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Inhaled steroids for bronchiectasis

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ABSTRACT

Background

Bronchiectasis is increasingly recognized as a major cause of respiratory morbidity especially in developing countries and in some ethnic populations of affluent countries. It is characterized by irreversible dilatation of airways, generally associated with chronic bacterial infection. Medical management largely aims to reduce morbidity by controlling the symptoms and by preventing the progression of bronchiectasis.

Objectives

To evaluate the efficacy of inhaled corticosteroids (ICS) in children and adults with bronchiectasis (a) during stable bronchiectasis; and for reducing; (b) the severity and frequency of acute respiratory exacerbations and (c) long term pulmonary decline.

Search methods

The Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Specialized Register of trials, MEDLINE and EMBASE databases were searched by the Cochrane Airways Group. The latest searches were performed in October 2010.

Selection criteria

All randomised controlled trials comparing ICS with a placebo or no medication. Children and adults with clinical or radiographic evidence of bronchiectasis were included, but patients with cystic fibrosis (CF) were excluded.

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion.

Main results

There were no paediatric studies. Six adult studies fulfilled the inclusion criteria. Of the 303 randomised, 278 subjects completed the trials. In the short term group (ICS for less than 6 months duration), adults on large doses of ICS (2g per day of budesonide equivalent) had significantly improved forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), Quality of life (QOL) score and sputum volume but no significant difference in peak flow, exacerbations, cough or wheeze, when compared to adults in the control arm (no ICS). When only placebo-controlled studies were included, there were no significant difference 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 effect of inhaled steroids in any of the outcomes.

Authors’ conclusions

The present review indicates that there is insufficient evidence to recommend the routine use of inhaled steroids in adults with stable state bronchiectasis. While a therapeutic trial may be justified in adults with difficult to control symptoms and in certain subgroups, this has to be balanced with adverse events especially if high doses are used. No recommendation can be made 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 in management of non CF bronchiectasis

People with bronchiectasis have significant morbidity (e.g. cough, wheeze, sputum production) and have more rapid lung function decline. As asthma like symptoms are common in people with bronchiectasis, the routine use of inhaled corticosteroids is potentially beneficial in reducing exacerbations, symptoms and pulmonary decline. The review found that there is insufficient evidence for the routine use of inhaled corticosteroids in people with bronchiectasis. While inhaled corticosteroids may be beneficial in a subgroup of people with bronchiectasis, its use has to be balanced with adverse effects that include potential increase in commensal bacterial density in the sputum.

BACKGROUND

Bronchiectasis, previously termed an ‘orphan disease’ is increasingly recognized as a major cause of respiratory morbidity especially in developing countries (Karadag 2005, Karakoc 2001) and in some ethnic populations of affluent countries (Chang 2002, Edwards 2003, Singleton 2000). The underlying aetiology of bronchiectasis varies from post recurrent respiratory infections to rare immune deficiencies. Other causes include primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis and Mycobacterial infection (Shoemark 2007). However, bronchiectasis is also a common pathway for a variety of diseases. Thus, the presence of bronchiectasis is also increasingly recognised in common (e.g. chronic obstructive pulmonary disease (COPD) (Patel 2004, O’Brien 2000) and uncommon respiratory diseases (e.g. bronchiolitis obliterans (Chang 1998) and sarcoidosis (Lewis 2002)) as well non primary respiratory (e.g. autoimmune) diseases. When bronchiectasis is present with another underlying disorder, it increases the morbidity and mortality of the underlying diseases (Lewis 2002, Keistinen 1997). For example, in diseases like COPD the presence of bronchiectasis has been reported in 29-50% (Patel 2004, O’Brien 2000) of cohorts and when present, increases the severity (Patel 2004) and frequency (Gursel 2006) of respiratory exacerbations. Thus, management of the symptoms and severity of bronchiectasis is important.

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 decline may occur (Keistinen 1997, Twiss 2006). In both children and adult cohort studies, asthma-like symptoms in people with bronchiectasis have been described and when present, is associated with accelerated pulmonary decline when compared to those with bronchiectasis but without asthma-like symptoms (Keistinen 1997, Field 1969).

Like patients with COPD, children and adults with bronchiectasis also suffer from recurrent acute exacerbations, some of whom require hospitalised treatment. Effective management regimes for bronchiectasis would reduce the frequency or severity of respiratory exacerbations, and/or the long term pulmonary decline. Based on Cole’s ‘vicious circle hypothesis’, microbial colonization/infection is important in the pathophysiology of bronchiectasis as it leads to bronchial obstruction and a normal or exaggerated inflammatory response (Cole 1986). Neutrophilic airway inflammation is dominant in people with bronchiectasis and COPD and ICS is likely beneficial in people with COPD (Abramson 2006). However use of ICS is associated with adverse events in children and adults that range from mild (candidiasis) to serious (adrenal insufficiency, osteoporosis, cataracts) events. Thus a systematic review on the efficacy of ICS in the management of children and adults with bronchiectasis would help guide clinical practice. This
current review was significantly revised from a previous review (Ram 2000).

**OBJECTIVES**

To evaluate the efficacy of inhaled corticosteroids (ICS) in children and adults with bronchiectasis:
(a) during stable bronchiectasis;
and for reducing
(b) the severity and frequency of acute respiratory exacerbations
and
(c) long term pulmonary decline

**METHODS**

Criteria for considering studies for this review

**Types of studies**
All randomised controlled trials using ICS in patients with bronchiectasis.

**Types of participants**
Children or adults with bronchiectasis (defined clinically or radiologically) not related to CF.
Exclusion criteria: Participants with cystic fibrosis.

**Types of interventions**
All types of ICS.

**Types of outcome measures**
It was planned that attempts would have been made to obtain data on at least one of the following outcome measures:
(A) for short term effectiveness (6 months or less)
 a) mean difference in bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, cough diary, etc),
b) total numbers of days with respiratory symptoms
c) mean difference in lung function indices (spirometry, other lung volumes, airway hyper-responsiveness)
d) participants who had respiratory exacerbations and/or hospitalisations,
e) total number of hospitalised days
f) mean difference in other objective indices (airway markers of inflammation, exhaled nitric oxide etc)
g) proportions experiencing adverse effects of the intervention, (e.g. pharyngeal candidiasis, voice change, etc)

(B) for medium to long term outcomes (> 6 months)
h) radiology scores (high resolution computed tomography scans or chest radiograph)
i) lung function
j) clinical indices of bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, etc),
k) relevant airway markers of inflammation.
l) mortality
m) proportions experiencing adverse effects of the intervention, (e.g. adrenal insufficiency, cataracts, linear growth etc)

Search methods for identification of studies

Trials were identified from the following sources:
1. The Cochrane Airways Group Specialized Trials Register (updated October 2010)
2. The Cochrane Central Register of Controlled Trials (CENTRAL): Issue 4, 2010
3. MEDLINE (1950 to October 2010).
4. EMBASE (1980 to October 2010).
5. The list of references in relevant publications.
6. Written communication with the authors of trials included in the review when necessary.
For the full database topic search strategies see Appendix 1.

Data collection and analysis

**Selection of studies**

From the title, abstract, or descriptors, two reviewers (NK, AC) independently reviewed the literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, the same two reviewers independently selected trials for inclusion. Agreement was measured using kappa statistics. Disagreement was resolved by consensus.

Data extraction and management

Trials that satisfied the inclusion criteria were reviewed and the following information recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible subjects), 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, co-interventions, numbers of patients 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. Data were extracted on the outcomes described previously. Further information was requested from the authors but only two (Martinez 2006; Joshi 2004) responded with limited further information.

**Assessment of risk of bias in included studies**

We assessed the risk of bias for each of the studies included in the review independently (by two reviewers: NK & AC).

Four components of quality were assessed:

1. Allocation concealment. Trials were scored as: Adequate concealment (low risk of bias); Unclear (unclear risk of bias); clearly inadequate concealment (high risk of bias).
2. Blinding. Trials were scored as: Participant and care provider and outcome assessor blinded and/or outcome assessor blinded (low risk of bias); unclear (unclear risk of bias); no blinding of outcome assessor (high risk of bias).
3. Reporting of participants by allocated group. Trials were scored as: Progress of all randomised participants in each group described (low risk of bias); Unclear or no mention of withdrawals or dropouts (high risk of bias).
4. Follow-up. Trials were scored as: Outcomes measured in >90% (where withdrawals due to complications and side-effects are categorised as treatment failures, low risk of bias), Grade B: Outcomes measured in 80-90%, Grade C: Unclear, Grade D: Outcomes measured in <80%. (Grade A = high quality).

All assessments were included in Characteristics of included studies. Inter-reviewer reliability for the identification of high quality studies for each component was measured by the Kappa statistic.

**Data synthesis**

For the dichotomous outcome variables of each individual study, odds ratio (OR) was calculated using a modified intention-to-treat analysis. 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.

Results from studies that met the inclusion criteria and reported any of the outcomes of interest were included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed effects model) were calculated (Cochrane statistical package, RevMan version 5). For cross-over studies, mean
treatment differences were calculated from raw data, extracted or imputed and entered as fixed effects generic inverse variance (GIV) outcome, to provide summary weighted differences and 95% confidence intervals. In cross-over trials, only data from the first arm were included in meta-analysis when the data were combined with parallel studies (Elbourne 2002). Numbers needed to treat (NNT) were calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2003). If studies reported outcomes using different measurement scales, the standardised mean difference was used. Any heterogeneity between the study results was described and tested to see if it reached statistical significance using a chi-squared test. The 95% confidence interval estimated using a random effects model were included whenever there are concerns about statistical heterogeneity.

**Subgroup analysis and investigation of heterogeneity**

The following a priori sub-group analysis was planned:
1. children (aged 18 years or less) and adults (>18 years)
2. dose of ICS; low (< 400 ug), moderate (400-800 ug), high (>800 ug) of budesonide equivalent
3. participant type (bronchiectasis as primary disease versus bronchiectasis as co-existent disease)
4. severity of bronchiectasis (based on lung function)

**Sensitivity analysis**

Sensitivity analyses were also planned to assess the impact of the 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. differences in outcome measures;
5. analysis using random effects model;
6. analysis by “treatment received”; and
7. analysis by “intention-to-treat”.

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.

**Results of the search**

From the 2006 and 2007 searches, the Airways Group specialised register/search identified 341 potentially relevant titles. After assessing the abstracts, 9 papers were obtained for consideration to be
included into review. Three studies were excluded as ICS were not
compared to placebo/ no treatment or were non-randomised stud-
ies or included subjects with pneumonia (Ghosh 2002; Monton
1999; O'Neil 2004) see Characteristics of excluded studies). The
searches from 2008-2010 identified a further 161 references, none
of which were eligible for inclusion.

Included studies
Six studies met the inclusion criteria (Elborn 1992; Joshi 2004;
Martinez 2006; Tsang 1998; Tsang 2004; Tsang 2005), all were uni-centre studies. The studies included patients with bronchiectasis
diagnosed on bronchography (Elborn 1992) or high resolu-
tion CT (HRCT) of the chest (Joshi 2004; Martinez 2006; Tsang
1998; Tsang 2004; Tsang 2005). All studies excluded patients with
CF with Joshi 2004; Martinez 2006; Tsang 1998; Tsang 2004 and
Tsang 2005 excluding patients with bronchial asthma as well. Pa-
tients with allergic bronchopulmonary aspergillosis (ABPA) were
also excluded from Elborn 1992 and Martinez 2006. No study
was conducted in children. All studies were published in English.
Joshi 2004 and Elborn 1992 were cross over studies and the others
were parallel group studies. All were double blind placebo con-
trolled trials except Martinez 2006 which did not use placebo in
the control group.

Patients with bronchiectasis were recruited during stable state de-
 fined as free from exacerbation for 4 weeks (Joshi 2004; Martinez
2006) or stable 24 hour sputum volume, FEV₁ and FVC (Tsang
1998; Tsang 2004; Tsang 2005). No study was performed in acute
respiratory exacerbation.

Moderate to high doses of inhaled steroids were used: beclometha-
sone 800 µg/ day (Joshi 2004), beclomethasone 1500 µg/day in
Elborn 1992 and fluticasone 1000 µg/day (2000ug/day BDP
equivalent) (Martinez 2006; Tsang 1998; Tsang 2004; Tsang
2005). Martinez 2006 had a third arm with inhaled fluticasone
500 mcg/day but that data was not included in the final primary
analyses to have uniformity of steroid dose with the other included
studies (Tsang 1998; Tsang 2004; Tsang 2005). The results from
the lower dose arm was included in the sensitivity analyses.

The study duration ranged from a short duration of 4-6 weeks
(Joshi 2004; Tsang 1998; Elborn 1992) to 6 months in Martinez
2006 with visits at 1, 3 and 6 months. Two studies were of one
year duration (Tsang 2004; Tsang 2005) with visits at 4, 12, 24,
36 and 52 weeks. Additional data were requested from all authors
but only 2 authors (Joshi 2004; Martinez 2006) responded and
provided additional data. Data on outcomes at 24 weeks for Tsang
2005 as well as the lung function values in actual volumes (instead
of % predicted) was also requested from the authors.

Lung functions were included as an outcome variable in all studies
except Tsang 2004 which reported only FeNO levels. FEV₁ and
FVC (in litres or % predicted) were available from all studies.
PEFR were reported by Elborn 1992; Joshi 2004 and Tsang 1998
with Martinez 2006 and Tsang 1998 giving details about TLC,
RV and diffusion capacity.

Clinical parameters of cough, wheeze and dyspnoea were measured
differently in different studies. Elborn 1992 used a visual analogue
scale to quantify these symptoms, Martinez 2006 defined significa-
cent cough as that persisting for > 50% of days. Dyspnea was mea-
sured by using the transition dyspnoea index by Martinez 2006.
Clinical parameters of cough, dyspnoea and wheezing though re-
ported by Tsang 2005 were not defined properly and were not
included in the analysis. 24 hour sputum volume was included as
an outcome variable in Elborn 1992; Martinez 2006; Tsang 1998
and Tsang 2005.

Quality of life was included as an outcome parameter by Martinez
2006 and it used the Spanish version of the St. George Respiratory
Questionnaire (SGRQ) to calculate total scores as well as symp-
toms, activity and impact score.

All studies which had exacerbation as an outcome variable
(Martinez 2006; Tsang 1998; Tsang 2005) defined exacerbation
as persistent (>24hours) 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 deteri-
oration in chest signs.

Risk of bias in included studies
Allocation concealment was unclear in all 6 studies (Elborn 1992;
Joshi 2004; Martinez 2006; Tsang 1998; Tsang 2004; Tsang
2005). All studies were double blind studies except Martinez 2006
which did not have a placebo arm and blinding was done only for
comparing two dosages of ICS. The baseline values for lung func-
tions, sputum amount and sputum inflammatory markers were
significantly different clinically in Tsang 1998 and thus were sub-
ject to bias. Four studies (Martinez 2006; Tsang 1998; Tsang 2004;
Tsang 2005) reported the progress of all randomised subjects in
each group described whereas in Joshi 2004 there was no mention
of withdrawals or dropouts. As the pre crossover arm data could
not be extracted, data from Elborn 1992 could not be included in
any of the meta-analysis. The follow up was between 80-90% in
Tsang 2005 and was unclear in Joshi 2004. The remaining studies
(Martinez 2006; Tsang 1998; Tsang 2004) reported outcomes in
> 90% of the subjects. The agreement between the two authors
was excellent (weighted kappa score for quality assessment scores
was 0.81).

Inclusion of only those patients who had a significant post bron-
chodiator response in Joshi 2004 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 re-
versibility in their airway.

Effects of interventions
The 6 trials (Elborn 1992; Joshi 2004; Martinez 2006; Tsang 1998; Tsang 2004 and Tsang 2005) involved 303 participants with 278 completing the studies. Data that could be included in the meta-analysis were very limited.

**Stable state short term (< 6 months) outcomes (Comparison 1)**

Data from Joshi 2004; Martinez 2006; Tsang 1998 and Tsang 2004 were included in the short term stable state analysis.

1. **Clinical severity indices (Outcome 1.1, Figure 1):** Only data from a single study (Martinez 2006 which was a non-placebo study) could be displayed for these clinical parameters. Using ITT analysis, the number of subjects without sputum reduction as well as without improvement in dyspnoea (comparison 1.1.3 and 1.1.4) were significantly more in the control arm compared to the ICS arm. Subjects in the ICS group were significantly better than the control arm in the parameters of sputum volume reduction (OR of 7.69, 95%CI 1.92 to 30.70) and improvement in dyspnoea (OR of 3.33, 95%CI 1.17 to 9.43). There was no difference between groups for the clinical parameters of cough and wheeze. Although the Martinez 2006 study described a significant difference between groups for the number of participants experiencing reduced cough, we found no difference between groups when ITT analyses was performed. Also as the methodology of subjective cough measures was not a validated method, this data is not displayed as a forest plot. The data from Elborn 1992 though not included in the final analysis reported that the ICS group had a significant improvement in cough (p=0.02) but not wheeze and dyspnoea. None of the other studies reported these clinical outcomes.

![Figure 1. Forest plot of comparison: 1 Stable State Bronchiectasis (6 months or less), outcome: 1.1 Clinical severity indices.](image)

2. **Lung Function indices (Outcome 1.2, Figure 2):** Data from 3 studies (Joshi 2004; Martinez 2006; Tsang 1998) were included in this meta-analysis. In view of clinically significant differences in the baseline values between the two groups in one of the study (Tsang 1998), a change from baseline was taken as the outcome variable. Though clinically small, the lung function indices of FEV\(_1\) and FVC showed an improvement in the inhaled steroid group. Elborn 1992 also reported an improvement in the FEV\(_1\) in the ICS group compared to the placebo group (P=0.03) but not in FVC.
For FEV₁ (end study minus baseline values) (Outcome 1.2.1), the pooled data showed an improvement between the groups; MD (fixed) = 0.09 (95% CI 0.03 - 0.15) and there was no significant heterogeneity between studies.

For FVC (end study minus baseline values) (Outcome 1.2.2), there was again small improvement in the ICS group; MD (fixed) = 0.09 (95% CI 0.02 - 0.16) with no significant heterogeneity between studies.

For both FEV₁ and FVC, when the Martinez study was excluded (no placebo in this study), there was no longer any difference between groups although the trend remained favouring the ICS group.

For Peak flow (end study minus baseline values) (Outcome 1.2.3) data was only available from 2 studies (Joshi 2004; Tsang 1998) which showed a MD (fixed) = 26.23 (95% CI -5.84 to 58.31). Tsang 1998 showed a significant improvement in PEFR from baseline values in the ICS group but the combined data was not statistically significant.

Inhaled corticosteroids showed a (non significant) trend towards improving the following outcomes: DLCO (MD (fixed) = 2.65 (95% CI -2.39 to 7.68)), TLC (MD (fixed) = 2.55 (95% CI -19.41 to 14.55)) and RV (MD (fixed) = -2.43 (95% CI -19.14 to 14.55)).
3. Exacerbations (Outcome 1.3): Data on average number of exacerbation per subject was available from only one study (Martinez 2006) which showed no difference between the two groups (MD (fixed) = 0.09 (95% CI -0.61 to 0.79)). In Tsang 1998, one patient in the fluticasone group experienced an exacerbation compared with three patients in the placebo group.

4. Sputum and biomarkers characteristics (Outcome 1.4): a) Sputum volume per day (Outcome 1.4.1): Martinez 2006 was the only study included in this analysis which showed a trend towards reduction in the sputum volume with a MD (fixed) of -8.80 [95% CI -16.55 to -0.05]. The data on sputum volume in sputum inflammatory markers from Tsang 1998 was not included in the final analysis due to clinically significant differences in the baseline value between the two groups. Elborn 1992 also described a significant improvement in the 24 hour sputum volume in the ICS group (P =0.003). The other studies did not include this as an outcome variable.
   b) FeNO at 24 weeks (Outcome 1.4.2): Tsang 2004 showed no change in the FeNO between the two groups at 24 weeks with a MD (fixed) of 3 [95% CI -4.17 to 10.17]. The data on density of total bacteria, commensal bacteria and Pseudomonas aeruginosa in sputum, though not included in the final analysis, showed an increasing trend after 4 week therapy with inhaled steroids. (Tsang 1998)

Stable state long term (> 6 months) outcomes (Comparison 2)

Data from Tsang 2004 and Tsang 2005 were included in the long term stable state analysis though Tsang 2004 had only FeNO as the outcome variable.

1. Clinical severity indices: No data was included for the clinical parameters from the two studies (Tsang 2004 & Tsang 2005) of more than 6 month duration.

2. Lung Function indices (Outcome 2.1): For FEV_1 % predicted (end study minus baseline values) (Outcome 2.1.1), data from the single study Tsang 2005 showed no difference between the two groups; MD (fixed) = 0.30 (95% CI 17.43 to 18.03). For FVC % predicted (end study minus baseline values) (Outcome 2.1.2), data from the single study Tsang 2005 showed no difference between the two groups; MD (fixed) = -0.90 (95% CI 14.59 to 12.79).

3. Exacerbations (Outcome 2.2): Tsang 2005 showed a non significant reduction in the average number exacerbations per person in the ICS group; MD (fixed) = 0.49 (95% CI -1.49 to 0.51).

4. Sputum and biomarkers characteristics (Outcome 2.3): a) Sputum volume per day: As an overall effect, ICS had no effect on the 24 hour sputum volume when given for a period of 52 weeks though the data for this outcome was not included in the analysis because only median and interquartile range were available and the data was very skewed. As a subgroup analysis, Tsang 2005 report a significant improvement in the amount of sputum volume/ day in the subgroup of patients with sputum volume < 30 ml/ day, exacerbation frequency <= 2/year, and sputum purulence score score >5 (Data not available).
   b) Sputum purulence score (Outcome 2.3.1): 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 and milky white grey, pale green, moderately green, and dark green sputum, respectively) in Tsang 2005. After 52 weeks, there was no difference in the purulence scores between the ICS and placebo group; MD (fixed) = 0.2 (95% CI -0.94 to 1.34).
   c) FeNO at 52 weeks (Outcome 2.3.2): Tsang 2004 showed no change in the FeNO between the two groups at 52 weeks with a MD (fixed) of -1.20 (95% CI -6.82 to 4.42)

Sensitivity analysis

As mentioned in comparisons 1 , removing the study with a poor quality score (no placebo) altered the results for FEV_1 and FVC from being significant to non significant between the ICS and control groups. On replacing the data from the fluticasone 1000µg arm of Martinez 2006 with the 500µg data in the meta-analysis, improvement in FEV_1 still favoured the ICS group with a mean difference (fixed) of 0.06 (95% CI 0.01, 0.10) though the effect was less, whereas the effect of ICS became non significant for the parameter of FVC (mean difference of 0.05, 95% CI 0.03, 0.12). For the clinical data, the difference between the groups was still significant (favouring ICS group) for number of subjects without sputum volume reduction of >50% (OR of 0.19, 95%CI 0.05 to 0.79) though the variable of amount of sputum became non significant with MD (fixed) = 2.7 (95% CI -14.9, 3.5). For the outcomes of wheeze (OR of 0.65, 95%CI 0.22, 1.87) and cough (OR of 0.59, 95%CI 0.21, 1.62), there was still no difference between the groups. For the outcome of dyspnoea, actual data was not provided for the 500µg arm but the authors mentioned that there was no difference between groups. Hence it is assumed that the significant effect present for the 1000µg/day group (outcome 1.1.4) was no longer present for the 500µg/day group. Also, there was no change (i.e. no difference between groups) in the other outcome variables (diffusion capacity, residual volume, total lung capacity and exacerbation frequency)..

Analysis using random effects did not alter the significance of any of the outcomes. None of the other planned sensitivity analysis were relevant.

DISCUSSION

The meta-analysis based on six studies involving 303 adults has shown that use of high dose inhaled corticosteroids in patients with non CF bronchiectasis leads to a statistically significant though clinically minor improvement in the lung function indices of FEV_1 and FVC but not for peak flow. However when the study that
was not placebo-controlled was excluded, there was no significant difference between groups in FEV1 or FVC. Also there was no difference between groups for the other outcomes (exacerbations, sputum volume, clinical symptoms and FeNO).

The three studies (Joshi 2004; Martinez 2006; Tsang 1998) included in the short term effect of inhaled steroids in bronchiectasis showed a clinically small benefit of ICS on lung function parameters of FEV1 and FVC. Two of the studies reported no significant difference between groups and the major contribution with a positive effect was that from Martinez 2006. Thus not surprisingly when Martinez’s study was excluded based on quality (no placebo), the groups no longer differed. Also there was no difference between groups for PEFR, diffusion capacity and TLC. Nevertheless, Ellerman 1992 data which could not be included in the meta-analysis showed a significant improvement in the FEV1 as well as the 24 hour sputum volume in the ICS group compared to placebo group.

Data on the short term effect of ICS on clinical parameters of cough, wheeze, dyspnoea and sputum volume was available only from one study (Martinez 2006). This showed a significant improvement in dyspnoea and sputum volume for the higher dose of fluticasone (1000µg/day) compared to the control group. The lack of a placebo arm in this study makes assessment of these outcomes biased. The effect was also lost when data from 1000µg/day fluticasone was substituted by that for 500µg/day. Data on sputum volume from Tsang 1998 was not included in the analysis in view of clinically significant difference in the baseline values. Martinez 2006 showed a significant improvement in the quality of life score in the ICS group using the St George’s Respiratory Questionnaire but was not included in the final analysis since it encompassed all the symptoms already included in the analysis.

Recurrent acute pulmonary exacerbations form part of the disease progression in patients with bronchiectasis and many of these exacerbations require hospital admission. Recurrent exacerbations not only lead to progressive deterioration of lung functions (Ellerman 1997) but are also one of the strong predictors of poor quality of life in bronchiectasis (Wilson 1997). In this review, short term use of ICS did not significantly influence frequency of exacerbations. Prolonged ICS administration also did not significantly influence exacerbation frequency (Tsang 2005). This becomes more relevant with the fact that ICS actually increased the bacterial density in the airways (Tsang 1998) and most exacerbations in bronchiectasis are likely of infective in origin. Though exacerbation was defined in a similar manner in all three studies, its definition in bronchiectasis, specially paediatric bronchiectasis, is not standardized (Chang 2008). For further research into prevention and treatment of bronchiectasis exacerbation to be useful, we need a consensus on the definition of exacerbation.

Administration of inhaled steroids for a longer duration (Tsang 2004; Tsang 2005) significantly increased the number of subjects 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. 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.

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

Moreover, even in CF, the clinical benefits of ICS have been difficult to demonstrate. A Cochrane review of ICS in CF concluded that there is insufficient evidence to determine if they are beneficial or harmful (Balfour-Lynn 2000). In a large prospective, multicenter study, withdrawal of inhaled corticosteroids for 6 months was not associated with significant worsening of CF lung disease (Balfour 2006). Patients in whom steroids 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 2006).

Nearly 50% of adults with COPD have bronchiectasis (Chang 2008). A recent Cochrane review (Yang 2007) concluded that ICS administration reduce the rate of exacerbations as well as the rate of decline in quality of life in patients with stable state COPD. As the Martinez 2006 study included subjects who were smokers, there is a possibility that some of these subjects had COPD and this may influence the positive findings in that study. It also indicates that COPD associated bronchiectasis may respond differently to treatment modalities when compared to bronchiectasis associated with other causes.

Also, the beneficial effect if any of long term administration of high dose ICS has to be weighed against the potential adverse effects associated with it. High dose ICS use is associated with adverse events in children and adults that range from mild events (candidiasis) to serious events (pneumonia, adrenal insufficiency, osteoporosis, cataracts), Sobieraj 2008. Martinez 2006 reported dry mouth, local irritation and transient dysphonia as the most common adverse effects. None of the other studies reported any adverse effects.

**Limitations of the Review**

This systematic review is limited to 6 adult studies with variable designs, variable doses and length of study. Also data extraction
was limited to only one to 4 studies for the outcomes examined. The small sample size (max 101) for the meta-analysis is also a significant limitation. The major contributor to the benefit of ICS was from a non-placebo controlled study.

Authors’ Conclusions

Implications for practice

The present review indicates that there is insufficient evidence to recommend the routine use of inhaled steroids in adults with stable state bronchiectasis. The only study (Martinez 2006) that showed a benefit was a non-placebo controlled trial. In a second study benefit was found only with subgroup analysis and very high doses were utilised. While a therapeutic trial may be justified in patients with difficult to control symptoms, this has to be balanced with adverse events especially if high doses are used. In bronchiectasis, the adverse effect of ICS includes increased bacteria density and thus surveillance sputum bacteriology is recommended. No recommendation can be made for the use of ICS in adults during an acute exacerbation, or in children (for any state) as there were no studies.

References to studies included in this review

Elborn 1992 {published data only}

Joshi 2004 {published data only}

Martinez 2006 {published and unpublished data}

Tsang 1998 {published data only}

Tsang 2004 {published data only}

Tsang 2005 {published data only}

References to studies excluded from this review

Ghosh 2002 {published data only}

Monton 1999 {published data only}

ONeill 2004 {published data only}

Implications for research

Further studies are required to examine the effect of inhaled corticosteroids on short and long term outcomes for children and adults with non-CF 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. A validated and standardised definition of acute respiratory exacerbation is also required. Adult studies should clearly differentiate co-existent COPD as the presence of this may influence effect of ICS. A priori analysis for those with AHR should also be defined since its presence may influence ICS response.

Acknowledgements

We thank Toby Lasserson and Chris Cates from the Airways Group for their advice, supportive role and comments to the protocol and review. We are also very grateful to Elizabeth Arnold for performing the relevant searches and obtaining the articles. This review was completely rewritten and reanalysed from a previous review by Ram and colleagues (Ram 2000) and we acknowledge their previous work.
Additional references

Abramson 2006

Balfour 2006

Balfour-Lynn 2000

Cates 2003

Chang 1998

Chang 2002

Chang 2008

Cole 1986

Edwards 2003

Elbourne 2002

Ellerman 1997

Field 1969

Gursel 2006

Ip 1993

Karadag 2005

Karakoc 2001

Keitinen 1997

Lewis 2002

O’Brien 2000

Patel 2004

Shoemark 2007

Singleton 2000

Sobieraj 2008
Twiss 2006

Van Haren 1995

Wilson 1997

Yang 2007

References to other published versions of this review

Ram 2000

* Indicates the major publication for the study
## 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 5 patients who dropped out- unsure when these occurred. Two patients declined to take part in second limb of study  
No wash out period mentioned. |
|---|---|
| Participants | Twenty patients (12 females, mean age 50 years, range 30-65) were studied with bronchiectasis diagnosed by bronchogram in 18 and CT scan in two. No patient received a course of antibiotics for at least 8 weeks prior to study  
Exclusion: Patients with hypogammaglobulinaemia, CF, allergic bronchopulmonary aspergillosis (ABPA) or primary ciliary dyskinesia as well as those taking oral or inhaled corticosteroids |
| Interventions | Inhaled beclomethasone dipropionate 750 microgram BD by MDI or placebo for 6 weeks |
| Outcomes | FEV₁, FVC, morning and evening PEFR, 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 wash out period. Separate results of first arm not available. Data not included in analysis |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
</table>
| Adequate sequence generation? | Yes | Quote: "Patients were randomised to take beclomethasone dipropionate"  
Comment: Probably done. |
| Allocation concealment? | Unclear | No mention how randomisation was done. |
| Blinding? All outcomes | Yes | Quote: "double-blinded" & "matched placebo" |
| Incomplete outcome data addressed? All outcomes | No | There were 5 patients who dropped out- unsure when these occurred. Two patients declined to take part in second limb of study |
| Free of selective reporting? | Yes | No suggestion that selective reporting may have been done. |
Elborn 1992  (Continued)

Free of other bias?  
No  
Cross over design with no wash out period.  
Separate results of first arm not available

Joshi 2004

Methods  
Randomized double blind placebo controlled cross over study with study duration of 4 weeks  
Two week washout period between cross over.  
Details of drop outs not clear.

Participants  
20 patients (9 females) age range 15-60 years were prospectively enrolled. All patients treated with oral salbutamol 2 mg four times daily and oral theophylline 200 mg four times daily throughout the trial period  
14 patients had unilateral disease and 6 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 microgram/day in two divided doses by MDI or placebo for 4 weeks

Outcomes  
FVC, FEV$_1$ and 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

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “patients were randomised in a double blind manner”. Comment: Probably done</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>No mention how randomisation was done.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Quote: “patients were randomised in a double blind manner”. Comment: Probably done</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear</td>
<td>No mention of drop outs.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>No suggestion that selective reporting may have been done.</td>
</tr>
</tbody>
</table>
Free of other bias? No

Inclusion of patients 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 2006

Methods Randomized (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 patients 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 steroids and had disease of significant severity). 93 patients enrolled in the study
7 drop outs during the study, 3 from the no steroid group and 2 each from the 500 µg and 1000µg group. Study completed in 86 patients
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 patients with HRCT diagnosed bronchiectasis diagnosed between 1993 and June 2003 in Requena General Hospital. The patients were required to be free from acute exacerbation for at least 4 weeks
Exclusion: Patients with asthma, CF and on whom inhaled steroids could not be stopped

Interventions Inhaled fluticasone 500 µg BD by MDI vs. 250 µg fluticasone BD vs. 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 few days prior to randomisation
During randomisation visit, information collected on dyspnoea score, daily sputum production (average of sputum produced over 3 days); cough and need for short acting bronchodilator in the 1 month prior to randomisation, and health-related quality of life (HRQol) using the validated Spanish version of the St. George Respiratory Questionnaire (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 All comparisons made only between no steroids and 500 µg BD group. Additional information provided by the authors
### Martinez 2006

(Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>No mention how randomisation was done.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>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 vs. 1000 µg/day)</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>No</td>
<td>The patient characteristics and outcome data of those excluded or dropped out not described and not compared with those included for analysis</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Information on TLC, RV and DLCO gathered but not reported.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Intention to treat analysis not done.</td>
</tr>
</tbody>
</table>

### Tsang 1998

**Methods**

Randomized double blind placebo controlled prospective trial with study duration of 4 weeks

There were no drop outs.

**Participants**

24 patients (mean age 51 years, 12 F) 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 > 10ml, absence of asthma or other unstable systemic disease; and “steady state” bronchiectasis (< 10% alteration of 24 hour sputum volume, FEV\textsubscript{1} and FVC).

Exclusion: Unreliable clinic attendance, known adverse reaction to fluticasone, regular use of ICS and asthma

**Interventions**

Inhaled Fluticasone 500 µg BD by accuhaler or placebo for 4 weeks

**Outcomes**

FEV\textsubscript{1}, FVC, TLC, RV, diffusion capacity, PEFR, 24 h sputum volume (mean of three days), sputum leukocyte density, bacterial densities and concentrations of interleukin (IL)1B, IL 8, tumour necrosis factor (TNF) alpha and leukotriene B4 were all measured at the time of randomization and at 4 weeks
Tsang 1998  (Continued)

Notes
SD estimated from 95% confidence intervals. Change from baseline used instead of post treatment values in view of clinically significant differences in the baseline values for fluticasone and placebo group. Values for number of females different in abstract compared with the table

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “randomly assigned into receiving either fluticasone (500 µg twice daily) or otherwise identical placebo”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: Probably done.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>No mention how randomization was done.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Quote: “performed a double blind, placebo controlled study”. Comment: Probably done</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>There were no drop outs.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>No suggestion that selective reporting may have been done.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>The baseline values for lung functions, sputum amount and sputum inflammatory markers were significantly different clinically in and thus were subject to bias</td>
</tr>
</tbody>
</table>

Tsang 2004

Methods
Randomized double blind prospective placebo controlled trial with study duration of 52 weeks
There were no drop outs.

Participants
60 patients (mean age 56.4 years, 38 F) 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 Pseudomonas colonized and 44 were not.
Inclusion: Absence of asthma or other unstable systemic disease; and “steady state” bronchiectasis (< 20% alteration of 24 hour sputum volume, FEV₁ 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 microgram BD by accuhaler or placebo for 52 weeks
Outcomes
The patients were followed up at -2, -1, 0, 4, 12, 24, 36, 48 and 52 weeks after commencement of therapy for measurement of fractional exhaled nitric oxide (FeNO).

Notes
SD calculated from interquartile (IQ) range. Medians used instead of means. Data at 24 weeks and 52 weeks included in the analysis.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: &quot;before randomization to receive fluticasone (500µg twice daily) or identical placebo&quot; Comment: Probably done.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>No mention how randomization was done.</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Yes</td>
<td>Quote: &quot;performed a double blind, placebo controlled study&quot;. Comment: Probably done</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td>There were no drop outs.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>No suggestion that selective reporting may have been done.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Baseline value of the 2 groups were significantly different.</td>
</tr>
</tbody>
</table>

Tsang 2005

Methods
Randomized 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. 3 patients withdrew. 86 patients (57 females, mean age 58.5 years) with HRCT proven bronchiectasis randomized 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 Pseudomonas colonized.
Inclusion: Absence of asthma or other unstable systemic disease; and "steady state" bronchiectasis (< 20% alteration of 24 hour sputum volume, FEV1 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
**Tsang 2005 (Continued)**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Inhaled fluticasone 500 microgram BD by accuhaler device or matched placebo for 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>The patients were followed up at -2, -1, 0, 4, 12, 24, 36, 48 and 52 weeks after commencement of therapy. Primary outcomes were: 24 hour sputum volume (mean of 3 days) and cumulative exacerbation frequency. Secondary outcomes were: Sputum purulence score, FEV$_1$%, and FVC%. Improvement or deterioration was defined as &gt;20% change from baseline.</td>
</tr>
<tr>
<td>Notes</td>
<td>SD calculated from P value for sputum volume and exacerbation frequency and from confidence interval for the rest</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “randomisation (block of 4)”. Comment: Probably done</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>Quote: “randomisation (block of 4)”. Comment: Probably not done</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Quote: “double blind, placebo controlled study”</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>No</td>
<td>Data of drop outs not compared to those included in analysis</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>No suggestion that selective reporting may have been done.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Significant differences at the baseline on clinical features of “Cough” and “Dyspnea” between the two groups to allow for post treatment comparison</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghosh 2002</td>
<td>Study compared effects of inhaled budesonide with inhaled ipratropium and not placebo</td>
</tr>
<tr>
<td>Monton 1999</td>
<td>Study included patients with pneumonia and not bronchiectasis. Used systemic steroids not inhaled</td>
</tr>
<tr>
<td>ONeil 2004</td>
<td>Study not a RCT. Studies subjective benefits of inhaler therapy including both ICS and bronchodilators</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. Stable State Bronchiectasis (6 months or less)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clinical severity indices</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.1 Number of subjects with regular wheeze</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.2 Number of subjects without sputum reduction of &gt;50%</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.3 Number of subjects with no improvement in dyspnoea score &gt; 1 (min important difference)</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2 Lung function indices</td>
<td>3</td>
<td>101</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 FEV₁ (in L, end study minus baseline values)</td>
<td>3</td>
<td>101</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.09 [0.03, 0.15]</td>
</tr>
<tr>
<td>2.2 FVC (in L, end study minus baseline values)</td>
<td>3</td>
<td>101</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.09 [0.02, 0.16]</td>
</tr>
<tr>
<td>2.3 Peak flow (L/min, end study minus baseline values)</td>
<td>2</td>
<td>44</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>26.23 [-5.84, 58.31]</td>
</tr>
<tr>
<td>2.4 Diffusion capacity % predicted (end of study)</td>
<td>2</td>
<td>81</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.65 [-2.39, 7.68]</td>
</tr>
<tr>
<td>2.5 RV % predicted (end of study values)</td>
<td>2</td>
<td>63</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.43 [-19.41, 14.55]</td>
</tr>
<tr>
<td>2.6 TLC % predicted (end of study values)</td>
<td>2</td>
<td>81</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.55 [-2.39, 7.49]</td>
</tr>
<tr>
<td>3 Average number of exacerbations per subject</td>
<td>1</td>
<td>57</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.09 [-0.61, 0.79]</td>
</tr>
<tr>
<td>4 Sputum and biomarkers characteristics</td>
<td>2</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4.1 Sputum volume or weight (per day)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>4.2 FeNO (ppb) at 24 weeks</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>
### Comparison 2. Stable State (>6 months)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lung Function Indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 FEV₁ % predicted (end study minus baseline values)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>1.2 FVC % predicted (end study minus baseline values)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>2 Average exacerbation per subject</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>3 Sputum and biomarker characteristics</td>
<td>2</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>3.1 Sputum purulence score</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>3.2 FeNO (ppb) at 52 weeks</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

### What’s New

Last assessed as up-to-date: 26 October 2010.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 October 2010</td>
<td>New search has been performed</td>
<td>Literature search run, no new studies identified.</td>
</tr>
</tbody>
</table>

### History


Review first published: Issue 2, 1999

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 August 2008</td>
<td>New citation required and conclusions have changed</td>
<td>Aug 2008: New author team, protocol changed and previous included studies data amended, new studies added, conclusions changed</td>
</tr>
<tr>
<td>5 May 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>10 September 2007</td>
<td>New search has been performed</td>
<td>New literature search performed.</td>
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</table>
CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

There is no conflict of interest.

SOURCES OF SUPPORT

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

External sources
- National Health and Medical Research Council, Australia.
  AC's Practitioner Fellowship and Project Grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, long term effect was defined as that measured at more than 12 months duration. This was changed to more than 6 months duration in the final review. Data from Martinez 2006 was included in the review though the comparison between the untreated and the ICS groups were not blinded. Also, for the clinical severity assessment in the Martinez 2006 study, outcome variables of sputum reduction > 50% and dyspnoea score improvement > 1 were used post hoc since these were the ones available from the study.

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]; Randomized Controlled Trials as Topic; Respiratory Function Tests

MeSH check words
Adult; Humans