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[Intervention Review]

Inhaled corticosteroids for bronchiectasis

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ABSTRACT

Background

Bronchiectasis is being increasingly diagnosed and recognised as an important contributor to chronic lung disease in both adults and children in high- and low-income countries. It is characterised by irreversible dilatation of airways and is generally associated with airway inflammation and chronic bacterial infection. Medical management largely aims to reduce morbidity by controlling the symptoms, reduce exacerbation frequency, improve quality of life and prevent the progression of bronchiectasis. This is an update of a review first published in 2000.

Objectives

To evaluate the efficacy and safety of inhaled corticosteroids (ICS) in children and adults with stable state bronchiectasis, specifically to assess whether the use of ICS: (1) reduces the severity and frequency of acute respiratory exacerbations; or (2) affects long-term pulmonary function decline.

Search methods

We searched the Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Register of trials, MEDLINE and Embase databases. We ran the latest literature search in June 2017.

Selection criteria

All randomised controlled trials (RCTs) comparing ICS with a placebo or no medication. We included children and adults with clinical or radiographic evidence of bronchiectasis, but excluded people with cystic fibrosis.

Data collection and analysis

We reviewed search results against predetermined criteria for inclusion. In this update, two independent review authors assessed methodological quality and risk of bias in trials using established criteria and extracted data using standard pro forma. We analysed treatment as 'treatment received' and performed sensitivity analyses.

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Main results

The review included seven studies, involving 380 adults. Of the 380 randomised participants, 348 completed the studies.

Due to differences in outcomes reported among the seven studies, we could only perform limited meta-analysis for both the short-term ICS use (6 months or less) and the longer-term ICS use (> 6 months).

During stable state in the short-term group (ICS for 6 months or less), based on the two studies from which data could be included, there were no significant differences from baseline values in the forced expiratory volume in the first second (FEV_1) at the end of the study (mean difference (MD) -0.09, 95% confidence interval (CI) -0.26 to 0.09) and forced vital capacity (FVC) (MD 0.01 L, 95% CI -0.16 to 0.17) in adults on ICS (compared to no ICS). Similarly, we did not find any significant difference in the average exacerbation frequency (MD 0.09, 95% CI -0.61 to 0.79) or health-related quality of life (HRQoL) total scores in adults on ICS when compared with no ICS, though data available were limited. Based on a single non-placebo controlled study from which we could not extract clinical data, there was marginal, though statistically significant improvement in sputum volume and dyspnoea scores on ICS.

The single study on long-term outcomes (over 6 months) that examined lung function and other clinical outcomes, showed no significant effect of ICS on any of the outcomes. We could not draw any conclusion on adverse effects due to limited available data.

Despite the authors of all seven studies stating they were double-blind, we judged one study (in the short duration ICS) as having a high risk of bias based on blinding, attrition and reporting of outcomes. The GRADE quality of evidence was low for all outcomes (due to non-placebo controlled trial, indirectness and imprecision with small numbers of participants and studies).

Authors' conclusions

This updated review indicates that there is insufficient evidence to support the routine use of ICS in adults with stable state bronchiectasis. Further, we cannot draw any conclusion for the use of ICS in adults during an acute exacerbation or in children (for any state), as there were no studies.

PLAIN LANGUAGE SUMMARY

Role of inhaled corticosteroids (ICS) in the management of bronchiectasis

Background

Bronchiectasis is a lung disease. People with bronchiectasis often experience long-term symptoms such as productive or wet cough, repeated flare-ups (exacerbations) and poor quality of life. People with bronchiectasis have airway inflammation and many have asthma-like symptoms (such as cough and wheeze). Because of this, inhaled corticosteroids (ICS), commonly used in asthma, might also improve symptoms, reduce flare-ups and/or reduce worsening of lung function for people with bronchiectasis. However, routine use of ICS may also cause unwanted side effects.

Review question

What are the benefits of using ICS regularly in the management of adults and children with bronchiectasis?

Study characteristics

We included studies that compared ICS with no ICS, or with a placebo (i.e. a medication made to look the same as ICS but with no active ingredients). We only included studies where it was decided at random who would receive ICS and who would not. The participants included in the seven studies were 380 adults who had bronchiectasis diagnosed by symptoms or from a detailed lung scan (computed tomography (CT)). We did not include studies that involved participants with cystic fibrosis, which can also cause bronchiectasis. Although we planned to include studies involving children with bronchiectasis, we did not find such studies.

What evidence did we find?

From available evidence up to June 2017, we found seven eligible studies involving adult participants that examined the role of ICS in bronchiectasis. The adults had stable bronchiectasis - they were not having a flare-up at the start of the study.

We were able to include results from two studies that gave ICS for less than six months to adults with stable bronchiectasis. ICS did not make a difference to lung function, number of exacerbations during the study or quality of life. In a different study, which also

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gave ICS for less than six months, we found a small reduction in sputum (phlegm) and improvement in breathlessness. However, as these results were from a study which did not use a placebo we cannot be certain about them.

The single study on long-term use of ICS (i.e. for over 6 months) showed no meaningful benefit of ICS for any of the outcomes.

There were no studies conducted when the participants were having a flare-up of their bronchiectasis. There were also no studies that involved children with bronchiectasis. Importantly, we do not know if ICS are linked to more unwanted side effects, because the studies did not provide much information about this.

Conclusion

The review found that there is not enough evidence for the routine use of ICS in adults with stable bronchiectasis. We can make no conclusions about the use of ICS for flare-ups of bronchiectasis, or about their use in children, because we did not find any studies.

Quality of evidence

Overall, we judged the quality of evidence to be low. We were concerned because the largest study, which showed some benefits, did not use a placebo. This means that participants and staff in the study would have known who was getting ICS and who was not, which could affect the results. Also, our confidence was reduced because we only found a small number of studies to include in our review and some of the studies may have included people with other types of lung disease, in addition to bronchiectasis.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Inhaled corticosteroids compared to placebo for bronchiectasis (< 6 months)

Patient or population: people with bronchiectasis
Setting: university hospital
Intervention: inhaled corticosteroids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Inhaled corticosteroids				
Lung function (spirometry indices) - FEV_1 (in L, end study minus baseline values)	Mean change from baseline ranged from -0.038 to 0.805	MD 0.09 lower (0.26 lower to 0.09 higher)	-	156 (2 studies)	⊕⊕◯◯ Low[1,2,3]	
Lung function (spirometry indices) - FVC (in L, end study minus baseline values)	Mean change from baseline ranged from -0.062 to 0.0218	MD 0.01 higher (0.16 lower to 0.17 higher)	-	156 (2 studies)	⊕⊕◯◯ Low[1,2,3]	
Lung function (other indices) - diffusion capacity % predicted (end of study)	Mean end of study value 84.2	MD 2.70 higher (2.49 lower to 7.89 higher)	-	57 (1 study)	⊕⊕◯◯ Low[1,2,3]	
Lung function (other indices) - RV % predicted (end of study values)	Mean end of study value 106	MD 2.00 higher (9.41 lower to 13.41 higher)	-	57 (1 study)	⊕⊕◯◯ Low[1,2,3]	
Lung function (other indices) - TLC % predicted (end of study values)	Mean end of study value 86.4	MD 3.20 higher (1.99 lower to 8.39 higher)	-	57 (1 study)	⊕⊕◯◯ Low[1,2,3]	

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Average number of exacerbations per participant	Average number of exacerbations per patient ranged from 0.97 to 1.31	MD 0.17 lower (0.56 lower to 0.22 higher)	-	127 (2 studies)	⊕⊕◯◯ Low[1,2,3]
Pseudomonas aeruginosa (*P aeruginosa*) colonisation	410 per 1000	395 per 1000 (238 to 576)	OR 0.94 (0.45 to 1.96)	156 (2 studies)	⊕⊕◯◯ Low[1,2,3]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__CI:__ confidence interval; __FEV$_1$:__ forced expiratory volume in 1 second; __FVC:__ forced vital capacity; __MD:__ mean difference; __OR:__ odds ratio; __RV:__ residual volume; __TLC:__ total lung capacity

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]The largest study was not a placebo controlled trial (Martinez-Garcia 2006).
[2]Study participant numbers are small; outcome downgraded one point for imprecision.
[3]One study had an issue with directness (Joshi 2004), but did not contribute to this outcome.

BACKGROUND

Description of the condition

Bronchiectasis, previously termed an 'orphan disease' is increasingly recognised as a major cause of respiratory morbidity, especially in low-income countries (Karadag 2005; Karakoc 2001), and in some ethnic populations of affluent countries (Chang 2002; Edwards 2003; Singleton 2000). More recently, it has also been increasingly reported from some high-income countries (Sanchez-Munoz 2016). Bronchiectasis is the end result of a variety of airway insults and predisposing conditions that culminate in airway injury, recurrent or persistent airway infection and destruction (Chang 2010). The underlying aetiology of bronchiectasis varies from being a consequence of recurrent respiratory infections to rare immune deficiencies. Other causes include primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis and mycobacterial infection (Olveira 2017; Shoemark 2007). A common feature of most patients is the impaired local and/or systemic host defences to infection.

The dominant symptoms and signs of bronchiectasis are productive or wet cough, dyspnoea on exertion and presence of other respiratory signs (clubbing, chest wall deformity, respiratory noises such as wheeze or crepitations on auscultation). In the long-term, pulmonary function decline may occur (Keistinen 1997; Twiss 2006). In studies involving both children and adult cohorts, asthma-like symptoms in people with bronchiectasis have been described and when present, are associated with accelerated pulmonary function decline when compared to those with bronchiectasis, but without asthma-like symptoms (Field 1969; Keistinen 1997).

Like people with chronic obstructive pulmonary disease (COPD) and cystic fibrosis, children and adults with bronchiectasis also suffer from recurrent acute exacerbations, some of whom require hospitalised treatment. Pulmonary exacerbations present with a worsening of the baseline clinical state (Kapur 2012a), and are associated with increased morbidity (Kapur 2009), progressive deterioration in lung function (Ellerman 1997; Kapur 2010), and poor quality of life in both adults and children with bronchiectasis (Kapur 2012; Wilson 1997). Effective management regimes for bronchiectasis would reduce the frequency or severity of respiratory exacerbations, and/or the long-term pulmonary function decline.

The hallmarks of bronchiectasis are stasis of infected airway secretions; reduced airway mucus clearance; and regional or diffuse airway wall dilatation, thickening and destruction with loss of airway structural integrity (Mandal 2013). Based on Cole's 'vicious circle hypothesis', microbial colonisation/infection is important in the pathophysiology of bronchiectasis, as it leads to bronchial obstruction and a normal or exaggerated inflammatory response (Cole 1986). As in COPD, chronic airway obstruction and bronchial hyper-responsiveness is known to occur in bronchiectasis. A variety of proinflammatory airway cells such as neutrophils, lymphocytes, macrophages and eosinophils have been implicated in the pathogenesis of both bronchiectasis and COPD (Mandal 2013; Kim 2008).

Although inflammation is considered an important driver of bronchial hyper-responsiveness and airway instability in airway diseases such as COPD and asthma (Berend 2008), evidence directly implicating it in bronchial hyper-responsiveness in bronchiectasis is unclear. Since bronchiectasis involves similar airway inflammatory mediators, suppression of this inflammatory process could potentially slow the rate of airway damage.

Description of the intervention

The anti-inflammatory effect of corticosteroids on the airways has been well documented in inflammatory airway diseases, such as asthma (Booth 1995), and COPD (Renkema 1996; Sobieraj 2008). Inhaled preparation of corticosteroids provide a non-specific, local anti-inflammatory effect with minimal systemic side effects. ICS are available as metered dose inhalers, dry powder devices or nebulised, and can be used for short or long durations. Short duration use of ICS likely has different effects compared to longer-term ICS use for our primary outcome of interest (lung function), as well as for other adverse event outcomes, such as bone metabolism (Kerstjens 1994), and children's growth (Pruteanu 2014), further discussed in the last paragraph of the 'Data synthesis' section.

Inhaled corticosteroids (ICS) are beneficial in some (but not all) people with COPD (Ernst 2015). However, use of ICS is associated with adverse events in children and adults that range from mild (candidiasis) to serious (adrenal insufficiency (Holme 2008), osteoporosis, cataracts, pneumonia) events. Recent evidence indicates increased risk of pneumonia and lower respiratory tract infections with use of ICS in adults with COPD (Wang 2016). Since bronchiectasis involves similar disruption of the host airway defences, it is plausible that this cohort is also at higher risk of respiratory infections with the use of ICS.

How the intervention might work

Airway eosinophilia and bronchial hyper-responsiveness has been reported in adults (Ip 1991; Tsikrika 2017), and children with bronchiectasis (Goyal 2016; Pizzutto 2013), hence ICS may be potentially beneficial for this group of patients, as ICS is usually efficacious in people with airway eosinophilia.

Why it is important to do this review

The role of ICS in bronchiectasis remains unclear. An update of the original systematic review on the efficacy of ICS in the

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management of children and adults with bronchiectasis (Kapur 2009) could help guide clinical practice.

OBJECTIVES

To evaluate the efficacy and safety of inhaled corticosteroids (ICS) in children and adults with stable state bronchiectasis, specifically to assess whether the use of ICS: (1) reduces the severity and frequency of acute respiratory exacerbations; or (2) affects long-term pulmonary function decline.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) using inhaled corticosteroids (ICS) in patients with bronchiectasis, in comparison to placebo.

Types of participants

Children or adults with bronchiectasis (defined clinically or radiologically) not related to cystic fibrosis.

Types of interventions

All types of ICS.

Types of outcome measures

Primary outcomes

1. Change in objective measures of lung function.

Secondary outcomes

(A) for short-term effectiveness (6 months or less)

1. Mean difference in bronchiectasis severity control (wheeze, dyspnoea, cough diary, etc).
2. Mean of respiratory exacerbations, or hospitalisations per participant, or both.
3. Sputum volume.
4. Mean difference in other objective indices (airway markers of inflammation, exhaled nitric oxide, etc).
5. Mean difference in quality of life indices.
6. Proportions experiencing adverse effects of the intervention, (e.g. pharyngeal candidiasis, voice change, pneumonia, etc).

(B) for medium- to long-term outcomes (greater than 6 months)

1. Clinical indices of bronchiectasis severity control (quality of life, cough diary, Likert scale, visual analogue scale, level of interference of cough, etc).
2. Relevant airway markers of inflammation.
3. Proportions experiencing adverse effects of the intervention, (e.g. adrenal insufficiency, cataracts, linear growth, etc).
4. Frequency of exacerbation per subject.

Search methods for identification of studies

Electronic searches

This is an update of a previous Cochrane Review (Kapur 2009). For this update, we identified studies from the following sources.

1. The Cochrane Airways Group Trials Register (updated June 2017).
2. The Cochrane Central Register of Controlled Trials (CENTRAL; Issue 5, 2016.
3. MEDLINE (1950 to June 2017).
4. Embase (1980 to June 2017).
5. The list of references in relevant publications.
6. Written communication with the study authors of the studies included in the review, when necessary.

For the full database topic search strategies, see Appendix 1. We searched all databases with no restriction on language of publication. We searched the CENTRAL database for handsearched conference abstracts and grey literature.

We also conducted searches of ClinicalTrials.gov (www.ClinicalTrials.gov), and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/), using the search strategy in Appendix 2. We searched all databases from their inception to 5 February 2018, and we imposed no restriction on language of publication.

Searching other resources

We wrote to the lead authors of all the studies included and three study authors replied; we incorporated any information provided.

Data collection and analysis

Selection of studies

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From the title, abstract, or descriptors, two review authors (NK, AC) independently reviewed the literature searches to identify potentially relevant studies for full review. There was no disagreement between the review authors as to which studies should be included. We recorded the selection process in sufficient detail to complete the PRISMA (PRISMA 2009) flow diagram (Figure 1) and Characteristics of excluded studies table.

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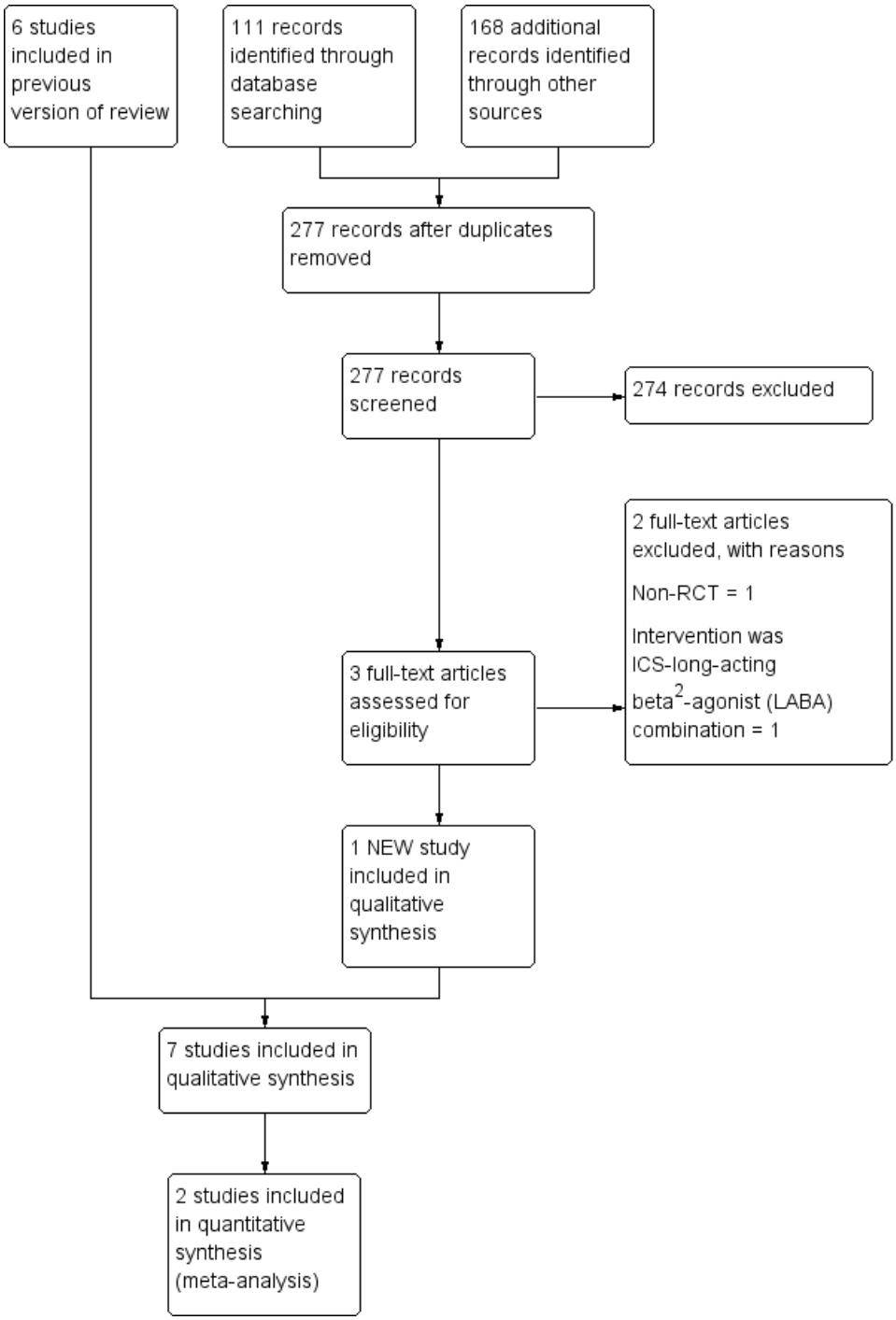
Figure 1. Study flow diagram.



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Data extraction and management

We reviewed studies that satisfied the inclusion criteria and recorded the following information: study setting, year of study, source of funding, participant recruitment details (including number of eligible participants), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, cointerventions, numbers of participants not followed up, reasons for withdrawals from study protocol (clinical, side effects, refusal and other), details on side effects of therapy, and whether intention-to-treat analyses were possible. We extracted data independently on the outcomes described previously. We requested further information from the study authors, but only three responded (Hernando 2012; Joshi 2004; Martinez-Garcia 2006); we incorporated the information received.

Assessment of risk of bias in included studies

We included all assessments in the 'Characteristics of included studies' table. We measured inter-reviewer reliability for the identification of high quality studies for each component using the Kappa statistic. Agreement between the two review authors was excellent (weighted kappa score for quality assessment scores was 0.81).

Two review authors (NK, AC) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreement by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We carried out blinding separately for different key outcomes, where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

The statistical analysis proposed, included calculation of a pooled estimate of treatment effect for each dichotomous outcome across all studies (odds of outcome in participants allocated to receive treatment compared with odds of outcome in participants allocated to control group); and calculation of a pooled estimate of treatment effect for each continuous outcome across all studies in the form of a mean difference (MD). For continuous variables, we recorded mean absolute change from baseline for each group and standard deviation (SD) for each group.

Unit of analysis issues

We used the participant as the unit of analysis.

Dealing with missing data

We sought data on a number of participants with each outcome event listed above, by allocated treatment group in order for us to conduct an intention-to-treat (ITT) analysis. We also contacted the study investigators for clarification and further information where necessary.

Assessment of heterogeneity

We described and tested any heterogeneity between the study results to see if it reached statistical significance using a chi^2 test. We estimated the 95% confidence interval (CI) using a random-effects model whenever there were concerns about statistical heterogeneity.

Assessment of reporting biases

We checked all reports of the included studies to check that all the stated outcomes were reported and the results were presented in the 'Risk of bias table' in the 'Characteristics of included studies' table.

Data synthesis

We calculated odds ratio (OR) using a modified ITT analysis for the dichotomous outcome variables of each individual study. This analysis assumes that participants not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies examined whether pooling of results (meta-analysis) is reasonable. This took into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

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We included results from studies that met the inclusion criteria and reported any of the outcomes of interest in the subsequent meta-analyses. We calculated the summary weighted risk ratio (RR) and 95% CI (fixed-effect model) using Review Manager 5 (Review Manager 2014). For cross-over studies, we calculated mean treatment differences from raw data. We extracted or imputed and entered the date as fixed-effect generic inverse variance outcomes to provide summary weighted differences and 95% CIs. In cross-over trials, we only included data from the first arm in meta-analysis when the data were combined with parallel studies (Elbourne 2002). We calculated numbers needed to treat to benefit (NNTB) were calculated from the pooled OR and applied its 95% CI to a specified baseline risk using an online calculator (Cates 2008). If studies had reported outcomes using different measurement scales, we planned to use the standardised mean difference (SMD).

'Summary of findings' table

We created 'Summary of findings' tables using the following outcomes.

Short-term ICS use ($\leq$ 6 months)

- Lung function indices forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) (in L, end of study minus baseline values)
- Lung function indices diffusion capacity % predicted (end of study values)
- Average number of exacerbations per participant
- *Pseudomonas aeruginosa (P aeruginosa)* colonisation

There are various types of lung function abnormality in people with bronchiectasis (Guan 2014). As this was our primary outcome measure, we included the various indices that reflect these abnormalities.

Longer-term ICS use (> 6 months)

- Lung function indices FEV_1 and FVC (in L, end of study minus baseline values)
- Average number of exacerbations per participant

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contributed data to the meta-analyses for the prespecified outcomes. We then used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

We evaluated the outcomes described above based on short (6 months or less) and long duration (> 6 months) use of ICS, as done previously in our Cochrane Review (Kapur 2009). This arbitrary cut-off is a commonly used time frame in studies (Daniel 2017; Kerstjens 1994; Lee 2012), when evaluating the effects of ICS, as duration of ICS use may impact on clinical and structural pulmonary outcomes (e.g. airway remodelling (Barnes 2010)), and adverse events (e.g. growth (Pruteanu 2014)), and bone metabolism (Kerstjens 1994). Lung function in people with bronchiectasis generally declines slowly over time and as this was our a priori defined primary outcome, the effect of short duration ICS theoretically could differ from longer duration ICS. Outcomes such as bronchial hyper-responsiveness takes months of ICS therapy to plateau (Barnes 2010). An example with respect to adverse events: in the Cochrane Review on the effect of ICS on height in growing children with asthma, the authors found no difference between groups (ICS versus placebo) in the first six months of ICS use, but a significant difference between groups was present in ICS use at the 12 months time point (Pruteanu 2014).

Subgroup analysis and investigation of heterogeneity

We planned the following a priori subgroup analysis.

1. Children (aged 18 years or less) and adults (> 18 years).
2. Dose of ICS; low (< 400 µg), moderate (400 µg to 800 µg), high (> 800 µg) of beclomethasone equivalent.
3. Severity of bronchiectasis (based on lung function).

Sensitivity analysis

We also planned sensitivity analyses to assess the impact of the following potentially important factors on the overall outcomes.

1. Study quality.
2. Variation in the inclusion criteria.
3. Differences in the medications used in the intervention and comparison groups.
4. Analysis using random-effects model.
5. Analysis by 'treatment received'.

RESULTS

Description of studies

Results of the search

For the updated review in 2009 the Airways Group Register identified 341 potentially relevant titles. After assessing the abstracts, we obtained nine papers for consideration for inclusion in the review. We excluded three studies as inhaled corticosteroids (ICS) were not compared to placebo/no treatment or were non-randomised

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studies or included participants with pneumonia (Ghosh 2002; Monton 1999; ONeil 2004; see Characteristics of excluded studies table).

For this 2018 update, we conducted searches from 2011 to 30 June 2017 and the Cochrane Airways Group's Register identified 111 new references; we identified an additional 277 titles through searches of ClinicalTrials.gov (www.ClinicalTrials.gov), and the WHO trials portal (www.who.int/ictrp/en/). After assessing the abstracts, we obtained three articles for consideration to be included in the review; we excluded two studies because ICS was compared to an ICS-long-acting beta^2-agonist (LABA) combination (Martinez-Garcia 2012), or was a non-randomised study (Guran 2008). We included one new study in this update (Hernando 2012) (Figure 1).

Included studies

See Characteristics of included studies and Table 1 'Summary of included studies characteristics'.

We identified one new study for this review update (Hernando 2012), including 77 participants. A total of seven studies met the inclusion criteria for this review update (Elborn 1992; Hernando 2012; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). All included studies identified were published in English. We requested additional data from all study authors but only three authors responded (Hernando 2012; Joshi 2004; Martinez-Garcia 2006), and provided additional data. We also requested data on outcomes at 24 weeks for the Tsang 2005 study as well as the lung function values in actual volumes (instead of percentage predicted) from the study authors.

Study design and population

All seven studies were single centre studies. The studies included participants with bronchiectasis diagnosed on bronchography (Elborn 1992), or high resolution computed tomography (HRCT) of the chest (Hernando 2012; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). All studies excluded participants with cystic fibrosis, with six studies excluding participants with bronchial asthma also (Hernando 2012; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). Participants with allergic bronchopulmonary aspergillosis were also excluded from the Elborn 1992 study and the Martinez-Garcia 2006 study. None of the studies included any children.

The Joshi 2004 and Elborn 1992 studies were cross-over studies and the others were parallel group studies. All were double-blind placebo controlled trials except the Martinez-Garcia 2006 study, which did not use placebo in the control group.

Participants with bronchiectasis were recruited during stable state, defined as "free from exacerbation for four weeks" (Hernando 2012; Joshi 2004; Martinez-Garcia 2006), or "stable 24-hour sputum volume, FEV_1 and FVC" (Tsang 1998; Tsang 2004; Tsang 2005). No study was performed during an acute respiratory exacerbation.

Interventions

Moderate to high doses of ICS were used: budesonide 800 µg/day (Hernando 2012), beclomethasone 800 µg/day (Joshi 2004), beclomethasone 1500 µg/day in the Elborn 1992 study and fluticasone 1000 µg/day (2000 µg/day budesonide equivalent) (Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). The Martinez-Garcia 2006 study had a third arm with inhaled fluticasone 500 µg/day and we combined this data with the 1000 µg/day arm and compared them as a single group with the control group wherever possible.

The study duration ranged from a short duration of four to six weeks in the Elborn 1992, Joshi 2004 and Tsang 1998 studies to six months in the Martinez-Garcia 2006 and Hernando 2012 studies. Two studies were of one year duration (Tsang 2004; Tsang 2005), with visits at four, 12, 24, 36 and 52 weeks.

Outcomes

Lung functions were available as an outcome variable in all studies except the Tsang 2004 study, which reported only fractional exhaled nitric oxide (FeNO) levels. Forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) (in litres or % predicted) were available from all studies. Peak expiratory flow rate (PEFR) was reported in the Elborn 1992, Joshi 2004 and Tsang 1998 studies, with the Martinez-Garcia 2006 and Tsang 1998 studies giving details about total lung capacity, residual volume and diffusion capacity. We did not include spirometric parameters from the Joshi 2004 study in the final analysis since the 'pre-treatment' values were reported for the whole 20 group together and these values were not available separately for the two groups at baseline. We also did not include data from the Tsang 1998 and Tsang 2004 studies in the final analysis, since geometric mean was used instead of arithmetic mean. We did not include any of the data from the Elborn 1992 study, since pre-cross-over data were not available separately.

Clinical parameters of cough, wheeze and dyspnoea were measured differently in different studies. The Elborn 1992 study used a visual analogue scale (VAS) to quantify these symptoms, the Martinez-Garcia 2006 study defined significant cough as that persisting for > 50% of days. Dyspnoea was measured by using the transition dyspnoea index in the Martinez-Garcia 2006 study. The Hernando 2012 study measured cough, sputum production and dyspnoea on a scale of 0 to 3 and combined these three as a total symptom score. Clinical parameters of cough, dyspnoea and wheezing, although reported by the Tsang 2005 study, were not defined properly and we did not include them in the analysis. Twenty-four-hour sputum volume was included as an outcome variable in the Elborn 1992, Martinez-Garcia 2006, Tsang 1998 and Tsang 2005 studies.

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Quality of life was included as an outcome parameter in the Martinez-Garcia 2006 and Hernando 2012 studies, with both using the St. George Respiratory Questionnaire to calculate total scores as well as symptoms, activity and impact score.

The Martinez-Garcia 2006, Tsang 1998 and Tsang 2005 studies defined exacerbation as persistent (> 24 hours) deterioration in at least three respiratory symptoms (including cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain), with or without fever, radiographic deterioration, systemic disturbances, or deterioration in chest signs. The Hernando 2012 study defined exacerbation as worsening of more than 48 hours duration of at least three of the four symptoms of cough, sputum production, dyspnoea and fever.

The study characteristics are described in the 'Characteristics of included studies' table.

Excluded studies

We excluded five studies from the review. The reason for their exclusion is discussed in the 'Characteristics of excluded studies' table. The most common reason for exclusion was the study not being a RCT (two studies).

Risk of bias in included studies

Risk of bias judgements for included studies are summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

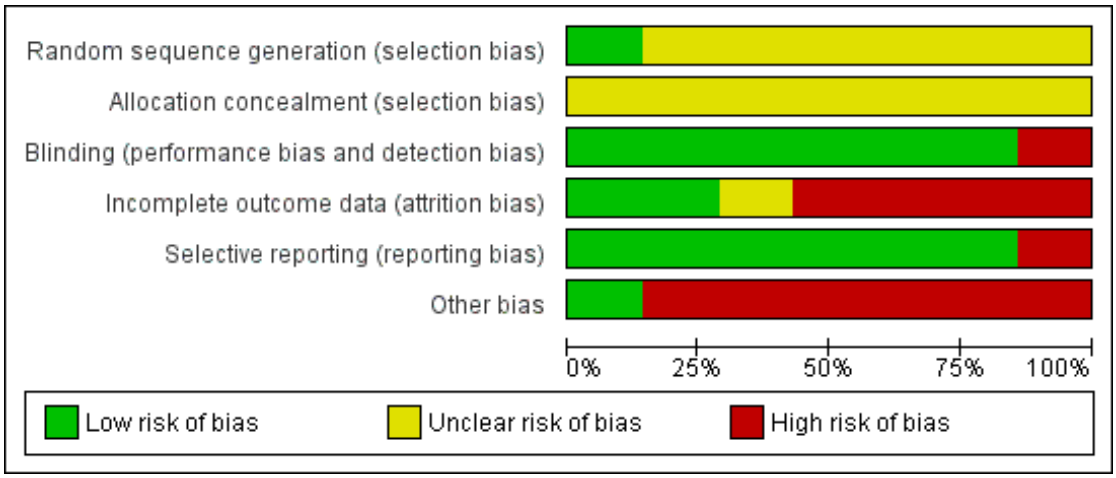

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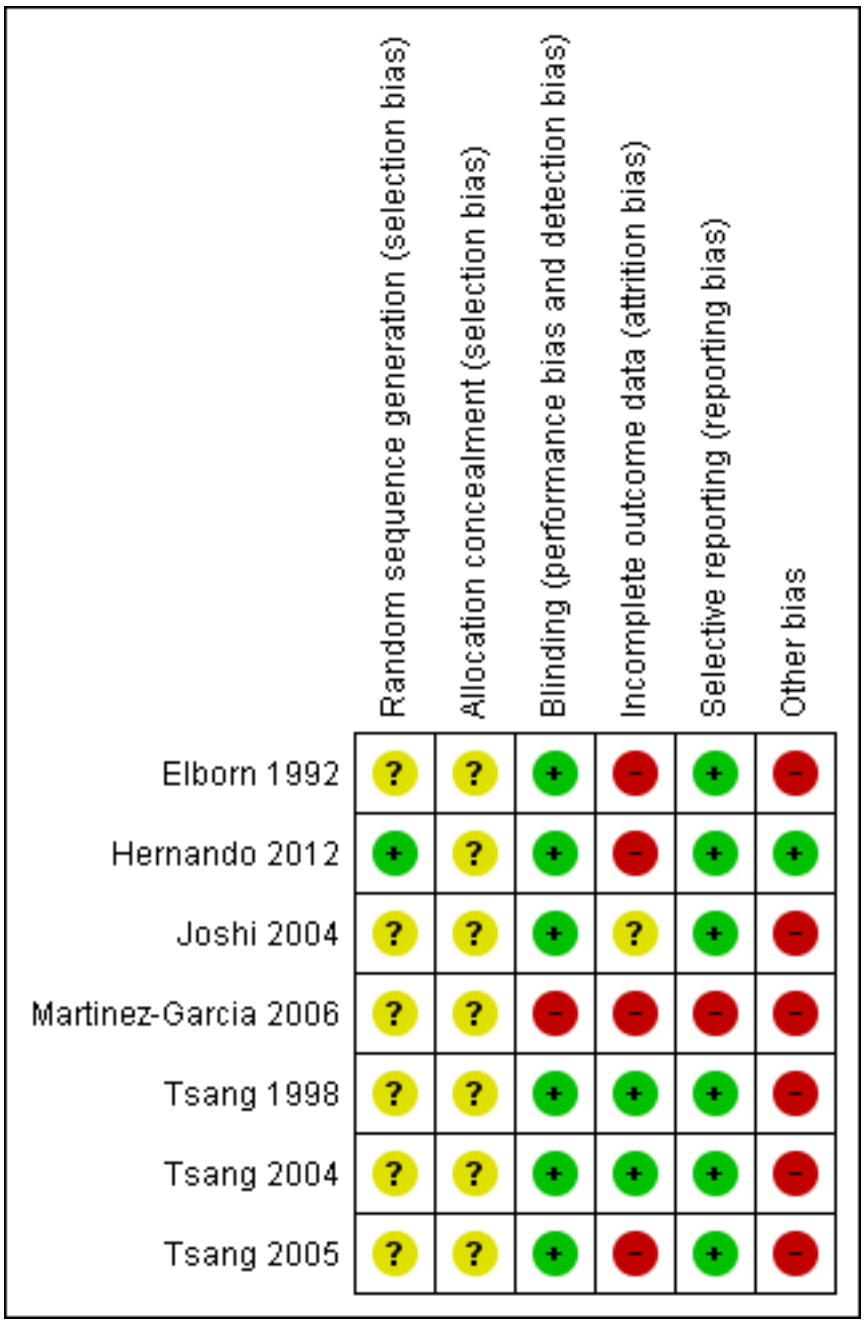
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

The generation of randomisation sequence was not reported in six studies and so we judged risk of bias to be unclear (Elborn 1992; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). Only one study stated how the random sequence was generated and we judged this to have low risk of bias (Hernando 2012). Allocation concealment was unclear in all seven studies (Elborn 1992; Hernando 2012; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005).

Blinding

We judged all studies as low risk as they were double-blind, except Martinez-Garcia 2006, which we judged as high risk as they did not have a placebo arm, and the blinding was done only for comparing two dosages of ICS.

Incomplete outcome data

Two studies reported the progress of all randomised participants in each group (Tsang 1998; Tsang 2004), resulting in low risk of bias, whereas in Joshi 2004, the bias was unclear as there was no mention of withdrawals or dropouts. We judged four studies as high risk of bias as they did not describe where their dropouts occurred (Elborn 1992; Hernando 2012; Martinez-Garcia 2006; Tsang 2005). Furthermore, we could not extract pre-cross-over arm data from Elborn 1992 or include it in any of the meta-analysis. Follow-up was between 80% to 90% in Tsang 2005 and was unclear in Joshi 2004. The remaining studies reported outcomes in > 90% of the participants (Hernando 2012; Martinez-Garcia 2006; Tsang 1998; Tsang 2004).

Selective reporting

We judged six studies to have low risk of bias (Elborn 1992; Hernando 2012; Joshi 2004; Tsang 1998; Tsang 2004; Tsang 2005), as they reported all data for outcomes. One study did not report all the outcome data for the 500 µg/day arm (Martinez-Garcia 2006), therefore we judged it at high risk of bias.

Other potential sources of bias

We judged six studies as potentially having high risk of bias in other areas (Elborn 1992; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). The baseline values for lung functions, sputum amount and sputum inflammatory markers were significantly different clinically between the arms in three studies (Tsang 1998; Tsang 2004; Tsang 2005). We judged Elborn 1992 as high risk due to the cross-over design with no washout period. Joshi 2004 included participants with significant post-bronchodilator response which indicates ICS would be beneficial. Martinez-Garcia 2006 did not complete ITT analysis.

Effects of interventions

See: **Summary of findings for the main comparison** Inhaled corticosteroids compared to placebo for bronchiectasis (short-term use of 6 months or less); **Summary of findings 2** Inhaled corticosteroids compared to placebo for bronchiectasis (longer-term use of > 6 months)

The seven studies involved 380 participants, with 348 completing the studies (Elborn 1992; Hernando 2012; Joshi 2004; Martinez-Garcia 2006; Tsang 1998; Tsang 2004; Tsang 2005). The data that we could include in the meta-analysis were very limited, with just two studies contributing most data (Hernando 2012; Martinez-Garcia 2006).

Stable state bronchiectasis: short-term (≤ 6 months) outcomes

We included data from the Hernando 2012 and Martinez-Garcia 2006 studies in the short-term stable state analysis. See Summary of findings for the main comparison for the main comparisons.

Primary outcome: lung function

We included date from two studies in this meta-analysis (Hernando 2012; Martinez-Garcia 2006). We used change from baseline data to remove bias in differences at baseline. For both FEV_1 and FVC, we combined data of the two steroid dose arms for the Martinez-Garcia 2006 study into a single intervention arm when comparing against the no steroid arm. For FEV_1, the pooled data showed no difference between the groups (mean difference (MD) -0.09, 95% confidence interval (CI) -0.26 to 0.09; participants = 156; Analysis 1.1). A similar result was seen for FVC (MD 0.01, 95% CI -0.16 to 0.17; participants = 156; Analysis 1.1), with no significant heterogeneity between studies. The Elborn 1992 study also reported an improvement in the FEV_1 in the ICS group compared to the placebo group (P = 0.03), but not in FVC; as the values were not reported, we were unable to pool this.

Based on a single study from which we could include data in the final analysis, ICS showed no difference in the following outcomes: diffusing capacity of the lungs for carbon monoxide (DLCO) (MD 2.70, 95% CI -2.49 to 7.89), residual volume (MD 2.00, 95% CI -9.41 to 13.41) and total lung capacity (MD 3.20, 95% CI -1.99 to 8.39) . We only used the 500 µg twice daily arm, since data on the lower dose ICS arm were not available (Martinez-Garcia 2006).

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Secondary outcome: clinical severity

We could only display data from a single non-placebo study for these clinical parameters (Martinez-Garcia 2006). We combined data from the two ICS dose arms for wheeze and sputum production, but not for dyspnoea, since lower dose steroid data were unavailable. The number of participants with sputum reduction as well as with improvement in dyspnoea was significantly higher in the ICS arm compared to the control arm (Analysis 1.3). There were no differences between groups for the clinical parameters of cough and wheeze. Although the Martinez-Garcia 2006 study described a significant difference between groups for the number of participants experiencing reduced cough, we found no difference between groups when we performed ITT analyses. Also, as the methodology of subjective cough measures was not a validated method, we did not display this data as a forest plot. Although we did not include date from the Elborn 1992 study in the final analysis, the study reported that the ICS group had a significant improvement in cough (P = 0.02) but not wheeze and dyspnoea. Again, only the P value was reported. The data from the Hernando 2012 study showed no significant improvement in the total symptom score in the group on ICS compared to control (MD -3.22, 95% CI -8.15 to 1.71), but we could not include the data since the subdivision of the score was not available. None of the other studies reported these clinical outcomes.

Secondary outcome: exacerbations

Data on average number of exacerbations per participant were available from two studies (Hernando 2012; Martinez-Garcia 2006). The combined data showed no difference between the two groups (MD -0.17, 95% CI -0.56 to 0.22; participants = 127; Analysis 1.4). In the Tsang 1998 study, one participant in the fluticasone group experienced an exacerbation compared with three participants in the placebo group. In the Hernando 2012 study, the mean numbers of exacerbations in the ICS group was 0.68 compared to 0.97 in the placebo group, though this was not reported to be statistically significant. In the same study, a much higher proportion of participants (12%) needed hospital admission in the placebo group compared to the ICS group (2.7%), but this was not statistically significant. We only used the 500 µg twice daily arm for the Martinez-Garcia 2006 study, since data on the lower dose ICS arm were not available for this parameter.

Secondary outcome: sputum and biomarker characteristics

The Martinez-Garcia 2006 study was the only study included in this analysis which showed a trend towards reduction in the sputum volume (MD -8.30, 95% CI -16.55 to -0.05; participants = 57; Analysis 1.5). We only used the 500 µg twice daily arm for the Martinez-Garcia 2006 study, since data on the low dose ICS arm were not available. We did not include data on sputum volume and sputum inflammatory markers from the Tsang 1998 study in the final analysis due to clinically significant differences in the baseline value between the two groups. The Elborn 1992 study also described a significant improvement in the 24-hour sputum volume in the ICS group (P = 0.003), but neither the size of the effect nor the CI was provided. The other studies did not include this as an outcome variable.

Secondary outcome: fractional exhaled nitric oxide (FeNO)

The Tsang 2004 study showed no change in the FeNO between the two groups at 24 weeks. Since the data were skewed and geometric means were reported, we did not include this data in the analysis. The proportion of eosinophils as a percentage of total cells were significantly less in the sputum at the end of ICS therapy compared to the end of placebo therapy in the Hernando 2012 study, although all other inflammatory sputum markers, including IL-8, did not show any significant difference.

Secondary outcome: Pseudomonas colonisation

Data on proportion of participants colonised with *P aeruginosa* at the end of treatment were available from two studies (Hernando 2012; Martinez-Garcia 2006), with pooled data showing no increased risk of *P aeruginosa* colonisation with ICS therapy. We used combined data for the two steroid dose arms for the Martinez-Garcia 2006 study for this parameter. We included extra data provided by the Hernando 2012 study in this analysis.

The Tsang 1998 study explained that the density of *P aeruginosa* in the sputum was similar between groups at the end of treatment (median density of 1.0 x 10E7 cfu/mL (inter-quartile range (IQR) 0.33 to 5.15) in the ICS group and 1.4 x 10E7 cfu/mL (IQR 0.7 to 4.67) in the placebo group.

However, the density of total bacteria and commensal bacteria in sputum increased after four weeks of therapy with ICS when compared to baseline (median baseline value was 2.6 x 10E7 cfu/mL (IQR 0.94 to 5.28) and median post-treatment value was 11.6 x 10E7 cfu/mL (IQR 0.34 to 33.8) whilst the corresponding value in the placebo group was lower post-treatment (median baseline value was 2.6 x 10E7 cfu/mL (IQR 0.34 to 4.3) and median post-treatment value was 1.3 x 10E7 cfu/mL (IQR 0.55 to 2.75). The post-treatment between-group comparisons P value did not reach statistical significance (P = 0.06) (Tsang 1998).

Secondary outcome: quality of life

Data were available from two studies (Hernando 2012; Martinez-Garcia 2006). When data of the two ICS dose arms were combined in the Martinez-Garcia 2006 study, and clinical improvement in health-related quality of life (HRQoL) analysed as a dichotomous variable, significantly more people in the ICS group experienced a clinically important improvement in their HRQoL score compared to the no treatment group (Analysis 1.3.4). The Hernando 2012 study reported worsening in total quality of life score in

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both the ICS and placebo group when compared to baseline, but the between-group difference was not statistically significant (MD -3.22, 95% CI -8.15 to 1.71; participants = 70; Analysis 1.7). When we pooled the data from the two included studies, there was a statistically significant improvement in activity score but not for total scores or symptom score (Analysis 1.7). Only 500 µg twice daily ICS data were available for these parameters. Impact score data were only available from the Hernando 2012 study.

Secondary outcome: adverse events

Only one study reported adverse events (Martinez-Garcia 2006), and it was more frequent in the treatment group receiving 1000 µg versus 500 µg (19 participants versus 7, P = 0.04). The most common side effects were dry mouth, local irritation and transient dysphonia.

Stable state bronchiectasis: long-term (> 6 months) outcomes

We included data from the Tsang 2004 study and Tsang 2005 study in the long-term stable state analysis, although the Tsang 2004 study had only FeNO as the outcome variable. See Summary of findings 2 for the main comparisons.

Primary outcome: lung function

For FEV_1 % predicted (end study minus baseline values), data from the single study, Tsang 2005, showed no difference between the two groups (MD 0.30, 95% CI -17.43 to 18.03; participants = 86; Analysis 2.1).
For FVC % predicted (end study minus baseline values), data from the single study, Tsang 2005, showed no difference between the two groups (MD -0.90, 95% CI -14.59 to 12.79; participants = 86; Analysis 2.1).

Secondary outcome: clinical severity

We did not include any data for the clinical parameters from the two studies of more than six months duration (Tsang 2004; Tsang 2005).

Secondary outcome: exacerbations

The Tsang 2005 study showed a non-significant improvement in exacerbation frequency in the ICS group compared to the control group (odds ratio (OR) 0.57, 95% CI 0.24 to 1.34; participants = 86; Analysis 2.2).

Secondary outcome: sputum and biomarker characteristics

As an overall effect, ICS had no effect on the 24-hour sputum volume when given for a period of 52 weeks, although we did not include the data for this outcome in the analysis because only median and interquartile ranges were available and the data were very skewed. As a subgroup analysis, the Tsang 2005 study reported a significant improvement in the amount of sputum volume/day in the subgroup of participants with sputum volume < 30 mL/day, exacerbation frequency ≤ two/year, and sputum purulence score > 5 (data not available).
Sputum purulence was scored as 0, 1, 2, 3, 4, 5, 6, 7 or 8 (absence of, completely transparent, almost transparent, translucent but colourless, opaque, milky white grey, pale green, moderately green, and dark green sputum, respectively) in the Tsang 2005 study. After 52 weeks, there was no significant difference in the purulence scores between the ICS and placebo groups (MD 0.2, 95% CI -0.94 to 1.34; participants = 86; Analysis 2.3).

Secondary outcome: FeNO

The Tsang 2004 study showed no change in the FeNO between the two groups at 52 weeks, although we did not include the data due to its skewed nature.

Secondary outcome: adverse events

None of the studies reported adverse events.

Sensitivity analysis

Removing the study with a poor quality score (no placebo) made no difference to the results for FEV_1 and FVC. The activity subscore of the St. George Respiratory Questionnaire (a measure of HRQoL) became non-significant when we removed the non-placebo controlled study (Martinez-Garcia 2006).
For the clinical data, when we analysed separately the data from the fluticasone 1000 µg arm of the Martinez-Garcia 2006 study and the 500 µg arm, in both arms in the meta-analysis, those on ICS still had a higher proportion of participants with sputum volume reduction of > 50%. For the outcomes of wheeze and cough there was still no difference between the groups. For the outcome of dyspnoea, actual data were not provided for the 500 µg arm but the study authors mentioned that there was no difference between groups. Hence it is assumed that the significant effect present for the 1000 µg/day group (outcome 1.3.3) was no longer present for the 500 µg/day group.
Analysis using random-effects did not alter the significance of any of the outcomes. None of the other planned sensitivity analysis were relevant.

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ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Inhaled corticosteroids compared to placebo for bronchiectasis (medium- to long-term outcomes)

Patient or population: people with bronchiectasis
Setting: university hospital
Intervention: inhaled corticosteroids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evi- dence (GRADE)	Comments
	Risk with placebo	Risk with Inhaled corti- costeroids				
Lung function indices - FEV_1% predicted (end study minus baseline values)	Mean change from baseline 0	MD 0.30 higher (17.43 lower to 18.03 higher)	-	86 (1 study)	⊕⊕◯◯ Low[1,2]	
Lung function indices - FVC % predicted (end study minus baseline values)	Mean change from baseline 0.9	MD 0.90 lower (14.59 lower to 12.79 higher)	-	86 (1 study)	⊕⊕◯◯ Low[1,2]	
Number of participants improved	628 per 1000	490 per 1000 (288 to 693)	OR 0.57 (0.24 to 1.34)	86 (1 study)	⊕⊕◯◯ Low[1,2]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **FEV_1:** forced expiratory volume in 1 second; **FVC:** forced vital capacity; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Only a single study with small participant numbers; we downgraded outcome one point for imprecision.
[2]Single study with high/unclear risk of bias in several domains; we downgraded outcome one point for limitations.

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DISCUSSION

Summary of main results

We did not identify any studies involving children in our searches. Seven studies involving adult participants fulfilled the inclusion criteria. Of the 380 randomised, 348 participants completed the trials. In the short-term group (inhaled corticosteroids (ICS) for ≤ 6 months), use of high dose ICS in adults with bronchiectasis did not lead to any statistical or clinically significant change in the lung function indices of forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC). Further, there was no statistically significant improvement in the overall health-related quality of life (HRQoL) indices except in the activity score. There was improvement in sputum production and dyspnoea scores in the ICS group from the single study with available data for this outcome (Martinez-Garcia 2006), but the result should be interpreted with caution as the study was not placebo controlled. When we only included placebo controlled studies, there were no significant differences between groups in all outcomes examined (spirometry, clinical outcomes of exacerbation or sputum volume, etc.). The single study on long-term outcomes showed no significant benefit of ICS in any of the outcomes.

Overall completeness and applicability of evidence

This Cochrane review is limited to seven studies involving adult participants with variable designs, variable doses and length of study. Also, data that could be combined for the meta-analyses were limited to only two studies for the various outcomes examined. As there were no paediatric studies, data from this review cannot be extrapolated to children. Further, in children, the adverse effect of high dose, or long-term ICS, or both, is likely to be more serious than in adults, in particular to the detrimental effect on linear growth (Philip 2014).

The meta-analyses derived from two studies of the short-term effect of ICS in bronchiectasis showed no benefit of ICS on lung function parameters of FEV_1 and FVC (compared to controls), though the data included were limited (Hernando 2012; Martinez-Garcia 2006). There was improvement in clinical parameters of dyspnoea and sputum production in the ICS group, based on data from the single study which was not placebo controlled. Similar improvement was also seen in the activity score of HRQoL in the ICS group, though the effect was marginal. We could not include data from Joshi 2004 and Tsang 1998 in the final analysis, but both studies had not reported any improvement in the lung function parameters between the steroid and placebo groups. On the contrary, data from the Elborn 1992 study (which we could not include in the meta-analysis) showed a significant improvement in the FEV_1 in the ICS group compared to the placebo group. Thus, it remains uncertain whether ICS confers any benefit in people with bronchiectasis.

Data on the short-term effect of ICS on clinical parameters of cough, wheeze, dyspnoea and sputum volume were available from two studies (Hernando 2012; Martinez-Garcia 2006). The Martinez-Garcia 2006 study showed a significant improvement in dyspnoea in the 1000 µg/day fluticasone group and sputum volume for the combined 500 µg/day and 1000 µg/day group compared to the control group, although no such effect was seen in the total symptom score from the Hernando 2012 study. We did not include data on sputum volume from the Tsang 1998 study in the analysis in view of the clinically significant difference in the baseline values. The Martinez-Garcia 2006 study showed a significant improvement in the quality of life score in the ICS group using the St. George Respiratory Questionnaire, though no such improvement was reported in the Hernando 2012 study. On pooling these data, the effect favoured ICS use largely due to the large effect of the non-placebo controlled study (Martinez-Garcia 2006).

Recurrent acute pulmonary exacerbations form part of the disease progression in patients with bronchiectasis and many of these exacerbations require hospital admission. Recurrent exacerbations are associated with progressive deterioration of lung functions (Kapur 2010), and are also one of the strong predictors of poor quality of life in bronchiectasis (Wilson 1997). In this review, based on limited data, short-term use of ICS did not influence frequency of exacerbations. Prolonged ICS administration also did not influence exacerbation frequency (Tsang 2005). This becomes more relevant with the fact that ICS actually increased the bacterial density in the airways and most exacerbations in bronchiectasis are likely to be infective in origin (Tsang 1998).

Administration of ICS for a longer duration significantly increased the number of participants who had a more than 20% reduction in the 24-hour sputum volume, but did not have any beneficial effect in the other clinical or spirometric parameters (Tsang 2004; Tsang 2005). This lack of effect again suggests that infection and not pure inflammation, is probably the more relevant underlying pathogenic mechanism of disease progression in bronchiectasis.

The ICS doses used in several studies were very high (up to 2000 µg/day budesonide equivalent). This limits applicability of the data to most patients in our current era where ICS doses used are generally lower, in light of the increased appreciation of adverse events related to prolonged use of high ICS doses, such as the effect on linear growth (Philip 2014). High dose ICS use is also associated with adverse events in children and adults that range from mild events (candidiasis) to serious events (pneumonia, adrenal insufficiency, osteoporosis, cataracts) (Sobieraj 2008). The Martinez-Garcia 2006 study reported dry mouth, local irritation and transient dysphonia as the most common adverse effects. None of the other studies reported any adverse effects. While there was no significant difference in adverse events between groups, the total sample size was small, rendering a likely type-1 error.

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The potential harm associated with prolonged ICS use, or high ICS doses, or both, need to be considered along with its potential benefit.

Bronchiectasis is a heterogenous condition, with a substantial overlap in people with chronic obstructive pulmonary disease (COPD). Not all the studies in this review excluded smokers and thus, whether data in our review can be universally applied is unknown. Nearly 50% of adults with COPD have bronchiectasis (Chang 2008). A Cochrane Review concluded that ICS administration reduces the rate of exacerbations as well as the rate of decline in quality of life in patients with stable state COPD (Yang 2012). As the Martinez-Garcia 2006 study included participants who were smokers, there is a possibility that some of these participants had COPD and this may influence the positive findings in that study. It is possible that COPD-associated bronchiectasis may respond differently to treatment modalities when compared to bronchiectasis associated with other causes.

Persistent inflammation plays a role in deterioration of lung function in bronchiectasis (Ip 1993). Studies in adults with cystic fibrosis suggest that ICS treatment improves bronchial hyper-responsiveness and spirometric parameters (Van Haren 1995). Thus, it is theoretically possible that ICS may improve lung function, and with it clinical parameters in non-cystic fibrosis bronchiectasis as well, although this review has shown that any benefit from ICS is inconsistent. However, given the increased presence of airway hyper-responsiveness in patients with non-cystic fibrosis bronchiectasis (Ip 1991), it is possible that ICS may have a role in this subgroup.

The bacteriology of sputum influences future morbidity and mortality; specifically, people with *Pseudomonas aeruginosa* (*P aeruginosa*) have more rapid lung function decline (Finch 2015). As the bacteriology in all the included studies were unclear, the applicability of this review in the different subsets of people with various bacteriology such as mycobacteria and *P aeruginosa* is also uncertain.

In the consideration of using ICS, especially long-term ICS (> 6 months) in patients, clinicians should be cognisant of the possible effect of corticosteroids on cell immunity dysregulation (Sabroe 2013). Biologically, this effect could lead to an increase in infections that could worsen clinical outcomes, such as lung function and exacerbations (Sabroe 2013). Indeed, adults with COPD on ICS have an increased unadjusted risk of having pneumonia (Festic 2016). Although this adverse event is a clinically important issue in people with bronchiectasis, only one study specifically reported on adverse events and thus we could not assess this in this review. However, in the ICS group of shorter duration (6 months or less), two studies found no increased risk of *P aeruginosa* in the ICS arm compared to placebo (Analysis 1.6). One study found a non-significant increase in sputum bacterial density in the ICS group (Tsang 1998), whilst there was a non-decrease in the placebo group (between-groups post-treatment P = 0.06).

Quality of the evidence

The overall quality of evidence was low (Summary of findings for the main comparison; Summary of findings 2). The sample size and number of studies were small. The major contributor to the benefit of ICS found in the meta-analyses was from a non-placebo controlled study. The studies also did not exclude participants with airway hyper-responsiveness or coexistent COPD, hence the potential of skewing the results in favour of ICS.

Potential biases in the review process

We conducted this review in accordance with a prespecified protocol. We have outlined changes from the protocol in the Differences between protocol and review section and we did not identify any major sources of bias in the review process.

Agreements and disagreements with other studies or reviews

Our findings are similar to that outlined in bronchiectasis guidelines of the British Thoracic Society (Pasteur 2010), and the Thoracic Society of Australia and New Zealand (Chang 2015). We found no other published systematic reviews on the use of ICS for people with bronchiectasis.

Whilst a separate disease, cystic fibrosis lung disease manifests with bronchiectasis. Studies in cystic fibrosis have also shown no benefits with ICS. A Cochrane Review of ICS in cystic fibrosis concluded that there is insufficient evidence to determine if they are beneficial or harmful (Balfour-Lynn 2014). In a large prospective, multicentre study, withdrawal of ICS for six months was not associated with significant worsening of cystic fibrosis lung disease (Balfour-Lynn 2006). Participants in whom ICS were discontinued did not have a change in lung function over time, an increased need for oral or intravenous antibiotics, or a shorter time to pulmonary exacerbation (Balfour-Lynn 2006).

AUTHORS' CONCLUSIONS

Implications for practice

In this review update, we identified one new study, adding a further 77 participants; however, these additional results did not change the original conclusions. The present review continues to indicate that there is insufficient evidence to suggest the routine use of inhaled corticosteroids (ICS) in adults with stable state bronchiectasis. The only study that showed a benefit was a non-placebo controlled trial (Martinez-Garcia 2006). Insufficient data precludes any definite conclusion on the use of ICS in adults during an acute exacerbation, or in children (for any state) as there were no studies.

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Implications for research

Further studies are required to examine the effect of ICS on short- and long-term outcomes for children and adults with non-cystic fibrosis bronchiectasis. Outcomes should include exacerbations (rate and hospital admission), symptoms, quality of life, lung function indices and inflammatory parameters and bacteriology. Studies are required in both stable state and during an acute exacerbation state. Studies involving adults should clearly differentiate co-existent COPD, as the presence of this may influence effectiveness of ICS. A priori analysis for those with bronchial hyper-responsiveness should also be defined, since its presence may influence ICS response.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Elborn 1992

Methods	A prospective, double-blind, placebo controlled, randomised cross-over design with study duration of 6 weeks There were five participants who dropped out; we are unsure when these occurred. Two participants declined to take part in second limb of study No washout period mentioned.
Participants	Twenty participants (12 females, mean age 50 years, range 30 to 65) were studied with bronchiectasis diagnosed by bronchogram in 18 and computed tomography scan in two. No participant received a course of antibiotics for at least 8 weeks prior to the study Exclusion: participants with hypogammaglobulinaemia, cystic fibrosis, ABPA or primary ciliary dyskinesia, as well as those taking OCS or ICS
Interventions	Inhaled beclomethasone dipropionate 750 µg twice daily by MDI or placebo for 6 weeks
Outcomes	• FEV_1 • FVC • PEFR (morning and evening) • 24-hour sputum amount collected weekly from patients • visual analogue scale for cough, wheeze and dyspnoea recorded on a diary card and on a 75 mm line (higher value better)
Notes	Cross-over design with no washout period. Separate results of first arm not available. Data not included in analysis. No funding source mentioned, though acknowledgement for ICS was given to Allen and Hanburys

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was provided within the published article about generation of randomisation
Allocation concealment (selection bias)	Unclear risk	No information about concealment was reported in the article
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blinded" and "matched placebo".
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 5 patients who dropped out; we are unsure when these occurred. Two patients declined to take part in second arm of study

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Elborn 1992 (*Continued*)

Selective reporting (reporting bias)	Low risk	No suggestion that selective reporting may have been done.
Other bias	High risk	Cross-over design with no washout period. Separate results of first arm not available

Hernando 2012

Methods	A prospective, double-blind, parallel group placebo controlled trial
Participants	77 participants included over a 3-year period. Age range 40 to 85 years, mean age 68. 06 years. Seven did not complete the study: three died from respiratory failure and four pulled out voluntarily. 37 analysed in the budesonide group and 33 in the placebo group. Mean age of the budesonide group was 68 years and that of the placebo group was 66 years. 19 (27.1%) participants in the budesonide group and 18 (25.7%) in the placebo group had *Pseudomonas aeruginosa* (*P aeruginosa)* cultured from their sputum. The mean (SD) baseline FEV_1% predicted in the budesonide and the placebo group was 64.6% (25.1) and 64.7% (27), respectively
Interventions	400 µg inhaled budesonide twice a day versus placebo for 6 months
Outcomes	Total symptom score which included I) cough and sputum production; and ii) dyspnoea • Proportion with exacerbations • Hospital admission • FEV_1 difference • FVC difference • SGRQ • Sputum IL-8 & cellularity • Microbiological changes including percentage *P aeruginosa* positive at the end of 6 months
Notes	Additional information provided by the authors. The study was supported by the Catalan Foundation of Pneumology grant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Hospital pharmacy (third party) performed randomisation and dispensed inhalers
Allocation concealment (selection bias)	Unclear risk	No mention how allocation was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote "parallel, placebo-masked clinical trial". Probably done

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Hernando 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	7 dropouts, 6 of whom were from the placebo group. Data of dropouts not included. Since 3 of these died of respiratory failure, all belonging to the placebo group, potential for bias on outcome if data not included
Selective reporting (reporting bias)	Low risk	No suggestion that selective reporting may have been done.
Other bias	Low risk	No other risk of bias identified

Joshi 2004

Methods	Randomised double-blind, placebo controlled, cross-over study with study duration of 4 weeks Two-week washout period between cross-over. Details of dropouts not clear.
Participants	20 participants (9 females) age range 15 to 60 years were prospectively enrolled. All participants treated with oral salbutamol 2 mg four times daily and oral theophylline 200 mg four times daily throughout the trial period 14 participants had unilateral disease and six had bilateral disease Inclusion: bronchiectasis confirmed by HRCT, chest in stable state (no exacerbation in previous 1 month) demonstrating significant post-bronchodilator response (> 12% change) on spirometry Exclusion: atopy, bronchial asthma or smoking
Interventions	Inhaled beclomethasone 800 µg/day in two divided doses by MDI or placebo for 4 weeks
Outcomes	• FVC at 4 weeks and 10 weeks • FEV_1 at 4 weeks and 10 weeks • PEFR at 4 weeks and 10 weeks
Notes	SD calculated from P value. Only first arm of the study before cross-over used in analysis. Additional information provided by the authors. Spirometeric data not included in the analysis since baseline values not reported separately for the two groups and a common mean given for the group of 20. No mention of funding source

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information was provided within the published article about generation of randomisation
Allocation concealment (selection bias)	Unclear risk	No mention how allocation was done.

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Joshi 2004 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "patients were randomised in a double blind manner". Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of dropouts.
Selective reporting (reporting bias)	Low risk	No suggestion that selective reporting may have been done.
Other bias	High risk	Inclusion of participants who had a significant post-bronchodilator response biased the study in favour of response to ICS since those with positive bronchodilator response are more likely to improve with ICS due to the asthma-like reversibility in their airway

Martinez-Garcia 2006

Methods	Randomised (stratified for prior smoking habit in pack year), double-blind (only for dose of steroid), non-placebo controlled prospective trial with study duration 6 months
Participants	Of the 132 participants initially included in the study, 39 were excluded prior to randomisation (23 had high probability of asthma, 4 did not give consent, 1 had Down's syndrome and 3 each had psychiatric disorder, systemic ICS and had disease of significant severity). 93 patients enrolled in the study Seven dropouts during the study, three from the no steroid group and two each from the 500 µg and 1000 µg group. Study completed in 86 participants • No steroid group n = 28: mean age 70.9 (SD 6.1), 17 males • 500 µg/day fluticasone group n = 29: mean age 66.4 (SD 12.6), 18 males • 1000 µg/day group n = 29: mean age 70.9 (SD 6), 21 males Inclusion: all participants with HRCT diagnosed bronchiectasis diagnosed between 1993 and June 2003 in Requena General Hospital. The participants were required to be free from acute exacerbation for at least 4 weeks Exclusion: participants with asthma, cystic fibrosis and on whom ICS could not be stopped
Interventions	Inhaled fluticasone 500 µg twice daily by MDI versus 250 µg fluticasone twice daily versus no treatment for 6 months
Outcomes	Baseline data collection started 6 months prior to randomisation. During this period data prospectively collected on number of acute exacerbations, antibiotic use and hospital admissions • FEV1, FVC, TLC, RV and diffusion capacity measured a few days prior to randomisation. During randomisation visit, information collected on dyspnoea score, daily sputum production (average of sputum produced over three days); cough and need for short-

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	acting bronchodilator in the 1-month prior to randomisation, and HRQoL using the validated Spanish version of the SGRQ After randomisation, TLC, RV and diffusion capacity analysed again after 6 months. HRQoL assessment at 3 and 6 months and all other tests at 1, 3 and 6 months > 4-point change in SGRQ considered significant. > 1-point change is dyspnoea score considered significant
Notes	Wherever available, data on the 250 µg twice daily group was combined with 500 µg twice daily group for comparison with no steroid group. Additional information provided by the authors. Study was supported by Grant Red Respira

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was provided within the published article about generation of randomisation
Allocation concealment (selection bias)	Unclear risk	No mention of how allocation was done.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The study was conducted on a double blind basis regarding the effective inhalatory steroid dose administered (500 vs. 1000 µg/day), but not as relates to the administration or not of steroid treatment (i.e. 0 vs. 500 or 1000 µg/day)." Comment: No blinding for the two groups assessed by us (0 versus 1000 µg/day)
Incomplete outcome data (attrition bias) All outcomes	High risk	The patient characteristics and outcome data of those excluded or dropped out not described and not compared with those included for analysis
Selective reporting (reporting bias)	High risk	Information on TLC, RV and DLCO gathered but not reported. Some outcomes that were reported in the 1000 µg group were not reported in the 500 µg group (such as sputum volume, TLC, RV and cough and wheeze clinical variables)
Other bias	High risk	Intention-to-treat analysis not done. Of the 39 participants excluded before randomisation, no details available for the reason for exclusion for 2 participants

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Tsang 1998

Methods	Randomised double-blind, placebo controlled prospective trial with study duration of 4 weeks There were no dropouts.
Participants	24 participants (mean age 51 years, 12 females) with HRCT proven bronchiectasis Fluticasone group: n = 12, 6 females, age: mean 43 (SD 11). Placebo group: n = 12, 8 females, age: mean 56.8 (SD 11) Inclusion: daily sputum > 10 mL, absence of asthma or other unstable systemic disease; and "steady state" bronchiectasis (< 10% alteration of 24-hour sputum volume, FEV_1 and FVC). Exclusion: unreliable clinic attendance, known adverse reaction to fluticasone, regular use of ICS and asthma
Interventions	Inhaled fluticasone 500 µg twice daily by accuhaler or placebo for 4 weeks
Outcomes	• FEV_1 • FVC • TLC • RV • Diffusion capacity • PEFR • 24-hour sputum volume (mean of 3 days) Sputum leukocyte density, bacterial densities and concentrations of interleukin (IL)1B, IL 8, TNF alpha and leukotriene B4 were all measured at the time of randomisation and at 4 weeks
Notes	Geometric mean was used instead of arithmetic mean. Hence, none of the lung function data were included in the final analysis. No mention of funding source

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information was provided within the published article about generation of randomisation
Allocation concealment (selection bias)	Unclear risk	No mention of how allocation was done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "performed a double blind, placebo controlled study". Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Low risk	No suggestion that selective reporting may have been done.

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Tsang 1998 (*Continued*)

Other bias	High risk	The baseline values for lung functions, sputum amount and sputum inflammatory markers were significantly different, thus were subject to bias

Tsang 2004

Methods	Randomised double-blind, prospective placebo controlled trial with study duration of 52 weeks There were no dropouts.
Participants	60 participants (mean age 56.4 years, 38 females) with HRCT proven bronchiectasis Fluticasone group: n = 30, age: mean 56.1 (SD 14). Placebo group: n = 30, age: mean 56.7 (SD 11.3) 16 were *P aeruginosa* colonised and 44 were not. Inclusion: absence of asthma or other unstable systemic disease; and "steady state" bronchiectasis (< 20% alteration of 24-hour sputum volume, FEV_1 and FVC) and absence of deterioration in respiratory symptoms at baseline visit Exclusion: unreliable clinic attendance, known adverse reaction to fluticasone and asthma
Interventions	Inhaled fluticasone 500 µg twice daily by accuhaler or placebo for 52 weeks
Outcomes	The participants were followed up at -2, -1, 0, 4, 12, 24, 36, 48 and 52 weeks after commencement of therapy for measurement of FeNO
Notes	Data not included in the final analysis since medians and inter-quartile range reported in this study. The study was supported by a CRCG Grant of the University of Hong Kong. The Accuhalers were donated by GlaxoWellcome, China

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information was provided within the published article about generation of randomisation
Allocation concealment (selection bias)	Unclear risk	No mention on allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "performed a double blind, placebo controlled study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Low risk	No suggestion that selective reporting may have been done.

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Tsang 2004 (*Continued*)

Other bias	High risk	Baseline value of the 2 groups were significantly different.

Tsang 2005

Methods	Randomised double-blind, prospective placebo controlled trial with study duration of 52 weeks 5 dropouts in the placebo arm (1 at 4 weeks, 3 at 24 weeks and 1 at 52 weeks) and 8 dropouts in the fluticasone arm (2 at 4 weeks and 1 each at 6, 22, 32, 36, 50 and 52 weeks)
Participants	89 patients recruited. Three participants withdrew. 86 participants (57 females, mean age 58.5 years) with HRCT proven bronchiectasis randomised between fluticasone and placebo Fluticasone group: n = 43, 23 females, age: mean 57.7 (SD 14.4). Placebo group: n = 43, 34 females, age: mean 59.2 (SD 14.2) 23 were *P aeruginosa* colonised. Inclusion: absence of asthma or other unstable systemic disease; and "steady state" bronchiectasis (< 20% alteration of 24-hour sputum volume, FEV_1 and FVC) and absence of deterioration in respiratory symptoms at baseline visit Exclusion: unreliable clinic attendance, known adverse reaction to fluticasone or quinolones and regular usage of ICS
Interventions	Inhaled fluticasone 500 µg twice daily by accuhaler device or matched placebo for 52 weeks
Outcomes	The participants were followed up at -2, -1, 0, 4, 12, 24, 36, 48 and 52 weeks after commencement of therapy Primary outcomes • 24-hour sputum volume (mean of 3 days) and cumulative exacerbation frequency Secondary outcomes • Sputum purulence score • FEV_1 % • FVC % Improvement or deterioration was defined as > 20% change from baseline
Notes	SD calculated from P value for sputum volume and exacerbation frequency and from confidence interval for the rest. The study was partially funded by GlaxoWelcome (Hong Kong)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation (block of 4)", however, no information about who generated the randomisation codes

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Tsang 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information about concealment was reported in the published article
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind, placebo controlled study".
Incomplete outcome data (attrition bias) All outcomes	High risk	Data of dropouts not compared to those included in analysis.
Selective reporting (reporting bias)	Low risk	No suggestion that selective reporting may have been done.
Other bias	High risk	Significant differences at the baseline on clinical features of "cough" and "dyspnoea" between the two groups to allow for post-treatment comparison

ABPA: allergic bronchopulmonary aspergillosis
DLCO: diffusing capacity of the lungs for carbon monoxide
FeNO: fractional exhaled nitric oxide
FEV_1: forced expiratory volume (in 1 second)
FVC: forced vital capacity
HRCT: high resolution computed tomography
HRQoL: health-related quality of life
ICS: inhaled corticosteroids
MDI: metered dose inhaler
OCS: oral corticosteroids
PEFR: peak expiratory flow rate
RV: residual volume
SD: standard deviation
SGRQ: St George's Respiratory Questionnaire
TLC: total lung capacity
TNF: tumour necrosis factor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ghosh 2002	Study compared effects of inhaled budesonide with inhaled ipratropium and not placebo
Guran 2008	Not a RCT, withdrawal study with before-and-after outcomes
Martinez-Garcia 2012	Study compared budesonide with budesonide-formoterol combination and not a placebo

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(*Continued*)

Monton 1999	Study included patients with pneumonia and not bronchiectasis. Used systemic steroids, not inhaled
ONeil 2004	Study not a RCT. Studies subjective benefits of inhaler therapy including both ICS and bronchodilators

ICS: inhaled corticosteroids
RCT: randomised controlled trial

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DATA AND ANALYSES

Comparison 1. Stable state bronchiectasis (6 months or less)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lung function (spirometry indices)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 FEV_1 (in L, end study minus baseline values)	2	156	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.26, 0.09]
1.2 FVC (in L, end study minus baseline values)	2	156	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.16, 0.17]
2 Lung function (other indices)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Diffusion capacity % predicted (end of study)	1	57	Mean Difference (IV, Fixed, 95% CI)	2.70 [-2.49, 7.89]
2.2 RV % predicted (end of study values)	1	57	Mean Difference (IV, Fixed, 95% CI)	2.0 [-9.41, 13.41]
2.3 TLC % predicted (end of study values)	1	57	Mean Difference (IV, Fixed, 95% CI)	3.20 [-1.99, 8.39]
3 Clinical severity indices	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Number of participants with regular wheeze (combined)	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Number of participants without sputum reduction of > 50% (combined)	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Number of participants with no improvement in dyspnoea score > 1 (min important difference) (1000F)	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Number of participants with no clinically significant improvement in HRQoL	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Exacerbations	2	127	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.56, 0.22]
4.1 Average number of exacerbations per participant	2	127	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.56, 0.22]
5 Sputum and biomarkers characteristics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Sputum volume or weight (per day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Pseudomonas aeruginosa colonisation	2	156	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.45, 1.96]
7 St George HRQoL (end of study minus baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Total score	2	127	Mean Difference (IV, Fixed, 95% CI)	-3.54 [-8.00, 0.92]
7.2 Symptom score	2	127	Mean Difference (IV, Fixed, 95% CI)	-4.75 [-10.42, 0.92]
7.3 Activity score	2	127	Mean Difference (IV, Fixed, 95% CI)	-6.21 [-12.40, -0.01]
7.4 Impact score	1	70	Mean Difference (IV, Fixed, 95% CI)	-3.63 [-9.35, 2.09]

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Comparison 2. Stable state (> 6 months)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lung function indices	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 FEV_1% predicted (end study minus baseline values)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 FVC % predicted (end study minus baseline values)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Number of participants improved	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Sputum and biomarker characteristics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Sputum purulence score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

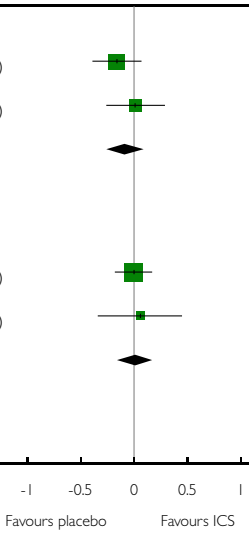
Analysis 1.1. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 1 Lung function (spirometry indices).

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 1 Lung function (spirometry indices)

Study or subgroup	Inhaled Corticos-teroids N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 FEV_1 (in L, end study minus baseline values)							
Hernando 2012	37	0.646 (0.46)	33	0.81 (0.515)		58.7 %	-0.16 [-0.39, 0.07]
Martinez-Garcia 2006	58	-0.023 (0.6848)	28	-0.04 (0.5662)		41.3 %	0.02 [-0.26, 0.29]
Subtotal (95% CI)	**95**		**61**			**100.0 %**	**-0.09 [-0.26, 0.09]**
Heterogeneity: Chi^2 = 0.91, df = 1 (P = 0.34); I^2 =0.0%							
Test for overall effect: Z = 0.97 (P = 0.33)							
2 FVC (in L, end study minus baseline values)							
Hernando 2012	37	0.0174 (0.387)	33	0.02 (0.375)		82.9 %	0.00 [-0.18, 0.17]
Martinez-Garcia 2006	58	-0.007 (0.6795)	28	-0.06 (0.95)		17.1 %	0.06 [-0.34, 0.45]
Subtotal (95% CI)	**95**		**61**			**100.0 %**	**0.01 [-0.16, 0.17]**
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 0.07 (P = 0.94)							



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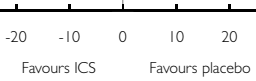
Analysis 1.2. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 2 Lung function (other indices).

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 2 Lung function (other indices)

Study or subgroup	Favours ICS N	Mean(SD)	Favours placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Diffusion capacity % predicted (end of study)							
Martinez-Garcia 2006	29	86.9 (10)	28	84.2 (10)		100.0 %	2.70 [-2.49, 7.89]
Subtotal (95% CI)	**29**		**28**			**100.0 %**	**2.70 [-2.49, 7.89]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 RV % predicted (end of study values)							
Martinez-Garcia 2006	29	108 (10)	28	106 (29.2)		100.0 %	2.00 [-9.41, 13.41]
Subtotal (95% CI)	**29**		**28**			**100.0 %**	**2.00 [-9.41, 13.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
3 TLC % predicted (end of study values)							
Martinez-Garcia 2006	29	89.6 (10)	28	86.4 (10)		100.0 %	3.20 [-1.99, 8.39]
Subtotal (95% CI)	**29**		**28**			**100.0 %**	**3.20 [-1.99, 8.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.21 (P = 0.23)							
Test for subgroup differences: Chi^2 = 0.04, df = 2 (P = 0.98), I^2 =0.0%							



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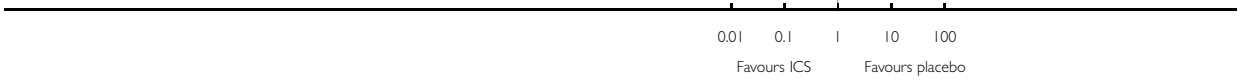
Analysis 1.3. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 3 Clinical severity indices.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 3 Clinical severity indices

Study or subgroup	Inhaled Corticos-teroids n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Number of participants with regular wheeze (combined)				
Martinez-Garcia 2006	18/58	9/28		0.95 [0.36, 2.50]
2 Number of participants without sputum reduction of > 50% (combined)				
Martinez-Garcia 2006	33/58	25/28		0.16 [0.04, 0.58]
3 Number of participants with no improvement in dyspnoea score > 1 (min important difference) (1000F)				
Martinez-Garcia 2006	10/29	18/28		0.29 [0.10, 0.87]
4 Number of participants with no clinically significant improvement in HRQoL				
Martinez-Garcia 2006	33/58	26/28		0.10 [0.02, 0.47]



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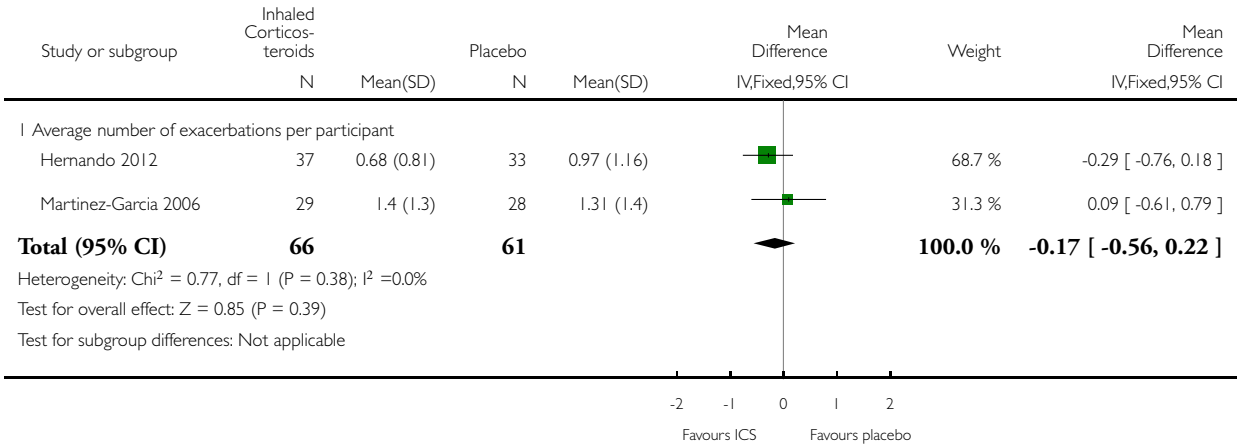
Analysis 1.4. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 4 Exacerbations.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 4 Exacerbations

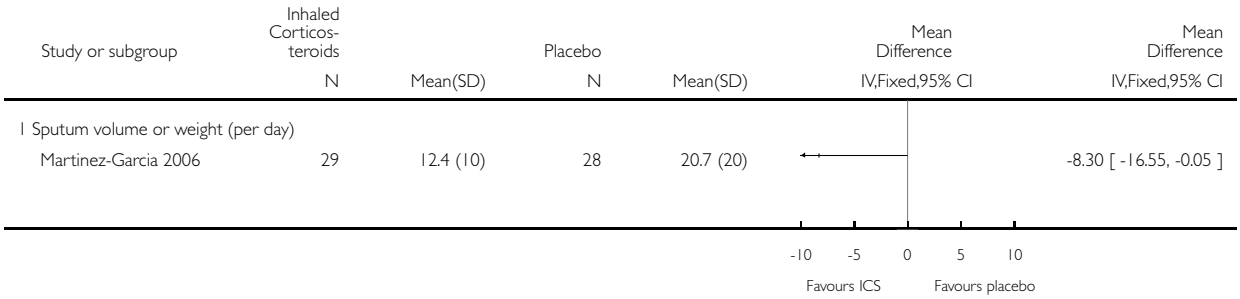


Analysis 1.5. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 5 Sputum and biomarkers characteristics.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 5 Sputum and biomarkers characteristics



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Analysis 1.6. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 6 Pseudomonas aeruginosa colonisation.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 6 Pseudomonas aeruginosa colonisation

Study or subgroup	Inhaled Corticos-teroids n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Hernando 2012	21/37	20/33		62.6 %	0.85 [0.33, 2.22]
Martinez-Garcia 2006	11/58	5/28		37.4 %	1.08 [0.33, 3.46]
Total (95% CI)	**95**	**61**		**100.0 %**	**0.94 [0.45, 1.96]**

Total events: 32 (Inhaled Corticosteroids), 25 (Placebo)

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Not applicable

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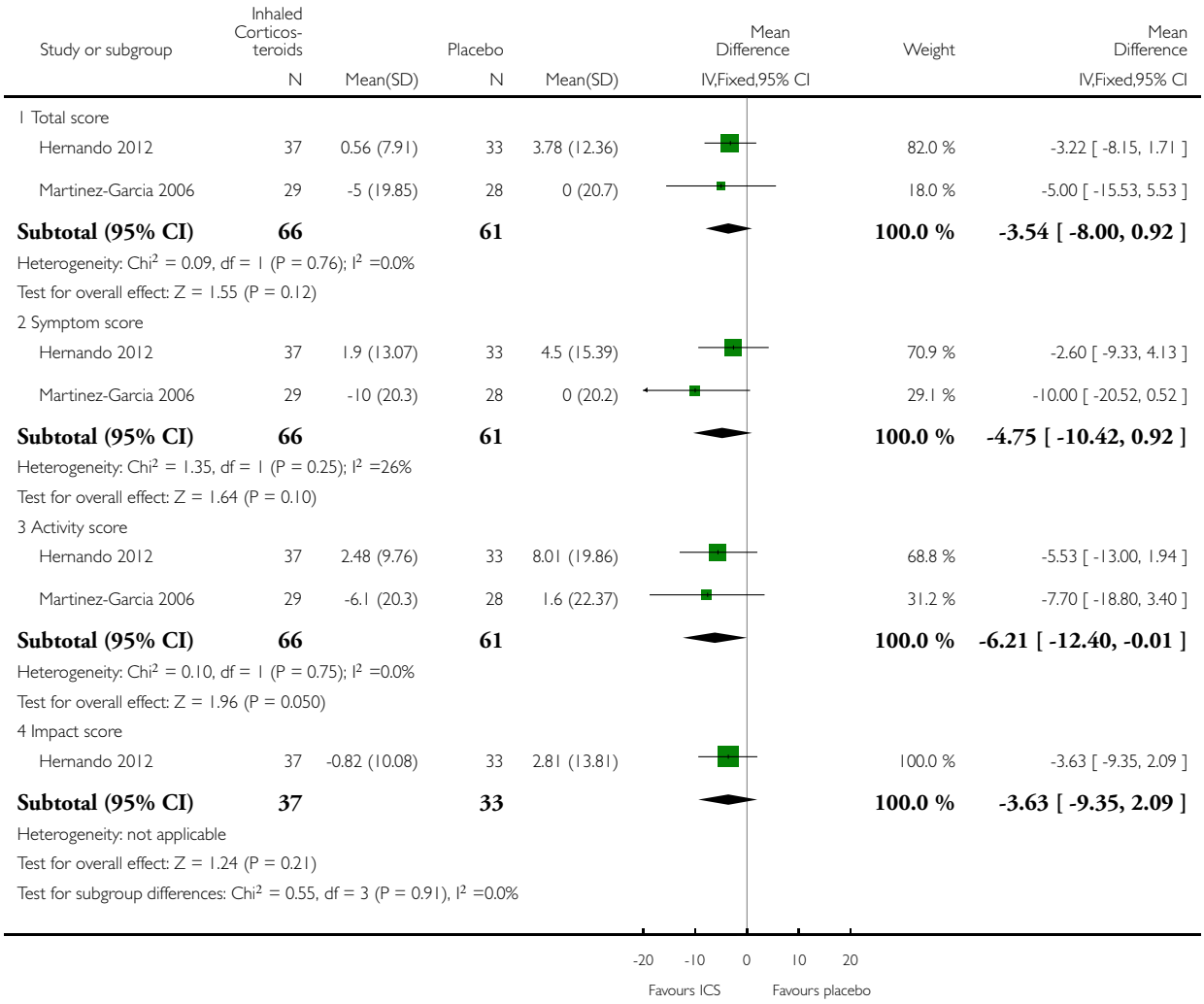
Analysis 1.7. Comparison 1 Stable state bronchiectasis (6 months or less), Outcome 7 St George HRQoL (end of study minus baseline).

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 1 Stable state bronchiectasis (6 months or less)

Outcome: 7 St George HRQoL (end of study minus baseline)



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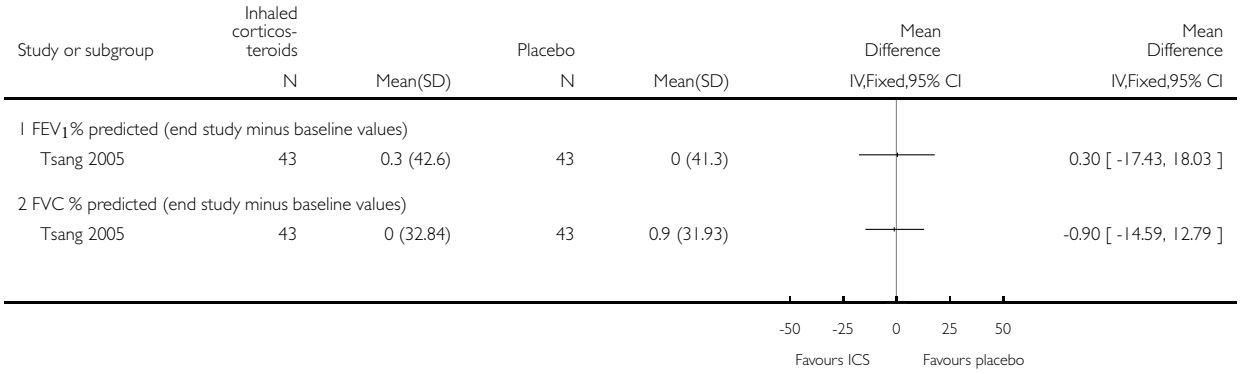
Analysis 2.1. Comparison 2 Stable state (> 6 months), Outcome 1 Lung function indices.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 2 Stable state (> 6 months)

Outcome: 1 Lung function indices

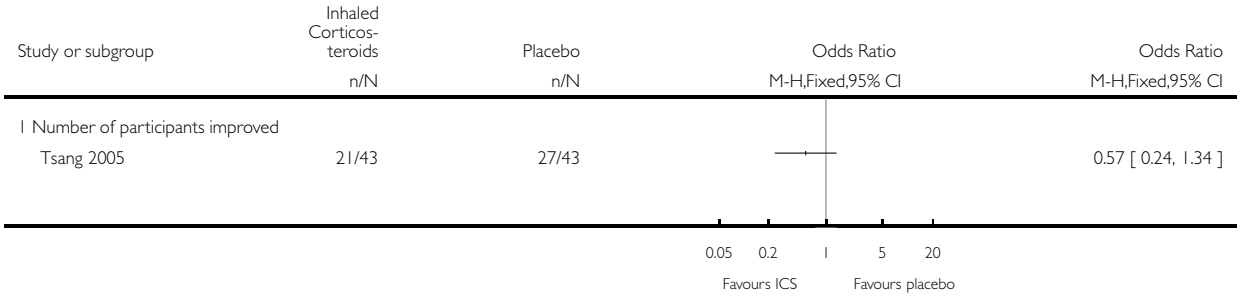


Analysis 2.2. Comparison 2 Stable state (> 6 months), Outcome 2 Exacerbations.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 2 Stable state (> 6 months)

Outcome: 2 Exacerbations



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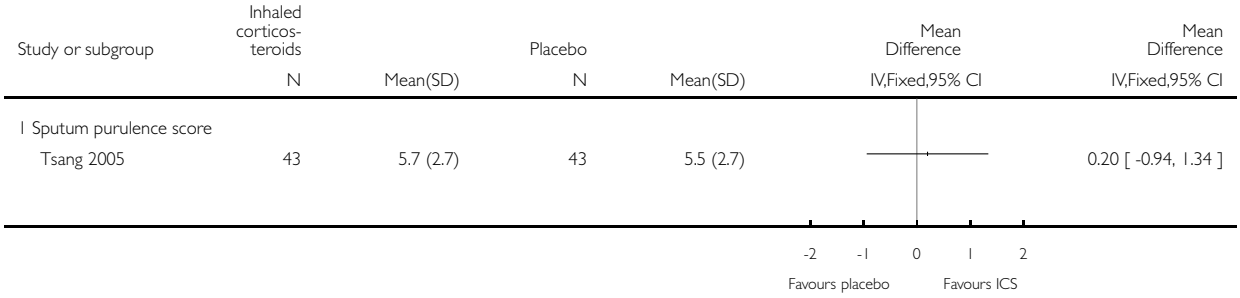
Analysis 2.3. Comparison 2 Stable state (> 6 months), Outcome 3 Sputum and biomarker characteristics.

Review: Inhaled corticosteroids for bronchiectasis

Comparison: 2 Stable state (> 6 months)

Outcome: 3 Sputum and biomarker characteristics



ADDITIONAL TABLES

Table 1. Summary of included studies characteristics

Study ID	Intervention	Control	Duration of intervention
Elborn 1992	Beclomethasone dipropionate 750 µg twice daily by MDI	Placebo	6 weeks
Hernando 2012	Budesonide 400 µg twice daily	Placebo	6 months
Joshi 2004	Beclomethasone 800 µg per day over 2 doses	Placebo	4 weeks
Martinez-Garcia 2006	Fluticasone 500 µg twice daily by MDI or 250 µg fluticasone twice daily	No treatment	6 months
Tsang 1998	Fluticasone 500 µg twice daily by accuhaler	Placebo	4 weeks
Tsang 2004	Fluticasone 500 µg twice daily by accuhaler	Placebo	52 weeks
Tsang 2005	Fluticasone 500 µg twice daily by accuhaler	Placebo	52 weeks

MDI: metered dose inhaler

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APPENDICES

Appendix 1. Database search strategies

Database	Search	
Airways Register (searched through the Cochrane Register of Studies)	steroid* or corticosteroid* or glucocorticoid* or beclomet* or budesonide or fluticasone OR ciclesonide or triamcinolone or flunisolide	
CENTRAL and MEDLINE (Ovid) strategy (MEDLINE search combined with RCT search filter)	#1 MeSH descriptor Bronchiectasis explode all trees #2 bronchiect* #3 (#1 OR #2) #4 MeSH descriptor Adrenal Cortex Hormones explode all trees #5 steroid* #6 corticosteroid* #7 glucocorticoid* #8 beclomet* #9 0fluticasone #11 ciclesonide #12 flunisolide #13 triamcinolone #14 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #12) #15 (#3 AND #14)	
Embase (Ovid) strategy (combined with RCT search filter)	#1 Emtree descriptor Bronchiectasis explode all trees #2 bronchiect* #3 (#1 OR #2) #4 Emtree descriptor Corticosteroid explode all trees #5 steroid* #6 corticosteroid* #7 glucocorticoid* #8 beclomet* #9 budesonide #10 fluticasone #11 ciclesonide #12 flunisolide #13 triamcinolone #14 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #12) #15 (#3 AND #14)	

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Appendix 2. Search strategy to identify relevant trials from ClinicalTrials.gov and WHO trials portal

"inhaled corticosteroid" AND "bronchiectasis" AND "clinical trials"

WHAT'S NEW

Last assessed as up-to-date: 30 June 2017.

Date	Event	Description
30 June 2017	New search has been performed	Literature search run.
30 June 2017	New citation required but conclusions have not changed	One new study included in the review. Addition of author. Review updated to reflect current Cochrane methods including addition of 'Summary of findings' table and PRISMA flow chart. See Differences between protocol and review.

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 2, 1999

Date	Event	Description
15 August 2008	New citation required and conclusions have changed	Aug 2008: new author team, protocol changed and previous included studies data amended, new studies added, conclusions changed
5 May 2008	Amended	Converted to new review format.
10 September 2007	New search has been performed	New literature search performed.

CONTRIBUTIONS OF AUTHORS

The protocol was written by NK and AC based on previous protocols on cough in children. For the review update: NK and AC performed selection of articles from the search, data extraction, data analysis and writing of the review. HP prepared the manuscript. SB and JK reviewed the manuscript.

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DECLARATIONS OF INTEREST

Nitin Kapur: none known.

Helen Petsky: none known.

Scott Bell: has received travel and accommodation support to attend investigator meetings (Vertex, Rempex), to participate in advisory boards and to speak at sponsored Symposia. Speakers fees and support to participate in preparation of educational materials and in advisory board have been paid to his Institution.

John Kolbe: has received funds of approximately NZ $500 from Novartis for lecture to GPs as part of an educational symposium. John also received funds to attend investigator meetings from Aradigm, GSK, Insmed, and Corus.

Anne Chang: grant provided by GSK is unrelated to this topic.

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.

Salary support from the Foundation for the 2009 version of this review

External sources

- National Health and Medical Research Council, Australia.

AC's Practitioner Fellowship and Project Grant

- Asthma Australia, Australia.

HP is supported through an Early Career Fellowship

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the original protocol, we defined 'long-term effect' as that measured at more than 12 months duration. We changed this to more than six months duration in the first review undertaken by the current group of review authors.

- We included data from the Martinez-Garcia 2006 study in the review, although the comparison between the untreated and the inhaled corticosteroids (ICS) groups were not blinded. Also, for clinical severity assessment in the Martinez-Garcia 2006 study, we used outcome variables of sputum reduction > 50% and dyspnoea score improvement > 1 posthoc, since these were the ones available from the study.

- We moved lung function to a primary outcome.

- We included 'Summary of findings' tables in the review.

- We added a study flow diagram.

- We specified the methods in more detail following the MECIR standards.

- We redrafted all sections under recommended headings.

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INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Androstadienes [administration & dosage]; Anti-Bacterial Agents [administration & dosage]; Beclomethasone [administration & dosage]; Bronchiectasis [*drug therapy]; Fluticasone; Randomized Controlled Trials as Topic; Respiratory Function Tests

MeSH check words

Adult; Humans

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