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Short courses of antibiotics for children and adults with bronchiectasis (Review)

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[Intervention Review]

Short courses of antibiotics for children and adults with bronchiectasis

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ABSTRACT

Background

Bronchiectasis is an important cause of respiratory morbidity in both developing and developed countries. Antibiotics are considered standard therapy in the treatment of this condition but it is unknown whether short courses (four weeks or less) are efficacious.

Objectives

To determine whether short courses of antibiotics (i.e. less than or equal to four weeks) for treatment of acute and stable state bronchiectasis, in adults and children, are efficacious when compared to placebo or usual care.

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE, EMBASE, OLDMEDLINE, CINAHL, AMED and PsycINFO and handsearching of respiratory journals and meeting abstracts were performed by the Cochrane Airways Group up to February 2011.

Selection criteria

Only randomised controlled trials were considered. Adults and children with bronchiectasis (defined clinically or radiologically) were included. Patients with cystic fibrosis were excluded.

Data collection and analysis

Two review authors independently reviewed the titles, abstracts and citations to assess eligibility for inclusion. Only one study fulfilled the inclusion criteria and thus meta-analysis could not be performed.

Main results

The single eligible study showed a small benefit, when compared to placebo, of four weeks of inhaled antibiotic therapy in adults with bronchiectasis and pseudomonas in their sputum. There were no studies in children and no studies on oral or intravenous antibiotics.

Authors' conclusions

There is insufficient evidence in the current literature to make reasonable conclusions about the efficacy of short course antibiotics in the management of adults and children with bronchiectasis. Until further evidence is available, adherence to current treatment guidelines is recommended.

PLAIN LANGUAGE SUMMARY

Short courses of antibiotics for children and adults with bronchiectasis

There is a paucity of evidence to conclude whether short courses of antibiotics (i.e. less than or equal to four weeks) are equivalent or superior to placebo in the treatment of stable or exacerbation state bronchiectasis. One single study showed some benefit of short-course inhaled antibiotics over placebo, in terms of microbiological response and subjective improvement in medical condition, although this was balanced against an increase in adverse effects and antimicrobial resistance in the treatment group. Given the potential benefits of shorter duration antibiotic therapy in bronchiectasis, further RCTs are clearly needed to answer this important question.

BACKGROUND

Non cystic-fibrosis bronchiectasis, previously termed an 'orphan disease' is increasingly recognised as a major cause of respiratory morbidity both in developing countries as well as affluent countries, and particularly within Indigenous populations (Chang 2008; Edwards 2003; Singleton 2000).

There are many known aetiological associations with bronchiectasis. Severe lower respiratory tract infection has previously been identified as the most common preceding medical condition in children diagnosed with bronchiectasis (Chang 2008b; Eastham 2004; Karakoc 2009; Singleton 2000), and continues to be a major cause of bronchiectasis worldwide (Callahan 2002; Edwards 2003; Karakoc 2009). However, diseases that affect the pulmonary system (such as immunodeficiency) have become increasingly identified as important causes of bronchiectasis within developed countries (Li 2005; Shoemark 2007).

In adults, the major aetiological associations include post-infection pneumonia or TB, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis and immunodeficiencies (Shoemark 2007). Primary lung diseases such as chronic obstructive pulmonary disease (COPD) (O'Brien 2000; Patel 2004), sarcoidosis (Lewis 2002), and bronchiolitis obliterans (Chang 1998) have been associated with bronchiectasis as a secondary manifestation. In children, immunodeficiency, aspiration, primary ciliary dyskinesia and congenital airway anomalies are important considerations (Li 2005). Despite intensive investigations, an underlying cause is often not found in many children and adults with bronchiectasis (Shoemark 2007).

Description of the condition

Bronchiectasis is a disease that primarily affects the airways in the initial disease phase. The postulated pathophysiology includes a 'vicious circle' of infection, inflammation and impairment of mucociliary clearance mechanisms eventually leading to airway destruction and bronchial dilatation (Cole 1986).

Adult patients usually present with cough, daily sputum production, dyspnoea, rhinosinusitis, haemoptysis and recurrent pleurisy (King 2004). Children usually present with chronic wet cough or recurrent pneumonia (Singleton 2000). They may have clinical signs such as crackles and wheeze on chest auscultation and sometimes peripheral clubbing (King 2004). With appropriate treatment (usually antibiotics and airway clearance), the chronic cough can totally resolve (Kapur 2009), as can radiological evidence of bronchiectasis (Gaillard 2003). High-resolution Computed Tomography (HRCT) of the chest is considered the gold-standard in diagnosis of bronchiectasis. However, controversy exists as to the normal cut-off of broncho-arterial ratio (particularly in children) (Chang 2008b). Hence, bronchiectasis is sometimes defined clinically in children (Chang 2008b; Singleton 2000). Recent studies suggest that volumetric scans acquired using multi-detector CT are substantially more sensitive and accurate than conventional HRCT for assessing bronchiectasis (Hill 2009).

A combination of airway clearance techniques and antibiotic therapy, with or without other therapies such as anti-inflammatory agents and bronchodilators, are current recommended treatment for non-cystic fibrosis bronchiectasis (Chang 2008b). Specific treatments targeted to the underlying aetiology (such as intravenous immunoglobulin for common variable immunodeficiency) is also important in the management of bronchiectasis.

Early recognition and treatment of bronchiectasis may improve long term outcomes (Kapur 2010).

Description of the intervention

Antibiotics are the mainstay of therapy in the management of bronchiectasis (Prasad 2007). There are various methods to deliver antibiotics to the pulmonary system (oral, intravenous or inhaled). The type of antibiotics given may be targeted to the patient's known airway organism(s) or used empirically.

How the intervention might work

Infection and inflammation are key components in the aetiopathogenesis of bronchiectasis (Cole 1986). Bronchiectatic airways facilitate chronic bacterial colonisation and predispose them to recurrent infections (Loebinger 2007). Chronic bacterial infection elicits a systemic inflammatory response with local release of inflammatory cytokines (including TNF-α and IL-8) causing migration of inflammatory cells such as neutrophils and lymphocytes (Gaga 1998; Shum 2000). Neutrophils release proteolytic enzymes e.g. neutrophil elastase (Amitani 1995) and reactive oxygen species (Anderson 1996), into the airway lumen which cause epithelial damage and stimulate mucous production (Adler 1990). Antibiotics can potentially halt the bacterial infection and subsequently limit ongoing neutrophilic inflammation.

An existing Cochrane Review found that prolonged courses of antibiotics for bronchiectasis, i.e. greater than four weeks in length, are effective in reducing sputum volume and purulence but have a limited impact on the natural history of the condition (Evans 2007). We have reviewed the literature to determine the impact of shorter courses of antibiotics during stable state and exacerbation state in bronchiectasis.

Why it is important to do this review

Most adults and children with bronchiectasis are given frequent courses of antibiotics, the optimal duration of which is unknown. The published Cochrane Review on antibiotics for bronchiectasis is limited to prolonged courses greater than four weeks in duration (Evans 2007).

In clinical practice, short courses of antibiotics during stable and exacerbation states of bronchiectasis often result in improvement in symptoms. Objective measures of airway inflammation also improve, as some studies have shown, for example use of short-course inhaled gentamicin resulted in improvement in airway hypersecretion and inflammation (Lin 1997).

There is currently a paucity of evidence on the optimal duration of antibiotics in stable and exacerbation states. However, there is a trend towards use of shorter courses (i.e. less than two weeks) amongst clinicians. The risks of antibiotic side effects and resistance are a significant concern when using longer courses of antibiotics. A review of the literature to determine the evidence for use of shorter courses of antibiotics in adults and children in stable and exacerbation states of bronchiectasis is important to assist in guiding clinical practice.

OBJECTIVES

To evaluate the efficacy of short courses (i.e. four weeks or less) of antibiotics in children and adults with bronchiectasis;

(a) during stable state bronchiectasis; and

(b) for reducing the severity and frequency of acute respiratory exacerbations.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled trial comparing outcomes with use of antibiotics (intravenous, oral or inhaled) versus placebo or usual care as the control, for periods of less than, or equal to, four weeks, in non-cystic fibrosis bronchiectasis. Participants are allowed to have adjunctive therapies (such as airway clearance) as long as they have equal chance of having these adjunctive therapies.

Types of participants

Adults and children with bronchiectasis (defined clinically or radiologically) not related to cystic fibrosis.

Types of interventions

Any short (four weeks or less) course of antibiotics given by intravenous, oral or nebulised routes.

Types of outcome measures

Primary outcomes

The primary outcome measures were change in:

1. Symptom score (e.g. bronchiectasis severity control, cough-specific/respiratory-specific quality of life (QoL) or generic health-specific QoL)

2. Lung function indices (airway resistance or airway calibre measurements)
3. Adverse events

Secondary outcomes

1. Sputum or airway markers (weight, purulence, colour (Bronkotest), inflammatory profiles)
2. Microbiological data (density, resistance patterns)
3. Exacerbation data (length, time to next exacerbation)

Search methods for identification of studies

Electronic searches

Randomised controlled trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, OLDMEDLINE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group search methods for further details). We searched all records in the Specialised Register coded as 'bronchiectasis' using the following terms:

antibiotic* OR *cillin OR *tetracycline OR *mycin OR macrolide* OR quinolone* OR *oxacin OR trimethoprim OR *sulpha OR *ceph or anti-bacteri* or "anti bacteri* OR anti-microbial* OR anti*
The search was conducted in February 2011.

Searching other resources

We handsearched all the papers and reviews identified for further references and contacted authors to request their identification of any unpublished or missed trials. We contacted researchers directly as required to establish whether other unpublished or ongoing studies were available for assessment. We handsearched clinical trials web sites (www.clinicalstudyresults.org; www.clinicaltrials.gov; www.fda.gov).

Data collection and analysis

Selection of studies

Following electronic literature searches, AC and DW independently reviewed the searches to identify potentially relevant trials for full review. We searched bibliographies and texts to identify additional studies. From the full text using specific criteria, AC and DW independently selected trials for inclusion. There was complete agreement between review authors.

Data extraction and management

We extracted information from each study for the following characteristics:
1. Design (description of randomisation, blinding, allocation, number of study centres and location, withdrawals)
2. Participants (N, mean age, age range of the study, baseline lung function, duration of antibiotics < 4 weeks versus no antibiotics)
3. Intervention (type and duration of antibiotic, appropriateness of antibiotic choice, dosing schedules of groups)
4. Outcomes (type of outcomes and results of outcomes)

We requested further information from the trial authors where required. This occurred with Barker 2000 as explained in the included studies section of the Results.
Studies were translated to English where possible.

Assessment of risk of bias in included studies

We assessed trial bias protection in the following domains and study quality according to whether studies met the following prespecified quality criteria (as met, unmet or unclear) using the risk of bias (RoB) table in Review Manager 5.
1. Sequence generation
2. Allocation concealment
3. Blinding of participants and investigators
4. Loss to follow-up

Measures of treatment effect

We extracted data for each of the outcomes (where data were available) from the trial publication that fulfilled the inclusion criteria.
We performed an initial qualitative comparison of all the individually analysed studies taking into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment and estimated effect size, to examine whether pooling of results (meta-analysis) was reasonable.

Unit of analysis issues

We sought to obtain data that were reported with patients (rather than events) as the unit of analysis for the primary outcomes.

Dealing with missing data

The proportion of randomised patients who provided data for the main outcomes was reported and we had planned to compare this with the number of patients with events in each outcome category.

Assessment of heterogeneity

We had planned to describe and explore heterogeneity between the study results, and to use the 95% confidence interval, estimated using a random-effects model, whenever there were concerns about statistical heterogeneity.

Assessment of reporting biases

If combining data was possible, we had planned to assess publication bias using a funnel plot. We planned to identify and report on any selective reporting in the included trials.

Data synthesis

We combined data using Review Manager 5, with a view to using a fixed-effect mean difference (calculated as a weighted mean difference) for continuous data variables. If different scales were combined, we had intended to use the standardised mean difference.

For the dichotomous outcome variables of each individual study, we had planned to calculate odds ratios using a modified intention-to-treat analysis (i.e. failure assumed if participant drops out of study). This analysis assumes that children or adults not available for outcome assessment have not improved (and probably represents a conservative estimate of effect).

For the primary outcomes we intended to calculate a number needed to treat (benefit or harm) when possible for the different levels of risk as represented by control group event rates over a specified time period using the pooled Odds Ratio and its confidence interval using an online calculator, Visual Rx (Cates 2003). A summary of findings (SoF) table would be constructed for the primary outcomes.

Subgroup analysis and investigation of heterogeneity

We had intended to perform an a priori subgroup analysis for:

1. Children versus adults (adult studies will be considered as those which recruited participants from 18 years upwards)
2. Type of antibiotics (oral, intravenous, inhaled)
3. Type of control arm (placebo/no treatment or control antibiotic i.e. prolonged duration antibiotics)
4. State during enrolment (stable state or exacerbation)

Sensitivity analysis

Sensitivity analyses were also planned to assess the impact of the potentially important factors on the overall outcomes:

1. variation in the inclusion criteria;
2. differences in the medications used in the intervention and comparison groups;
3. analysis using random-effects model;
4. analysis by "treatment received"; and
5. analysis by "intention-to-treat".

RESULTS

Description of studies

Results of the search

From the searches, the Cochrane Airways Group specialised register/search identified 187 potentially relevant titles. After assessing the titles/abstracts, we obtained19 papers for consideration for inclusion in the review. We reviewed 11 full text articles and 8 further abstracts. We excluded 18 studies (see Excluded studies). We found two potentially eligible studies, however they appeared to have used the same patient population, leaving only one eligible study in adults. We identified no studies in children.

Included studies

The included studies were Barker 2000 and Couch 2001a, which described the same study populations. Couch 2001a was an "early review of data" for a chest supplement on aerosolised therapeutics as discussed by Fiel 2001 in his editorial. For this reason, we used the final data in Barker's paper in this Cochrane Review.

The sole study was a multicentre parallel RCT that examined the effect of nebulised tobramycin (Tobramycin Solution for Inhalation) versus placebo, in adults with CT confirmed bronchiectasis and *Pseudomonas aeruginosa* infection. There were 16 study sites, 74 adults enrolled with completion rate of 81% (60/74). Further details are described in the Characteristics of included studies.

Excluded studies

Eighteen studies were excluded as they did not fulfil criteria for the review. Fifteen of the eighteen studies excluded had no suitable comparator/placebo group, one study did not specify bronchiectasis as an inclusion criterion, one study had treatment periods greater than four weeks, two studies shared a common study population, resulting in the exclusion of one.

Bilton 2006 and Shrewsbury 2004 examined short courses of antibiotics in bronchiectasis and compared oral ciprofloxacin (in treatment doses) plus placebo to oral ciprofloxacin plus inhaled tobramycin. Although these studies almost fulfilled criteria for inclusion, there was no "antibiotic-free" placebo for comparison, resulting in their exclusion from this review.

Couch 2001a was excluded as it was an early review of the same data used in the included study Barker 2000. Attempts to contact the corresponding author were unsuccessful, but this was confirmed in the editorial Fiel 2001 which accompanied the paper.

Risk of bias in included studies

Allocation concealment was unclear in this study (Barker 2000). Block randomisation was utilised to balance group sizes. The study was double-blinded, with both investigators and participants being blinded to study group allocation to reduce selection bias. Six patients were withdrawn from the placebo group due to need for an antibiotic other than the study drug.

Allocation

Block randomisation of patients was used. Eligible patients were randomly assigned in blocks of two to parallel groups at each study centre to receive either inhaled tobramycin or placebo.

Blinding

The study was double-blinded i.e. both participants and investigators were blinded to the study drug assignment until completion of the follow-up visit and data were collected from all study sites. The placebo used (quinine sulphate) was chosen because of its similar taste to tobramycin. It was unclear whether investigators were blinded to the study hypothesis.

Incomplete outcome data

The number of participants withdrawn (due to adverse events or use of antibiotic other than the study drug) and those lost to follow-up were reported for both inhaled tobramycin and placebo groups.

Selective reporting

There was no suggestion that selective reporting had occurred.

Effects of interventions

The included trial involved 74 patients with 60 completing the study. In the absence of additional suitable studies, there were insufficient data to perform a meta-analysis. The outcomes from the single study (also presented in the forest plot) were:

Primary Outcomes

1. Symptom score (e.g. bronchiectasis severity control, cough-specific/respiratory-specific quality of life (QoL) or generic health-specific QoL)

The study did not specifically measure any symptoms to determine a symptom score. Instead, the investigator's subjective assessment of a change in the patient's general medical condition ("improved" or "not improved") was recorded at week six: 23 of 37 (62%) patients in the tobramycin-treated group significantly improved compared to 14 of 35 (40%) in the placebo group that improved (Analysis 1.1; OR 0.37; 95% CI 0.14 to 0.95).

2. Lung function indices (airway resistance or airway calibre measurements)

Percent change in forced expiratory volume in one second (FEV_1) percent predicted and in Forced Vital Capacity (FVC) percent predicted from baseline to week four were not statistically significant between the tobramycin and placebo groups (-2.2% versus 1.5% respectively, P = 0.41) for FEV_1 % predicted and FVC % predicted (-2.8% versus 2.2%, P = 0.19). Airway reactivity (percent change in FEV1 from pre- to post-study drug administration) was not significantly different from zero percent for either the tobramycin group (mean = -1%, Week 0, -3% Week 4) or placebo group (mean = -3% Week 0, -1% Week 4).

3. Adverse events

Thirty-one of 37 (84%) patients in each treatment group reported at least one adverse event. Respiratory system adverse events were reported by 26 (70%) tobramycin patients and by 19 (51%) placebo patients. There was no statistical significance, but results favoured the placebo group (OR 2.24; 95% CI 0.86 to 5.82; Analysis 2.1). Five patients in the tobramycin group and one patient in the placebo group were hospitalised and treated for an exacerbation of their pulmonary disease (OR 5.63; 95% CI 0.62 to 50.73; Analysis 2.2).

Secondary outcomes

1. Microbiological response (i.e. change in *P. aeruginosa* density from baseline to week 4 and week 6 and antibiotic resistance)

At the end of the trial, significantly more subjects in the tobramycin group (13 of 37) had *P. aeruginosa* eradicated from their sputum compared to the placebo group (0 of 37); (OR 0.03; 95% CI 0.01 to 0.14; Analysis 3.1.) Furthermore, a further 12 patients in the tobramycin group had reduced *P. aeruginosa* carriage (PA cfu/g decreased by at least 2 $\log_{10}$ at week 4), compared to two patients with reduced carriage in the placebo group.

However, at follow-up two weeks post cessation of antibiotics, the mean reduction in the tobramycin group was smaller than in previous weeks, suggesting some regrowth of organisms after ceasing the antibiotic.

Four of 36 patients in the tobramycin group and one of 32 in the placebo group, who began the study with susceptible *P. aeruginosa*, had resistant *P. aeruginosa* at their last visit (P = 0.36). Three of the four patients in the tobramycin group who developed resistant *P. aeruginosa* showed no microbiological response. All four patients

were considered to have not improved when their general medical condition was assessed.

DISCUSSION

This review is limited to a sole study in adults. The data suggest that short term inhaled antibiotics show some benefit in the treatment of patients with bronchiectasis and *P. aeruginosa*. The study followed the patients for only two weeks post-treatment to assess longevity of response. Despite its weaknesses, this single study supports previous Cochrane Reviews on the use of longer term antibiotics in bronchiectasis (Evans 2007), in showing subjective improvement in general medical condition as assessed by an investigator.

This review has highlighted the fact that, although antibiotics are the mainstay of treatment in adults and children with bronchiectasis, there remains a paucity of data, particularly high quality data, to support this practice. In today's evidence based medical era and with bronchiectasis becoming increasingly recognised as a major cause of respiratory morbidity, there will be an increasing need to provide evidence-based answers to these common questions.

A small number of patients in the study antibiotic arm developed "resistant" pseudomonas. This highlights an important complication of antibiotic therapy, particularly when antibiotic use in any one patient is prolonged or recurrent. Previous research by Hillier 2007 has shown that antibiotic resistance increases with increased duration of antibiotic therapy. These findings are related to urinary tract infections but are likely to be applicable to infections elsewhere in the body including the lung. This issue, combined with the likely improved quality of life for patients receiving shorter courses of antibiotics, highlights the need for further studies to determine the optimal duration of antibiotic therapy in bronchiectasis.

The included study followed patients for only two weeks post-therapy. Given that antibiotics are known to indirectly limit neutrophilic inflammation in the airways and ideally eradicate the bacterial infection, it is not surprising that patients showed improvement over this follow-up period. It is unknown if two weeks is an optimal timeframe to assess bacterial eradication adding further to the limitations of this study. To assess longevity of symptom response and microbiological eradication, a longer timeframe of follow-up would have been required.

Evans 2007's Cochrane Review on prolonged antibiotics found a significant benefit of prolonged antibiotics (i.e. four or more weeks) in terms of response rates. They found no significant difference between placebo and prolonged antibiotics in terms of exacerbation rates and lung function. This would concur with Barker 2000, which found a subjective improvement in patients' general medical condition with inhaled tobramycin therapy as compared to placebo, with no significant differences in lung function between treatment groups.

The single included study (Barker 2000) showed some benefit of four weeks of inhaled antibiotic therapy compared with placebo in patients with bronchiectasis and *P. aeruginosa* infection in terms of microbiological response (at the expense of increased resistance) and improvement in general medical condition. The lack of other suitable studies for this Cochrane Review precluded a meta-analysis, and as a result we could not draw any firm conclusions on the topic.

AUTHORS' CONCLUSIONS

Implications for practice

When considering implications for practice, one must acknowledge the fact that this review was based on one study of adult patients and the intervention was "inhaled" antibiotics. This study showed a small benefit in microbiological response and overall subjective improvement in general medical condition, with no effect on lung function and an increase in adverse events in the intervention group. The study failed to address primary outcome measures with symptom scores or objective outcomes. Therefore, although this one study is suggestive of benefit of short courses of antibiotics for bronchiectasis, one would conclude, for current practice implications, that there is insufficient evidence available in the current literature to make any reasonable conclusions. However until further evidence is available, clinicians should adhere to guidelines (Chang 2010; Pasteur 2010) that include data from non RCTs.

Implications for research

Well-designed, double-blinded, parallel, randomised controlled trials are required to assess the role of short courses of antibiotics in the treatment of bronchiectasis. These studies should include validated outcome measures such as improvements in symptom score, QOL and lung function, balanced against adverse effects as primary outcome measures. Trials including oral, inhaled and intravenous antibiotic administration methods are needed. Future RCTs should be undertaken in paediatric as well as adult patients. Well-designed studies should include sufficient longitudinal follow-up of patients to assess longevity of intervention response and therefore applicability of evidence to practice. Such well-designed research would have the potential to improve the quality of life for individuals with bronchiectasis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Barker 2000

Methods	The study was a randomised placebo-controlled, double-blinded trial with antibiotics administered for 4 weeks. Eligible patients were randomly assigned in blocks of two to parallel groups at each of 16 study sites across the United States to receive either Tobramycin solution for inhalation or placebo. This was administered twice daily for 4 weeks in bronchiectasis patients whose sputum contained *Pseudomonas aeruginosa*. Patients were then observed for 2 weeks after administration of their last dose. Of patients enrolled, they were divided equally between the two treatment groups. Patients were withdrawn if they required any additional antibiotics at any stage during study participation Patients were screened 2 weeks prior to their initial dose of the study drug, were dosed for 4 weeks, and then observed for 2 weeks after their last dose. Thus the total duration of the study was 8 weeks. At each visit a sputum sample was obtained and the density of the *P. aeruginosa* in sputum was measured. Pulmonary function testing (FEV1 and FVC) was performed at baseline and at the final treatment visit (week 4). Tobramycin levels were measured. Adherence was measured at week 4 by counting the number of vials of study drug used. A subjective clinical assessment of the patient's general medical condition was made, by a study investigator, at the follow-up visit on week 6 There were 6 patients who withdrew from the tobramycin group (3 for adverse events, 2 for use of antibiotics other than study drug, and 1 was lost to follow-up.) 8 withdrew from the placebo group (2 for adverse events, and 6 for use of antibiotics other than the study drug.)
Participants	125 patients were screened and 74 patients (45 female), mean age 66.6 (tobramycin group) and 63.2 (placebo group) were enrolled. Patients were block randomised to receive either 300 mg of inhaled tobramycin or placebo twice daily for 4 weeks. 37 received inhaled tobramycin and 37 received placebo Inclusion: Bronchiectasis diagnosed by conventional or high-resolution CT and sputum containing at least 10^4 cfu/mL *P. aeruginosa*. Exclusion: cystic fibrosis, allergic bronchopulmonary aspergillosis, acute pulmonary process requiring medical intervention as indicated by a new infiltrate on a chest radiograph, significant recent haemoptysis, or had received antibiotics within 2 weeks of the screening visit
Interventions	Nebulised tobramycin solution for inhalation (300 mg tobramycin) twice daily or placebo for 4 weeks
Outcomes	Primary end point was (1) Change in *P. aeruginosa* density from baseline to week 4. Additional endpoints included: (1) change in *P. aeruginosa* density from baseline values to week 2 and to week 6; (2) an investigator's subjective assessment of a change in the patient's general medical condition ("improved" or "not improved") was made and recorded at week 6, (3) the percent change in FEV1 percent predicted and in FVC percent predicted from week 0 to week 4 and (4) Safety endpoints included the incidence of adverse events, change in serum chemistry and haematology measurements, and airway reactivity

	Each patient's microbiological response was categorised according to whether *P. aeruginosa* was eradicated, reduced by treatment, or did not respond to treatment. *P. aeruginosa* was considered eradicated if it was not detected at week 6 or if it was not detected at week 4 and the patient was unable to produce sputum at week 6. A patient's response was defined as reduced by treatment if *P. aeruginosa* was recovered from the week 6 sputum and reduced by at least 2 log 10 cfu/g at week 4 compared with baseline. A patient had no microbiological response if *P. aeruginosa* did not decrease 2 log 10 cfu/g at week 4 or if the patient withdrew from the study
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and investigators.	Low risk	Patients and investigators were blinded to the study drug assignment
Incomplete outcome data assessed?	Low risk	Number of dropouts and loss to follow-up included.
Free of selective reporting?	Low risk	No suggestion that selective reporting may have occurred.
Free of other bias?	Low risk	No other bias identified
Sequence generation.	Low risk	Sequence generation was referred to, however details were not provided

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

Study	Reason for exclusion
Bilton 2006	No suitable placebo/comparator group. (Comparator was not adequate to satisfy inclusion criteria, i.e. no "antibiotic-free/placebo" or long-term antibiotic group for comparison.)
Chrysanthopoulos 1989	No suitable placebo/comparator group.
Couch 2001a	Overlap of study participants with included study.
Douglas 1957	No suitable placebo/comparator group.
Howie 1976	Study participants had unknown bronchiectasis status.

(*Continued*)

Lam 1989	No suitable placebo/comparator group.
Lin 1996	No suitable placebo/comparator group.
Matsumoto 1986	No suitable placebo/comparator group. Not an RCT.
May 1972	No suitable placebo/comparator group.
Mehta 1991	No suitable placebo/comparator group.
Messens 1973	Translated from French. No suitable placebo/comparator group
Mijuskovic 1972	No suitable placebo/comparator group.
Nagy 1968	No suitable placebo/comparator group. (Compared antibiotic treatment to surgery.)
Oki 1993	No suitable placebo/comparator group. (Examined long term antibiotic treatment, no short course treatment arm.)
Santiveri 1995	No suitable placebo/comparator group.
Shrewsbury 2004	No suitable placebo/comparator group. (Comparator was not adequate to satisfy inclusion criteria, i.e. no "antibiotic-free/placebo" or long-term antibiotic group for comparison.)
Tagaya 2002	No suitable placebo/comparator group.
Twiss 2008	Longer-course antibiotics (i.e. 2 to 3 months) compared to placebo. No short course group

DATA AND ANALYSES

Comparison 1. Change in general medical condition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in general medical condition	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Respiratory system adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory system adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Hospitalised for respiratory events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. Microbiological response

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological response	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 4. Development of pseudomonas resistance (when initially sensitive)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pseudomonas resistance	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Change in general medical condition, Outcome 1 Improvement in general medical condition.

Review: Short courses of antibiotics for children and adults with bronchiectasis

Comparison: 1 Change in general medical condition

Outcome: 1 Improvement in general medical condition

Study or subgroup	TSI n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Barker 2000	14/37	23/37			0.37 [0.14, 0.95]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 14 (TSI), 23 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

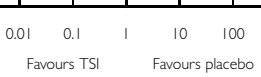
Analysis 2.1. Comparison 2 Respiratory system adverse events, Outcome 1 Respiratory system adverse events.

Review: Short courses of antibiotics for children and adults with bronchiectasis

Comparison: 2 Respiratory system adverse events

Outcome: 1 Respiratory system adverse events

Study or subgroup	TSI n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Barker 2000	26/37	19/37			2.24 [0.86, 5.82]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 26 (TSI), 19 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



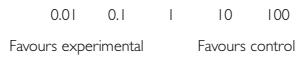
Analysis 2.2. Comparison 2 Respiratory system adverse events, Outcome 2 Hospitalised for respiratory events.

Review: Short courses of antibiotics for children and adults with bronchiectasis

Comparison: 2 Respiratory system adverse events

Outcome: 2 Hospitalised for respiratory events

Study or subgroup	Tobramycin n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Barker 2000	5/37	1/37			5.63 [0.62, 50.73]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 5 (Tobramycin), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



Analysis 3.1. Comparison 3 Microbiological response, Outcome 1 Microbiological response.

Review: Short courses of antibiotics for children and adults with bronchiectasis

Comparison: 3 Microbiological response

Outcome: 1 Microbiological response

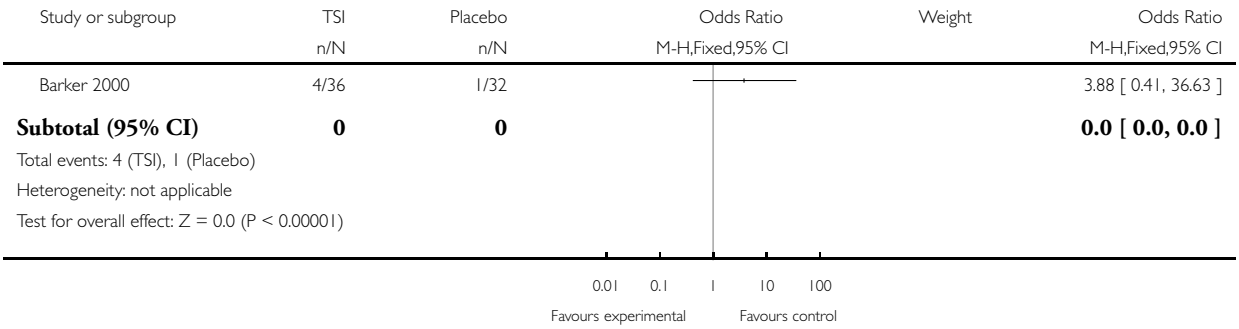
Study or subgroup	TSI n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Barker 2000	12/37	33/35			0.03 [0.01, 0.14]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 12 (TSI), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Analysis 4.1. Comparison 4 Development of pseudomonas resistance (when initially sensitive), Outcome 1 Pseudomonas resistance.

Review: Short courses of antibiotics for children and adults with bronchiectasis

Comparison: 4 Development of pseudomonas resistance (when initially sensitive)

Outcome: 1 Pseudomonas resistance



CONTRIBUTIONS OF AUTHORS

DW and AC wrote the protocol, based on previous protocols on cough in children. DW and AC selected articles from the search and together with JM, wrote the manuscript. BM, JU and SY contributed by reviewing the manuscript.

DECLARATIONS OF INTEREST

No conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Australian Cochrane Airways Group Network Graduate Scholarship, Australia.

Support to attend Cochrane Airways course

External sources

- TSANZ Allen and Hanbury's Paediatric Respiratory Grant-in-aid, Australia.

To support paediatric respiratory training for DW

- Queensland Children's Medical Research Institute, Australia.

Top-up scholarship for DW; Program grant for AC

- NHMRC, Australia.

Practitioner Fellowship for AC

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The duration of short course antibiotics was originally specified in the protocol as less than four weeks, however, in the actual review this was amended to four weeks or less to enable inclusion of Barker 2000.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [administration & dosage; *therapeutic use]; Bronchiectasis [*drug therapy]; Drug Administration Schedule; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans