Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis

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[Intervention Review]

Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis

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ABSTRACT

Background

Bronchiectasis is a major contributor to chronic respiratory morbidity and mortality worldwide. Wheeze and other asthma-like symptoms and bronchial hyperreactivity may occur in people with bronchiectasis. Physicians often use asthma treatments in patients with bronchiectasis.

Objectives

To assess the effects of inhaled long-acting beta$_2$-agonists (LABA) combined with inhaled corticosteroids (ICS) in children and adults with bronchiectasis during (1) acute exacerbations and (2) stable state.

Search methods

The Cochrane Airways Group searched the the Cochrane Airways Group Specialised Register of Trials, which includes records identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and other databases. The Cochrane Airways Group performed the latest searches in October 2013.

Selection criteria

All randomised controlled trials (RCTs) of combined ICS and LABA compared with a control (placebo, no treatment, ICS as monotherapy) in children and adults with bronchiectasis not related to cystic fibrosis (CF).

Data collection and analysis

Two review authors extracted data independently using standard methodological procedures as expected by The Cochrane Collaboration.

Main results

We found no RCTs comparing ICS and LABA combination with either placebo or usual care. We included one RCT that compared combined ICS and LABA with high-dose ICS in 40 adults with non-CF bronchiectasis without co-existent asthma. All participants received three months of high-dose budesonide dipropionate treatment (1600 micrograms). After three months, participants were randomly assigned to receive either high-dose budesonide dipropionate (1600 micrograms per day) or a combination of budesonide with formoterol (640 micrograms of budesonide and 18 micrograms of formoterol) for three months. The study was not blinded. We assessed it to be an RCT with overall high risk of bias. Data analysed in this review showed that those who received combined ICS-LABA (in stable state) had a significantly better transition dyspnoea index (mean difference (MD) 1.29, 95% confidence interval (CI) 0.40 to 2.18) and cough-free days (MD 12.30, 95% CI 2.38 to 22.2) compared with those receiving ICS after three months of treatment. No significant difference was noted between groups in quality of life (MD -4.57, 95% CI -12.38 to 3.24), number of hospitalisations (odds ratio (OR) 0.26, 95% CI 0.02 to 2.79) or lung function (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)). Investigators reported 37 adverse events in the ICS group versus 12 events in the ICS-LABA group but did not mention the number of individuals experiencing adverse events. Hence differences between groups were not included in the analyses. We assessed the overall evidence to be low quality.

Authors' conclusions

In adults with bronchiectasis without co-existent asthma, during stable state, a small single trial with a high risk of bias suggests that combined ICS-LABA may improve dyspnoea and increase cough-free days in comparison with high-dose ICS. No data are provided for or against, the use of combined ICS-LABA in adults with bronchiectasis during an acute exacerbation, or in children with bronchiectasis in a stable or acute state. The absence of high quality evidence means that decisions to use or discontinue combined ICS-LABA in people with bronchiectasis may need to take account of the presence or absence of co-existing airway hyper-responsiveness and consideration of adverse events associated with combined

ICS-LABA.

PLAIN LANGUAGE SUMMARY

Combined ICS-LABA for children and adults with bronchiectasis

A paucity of evidence is available to allow conclusions on whether combined inhaled corticosteroids (ICS)-long-acting $beta_2$-agonists (LABA) are equivalent or superior to placebo or ICS monotherapy for the treatment of stable or exacerbation (flare-up) state bronchiectasis (Appendix 2).

Review question: Is any evidence available to show that combined ICS-LABA is superior to placebo or ICS monotherapy for the treatment of stable or exacerbation state bronchiectasis in children and adults?

Study characteristics: A small, single-centre, non-blinded study that compared inhaled ICS-LABA with high-dose ICS.

Key results: A single study showed some benefit of the inhaled ICS-LABA combination over high-dose ICS in terms of indices of clinical stability such as dyspnoea (shortness of breath), cough-free days and number of exacerbations but failed to show significant improvement in lung function or microbiology. No data are available on children with bronchiectasis or adults with bronchiectasis during an exacerbation phase. Until further evidence becomes available, we recommend that use of combined ICS-LABA should be individualised according to the presence or likelihood of co-existing asthma features and risks of medications.

Quality of the evidence: This review is based on a single study, hence the quality of evidence is substantially limited.

Bottom line: The decision to use combined ICS-LABA in bronchiectasis must be made for individual patients on the basis of the presence or absence of bronchial hyperreactivity, until further randomised controlled trials are conducted to answer this important question.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Combination inhaled budesonide with formoterol (corticosteroids and long-acting beta$_2$-agonists) compared with high-dose budesonide for bronchiectasis

Patient or population: 18 to 80 years of age with bronchiectasis
Settings: community
Intervention: medium-dose budesonide with formoterol (ICS-LABA)
Comparison: high-dose budesonide (ICS)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ICS	ICS and LABA				
SGRQ Scores range from 0 to 100, with higher scores indicating more limitations Follow-up: 3 months	Mean score 0.73 points lower than baseline	Mean score in the ICS-LABA groups was 4.57 lower than that in the ICS groups (12.38 lower to 3.24 higher)	MD -4.57 (-12.38 to 3.24)	40 (1 study)	⊕⊕◯◯ **low**	The difference between groups for change in SGRQ was not significant. Quality of evidence was downgraded for imprecision and risk of bias
TDI Total scores range from -9 to +9. The lower the score, the greater the deterioration in severity of dyspnoea, MCID $\geq$ 1 Follow-up: 3 months	Mean score 0.1 point higher than baseline	1.29 higher (0.40 to 2.18 higher)	MD 1.29 (0.40 to 2.18)	40 (1 study)	⊕⊕◯◯ **low**	No significant difference between groups. Quality of evidence was downgraded for imprecision and risk of bias
Cough-free days Percentage of days free of cough Follow-up: 3 months	3 per 100	12.30 per 100 higher (2.38% to 22.22% more)	MD 12.30 (2.38 to 22.22)	40 (1 study)	⊕⊕◯◯ **low**	The difference is significant but is based on only 1 study. Quality of evidence was downgraded for imprecision and risk of bias

Hospitalisations, number of participants with 1 or more exacerbations Follow-up: 3 months	167 per 1000	49 per 1000 (4 to 358)	OR 0.26 (0.02 to 2.79)	38 (1 study)	⊕⊕◯◯ **low**	These results should be interpreted with caution, as data are based on a single study with a high risk of bias. CI for comparative risk could not be calculated. Quality of evidence was downgraded for imprecision and risk of bias

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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). As only one study was included in the review, assumed risk is not expressed as a range.
CI: confidence interval; **ICS**: Inhlaed corticosteroids (budesonide); **LABA**: long-acting beta$_2$-agonists; **MCID:** minimal clinically important difference; **OR:** odds ratio; **SGRQ:** St George's Respiratory Questionnaire; **TDI**: transition dyspnoea index.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

These results come from a single study with a small number of participants and require confirmation in other, larger studies.

BACKGROUND

Although bronchiectasis is regarded in affluent countries as an 'orphan disease,' it remains a major contributor to chronic respiratory morbidity (Santamaria 2009; Seitz 2010; Weycker 2005) and mortality (Roberts 2010) worldwide. Recent studies have reported increased prevalence and hospitalisation due to bronchiectasis over the past two decades (Santamaria 2009; Seitz 2010; Weycker 2005). Estimated prevalence rates in the USA, based on a retrospective cohort study, ranged from 4.2 cases per 100,000 persons aged 18 to 34 years to 271.8 per 100,000 among those aged over 75 years (Weycker 2005). The prevalence of bronchiectasis is particularly high in some populations, such as among indigenous Australian children (1470 per 100,000) (Chang 2003) and Alaskan Native children in the USA (1600 per 100,000) (Singleton 2000). Indeed, non-cystic fibrosis (CF) bronchiectasis is far more common globally than CF bronchiectasis in both developing and affluent countries (Chang 2011).

Description of the condition

Bronchiectasis, defined as abnormal widening of the bronchi with airway suppuration, is a heterogeneous condition (King 2006). People with bronchiectasis typically have prolonged and/or recurrent periods of wet or productive cough, with or without features such as haemoptysis, chest pain, exertional dyspnoea, wheeze and asthma-like symptoms, fatigue, recurrent chest infection, growth failure, digital clubbing, hyperinflation and chest wall deformity (Chang 2003; King 2006).

The underlying aetiology of bronchiectasis varies from recurrent respiratory infections to rare immune deficiencies. Other causes include primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis and mycobacterial infection. However, bronchiectasis is a common pathway for a variety of diseases. Thus, the presence of bronchiectasis is increasingly recognised in common respiratory diseases (e.g. chronic obstructive pulmonary disease (COPD) (Keistinen 1997), asthma (Gupta 2009)), uncommon diseases (e.g. bronchiolitis obliterans, sarcoidosis) and non-primary respiratory (e.g. autoimmune) diseases (Chang 2010). When bronchiectasis is present along with another underlying disorder, the morbidity and mortality of the underlying diseases are increased (Keistinen 1997; Lewis 2002). For example, in diseases like COPD, the presence of bronchiectasis has been reported in 29% to 50% (O'Brien 2000; Patel 2004) of cohorts and, when present, increases the severity (Patel 2004) and frequency (Gursel 2006) of respiratory exacerbations.

Description of the intervention

Different types of long-acting beta$_2$-agonists (LABA) (e.g. salmeterol, formoterol) are available. New ultra-LABA (e.g. indacaterol, olodaterol) are emerging. These LABA medications are available through a variety of delivery systems (i.e. metered-dose inhalers and various types of dry powder inhalers). Likewise, different types of inhaled corticosteroids (ICS) (e.g. fluticasone, budesonide, ciclesonide, mometasone) and various methods of delivery are available. LABA with ICS can be delivered via separate inhalers or via a single inhaler as combined therapy. Both delivery types will be included in this review.

How the intervention might work

Asthma-like symptoms and airway hyperresponsiveness may occur in people with bronchiectasis (Chang 2010). When they are present, this disorder may be associated with accelerated pulmonary decline when compared with bronchiectasis without asthma-like symptoms (Keistinen 1997; King 2005). Thus, medications beneficial for people with asthma, such as combined LABA with ICS (Ducharme 2010), may also be beneficial for those with bronchiectasis.

Inhaled beta$_2$-agonists induce bronchodilation by acting on airway smooth muscle beta$_2$-adrenoceptors (Walker 2011). LABA have a duration of action of approximately 12 hours, in contrast to short-acting beta$_2$-agonists (SABA), which have a duration of four to six hours. LABA are available in single inhalers (i.e. used as monotherapy) or in combination with ICS (Cazzola 2011). Cochrane reviews on SABA (Franco 2003) and LABA used as monotherapy for people with bronchiectasis (Sheikh 2001) found no eligible studies.

ICS may be beneficial in people with bronchiectasis by impacting the inflammatory pathway. However, the Cochrane review on ICS for people with bronchiectasis (Kapur 2009) that described six studies in adults and no paediatric data found no significant difference between those who received ICS and those given placebo for all outcomes examined (spirometry, clinical outcomes of exacerbation or sputum volume) when only placebo-controlled studies were included (Kapur 2009).

LABA and ICS as individual monotherapy may have separate beneficial effects in the management of people with bronchiectasis during acute (exacerbation) and/or stable states. Thus, combining LABA and ICS therapy may confer additional benefits. This may be related to ICS negating the proinflammatory effects of long-term beta$_2$-adrenoceptor exposure (Cazzola 2011).

In COPD, LABA combined with ICS (compared with ICS alone) reduces morbidity and mortality (Nannini 2013). In adults with asthma, the addition of LABA to ICS reduces the exacerbation rate and improves lung function (Ducharme 2010). Thus LABA combined with ICS may also be beneficial in children and adults with bronchiectasis.

Why it is important to do this review

As asthma-like symptoms and airway hyperresponsiveness may occur in people with bronchiectasis, asthma medications such as beta$_2$-agonists and ICS as monotherapy or combined therapy are often used. Although asthma may co-exist with bronchiectasis, audible wheeze may reflect small airway obstruction related to airway oedema and secretions rather than bronchospasm. A history of use of asthma medication has been associated with both increased (King 2005) or reduced rate of decline in forced expiratory volume in one second (FEV_1) (Twiss 2006). As described above, LABA combined with ICS may confer additional clinical benefit over either medication alone. Thus, a systematic review of the benefits, or otherwise, of using LABA combined with ICS in people with bronchiectasis will be useful in guiding clinical practice.

OBJECTIVES

To assess the effects of inhaled long-acting beta$_2$-agonists (LABA) combined with inhaled corticosteroids (ICS) in children and adults with bronchiectasis during (1) acute exacerbations and (2) stable state.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials for inclusion in this review. Long-term cross-over trials are contentious for the target population, as recent data have shown that bronchiectasis in adults is generally a progressive condition. Nevertheless, to maintain consistency with the Cochrane review on ICS for bronchiectasis (Kapur 2009), we also included cross-over studies.

Types of participants

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

We planned to exclude participants with other diseases in which bronchiectasis is not present, such as participants with asthma and COPD who do not have co-existent bronchiectasis.

Types of interventions

All types of combined ICS and LABA compared with a control (placebo, no treatment, ICS as monotherapy). ICS and LABA can be delivered through separate inhalers or by a combined inhaler.

Types of outcome measures

Primary outcomes

1. For acute exacerbations.
   i) Mean difference in symptom scores at end of trial.
   ii) Duration of exacerbation.
2. For stable state.
   i) Clinical indices of bronchiectasis control (quality of life (QOL), Likert scale, visual analogue scale, level of interference of cough, etc).
   ii) Exacerbation frequency.

Secondary outcomes

1. For acute exacerbations.
   i) Proportion of participants requiring hospitalisation and total number of hospitalised days.
   ii) Mean difference in other objective indices (airway markers of inflammation, exhaled nitric oxide, etc).
   iii) Mean difference in lung function indices (spirometry, other lung volumes, airway hyperresponsiveness).
   iv) Proportion of participants experiencing adverse effects of the intervention (e.g. pharyngeal candidiasis, voice change).
2. For stable bronchiectasis.
   i) Mortality.
   ii) Radiology scores (high-resolution computed tomography scans or chest radiographs).
   iii) Lung function.
   iv) Relevant airway markers of inflammation.
   v) Proportion experiencing adverse effects of the intervention (e.g. adrenal insufficiency, cataracts, linear growth).

Search methods for identification of studies

Electronic searches

The search was performed by the Cochrane Airways Group. We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), part of *The Cochrane LIbrary*, as well as MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and from handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details) and records in the CAGR coded as 'bronchiectasis' using the following terms:

(steroid* or corticosteroid or ICS or fluticasone or budesonide or beclomet* or flunisolide or mometasone or ciclesonide) AND (LABA or beta* or long-acting* or "long acting*" or *formoterol or salmeterol or indacaterol or olodacaterol)

We also conducted a search of ClinicalTrials.gov and the World Health Organization (WHO) trial portal using appropriate keywords. We searched all databases from their inception up to October 2013 with no restriction on language of publication or publication status.

Searching other resources

We checked the reference lists of all relevant primary studies and review articles for additional references. We contacted the primary author of the identified trial.

Data collection and analysis

Selection of studies

Both review authors independently assessed titles and abstracts of studies identified by the search to identify potentially relevant studies. For appropriate articles, we assigned each reference to a study identifier and assessed the full text against the inclusion criteria of this protocol. There was no disagreement between the review authors on selection of studies.

Data extraction and management

We extracted data onto a data collection form. We discussed and resolved discrepancies in the data. We transferred data from the data collection form into Review Manager 5.1 (RevMan Version 5.1) and managed it according to recommendations provided in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011).

We extracted information from the single identified study for the following characteristics.

1. Design (design, total duration of study and run-in, number of study centres and locations, withdrawals, date of study).
2. Participants (N, mean age, age range, gender, bronchiectasis severity, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria).
3. Interventions (run-in, intervention treatment and inhaler type, control treatment and inhaler type).
4. Outcomes (primary and secondary outcomes specified and collected, time points reported).

Assessment of risk of bias in included studies

Both review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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 bias domain as high, low or unclear for each study.

Measures of treatment effect

For dichotomous variables, we calculated individual and pooled statistics as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes measured on the same metrics, we calculated individual and pooled statistics as mean differences (MDs) with 95% CIs. For continuous outcomes measured on different metrics, we planned to combine data using standardised mean differences (SMDs).

For cross-over studies, we planned to include only the first arm and to calculate mean treatment differences from raw data, with variances extracted or imputed and entered as fixed-effect generic inverse variance (GIV) outcomes, to provide summary weighted differences and 95% CIs.

Unit of analysis issues

The unit of analysis was the participant. In cross-over trials, because there might be a carry-over effect from both ICS and LABA, we planned that only data from the first arm would be included in the meta-analysis when the data are combined with those from parallel studies, as was previously done (Kapur 2009).

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible. We planned to conduct intention-to-treat (ITT) analysis by assuming that missing values would have had poor outcomes. The single study included had analysed data using ITT analysis.

Assessment of heterogeneity

We had planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis. As only one eligible study was identified, assessment of heterogeneity was not applicable. If we had identified substantial heterogeneity, we planned to explore this through prespecified subgroup analysis (see Subgroup analysis and investigation of heterogeneity). We would have considered levels of heterogeneity greater than 50% as substantial.

Assessment of reporting biases

We planned to attempt to contact study authors and ask them to provide missing outcome data in cases of suspected reporting bias. When this was not possible, and the missing data were thought to

introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis**.** We planned to investigate publication bias by visually inspecting a funnel plot if at least 10 trials were included in a meta-analysis for a single outcome. As the review is based on a single study, we have not done a funnel plot of studies.

Data synthesis

We analysed data using Review Manager 5 (RevMan Version 5.1), with a view toward using a fixed-effect MD (calculated as a weighted MD) for continuous data variables. For dichotomous outcome variables of each individual study, we calculated the ORs using a modified ITT analysis (i.e. failure assumed if participant drops out of study). This analysis assumes that participants not available for outcome assessment have not improved (and probably represents a conservative estimate of effect).

We intended to calculate a number needed to treat (for an additional beneficial or harmful outcome) when possible for the different levels of risk as represented by control group event rates over a specified time period using the pooled OR, and its CI using an online calculator, Visual Rx (Cates 2003). We constructed a 'Summary of findings' table according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses on the primary outcomes of both exacerbation and stable states.

1. Children versus adults.
2. Type of ICS-LABA combination.
3. Type of control arm (placebo/no treatment/ICS).

As only one included study was identified, subgroup analysis was not possible.

Sensitivity analysis

We planned to assess the impact of the following important factors on overall outcomes.

1. Study quality.
2. Variation in inclusion criteria.
3. Differences in medications used in the intervention and comparison groups.
4. Differences in outcome measures.
5. Analysis using random-effects model.
6. Analysis by "treatment received" and analysis by "intention-to-treat."

We planned to remove from the meta-analysis studies considered to be at high or unclear risk of bias for methodological quality (as per the risk of bias table), and to examine any changes in the summary statistics. As only one study was eligible for inclusion in the review, sensitivity analysis was not undertaken.

Summary of findings table

We created a 'Summary of findings' table using the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and by using GRADEpro software. We included only the primary outcomes and one secondary outcome.

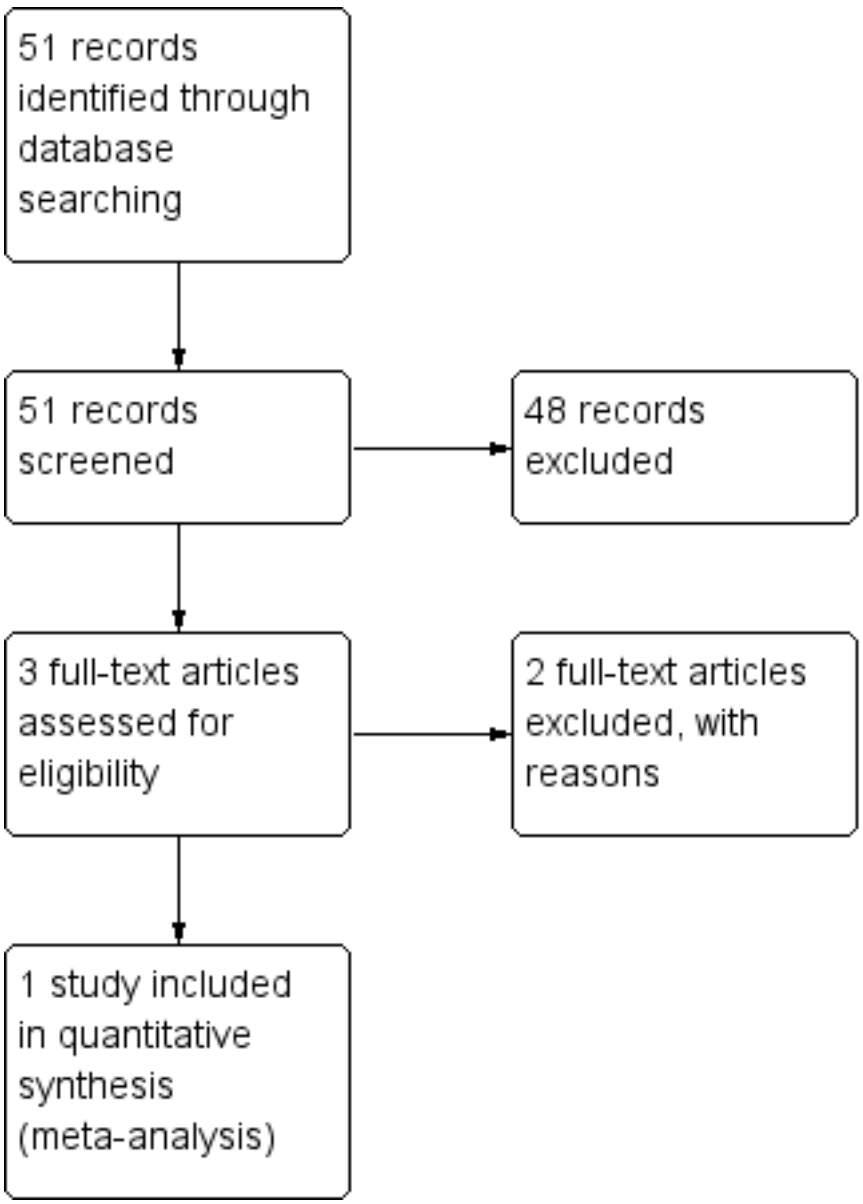
RESULTS

Description of studies

Results of the search

The Airways Group search identified 51 potentially relevant titles (Figure 1). Two review authors (VG and AC) independently assessed the abstracts and retrieved three papers. Of these,only one study fulfilled the study eligibility criteria (Included studies), and the other two studies were excluded (Excluded studies). No paediatric studies were identified. No studies were identified that compared ICS-LABA versus placebo or usual care.

Figure 1. Study flow diagram.



Included studies

The single included study (Martinez-Garcia 2012) was conducted in Spain in 40 adults between 18 and 80 years of age with non-CF bronchiectasis. The study excluded patients with co-existent asthma. The study authors reported it as a double-blinded, parallel-group RCT comparing high-dose budesonide dipropionate treatment versus the combination of budesonide with formoterol. However, on writing to the primary author, we were informed that participants were aware of the different coloured turbuhalers. The trial was carried out in two stages. During the first stage, all participants received three months of high-dose budesonide dipropionate treatment (1600 micrograms). All other non-study drugs and steroids were stopped. After three months, participants were randomly assigned to receive either high-dose budesonide dipropionate (1600 micrograms per day) or a combination of budesonide with formoterol (640 micrograms of budesonide and 18 micrograms of formoterol) for three months. Bronchiectasis exacerbation was defined as subjective and persistent (24 hours) deterioration in at least three respiratory symptoms, including cough, dyspnoea, haemoptysis, increased sputum purulence or volume, chest pain (with or without fever), radiographic deterioration, systemic disturbances or changes in chest auscultation (Tsang 1998). Outcomes for this study were health-related quality of life (as measured by St George's Respiratory Questionnaire), transition dyspnoea index, cough-free days, rescue beta$_2$-agonist inhalation as needed, change in lung function, microbiology data, number of exacerbations and adverse effects of the medications.

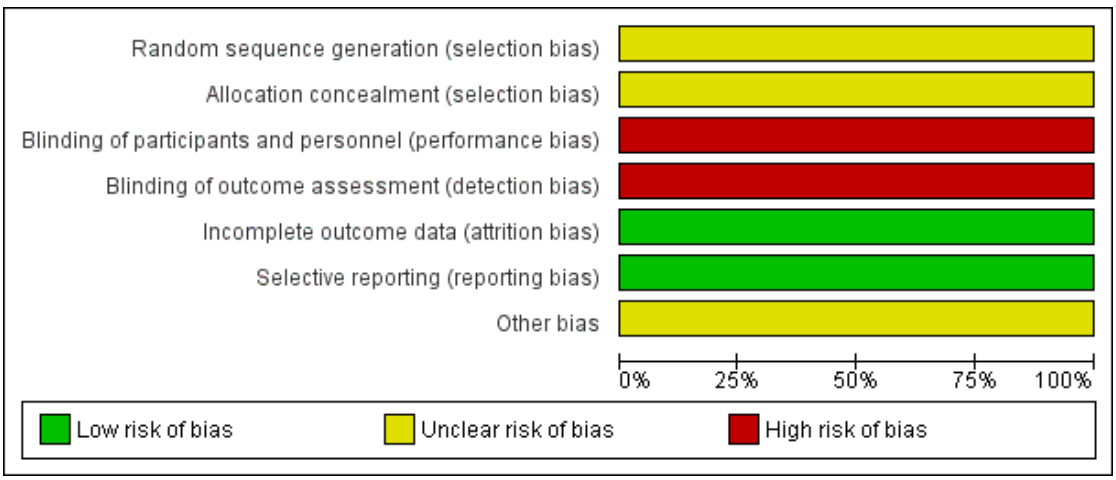
Excluded studies

We found two additional studies that were excluded, as they did not fulfil the inclusion criteria (see Characteristics of excluded studies). The first study (Mostafapour 2009) was published in Croatian. Investigators reported significant improvement in lung function parameters among 12 participants enrolled in the study, all of whom received a combination of salmeterol and fluticasone. This study was excluded because it was not an RCT. The second study, published in Chinese (Ding 2006), used SABA. Investigators reported that those receiving combined ICS-SABA had a reduced quantity of sputum and fewer hospitalised days compared with those given SABA alone or no therapy. Although this was an RCT, the study was excluded because the inclusion criteria required LABA, not SABA.

Risk of bias in included studies

Overall we assessed the sole included study (Martinez-Garcia 2012) to be at high risk of bias, as detailed in the 'Risk of bias' table and summarised in Figure 2.

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



Allocation

Participants were randomly assigned using a computer-generated programme, but the details were not provided. Drugs were dispensed by an independent pharmacist, but details of this were not provided in the paper.

Blinding

This study was described as double-blind. The two groups received drugs in a similar regimen (i.e. two puffs two times a day). We contacted the original study authors, who suggested that the two inhalers did not look similar and hence did not fulfil the criteria for adequate blinding.

Incomplete outcome data

The number of participants withdrawn because of adverse effects (two in the high-dose budesonide group and one lost to follow-up in the combination group) was reported, and ITT analysis was used; therefore we judged the trial to be at low risk of attrition bias.

Selective reporting

It was not suggested that selective reporting had occurred.

Other potential sources of bias

The study was sponsored by pharmaceutical companies, but the study authors reported that the company had no role in the design of the study, in collection and analysis of the data, or in preparation of the manuscript.

Effects of interventions

See: **Summary of findings for the main comparison**

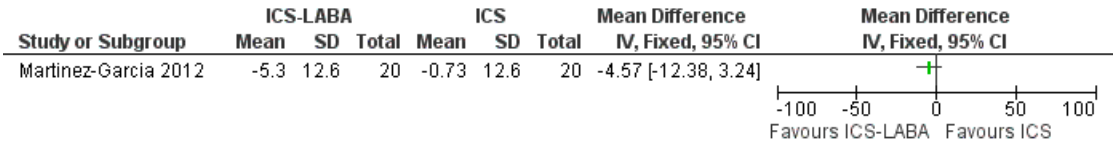
Primary outcomes

The included study was conducted during stable state. Thus, only outcomes related to 'stable state' are described below.

Clinical indices of bronchiectasis control: quality of life and dyspnoea

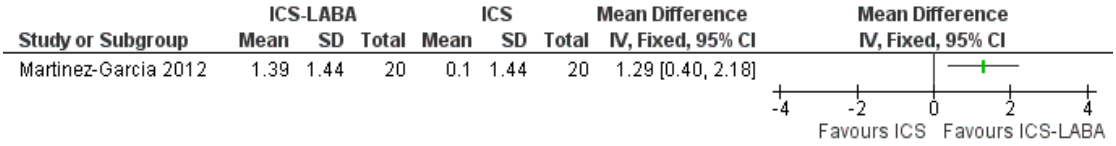
Using the Spanish version of St George's Respiratory Questionnaire (SGRQ), Martinez-Garcia 2012 and colleagues in their paper reported significant improvement (5.3 point reduction in SGRQ score) among participants using combined ICS and LABA but no improvement in the ICS group (0.73 points). SGRQ score ranges from 0 to 100, with higher scores indicating more severe limitations. Data on differences between the groups were not mentioned in the paper. The standard deviation (SD) for mean change in the ICS-LABA group was calculated from the P value provided in the paper. As no numbers were provided for the ICS group (controls), we requested data from the study authors, who reported that the change in the ICS group was 0.73 points. Because the P value was not provided for the ICS group, we assumed the SD to be the same as that in LABA-ICS group. No significant differences between groups were reported (MD -4.57, 95% CI -12.38 to 3.24; Analysis 1.1, Figure 3) for SGRQ.

Figure 3. Forest plot of comparison: quality of life (total SGRQ score).



For the outcome of transition dyspnoea index, those receiving combined ICS-LABA were significantly better than the ICS group (MD 1.29, 95% CI 0.40 to 2.18; Analysis 1.2, Figure 4).

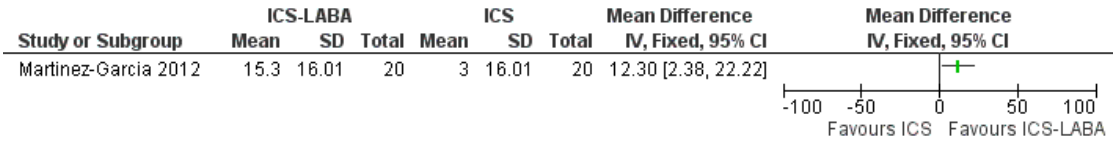
Figure 4. Forest plot of comparison: transient dyspnoea index.



Cough-free days

A significant difference between groups was reported for cough-free days; those in the combined ICS-LABA group had 15.3% of days cough-free compared with 3% in the ICS group (MD 12.30, 95% CI 2.38 to 22.2; Analysis 1.3, Figure 5).

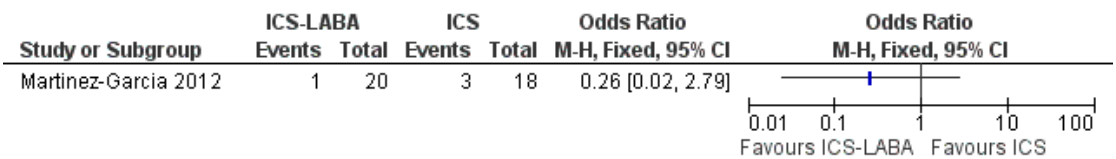
Figure 5. Forest plot of comparison: cough-free days.



Exacerbations

No significant difference in the number of participants who experienced exacerbations was reported (seven in the ICS group and four in the ICS-LABA group). No significant differences in hospitalisation were described between groups (OR 0.26, 95% CI 0.02 to 2.79; Analysis 1.4, Figure 6). We did not include exacerbations in a forest plot because it was not mentioned in the study whether seven and four participants, respectively, were having at least one exacerbation, or whether few participants experienced more than one exacerbation.

Figure 6. Forest plot of comparison: exacerbations.



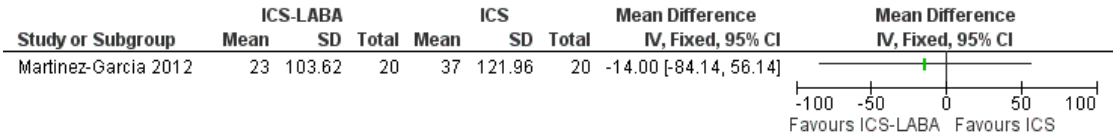
Secondary outcomes

The single included study reported the results for other secondary outcomes including lung function and proportions of participants experiencing adverse effects of the intervention. Investigators did not use change in radiology scores as an outcome, and no deaths were reported in the trial period. Relevant inflammatory markers for the airway were not tested.

Lung function

No significant change in lung function indices was reported in the sole included study. Although FEV_1 seemed to improve more in the high-dose budesonide group (MD -14.00, 95% CI -86.83 to 58.83; Analysis 1.5, Figure 7) and forced vital capacity (FVC) improved more in the combination group (MD 14.00, 95% CI -63.17 to 91.17; Analysis 1.6), the differences were not significant .

Figure 7. Forest plot of comparison: FEV1 (change from baseline in mL).



Adverse events

Study authors reported a significant difference in the number of adverse events, with the ICS group experiencing more events. They described 37 adverse events in the ICS group versus 12 events in the ICS-LABA group but did not mention the number of individuals who experienced adverse events.

DISCUSSION

This review included data from only one study, and the results of the review are different from those reported in the study, as the study authors had described the study as double-blinded when it was not, and the difference in QOL between the two groups was not significant, as was stated in the study. We found that the LABA-ICS group had significantly better control of bronchiectasis in terms of cough-free days and transitional dyspnoea index, but no significant difference between groups could be found for QOL (as measured by SGRQ), lung function, number of participants with one or more exacerbations or adverse events. Given the high risk of bias and the small number of participants in the single included study, widespread applicability of these results is substantially limited.

This review summarises the best evidence available up to September 2013 and emphasises the paucity of trials testing the combination of LABA with ICS for bronchiectasis in adults and children.

Summary of main results

This review is limited to a single study eligible for inclusion (Martinez-Garcia 2012). The combination of LABA-ICS was marginally better than high-dose ICS in improving only a few clinical indices of bronchiectasis symptom control in adults with stable state non-CF bronchiectasis without co-existent asthma. Although the study has been reported as a double-blinded trial, we assessed it as having high risk of blinding and performance bias, as well as detection bias, as the two inhalers were of different colours therefore quality of evidence across the outcomes from the study were downgraded to low quality evidence. There were no studies in support or otherwise for the ICS-LABA combination for non-CF bronchiectasis in children or adults with acute exacerbations. Overall the quality of evidence based on this review is low, and conclusions are likely to change as more evidence becomes available.

Overall completeness and applicability of evidence

Although this review provides some evidence of possible benefit derived from using combined LABA-ICS rather than high-dose inhaled steroids in patients with non-CF bronchiectasis, the results from a single study on clinical efficacy and safety of budesonide-formoterol over three months cannot be applied to all LABA and ICS combinations. This review highlights the fact that there remains a paucity of high-quality data to support the routine use of combined ICS-LABA. We need more robust evidence for the

use of combination LABA-ICS in stable and exacerbation states of non-CF bronchiectasis.

The reason why we cannot make any significant recommendations based on the results of this review are manifold: First, this review is based on a single study in adults, and no studies in children have been identified. Second, no studies were identified for use of the LABA-ICS combination for acute exacerbations. Third, the number of participants (20 in each group) and the duration of follow-up (three months) were small. Fourth, the sole included study has a high risk of bias. Last, even though the study authors excluded participants with asthma and COPD, participants were not tested for airway hyperreactivity, and this could be a reason for the non-significant difference between the two groups.

With no paediatric trial available at the time of this review, extrapolation of results to children cannot be recommended. As this was a single-study review, it was not possible to examine whether the duration of the intervention affected the findings.

Quality of the evidence

Only a single study was included in this review, hence the quality of evidence is substantially limited.

Potential biases in the review process

The Cochrane Airways Group conducted an extensive search for RCTs in children and adults with bronchiectasis. Two review authors independently screened the searches and identified one study for inclusion. We identified the sole included study itself as having overall high risk of bias. We contacted the original investigators, who kindly provided additional information about randomisation and blinding.

Agreements and disagreements with other studies or reviews

Evidence shows that a proportion of patients with bronchiectasis have increased airway hyperreactivity (Müsellim 2013; Pang 1989), and in adults with bronchiectasis, bronchodilator use is associated with greater decline in lung function over two-year follow-up (King 2005). Further, the ICS-LABA combination has proved better than ICS alone in asthma and COPD (Chroinin 2009; Nannini 2013). These results have been extrapolated to adults and children with bronchiectasis for use of a combination of ICS with LABA, but evidence to support it is lacking.

AUTHORS' CONCLUSIONS

Implications for practice

Results of a small single trial at high risk of bias suggest that LABA combined with ICS (compared with high-dose ICS) may be beneficial in adult patients with stable bronchiectasis without co-existent asthma in improving symptom control. However, in the absence of sufficient evidence, combined ICS-LABA cannot be routinely recommended for adults or children with bronchiectasis. Until further evidence becomes available, we recommend that therapy be individualised on the basis of the presence or absence of co-existing airway hyperresponsiveness and consideration of adverse events associated with combined ICS-LABA.

Implications for research

This review highlights the fact that we need large RCTs comparing the combination of inhaled LABA with ICS versus placebo or ICS in adults and children in stable and exacerbation states of bronchiectasis. Future RCTs should consider the following features.

- Double-blind, randomised, parallel studies.
- Inclusion of placebo and inhaled steroids alone.
- In the case of different coloured inhalers, a double-dummy trial.
- Minimal intervention period of six to 12 months to account for the long-term adverse effects of steroids.
- Clearly defined outcome measures, including validated QOL indices and changes in lung function, sputum volume, microbiology data and sputum and/or blood inflammatory markers.
- A priori definition of bronchial hyperreactivity with a planned subgroup analysis in participants with hyperreactivity.
- Powered to enable treatment stratification (co-existent asthma vs overall effect).
- Complete reporting of continuous (N, mean change and mean standard deviation of change) and dichotomous (denominators and event rate) data.
- Protocol-defined exacerbations and adverse events and data presented as numbers of participants as well as numbers of events.
- Well-defined adverse events, including pharyngeal candidiasis, voice change, adrenal suppression, osteopenia, effect on linear growth etc.
- Stratification based on causes of bronchiectasis and the presence or absence of *Pseudomonas aeruginosa.*
- Use of ITT analysis.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Martinez-Garcia 2012 *{published data only}*
Martínez-García MA, Soler-Cataluña JJ, Catalán-Serra P, Román-Sánchez P, Tordera MP. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. *Chest* February 2012;**141**(2):461–8.

References to studies excluded from this review

Ding 2006 *{published data only}*
Ding H, Wang JG, Sun XY, Xu LJ. Responsibility to bronchodilator and glucocorticosteroid in patients with bronchiectasia and reversible airflow limitation. *Journal of Jilin University Medicine Edition* 2006;**32**(5):872–5.

Mostafapour 2009 *{published data only}*
Mostafapour E, Mousavi S-AJ, Shahmiri SS, Fereshtehnejad S-M. Effects of combination of fluticasone propionate and salmeterol xinafoate on lung function improvement in patients with bronchiectasis. *Lijecnicki Vjesnik* 2009;**131** (Suppl 6):8–11.

Additional references

Cates 2003
Cates C. Visual Rx. Online NNT Calculator. Cates C, 2003.

Cazzola 2011
Cazzola M, Calzetta L, Matera MG. Beta(2) -adrenoceptor agonists: current and future direction. *British Journal of Pharmacology* 2011;**163**:4–17.

Chang 2003
Chang AB, Masel JP, Boyce NC, Wheaton G, Torzillo PJ. Non-CF bronchiectasis-clinical and HRCT evaluation. *Pediatric Pulmonology* 2003;**35**(6):477–83.

Chang 2010
Chang AB, Bell SC, Byrnes CA, Grimwood K, Holmes PW, King PT, et al.Bronchiectasis and chronic suppurative lung disease (CSLD) in children and adults in Australian and New Zealand: Thoracic Society of Australia and New Zealand and Australian Lung Foundation Position Statement. *Medical Journal of Australia* 2010;**193**(6): 356–65.

Chang 2011
Chang AB. Editorial. Bronchiectasis: so much yet to learn and to do. *Paediatric Respiratory Review* 2011;**12**:89–90.

Chroinin 2009
Chroinin MN, Greenstone I, Lasserson TJ, Ducharme FM. Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD005307.pub2]

Ducharme 2010
Ducharme FM, Ni CM, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD005535.pub2]

Franco 2003
Franco F, Sheikh A, Greenstone M. Short acting beta2-agonists for bronchiectasis. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD003572]

Gupta 2009
Gupta S, Siddiqui S, Haldar P, Raj JV, Entwisle JJ, Wardlaw AJ, et al.Qualitative analysis of high resolution computed tomography scans in severe asthma. *Chest* 2009;**136**(6): 1521–8.

Gursel 2006
Gursel G. Does coexistence with bronchiectasis influence intensive care unit outcome in patients with chronic obstructive pulmonary disease?. *Heart and Lung* 2006;**35** (1):58–65.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Kapur 2009
Kapur N, Bell S, Kolbe J, Chang AB. Inhaled steroids for bronchiectasis. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD000996.pub2]

Keistinen 1997
Keistinen T, Saynajakangas O, Tuuponen T, Kivela SL. Bronchiectasis: an orphan disease with a poorly-understood prognosis. *European Respiratory Journal* 1997;**10**(12): 2784–7.

King 2005
King PT, Holdsworth SR, Freezer NJ, Villanueva E, Gallagher M, Holmes PW. Outcome in adult bronchiectasis. *COPD* 2005;**2**(1):27–34.

King 2006
King P, Holdsworth S, Freezer N, Holmes P. Bronchiectasis. *Internal Medicine Journal* 2006;**36**(11):729–37.

Lewis 2002
Lewis MM, Mortelliti MP, Yeager H, Tsou E. Clinical bronchiectasis complicating pulmonary sarcoidosis: case series of seven patients. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases* 2002;**19**(2):154–9.

Müsellim 2013
Müsellim B. Bronchial hyperreactivity in non-cystic fibrosis bronchiectasis. *Journal of Clinical and Analytical Medicine* 2013;**4**(3):224–7.

Nannini 2013
Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD006826.pub2]

O'Brien 2000
O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000;**55**(8):635–42.

Pang 1989
Pang J, Chan HS, Sung JY. Prevalence of asthma, atopy, and bronchial hyperreactivity in bronchiectasis: a controlled study. *Thorax* 1989;**44**(11):948–51.

Patel 2004
Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, et al.Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2004;**170**:400–7.

RevMan Version 5.1
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Roberts 2010
Roberts HJ, Hubbard R. Trends in bronchiectasis mortality in England and Wales. *Respiratory Medicine* 2010;**104**(7): 981–5.

Santamaria 2009
Santamaria F, Montella S, Pifferi M, Ragazzo V, De SS, De PN, et al.A descriptive study of non-cystic fibrosis bronchiectasis in a pediatric population from central and southern Italy. *Respiration* 2009;**77**(2):160–5.

Seitz 2010
Seitz AE, Olivier KN, Steiner CA, De Oca RM, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations: USA, 1993-2006. *Chest* 2010; **138**(4):944–9.

Sheikh 2001
Sheikh A, Nolan D, Greenstone M. Long-acting beta-2-agonists for bronchiectasis. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD002155]

Singleton 2000
Singleton RJ, Morris A, Redding G, Poll J, Holck P, Martinez P, et al.Bronchiectasis in Alaska Native children: causes and clinical courses. *Pediatric Pulmonology* 2000;**29** (3):182–7.

Tsang 1998
Tsang KW, Ho PL, Lam WK, Ip MS, Chan KN, Ho CS, et al.Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 1998;**158**(3):723–7.

Twiss 2006
Twiss J, Stewart AW, Byrnes CA. Longitudinal pulmonary function of childhood bronchiectasis and comparison with cystic fibrosis. *Thorax* 2006;**61**:414–8.

Walker 2011
Walker JK, Penn RB, Hanania NA, Dickey BF, Bond RA. New perspectives regarding beta(2) -adrenoceptor ligands in the treatment of asthma. *British Journal of Pharmacology* 2011;**163**(1):18–28.

Weycker 2005
Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clinical Pulmonary Medicine* 2005;**12**(4):205–9.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Martinez-Garcia 2012

Methods	Randomised, non-blinded, parallel-group clinical trial from a single centre: La Fe University Hospital, Valencia, Spain 3 -month run-in period followed by 3 months of intervention. 2 withdrawals in ICS because of adverse events; 1 in the LABA-ICS group did not return
Participants	40 participants between 18 and 80 years of age with non-CF bronchiectasis 1. Mean age 70.1 years 2. 45% male participants 3. Mean smoking history of 4.7 pack-years with no differences between the 2 groups 4. Baseline lung function FEV_1 1297 mL (61% of predicted) with no differences between groups Diagnosis of bronchiectasis established by chest high-resolution CT (HRCT) scan performed a maximum of 12 months before the start of the study Inclusion criteria 1. Known chronic airflow obstruction 2. Clinically stable phase (i.e. free from acute exacerbation for at least 6 weeks) Exclusion criteria 1. Cigarette smoking history of 10 pack-years 2. Occupational risk for COPD 3. Long-term oral steroid treatment 4. Traction bronchiectasis due to advanced fibrosis 5. Known intolerance for ICS or LABA 6. Asthma 7. Cardiopulmonary conditions that could modify spirometric values or its course
Interventions	Interventions During the first stage (run-in period): All participants received 3-month high-dose budesonide dipropionate (1600 microgram) treatment In the second stage, participants were randomly assigned to either 1. Continuing high-dose budesonide dipropionate (1600 microgram) treatment dosed in two inhalations every 12 hours, or 2. A single Turbuhaler inhaler with half of the budesonide daily dose and formoterol (18 micrograms of formoterol furoate and 640 micrograms of budesonide dipropionate), dosed in 2 inhalations every 12 hours
Outcomes	Clinical and health-related quality of life (HRQOL) measures at randomisation and at 3 months Pulmonary function at randomisation and at 3 months Microbiologic data at randomisation and at 3 months Exacerbations
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence was generated by a computer, but details were not provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the study, although the drug was dispensed by an independent pharmacist
Blinding of participants and personnel (performance bias) All outcomes	High risk	The 2 inhalers were different in colour, hence we judged that the participants were not blinded (although the manuscript mentioned it was a double-blinded study). These data were obtained from the primary author of the study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary outcome (mentioned in trial registration but not in paper) was St George's Respiratory Questionnaire (SGRQ) at 3 months and at 6 months. As participants were not blinded, risk of detection bias was high
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants withdrawing from each group accounted for and final intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	Study partially sponsored by a company with pharmaceutical interest

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

Study	Reason for exclusion
Ding 2006	Article in Chinese; a study of 34 participants compared 3 groups given routine care (n = 11) vs nebulised terbutaline (n = 11) vs terbutaline + budesonide (n = 12). Excluded, as terbutaline is not a LABA
Mostafapour 2009	Excluded because this was a non-randomised study; all 12 participants recruited into the study were given the study medication

DATA AND ANALYSES

Comparison 1. Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (change in total SGRQ score from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Transition dyspnoea index (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Cough-free days (percentage)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Hospitalisations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 FEV_1 (change from baseline in mL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 FVC (change from baseline in mL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

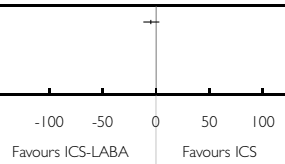
Analysis 1.1. Comparison 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control, Outcome 1 Quality of life (change in total SGRQ score from baseline).

Review: Combination inhaled corticosteroids and long-acting $beta_2$-agonists for children and adults with bronchiectasis

Comparison: 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome: 1 Quality of life (change in total SGRQ score from baseline)

Study or subgroup	ICS-LABA N	Mean(SD)	ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Martinez-Garcia 2012	20	-5.3 (12.6)	20	-0.73 (12.6)		-4.57 [-12.38, 3.24]



Analysis 1.2. Comparison 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control, Outcome 2 Transition dyspnoea index (change from baseline).

Review: Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis

Comparison: 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome: 2 Transition dyspnoea index (change from baseline)

Study or subgroup	ICS-LABA N	Mean(SD)	ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Martinez-Garcia 2012	20	1.39 (1.44)	20	0.1 (1.44)		1.29 [0.40, 2.18]

Analysis 1.3. Comparison 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control, Outcome 3 Cough-free days (percentage).

Review: Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis

Comparison: 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome: 3 Cough-free days (percentage)

Study or subgroup	ICS-LABA N	Mean(SD)	ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Martinez-Garcia 2012	20	15.3 (16.01)	20	3 (16.01)		12.30 [2.38, 22.22]

Analysis 1.4. Comparison 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control, Outcome 4 Hospitalisations.

Review: Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis

Comparison: 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome: 4 Hospitalisations

Study or subgroup	ICS-LABA n/N	ICS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Martinez-Garcia 2012	1/20	3/18		0.26 [0.02, 2.79]

Analysis 1.5. Comparison 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control, Outcome 5 FEV1 (change from baseline in mL).

Review: Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis

Comparison: 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome: 5 FEV_1 (change from baseline in mL)

Study or subgroup	ICS-LABA N	Mean(SD)	ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Martinez-Garcia 2012	20	23 (103.62)	20	37 (121.96)		-14.00 [-84.14, 56.14]

Analysis 1.6. Comparison 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control, Outcome 6 FVC (change from baseline in mL).

Review: Combination inhaled corticosteroids and long-acting beta$_2$-agonists for children and adults with bronchiectasis

Comparison: 1 Combined ICS-LABA vs high-dose ICS; clinical indices of bronchiectasis control

Outcome: 6 FVC (change from baseline in mL)

Study or subgroup	ICS-LABA N	Mean(SD)	ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Martinez-Garcia 2012	20	74 (128.2)	20	60 (120.7)		14.00 [-63.17, 91.17]

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*The Cochrane Library*)	Monthly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Bronchiectasis search

1. exp Bronchiectasis/
2. bronchiect$.mp.
3. bronchoect$.mp.
4. kartagener$.mp.
5. (ciliary adj3 dyskinesia).mp.
6. (bronchial$ adj3 dilat$).mp.
7. or/1-6

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and the RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Terms used in plain language summary

Scientific Term	Plain language
Bronchiectasis	Refers to dilatation of bronchi (breathing tubes) identified on CT scan of chest in the presence of relevant clinical features
Exacerbation	Flare-up, worsening of symptoms of cough, shortness of breath, etc
Indices of clinical stability	Clinical signs pointing to stability of the disease
Dyspnoea	Shortness of breath
Bronchial hyperreactivity	Inappropriate reaction of the airway smooth muscle to different stimuli
Placebo	Simulated or otherwise medically ineffectual treatment

CONTRIBUTIONS OF AUTHORS

The protocol was written by both review authors on the basis of previous protocols on bronchiectasis (Kapur 2009). VG and AC selected articles from the search, analysed the data independently and wrote the manuscript. VG contacted the authors of the included study to ask for further information.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- No sources of support supplied

External sources

- National Health & Medical Research Council, Australia.

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- National Health & Medical Research Council, Australia.

Centre for Research Excellence in Lung Health of Aboriginal and Torres Straits Islander children (grant number 1040830)

- Australian Cochrane Airways Group/Australian Lung Foundation Scholarship, Australia.

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