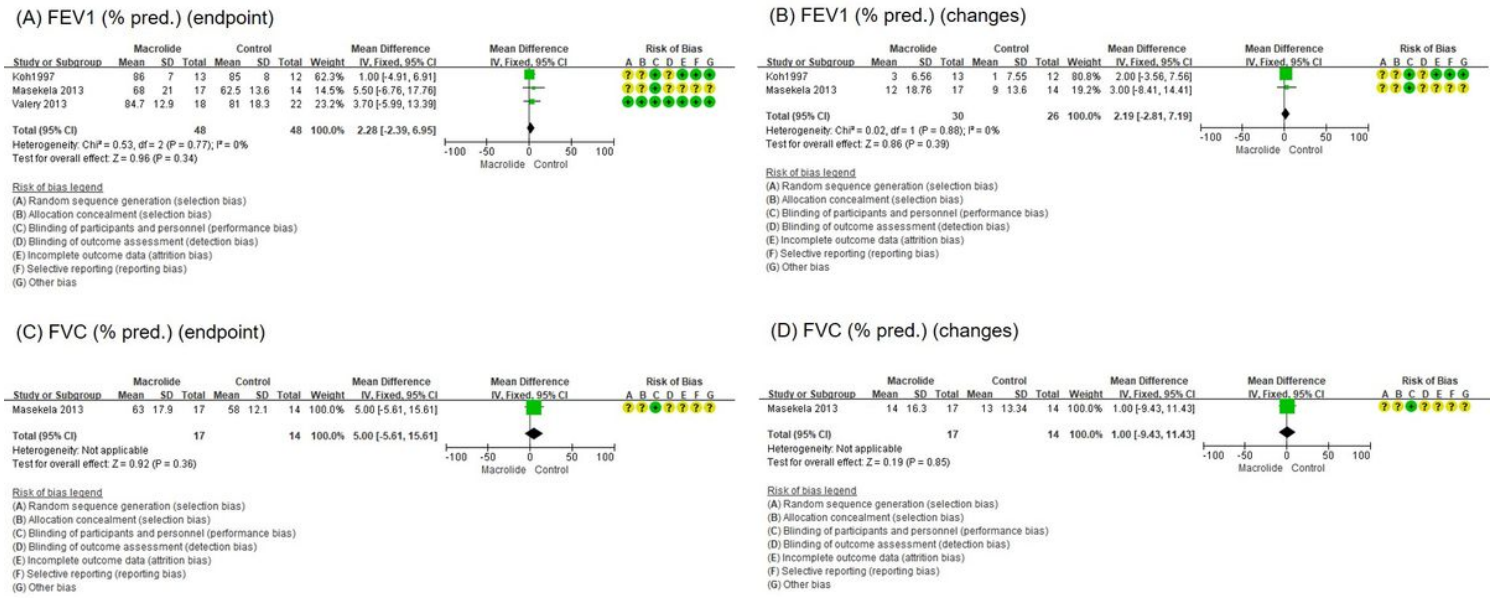

Figure 3

Forest plot of the effects of long-term macrolide treatment on pulmonary functions in children with non-cystic fibrosis bronchiectasis. (A) FEV1 % predicted at endpoint, (B) FEV1 % predicted changes, (C) FVC % predicted at the endpoint, and (D) FVC % predicted changes.

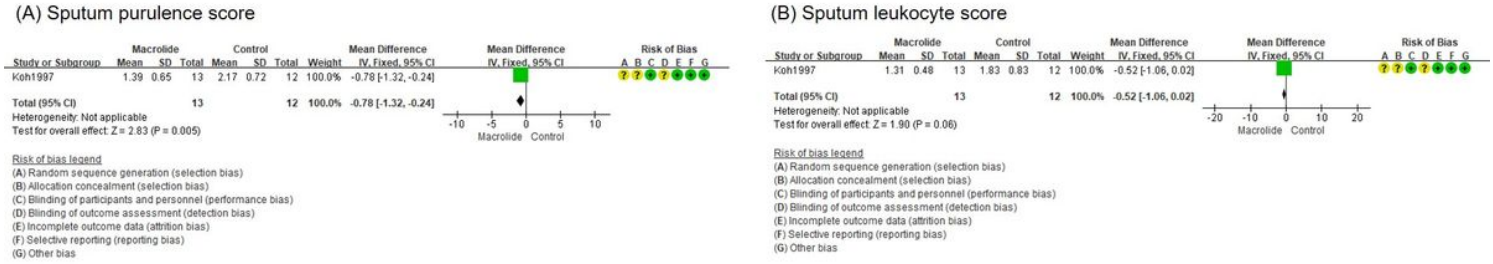

Figure 4

Forest plot of the sputum scores of long-term macrolide treatment on children with non-cystic fibrosis bronchiectasis. (A) Sputum purulent score, and (B) sputum leukocyte score in children with bronchiectasis.

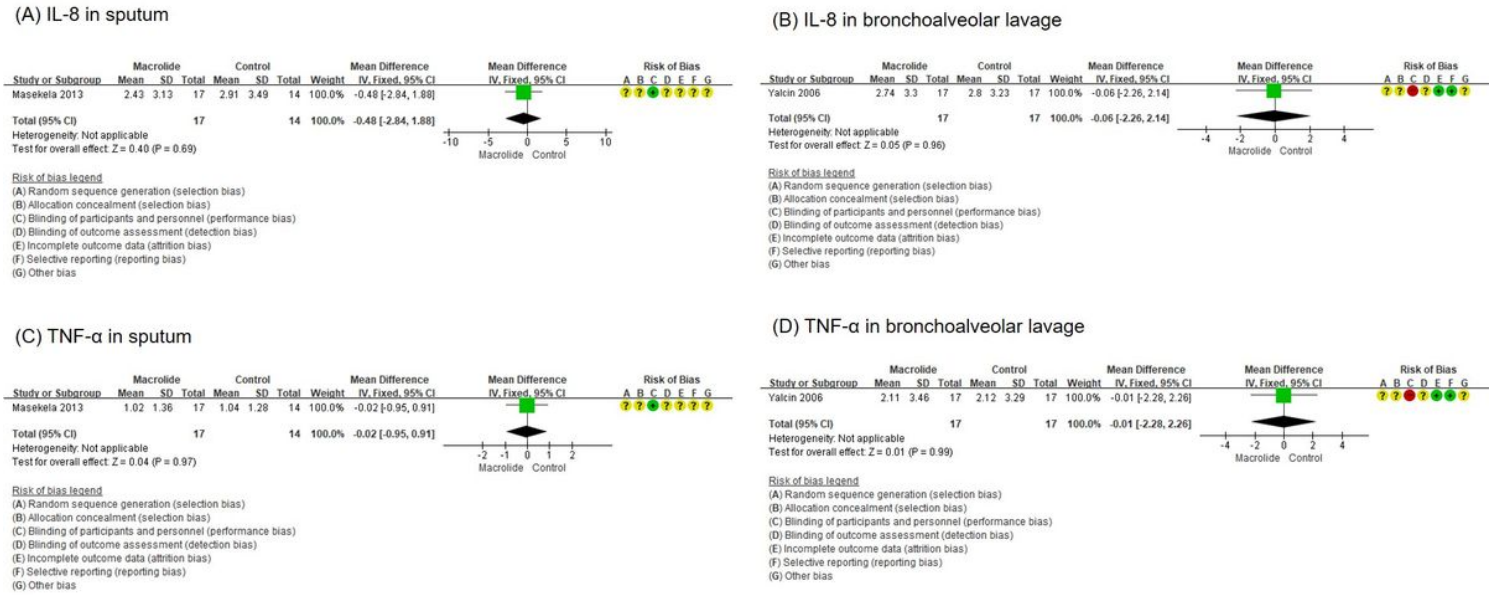

Figure 5

Forest plot of the effects of long-term macrolide treatment on cytokine levels from the sputum in children with bronchiectasis. (A) Log-transformed IL-8 levels in the sputum, (B) Log-transformed IL-8 levels in bronchoalveolar lavage fluid, (C) Log-transformed TNF-α level in the sputum, and (D) Log-transformed TNF-α level in bronchoalveolar lavage fluid.

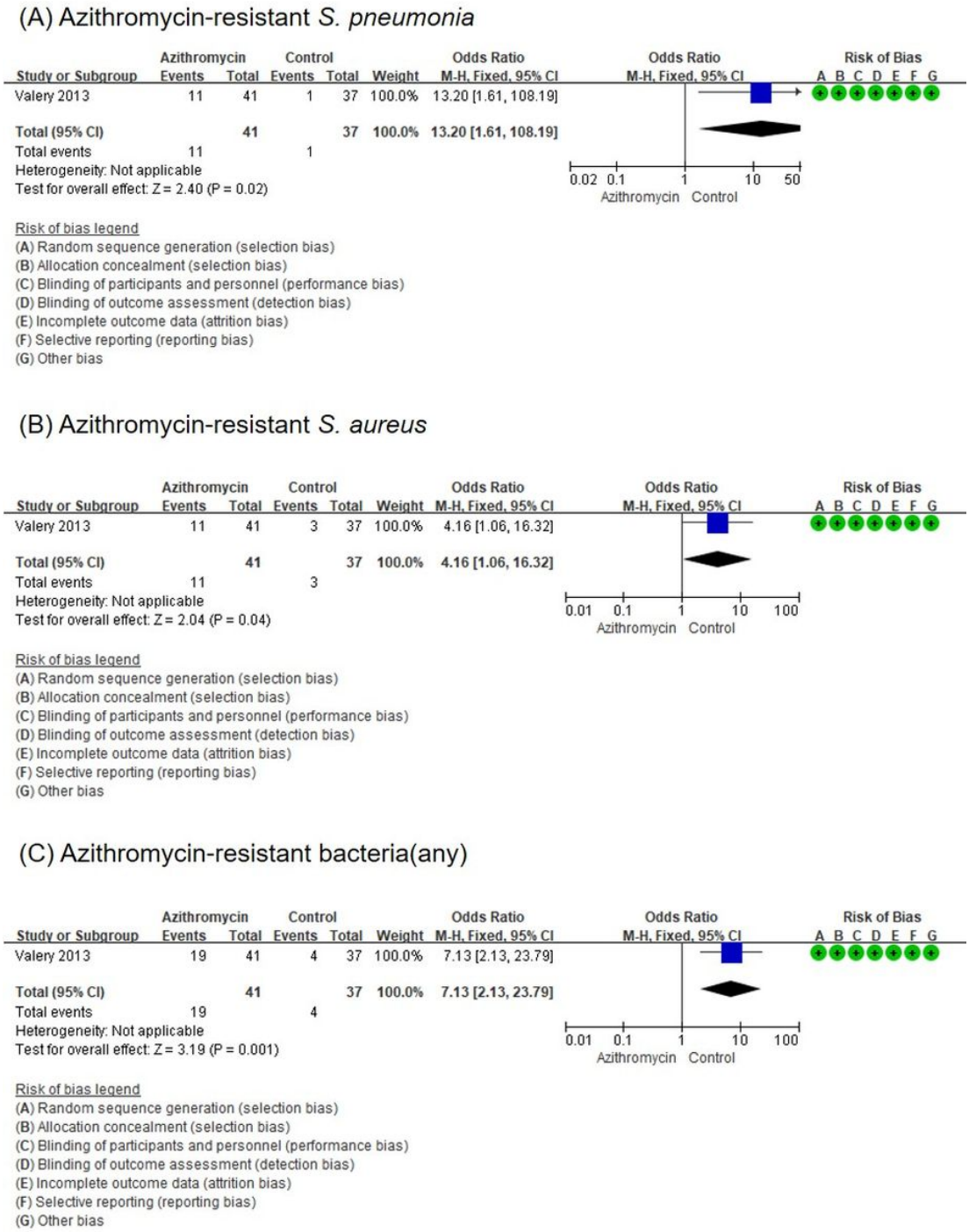

Figure 6

Forest plot of the effects of long-term macrolide treatment on the development of resistance to antibiotics in children with bronchiectasis. (A) Azithromycin-resistant Streptococcus pneumoniae, (B) azithromycin-resistant Staphylococcus aureus, and (C) azithromycin-resistant any bacteria.

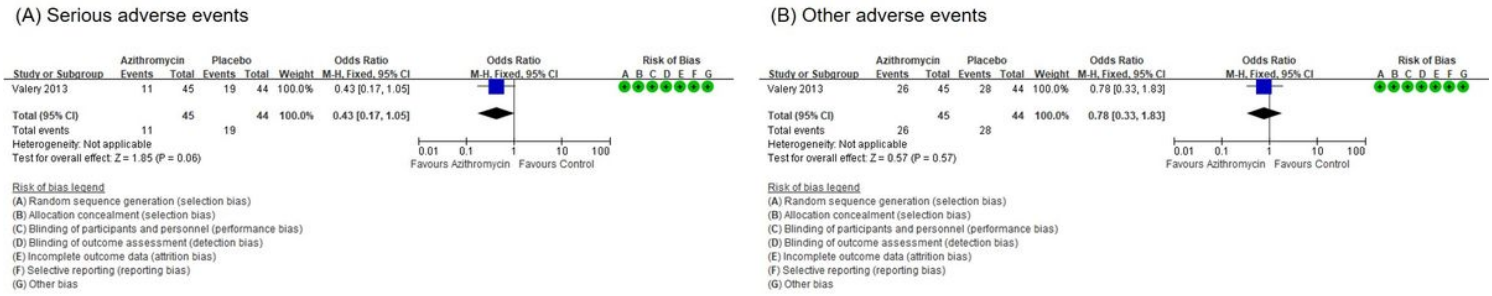

Figure 7

Forest plot for adverse events with long-term macrolide treatment in children with bronchiectasis. (A) Serious adverse events and (B) other adverse events.