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Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

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ABSTRACT

Background

Chronic neutrophilic inflammation, both in the presence and absence of infection, is a feature of bronchiectasis in adults and children. The anti-inflammatory properties of non-steroid anti-inflammatory drugs (NSAIDs) may be beneficial in reducing airway inflammation and thus potentially improve lung function and quality of life in patients with bronchiectasis.

Objectives

To evaluate the efficacy of inhaled NSAIDs in the management of non-cystic fibrosis bronchiectasis in children and adults.

Search methods

We searched the Cochrane Airways Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 3), MEDLINE, OLDMEDLINE and EMBASE databases. The latest searches were carried out in October 2009.

Selection criteria

All randomised controlled trials comparing inhaled NSAIDs to a control group (placebo or usual treatment) in children or adults with bronchiectasis not related to cystic fibrosis.

Data collection and analysis

We reviewed the results of the searches against pre-determined criteria for inclusion.
Main results

One small, short-term trial was eligible for inclusion. We included this study of 25 adults with chronic lung disease (including bronchiectasis) as the other conditions were linked to development of bronchiectasis and all had chronic sputum production.

The single trial in adults reported a significant reduction in sputum production over 14 days in the treatment group (inhaled indomethacin) compared to placebo (difference -75.00 g/day; 95% CI -134.61 to -15.39) and a significant improvement in a dyspnoea score (difference -1.90; 95% CI -3.15 to -0.65). There was no significant difference between groups in lung function or blood indices. No adverse events were reported.

Authors’ conclusions

There is currently insufficient evidence to support or refute the use of inhaled NSAIDs in the management of bronchiectasis in adults or children. One small trial reported a reduction in sputum production and improved dyspnoea in adults with chronic lung disease who were treated with inhaled indomethacin, indicating that further studies on the efficacy of NSAIDs in treating patients with bronchiectasis are warranted.

Plain Language Summary

Inhaled non-steroid anti-inflammatories (NSAIDs) for children and adults with bronchiectasis

The airways of patients with bronchiectasis are characterised by chronic inflammation. The anti-inflammatory effects of inhaled non-steroid anti-inflammatory drugs (NSAIDs) may be beneficial in patients with bronchiectasis. However, the short and long-term benefits in both adults and children require investigation, in addition to the potential side effects of the long-term use of NSAIDs. For this review we found one small study that reported an improvement in sputum production and dyspnoea (shortness of breath) in adults with chronic lung disease (chronic bronchitis, bronchiectasis or diffuse panbronchiolitis) who received inhaled indomethacin compared to the placebo group. There was no significant improvement in lung function (forced expiratory volume in one second (FEV1) and vital capacity (VC)). However, the small scale of this study and the collective analysis of data from the three disease states made it difficult to draw any solid conclusions on the benefit of using NSAIDs to treat adults with bronchiectasis. There were no studies identified on the use of NSAIDs in children with bronchiectasis.

Background

Description of the condition

Bronchiectasis, previously termed an ‘orphan disease’, is increasingly recognised as a major cause of respiratory morbidity, especially in developing countries (Karadag 2005; Karakoc 2001) and in pockets of affluent countries (Chang 2008). The underlying aetiology of bronchiectasis varies; it may follow recurrent respiratory infections or be secondary to rare immune deficiencies. 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) (O’Brien 2000) and uncommon respiratory diseases (e.g. bronchiolitis obliterans and sarcoidosis (Lewis 2002)) as well as non-primary respiratory (e.g. autoimmune) diseases. When bronchiectasis is present with another underlying disorder, it increases the morbidity and mortality of the underlying disease (Keistinen 1997; Lewis 2002). For example, in diseases such as COPD the presence of bronchiectasis has been reported in 29% to 50% (O’Brien 2000) of cohorts and when present increases the severity and frequency (Gursel 2006) of respiratory exacerbations.

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). Also, as in patients with COPD, children and adults with bronchiectasis also suffer from recurrent acute exacerbations, some of which require hospitalised treatment (Chang 2008). Effective management regimes for bronchiectasis improve quality of life (Courtney 2008; Martinez-Gracia 2005; Murthalithas 2008), and could reduce the frequency or severity of respiratory exacerbations (Cymbala 2005).
and/or the long-term pulmonary decline (Chang 2008). Thus, management of the symptoms and severity of bronchiectasis is important.

**Description of the intervention**

Non-steroid anti-inflammatory drugs (NSAIDs) are a class of medication that act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Non-steroidal anti-inflammatories have analgesic, antipyretic and anti-inflammatory effects and reduce pain, fever and inflammation. NSAIDs are usually given orally but the inhaled formulation has been also used in people with bronchorrhoea, a feature present in many patients with bronchiectasis (Tamaoki 1992). A Cochrane Review of oral NSAIDs for people with bronchiectasis did not find any suitable randomised controlled trials (Kapur 2007).

**How the intervention might work**

Based on Cole’s ‘vicious circle hypothesis’, microbial colonisation/infection is important in the pathophysiology of bronchiectasis as it leads to bronchial obstruction and an abnormal or exaggerated inflammatory response (Cole 1986). Anti-inflammatory drugs may reduce the inflammatory cascade and thus ameliorate symptoms and reduce long-term pulmonary decline.

As the airways of patients with bronchiectasis have intense neutrophilic inflammation (Cole 1986), the anti-inflammatory effect of NSAIDs may have a beneficial effect for patients with bronchiectasis. “Blockade of cyclooxygenase pathway with indomethacin could decrease respiratory tract fluid and mucus by inhibiting chloride secretion and glandular secretion and by enhancing Na absorption across airway mucosa” (Tamaoki 1992). Animal studies have shown that pre-treatment with inhaled indomethacin protects the airway from distilled water and ozone which increases lung resistance through swelling of airway epithelial cells (Mochizuki 2002).

**Why it is important to do this review**

Although NSAIDs may have potential benefits for those with bronchiectasis, oral NSAIDs are associated with a number of adverse events, particularly of the gastrointestinal tract (Behrman 2003). NSAIDs may be better tolerated when inhaled, however transient upper airway irritation has been reported (Ong 2004; Sestini 1999). It is therefore important to assess any additional side affects associated with the inhalation of NSAIDs.

In cystic fibrosis (CF), preliminary evidence suggests that NSAIDs may prevent pulmonary deterioration in people with mild lung disease due to CF (Lands 2007). However, extrapolation of treatment for CF to non-CF bronchiectases may be harmful (e.g. recombinant human DNase efficacious in CF causes harm in non-CF bronchiectasis (Crockett 2001)). Thus, a systematic review on the efficacy of inhaled NSAIDs in the management of children and adults with bronchiectasis would help guide clinical practice.

**OBJECTIVES**

To evaluate the efficacy of inhaled NSAIDs in children and adults with bronchiectasis:

(a) during stable bronchiectasis;
(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 (RCTs) comparing inhaled NSAIDs to a control group (placebo or usual treatment) in patients with bronchiectasis.

**Types of participants**

Children or adults with bronchiectasis (defined clinically or radiologically) not related to cystic fibrosis. We excluded participants with cystic fibrosis or with other diseases where bronchiectasis was not present.

**Types of interventions**

All types of inhaled NSAIDs.

**Types of outcome measures**

**Primary outcomes**

We planned to obtain data on at least one of the following outcome measures:

(A) For short-term effectiveness (12 months or less): mean difference in bronchiectasis severity control (quality of life (QOL), cough scores).
(B) For medium to long-term outcomes (> 1 year): lung function data (forced expiratory volume in one second (FEV_{1}) % predicted).

Secondary outcomes

(A) For short-term effectiveness (12 months or less):
- a) total numbers of days with respiratory symptoms;
- b) mean difference in lung function indices (spirometry, other lung volumes, airway hyper-responsiveness);
- c) proportions of participants who had respiratory exacerbations and/or hospitalisations;
- d) total number of hospitalised days;
- e) mean difference in other objective indices (airway markers of inflammation, exhaled nitric oxide etc.);
- f) proportions experiencing adverse effects of the intervention (e.g. gastritis, haematemesis, ecchymoses, etc.);
- g) serious adverse events (e.g. haemoptysis, bronchospasm etc.).

(B) For medium to long-term outcomes (> 1 year):
- h) radiology scores (high resolution computed tomography scans or chest radiograph);
- i) clinical indices of bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, etc.);
- j) mortality;
- k) proportions experiencing adverse effects of the intervention (e.g. gastric bleeding, gastritis, haematemesis, cardiac events, etc.);
- l) serious adverse events (e.g. haemoptysis, bronchospasm etc.).

Search methods for identification of studies

Electronic searches

We used the following topic search strategy to identify the relevant randomised controlled trials listed in the electronic databases: ("bronchiectasis" OR "suppurative lung disease" as (textword) or (MeSH )) AND ("inhaled" OR "nebulised" OR "nebulised" as (textword) or (MeSH )) AND ("anti-inflammatory" OR "dicyclofenac" OR "etodolac" OR "keto..."

Searching other resources

We also searched the references in relevant publications. We planned to communicate with the authors of trials included in the review, if necessary.

Data collection and analysis

Selection of studies

From the title, abstract or descriptors, two authors (SP, AC) independently reviewed the literature searches to identify potentially relevant trials for full review. We conducted searches of bibliographies and texts to identify additional studies. From the full text and using the specified criteria, the same two authors independently selected trials for inclusion. We planned to resolve any disagreement by third party adjudication (JU).

Data extraction and management

We reviewed trials that satisfied the inclusion criteria for the following information: 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 used where possible. We would have extracted data on the outcomes described previously. Where required we planned to obtain further information from the authors.

Assessment of risk of bias in included studies

In order to assess the risk of bias, two review authors (SP, AC) independently assessed the quality of the studies according to the criteria described by Jüni (Jüni 2001).

Allocation concealment

We assessed allocation concealment as follows.
- 1. Adequate: if the allocation of participants involved a central independent unit, on-site locked computer, identically appearing
numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes.

2. Unclear: if the method used to conceal the allocation was not described.

3. Inadequate: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

**Generation of the allocation sequence**

Each study was to be graded for allocation concealment as follows.

1. Adequate: if methods of randomisation included using a random number table, computer-generated lists or similar methods.

2. Unclear: if the trial was described as randomised, but no description of the methods used to allocate participants to treatment group was described.

3. Inadequate: if methods of randomisation included alternation, the use of case record numbers, dates of birth or day of the week, and any procedure that was entirely transparent before allocation.

**Blinding (or masking)**

Each study was graded for blinding as follows.

1. Blinding of clinician (person delivering treatment) to treatment allocation.

2. Blinding of participant to treatment allocation.

3. Blinding of outcome assessor to treatment allocation.

**Follow up**

Each study was graded as to whether numbers of and reasons for drop-outs and withdrawals in all intervention groups were described, or if it was specified that there were no drop-outs or withdrawals.

**Dealing with missing data**

The authors planned to request further information from the primary investigators where required but as the only included study was published in 1992, we did not contact the authors (Tamaoki 1992).

**Assessment of heterogeneity**

We planned to describe any heterogeneity between the study results and test this to see if it reached statistical significance using the Chi² test. We would have considered heterogeneity to be significant if the P value was less than 0.10 (Higgins 2008). We also planned to use the I² statistic, where heterogeneity is categorised such that a value of under 25% is considered low, around 50% is considered moderate and over 75% is considered a high degree of heterogeneity (Higgins 2003).

**Assessment of reporting biases**

If meta-analysis had been possible, we would have assessed publication bias using a funnel plot. We intended to investigate and report on any selective reporting.

**Data synthesis**

For the dichotomous outcome variables of each individual study, we would have calculated the odds ratios (OR) using a modified intention-to-treat analysis. This analysis assumes that children 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 examines whether pooling of results (meta-analysis) is reasonable. This would take into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment and estimated effect size.

The results from studies that met the inclusion criteria and reported any of the outcomes of interest were to be included in the subsequent meta-analyses. We planned to calculate the summary weighted odds ratio and 95% confidence interval (CI) (fixed-effect model) (Cochrane statistical package, RevMan version 5 (RevMan 2008)). We would only have combined data from parallel studies. We planned to calculate numbers needed to treat (NNT) 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, we planned to estimate the standardised mean difference (SMD). We would have described and explored any heterogeneity between the study results. We would have included the 95% CI estimated using a random-effects model whenever there were concerns about statistical heterogeneity.

**Subgroup analysis and investigation of heterogeneity**

The following a priori subgroup analyses were planned:

1. children (aged 18 years or less) and adults (> 18 years);

2. severity of bronchiectasis (based on FEV₁: > 80% classified as mild, 50% to 79% classified as moderate, 30% to 49% classified as severe, < 30% classified as very severe).

**Sensitivity analysis**

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

- variation in the inclusion criteria;

- differences in the medications used in the intervention and comparison groups;

- differences in outcome measures;
• analysis using random-effects model;
• analysis by treatment received; and
• analysis by intention-to-treat.

R E S U L T S

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
See the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search
The Airways Group specialised register/literature search performed in Oct 2008 and October 2009 yielded 173 (153 and 20 respectively) references. There were no RCTs which focused specifically on adults or children with bronchiectasis. We identified two publications which were considered for inclusion in this review. One study Tamaoki 1992 was included; the second (Llewellyn-Jones 1995) did not meet the eligibility criteria and was excluded.

Included studies
There were no studies identified which focused solely on bronchiectasis in either adults or children. However a single, small study on adults with chronic lung disease, including bronchiectasis, was included in this review as the additional two chronic lung disease conditions in the study lead to bronchiectasis, and bronchorrhoea is a key clinical feature of bronchiectasis. The detail of this study is described in the 'Characteristics of included studies' table. Tamaoki and colleagues (Tamaoki 1992) examined the short-term effect (14 days) of inhaled indomethacin on sputum and blood indices, dyspnoea scale and lung function in 25 adults with chronic lung disease (eight with bronchiectasis, 12 with chronic bronchitis and five with diffuse panbronchiolitis).

Excluded studies
We excluded one study (Llewellyn-Jones 1995) as it was not a randomised controlled trial.

Risk of bias in included studies

Allocation
The method used for allocating treatment groups was not described.

Blinding
The patients and investigators responsible for disease follow up and data analysis were blinded. The doctor responsible for allocating treatment groups was not blinded but was not involved in follow up or data analysis.

Incomplete outcome data
Data were complete for all participants. However, data analysis did not distinguish bronchiectasis patients from the other respiratory groups, other than that for sputum production.

Selective reporting
We identified no selective reporting bias in the study.

Other potential sources of bias
We identified no other potential sources of bias.

Effects of interventions
The one study included in this review evaluated the effect of inhaled indomethacin on sputum production, quality of life and lung function in 25 patients with chronic lung disease, including eight patients with bronchiectasis.

Respiratory symptoms
The only clinical data reported were in the form of the Borg score, which showed a significant difference between groups (difference of -1.90; 95% CI -3.15 to -0.65) (Analysis 1.1). (The minimum clinically important difference (in COPD) is 1 unit (Ries 2005)). Days with respiratory symptoms (our primary outcome measure) was not reported in the study.

Lung function
There was no significant difference between groups for FEV₁ % predicted (difference between groups of -2.90%; 95% CI -13.30 to 7.50) or for vital capacity (VC) % predicted (difference -2.90%; 95% CI -10.58 to 4.78) (Analysis 2.1 and Analysis 2.2).
Other indices

For sputum indices (Analysis 3.2), a significant decrease in sputum production in the indomethacin group was found compared with the placebo group (difference -75.00 g/day; 95% CI -134.61 to -15.39) but there was no difference in the density of bacteria per gram of sputum (difference -0.30; 95% CI -1.71 to 1.11). For blood indices (Analysis 3.3) no significant difference between groups was found for either erythrocyte sedimentation rate (ESR) (difference -2.00 mm/hr; 95% CI -13.42 to 9.42) or total white cell count (difference -400.00 cells/ml; 95% CI -1654.94 to 854.94).

Adverse events

No adverse events were reported in the study.

DISCUSSION

Summary of main results

Data from one small, short-term (14-day) study of 25 adults with chronic lung disease (12 with chronic bronchitis, eight with bronchiectasis and five with panbronchiolitis) suggest that inhaled indomethacin (a type of NSAID) was significantly beneficial in reducing sputum production and improving dyspnoea compared to placebo. The clinically important difference for the Borg scale in bronchiectasis is unknown but that for COPD is 1 unit (Ries 2005) and thus the difference between groups for dyspnoea (-1.90; 95% CI -3.15 to -0.65) is likely to be clinically important. There was no difference between groups for lung function or blood indices.

Overall completeness and applicability of evidence

The small study and limited number of patients with bronchiectasis in the sole included study limits any definitive conclusion. We included this study on the same basis for inclusion as a study in the Cochrane Review of pneumococcal vaccination for bronchiectasis (Chang 2009). No randomised controlled trials of inhaled NSAIDs in children with bronchiectasis were identified.

Quality of the evidence

The sole included study in this review (Tamaoki 1992) was a double-blind, randomised study but the sample size was small and allocation concealment remains unknown. Data from the three disease states were described and analysed collectively, thus bronchiectasis-specific data are unknown. Data were expressed as means +/-SEM (standard error of the mean). Two-way analysis of variance and Student’s paired t test were used for normally distributed variables. The Newman-Keuls test was used for multiple comparisons. A P value of less than 0.05 was considered statistically significant.

Agreements and disagreements with other studies or reviews

The Cochrane Review of oral NSAIDs for cystic fibrosis concluded that NSAIDs are likely to slow the progression of lung disease (Lands 2007). Data on sputum production or dyspnoea were not reported in the review. The Cochrane Review of oral NSAIDs for bronchiectasis (Kapur 2007) did not find any relevant studies.

AUTHORS’ CONCLUSIONS

Implications for practice

Although a single study has shown some benefit in the short-term use of inhaled indomethacin in adults with chronic lung disease (including bronchiectasis and those at risk of bronchiectasis), there is currently insufficient evidence to support or refute the use of inhaled NSAIDs in children or adults with bronchiectasis. NSAIDs may be beneficial in the immediate term in reducing sputum production and therefore improving quality of life in adults with chronic lung disease. However, there were too few bronchiectasis patients included in the study group and the duration of treatment was too short to provide adequate information on the beneficial or adverse effects of inhaled NSAIDs in adults with bronchiectasis. There is no data currently available on the effectiveness of inhaled NSAIDs in children with bronchiectasis.

Implications for research

The data presented in the one study included in this review indicate that a double-blind, randomised, placebo-controlled trial is warranted to investigate the short-term (<12 months) and long-term (>12 months) beneficial and adverse effects of inhaled NSAIDs in both adults and children with bronchiectasis. Randomised controlled trials should investigate children and adults separately and include data as highlighted in the ‘Types of outcome measures’ section of this review.

ACKNOWLEDGEMENTS

We thank Toby Lasserson, Dr Chris Cates, Elizabeth Arnold and Susan Ann Hansen from the Airways Group for their advice, supportive role and comments on the protocol and review. We also
thank Dr Andre Wattiaux from Menzies School of Health Research for translating a French article identified by the literature search.

REFERENCES

References to studies included in this review

Tamaoki 1992 [published data only]

References to studies excluded from this review

Llewellyn-Jones 1995 [published data only]

Additional references

Behrman 2003

Cates 2003

Chang 2008

Chang 2009

Cole 1986

Courtney 2008

Crockett 2001

Cymbala 2005

Gursel 2006

Higgins 2003

Higgins 2008

Jüni 2001

Kapur 2007

Karadag 2005

Karakoc 2001

Keistinen 1997

Lands 2007

Lewis 2002
Lewis MM, Mortelliti MP, Yeager H Jr, Tsou E. Clinical bronchiectasis complicating pulmonary sarcoidosis: case

**Martinez-Gracia 2005**

**Mochizuki 2002**

**Muthalithas 2008**

**O’Brien 2000**

**Ong 2004**

**RevMan 2008**

**Ries 2005**

**Sestini 1999**

* Indicates the major publication for the study
Characteristics of included studies  

**Tamaoki 1992**

| Methods |
|-----------------|----------------|
| Double-blind, randomised, placebo-controlled trial |
| Pulmonary function was assessed by a change in vital capacity (VC) and FEV<sub>1</sub> pre-treatment (day 0) and on day 14. Quality of life was assessed by Borg’s ratio scale to questions related to breathlessness and dyspnoea |
| Sputum was analysed for change in production (g/day), cyclooxygenase products (PGE<sub>2</sub>, PGF<sub>2α</sub>, 6-oxo-PGF<sub>1α</sub>, TxB<sub>2</sub>) and microbiological culture |
| Statistical analysis: data were expressed as means +/- SEM. Two-way analysis of variance and Student’s paired t test were used for normally distributed variables. The Newman-Keuls test was used for multiple comparisons. A P value of less than 0.05 was considered statistically significant |

<table>
<thead>
<tr>
<th>Participants</th>
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<tbody>
<tr>
<td>25 adults (age 29 to 78 years) diagnosed with chronic lung disease (chronic bronchitis, diffuse panbronchiolitis or bronchiectasis) and bronchorrhea of at least 4 weeks. Eight of the 25 participants had bronchiectasis but all had symptoms of bronchiectasis and 21 had chronic colonisation with respiratory pathogens present in adults with bronchiectasis - 17 had <em>Pseudomonas aeruginosa</em>, 3 with <em>Haemophilus influenzae</em> and one with <em>Staphylococcus aureus</em>. Of the 8 subjects with bronchiectasis, 4 were allocated to the indomethacin group and 4 to the placebo group. All had no history of respiratory allergy</td>
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<table>
<thead>
<tr>
<th>Interventions</th>
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<tbody>
<tr>
<td>Treatment group 1: inhaled indomethacin, 2 ml aerosol preparation of 1.2 µg/ml in saline 3 times daily for 14 days</td>
</tr>
<tr>
<td>Treatment group 2: inhaled placebo, 2 ml aerosolised saline alone 3 times daily for 14 days</td>
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<tr>
<td>Method of delivery: nebuliser delivering aerosolised particles with a median particle diameter of 4.5 to 5 µm</td>
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<th>Outcomes</th>
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<tr>
<td>Data for all 3 disease states were analysed collectively. Outcomes were sputum indices (% solid composition, sputum bacterial density and inflammatory markers - prostaglandin E2, PGF&lt;sub&gt;2α&lt;/sub&gt;, 6-oxo-PGF&lt;sub&gt;1α&lt;/sub&gt;, TxB&lt;sub&gt;2&lt;/sub&gt;), Borg score ratio scale for breathlessness and dyspnoea, white cell count (WCC), erythrocyte sedimentation rate (ESR) and spirometry</td>
</tr>
<tr>
<td>The only outcome for which results were reported separately for bronchiectasis patients was effect on sputum production</td>
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<tr>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>We elected to include all outcomes as although not all had the diagnosis of bronchiectasis, the additional 2 diseases (chronic bronchitis and panbronchiolitis) overlap with bronchiectasis and can eventually lead to bronchiectasis. Furthermore, the high number colonised with bacteria especially with <em>Pseudomonas</em> indicates that bronchiectasis would have been likely to be present if a multidetector high resolution CT scan was performed in all subjects</td>
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**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Not described</td>
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</table>
Tamaoki 1992  (Continued)

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<th>Allocation concealment?</th>
<th>Unclear</th>
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<tbody>
<tr>
<td></td>
<td>The authors state that the study is a double-blind, randomised, placebo-controlled trial but do not describe the randomisation process, including allocation concealment</td>
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<table>
<thead>
<tr>
<th>Blinding?</th>
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<tbody>
<tr>
<td>Sputum volume</td>
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<td>Yes</td>
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<tr>
<td>The patients and investigators responsible for disease follow up and data analysis were blinded. The doctor responsible for allocating treatment groups was not blinded but was not involved in follow up or data analysis</td>
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**Characteristics of excluded studies  [ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llewellyn-Jones 1995</td>
<td>Study using oral indomethacin</td>
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</table>
### DATA AND ANALYSES

**Comparison 1. Clinical symptoms**

<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 Borg score</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

**Comparison 2. Lung function**

<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 FEV1 % predicted (end of study)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2 VC % predicted (end of study)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

**Comparison 3. Other indices**

<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 Wet weight of sputum at end of study (g/day)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Bacterial load of sputum at end of study (Log10 cfu/g)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 White cell count at end of study (per mm3)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 ESR at end of study (mm/h)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
**Analysis 1.1. Comparison 1 Clinical symptoms, Outcome 1 Borg score.**

Review: Inhaled non-steroid anti-inflammatory for children and adults with bronchiectasis

Comparison: 1 Clinical symptoms

Outcome: 1 Borg score

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Mean(SD))</td>
<td>N (Mean(SD))</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Tamaoki 1992</td>
<td>13 (4.5 (1.44))</td>
<td>12 (6.4 (1.73))</td>
<td>-1.90 [-3.15, -0.65]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>0</td>
<td>0</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

---

**Analysis 2.1. Comparison 2 Lung function, Outcome 1 FEV1 % predicted (end of study).**

Review: Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

Comparison: 2 Lung function

Outcome: 1 FEV1 % predicted (end of study)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Mean(SD))</td>
<td>N (Mean(SD))</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Tamaoki 1992</td>
<td>13 (72.7 (12.98))</td>
<td>12 (75.6 (13.51))</td>
<td>-2.90 [-13.30, 7.50]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>0</td>
<td>0</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable
### Analysis 2.2. Comparison 2 Lung function, Outcome 2 VC % predicted (end of study).

**Review:** Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

**Comparison:** 2 Lung function

**Outcome:** 2 VC % predicted (end of study)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Tamaoki 1992</td>
<td>13</td>
<td>82.6 (8.65)</td>
<td>12</td>
<td>85.5 (10.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2.90 [-10.58, 4.78]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0</td>
<td>0</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

---

### Analysis 3.1. Comparison 3 Other indices, Outcome 1 Wet weight of sputum at end of study (g/day).

**Review:** Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

**Comparison:** 3 Other indices

**Outcome:** 1 Wet weight of sputum at end of study (g/day)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Tamaoki 1992</td>
<td>13</td>
<td>95 (75.72)</td>
<td>12</td>
<td>170 (76.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-75.00 [-134.61, -15.39]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis (Review)*

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Analysis 3.2. Comparison 3 Other indices, Outcome 2 Bacterial load of sputum at end of study (Log10 cfu/g).

Review: Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

Comparison: 3 Other indices

Outcome: 2 Bacterial load of sputum at end of study (Log10 cfu/g)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Tamaoki 1992</td>
<td>13</td>
<td>7.8 (2.16)</td>
</tr>
</tbody>
</table>

Analysis 3.3. Comparison 3 Other indices, Outcome 3 White cell count at end of study (per mm3).

Review: Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

Comparison: 3 Other indices

Outcome: 3 White cell count at end of study (per mm3)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>Tamaoki 1992</td>
<td>13</td>
<td>6500 (1442)</td>
</tr>
</tbody>
</table>
Analysis 3.4. Comparison 3 Other indices, Outcome 4 ESR at end of study (mm/h).

Review: Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis

Comparison: 3 Other indices

Outcome: 4 ESR at end of study (mm/h)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
</tbody>
</table>

HISTORY
Protocol first published: Issue 1, 2009
Review first published: Issue 4, 2010

CONTRIBUTIONS OF AUTHORS
SP and AC wrote the protocol and review based on previous protocols and reviews. JU and ST contributed to writing the protocol and review.

DECLARATIONS OF INTEREST
None of the authors have any conflict of interest.

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INDEX TERMS

Medical Subject Headings (MeSH)
Administration, Inhalation; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Bronchiectasis [*drug therapy]; Dyspnea [drug therapy]; Sputum [secretion]

MeSH check words
Adult; Child; Humans