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Inhaled antibiotics in non-cystic fibrosis bronchiectasis: A meta-analysis

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Objective: To evaluate the efficacy and safety of inhaled antibiotics for the treatment of non-cystic fibrosis bronchiectasis (NCFB). *Methods:* Pubmed, Cochrane library, Embase, Elsevier, OVID, Springerlink, Web of knowledge and NEJM were searched for randomized controlled trials (RCTs) on inhaled antibiotics in treatment of NCFB from inception until April 2015. Meta-analysis was conducted to assess the efficacy and safety of inhaled antibiotics in the treatment of NCFB. *Results:* Twelve RCTs involving 1154 participants were included. They showed that inhaled antibiotics were more effective in reduction of sputum bacterial density, eradication of *P*. aeruginosa, prolonged time to exacerbation and reduction of new pathogens emergence with no significant difference in adverse events compared with control groups. However, we did not find significant benefits of inhaled antibiotics in reducing the risk of acute exacerbation, improving health-related quality of life and reduction of *P*. aeruginosa resistance. Moreover, inhaled antibiotics exerted a statistically significant reduction in FEV1%. **Conclusions:** Inhaled antibiotics may be an alternative pathway to inhibit airway inflammation with no more adverse events in patients with NCFB.

1. Introduction

Non-cystic fibrosis bronchiectasis (NCFB) as the outcome of various insults to the lungs is defined as cycles of recurrent infection, local inflammation and bronchial wall damage (Cohen and Sahn 1999). Frequent exacerbation caused by recurrent infection leads to a significant burden of morbidity, health-related quality of life, and socioeconomic cost (Mcdonnell et al. 2014). So treatment of the known underlying cause and control of recurrent infections were effective in the management of NCFB.

Long-term antibiotics offer a therapeutic option in bronchiectasis. The chronic nature of the infections in this disease provides the rationale for using aerosolized antibiotics, which can maximize the concentration of antimicrobial delivered into the airway while minimizing systemic side-effects (Martínez et al. 2011). Some authors (Yang et al 2015; Vendrell et al. 2015) have reported the efficacy of inhaled antibiotics on patients with NCFB, however, there are inconsistent conclusions remaining. In this meta-analysis we evaluated the efficacy and safety of inhaled antibiotics on patients with NCFB based on more included studies.

2. Investigations and results

2.1. Study identification and selection

According to the specified search strategy, 245 articles were retrieved. After screening by inclusion and exclusion criteria, 12 articles (Haworth et al. 2014; Barker et al. 2014; Couch 2001; Murray et al. 2011; Wilson et al. 2013; Serisier et al. 2013; Bilton et al. 2006; Wong et al. 2012; Orriols et al. 1999; Antoniu and Azoicai 2013; Barker et al. 2000; Drobnic et al. 2005) were eventually included in this review. Reasons for exclusion of articles are shown in Fig. 1.

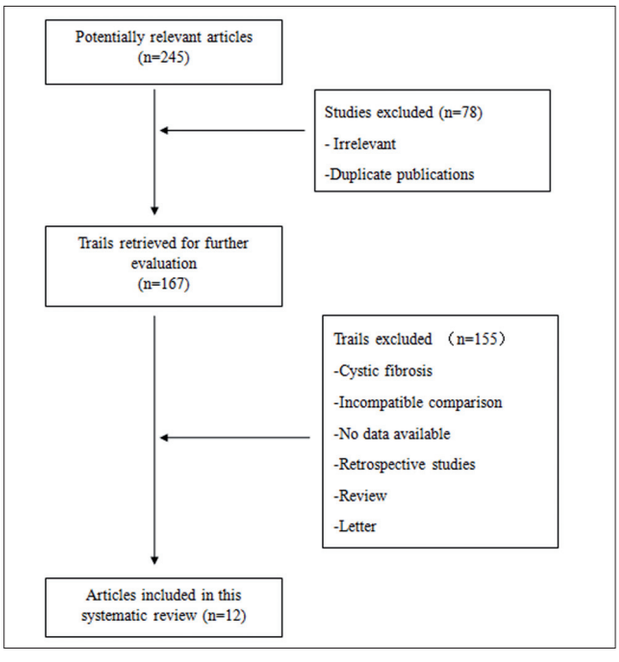

Fig. 1: Flow diagram of study selection

2.2. Characteristics of included studies

As shown in Table 1, 12 articles designed as RCTs involving 1154 patients were included in our review. Of all studies included, tobramycin was used as experimental control in 4 studies, which was the most commonly used inhaled antibiotic. Ciprofloxacin was used in 3 studies as experimental group. Polymyxin, gentamicin, aztreonam, azithromycin, combined medication of ceftazidime with tobramycin were used as experimental group only once. Placebo or symptomatic treatments were used as control groups in all studies.

Table: Characteristics of included studies

Study ID	Number of patients (n,T/C)	Male (n, T/C)	The average age (years T/C)	Interventions		Frequency	Duration
				T	C		
Antoniu and Azoicai (2013)	60/64	NA	64.7/61.4	Ciprofloxacin 50 mg	Placebo	Twice daily	4 weeks
Barker et al. (2000)	37/37	14/15	66.6/63.2	Tobramycin 300 mg	Placebo	Twice daily	4 weeks
Barker et al. (2014)	134/132	50/35	64.2/64.9	Aztreonam 75 mg	Placebo	Three-times daily	4 weeks
Bilton et al. (2006)	26/27	6/9	61.9/63.7	Tobramycin 300 mg	Placebo	Twice daily	2 weeks
Couch (2001)	37/37	NA	NA	Tobramycin 300 mg	Placebo	Twice daily	4 weeks
Drobnic et al. (2005)	20/20	NA	64.5/64.5	Tobramycin 300 mg	Placebo	Twice daily	6 months
Haworth et al. (2014)	73/71	27/34	58.3/60.3	Polymyxin 10000 IU	0.45% sodium chloride 1 ml	Twice-daily	6 months
Murray et al. (2011)	27/30	9/15	58/64	Gentamicin 80 mg	0.9% saline 5 ml	Twice daily	12 months
Orriols et al. (1999)	7/8	6/4	62/61.4	Ceftazidime 1000 mg+ tobramycin 100 mg	Symptomatic treatment	Twice daily	12 months
Serisier et al. (2013)	20/22	10/9	70/59.5	Ciprofloxacin	Placebo	Once-daily	4 weeks
Wilson et al. (2013)	60/64	21/21	64.7/61.4	Ciprofloxacin DPI 32.5 mg	Placebo	Twice daily	4 weeks
Wong et al. (2012)	71/70	23/20	60.9/59	Azithromycin 500 mg	Placebo	Three times a week	6 months

T: test group; C: control group; NA: data not available

2.3. Quality assessment

As shown in Fig. 2, bias risk assessment was evaluated by Revman 5.3 in seven aspects. Each of the components was classified as "low risk", "unclear" and "high risk" according to "yes", "unclear"and "no" in relevant aspect respectively.

2.4. Efficacy

2.4.1. Reduction of sputum bacterial density

As shown in Fig. 3, five studies reported the effect of inhaled antibiotics on sputum bacterial density (log_{10} CFU·g^{-1}) and five trials reported reduction of *P. aeruginosa* density in sputum (log_{10} CFU·g^{-1}). The meta-analysis of five studies showed that inhaled antibiotics produced a greater reduction in sputum bacterial density than placebo [WMD = 2.86, 95% CI (1.73- 4.00), P <0.00001]. Reduction of sputum *P. aeruginosa* density was also significantly different in inhaled antibiotics compared with control groups [WMD = 3.12, 95% CI (1.48- 4.76), P =0.0002].

2.4.2. Eradication of sputum P. aeruginosa

As shown in Fig. 4, six studies compared the eradication of sputum *P. aeruginosa* by inhaled antibiotics with control groups. Inhaled antibiotics achieved a higher eradication of *P. aeruginosa* than placebo [RR = 2.35, 95% CI (1.62- 3.42), P <0.00001].

2.4.3. Exacerbation

As shown in Fig. 5, eight trials compared exacerbation and six studies reported exacerbation requiring systematic antibiotics between inhaled and control groups. No differences were found in exacerbation [RR 0.84, 95% CI 0.68-1.04, P=0.011] and exacerbation requiring systematic antibiotics [RR 0.95, 95% CI 0.79-1.16, P=0.63].
Four studies discussed time to exacerbation in inhaled antibiotics and control groups. Longer time to exacerbation was found in treatment groups [WMD 86.34, 95% CI 30.34-142.33, P=0.003].

2.4.4. Pulmonary function

As shown in Fig. 6, eight studies reported effect of inhaled antibiotics on pulmonary function. No difference was found in FEV1(L) in treatment groups compared with control groups, however, inhaled antibiotics decreased FEV1(%) [WMD -2.26, 95% CI -2.66- -1.87, P<0.00001]. Subgroup analysis showed no statistically significant difference in FEV1 (L) and FEV1 (%) between inhaled antibiotics and control groups in any duration.

2.4.5. Systemic inflammation

As shown in Fig. 7, four studies reported effect of inhaled antibiotics on change in CRP from baseline. It demonstrated that inhaled antibiotics exerted no statistically significant difference in CRP expression change compared with placebo groups [WMD 1.96, 95% CI 0.85- 3.07, P=0.0005].

2.4.6. Quality of life

As shown in Fig. 8, four studies compared change in SGQR and 6MWT from baseline between inhaled antibiotics groups and control groups. No significant difference was found in SGQR [WMD -1.42, 95% CI -7.45- 4.61, P=0.64] and 6MWT changes [WMD 6.76, 95% CI -9.16- 22.68, P=0.41] between the two groups.

2.5. Safety

2.5.1. Adverse events

As shown in Fig. 9, eight studies reported effects of inhaled antibiotics on any adverse events (AEs) and six studies observed serious AEs induced by inhaled antibiotics. There were no statistically significant differences in AEs [RR 1.01, 95% CI 0.94- 1.09, P=0.77] and serious AEs [RR 1.35, 95% CI 0.94- 1.94, P=0.10] between inhaled antibiotics and control groups.

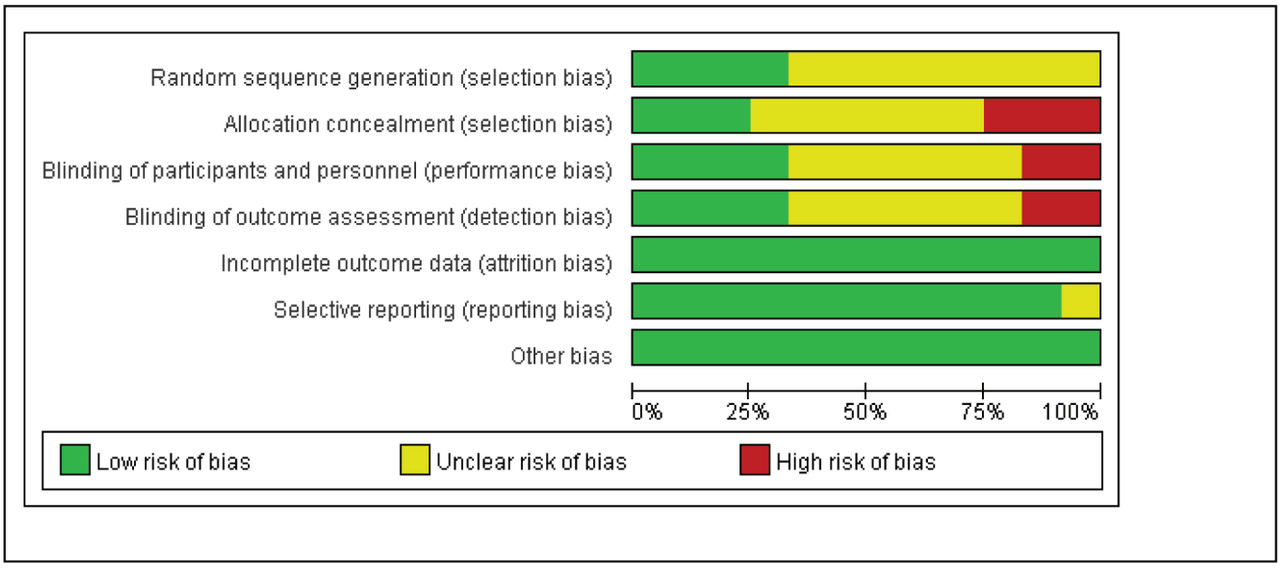

Fig. 2: Risk of bias assessment of included studies

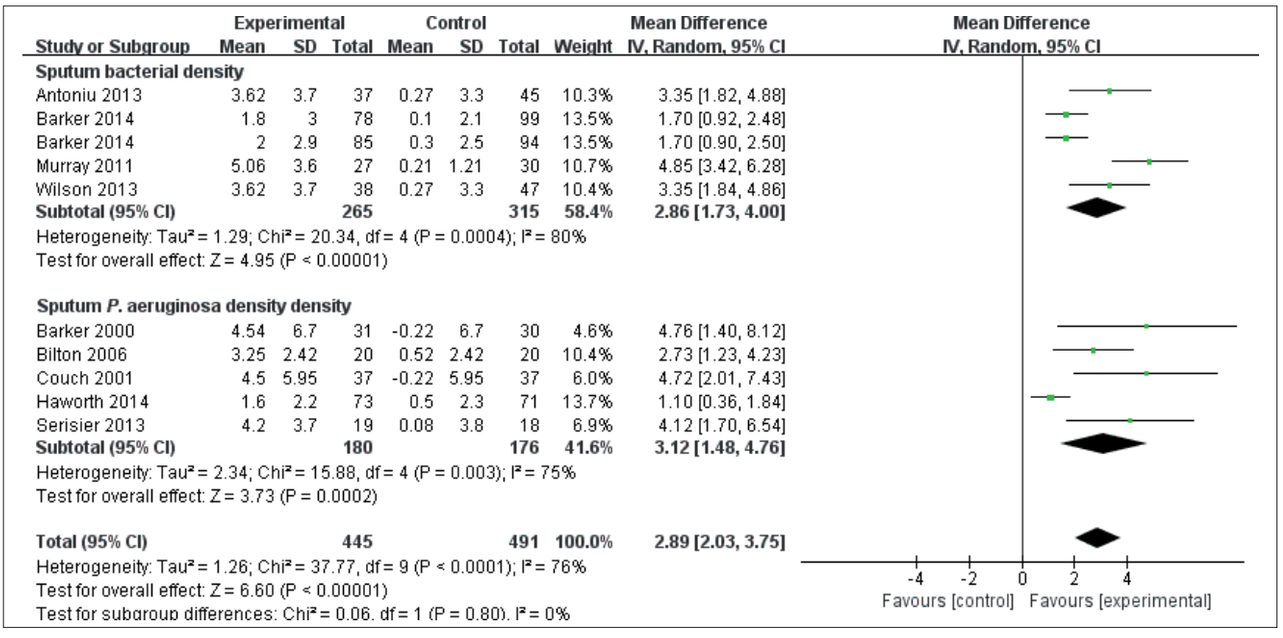

Fig. 3: Effects of inhaled antibiotics on reduction of bacterial density in sputum (log10 CFU•g-1)

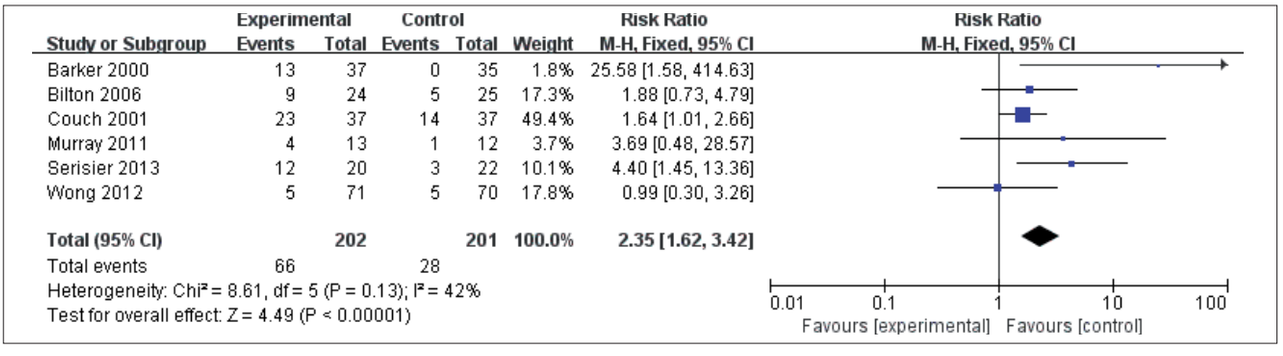

Fig. 4: Effects of inhaled antibiotics on eradication of P. aeruginosa

2.5.2. *Risk of P. aeruginosa resistance*

As shown in Fig. 10, five studies compared the risk of *P. aeruginosa* resistance between inhaled antibiotics and placebo groups. Risk of *P. aeruginosa* resistance did not differ significantly between treatment and control groups [RR 1.35, 95% CI 0.61- 2.96, *P*=0.46].

2.5.3. *Emergence of new pathogens*

As shown in Fig. 11, three trials reported the emergence of new pathogens after inhalation of antibiotics. Inhaled antibiotics significantly reduced the emergence of new pathogens compared with placebo groups [RR 0.62, 95% CI 0.42- 0.92, *P*=0.02].

3. Discussion

Twelve randomized trials involving 1154 participants were included in this systematic review to describe the efficacy and safety of inhaled antibiotics in the treatment of NCFB. It could be shown that inhaled antibiotics are more effective in decreased sputum bacterial density, eradication of *P.* aeruginosa, extended

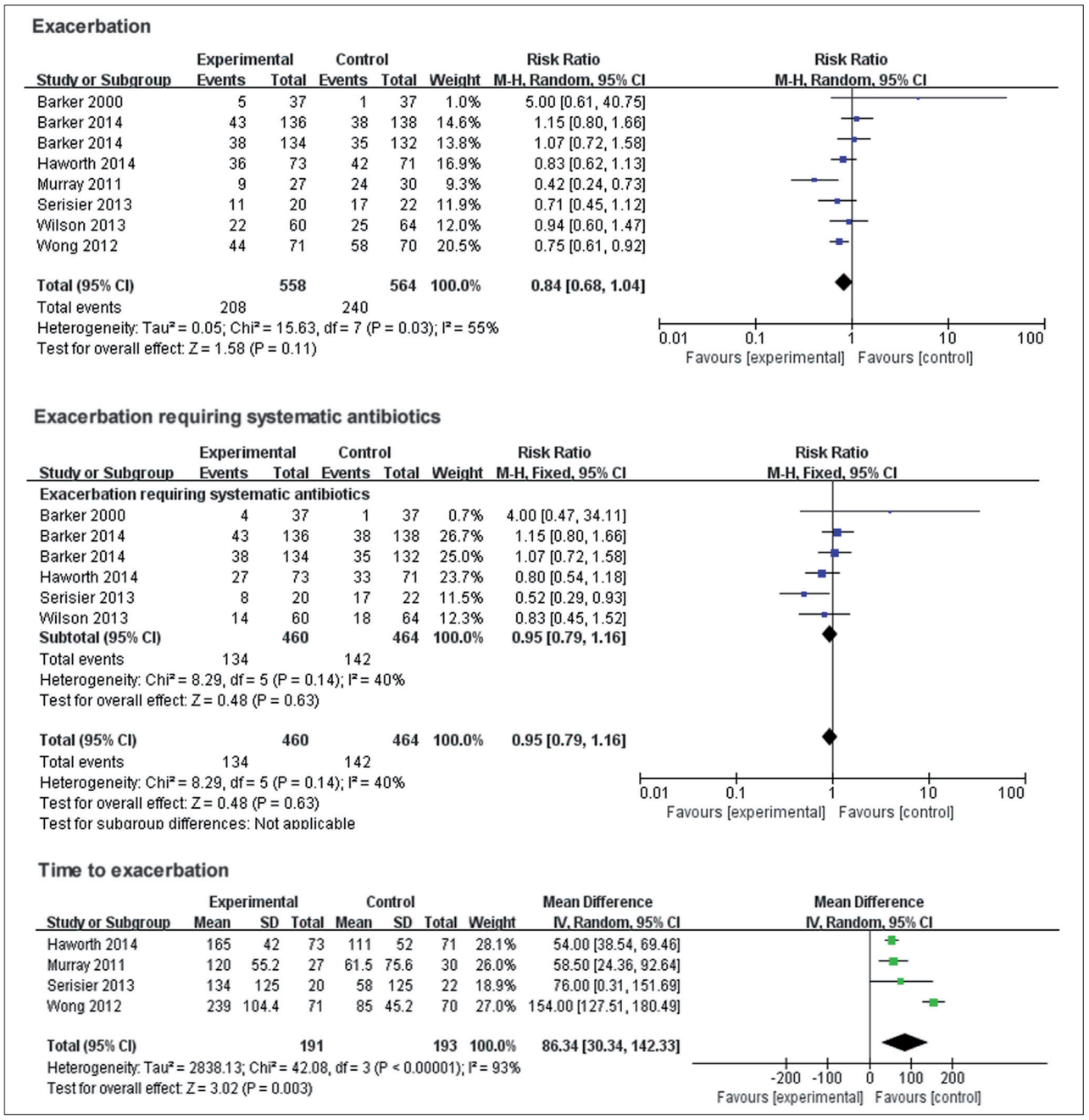

Fig. 5: Effects of inhaled antibiotics on exacerbation

time to exacerbation and reduction of emergence of new pathogens with no more AEs. However, we did not find a significant advantage regarding decreased risk of acute exacerbation, improvement of health-related quality regarding life and reduction of *P. aeruginosa* resistance in inhalation groups. Moreover, inhaled antibiotics exerted a statistically significant reduction in FEV1%.

Exacerbation of NCFB occurs at rates of 1.5~6.5 per patient per year (Pasteur et al. 2010), which is a significant cause of morbidity

in patients with NCFB (Yap 2015). Recurrent exacerbations lead to increased symptoms, a decline in FEV1 (White et al. 2012) and a decreased quality of life. Exacerbation is an independent predictor of mortality (Chalmers et al. 2014). So reducing exacerbations is the object of NCFB management (Altenburg et al. 2015). In our review, there was no significant difference in exacerbation frequency and exacerbation requiring systematic antibiotics between the inhaled antibiotics and control groups, however, the time to exacerbation was prolonged by inhaled antibiotics.

Increase in FEV1

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Increase in FEV1(L)								
Haworth 2014	-0.1	0.45	73	0	0.26	71	17.8%	-0.10 [-0.22, 0.02]
Murray 2011	-0.2	0.65	27	0.01	0.22	30	15.2%	-0.21 [-0.47, 0.05]
Orriols 1999	-0.1	0.08	7	-0.06	0.2	8	17.4%	-0.04 [-0.19, 0.11]
Serisier 2013	-0.05	0.12	20	0	0.1	22	18.4%	-0.05 [-0.12, 0.02]
Wong 2012	-0.02	0.17	71	-0.06	0.17	70	18.5%	0.04 [-0.02, 0.10]
Subtotal (95% CI)			**198**			**201**	**87.4%**	**-0.04 [-0.11, 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 8.98, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 1.10 (P = 0.27)								
Increase in FEV1(%)								
Barker 2000	-2.2	19.4	37	1.5	19.4	37	0.1%	-3.70 [-12.54, 5.14]
Drobnic 2005	-3.5	0.82	20	-1.2	0.4	20	12.0%	-2.30 [-2.70, -1.90]
Murray 2011	-2.9	18.23	27	1.9	23.73	30	0.0%	-4.80 [-15.73, 6.13]
Orriols 1999	-0.6	21.68	7	-0.1	19.28	8	0.0%	-0.50 [-21.39, 20.39]
Wilson 2013	0.06	8.36	60	-0.4	10.06	64	0.5%	0.46 [-2.79, 3.71]
Subtotal (95% CI)			**151**			**159**	**12.6%**	**-2.26 [-2.66, -1.87]**
Heterogeneity: Tau² = 0.00; Chi² = 3.07, df = 4 (P = 0.55); I² = 0%								
Test for overall effect: Z = 11.20 (P < 0.00001)								
Total (95% CI)			**349**			**360**	**100.0%**	**-0.34 [-0.57, -0.11]**
Heterogeneity: Tau² = 0.07; Chi² = 134.70, df = 9 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 2.86 (P = 0.004)								
Test for subgroup differences: Chi² = 117.75, df = 1 (P < 0.00001), I² = 99.2%								

Mean Difference IV, Random, 95% CI

-20 -10 0 10 20

Favours [experimental] Favours [control]

Subgroup of increase in FEV1(L)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4W								
Haworth 2014	-0.03	0.4	73	0.02	0.18	71	9.1%	-0.05 [-0.15, 0.05]
Serisier 2013	-0.05	0.12	20	0	0.1	22	20.5%	-0.05 [-0.12, 0.02]
Subtotal (95% CI)			**93**			**93**	**29.6%**	**-0.05 [-0.11, 0.01]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 1.75 (P = 0.08)								
12W								
Haworth 2014	0.01	0.43	73	-0.09	0.34	71	5.8%	0.10 [-0.03, 0.23]
Murray 2011	-0.06	1.2	27	0.07	1.41	30	0.2%	-0.13 [-0.81, 0.55]
Subtotal (95% CI)			**100**			**101**	**6.0%**	**0.09 [-0.03, 0.22]**
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.46 (P = 0.15)								
6 month								
Haworth 2014	-0.14	1.11	27	0.05	1.38	30	0.2%	-0.19 [-0.84, 0.46]
Murray 2011	-0.1	0.45	73	0	0.26	71	6.5%	-0.10 [-0.22, 0.02]
Wong 2012	0	0.18	71	-0.04	0.18	70	26.2%	0.04 [-0.02, 0.10]
Subtotal (95% CI)			**171**			**171**	**32.8%**	**0.01 [-0.04, 0.06]**
Heterogeneity: Chi² = 4.59, df = 2 (P = 0.10); I² = 56%								
Test for overall effect: Z = 0.40 (P = 0.69)								
12 month								
Murray 2011	-0.2	0.65	27	0.01	0.22	30	1.4%	-0.21 [-0.47, 0.05]
Orriols 1999	-0.1	0.08	7	-0.06	0.2	8	4.1%	-0.04 [-0.19, 0.11]
Wong 2012	-0.02	0.18	71	-0.06	0.18	70	26.2%	0.04 [-0.02, 0.10]
Subtotal (95% CI)			**105**			**108**	**31.6%**	**0.02 [-0.04, 0.07]**
Heterogeneity: Chi² = 4.11, df = 2 (P = 0.13); I² = 51%								
Test for overall effect: Z = 0.68 (P = 0.50)								
Total (95% CI)			**469**			**473**	**100.0%**	**0.00 [-0.03, 0.03]**
Heterogeneity: Chi² = 14.94, df = 9 (P = 0.09); I² = 40%								
Test for overall effect: Z = 0.02 (P = 0.99)								
Test for subgroup differences: Chi² = 5.81, df = 3 (P = 0.12), I² = 48.4%								

Mean Difference IV, Fixed, 95% CI

-0.5 -0.25 0 0.25 0.5

Favours [experimental] Favours [control]

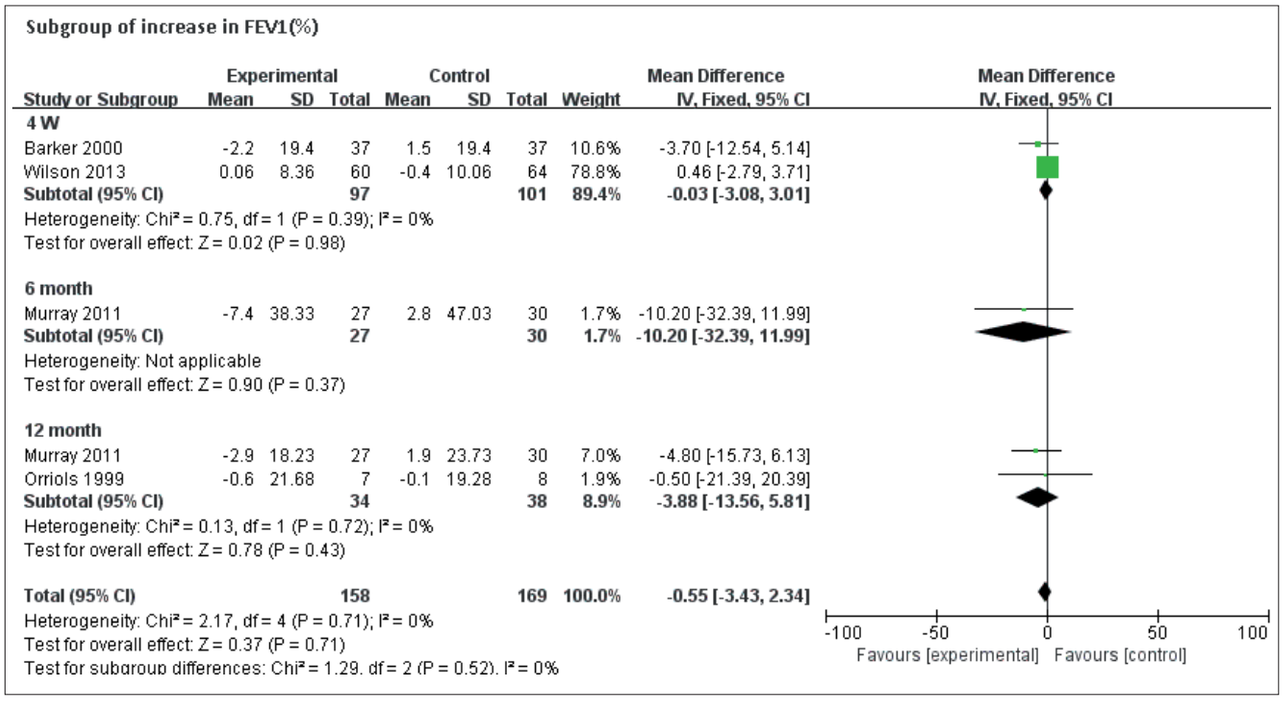

Fig. 6: Effects of inhaled antibiotics on pulmonary function

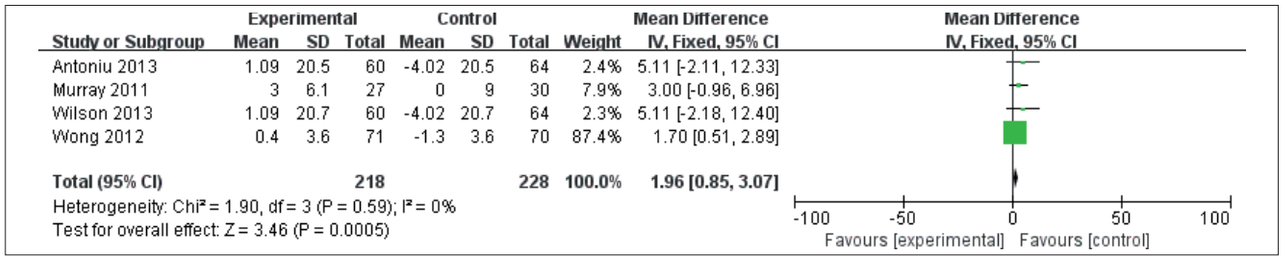

Fig. 7: Effects of inhaled antibiotics on CRP expression

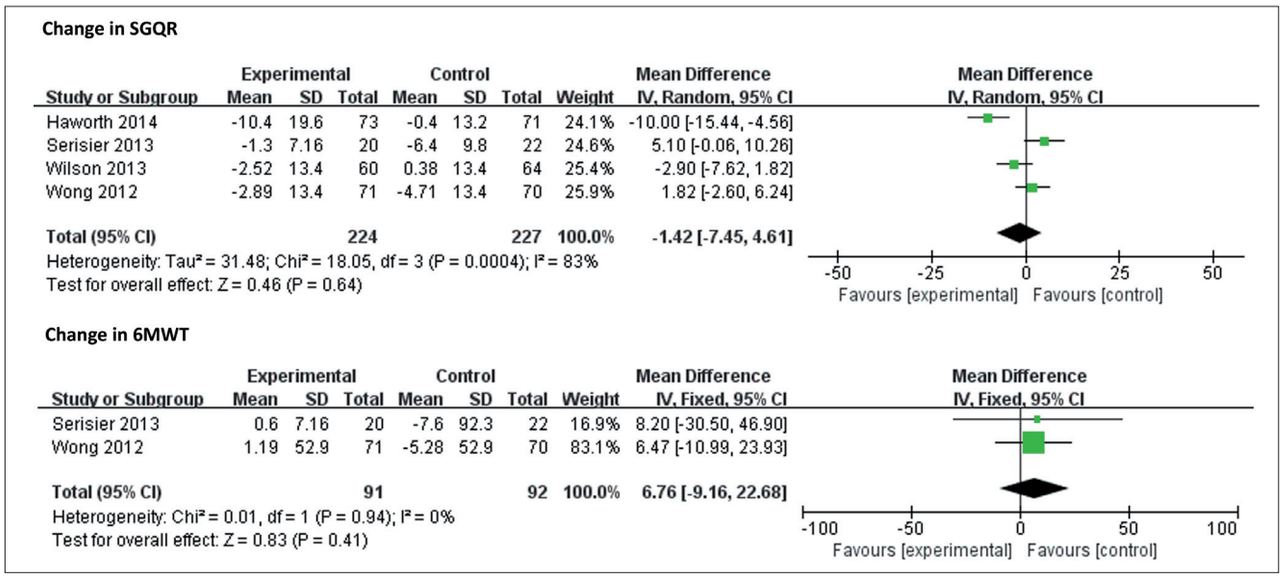

Fig. 8: Effects of inhaled antibiotics on quality of life

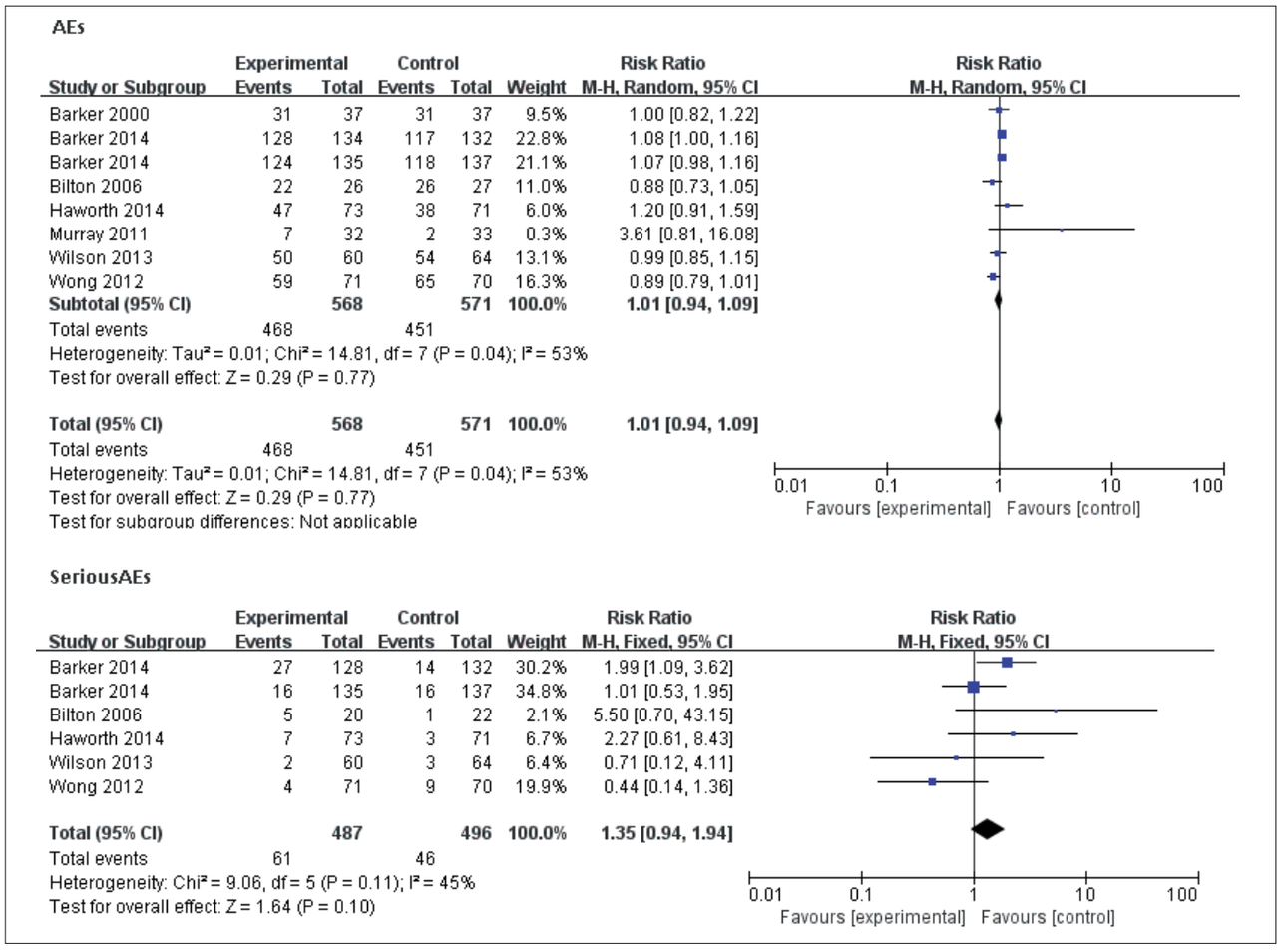

Fig. 9: Effects of inhaled antibiotics on adverse events

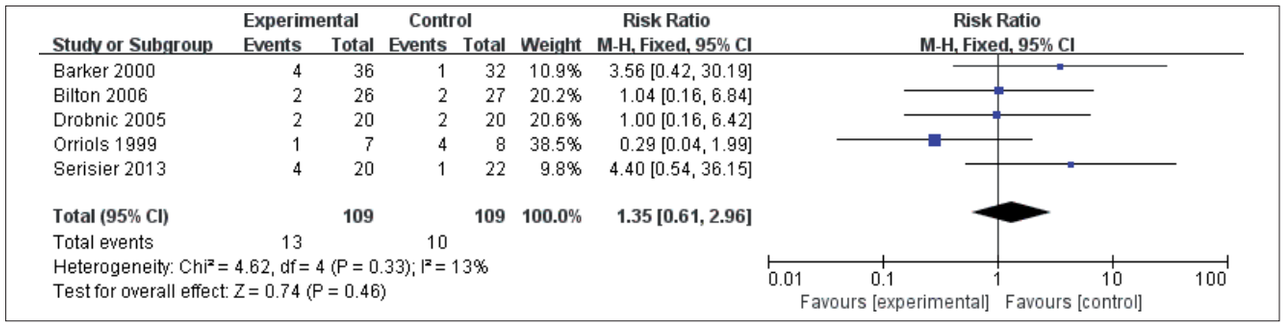

Fig. 10: Effects of inhaled antibiotics on risk of P. aeruginosa resistance

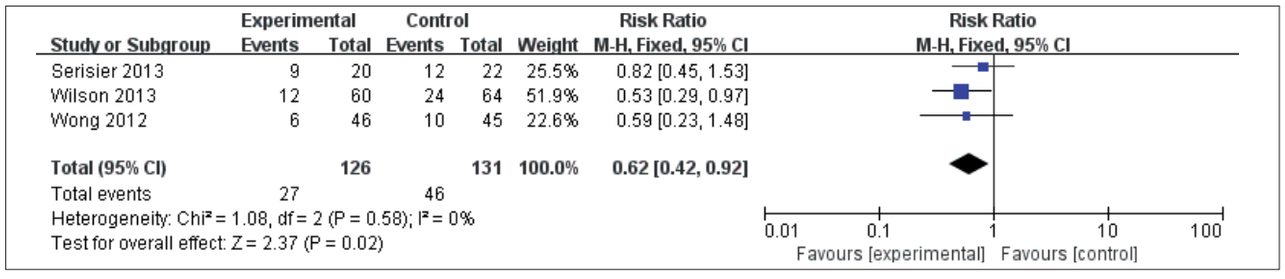

Fig. 11: Effects of inhaled antibiotics on emergence of new pathogens

More than a half of bronchiectasis patients are commonly infected with pathogens, even in clinically stable periods (Angrill et al. 2002). Bacterial load is related to severe systemic inflammation and increased exacerbation (Chalmers et al. 2012). The most common isolated pathogens in bronchiectatic patients are *Pseudomonas aeruginosa, Haemophilus influenza, Streptococcus puneumoniae, Staphylococcus aureus*, and *Moraxella catarrhalis*. 24 to 33% bronchiectatic patients are infected with *P. aeruginosa* (Bilton 2006), which is related to decreased pulmonary function (Finch et al. 2015). Reduction of the bacterial burden in the airways may relieve inflammation, decrease exacerbation, and improve health-related quality of life. This systematic review showed that inhaled antibiotics significantly reduce sputum bacterial density (2.86 $\log_{10}$ CFU•g^{-1}), especially *P. aeruginosa* density (3.12 $\log_{10}$ CFU•g^{-1}). Different to previous reports, a reduction in FEV1% pred was found under antibiotic treatment. However, a reduction of 2.26% in FEV1% may not be clinically relevant. Subgroup analysis showed that there was no difference in FEV1 or FEV1% pred between inhalation and control groups in any duration. Further studies are needed to elucidate the effect of inhaled antibiotics on lung function.

The potential for development of antimicrobial resistance is inherent to any antibiotic therapy, particularly when used as a chronic maintenance therapy (Serisier et al. 2013). Fortunately, inhaled antibiotics did not increase resistance of *P. aeruginosa* in our review. Furthermore, we found that inhalation of antibiotics decreased the emergence of new pathogens compared with placebo group.

Our review suggests that inhaled antibiotics have an acceptable safety profile. No difference was found in AEs and serious AEs between inhaled antibiotics and placebo groups. The most commonly reported adverse events were bronchospasm, cough and haemoptysis, which were low throughout the period of treatment (Brodt et al. 2014).

Limitations should be considered when interpreting the presented results of this systematic review. Firstly, in a few articles, direct descriptions on standard deviation were not applied, they were calculated based on 95% CI and *P* value. This may lead to a little bias on final results. Secondly, medication compliance was not assessed in this meta-analysis. Finally, the underlying reasons of adverse events of inhaled antibiotics were not elucidated.

In conclusion, inhaled antibiotics may be useful to inhibit airway inflammation, extend time to exacerbation and reduce new pathogens with no more adverse events and *P. aeruginosa* resistance in patients with NCFB.

4. Experimental

4.1. Study selection

Pubmed, Cochrane library, Embase, Elsevier, OVID, Springerlink, Web of knowledge and NEJM were searched from inception to April 2015. The search strategy was used as follows: (inhaled or neublized or aerosolized or inhalation or nebulization) and (antibiotics or antibacterial or anti-bacterial or antimicrobial) and (bronchiectasis or non-cystic fibrosis bronchiectasis or chronic bronchial infection)

4.2. Inclusion criteria:

1) Studies designed as randomized control trails (RCTs); 2) adult patients with NCFB; 3) inhaled antibiotics used as intervention; 4) placebo or symptomatic treatment used as control; 5) outcomes at least one of the measures including reduction of sputum bacterial density, eradication of *P.* aeruginosa, exacerbation, pulmonary function, markers of systemic inflammation, quality of life, adverse events, risk of *P*. aeruginosa resistance, emergence of new pathogens.

4.3. Exclusion criteria:

1) Retrospective cohort studies; 2) patients diagnosed of cystic fibrosis; 3) incompatible comparison; 4) review; 5) letter.

4.4. Data extraction and quality assessment

Two investigators independently extracted data from the included studies and then assessed the risk of bias for RCTs according to the recommendations of the Cochrane Collaboration. Any disagreement between the two investigators about data extraction was resolved by discussion.

4.5. Statistical analysis

Meta-analysis was performed by Revman 5.3. Weighted mean difference (WMD) and 95% confidence intervals were used to measure continuous outcomes. Dichotomous data were synthesized using risk ratios and 95% confidence intervals. Heterogeneity was measured by I^2. I^2 >50% indicates significant heterogeneity. Mantel-Haenszel fixed-effects model was used when no heterogeneity was found. Conversely, random-effect model was applied [Review Manager Version (Revman) 5.3]

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