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[Intervention Protocol]

Exercise training for bronchiectasis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effects of exercise training compared to usual care on exercise tolerance, HRQoL, incidence of acute exacerbations and hospitalisation, clinical respiratory and mental health symptoms, and physical function in people with stable or an acute exacerbation of bronchiectasis.

BACKGROUND

Description of the condition

Bronchiectasis is a chronic and progressive respiratory condition characterised clinically by chronic cough, sputum production and bronchial infection, and radiologically by abnormal and permanent dilation of the bronchial lumen (Polverino 2017). Peripheral muscle dysfunction is a common feature of the disease associated with muscle weakness, reduced endurance, and high levels of fatigue and dyspnoea (Ozalp 2012; Inal-Ince 2014; De Carmargo 2018). Although the causes of dyspnoea in bronchiectasis are multifactorial, key factors include altered respiratory mechanics and insufficient gas exchange (Ozalp 2012). Expiratory airflow limitation has been identified in people with moderate-to-severe bronchiectasis, with an increase in dynamic hyperinflation and corresponding heightened levels of dyspnoea (Koulouris 2003; Ozalp 2012). Both respiratory muscle weakness (Newall 2005; Moran 2010; Liaw 2011) and reduced exercise tolerance have been reported in people with bronchiectasis compared to age-matched healthy controls (Koulouris 2003; Ozalp 2012). Children with bronchiectasis have also demonstrated reduced maximal exercise capacity (Swaminathan 2003). Reduced quadriceps strength is common (Ozalp 2012), and fatigue has been reported in 27% to 74% of people with bronchiectasis (King 2005; King 2006; Hester 2011). People with bronchiectasis have also been shown to be highly physically inactive, with lower proportions of physical activity undertaken each day compared to healthy controls (Gale 2012; Bradley 2015; De Carmargo 2018).

While the aetiology of bronchiectasis is heterogeneous and includes severe infections, immune deficiencies, autoimmune disorders and ciliary disorders (Chalmers 2015), between 50% and 70% of adults with bronchiectasis are classed as idiopathic (Kelly 2003). In children, common aetiologies are immunodeficiency, aspiration and primary ciliary dyskinesia (Li 2005). Despite the global prevalence of bronchiectasis being unclear, various reports

provide an estimate according to country. In the USA, between 139 and 1106 cases per 100,000 population have been reported from data collected between 2000 and 2013 (Seitz 2012; Weycker 2017). In the UK, the prevalence in 2013 was approximately 566 per 100,000 females and 485 per 100,000 males diagnosed with bronchiectasis (Quint 2016), with the incidence increasing with age (Quint 2016). The prevalence was slightly lower in Germany in 2013, with an estimated 67 cases per 100,000, but a higher rate is reported for people aged over 75 years (Ringshausen 2015). The prevalence of bronchiectasis in children has been reported as 1 in 5800 in north-east England (Eastham 2004), and 1 in 1700 in New Zealand (Twiss 2005). Among some indigenous populations, there is a higher prevalence. In Australia, an estimated 1470 per 100,000 indigenous children are diagnosed with bronchiectasis (Chang 2002); in New Zealand, between 4.8 and 7.9 per 100,000 in the Maori population and 17.8 and 18.3 per 100,000 among the Pacific Islander population are diagnosed with bronchiectasis (Edwards 2003). Bronchiectasis is associated with significant mortality, accounting for between 1438 and 1914 deaths per 100,000 people with bronchiectasis in the UK (Quint 2016). In Belgium, over a five-year follow-up period, there was a mortality rate of 20.4% (Goeminne 2014). With bronchiectasis characterised by recurrent acute exacerbations, the rate of hospitalisations is ever increasing, particularly among the older population (Seitz 2010; Seitz 2012; Ringshausen 2013). Acute exacerbations, peripheral and respiratory muscle dysfunction, and respiratory and psychological symptoms of anxiety and depression (O'Leary 2002; Giron Moreno 2013; Olveira 2013) all contribute to the reductions in health-related quality of life (HRQoL) observed in people with bronchiectasis (Martinez-Garcia 2005; Pifferi 2010; Chalmers 2018).

Description of the intervention

International guidelines for managing bronchiectasis have highlighted the importance of minimising inflammation and infection, optimising airway clearance and addressing structural lung disease (Pasteur 2010; Chang 2015; Polverino 2017). Several interventions are applied to achieve optimal management of bronchiectasis, including antibiotics, anti-inflammatory agents, mucolytics, airway clearance therapy and exercise training. Exercise training refers to structured programmes of activities that involve physical exertion and skeletal muscle contractions targeting improvements in physical function or exercise tolerance (or both). Exercise training may be undertaken in isolation or as part of a pulmonary rehabilitation programme. Pulmonary rehabilitation has been defined as "comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies, that include, but are not limited to, exercise training, education, and behavioural change, designed to improve the physical and psychological conditions of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" (Spruit 2013). It is well recognised that exercise training is a critical component of pulmonary rehabilitation; this may be complemented by formal education sessions focusing on self-management, behavioural modification and counselling (Spruit 2013). Regardless of the circumstances in which exercise training in people with bronchiectasis is completed, any individually tailored exercise training programme prescribed for people with bronchiectasis may consist of lower and upper limb endurance exercise (of low or high intensity) and strength training (Spruit 2013). The exercise training may be completed in a hospital, community or home-based environment (O'Neill 2002; Lee 2008; Spruit 2013; Jose 2017), may or may not be undertaken in a group setting, and prescribed for a person who is in a stable clinical state or experiencing an acute exacerbation (Greening 2014). Exercise training may additionally be undertaken under the supervision of a suitably trained healthcare professional or conducted unsupervised across any of these settings.

The majority of research in exercise training in people with chronic respiratory conditions has been undertaken in those diagnosed with chronic obstructive pulmonary disease (COPD) (Nici 2006; Spruit 2013). In this patient group, there are clinically significant improvements in respiratory symptoms, functional ability, exercise tolerance, exacerbation frequency and HRQoL (Spruit 2013). As many symptoms are common between the two conditions, it has been postulated that exercise training may offer equivalent effects in people with bronchiectasis (Rochester 2015).

How the intervention might work

The theoretical rationale for performing exercise training in people with bronchiectasis relates to the respiratory and peripheral skeletal muscle manifestations of bronchiectasis. Exercise training targets improvements in physical function or exercise tolerance (or both). This is commonly associated with improvements in respiratory symptoms. Endurance and strength exercise training has been associated with improvement in peripheral muscle strength and aerobic capacity; reduced symptoms of dyspnoea and fatigue; and improved HRQoL in other chronic respiratory conditions such as COPD (Spruit 2013; McCarthy 2015). It is hypothesised that a similar effect may occur in bronchiectasis, although the precise mechanisms are unclear. Despite this, clinical guidelines support the inclusion of people with respiratory conditions other than COPD into rehabilitation programmes (Spruit 2013; Alison 2017). However, it is not clear whether the magnitude of effect of exercise training in bronchiectasis is similar to that of COPD and the longevity of these effects. Exercise training has not been previously associated with modifying disease severity in chronic respiratory conditions (Spruit 2013), so this is not anticipated to be a likely mechanism of action in bronchiectasis (Mandal 2012). Exercise training may additionally benefit respiratory symptoms such as dyspnoea, chronic cough and sputum expectoration in

people with bronchiectasis due to its effects on breathing pattern and sputum clearance.

Why it is important to do this review

An international policy statement for pulmonary rehabilitation supported the inclusion of people with bronchiectasis within pulmonary rehabilitation programmes (Rochester 2015). The 2017 Australian and New Zealand Pulmonary rehabilitation guidelines also state that people with bronchiectasis can achieve improvements in exercise capacity and HRQoL following pulmonary rehabilitation compared to usual care (Alison 2017). Surveys of clinical practice have indicated that clinicians prescribe exercise training for people with bronchiectasis or refer people to pulmonary rehabilitation programmes (or both) (O'Neill 2002; Lee 2008). Although review authors previously completed a systematic review and meta-analysis in 2017 comparing the effects of pulmonary rehabilitation in bronchiectasis to usual care (Lee 2017), this was isolated to pulmonary rehabilitation and did not include broader definitions of exercise training, which may be completed in other environments. With a lack of ready access to pulmonary rehabilitation for people with chronic respiratory disease (Rochester 2015), including those diagnosed with bronchiectasis, it is important to consider a broad range of options for exercise training and its effects on clinical parameters compared to usual care, in order to guide future clinical practice.

OBJECTIVES

To determine the effects of exercise training compared to usual care on exercise tolerance, HRQoL, incidence of acute exacerbations and hospitalisation, clinical respiratory and mental health symptoms, and physical function in people with stable or an acute exacerbation of bronchiectasis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) of a parallel-group design. We will include studies reported in full text, published as an abstract only and unpublished data. Studies published in languages other than English will be eligible for inclusion, with translations sought via the Cochrane Airways network. We will record studies that are included but lacking available data as 'awaiting classification.'

Types of participants

We will include people of any age with a diagnosis of bronchiectasis according to high-resolution computed tomography (HRCT) or physician diagnosis (Pasteur 2010). Studies comprising patient groups of mixed respiratory pathology must have at least 75% with a primary diagnosis of bronchiectasis or available data on a bronchiectasis subgroup. No participants will be excluded on the basis of coexisting respiratory disease (e.g. COPD). However, people with bronchiectasis due to cystic fibrosis will not be eligible for inclusion. Participants will be eligible for inclusion irrespective of whether they are experiencing an acute exacerbation of their bronchiectasis or are in a period of disease stability.

Types of interventions

We will include studies comparing exercise training with usual care. Exercise training will be defined as any structured exercise programme that targets improvements in physical function or exercise tolerance (or both). The intervention must be applied for a minimum duration of four weeks or eight sessions and may have been undertaken as part of an inpatient, outpatient, community or home-based programme, as an individual or in a group setting. Both supervised and unsupervised exercise training interventions will be allowed. Co-interventions such as respiratory muscle training, airway clearance techniques and patient education will be permitted, as these are commonly integrated in routine clinical bronchiectasis care (Chang 2015; Polverino 2017). Such co-interventions must, however, have been provided to both the intervention and usual care groups. The effects of exercise training may endure for differing lengths of time depending upon the duration of the initial intervention. Therefore, we will distinguish between studies of 12 weeks' duration or less and more than 12 weeks' duration. In a previous large Cochrane systematic review of pulmonary rehabilitation for people with COPD (McCarthy 2015), 55/64 (86%) of included studies involved training programmes of 12 weeks' duration or less, hence use of this threshold as a marker of 'conventional' versus 'long-term' interventions appears justified. Usual care will be defined as treatment that does not include a structured physical exercise training programme. Usual care may include adjunct therapies, such as medical interventions (i.e. antibiotic prescription), regimen of airway clearance therapy, respiratory muscle training or a combination of these.

Types of outcome measures

Primary outcomes

1. Exercise tolerance: may be measured via field walking tests (e.g. 6-minute walking test (6MWT), incremental shuttle walk test (ISWT), endurance shuttle walk test (ESWT)) or cardiopulmonary exercise testing (i.e. maximal incremental

treadmill or cycle ergometer cardiopulmonary exercise test (CPET), constant-load exercise test (CLET)). The principal unit of analysis for these tests will be: distance (metres) for 6MWT and ISWT; time (minutes) for endurance or CLET; and peak oxygen uptake (VO_2peak) for maximal incremental CPET. We will report these outcomes separately. This will be assessed upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion.

2. Health-related quality of life (HRQoL): may be measured via disease-specific questionnaires (i.e. Quality of life-Bronchiectasis, St. George's Respiratory Questionnaire, Chronic Respiratory Disease Questionnaire (CRDQ), Leicester Cough Questionnaire (LCQ)) or generic health questionnaires (i.e. Short Form-36, Euro-Qol). Both total scores and symptom-specific subdomain scores will be used but reported separately. Data from both disease-specific and generic instruments will be pooled for analysis; however, disease-specific quality-of-life total scores will be considered the principal analysis of interest. This will be assessed upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion.

Secondary outcomes

1. Exacerbations/hospitalisations: measured as the incidence or rate of acute exacerbations or respiratory-related hospitalisation, with each defined according to study authors. For this outcome, data will be sourced from the longest time point available up to 12 months after intervention completion.

2. Peripheral skeletal muscle force: may include measures of muscle strength (kilograms), power (Newtons) or torque (Newton.metres). Data from muscle groups of the upper limb will be pooled together, while data from muscle groups of the lower limb will be pooled together. Upper limb muscle force will be analysed separately from lower limb muscle force. This will be assessed upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion.

3. Physical activity: will comprise objectively measured outcomes of movement (e.g. steps, time spent in light/moderate/vigorous activity) but not sedentarism. This will be assessed upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion.

4. Mental health: will comprise measures of anxiety and depression (e.g. Hospital Anxiety and Depression Scale [HADS], Beck Depression Inventory, Hamilton Anxiety/Depression Rating Scale). Anxiety data will be analysed distinct from depression data. This will be assessed upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion.

5. Clinical symptoms: will comprise symptoms such as dyspnoea, cough or fatigue, with all measures of symptoms eligible for inclusion. Symptoms measured at rest will be the principal unit of interest; however, data obtained at the end of exercising will be accepted where resting data are unavailable provided the outcome is measured in the same manner for each group within individual trials. This will be assessed upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion.

6. Mortality: measured as the incidence or rate of death, assessed at the longest time point available up to 12 months after intervention completion.

7. Adverse events: will comprise events such as falls or injury, measured upon completion of the exercise training intervention.

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org).
2. Weekly searches of MEDLINE OvidSP 1946 to date.
3. Weekly searches of Embase OvidSP 1974 to date.
4. Monthly searches of PsycINFO OvidSP 1967 to date.
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date.
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine).
7. Monthly searches of PEDro (Physiotherapy Evidence Database).
8. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will search the following trials registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search the Cochrane Airways Trials Register and additional sources from inception to present, with no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and experts in the field to identify other published or unpublished studies where possible. We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (CG, AL) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve.' We will retrieve the full-text study reports of all potentially eligible studies and two review authors (CG, AL) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. This will be undertaken using Covidence software (Covidence). We will resolve any disagreement through discussion or, if required, we will consult a third person (CO). We will identify and exclude duplicates and 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 'Characteristics of excluded studies' table (Moher 2009). Any records identified through the search that involve members of the review team will be handled by team members who were not involved with the relevant study to avoid perceived conflicts of interest.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. This will be undertaken using Covidence software. Two review authors (CG, AL) 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 location, study setting, withdrawals and date of study.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (CG, AL) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (CO). One review author (CG) will transfer data into Review Manager 5 (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CO) will spot-check study characteristics for accuracy against the study report. We will contact authors of included studies to verify data extracted from their study when required and to request details of missing data when applicable.

No study data will be extracted or analysed by review members directly involved with included studies.

Assessment of risk of bias in included studies

Two review authors (AL, CG) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (CO). 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.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. 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 where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

We will conduct analyses and report findings from people aged less than 18 years separately from people aged 18 years or older.
We will conduct analyses and report findings from studies describing interventions commencing during or within two weeks of discharge from an acute exacerbation separately from those applicable to the stable disease state. We will accept study authors' definitions of acute exacerbations or stable disease state.
We will conduct analyses and report findings from interventions of a 'conventional' (12 weeks or less) duration separate from those of a 'long-term' (greater than 12 weeks) duration.
We will report findings from outcome data collected at more than one time point (e.g. upon completion of the exercise training intervention and the longest time point available up to 12 months after intervention completion) separately to avoid issues associated with participant double-counting.
We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals (CI). We will use SMDs where outcome data are reported via different metrics but deemed clinically homogenous (e.g. data from different field walking tests or different quality-of-life instruments). They will not be used where such outcome data comprises a combination of both endpoint and change data. Where SMDs are to be used for outcome data expressed as change from baseline, we will use the standard deviation (SD) of baseline values as the unit of measurement to calculate the SMD and adjust standard errors to take correlation into account, where appropriate data are available. Results from analyses using SMDs will be transformed back to native metrics for ease of interpretation. If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).
We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.
We will describe skewed data narratively (e.g. as medians and interquartile ranges for each group).
Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (i.e. exercise training approach one versus usual care and exercise training approach two versus usual care) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.
If adjusted analyses are available (ANOVA or ANCOVA), we will use these as a preference in our meta-analyses. If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline unless a low correlation between measurements in individuals is reported. If a study reports outcomes at multiple time points, we will use the data closest to the primary time point of interest, as defined in the Types of outcome measures section.
We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

For continuous outcomes, we will use endpoint, rather than change, data as the principal unit of analysis. Change data will only be included in pooled meta-analyses where endpoint data are not reported, with discussion provided regarding the potential for exaggerated weighting given to such studies.
For dichotomous outcomes, we will use the number of people experiencing an event as the unit of analysis (e.g. number of exacerbations). However, if a study reports rate ratios, we will analyse them on this basis. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity, we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

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

Data synthesis

We will meta-analyse data using a random-effects model, and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' tables

We will create separate 'Summary of findings' tables for each of our main comparisons (paediatric versus adult populations; acute versus stable disease; intervention duration 12 weeks or less versus more than 12 weeks). No tables will be generated for the level of the two subgroups (as defined in Subgroup analysis and investigation of heterogeneity). We will report upon the following primary outcomes for each table:

1. exercise tolerance;
2. disease-specific or generic HRQoL (total scores only).

We will use the five GRADE considerations (risk of bias, 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 for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. exercise training interventions characterised as being unicomponent (e.g. exercise training alone) versus those characterised as multicomponent (e.g. exercise training plus at least one adjunct therapy).

We will use the following outcomes in subgroup analyses:

1. exercise tolerance;
2. disease-specific or generic HRQoL (total scores only).

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014), with corresponding P values less than 0.05 denoting statistical significance.

Sensitivity analysis

We plan to carry out the following sensitivity analysis, removing the following from the primary outcome analyses:

1. studies identified as being of high risk of bias for domains other than performance bias, considering blinding of participants and personnel to knowledge of group allocation is inherently challenging in studies of exercise interventions.

We will compare results from the principal random-effects model with those of a fixed-effect model.

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REFERENCES

Additional references

Alison 2017
Alison JA, McKeough Z, Johnston K, McNamara R, Spencer L, Jenkins S, et al. Australian and New Zealand pulmonary rehabilitation guidelines. *Respirology* 2017;**22**: 800–19.

Bradley 2015
Bradley J, Wilson J, Hayes K, Kent L, McDonough S, Tully M, et al. Sedentary behaviour and physical activity in bronchiectasis: a cross-sectional study. *BMC Pulmonary Medicine* 2015;**15**:61.

Chalmers 2015
Chalmers J, Elborn JS. Reclaiming the name 'bronchiectasis'. *Thorax* 2015;**70**(5):399–400.

Chalmers 2018
Chalmers JD, Aliberti S, Filonenko A, Shteinberg M, Goeminne PC, Hill AT, et al. Characterisation of the 'frequent exacerbator phenotype' in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2018;**197**(11):1410–20. DOI: 10.1164/rccm.201711-2202OC

Chang 2002
Chang AB, Grimwood K, Mulholland EK, Torzillo PJ, for the working group on indigenous Paediatric Respiratory Health. Bronchiectasis in indigenous children in remote Australian communities. *Medical Journal of Australia* 2002; **177**(4):200–4.

Chang 2015
Chang AB, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Medical Journal of Australia* 2015;**202**(1):21–3.

Covidence [Computer program]
Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation.

De Carmargo 2018
De Carmargo A, Boldorini J, Holland A, de Castro R, Lanza F, Athanazio R, et al. Determinants of peripheral muscle strength and activity in daily life in people with bronchiectasis. *Physical Therapy* 2018;**98**(3):153–61. DOI: 10.1093/ptj/pzx123.

Eastham 2004
Eastham KM, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosis bronchiectasis in childhood. *Thorax* 2004;**59**(4):324–7.

Edwards 2003
Edwards EA, Metcalf R, Milne DG, Thompson J, Byrnes CA. Retrospective review of children presenting with non cystic fibrosis bronchiectasis: HRCT features and clinical relationships. *Pediatric Pulmonology* 2003;**36**:87–93.

Gale 2012
Gale N, Bolton C, Duckers J, Enright S, Cockcroft J, Shale D. Systemic comorbidities in bronchiectasis. *Chronic Respiratory Disease* 2012;**9**(4):231–8.

Giron Moreno 2013
Giron Moreno RM, Fernandes Vasconcelos G, Cisneros C, Gomez-Punter RM, Segrelles Calvo G, Ancochea J. Presence of anxiety and depression in patients with bronchiectasis unrelated to cystic fibrosis. *Archivos de Bronconeumologia* 2013;**49**(10):415–20.

Goeminne 2014
Goeminne PC, Nawrot TS, Ruttens D, Seys S, Dupont LJ. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respiratory Medicine* 2014;**108**(2):287–96.

GRADEpro GDT [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed prior to 29 March 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Greening 2014
Greening N, Williams J, Hussein S, Harvey-Dunstan T, Bankart M, Chaplin E, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: a randomised controlled trial. *BMJ* 2014;**349**:g4315.

Hester 2011
Hester K, Macfarlane J, Tedd H, Jary H, McAlinden P, Rostron L, et al. Fatigue in bronchiectasis. *QJM : Monthly Journal of the Association of Physicians* 2011;**105**(3):235–40.

Higgins 2011
Higgins J, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Inal-Ince 2014
Inal-Ince D, Sabasi S, Saglam M, Calik Kutukcu E, Vardar Yagli N, Arikan H, et al. Effects of endurance on strength, fatigue and quality of life in bronchiectasis. *European Respiratory Journal* 2014;**44**:P4278.

Jose 2017
Jose A, Holland A, de Oliveira C, Selman J, de Castro R, Athanazio R, et al. Does home-based pulmonary rehabilitation improve functional capacity, peripheral muscle strength and quality of life in patients with bronchiectasis compared to standard care?. *Brazilian Journal of Physical Therapy* 2017;**21**(6):473–80.

Kelly 2003
Kelly MG, Murphy S, Elborn JS. Bronchiectasis in secondary care: a comprehensive profile of a neglected disease. *European Journal of Internal Medicine* 2003;**14**: 488–92.

King 2005
King P, Holdsworth S, Freezer N, Villanueva E, Gallagher M, Holmes P. Outcome in adult bronchiectasis. *Chronic Obstructive Pulmonary Disease* 2005;**2**(1):27–34.

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

Koulouris 2003
Koulouris N, Retsou S, Kosmas E, Dimakou K, Malagari K, Mantzikopoulos G, et al. Tidal expiratory flow limitation, dyspnoea and exercise capacity in patients with bilateral bronchiectasis. *European Respiratory Journal* 2003;**21**(5): 743–8.

Lee 2008
Lee AL, Button BM, Denehy L. Current Australian and New Zealand physiotherapy practice in the management of patients with bronchiectasis and COPD. *New Zealand Journal of Physiotherapy* 2008;**36**(2):49–58.

Lee 2017
Lee AL, Hill CJ, McDonald CF, Holland AE. Pulmonary rehabilitation in non-cystic fibrosis bronchiectasis: a systematic review. *Archives of Physical Medicine and Rehabilitation* 2017;**98**(4):774–82.

Li 2005
Li AM, Sonnappa S, Lex C, Wong E, Zacharasiewicz A, Bush A, et al. Non-CF bronchiectasis: does knowing the aetiology lead to changes in management?. *European Respiratory Journal* 2005;**26**(1):8.

Liaw 2011
Liaw MY, Tsai YC, Huang KT, Chang PW, Chen YC, Lin MC. Inspiratory muscle training in bronchiectasis patients: a prospective randomised controlled study. *Clinical Rehabilitation* 2011;**25**(6):524–36.

Mandal 2012
Mandal M, Sidhu MK, Kope L, Pollock W, Stevenson LM, Pentland JL, et al. A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. *Respiratory Medicine* 2012;**106**:1647–54.

Martinez-Garcia 2005
Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ. Quality-of-life determinants in patients with clinically stable bronchiectasis. *Chest* 2005;**128**: 739–45.

McCarthy 2015
McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 2. DOI: 10.1002/14651858.CD003793.pub3; CD003793

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7): e1000097. DOI: 10.1371/journal.pmed.1000097

Moran 2010
Moran F, Piper A, Elborn JS, Bradley J. Respiratory muscle pressures in non-CF bronchiectasis: repeatability and reliability. *Chronic Respiratory Disease* 2010;**7**:165–71.

Newall 2005
Newall C, Stockley RA, Hill SL. Exercise training and inspiratory muscle training in patients with bronchiectasis. *Thorax* 2005;**60**(11):943–8.

Nici 2006
Nici L, Donner C, Wouters E, ZuWallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**(12):1390–413.

O'Leary 2002
O'Leary CJ, Wilson CB, Hansell DM, Cole PJ, Wilson R, Jones PW. Relationship between psychological well-being and lung health status in patients with bronchiectasis. *Respiratory Medicine* 2002;**96**(9):686–92.

O'Neill 2002
O'Neill B, McArdle N, MacMahon J. The current physiotherapy management of patients with bronchiectasis: a UK survey. *International Journal of Clinical Practice* 2002; **56**(1):34–5.

Olveira 2013
Olveira C, Gaspar I, Dorado A, Cruz I, Sorignuer F, Quittner AL, et al. Depression and anxiety symptoms in bronchiectasis: association with health-related quality of life. *Quality of Life Research* 2013;**22**:597–605.

Ozalp 2012
Ozalp O, Inal-Ince D, Calik E, Vardar-Yagli N, Saglam M, Savci S, et al. Extrapulmonary features of bronchiectasis: muscle function, exercise capacity, fatigue, and health status. *Multidisciplinary Respiratory Medicine* 2012;**7**:3. DOI: 10.1186/2049-6958-7-3.

Pasteur 2010
Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; **65**(Suppl 1):1–58.

Pifferi 2010
Pifferi M, Bush A, Di Cicco M, Pradal U, Ragazzo V, Macchia P, et al. Health-related quality of life and unmet needs in patients with primary ciliary dyskinesia. *European Respiratory Journal* 2010;**35**(4):787–94.

Polverino 2017
Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Leobinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *European Respiratory Journal* 2017;**50**(3): 1–23.

Quint 2016
Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *European Respiratory Journal* 2016;**47**(1):186–93.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ringshausen 2013
Ringshausen FC, de Roux A, Pletz MW, Hamalainen N, Welte T, Rademacher J. Bronchiectasis-associated hospitalisations in Germany, 2005-2011: a population-based study of disease burden and trends. *PloS One* 2013;**8** (8):e71109. DOI: 10.1371/journal.pone.0071109

Ringshausen 2015
Ringshausen FC, de Roux A, Diel R, Hohmann D, Welte T, Rademacher J. Bronchiectasis in Germany: a population-based estimation of disease prevalence. *European Respiratory Journal* 2015;**46**:1805–7.

Rochester 2015
Rochester C, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An official American Thoracic Society/European Respiratory Society Policy statement: enhancing implementation, use and delivery of pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2015;**192**(11):1373–86.

Seitz 2010
Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burdens of bronchiectasis-associated hospitalisations in the United States, 1993-2006. *Chest* 2010;**138**(4):944–9.

Seitz 2012
Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among Medicare beneficiaries in the United States, 2000 to 2007. *Chest* 2012;**142**(2): 432–9.

Spruit 2013
Spruit MA, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, et al. An official American Thoracic Society/ European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2013;**188**:13–64.

Swaminathan 2003
Swaminathan S, Kuppurao KV, Somu N, Vijayan VK. Reduced exercise capacity in non-cystic fibrosis bronchiectasis. *Indian Journal of Pediatrics* 2003;**70**(7): 553–6.

Twiss 2005
Twiss J, Metcalfe R, Edwards E, Byrnes C. New Zealand national incidence of bronchiectasis "too high" for a developed country. *Archives of disease in childhood* 2005;**90** (7):737–40.

Weycker 2017
Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of non-cystic fibrosis bronchiectasis among US adults in 2013. *Chronic Respiratory Disease* 2017;**14**(4): 377–84.

* *Indicates the major publication for the study*

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (OvidSP)	Weekly
Embase (OvidSP)	Weekly
PsycINFO (OvidSP)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify studies for the Cochrane Airways Trials Register

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 randomised controlled trials

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 studies in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

#1 BRONCH:MISC1
#2 MeSH DESCRIPTOR Bronchiectasis Explode All
#3 bronchiect*
#4 #1 or #2 or #3
#5 MESH DESCRIPTOR Rehabilitation EXPLODE ALL
#6 MESH DESCRIPTOR Respiratory Therapy EXPLODE ALL
#7 MESH DESCRIPTOR Exercise EXPLODE ALL
#8 MeSH DESCRIPTOR Physical Therapy Modalities Explode All
#9 rehabilitat* or fitness* or exercis* or train* or physiotherap* or (physical* NEXT therap*)
#10 {OR #5-#9}
#11 #10 AND #4

CONTRIBUTIONS OF AUTHORS

AL: protocol drafting and critical review, and will be involved in all aspects of review production.

CG: protocol drafting and critical review, and will be involved in all aspects of review production.

CO: protocol conception, drafting and critical review, and will be involved in all aspects of review production.

DECLARATIONS OF INTEREST

AL: no real or perceived conflicts of interest to declare; however, is an author on research that is likely to be included within this review.

CG: no real or perceived conflicts of interest to declare.

CO: Editor with Cochrane Airways. CO is a current recipient of a Lung Foundation Australia/Boehringer-Ingelheim COPD Research Fellowship, unrelated to this review. CO has no real or perceived conflicts of interest to declare related to this work.

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