Interventions for enhancing adherence to treatment in adults with bronchiectasis


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Interventions for enhancing adherence to treatment in adults with bronchiectasis (Protocol)

McCullough A, Ryan C, Bradley JM, O’Neill B, Elborn S, Hughes C

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Interventions for enhancing adherence to treatment in adults with bronchiectasis

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Editorial group: Cochrane Airways Group.


ABSTRACT
This is the protocol for a review and there is no abstract. The objectives are as follows:
To assess the effects of interventions to enhance adherence to any aspect of treatment in adults with bronchiectasis in terms of adherence and health outcomes, such as pulmonary exacerbations, health-related quality of life and healthcare costs.

BACKGROUND
Description of the condition
More than 600 million people worldwide suffer from chronic respiratory disease (WHO 2007), leading to 4.2 million deaths annually (WHO 2010). Bronchiectasis is an underdiagnosed and underinvestigated condition; research into new treatments is urgently required to improve the health status of patients with this condition (Gibson 2013). The global prevalence of bronchiectasis is currently not known. The most recent prevalence study, which was conducted in the United States, demonstrated that prevalence of the condition is increasing at a rate of 8.7% annually, with an eight-year prevalence of 1106 per 100,000 of the population (Seitz 2012). Bronchiectasis-associated annual healthcare costs are estimated at US$630 million (Weycker 2005), and bronchiectasis-associated hospital admissions range between two and six per 100,000 in Europe (Gibson 2013). Given the recognised under-diagnosis of this condition, it is likely that prevalence and the associated healthcare burden are even greater than reported.

Description of the intervention
No treatments have been licenced for use in patients with bronchiectasis. Patients are treated with a complex regimen of medication and airway clearance techniques that have been extrapolated from other chronic respiratory diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma. Airway clearance techniques such as the Acapella® and the active cycle of breathing technique are recommended to be
prescribed for patients with this condition (Pasteur 2010), but evidence of their long-term effectiveness is insufficient (Lee 2013). The aim of prescribed treatments in bronchiectasis is to reduce pulmonary exacerbations, improve health-related quality of life and reduce hospital admissions (Pasteur 2010). However, we recently reported that adherence was low in bronchiectasis, with as few as 53% of patients categorised as adherent to medication and 41% categorised as adherent to airway clearance (McCullough 2013). We have also demonstrated that those who were adherent to inhaled antibiotics had significantly fewer pulmonary exacerbations than those who were non-adherent (McCullough 2013). The first randomised controlled trial to test the effectiveness of colistin (inhaled antibiotic therapy) for use in bronchiectasis demonstrated that individuals who were adherent to treatment (i.e. took 80% or more of prescribed medication) had a longer time to first exacerbation and better health-related quality of life (Haworth 2013). This illustrates the importance of adherence to treatment in determining health outcomes and highlights the need to enhance adherence in this patient population. New therapies are being adapted and tested in patients with bronchiectasis (Altenburg 2013; Bilton 2013; Haworth 2013; Serisier 2013; Wilson 2013), and it is likely that the burden of treatment for those with bronchiectasis will continue to grow. This increasing treatment complexity may affect adherence to new and existing treatments. However, little is known about the types of adherence interventions that have been used in bronchiectasis or which, if any, are effective.

How the intervention might work
Adherence is a complex behavioural process; thus, no single mechanism is known for adherence to behaviour change. Adherence interventions use educational, psychological and behavioural techniques, in isolation or in combination with each other, to alter adherence behaviour. However, education alone is insufficient to alter adherence behaviour (Haynes 2008). Enhanced adherence may lead to improved health outcomes, including reductions in pulmonary exacerbations and in healthcare costs with bronchiectasis. Patients may experience improved health-related quality of life as a consequence of enhanced adherence.

Why it is important to do this review
Low adherence is associated with more frequent pulmonary exacerbations for patients with bronchiectasis (McCullough 2013). Therefore, enhancing adherence has the potential to lead to improved health outcomes in this patient population. Little is known about the types of adherence interventions that have been used in bronchiectasis or which, if any, are effective. We will analyse existing randomised controlled trials to determine the content of the interventions that have been tested in this population and their effectiveness in enhancing adherence and health outcomes.

**OBJECTIVES**
To assess the effects of interventions to enhance adherence to any aspect of treatment in adults with bronchiectasis in terms of adherence and health outcomes, such as pulmonary exacerbations, health-related quality of life and healthcare costs.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
We will include randomised controlled trials (RCTs). We will include studies reported as full text, those published as abstract only and unpublished data. Both parallel and cross-over group designs will be included.

**Types of participants**
We will include adults (18 years of age or older) with bronchiectasis diagnosed by high-resolution computed tomography. We will include both those who are acutely unwell and those who are stable. We will exclude participants with bronchiectasis caused by underlying cystic fibrosis. Studies that include only a subset of relevant participants will be included when data from those participants are analysed and reported separately.

**Types of interventions**
We will include trials comparing any intervention aimed at enhancing adherence (including self management, education, service developments, reminders and other psychological and behavioural techniques) versus no intervention, usual care or another adherence intervention. Studies comparing two different treatment interventions (e.g. those comparing one type of medication, airway clearance technique, inhaler, mask or nebuliser versus another) and those that merely report adherence to treatment will be excluded.

**Types of outcome measures**
Reporting in the trial one or more of the outcomes listed here is not an inclusion criterion for the review. Studies will be included on the basis of type of study, participants and interventions. We will extract data collected at the end of the intervention period (i.e. after the last intervention) and at the end of the study follow-up (i.e. the end of the study), if different from data obtained at the end of the intervention period. When appropriate, we will also extract data collected at interim time points (i.e. data collected at time points other than end of the intervention and end of the study).
Primary outcomes

1. Adherence to at least one aspect of treatment (medication, airway clearance, medical devices or physical activity) as measured by direct (e.g. electronic monitoring, directly observed therapy) or indirect methods (e.g. self report, prescription refill data).
2. Rate of, duration of or time to first pulmonary exacerbation of bronchiectasis, defined according to the investigators’ definition.

Secondary outcomes

1. Time to hospitalisation, number of hospital admissions or hospital days for a pulmonary exacerbation of bronchiectasis.
2. Pulmonary function measures (forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow (FEF25–75, peak expiratory flow (PEF)).
3. Health-related quality of life measured using a generic or disease-specific tool (e.g. St George’s Respiratory Questionnaire, Quality of Life Questionnaire-Bronchiectasis).
4. Exercise capacity as measured by any exercise capacity tool (e.g. six-minute walk test, incremental shuttle walk test).
5. Healthcare costs including costs of intervention, costs of devices and overall expenditures.
6. Any adverse events associated with adherence or non-adherence to treatment.

Adherence to treatment is a primary outcome of this review, as this is the key outcome that adherence interventions aim to change. Reducing the frequency, duration of or time to pulmonary exacerbations, minimising hospital admissions, improving health-related quality of life and maintaining pulmonary function are key clinical outcomes of bronchiectasis treatments (Pasteur 2010) and thus have been chosen as the clinical outcomes for this review. To judge whether interventions can be implemented in clinical practice, it is necessary to know the cost-effectiveness of the intervention. Finally, to ensure patient safety, it is important to be aware of any adverse events associated with the intervention.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO and by handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We will search all records in the CAGR using the search strategy provided in Appendix 2. We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We will search all databases from the time of their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers’ websites for trial information. We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and will report within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (AMcC and CR) will independently screen titles and abstracts for inclusion of all potential studies identified as a result of the search and will code them as ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will retrieve the full-text study reports/publications, and two review authors (AMcC and CR) will independently screen the full text and identify studies for inclusion, and will identify and record reasons for exclusion of ineligible studies. We will resolve disagreements through discussion, or, if required, we will consult a third review author (CH). We will identify and exclude duplicates and will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a ‘Characteristics of excluded studies’ table.

Data extraction and management

We will document study characteristics and outcome data using a data collection form that has been piloted on at least one study in the review. Two review authors (AMcC and CR) will extract the following study characteristics from included studies.
1. Methods: study design, total duration of study, details of any ‘run-in’ period, number of study centres and locations, study setting, withdrawals and date of study.
2. Participants: number of participants, mean age, age range, gender, ethnicity, educational level, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: description of the intervention including duration of run-in, intervention and follow-up; type of intervention (including its components (e.g. self management,
Assessment of bias in included studies

Two review authors (AMcC and CR) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve disagreements by discussion or by involving another review author (CH). We will assess the risk of bias according to the following domains.

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

We will grade each potential source of bias as high, low or unclear and will provide in the ‘Risk of bias’ table a quote from the study report together with a justification for our judgement. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for hospital admissions may be very different than for patient-reported adherence). When information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the ‘Risk of bias’ table. We will take into account the risk of bias of the included studies when considering treatment effects for each outcome.

Assessment of risk of bias in conducting the systematic review

We will conduct the review according to this published protocol and will report any deviations from it in the ‘Differences between protocol and review’ section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios and continuous data as mean differences or standardised mean differences. We will enter presented data as a scale with a consistent direction of effect. We will undertake meta-analyses only when this is meaningful (i.e. when treatments, participants and the underlying clinical question are similar enough for pooling to make sense). We will narratively describe skewed data reported as medians and interquartile ranges. When multiple trial arms are reported in a single trial, we will include only the relevant arms. When two comparisons (e.g. intervention A vs control and intervention B vs control) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

For dichotomous data, we will report the proportion of participants contributing to each outcome in comparison with the total number randomly assigned. For continuous data, the mean difference based on change from baseline will be preferred over the mean difference based on absolute. The unit of analysis will be the person. For cluster-randomised trials, to avoid a unit of analysis error, sensitivity analysis will occur at the participant level and will incorporate adjustment using the intra class correlation coefficient (ICC).

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study is identified as an abstract only). When this is not possible and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis.

Assessment of heterogeneity

We will use the $I^2$ statistic to measure heterogeneity among the trials in each analysis. If we identify moderate ($I^2 = 30\%$ to $60\%$) or substantial heterogeneity ($I^2 = 50\%$ to $90\%$) (Higgins 2011), we will report this and will explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small-study biases.
Data synthesis

If a meta-analysis is appropriate, we will use a fixed-effect model. If heterogeneity cannot be explained by the prespecified subgroup and sensitivity analyses, we will perform a sensitivity analysis using the random-effects model. If a meta-analysis is not appropriate, we will conduct a narrative synthesis of included studies.

Summary of findings table

We will create a ‘Summary of findings’ table using the primary and secondary outcomes stated previously. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and will use GRADEpro software. We will justify all decisions to downgrade or upgrade the quality of studies by using footnotes, and we will make comments to aid readers’ understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.
1. Type of intervention delivered.
2. Healthcare professional who delivered intervention (physician vs non-physician led, e.g. nurses compared with physiotherapists, pharmacists and other professionals).
3. Clinical setting (hospital care vs community services).
4. Duration of intervention (one-off intervention compared with more than one intervention).
5. Disease status (acute vs stable participants).

We will use the following outcomes in subgroup analyses.
1. Adherence to at least one aspect of treatment (medication, airway clearance, medical devices or physical activity) as measured by direct (e.g. electronic monitoring, directly observed therapy) or indirect methods (e.g. self report, prescription refill data).
2. Rate of, duration of or time to first pulmonary exacerbation of bronchiectasis, defined according to the investigators’ definition.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2012). When both acute and stable participants are included in a study, we will explore them by subgroup analysis only if the results are reported separately.

Sensitivity analysis

We plan to carry out the following sensitivity analyses.
1. Sensitivity analysis excluding studies with a high risk of bias based on the ‘Risk of bias’ assessment.
2. Studies with less than 80% follow-up.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and will outline remaining uncertainties.

References

Additional references

Altenburg 2013

Bilton 2013

Gibson 2013
Haworth 2013

Haynes 2008

Higgins 2011

Lee 2013

McCullough 2013

Pasteur 2010

RevMan 2012

Seitz 2012

Serisier 2013

Weycker 2005

WHO 2007

WHO 2010

Wilson 2013

* Indicates the major publication for the study

APPENDICES

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

Electronic searches: core databases
### Database Frequency of search

<table>
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<th>Database</th>
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<tr>
<td>CENTRAL</td>
<td>Monthly</td>
</tr>
<tr>
<td>MEDLINE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>EMBASE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>PsycINFO (Ovid)</td>
<td>Monthly</td>
</tr>
<tr>
<td>CINAHL (EBSCO)</td>
<td>Monthly</td>
</tr>
<tr>
<td>AMED (EBSCO)</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

### Handsearches: core respiratory conference abstracts

<table>
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<tr>
<th>Conference</th>
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<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>American Thoracic Society (ATS)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>Asia Pacific Society of Respirology (APSR)</td>
<td>2004 onwards</td>
</tr>
<tr>
<td>British Thoracic Society Winter Meeting (BTS)</td>
<td>2000 onwards</td>
</tr>
<tr>
<td>Chest Meeting</td>
<td>2003 onwards</td>
</tr>
<tr>
<td>International Primary Care Respiratory Group Congress (IPCRG)</td>
<td>2002 onwards</td>
</tr>
<tr>
<td>Thoracic Society of Australia and New Zealand (TSANZ)</td>
<td>1999 onwards</td>
</tr>
</tbody>
</table>

### MEDLINE search strategy used to identify trials for the CAGR

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

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

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

**Appendix 2. Search strategy to identify relevant trials from the CAGR**
#1 BRONCH:MISC1  
#2 MeSH DESCRIPTOR Bronchiectasis Explode All  
#3 bronchiect*  
#4 #1 or #2 or #3  
#5 MeSH DESCRIPTOR Medication Adherence  
#6 MeSH DESCRIPTOR Patient Acceptance of Health Care Explode All  
#7 MeSH DESCRIPTOR Patient Dropouts  
#8 complian* or noncomplian* or non-complian*  
#9 adhere* or nonadhere* or non-adhere*  
#10 persist*  
#11 refusal or refuse*  
#12 concord*  
#13 co-operate*  
#14 conform*  
#15 accept*  
#16 comply*  
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16  
#18 #4 and #17

[In search line #1, MISC1 denotes the field in which the reference record has been coded for condition, in this case, bronchiectasis]
CONTRIBUTIONS OF AUTHORS
All authors contributed to the protocol design.

DECLARATIONS OF INTEREST
None known.

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Internal sources
• No sources of support supplied

External sources
• Public Health Agency HSC Research & Development Division, UK.
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