

# Meta-analysis of macrolide maintenance therapy for prevention of disease exacerbations in patients with noncystic fibrosis bronchiectasis

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## Abstract

**Background:** Macrolide maintenance treatment remains controversial for patients with noncystic fibrosis (non-CF) bronchiectasis, we performed a meta-analysis to estimate the benefits and safety of macrolides therapy in adults and children with non-CF bronchiectasis.

**Methods:** PubMed, Embase, the Cochrane Library, and Web of Science databases were searched for all the randomized controlled trials of macrolides for treating non-CF bronchiectasis. The primary outcome was improvement of bronchiectasis exacerbations. Secondary outcomes included adverse events and macrolide resistance.

**Results:** A total of 10 studies involving 602 patients were included in the analysis. Pooled results showed that macrolide therapy significantly reduced the number of patients who suffered from exacerbations (RR=1.56, 95% CI=1.14–2.14,  $P=.006$ ,  $I^2=72\%$ ), number of patients who experienced at least 3 exacerbations (RR=0.55, 95% CI=0.39–0.77,  $P=.0005$ ,  $I^2=40\%$ ), average exacerbations per patient during the observation time (SMD=−0.69, 95% CI=−1.06 to −0.32,  $P=.0002$ ,  $I^2=60\%$ ), and bronchiectasis exacerbation-related admissions (RR=0.46, 95% CI=0.23–0.96,  $P=.04$ ,  $I^2=0\%$ ). Specified subgroup analyses of the number of patients free from exacerbations were further performed; macrolide therapy showed a significant benefit in both children (RR 5.03, 95% CI 2.02–12.50,  $P=.0005$ ,  $I^2=45\%$ ) and adults (RR=1.66, 95% CI=1.37–2.02,  $P<.00001$ ,  $I^2=79\%$ ); azithromycin showed a significant reduction on the number of patients who suffered from exacerbations (RR=2.25, 95% CI=1.67–3.02,  $P<.00001$ ,  $I^2=0\%$ ), was different from erythromycin (RR=1.33, 95% CI=0.92–1.94,  $P=.13$ ,  $I^2=0\%$ ) and roxithromycin (RR=1.14, 95% CI=0.97–1.35,  $P=.11$ ,  $I^2=0\%$ ). The pooled results also showed no higher risk of adverse events (RR=0.98, 95% CI=0.85–1.13,  $P=.80$ ,  $I^2=8\%$ ), even a lower risk of severe adverse events (RR=0.53, 95% CI=0.33–0.85,  $P=.009$ ,  $I^2=0\%$ ). However, a higher risk of macrolide resistance (RR=3.59, 95% CI 2.6–4.96,  $P<.00001$ ,  $I^2=0\%$ ) was observed.

**Conclusion:** For both children and adults with non-CF bronchiectasis, macrolide maintenance therapy can effectively reduce bronchiectasis exacerbations, especially for patients with more frequent exacerbations and needing hospital treatment. Azithromycin was more effective than other macrolides. Macrolide maintenance therapy did not increase the risk of adverse events, but may increase the risk of macrolide resistance.

**Abbreviations:** CF = cystic fibrosis, CI = confidence intervals, COPD = chronic obstructive pulmonary disease, ECG = electrocardiograph, non-CF = noncystic fibrosis, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, RR = relative risk, SMD = standard mean differences.

**Keywords:** bronchiectasis, exacerbations, macrolides, meta-analysis

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## 1. Introduction

Noncystic fibrosis (non-CF) bronchiectasis is a chronic respiratory disease characterized by abnormal dilatation and distortion of the bronchi and bronchioles,<sup>[1]</sup> mainly due to the vicious circle of frequent bacterial infections, chronic airway inflammation, retention of secretions, and airway destruction.<sup>[2,3]</sup> During the last 2 decades, the prevalence of bronchiectasis has not decreased as expected with a better control of airway infections. From 2000 to 2007, the prevalence of bronchiectasis in the United States has increased with an annual percentage of 8.74%.<sup>[4]</sup> The prevalence of bronchiectasis is particularly high among indigenous children in Central Australian, Maori, and Pacific Island in New Zealand, with at least 1470 cases for every 100,000 children.<sup>[5]</sup> Therefore, there is still a heavy health care burden associated with bronchiectasis worldwide.

Patients with non-CF bronchiectasis suffer from recurrent exacerbations, resulting in the destruction of airways and

reduced lung function, life quality and lifespan.<sup>[6]</sup> There is a strong interest in developing approaches that can mitigate this substantial problem. The current therapy of non-CF bronchiectasis mainly includes airway clearance techniques, exercise, inhaled hyperosmolar agents and mucolytic agents, and other anti-inflammatory agents.<sup>[2]</sup> While the available non-CF treatments can provide some benefits, the above strategies are insufficient and the specific indications of the above strategies are not clearly defined. Better strategies are urgently needed.

To the best of our knowledge, the important step of preventing exacerbations is to interrupt the vicious circle of infection, obstruction, inflammation and destruction. Macrolide antibiotics are antibacterial agents with anti-inflammatory and immunomodulatory properties,<sup>[2]</sup> which indicates that macrolide maintenance treatment may be effective in preventing exacerbations of patients with non-CF bronchiectasis. Since the 1980s, macrolide antibiotics have been used to reduce the incidence of non-CF bronchiectasis exacerbations. In addition, macrolide antibiotics have the advantages of high plasma concentration, long half-life, and broad antimicrobial spectrum.<sup>[7]</sup> All of these provide the rationale for using macrolide maintenance therapy in patients with non-CF bronchiectasis, which would be the first choice for prevention of non-CF bronchiectasis exacerbations. However, antibiotic maintenance therapy is not currently recommended as part of conventional management to control the disease and macrolides are only recommended in selected patients (e.g., those with frequent exacerbations,  $\geq 3$  exacerbations and/or  $\geq 2$  hospitalizations in the previous 12 months).<sup>[5]</sup> Recently, several randomized controlled trials (RCTs) focusing on the benefits of reducing exacerbations have been carried out to evaluate the benefits and safety on macrolides maintenance therapy in non-CF bronchiectasis. However, individual studies obtained varied results. The current meta-analysis aimed to determine the benefits and safety of macrolide maintenance treatment for non-CF bronchiectasis exacerbations.

## 2. Methods

### 2.1. Search strategy

We operated a literature search using PubMed, Embase, Web of Science, and the Cochrane Library, with the last report up to May 2018. No language and date restriction were applied. Searches were limited to human only and RCTs. We searched the following MeSH terms: “Macrolides,” “Macrolide,” “Azithromycin,” “Erythromycin,” “Clarithromycin,” “Roxithromycin,” “Bronchiectasis,” “noncystic fibrosis bronchiectasis,” “non-CF bronchiectasis,” “NCFB.” In addition, the reference lists of the articles were manually searched for other potentially eligible studies. Abstracts published in academic conferences or website materials were excluded. The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>[8]</sup>

### 2.2. Inclusion criteria, exclusion criteria, and study selection

The inclusion criteria were: a clinical randomized controlled trial (RCT); aimed to evaluate the benefits or safety of macrolides in comparison with control group (placebo, another class of antibiotic or blank control) in the treatment of patients with non-CF bronchiectasis; reported the number of exacerbations as

the outcome; published in peer-reviewed journal. A study was excluded if: it is presented as a review article or protocol; involved patients with other chronic respiratory conditions, such as cystic fibrosis, COPD, or asthma; data could not be obtained by original manuscripts or e-mail to authors. Two reviewers independently managed the study selection, differences were resolved by consensus after discussion. Ethical approval was not necessary because this was a meta-analysis.

### 2.3. Assessment of risk of bias in included studies

The risk of bias of each study was assessed by 2 authors independently according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Disagreements were resolved by discussion or arbitration involving a third reviewer. The detail domains of risk of bias included: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Each potential source of bias was graded as high, low, or unclear and the assessment outcome was noted in the “Risk of bias” table.

### 2.4. Data extraction and outcome measures

The following data were extracted: the year when the study was performed, location, age range of patients, number of patients, diagnostic criteria, total duration of study, macrolides intervention (the type of macrolide, medicine dose, interval of drug administration), reported outcomes, adverse events. We extracted data from the original manuscripts when possible; we also contacted the corresponding authors for original data.

The primary outcome measurement was the number of patients stratifying by different exacerbation times, the rate of exacerbation per patient per year and exacerbation-related admissions. A bronchiectasis exacerbation was defined using the study author’s criteria, almost all of the criteria included intense coughing, dyspnea, wheezing, fever, chest pain, increased purulent sputum, requirement for oral or intravenous antibiotics. Secondary outcomes were adverse events and macrolide resistance.

### 2.5. Data analysis

Relative risk (RR) with 95% confidence intervals (95% CI) was used to evaluate dichotomous variables and standard mean differences (SMD) with 95% CI were used to evaluate continuous variables. Sensitivity analysis was performed for missing data. Cochran’s  $X^2$  statistics with  $P$  value and  $I^2$  was used to measure the heterogeneity among studies. If  $P < .10$  or  $I^2 > 50\%$ , suggesting significant heterogeneity, a random-effects model was chosen. Otherwise, calculations were performed with a fixed-effects model. Subgroup analyses were performed to explore heterogeneity when substantial heterogeneity was presented. For the primary outcome, subgroup analyses were also performed based on: type of macrolides: azithromycin vs erythromycin; children vs adults. For the data that cannot be merged, a descriptive analysis was performed.  $P < .05$  was considered statistically significant. Publication bias was assessed by the funnel plot. All statistical analyses were performed using Review Manager Software (version 5.3; Cochrane Collaboration, Oxford, United Kingdom).

### 3. Result

#### 3.1. Literature review and selection

Initial literature searches retrieved 541 articles, 85 articles were included after initial title and abstract screening. Another 75 articles were excluded for various reasons, and 10 RCTs were finally identified for meta-analysis (see figure, supplemental digital content S1, <http://links.lww.com/MD/C926>, which illustrates the flowchart of the study selection process).

#### 3.2. Characteristics of included trials

The year of publication for eligible studies ranged from 1997 to 2013. Except one cross-over study with 1 month washout period,<sup>[9]</sup> others were all parallel group studies.<sup>[10–18]</sup> Both children and adult patients were included. Seven trials recruited adult patients<sup>[9,11–13,16–18]</sup> and 3 trials recruited children.<sup>[10,14,15]</sup> Five trials<sup>[9,13,15,17,18]</sup> used azithromycin as the therapy intervention, 3 trials<sup>[11,14,16]</sup> used erythromycin, the other 2 trials<sup>[10,12]</sup> used roxithromycin, no trial on clarithromycin met inclusion criteria. Duration of the observation period ranged from 8 weeks to 24 months, the observation period of 4 trials<sup>[9–11,18]</sup> were <6 months, others were more than 6 months. The observation period refers to the whole of “treatment period” and “follow-up after finishing treatment period.” The characteristics of the included trials are shown in Table 1.

The methodological quality of the included studies was evaluated using the risk of bias (see figure, supplemental digital content S2, <http://links.lww.com/MD/C926>, which illustrates the quality assessment of the studies). Seven trials described random sequence generation, 5 trials described allocation concealment, all the trials reported incomplete outcome data and described the selective reporting, only 4 indicated no other bias. Three trials did not describe blinding of the patients or executors, one trial described no blinding of outcome assessment.

#### 3.3. Outcomes

The detailed outcome measurements of the included trials are shown in Table 2.

##### 3.3.1. Primary outcome: clinic exacerbations

**3.3.1.1. Number of patients free from exacerbations.** Nine trials (n=572) reported the number of patients free from exacerbations. Six trials were conducted in adults and the other 3 in children; 4 trials used azithromycin as the intervention, 3 used erythromycin, and the other 2 used roxithromycin. Compared with the standard group, the number of patients without exacerbation in the macrolides group significantly increased during the observation time (RR=1.56, 95% CI=1.14–2.14, P=.006; Fig. 1). Since significant heterogeneity was detected (I<sup>2</sup>=72%), random-effects model were chosen. To identify and measure heterogeneity, specified subgroup analyses were further performed (Fig. 2). There was a significant benefit in azithromycin group (RR=2.25, 95% CI=1.67–3.02, P<.00001), but no significant benefit for neither erythromycin (RR=1.33, 95% CI=0.92–1.94, P=.13) nor roxithromycin (RR=1.14, 95% CI=0.97–1.35, P=.11). The heterogeneity in the subgroup of azithromycin, erythromycin, and roxithromycin exhibited was all unremarkable (I<sup>2</sup>=0%), suggesting the result in azithromycin, erythromycin, roxithromycin was reliable. There was a significantly benefit of macrolide therapy in reducing the exacerbations both in children (RR 5.03, 95% CI 2.02–12.50, P=.0005) and adults (RR=1.66, 95% CI=1.37–2.02, P<.00001). The heterogeneity in the subgroup of children was not significant (I<sup>2</sup>=45%), suggesting the result in children may be credible; while the heterogeneity exhibited in the subgroup of adults was significant (I<sup>2</sup>=79%), indicating the result in adults may be not reliable. It can be concluded that there was a significant benefit of macrolide therapy in preventing the exacerbation for patients with non-CF bronchiectasis and reducing the number of patients experiencing one or more exacerbations in children, while in

**Table 1**  
Characteristics of randomized clinical trials included in the meta-analysis.

Study period	Location	Study design	Total Sample (T/C)(F/M)	Age range	Diagnosis criteria	Exacerbation history and bronchiectasis states	Macrolides dose and frequency	Therapy duration Follow-up duration
Koh Y.Y 1995.10–1996.2	Korea	DB,RCT	25 (13/12) (11/14)	10–18	Clinical features and CT	Stable bronchiectasis, increased AR	Roxithromycin 4mg/kg twice daily	12 weeks 12 weeks
Tsang KW 1996.10–1997.4	China	DB,RCT	21 (11/10) (16/5)	35–75	HRCT	Stable idiopathic bronchiectasis	Erythromycin 500 mg twice daily	8 weeks 8 weeks
Cymbala AA 2005	America	Open label, crossover, RCT	22 (11/11) (NR)	≥18years	HRCT	NR	Azithromycin 500mg twice weekly	6 months 6 months
JF Liu 2007.6–2010.6	China	DB,RCT	43 (22/21) (20/23)	18–65	Meeting the criteria of O'Donnell	Stable bronchiectasis	Roxithromycin 150mg once daily	6 months 18 months
Wong C 2008.2–2009.10	New Zealand	DB,RCT	141 (71/70) (98/43)	≥18years	HRCT	Stable bronchiectasis, ≥1 exacerbation in the past year	Azithromycin 500mg thrice weekly	6 months 12 months
Masekela R 2009.1–2011.6	South Africa	DB,RCT	31 (17/14) (13/18)	6–18	HRCT	Bronchiectasis associated with HIV	Erythromycin, <15 kg 125 mg, >15 kg 250 mg per day	52 weeks 52 weeks
Valery PC 2008.12–2010.12	Australia	DB,RCT	89 (45/44) (47/42)	1–8	HRCT	Stable bronchiectasis, ≥1 exacerbation in the past year	Azithromycin 30 mg/kg once a week	12–24 months 12–24 months
Serisier DJ 2008.10–2011.12	Australia	DB,RCT	117 (59/58) (71/46)	20–85	HRCT	Stable bronchiectasis, ≥2 exacerbations in the past year	Erythromycin 400mg twice daily	48 weeks 52 weeks
Altenburg J 2008.4–2010.9	Nether-land	DB,RCT	83 (43/40) (53/30)	≥18years	HRCT or plain bronchography	Stable bronchiectasis, ≥3 LRTIs in the past year	Azithromycin 250mg once daily	52 weeks 52 weeks
De Diego 2005.1–2005.12	Spain	Open label, RCT	30 (16/14) (16/14)	≥18years	Clinic data and HRCT	Stable bronchiectasis	Azithromycin 250mg thrice weekly	3months 3months

AR = airway responsiveness, C = control group, DB = double-blinded, F = female, HIV = human immunodeficiency virus, HRCT = high Resolution CT, LRTIs = lower respiratory tract infection, M = male, NR = not reported, RCT = randomized controlled trial, T = treat group.

**Table 2**  
The non-CF exacerbations of the trials included in the meta-analysis.

Study		Exacerbations					The mean exacerbations per patient	Adverse events			
		No. of patients who suffered from any exacerbation						Exacerbations related admissions	Any adverse event	Severe adverse events	Macrolide resistance
		0	≥1	1	2	≥3					
Koh Y.Y 1995.10–1996.2	T	13/13	0/13	0/13	0/13	0/13	NR	NR	NR	NR	NR
	C	10/12	2/12	2/12	0/12	0/12					
Tsang KW 1996.10–1997.4	T	11/11	0/11	0/11	0/11	0/11	NR	NR	1/11	NR	NR
	C	8/10	2/10	2/10	0/10	0/10			0/10		
Cymbala AA 2005	T	9/11	2/11	NR	NR	NR	NR	NR	NR	NR	NR
	C	3/11	8/11								
JF Liu 2007.6–2010.6	T	21/22	1/22	1/22	0/22	0/22	NR	NR	8/22	NR	NR
	C	18/21	3/21	3/21	0/21	0/21			3/21		
Wong C 2008.2–2009.10	T	49/71	22/71	NR	NR	NR	NR	1/71	59/71	4/71	2/71
	C	24/70	46/70						65/70	9/70	0/70
Masekel R 2009.1–2011.6	T	3/17	14/17	NR	NR	NR	2.14 ± 2.28	NR	NR	NR	NR
	C	0/14	14/14				2.18 ± 1.59				
Valery PC 2008.12–2010.12	T	9/45	36/45	7/45	9/45	20/45	2.13 ± 1.85	3/45	26/45	11/45	19/41
	C	4/44	40/44	7/44	5/44	28/44	4.43 ± 3.28	9/44	28/44	19/44	4/37
Serisier DJ 2008.10–2011.12	T	20/59	39/59	20/59	9/59	10/59	1.29 ± 1.38	5/59	17/59	0/59	NR
	C	16/58	42/58	12/58	12/58	18/58	1.97 ± 1.98	7/58	15/58	1/58	
Altenburg J 2008.4–2010.9	T	23/43	20/43	10/43	6/43	4/43	0.84 ± 1.1	1/43	18/43	5/43	53/60
	C	8/40	32/40	8/40	10/40	14/40	2.05 ± 1.6	2/40	17/40	8/40	29/112
De Diego 2005.1–2005.12	T	NR	NR	NR	NR	NR	0.1 ± 0.6	NR	NR	NR	NR
	C						1.2 ± 0.9				

C=control group, NR=not reported, T=treat group.

adults more evidences were needed; azithromycin showed significant benefit, while erythromycin and roxithromycin did not show significant benefit.

3.3.1.2. Number of patients who experienced only one exacerbation during the observation time. Six trials (n=378) reported the number of patients who experienced only one

exacerbation. Compared with the control group, the macrolides group exhibited no significant reduction in the number of patients experienced only one exacerbation (RR=1.07, 95% CI=0.71–1.60, P=.74) (see figure, supplemental digital content S3, <http://links.lww.com/MD/C926>, which illustrates the effects of macrolide therapy on the number of patients who experienced only one exacerbation during the observation time). No significant

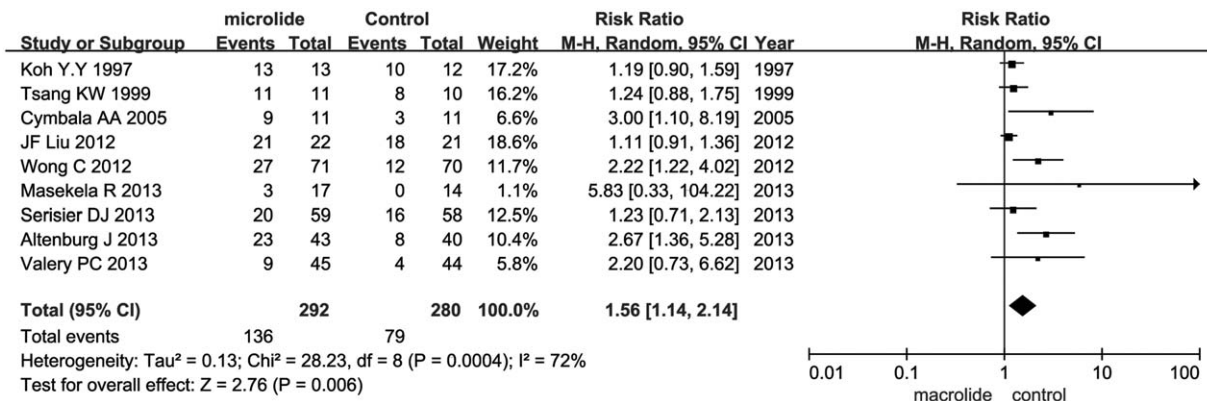


Figure 1. Effects of macrolide therapy on the number of patients with non-CF bronchiectasis free from exacerbations.

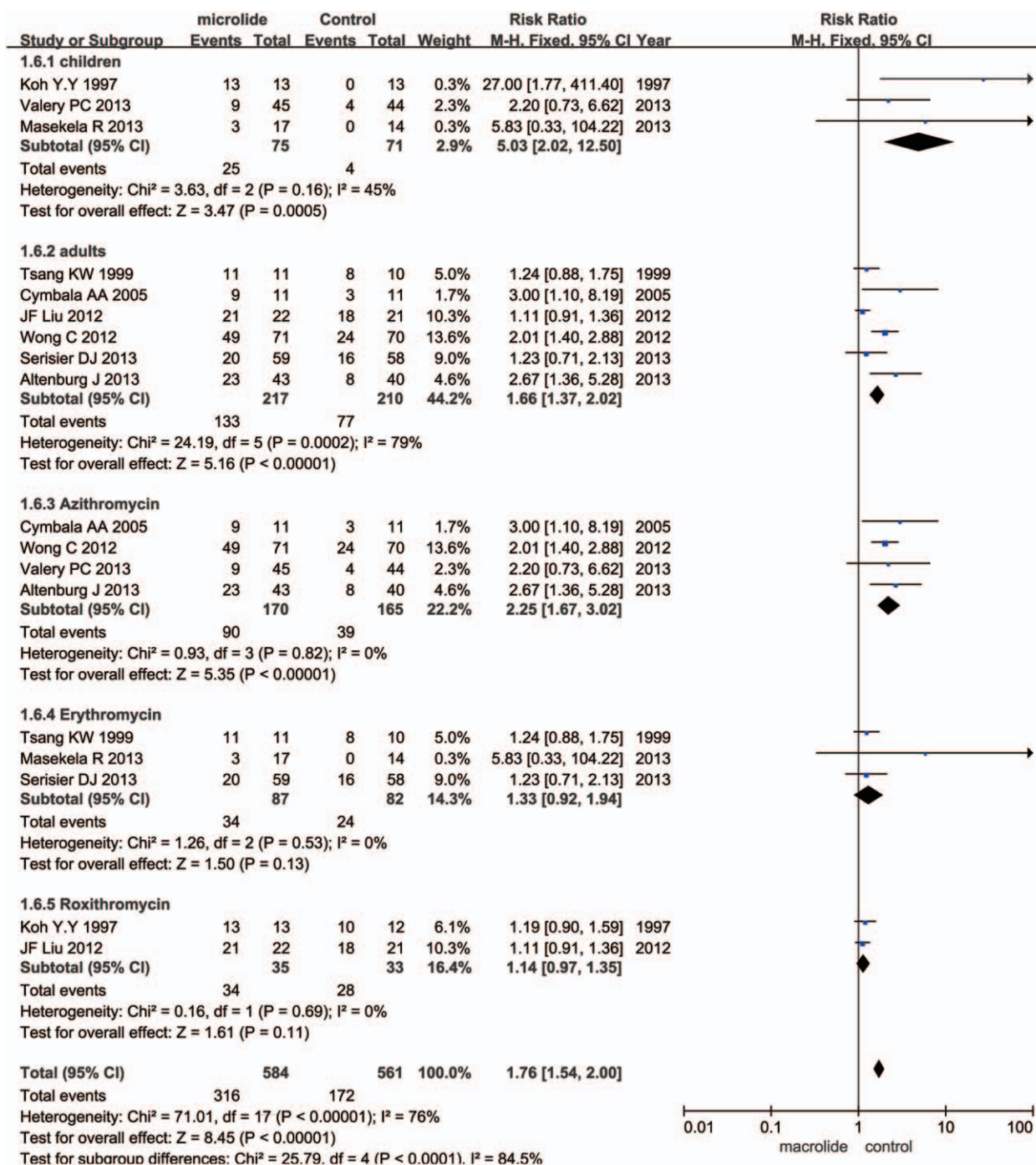


Figure 2. Subgroup analysis of effects of macrolide therapy on the number of patients with non-CF bronchiectasis free from exacerbations.

heterogeneity was detected ( $I^2=14\%$ ), thus fixed-effects model was chosen. It can be concluded that there was no significant benefit for patients with non-CF bronchiectasis who experienced only one exacerbation.

**3.3.1.3. Number of patients who experienced 2 exacerbations during the observation time.** Three trials (n=293) reported the number of patients who experienced 2 exacerbations. Compared with the control group, the macrolides group exhibited no significant reduction in the number of patients who experienced 2 exacerbations (RR=0.88, 95% CI=0.53–1.46, P=.63) (see

figure, supplemental digital content S4, <http://links.lww.com/MD/C926>, which illustrates the effects of macrolide therapy on the number of patients who experienced 2 exacerbations during the observation time). Since no significant heterogeneity was detected ( $I^2=23\%$ ), fixed-effects model was chosen. It can be concluded that there was no significant benefit for patients with non-CF bronchiectasis who experienced 2 exacerbations.

**3.3.1.4. Number of patients who experienced at least 3 exacerbations during the observation time.** Three trials (n=289) reported the number of patients who experienced at least 3

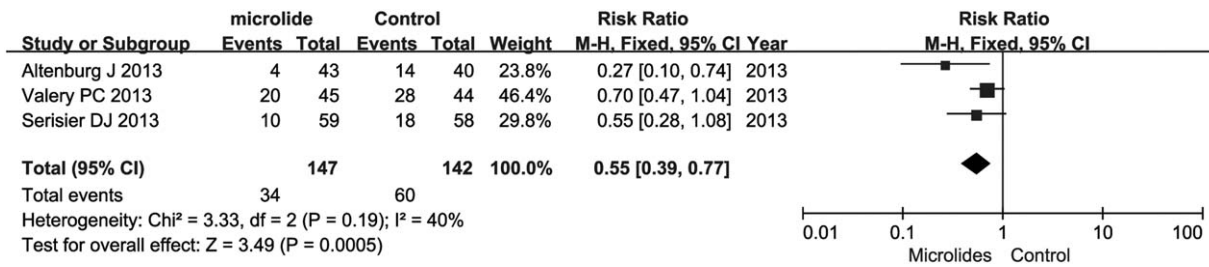


Figure 3. Effects of macrolide therapy on the number of patients who experienced at least 3 exacerbations during the observation time.

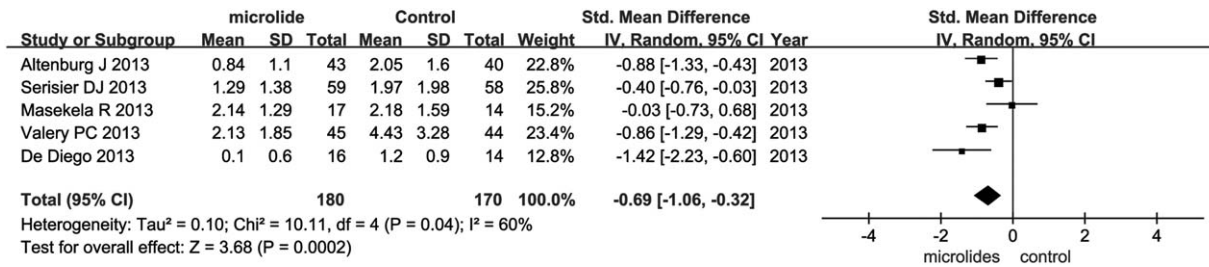


Figure 4. Effects of macrolide therapy on the frequency of exacerbations.

exacerbations. Compared with the control group, the macrolides group exhibited significant reduction in the number of patients who experienced at least 3 exacerbations (RR=0.55, 95% CI=0.39–0.77, P=.0005; Fig. 3). Since no significant heterogeneity was detected (I<sup>2</sup>=40%), fixed-effects model was chosen. It can be concluded that there was a significant benefit for patients with non-CF bronchiectasis who experienced frequent exacerbations.

**3.3.1.5. Average exacerbations per patient during the observation period.** Five trials (n=350) reported the average exacerbations per patient. Three trials were conducted in adults and the other 2 in children; 3 trials used azithromycin as the intervention, and the other 2 used erythromycin. Compared with the control group, the macrolides group exhibited significant reduction in the frequency of exacerbations (SMD=−0.69, 95% CI=−1.06 to −0.32, P=.0002; Fig. 4). Since significant heterogeneity was detected (I<sup>2</sup>=60%), random-effects model was chosen. To identify and measure heterogeneity, specified subgroup analyses were further performed (see figure, supplemental digital content S5, <http://links.lww.com/MD/C926>, which illustrates the subgroup analysis of effects of macrolide therapy

on the frequency of exacerbations). There was a significant benefit of macrolide therapy in reducing the frequency of exacerbations for both adults (SMD=−1.01, 95% CI=−1.35 to −0.67, P<.00001) and children (SMD=−1.09, 95% CI=−1.85 to −0.33, P=.005). The heterogeneity in the subgroup of children was significant (I<sup>2</sup>=88%), suggesting the result in children may be not precisely credible; while the heterogeneity in the subgroup of adults was not significant (I<sup>2</sup>=0%). The heterogeneity in the subgroup of both azithromycin and erythromycin was not significant (I<sup>2</sup>=46%, I<sup>2</sup>=8%), suggesting the results in azithromycin and erythromycin exhibited may be reliable. Azithromycin showed significant benefit (P<.00001), while erythromycin did not show significant benefit (P=.06).

**3.3.1.6. Bronchiectasis exacerbation-related admissions.** Four trials (n=430) reported admission associated with bronchiectasis exacerbation. Pooled analyses showed that macrolide therapy reduced the risk of admissions for infective exacerbations compared with the control group (RR=0.46, 95% CI=0.23–0.96, P=.04; Fig. 5). As no significant heterogeneity was detected (I<sup>2</sup>=0%), fixed-effects model was chosen.

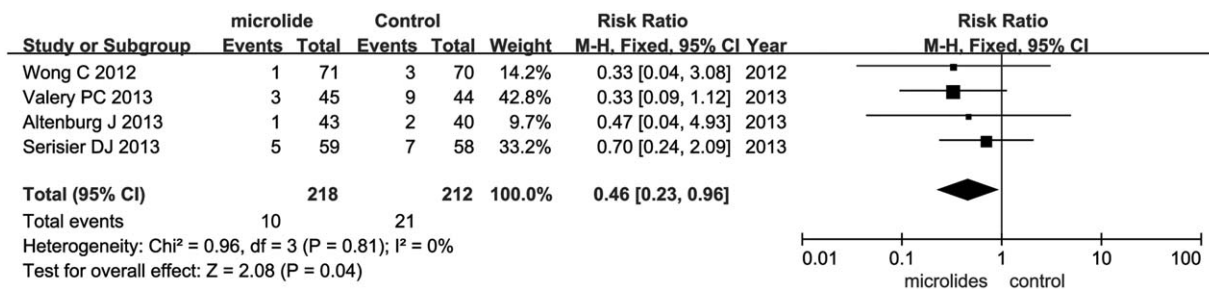


Figure 5. Effects of macrolide therapy on bronchiectasis exacerbation-related admissions.

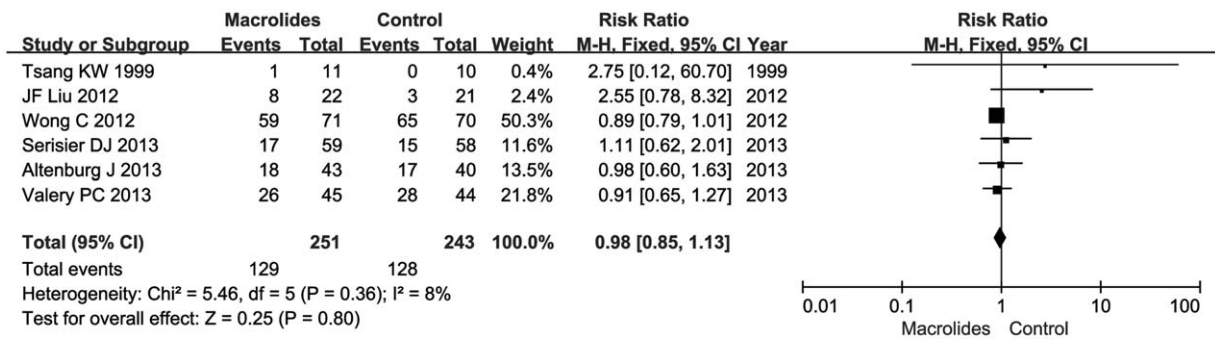


Figure 6. Effects of macrolide therapy on the number of patients suffered from any adverse event.

3.3.1.7. *Secondary outcome: adverse events and macrolide resistance.* Six studies with a total of 494 patients reported clinical and laboratory monitoring for adverse events. The main side effects included diarrhea, nausea, vomiting, abdominal discomfort, and headache, rash, or sinusitis. Six trials (n=494) reported the number of patients with one or more adverse events. The number of patients who experienced any adverse event was found to have no statistical difference among participants receiving macrolides compared to those receiving placebo (RR=0.98, 95% CI=0.85–1.13, P=.80; Fig. 6). No significant heterogeneity was detected (I<sup>2</sup>=8%), fixed-effects model was chosen. Three trials reported the gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal discomfort, etc.) of the adverse events. Gastrointestinal symptoms were more common in the macrolide therapy group (RR=3.62, 95% CI=1.93–6.79, P<.0001, I<sup>2</sup>=0%) (see figure, supplemental digital content S6, <http://links.lww.com/MD/C926>, which illustrates the effects of macrolide therapy on the number of patients suffering from gastrointestinal adverse events). Four trials (n=430) reported the number of patients with one or more severe adverse events. The

severe adverse events mainly included disease needed surgery, heart failure, stroke, corrected QT interval (QTc) prolongation, and even death. The number of patients who experienced any severe adverse event was significantly reduced in the macrolides group, compared with the control group (RR=0.53, 95% CI=0.33–0.85, P=.009; Fig. 7). No significant heterogeneity was detected (I<sup>2</sup>=0%), fixed-effects model was chosen. Three trials reported the macrolide resistance and the rate in macrolides group is higher than the control group (RR=3.59, 95% CI=2.60–4.96, P<.00001; Fig. 8). No significant heterogeneity was detected (I<sup>2</sup>=0%), fixed-effects model was chosen. The 3 trials were all about azithromycin. Unfortunately, no data on erythromycin and roxithromycin was reported about the macrolide resistance. So we could draw a conclusion that azithromycin was associated with a higher risk of developing resistance, but that no data was available for other macrolide agents to allow a comparison.

It can be concluded that, compared with the control group, macrolides therapy would not increase the risk of adverse events, would decrease the risk of severe adverse events, but would

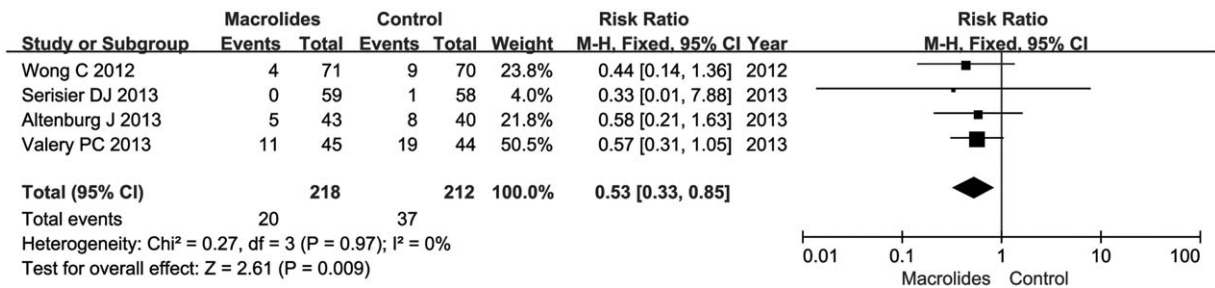


Figure 7. Effects of macrolide therapy on the number of patients suffered from any severe adverse event.

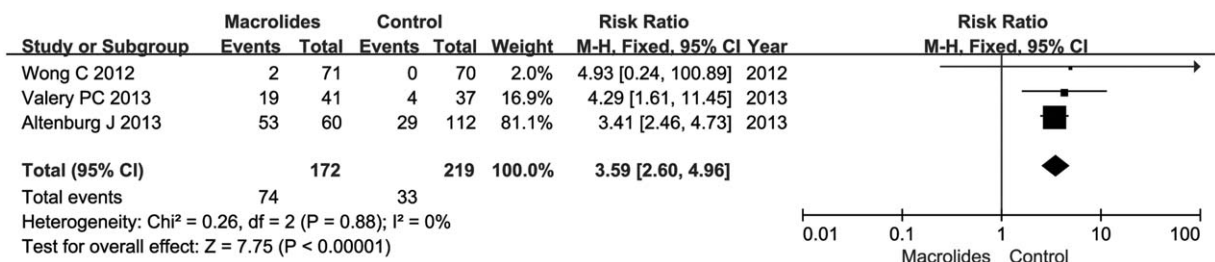


Figure 8. Effects of macrolide therapy on the macrolide resistance.

increase the gastrointestinal complications and the risk of macrolide resistance.

### 3.4. Publication bias

There is an asymmetrical appearance of the funnel plot with a gap in a bottom corner for the number of patients free from bronchiectasis exacerbations. (see figure, supplemental digital content S7, <http://links.lww.com/MD/C926>, which illustrates the funnel plot of included trials for the number of patients free from bronchiectasis exacerbations). However, Egger's test did not show a significant publication bias ( $P = .09$ ). Publication bias for the rate of exacerbation was not assessed due to the limited number of studies.

## 4. Discussion

The overall aim of the treatment of patients with non-CF bronchiectasis is to reduce symptoms, to prevent exacerbations, and thereby maintain lung function and improve the quality of life.<sup>[1]</sup> As a group of antibiotics with a wide antimicrobial spectrum, macrolides has been demonstrated to have the effect of preventing exacerbations in patients with CF<sup>[19]</sup> and COPD.<sup>[20]</sup> We performed the systematic review and meta-analysis to explore the evidence for a beneficial therapy of macrolide treatment on non-CF bronchiectasis.

In spite of the 2 meta-analyses conducted by Gao et al<sup>[21]</sup> and Fan et al<sup>[22]</sup> assessing the benefits and safety of macrolides in patients with non-CF bronchiectasis, the current study utilized different perspectives in assessing macrolide effect and included more eligible articles. For primary outcome, our study concluded that macrolide therapy could significantly decrease the number of patients with exacerbations and the average exacerbations per patient during the observation time. However, we further analyzed the number of patients stratifying by different exacerbations (0, 1, 2,  $\geq 3$ ), and found that there is a significant decrease of the number of participants with 0 and  $\geq 3$  exacerbations in the macrolide-treated group compared with the control group. There is no significant decrease of the number of participants with 1 and 2 exacerbations. Different from the result of Gao's study, we found that macrolides therapy can reduce the risk of admissions for infective exacerbations compared with the control group. Our results suggested that macrolides seem to have a positive net effect among individuals with more frequent exacerbations of non-CF. In addition, to address the degree of heterogeneity in the findings, subgroup analyses were performed for the number of patients free from exacerbations and the average exacerbations per patient by adults or children, azithromycin or erythromycin or roxithromycin. We concluded that exacerbations could be prevented in children as well as adults, but we cannot eliminate the heterogeneity in adults about the number of patients with 0 exacerbation and in children about the average exacerbations per patient. Due to the limited number of studies, we cannot employ further analysis to decrease the heterogeneity. We also concluded that only azithromycin could prevent the exacerbations, erythromycin and roxithromycin did not show significant effect in patients with non-CF bronchiectasis, no trial on clarithromycin met inclusion criteria.

Except the benefits, the safety is another important matter of concern for the widespread implementation of the macrolides. So we collected the data about the adverse events of included studies.

Macrolides might have gastrointestinal reaction, ototoxicity, and cardiovascular risks, even proarrhythmic effect.<sup>[23]</sup> The main adverse events included gastrointestinal complications, such as nausea, vomiting, diarrhea, and abdominal discomfort, as well as headache, sinusitis, and rash in some participants. In our study, the gastrointestinal adverse events of the macrolide antibiotic treatment group were significantly more common than the control group. Diarrhea was the most common side effect, followed by nausea and vomiting. A few patients had abdominal pain. But the symptoms were mild and can be relieved by expectant treatment, which would not result in patient withdrawal.

Neither ototoxicity nor cardiovascular risks were systematically assessed in our selected studies, and only one study<sup>[16]</sup> monitored electrocardiogram changes and reported the QTc prolongation with one participant (1/59) in the macrolides group. However, clinicians should pay attention to monitor the ECG to prevent cardiovascular events. According to meta-analysis results, the pooled estimate of the number of patients suffering from any adverse event was not significantly different in the macrolides treatment group than that in the control group ( $P = .92$ ). Compared with the control group, there was a significant decrease of the number of patients who experienced any severe adverse event in the macrolides treatment group ( $P = .02$ ). Severe adverse events mainly included disease needed admission or surgery, heart failure, stroke, QTc prolongation, even death. Both Li and Gao did not report severe adverse events in their meta-analyses. Due to the emergence of multidrug resistant strains, macrolide resistance is another critical issue for the use of long-term macrolide therapy. Comparing with the control group, we observed a significant increase of antimicrobial resistance in the macrolides group. This is in accordance with Li's study, but there was an obvious mistake in the forest plot of antimicrobial resistance in Li's study. In Li's study, he extracted the data reported by Valery et al<sup>[15]</sup> as the same as reported by Wong et al<sup>[13]</sup> (macrolides group 2/71 vs control group 0/70). However, the exact data reported by Valery et al<sup>[15]</sup> was macrolides group 19/41 vs control group 4/37. Macrolide resistance has become an increasing concern worldwide,<sup>[24]</sup> particularly in Asia,<sup>[25]</sup> which probably is the most hazardous shortcoming of the widespread use of macrolides.

Certain limitations of our study should be noted. Our analyses were based on pooled data from various trials with different macrolide antibiotics, populations, duration, in particular, of heterogeneous illness states (different exacerbation history, age and disease severity) before the participants were recruited, and without more details, we cannot employ meta-regression to detect whether the effect size is related to clinical heterogeneity. In addition, the random-effect model and subgroup analyses were used to account for the heterogeneity. Finally, studies recruited participants without CT scan to confirm the presence of bronchiectasis, which may induce bias.

## 5. Conclusion

In conclusion, the result from this meta-analysis strongly supported that macrolide maintenance treatment had a benefit in preventing exacerbations both in adults and children with bronchiectasis compared with controls. Azithromycin showed significant benefits comparing with other macrolides. In addition, macrolides would not increase the risk of adverse events, could decrease the risk of severe adverse events, but would increase the



risk of antimicrobial resistance. Nonetheless, randomized controlled trials involving larger patient samples are needed to confirm the optimal agents, dose, duration, and the potential antimicrobial resistance following macrolide therapy for patients with non-CF bronchiectasis.

### Author contributions

Donghai Wang and Jihong Dai conceived and designed the study, Donghai Wang and Wenlong Fu carried out the databases and did the data extraction and analysis, Donghai Wang wrote the first draft of the manuscript, and all the authors read and approved the final manuscript.

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