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Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis (Review)

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[Intervention Review]

Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Annemarie L Lee[1,2], Angela T Burge[1], Anne E Holland[1,2,3]

[1]Discipline of Physiotherapy, Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne, Australia. [2]Institute for Breathing and Sleep, Austin Health, Melbourne, Australia. [3]Department of Physiotherapy, The Alfred Hospital, Melbourne, Australia

Contact address: Annemarie L Lee, Discipline of Physiotherapy, Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Plenty Road and Kingsbury Drive, Melbourne, Victoria, Australia. A.Lee3@latrobe.edu.au, annemarielee257@gmail.com.

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ABSTRACT

Background

People with bronchiectasis experience chronic cough and sputum production and require the prescription of airway clearance techniques (ACTs). A common type of ACT prescribed is positive expiratory pressure (PEP) therapy. A previous review has suggested that ACTs including PEP therapy are beneficial compared to no treatment in people with bronchiectasis. However, the efficacy of PEP therapy in a stable clinical state or during an acute exacerbation compared to other ACTs in bronchiectasis is unknown.

Objectives

The primary aim of this review was to determine the effects of PEP therapy compared with other ACTs on health-related quality of life (HRQOL), rate of acute exacerbations, and incidence of hospitalisation in individuals with stable or an acute exacerbation of bronchiectasis.

Secondary aims included determining the effects of PEP therapy upon physiological outcomes and clinical signs and symptoms compared with other ACTs in individuals with stable or an acute exacerbation of bronchiectasis.

Search methods

We searched the Cochrane Airways Group Specialised Register of Trials, PEDro and clinical trials registries from inception to February 2017 and we handsearched relevant journals.

Selection criteria

Randomised controlled parallel and cross-over trials that compared PEP therapy versus other ACTs in participants with bronchiectasis.

Data collection and analysis

We used standard methodological procedures as outlined by Cochrane.

Main results

Nine studies involving 213 participants met the inclusion criteria, of which seven were cross-over in design. All studies included adults with bronchiectasis, with eight including participants in a stable clinical state and one including participants experiencing an acute exacerbation. Eight studies used oscillatory PEP therapy, using either a Flutter or Acapella device and one study used Minimal PEP therapy. The comparison intervention differed between studies. The methodological quality of studies was poor, with cross-over studies including suboptimal or no washout period, and a lack of blinding of participants, therapists or personnel for outcome measure assessment in most studies. Clinical heterogeneity between studies limited meta-analysis.

Daily use of oscillatory PEP therapy for four weeks was associated with improved general health according to the Short-Form 36 questionnaire compared to the active cycle of breathing technique (ACBT). When applied for three sessions over one week, minimal PEP therapy resulted in similar improvement in cough-related quality of life as autogenic drainage (AD) and L'expiration Lente Totale Glotte Ouverte en Decubitus Lateral (ELTGOL). Oscillatory PEP therapy twice daily for four weeks had similar effects on disease-specific HRQOL (MD -0.09, 95% CI -0.37 to 0.19; low-quality evidence). Data were not available to determine the incidence of hospitalisation or rate of exacerbation in clinically stable participants.

Two studies of a single session comparison of oscillatory PEP therapy and gravity-assisted drainage (GAD) with ACBT had contrasting findings. One study found a similar sputum weight produced with both techniques (SMD 0.54g (-0.38 to 1.46; 20 participants); the other found greater sputum expectoration with GAD and ACBT (SMD 5.6 g (95% CI 2.91 to 8.29: 36 participants). There was no difference in sputum weight yielded between oscillatory PEP therapy and ACBT with GAD when applied daily for four weeks or during an acute exacerbation. Although a single session of oscillatory PEP therapy was associated with less sputum compared to AD (median difference 3.1 g (95% CI 1.5 to 4.8 g; one study, 31 participants), no difference between oscillatory PEP therapy and seated ACBT was evident. PEP therapy had a similar effect on dynamic and static measures of lung volumes and gas exchange as all other ACTs. A single session of oscillatory PEP therapy (Flutter) generated a similar level of fatigue as ACBT with GAD, but greater fatigue was noted with oscillatory PEP therapy compared to ACBT alone. The degree of breathlessness experienced with PEP therapy did not differ from other techniques. Among studies exploring adverse events, only one study reported nausea with use of oscillatory PEP therapy.

Authors' conclusions

PEP therapy appears to have similar effects on HRQOL, symptoms of breathlessness, sputum expectoration, and lung volumes compared to other ACTs when prescribed within a stable clinical state or during an acute exacerbation. The number of studies and the overall quality of the evidence were both low. In view of the chronic nature of bronchiectasis, additional information is needed to establish the long-term clinical effects of PEP therapy over other ACTs for outcomes that are important to people with bronchiectasis and on clinical parameters which impact on disease progression and patient morbidity in individuals with stable bronchiectasis. In addition, the role of PEP therapy during an acute exacerbation requires further exploration. This information is necessary to provide further guidance for prescription of PEP therapy for people with bronchiectasis.

PLAIN LANGUAGE SUMMARY

PEP therapy in bronchiectasis

Review question: We reviewed the evidence to identify the effects of positive expiratory pressure (PEP) therapy compared to other airway clearance techniques (ACTs) in people with bronchiectasis.

Background: People with bronchiectasis have a chronic cough and frequently produce mucus. ACTs assist in the removal of mucus in people with bronchiectasis, with PEP therapy a technique which is commonly prescribed. A previous review suggested that ACTs may be beneficial compared to no treatment, although the strength of this evidence was low. We wanted to discover what the effects were of PEP therapy compared to other ACTs when used by people with bronchiectasis, and whether it provided advantages over other ACTs.

Study characteristics: Nine studies were included, with a total of 213 people. The average age of participants ranged from 45 to 74 years. Treatment duration ranged from a single session to up to four weeks of treatment. Eight studies examined people who were stable and one study examined people who were experiencing an exacerbation (flare-up) of bronchiectasis. PEP therapy was compared to a range of ACTs.

Key results: Two small studies indicated that PEP therapy is as effective as other ACTs at improving quality of life. The duration of hospitalisation when using PEP therapy or other ACTs during a flare-up was similar. Both PEP therapy and other techniques appear to

have a similar effect on the clearance of mucus from the lungs and on lung function. Similiar levels of breathlessness were experienced with PEP therapy and other ACTs. Other outcomes of interest were the rate of hospitalisation but these have not yet been reported. On the basis of this information, the prescription of PEP therapy for people with bronchiectasis is as suitable as any other type of ACT, with no greater advantage of PEP therapy.

Quality of the evidence: Because of inadequate reporting of methods and small number of participants, the quality of evidence was low.

This Cochrane plain language summary is current to May 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Positive expiratory pressure (PEP) therapy compared with other airway clearance techniques for bronchiectasis

Patient or population: people with bronchiectasis
Settings: hospital inpatient and outpatient department, home-based therapy
Intervention: positive expiratory pressure (PEP) therapy
Comparison: other airway clearance techniques (ACTs)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other airway clearance techniques (ACTs)	Positive expiratory pressure (PEP) therapy				
Cough-related quality of life (QOL) assessed with: Leicester cough questionnaire total score. Higher score indicates better QOL. 19 questions on 7-point Likert scale Scale from: 3 to 21 follow-up: mean 1 week	The median change in cough-related quality of life (QOL) was 0.5 points (95% CI 0.1 to 0.5)	The median change in cough-related quality of life (QOL) in the intervention group was 0.1 points lower	-	31 participants (one study)	⊕⊕◯◯ **low**[1,2]	Randomised cross-over trial of minimal PEP therapy vs Autogenic drainage. Duration of intervention of 1 week per ACT
Cough-related quality of life (QOL) assessed with: Leicester cough questionnaire total score. Higher score indicates better QOL. 19 questions on 7-point Likert scale Scale from: 3 to 21 follow-up: mean 1 week	The median change in cough-related quality of life (QOL) was 0.9 points (95% CI 0.5 to 2.1)	The median change in cough-related quality of life (QOL) in the intervention group was 0.4 points lower	-	31 participants (one study)	⊕⊕◯◯ **low**[1,2]	Randomised cross-over trial of minimal PEP therapy vs ELTGOL. Duration of intervention of 1 week per ACT

Health-related quality of life (HRQOL) disease-specific HRQOL assessed with: Chronic respiratory disease questionnaire total score Scale from: 0 to 28 follow-up: mean 4 weeks	not provided	not provided	The mean difference (95% CI) between groups was -0.09 points per item (-0.37 to 0.19) in favour of oscillatory PEP therapy	17 participants (one study)	⊕⊕◯◯ **low**[1,3]	Randomised cross-over trial of ACBT vs Oscillatory PEP therapy (Flutter). Duration of intervention of 4 weeks per ACT
Incidence of acute exacerbations of bronchiectasis - not reported	see comment	see comment	not estimable			No studies examined this outcome
Duration of acute exacerbation of bronchiectasis - not reported	see comment	see comment	not estimable			No studies examined this outcome
Incidence of hospitalisation - not reported	not provided	not provided	not estimable			No studies examined this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Small participant numbers
[2]Insufficient power for quality of life comparison
[3]Method of randomisation and allocation concealment unclear, lack of blinding of participants and personnel, no washout period applied

BACKGROUND

Description of the condition

Bronchiectasis is a chronic respiratory condition that is defined by a clinical profile of chronic cough with sputum (mucus) production, dyspnoea (uncomfortable breathlessness) and fatigue (Barker 2002; McShane 2013). Several aetiologies of bronchiectasis are known; it may develop secondary to a severe respiratory infection or in association with other conditions, including alpha-1 antitrypsin deficiency, which are characterised by inflammation or impaired mucociliary clearance (mucus transport system), or the cause may be idiopathic (unknown) (Pasteur 2000; Goeminne 2012; Cortese 2016). Bronchiectasis unrelated to cystic fibrosis (CF) has been previously referred to as non-CF bronchiectasis, but a recent consensus agreed that this term undermines the severity, morbidity, and prognosis associated with bronchiectasis not originating from CF (Aliberti 2016); therefore bronchiectasis is now the accepted term to describe this condition. Bronchiectasis originates from a recurring cycle of infection and inflammation, with infection causing chronic inflammation leading to tissue damage and impaired mucociliary clearance (Cole 1986). These pathophysiological (disease) processes increase the risk of further infection, with a cycle of progressive inflammation resulting in structural changes to the airways (Cole 1986; Gaga 1998). The pathophysiology is characterised by a history of recurrent acute exacerbations (flare-ups) (King 2006), which often require hospitalisation. This condition may affect both children and adults (Karadag 2005; Chang 2008; Chang 2010; Pasteur 2010).

The global prevalence is not accurately known but estimates from earlier studies have ranged from 0.5 cases per 100,000 in Finland (Säynäjäkangas 1997) to 1106 cases per 100,000 population over an eight-year period in the United States of America (USA) (Seitz 2012). More recently, higher prevalence rates were reported in the UK in 2013, with 566.1 per 100,000 in females and 485.5 per 100,000 in males (Quint 2016), while the prevalence was 3.6 cases per 1000 in 2012 in Catalonia (Monteagudo 2016). In New Zealand, the reported prevalence is 3.7 per 100,000 population, but this varies according to ethnicity (Twiss 2005), and in Australia, the prevalence amongst indigenous children is 1470 per 100,000 (Chang 2002). With increased use of high-resolution computed tomography (HRCT), bronchiectasis is more frequently identified (Weycker 2005; Kwak 2010), and hospitalisation rates associated with bronchiectasis are on the rise, particularly in older individuals (Seitz 2010; Seitz 2012; Ringshausen 2013). The frequency of these respiratory infections is linked to rising morbidity and mortality (Weycker 2005; Martinez-Garcia 2007; Roberts 2010; Goeminne 2012; Chalmers 2014; Goeminne 2014) and is a key predictor of reduced health-related quality of life (HRQOL) in those with bronchiectasis (Martinez-Garcia 2005).

Description of the intervention

Current international guidelines for the management of bronchiectasis focus on minimising further damage to the airways by reducing inflammation and infection and optimising airway clearance (Chang 2008; Chang 2010; Pasteur 2010; Chang 2015). To achieve this, recommended approaches incorporate the prescription of antibiotics, anti-inflammatory therapy and mucolytics (mucus loosening agents), together with airway clearance techniques to facilitate sputum clearance (Chang 2008; Chang 2010; Pasteur 2010; Chang 2015). A regular programme of airway clearance therapy has been associated with reduced symptoms of coughing and improved HRQOL (Mutalithas 2008). A recent updated review found that compared with no treatment, performing airway clearance techniques (ACTs) was associated with improvement in sputum expectoration (production), lung function and HRQOL (Lee 2013). When undertaken by individuals with stable bronchiectasis, oscillatory PEP therapy (with repetitive vibrations) was associated with greater sputum expectoration and improved disease-specific HRQOL and cough-related QOL compared to no treatment (Lee 2015). Less pulmonary hyperinflation (overinflated) was evident with selected ACTs, including oscillatory PEP therapy (Lee 2013). However, when compared to other ACTs, oscillatory PEP therapy in people with stable bronchiectasis led to equivalent changes in sputum volume, dynamic lung volumes and degree of breathlessness (Lee 2015). Multiple types of ACTs may be applied in individuals with bronchiectasis. Selected techniques have included forms of breathing exercises, forced expirations or controlled coughing, gravity-assisted drainage (GAD) and manual techniques, which often are used in combination and may or may not require the assistance of the therapist for maximal efficacy. Other ACT options for promoting sputum clearance include the application of positive expiratory pressure (PEP) therapy through the use of hand-held devices, which generally do not require the hands-on assistance of a therapist and therefore may facilitate independent treatment.

How the intervention might work

The theoretical rationale behind the physiological effects of PEP therapy is that in the presence of small airway obstruction caused by secretion retention, the reduced diameter of the airway lumen (internal space) increases expiratory (exhalation) resistance and encourages airway collapse, which may lead to reduced expiratory flow, insufficient expiration and dynamic hyperinflation (Olsen 2015). PEP therapy has been hypothesised to promote airflow through collateral channels during inspiration to improve ventilation distribution, which allows accumulation of an increased volume of air behind secretions. The pressure gradient across the sputum plug is believed to force secretions centrally towards the larger airways, where expectoration may occur (Falk 1984; Van der Schans 1991). During expiration, the positive pressure gen-

erated is thought to encourage airway splinting to stabilise peripheral airways and prevent premature airway collapse during expiration (Oberwaldner 1986; Darbee 2004). Despite these theoretical principles, a study of PEP therapy in participants with chronic obstructive pulmonary disease did not show differences in ventilation distribution (Osadnik 2014), which suggests that the precise mechanism behind PEP therapy is not understood. PEP therapy is applied by inspiring and expiring through a facemask or mouthpiece for a series of breaths via a one-way valve, followed by forced expiratory manoeuvres (huffing) or a slow expiratory manoeuvre in order to expectorate secretions. PEP therapy may apply low pressure (10 to 25 cmH_2O) (Falk 1984; Groth 1985) or high pressure (Hi-PEP) at 40 to 120 cmH_2O (Oberwaldner 1986). In contrast to low-pressure PEP therapy, during Hi-PEP, forced expiratory manoeuvres are also performed through the facemask to prevent dynamic airway collapse during expiration and to facilitate more peripheral secretion clearance (Oberwaldner 1986; Oberwaldner 1991). Forced expiration against a resistive load is thought to direct air from hyperinflated lung units to unobstructed and atelectatic (collapsed) lung units to encourage a homogenised slow expiratory flow.

In comparison, oscillatory PEP therapy offers the combination of PEP and high-frequency oscillations within the airways during exhalation to facilitate secretion clearance. The PEP component is thought to encourage airflow behind secretions, and the oscillation induces vibrations within the airway wall to displace secretions into the airway lumen; repeated accelerations of expiratory airflow favour movement of secretions from the peripheral to the central airways (App 1998; Tambascio 2011). Sputum rheology (mucus flow) may also be altered, with oscillations reducing the viscoelasticity (thickness) of the secretions (Altaus 2009). Several oral devices such as a Flutter valve or Acapella may be used to provide oscillatory PEP therapy.

Comparisons of PEP therapy versus oscillatory PEP therapy have been undertaken in both children and adults with cystic fibrosis (Van Winden 1998; McIlwaine 2001; Newbold 2008). Although oscillatory PEP therapy was associated with a greater decline in lung function and an increased rate of hospitalisation compared with PEP therapy over the longer term in children (McIlwaine 2001), other studies have reported no difference in effects on lung function between the two types of therapy (Van Winden 1998; Newbold 2008). In individuals with bronchiectasis, oscillatory PEP therapy was associated with a greater increase in secretion transport compared with PEP therapy (Tambascio 2011). This mix of results suggests that the various modes of PEP therapy may have differing clinical and physiological effects. For this reason, it may be important to evaluate the distinct effects of each type of PEP therapy.

Why it is important to do this review

Surveys of clinical practice have illustrated considerable variation in the prescription of ACTs, including use of PEP therapy for both adults and children with bronchiectasis, both in a stable clinical state and during an acute exacerbation (O'Neill 2002; Butler 2008; Lee 2008; Johnstone 2013). Selection of ACTs in this population may be influenced by underlying airway pathophysiology, participant compliance and perception of efficacy, as well as by participant resources (Lapin 2002). Of the five studies included in the previous review (Lee 2013), although four applied oscillatory PEP therapy, only a small number of participants (ranging from eight to 20) were included, and the effects were compared with a control condition only. Although the independence of PEP therapy options compared with other treatment options may appeal to both patients and clinicians, the effects of each mode of PEP therapy must be clarified in terms of both physiological and clinical impact when compared with other types of ACTs in individuals with bronchiectasis, to further guide clinical practice.

OBJECTIVES

The primary aim of this review was to determine the effects of any type of PEP therapy compared with other ACTs on HRQOL, rate of acute exacerbations, and incidence of hospitalisation in individuals with stable or an acute exacerbation of bronchiectasis.

Secondary aims included determining the effects of PEP therapy upon physiological outcomes and clinical signs and symptoms compared with other ACTs in individuals with stable or an acute exacerbation of bronchiectasis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of both parallel and cross-over design, in which a prescribed mode of PEP therapy was compared with other ACTs in individuals with stable or an acute exacerbation of bronchiectasis.

Types of participants

We included studies of both adults and children with a diagnosis of bronchiectasis of any origin, with the exception of CF. The diagnosis of bronchiectasis was based on a physician diagnosis or on HRCT with any degree of disease severity. We included studies of participants in a stable clinical state and experiencing an acute exacerbation. We classified participants as experiencing an acute

exacerbation if they met the investigators' definition, or if they had worsening symptoms (increased sputum production, clinical signs of infection or dyspnoea) requiring medical treatment, including antibiotic therapy, and required or didn't require hospitalisation. We classified participants as stable if they met the investigators' definition, or if no change were made to medical therapy and stable symptoms persisted over the previous four weeks. We analysed separately studies of participants diagnosed with an acute exacerbation of bronchiectasis and studies of participants in a stable clinical state, as the prescription for treatment and physiological and clinical effects may differ.

We excluded participants diagnosed (on the basis of physician reporting) with concurrent asthma, chronic obstructive pulmonary disease or interstitial lung disease, and those breathing through an artificial airway. Studies of children included participants up to the age of 18 years, and studies of adults included participants older than 18 years. We included studies that incorporated a mix of diagnostic groups only if data on any of the review outcomes could be obtained separately for participants with bronchiectasis.

Types of interventions

We included trials comparing PEP therapy with other ACTs (which may include a combination of techniques), with PEP therapy applied as a single technique or in conjunction with other recognised ACTs (e.g. oscillatory PEP therapy with active cycle of breathing technique vs active cycle of breathing technique alone). Types of PEP therapy included any of the following options, which were applied for the primary purpose of sputum removal.

- PEP therapy, with pressures ranging from 10 to 25 cmH_2O (Falk 1984; Groth 1985), delivered via mask or mouthpiece (including Bottle PEP) (Campbell 1986).
- Hi-PEP therapy, with pressures ranging from 40 to 120 cmH_2O (Oberwaldner 1986), delivered via mask.
- Oscillatory PEP therapy, delivered by a device (e.g. Flutter, Acapella, RC-Cornet, Quaker or Lung Flute) (App 1998; Altaus 2009; Shabari 2011).
- Minimal PEP therapy with pressure less than 5 cmH_2O, delivered via mask or mouthpiece (Venturelli 2012).

We excluded any type of PEP therapy delivered in conjunction with aerosol inhalation.

Comparative ACTs could include any of the following techniques, which could be applied in combination.

- Gravity-assisted drainage (GAD), which uses specific positioning of bronchopulmonary segments to facilitate sputum clearance (Prasad 1993). GAD and manual techniques are often combined as an ACT. Manual techniques, including any combination of percussion, vibration, rib springing, or rib shaking, apply external forces to the chest wall to encourage mobilisation of mucus (Gallon 1992; McCarren 2006).
- Slow expiration with the glottis open in lateral posture (ELTGOL), which uses GAD with slow expirations performed in a lateral decubitus position (Martins 2012).
- Active cycle of breathing technique (ACBT), which utilises a combination of thoracic expansion exercises, breathing control (BC) and the forced expiration technique (FET) to maximise collateral channel ventilation and sputum movement (Pryor 1979), and which may be applied with or without GAD and manual techniques.
- Autogenic drainage (AD), which incorporates breathing of variable volume to generate high expiratory flows while minimising airway collapse (Schoni 1989).
- Exercise performed for the purpose of sputum clearance, which could include endurance or strength training (Dwyer 2011).
- High-frequency chest wall oscillation, which applies external chest wall oscillations at variable frequencies and intensities through an inflatable vest attached to a machine (Warwick 1991).

We included treatments applied over a single session or on a medium-term (one to seven days) or longer-term basis (longer than seven days).

Types of outcome measures

Primary outcomes

- HRQOL, measured by disease-specific, generic, or symptom-specific questionnaires, which may or may not have been validated in this population.
- Rate of, duration of, or time to acute exacerbation of bronchiectasis, defined according to symptoms, physician diagnosis, or participant diaries.
- Incidence of hospitalisation for bronchiectasis.
    - For stable bronchiectasis, this included time to hospitalisation, number of hospital admissions, or number of hospital days.
    - For acute exacerbation of bronchiectasis, this included length of hospital stay, time to re-admission, number of hospital admissions, or number of hospital days.

These could be measured over the short, medium, or longer term according to the time frames previously defined.

Secondary outcomes

Secondary outcomes, including physiological outcomes consisted of the following:

- Sputum volume (wet and dry weight (g) or volume (mL)). Sputum weight was measured in the short term (within 24 hours of treatment), in the medium term (within one to seven days of treatment) and over the long term (more than seven days of treatment), with successful treatment indicated by an increase in sputum volume.

- Measures of mucociliary clearance (e.g. radioaerosol clearance).
- Lung function (e.g. spirometry - forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow (FEF), forced expiratory flow at 25% to 75% of pulmonary volume ($FEF_{25–75}$), peak expiratory flow rate (PEFR); lung volumes - total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), inspiratory capacity (IC), TLC/RV ratio.
- Participant symptoms reported on any scale (dyspnoea or breathlessness, fatigue, discomfort), which may or may not have been validated in this population.
- Adverse events (pneumothorax, barotrauma, haemoptysis, bronchospasm, nausea).

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the information specialist for the Group. The Register contains trial reports 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 Ovid SP 1946 to date;
3. Weekly searches of Embase Ovid SP 1974 to date;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. 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 also searched the Physiotherapy Evidence Database (PEDro) using similar terms (Appendix 3).

We conducted a search of the clinical trials registries ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to February 2017, and we imposed no restriction on language of publication.

Searching other resources

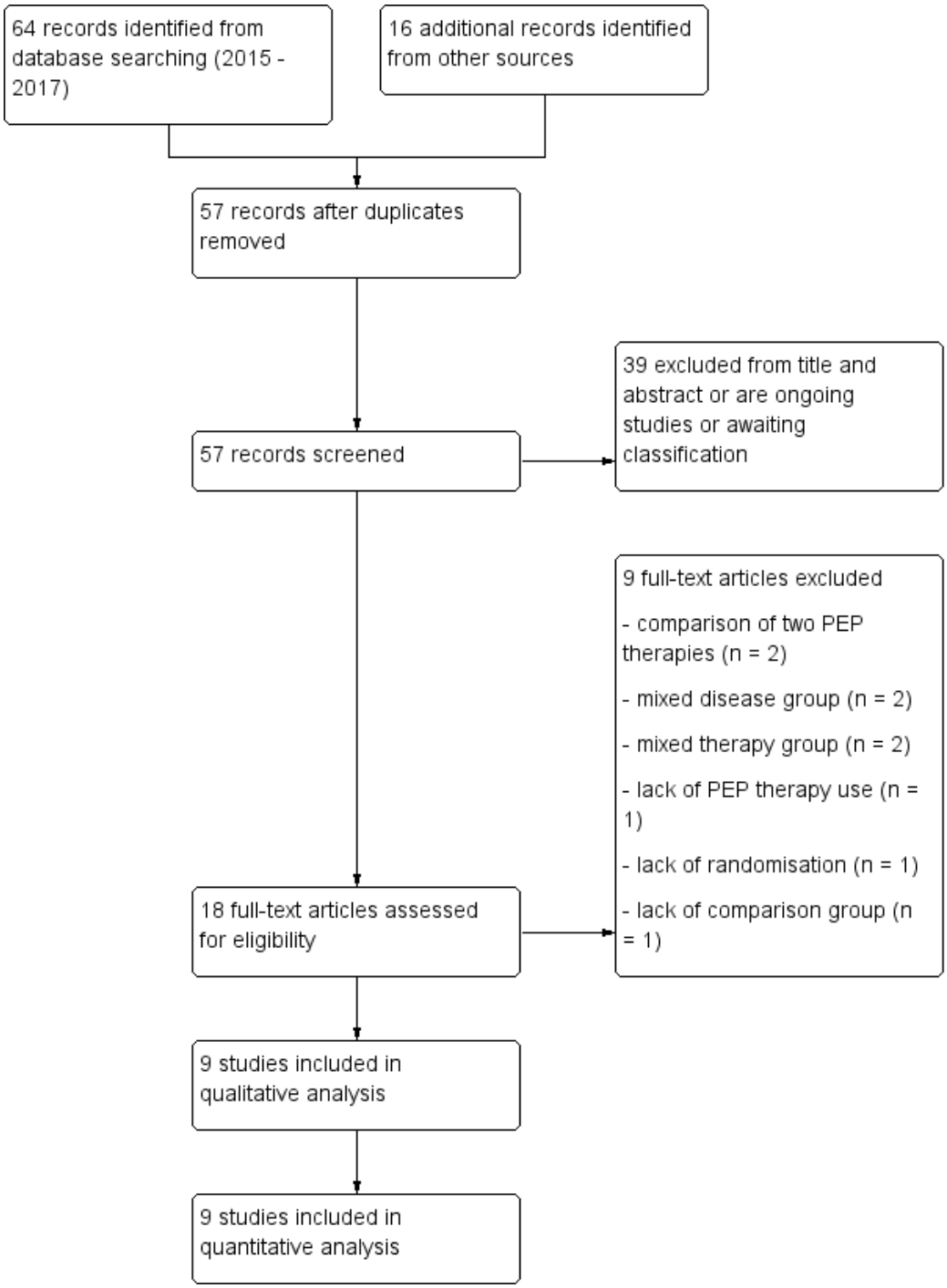
We checked reference lists of all primary studies and review articles for additional references. We searched the websites of manufacturers of relevant PEP devices (e.g. Flutter®, Acapella®, RC-Cornet®, Quaker®, Lung Flute®) for trial information.

Data collection and analysis

Selection of studies

Two review authors (AL and AB) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (not eligible). We included studies reported as full text, those published as abstract only, and unpublished data when sufficient information was available. We retrieved full-text study reports/publications, and two review authors (AL and AB) independently screened the full text, identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted a third person (AH). We calculated the degree of agreement between review authors with a kappa statistic. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1) and a 'Characteristics of excluded studies' table (Characteristics of excluded studies).

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form that was piloted on at least one study in the review to record study characteristics and outcome data. Two review authors (AL and AB) extracted the following study characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals, date of study.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria.
- Interventions: intervention, comparison, concomitant interventions.
- Outcomes: primary and secondary outcomes specified and collected, time points reported.
- Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (AL and AB) independently extracted outcome data from included studies. We noted in the 'Characteristics of included studies' table (Characteristics of included studies) if outcome data were not reported in a useable way. We resolved disagreements by reaching consensus, or by involving a third person (AH). One review author (AL) transferred data into the Review Manager (Review Manager (RevMan) file. We double-checked that data were entered correctly by comparing data presented in the systematic review with those provided in the study reports. A second review author (AB) performed spot-checks of study characteristics for accuracy against the trial report. We contacted authors of studies to verify extracted data, when necessary, and provided details of missing data when possible.

Assessment of risk of bias in included studies

Two review authors (AL and AB) independently assessed risk of bias for each RCT using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by involving another review author (AH). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report, together with a justification for our judgement in the 'Risk of bias' table. We summarised 'risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for rate of hospitalisation may be very different than for a participant-reported symptom scale). When information on risk of bias was related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table. We graded bias as low, high or unclear, and resolved discrepancies by consensus. We summarised results in a 'Risk of bias' table.

When considering treatment effects, we considered the risk of bias for studies that contributed to this outcome.

For randomised cross-over trials, additional considerations for risk of bias included appropriateness of cross-over design, randomisation of treatment order, possibility of carry-over effects, and availability of unbiased data (Higgins 2011).

Assesment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported deviations from it in the 'Differences between protocol and review' section (Differences between protocol and review) of the systematic review.

Measures of treatment effect

We analysed data for each outcome, irrespective of whether participants were stated to drop out (intention-to-treat analysis). We analysed dichotomous data as odds ratios and continuous data as means and standard deviations. We undertook meta-analyses for continuous data only when this was meaningful (i.e. if treatments, participants and the underlying clinical question were similar enough for pooling to make sense). We calculated mean differences (MDs: same metric scale) or standardised mean differences (SMDs: different metric scale) with 95% confidence intervals (95% CIs). We narratively described skewed data reported as medians and interquartile ranges, where available, or medians and 95% confidence intervals.

Unit of analysis issues

We analysed data from HRQOL, symptom questionnaires, lung function, or sputum clearance as continuous or ordinal data. We analysed exacerbation rates or hospitalisations as dichotomous (yes/no) or ratio (frequency, rate) data. We analysed cross-over trials using generic inverse variance methods, when possible. In the event of inadequate washout for a cross-over trial, we included only results from the first phase of the trial, where available. One

study applied independent t-tests for a cross-over trial (Semwal 2015); as raw data were not available, the results were reported narratively. One study applied a Student's t-test to compare different techniques (Antunes 2001); results were reported narratively.

Dealing with missing data

In the event of missing data, we contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only). When this was not possible, and missing data were related to the intervention, we planned to analyse the impact of including such studies in the overall assessment of results by performing a sensitivity analysis**.** However, with limited pooling of data, this analysis was not performed.

Assessment of heterogeneity

Where data was able to be pooled, we used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity ($\geq$ 50%), we would have explored possible causes through prespecified sensitivity analyses. For those studies in which homogeneity was evident, we planned to use a fixed-effect model for analysis. For studies of substantial heterogeneity ($I^2 \geq 50\%$), we used a random-effects model (Deeks 2008). For those with heterogeneity with an $I^2 > 75\%$, results of included studies were presented in a forest plot, but the pooled estimate was suppressed.

Assessment of reporting biases

If we had more than 10 trials, we planned to create a funnel plot and analyse this for small-study and publication biases (Egger 1997). However, a total of only nine trials were identified in this review.

Data synthesis

We analysed separately data from studies related to acute exacerbation compared with studies related to stable bronchiectasis. In addition, we planned to compare studies of low- or Hi-PEP therapy; however no studies using Hi-PEP therapy were included. Studies providing data on oscillatory PEP therapy were analysed separately. Within each group, we planned to pool data that were clinically homogeneous using a fixed-effect model; data that were clinically homogeneous using a random-effects model. However, the differences between interventions and differing units of reporting limited this pooling. We did not pool data that were clinically heterogeneous.

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: HRQOL, exacerbation rates, and hospitalisation. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to aid readers' understanding of the review, when necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

- Oscillatory PEP therapy vs other ACTs.
- Non-oscillatory PEP therapy vs other ACTs.
- Level of PEP (minimal/low pressure ((< 5 cmH_20 vs 10 to 25 cm H_2O) vs high pressure (40 to 120 cm H_2O)).

We used the following outcomes in subgroup analyses:

- HRQOL
- Exacerbation rates.
- Hospitalisation rates.

We used the formal test for subgroup interactions in Review Manager (Review Manager (RevMan).

Sensitivity analysis

We planned to perform a sensitivity analysis to determine the effects of methodological quality on the pooled estimate by removing studies that were at high or unclear risk of bias for the domains of blinding and incomplete outcome data. We had planned to examine the effects of the method of diagnosing bronchiectasis (physician-based or HRCT). However, insufficient numbers of included studies precluded these analyses.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies and Characteristics of studies awaiting classification for complete details.

Results of the search

The 2017 search of databases (CAGR and Pedro) and clinical trial registries of potential studies and reference checks yielded 81 studies. After removal of duplicates, a total of 57 studies were screened. We excluded 39 studies on the basis of title and abstract, including eight which are currently awaiting classification or are ongoing studies; these were not included in the analysis. A total of 18 full-text studies were assessed for eligibility. We excluded nine studies, as they did not meet the review criteria. We included nine studies in the qualitative analysis. Review authors agreed on 14 out of 18 studies following full-text review (82%), with kappa = 0.90, indicating substantial agreement. In this review, a total of nine studies were included (Figure 1). The full details of excluded studies and those awaiting classification are outlined in Characteristics of excluded studies and Characteristics of studies awaiting classification tables.

Included studies

Design

This review included seven randomised cross-over trials (Antunes 2001; Thompson 2002; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015) and two randomised controlled trials (Tsang 2003; Altiay 2012).

Participants

The nine included studies involved 213 participants with sample sizes ranging from 10 to 36. Eight studies included clinically stable adult participants (Antunes 2001; Thompson 2002; Patterson 2005; Eaton 2007; Altiay 2012; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015) and one study included adult participants experiencing an acute exacerbation of bronchiectasis (Tsang 2003). Bronchiectasis was diagnosed on the basis of HRCT in six studies (Antunes 2001;Thompson 2002; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015) and by physician diagnosis in two studies, as per the inclusion criteria (Altiay 2012; Semwal 2015). The study of participants with an acute exacerbation stated inclusion criteria of diagnosis of bronchiectasis of at least one year in duration, with symptoms of cough and sputum production (Tsang 2003). The age range of participants was 46 to 74 years in eight studies (Antunes 2001; Thompson 2002; Tsang 2003; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015); one study did not report age (Altiay 2012). Of the eight studies in those with stable disease, five reported disease severity according to spirometry, FEV_1 ranged from 53 to 64% predicted (Antunes 2001; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015) or 0.67 to 0.7 L (Thompson 2002). In those with an acute exacerbation of bronchiectasis, FEV_1 ranged from 36 to 49% predicted (Tsang 2003).

Intervention

The duration of each intervention ranged from a single treatment in five studies (Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015), twice over one week (Antunes 2001), daily for four weeks (Altiay 2012) or twice daily for four weeks (Thompson 2002). In those with an acute exacerbation, the frequency was three times per day from day two of admission until day of discharge (Tsang 2003). A washout period of one week was applied in two studies (Guimaraes 2012; Herrero-Cortina 2015), while three studies did not apply a washout period (Antunes 2001; Patterson 2005; Eaton 2007), one study applied a three hour washout (Semwal 2015), and one study did not mention the use of a washout period (Thompson 2002). Outcome measures were only collected throughout the intervention period, with no long-term follow-up beyond the intervention applied in any study.

Two studies compared oscillatory PEP therapy (Flutter) to slow expiration with the glottis open from the FRC to the RV, performed in the lateral decubitus position, with the affected lung in the dependent position ('L'expiration Lente Totale Glotte Ouverte en Decubitus Lateral' (ELTGOL) (Guimaraes 2012)) with one study adding chest clapping, vibrocompression and coughing (Antunes 2001). Three studies compared oscillatory PEP therapy (Flutter) to ACBT (Thompson 2002; Eaton 2007; Altiay 2012), with two studies applying ACBT in a seated (Eaton 2007) or a GAD position (Thompson 2002; Eaton 2007) or both. One study compared oscillatory PEP therapy (Flutter) to GAD with BC, deep inspiration, relaxation, and coughing (Tsang 2003). One study applied oscillatory PEP therapy (Acapella) in a GAD position versus ACBT with GAD (Patterson 2005). One study compared minimal PEP therapy to AD and to ELTGOL (Herrero-Cortina 2015). One study compared oscillatory PEP therapy (Acapella) to AD (Semwal 2015).

Outcome measures

Eight studies included a measure of sputum volume or weight, which could be wet or dry, and a measure of spirometry (Antunes 2001; Thompson 2002;Tsang 2003; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015). Health-related quality of life was assessed using the Short-Form-36 (SF-36) (Altiay 2012) or the Chronic Respiratory Questionnaire (CRQ) (Thompson 2002), while cough-related quality of life was assessed with the Leicester Cough Questionnaire (LCQ) in one study (Herrero-Cortina 2015). Breathlessness was measured using the Borg scale in four studies (Thompson 2002; Eaton 2007; Altiay 2012; Semwal 2015), while the Medical Research Council score for Dyspnoea (Altiay 2012) and the 15-count breathlessness score (Patterson 2005) were each applied in one study. Symptoms of tiredness and discomfort (Eaton 2007) and coughing (Altiay 2012) were assessed in one study each. Lung function was measured in seven studies, with spirometry (Thompson 2002;Tsang 2003;

Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015), peak expiratory flow (Semwal 2015), and lung volumes included (Guimaraes 2012).

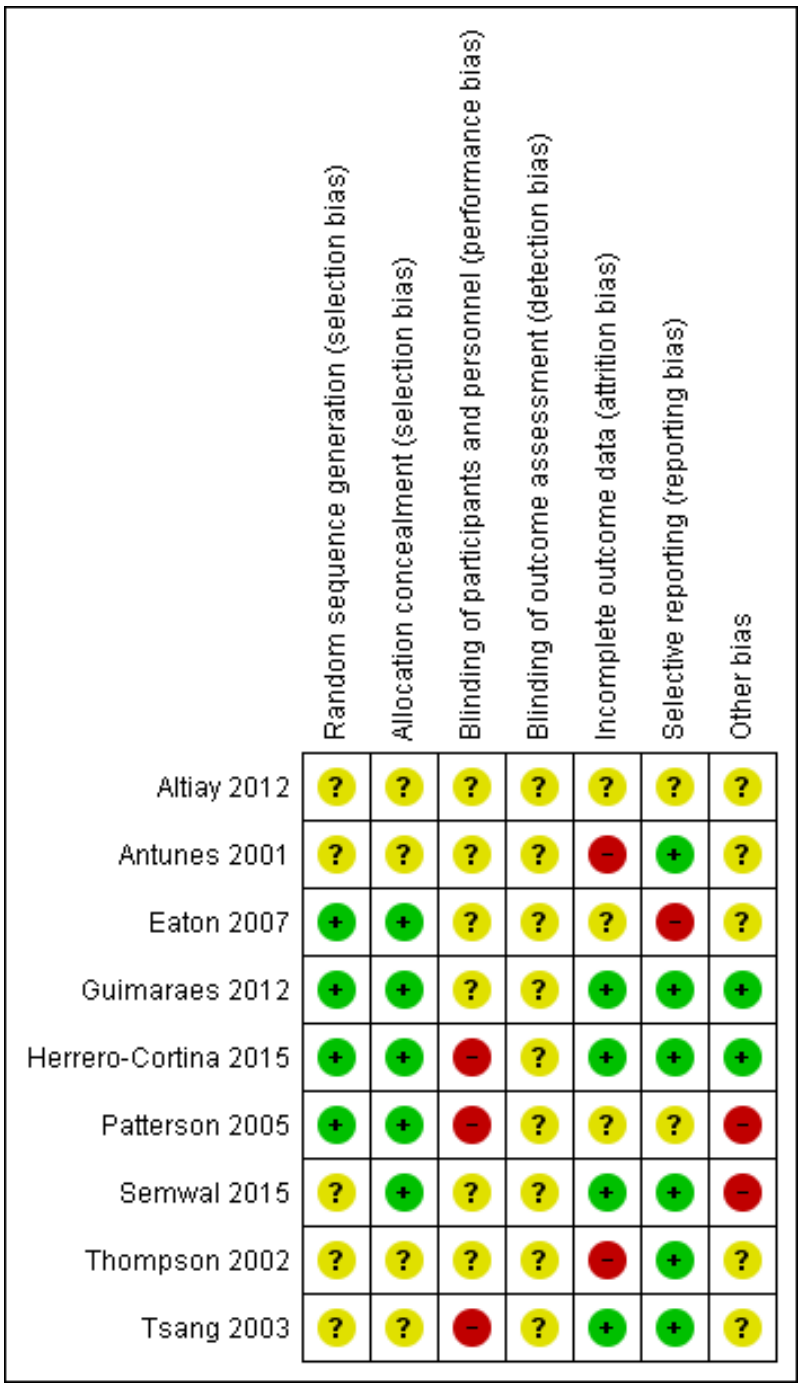
Excluded studies

We excluded a total of 48 studies. Reasons for exclusion of full-text reviewed studies were comparison between two types of PEP therapy (n = 2), mixed disease group from which data related to bronchiectasis could not be extracted (n = 2), mixed therapy group from which data related to PEP therapy could not be extracted (n = 2), lack of PEP therapy use (n = 1), lack of randomisation (n = 1) and lack of comparison group (n = 1). Full details of reasons for exclusion are provided in the Characteristics of excluded studies table. A further six studies are ongoing (Characteristics of ongoing studies) and two are awaiting classification. These will be assessed for eligibility in further updates of this review.

Risk of bias in included studies

Risk of bias was able to be completed for eight studies (Antunes 2001; Thompson 2002; Tsang 2003; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015). One study was available only in abstract form, therefore all criteria for 'risk of bias' assessment were indicated as unclear (Altiay 2012). An overview of the risk of bias for the domains listed below is outlined in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies reported random allocation to groups, but the methods by which this was applied were stated in only four studies (Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015). Five studies stated the use of either sealed, opaque envelopes, or a method of concealment was used for allocation (Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015); three studies did not provide sufficient information to determine the method used (Antunes 2001; Thompson 2002; Tsang 2003).

Blinding

Insufficient information was provided in seven studies regarding the blinding of participants and personnel delivering the interventions (Antunes 2001; Thompson 2002; Eaton 2007; Altiay 2012; Guimaraes 2012; Semwal 2015), while three studies specifically stated the absence of blinding of personnel (Patterson 2005; Tsang 2003) and participants and personnel (Herrero-Cortina 2015). The physical nature of the intervention is likely to impose limits on blinding participants in these studies. One study stated the use of an independent assessor for recording pre and post treatment outcome measures (Patterson 2005). Insufficient data were available to show whether assessors were blinded in other studies (Antunes 2001; Thompson 2002;Tsang 2003; Eaton 2007; Altiay 2012; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015). No studies reported whether data analysts were blinded to group allocation.

Incomplete outcome data

Three studies stated withdrawal of participants (Antunes 2001; Thompson 2002; Herrero-Cortina 2015). One study outlined that three participants were unable to conclude the study and their results were not included in the analysis (Antunes 2001). Thompson stated that of the five participants who withdrew, three dropped out because of an infective exacerbation (two during the oscillatory PEP therapy arm and one during the ACBT arm) and two recorded insufficient data for analysis (Thompson 2002). The third study outlined that two participants dropped out due to acute low back pain and pulmonary exacerbation (Herrero-Cortina 2015). The data of withdrawn participants were not included in analysis in any study (Antunes 2001; Thompson 2002; Herrero-Cortina 2015).

Selective reporting

Three studies were reported on a clinical registry prospectively (Guimaraes 2012; Altiay 2012; Herrero-Cortina 2015). Results were reported for all outcomes at each time point for six studies (Antunes 2001; Thompson 2002;Tsang 2003; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015). With one study reporting only in abstract form, it is possible that not all data were reported in this study (Altiay 2012).

Other potential sources of bias

An adequate washout period of one week was applied in two studies (Guimaraes 2012; Herrero-Cortina 2015). No washout period was applied in three studies (Antunes 2001; Thompson 2002; Patterson 2005), which may have influenced the findings of two studies, with consecutive days of treatment applied in one study (Patterson 2005) and a four-week intervention applied in another study (Thompson 2002). One study used a three-hour washout period between interventions, which may have influenced findings (Semwal 2015). One study did not mention the inclusion of a washout period between interventions (Eaton 2007).

Effects of interventions

See: **Summary of findings for the main comparison**

See Summary of findings (Summary of findings for the main comparison) for the primary outcome comparisons. We were able to include data from nine studies, in a quantitative and narrative synthesis, with all studies conducted in the adult population (Antunes 2001; Thompson 2002; Tsang 2003; Patterson 2005; Eaton 2007; Guimaraes 2012; Altiay 2012; Herrero-Cortina 2015; Semwal 2015;).

Primary outcomes

Health-related quality of life

Three studies examined the effects of PEP therapy compared to other techniques on HRQOL (Thompson 2002; Altiay 2012; Herrero-Cortina 2015). Due to clinical heterogeneity in comparison of treatment techniques, follow-up, and outcome measures, no studies could be combined in meta-analysis. Using oscillatory PEP therapy (Flutter) daily for four weeks improved general health (P = 0.048) based on the SF-36 compared to daily ACBT (Altiay 2012). Minimal PEP, AD, and ELTGOL, when applied for three sessions over one week, all significantly increased (better) cough-related quality of life according to the LCQ total scores, with no difference between minimal PEP therapy and AD (median 0.4 (95% CI 0.1 to 1.2) vs 0.5 (95% CI 0.1 to 0.5)) or minimal PEP therapy and ELTGOL (median 0.4 (95% CI 0.5 to 2.1) vs 0.9 (95% CI 0.1 to 1.2)) (P = 0.60) (Herrero-Cortina 2015). Performing oscillatory PEP therapy (Flutter) compared to ACBT in a GAD position twice daily for four weeks had a similar effect

on HRQOL for dyspnoea (MD 0.01, 95% CI -0.48 to 0.50; one study, 17 participants, low-quality evidence) (Analysis 1.1), fatigue (MD -0.19, 95% CI -0.82 to 0.45; one study, 17 participants, low-quality evidence) (Analysis 1.2), emotional function (MD -0.06, 95% CI -0.63 to 0.52; one study, 17 participants, low-quality evidence) (Analysis 1.3), mastery (MD -0.10, 95% CI -0.65 to 0.46; one study, 17 participants, low-quality evidence) (Analysis 1.4) and total score (MD -0.09, 95% CI -0.37 to 0.19; one study, 17 participants, low-quality evidence) (Analysis 1.5) (Thompson 2002). The results of all studies are outlined in Table 1.

Rate of exacerbation or time to first exacerbation

No studies reported on the rate of or time to first exacerbation.

Incidence of hospitalisation

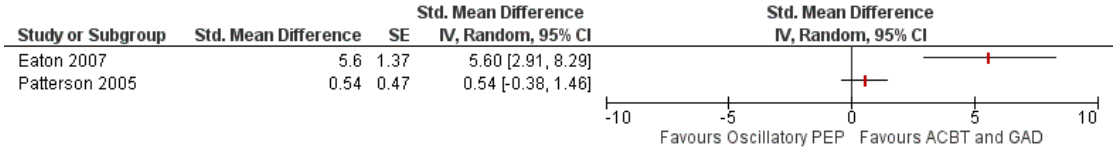
No studies reported on the incidence of hospitalisation for those in a stable clinical state.

Secondary outcomes

Sputum volume or weight

Eight studies compared the effects of PEP therapy to other ACTs on sputum yield (Antunes 2001; Thompson 2002; Tsang 2003; Patterson 2005; Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015). Two studies investigating a single session of oscillatory PEP therapy (Acapella or Flutter) compared to GAD with ACBT are presented together, but due to significant clinical heterogeneity, a pooled estimate of results was not calculated. A single session of oscillatory PEP therapy (Acapella) produced a similar sputum weight compared to GAD with ACBT (SMD 0.54 g, 95% CI -0.38 to 1.46 g; 20 participants); while a single session of oscillatory PEP therapy (Flutter) produced less sputum compared to GAD with ACBT (SMD 5.6 g (95% CI 2.91 to 8.29 g; 36 participants) (Analysis 2.1) (Figure 3). Less sputum volume was produced with oscillatory PEP therapy (Flutter) compared to GAD with ACBT (MD 5.1 mL (95% CI 2.24 to 7.96 mL; one study, 36 participants) (Analysis 2.2) (Eaton 2007). There was no difference in sputum weight between oscillatory PEP therapy (Flutter) and ACBT in a seated position (MD -0.3 g (95% CI -1.42 to 0.82 g; one study, 36 participants) (Analysis 3.1) or in sputum volume (MD -0.60 mL, 95% CI -1.87 to 0.67 mL; one study, 36 participants) (Analysis 3.2) (Eaton 2007). A single treatment of oscillatory PEP therapy (Flutter) yielded a lower sputum weight compared to ELTGOL (median 0.15 g (minimum to maximum 0.05 to 0.13 g) versus median 0.38 (minimum to maximum 0.06 to 2.63 g; one study, 10 participants), P < 0.05) (Guimaraes 2012). Less sputum was expectorated during a single treatment of minimal PEP therapy compared to AD (median difference 3.1 g, 95% CI 1.5 to 4.8 g) or ELTGOL (MD 3.6 g, 95% CI 2.8 to 7.1 g; one study, 31 participants) (Herrero-Cortina 2015). However, mean clearance over 24 hours was similar for each of these techniques (P = 0.8) (Herrero-Cortina 2015). A comparison of AD to oscillatory PEP therapy (Acapella) did not yield a difference in sputum volume (mean 16.1 mL (SD 7.9) vs 16.3 mL (10.3), P = 0.92) or sputum weight (mean 15.8 g (5.7) vs 16.2 g (7.9) (P = 0.85) immediately post treatment (Semwal 2015). Comparing four sessions of oscillatory PEP therapy (Flutter) to ELTGOL, there was no significant difference in average sputum dry weight per session (0.28 g (SD 0.28) vs 0.16 g (0.06), P < 0.05 or wet weight (7.2 g (SD 2.3) vs 6.3 g (0.7), P > 0.05) (Antunes 2001). Four weeks of twice daily oscillatory PEP therapy compared to ACBT with GAD did not increase sputum weight (median difference 7.64 g, P = 0.77) (Thompson 2002). When applied during an acute exacerbation, oscillatory PEP therapy (Flutter) and GAD yielded a similar sputum weight on day two of admission (MD favouring GAD 19.86 g, 95% CI -7.95 to 47.67 g; one study, 10 participants) (Analysis 4.1), day four of admission (MD 22.46 favouring GAD, 95% CI -10.71 to 55.63 g; one study, 10 participants) (Analysis 4.2) or day of discharge (MD favouring GAD, 21.03 g 95% CI -11.29 to 53.35 g; one study, 10 participants) (Analysis 4.3) (Tsang 2003).The results of all studies are outlined in Table 2.

Figure 3. Forest plot of comparison: Oscillatory PEP therapy vs ACBT with GAD (single session), Sputum weight (g)



Sputum clearance

No studies reported on sputum clearance using radioaerosol clearance.

Lung function

Eight studies compared the effects of PEP therapy to other ACTs on measures of lung function (Antunes 2001; Thompson 2002; Tsang 2003; Patterson 2005; Altiay 2012; Guimaraes 2012; Herrero-Cortina 2015; Semwal 2015). None could be combined in meta-analysis due to clinical heterogeneity. A single treatment session of oscillatory PEP therapy (Acapella) and ACBT with GAD yielded a similar effect on FEV_1, FVC and PEF % predicted (Patterson 2005). There was no difference in lung function (FEV_1, FVC, FEF_{25-75}) at treatment conclusion between minimal PEP therapy and ELTGOL or minimal PEP therapy and AD (P > 0.05) (Herrero-Cortina 2015). Similarly, a single session of oscillatory PEP therapy (Acapella) compared to AD did not change PEFR immediately following treatment (176.1 L/min (72.6) vs 179.1 L/min (72.6), P = 0.87) (Semwal 2015). There was no difference in PEFR between oscillatory PEP therapy (Flutter) vs ELTGOL between four occasions of treatment (P > 0.05) (Antunes 2001). One session of oscillatory PEP therapy (Flutter) had a similar effect to ELTGOL on change in FEV_1 (median 1.6 L (minimum to maximum -6.8 to 21.4) vs median 2.2 L (-20.2 to 20.9)), change in FVC (median 2.44 L (minimum to maximum -3.9 to 8.1) vs median 0.96 L (-11.8 to 22.1)), change in FEV_1/FVC (median 0.7 L (minimum to maximum -11.3 to 19.6) vs median 0 L (-8.6 to 10.6)), change in FEF_{25-75} (median 4.5 L (minimum to maximum -21.4 to 160) vs median 6 L (-90.51 to 236)), change in IC (median 3.49 L (minimum to maximum -28.47 to 33.78) vs median 2.65 L (-15.65 to 27.66)), change in TLC (median -18.27 L (minimum to maximum -42.83 to -6.43) vs median 9.66 L (-40.03 to -1.96)), change in FRC (median -25.81 L (minimum to maximum -52.02 to -5.14) vs median -14.48 L (-55.65 to -3.6)), change in RV (median -29.55 L (minimum to maximum -54.66 to -8.86) vs median -18.72 L (-71.85 to -10.73)) or change in RV/TLC ratio (median -5.21 L (minimum to maximum -22.81 to 27.59) vs median -8.48 L (-25.46 to 113.04)) (Guimaraes 2012). Four weeks of treatment with oscillatory PEP therapy (Flutter) compared to ACBT with GAD did not affect PEFR for the morning session (median difference -2.5 L/min, P = 0.38) or the evening session (median -2.72 (95% CI -6.95 to 1.52), P = 0.30) (Thompson 2002). Four weeks of daily ACBT or oscillatory PEP therapy (Flutter) did not yield a difference in FEV_1 or FVC between techniques (Altiay 2012).

During an acute exacerbation, there was no difference in FEV_1 post treatment between oscillatory PEP therapy (Flutter) and GAD on day two of admission (MD 0.12 L (95% -0.32 to 0.56 L)) (Analysis 4.4), day four (MD 0.15 L (95% CI -0.27 to 0.57 L)) (Analysis 4.5) or day of discharge (MD 0.12 L (95% CI -0.52 to 0.76 L)) (Analysis 4.6) (Tsang 2003). Similarly, there was no difference between these interventions for FVC on day two of admission (MD -0.22 L (95% CI -0.81 to 0.37 L)) (Analysis 4.7), Day four of admission (MD 0.2 L (95% CI -0.48 to 0.88 L)) (Analysis 4.8) or day of discharge (MD 0.12 L (95% CI -0.52 to 0.76 L)) (Analysis 4.9). Equivalent results were evident for PEFR for day two (MD 22.2 L/min (95% CI -48.88 to 93.28 L/min)) (Analysis 4.10), day four (MD 22.6 L/min (95% CI -40.69 to 85.89 L/min)) (Analysis 4.11) and day of discharge (MD 23.2 L/min (95% CI -39.56 to 85.96 L/min)) (Analysis 4.12) (Tsang 2003).The results of all studies are outlined in Table 3.

Symptoms

A single session of oscillatory PEP therapy (Flutter), when compared to ACBT with GAD, generated a similar level of fatigue (MD -0.3, 95% CI -0.35 to 0.95) (Analysis 2.3). However, using the Flutter was more tiring compared to ACBT alone (MD 0.7, 95% CI 0.15 to 1.25) (Analysis 3.3) (Eaton 2007). There was no difference in discomfort level between the Flutter compared to ACBT alone (MD 0.40, 95% CI -0.12 to 0.92) (Analysis 3.4), or between Flutter and ACBT combined with GAD (MD -0.3, 95% CI -0.82 to 0.22) (Analysis 2.4) (Eaton 2007). Similarly, there was no difference in dyspnoea (Borg score) between oscillatory PEP therapy (Acapella) and AD (mean 1.8 (SD 1.1) vs 1.8 (1.2), P = 1.00) (Semwal 2015) or in a comparison of oscillatory PEP therapy (Flutter) vs ACBT or ACBT with GAD (Eaton 2007). The 15-count breathlessness score did not differ between a single session of oscillatory PEP therapy (Acapella) and ACBT with GAD (Patterson 2005). Four weeks of daily oscillatory PEP therapy (Flutter) compared to ACBT had a similar effect on the degree of dyspnoea (Borg score), and symptoms of cough and feelings of weakness when compared to ACBT (Altiay 2012). Four weeks of twice daily oscillatory PEP therapy (Flutter) generated similar levels of breathlessness following morning therapy session (MD 0.13, 95% CI -0.078 to 0.34), P = 0.36) and evening sessions (median difference -0.04, P > 0.99) (Thompson 2002).The results of all studies are outlined in Table 4.

Adverse events

One study reported the occurrence of nausea in one participant when using oscillatory PEP therapy (Flutter) (Thompson 2002). No other reports of adverse events were made from other studies; it is unknown if any adverse events occurred in these studies.

DISCUSSION

Summary of main results

This review compared the effects of PEP therapy to other forms of ACTs in individuals with bronchiectasis. Results from nine studies of 213 individuals were mixed. In individuals with stable bronchiectasis, data from a small number of studies illustrated that PEP therapy offered similar effects on HRQOL, cough-related quality of life and symptoms of breathlessness as other ACTs. Short and medium-term use of PEP therapy offered no greater advantage in sputum expectoration compared to other types of techniques, irrespective of clinical disease state. No difference in effects on measures of lung function were evident between PEP therapy and other ACTs. According to the GRADE criteria, all review outcomes were rated as low-quality. Future, longer term studies are required to confirm the magnitude of effect on HRQOL, exacerbation frequency, and hospitalisation rates. Further information is needed regarding the effect of PEP therapy during an acute exacerbation of bronchiectasis.

Overall completeness and applicability of evidence

Key clinical features of bronchiectasis are cough, fatigue, and breathlessness (King 2006); for this reason, a reduction in these symptoms is beneficial. It is therefore encouraging that minimal PEP therapy, AD, and ELTGOL lead to improvement in cough-related quality of life, even when used for a short duration (Herrero-Cortina 2015). This is despite each of these techniques differing in their underlying rationale. The proposed physiological basis for ELTGOL is the promotion of two-phase gas-liquid interaction to facilitate mucociliary clearance (Guimaraes 2012), while the proposed primary mechanism of oscillatory PEP therapy involves a splinting effect on the airways to improve collateral ventilation and altering sputum rheology (Tambascio 2011). In contrast, AD relies on the generation of shearing forces induced by airflow at different lung volumes to loosen and mobilise secretions (Schoni 1989). This suggests that, regardless of the type of technique, use of either PEP therapy, AD, or ELTGOL may lead to more efficient expectoration in the short term. However, with a lack of sustained improvement following the washout period between treatment techniques, improvement in this domain of quality of life may only be able to be maintained with regular treatment.

The degree of breathlessness was not greater with PEP therapy compared to other techniques, including AD or ACBT with GAD (Thompson 2002; Patterson 2005; Eaton 2007; Altiay 2012; Semwal 2015). Although not specifically stated, this may be related to the approach with these techniques, with the inclusion of sessions of breathing control (Thompson 2002). However, for those experiencing fatigue, use of oscillatory PEP with a Flutter may be less tiring compared to ACBT in a seated position (Eaton 2007). The reason for this is unclear, with both techniques undertaken in a seated position. It is possible that a greater degree of breathing control was incorporated into the performance of ACBT, but in the absence of a specific description of the PEP therapy, this finding should be interpreted with caution. The lack of difference in disease-specific HRQOL between oscillatory PEP therapy and ACBT with GAD (Thompson 2002) suggests that any type of ACT may offer equal benefit in HRQOL. Evaluating the effects of ACTs on HRQOL is difficult with a treatment duration of only four weeks; a longer length of time of six or 12 months is required to fully evaluate treatment effect. With reports of greater preference for independent techniques such as oscillatory PEP therapy (Eaton 2007), longer term studies which factor in adherence would provide a clearer indication of the effect on HRQOL. In addition, alternative options for evaluating HRQOL have now been developed for bronchiectasis and which specifically consider all clinical symptoms which are of importance to people with this condition (Quittner 2015). Including this tool as an outcome measure in future studies of PEP therapy and other ACTs may provide more definitive information. Experiencing less pain with oscillatory PEP therapy is likely to influence adherence. However, with this study only available in abstract form and the lack of detail in location of pain (Altiay 2012), this finding requires further clarification. Using PEP therapy compared to GAD during an acute exacerbation offers no additional advantage in the duration of hospital stay. With the lack of studies including exacerbation rates and hospitalisation rates, there is a need of further long-term research which incorporate these clinically important outcomes.

The effect on sputum expectoration is variable, with some single treatments with oscillatory PEP therapy (either Flutter or Acapella) producing less sputum expectoration compared to GAD with ACBT or with AD or ELTGOL (Eaton 2007; Guimaraes 2012; Herrero-Cortina 2015), while other studies found no difference in the use of oscillatory PEP therapy and ACBT, with or without GAD, AD, or GAD with chest clapping and vibrocompression and coughing (Antunes 2001; Thompson 2002; Tsang 2003; Patterson 2005; Eaton 2007; Semwal 2015), irrespective of clinical state. Reasons for these contrasting findings are likely to be related to the differences in treatment approaches as well as the duration of treatment sessions. Greater sputum expectoration in a single session or with four weeks of daily treatment with ACBT and GAD compared to oscillatory PEP therapy was achieved only when the selection of GAD positions was based on HRCT results (Eaton 2007), rather than right and left lateral decubitus positions or two positions based on unknown criteria (Antunes 2001; Thompson 2002; Patterson 2005). This may be an important factor when choosing between PEP therapy and ACBT with GAD and the approach adopted in position selection. The addition of chest clapping and vibrocompression offered no greater advantage over oscillatory PEP therapy (Antunes 2001). However, as ACBT and GAD are perceived to be more time-consuming (Eaton 2007), the degree of interference in daily life may be an important clinical consideration. If GAD is not included, equivalent benefits for

sputum production were achieved with ACBT in a seated position or oscillatory PEP therapy (Flutter). This illustrates the role of patient preference, with oscillatory PEP therapy a well accepted and preferable technique to patients with bronchiectasis (Thompson 2002; Patterson 2005; Eaton 2007).

The greater sputum weight immediately post treatment achieved with ELTGOL over oscillatory PEP therapy (Flutter) or minimal PEP highlight that the components of ELTGOL may be of greater advantage. In one study of ELTGOL, participants performed slow expirations with an open glottis from FRC to RV in a lateral decubitus positions while oscillatory PEP therapy was undertaken in a seated position also for 15 minutes (Guimaraes 2012). Herrero-Cortina 2015 applied ELTGOL and compared this to minimal PEP therapy, with each session lasting 40 minutes. However, with the difference in sputum weight in one study being only 0.23 g (Guimaraes 2012) and in the second 3.6 g (Herrero-Cortina 2015), the clinical significance of these findings is unclear. However, it should be noted that differing approaches to sputum expectoration were applied between these two studies. Prior to any intervention, a series of five minutes of voluntary coughing was administered to all participants to clear central airway secretions (Guimaraes 2012); this approach was not used in the study conducted by Herrero-Cortina 2015. Although clearance of central secretions prior to commencing ACTs may provide a more accurate estimate of the effectiveness of a specific ACT upon sputum expectoration and could avoid an overestimation of the impact of the technique, it is a challenge to directly image the airways and determine whether secretions are originating from peripheral or central airways. Further studies could employ similar methods to allow direct comparison of techniques. The lack of difference in sputum clearance over a 24 hour period between ELTGOL and minimal PEP therapy may be related to a slower action timing for minimal PEP therapy in sputum clearance, with only 28% of sputum cleared during the physiotherapy session compared to 42% for ELTGOL (Herrero-Cortina 2015). The amount of pressure applied in PEP therapy may also influence sputum expectoration. Minimal PEP generated pressure of 1 cmH_2O rather than 10 to 25 cmH_2O reached with PEP therapy or oscillatory PEP therapy (Falk 1984; Darbee 2004). This may be insufficient to promote airflow through collateral ventilation and allow an increased volume of air behind secretions which supports sputum movement towards the larger airways (Falk 1984; Van der Schans 1991). This degree of pressure may account for the contrasting findings between studies comparing AD and PEP therapy. Comparing AD and oscillatory PEP therapy, a similar sputum volume is achieved after four weeks of treatment (Semwal 2015), while a single session of minimal PEP therapy yielded less expectoration during a physiotherapy session (Herrero-Cortina 2015). Although exacerbations of bronchiectasis are characterised by an increase in sputum production, both oscillatory PEP therapy and GAD appear to be equally effective (Tsang 2003); this emphasises the value in considering patient preference for technique in this clinical state. A confounding factor is the difference between studies in the measurement of sputum expectoration, with five studies using wet weight/volume (Thompson 2002; Tsang 2003; Eaton 2007; Herrero-Cortina 2015; Semwal 2015), one study using dry weight Guimaraes 2012), one using wet and dry weight (Antunes 2001) and one not stated (Patterson 2005). Wet volume may be influenced by an individual's reluctance to expectorate, saliva contamination and the swallowing of secretions (Williams 1994). Contamination with saliva may be corrected by drying sputum and measuring dry weight (Boucher 2010), which may lend more support to studies which have applied this technique. Hydration levels will also influence sputum volume and has been identified as a mode of supporting airway clearance and sputum expectoration (Wilkinson 2014). In the absence of commentary about hydration levels in the studies included in this review, it is difficult to determine its contribution.

That oscillatory PEP therapy has similar effects after a single session of treatment on measures of spirometry as other techniques (ranging from ACBT with GAD, AD, and ELTGOL in clinically stable participants (Patterson 2005; Eaton 2007; Guimaraes 2012; Semwal 2015)) is not surprising. Single sessions of treatment offer little opportunity to make a substantial change in spirometry, even when experiencing an acute exacerbation. Similar effects were noted for minimal PEP therapy compared to ELTGOL or AD (Herrero-Cortina 2015). Even the use of four sessions of treatment or four weeks of treatment of either oscillatory PEP therapy or ACBT with GAD or GAD with chest clapping and compression suggested there was no greater advantage or detriment between techniques in measures of spirometry or peak expiratory flow rates (Antunes 2001; Thompson 2002; Altiay 2012). The lack of advantage of oscillatory PEP therapy over GAD during an acute exacerbation upon spirometry measurements may be influenced by concurrent medical therapy administered as part of exacerbation management for all patients (Tsang 2003). For this reason, the opportunity to identify a difference between techniques on measures of FEV_1 and FVC is limited. The same degree of reduction in FRC, RV, and TLC with oscillatory PEP therapy as ELTGOL indicates that both types of ACTs reduce pulmonary hyperinflation (Guimaraes 2012), a feature of bronchiectasis (Koulouris 2003). The splinting effect of the oscillatory PEP therapy is believed to stabilise airways during expiration to avoid dynamic collage and favour pulmonary deflation (Calverley 2005; Guimaraes 2012). This suggests that issues affecting patient compliance, such as preference for techniques, practical considerations, and cost are of greater importance and significance in selecting a technique. Similar findings were evident in a single session or up to three months of treatment with PEP therapy compared to other techniques in individuals with cystic fibrosis (McIlwaine 2015). Other measurements of lung function such as the lung clearance index, a measure of abnormal ventilation distribution, may provide more detailed information about the effects of specific ACTs on lung function (Horsley 2009). With ventilation heterogeneity a clini-

cal feature of bronchiectasis (Gonem 2014), including this as an outcome in studies of PEP therapy may offer more insight into the physiological effects of this type of ACT.

A key limitation of this review is the assumption that all ACTs are equivalent and effective compared to no treatment. While previous reviews have illustrated that, compared to no treatment, some types of ACTs are effective in improving sputum expectoration, lung function, HRQOL, and symptoms (Lee 2013; Lee 2015), this has not been proven for all types of ACTs. For this review, the comparator ACTs were variable. This may influence individual study findings and therefore the interpretation and findings of this current review need to be considered in view of the differing physiological rationale behind each comparator technique.

A mix of cross-over and randomised controlled trials have been included in this review. Cross-over trials are more appropriate for comparing physiological outcomes between techniques, while controlled trials are more suited to comparing clinical outcomes. Despite this being a limitation of the current review, no meta-analysis which combined cross-over and controlled trials was undertaken. Being the first review to examine this question, future reviews may be better suited to separately examine the physiological and clinical impact of PEP therapy compared to other ACTs in this population.

Six studies included participants whose diagnosis of bronchiectasis was according to HRCT (Antunes 2001; Thompson 2002; Eaton 2007; Patterson 2005; Guimaraes 2012; Herrero-Cortina 2015). Given this is the gold standard for diagnosis, to minimise the likelihood of errors in diagnostic criteria, an update of this review could include studies in which a diagnosis of bronchiectasis was confirmed by HRCT only. In addition, while it is stated that studies which included participants with concurrent asthma or COPD were excluded, this relies on the original reporting of this information. The potential for some participants included in the current review having a concurrent respiratory condition cannot be excluded. The underlying causes of bronchiectasis or the extent of disease severity, including the number of lobes affected, were not specified in any study. Bronchiectasis severity can be determined by HRCT scan scoring (Bhalla 1991) or a combination of clinical signs and symptoms (Chalmers 2014). Knowledge of the severity of disease and the presence and degree of airway hyperresponsiveness does influence the selection of ACTs in cystic fibrosis (Volsko 2013); this may be equally important in bronchiectasis. The range of intervention durations between studies (from single sessions to four weeks) makes it difficult to generalise the findings to broader clinical practice, which reflects the long-term use of ACTs (Butler 2008; Lee 2008; O'Neill 2002), regardless of the chosen intervention. With a single study of PEP therapy during an acute exacerbation, further research is required to determine the impact of PEP therapy during this clinical state.

The method of prescription of the common types of ACTs, including PEP therapy, aligned with current clinical guidelines for bronchiectasis, which have largely been extrapolated from the CF population and the findings are comparable to those described in the CF population (McIlwaine 2015). A large proportion of studies comparing PEP therapy to other ACTs have been undertaken in this group, due to the acceptance that airway clearance therapy is the cornerstone of CF management. The efficacy of PEP therapy is similar to GAD with manual techniques, ACBT, AD, and high frequency chest oscillation, with no differences in lung function or sputum volumes between techniques (McIlwaine 2015).

A key factor is the consideration of patient preference. Adherence to treatment is increasingly recognised as important in bronchiectasis (McCullough 2014), with poor adherence influencing the rate of acute exacerbations. Adherence to ACT is associated with a higher burden of treatment and worsening respiratory symptoms (McCullough 2014). In people with bronchiectasis, adherence decision-making involves patient evaluation of the advantages and disadvantages of adhering to treatment (McCullough 2014a). Five studies included in the current review reported a preference for PEP therapy compared to ACBT with or without GAD or AD (Thompson 2002; Tsang 2003; Patterson 2005; Eaton 2007; Semwal 2015); in view of similar effects on selected physiological outcomes, patient preference for a technique may be an important clinical consideration, particularly if this influences adherence rates in the longer term. In studies of individuals with cystic fibrosis (Elkins 2006; McIlwaine 2015) and in some studies in the current review (Tsang 2003; Eaton 2007), the independence, ease of use, and perception of effectiveness have been reported to be higher with PEP therapy. While no studies in the current review have considered participant adherence and its influence on the clinical outcomes of PEP therapy over other techniques, these may be important outcomes in future research.

Quality of the evidence

The quality of the nine studies included in this review is mixed, with small sample sizes and often unclear or high risk of bias for blinding of participants and of outcome assessors. Differing intervention duration and different comparative airway clearance techniques limited meta-analysis. Little information on the primary outcomes of interest of quality of life, rate of acute exacerbations, and incidence of hospitalisations were available. While blinding of participants is difficult to achieve in cross-over trials, which was the design of seven out of nine included studies, inclusion of assessor blinding and therapist blinding were not consistently undertaken. The absence of an adequate washout period within studies, particularly for those which applied treatment techniques on the same or consecutive days, may have influenced the short-term outcomes.

Review outcomes were rated as low quality (all outcomes) using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system. Imprecision was increased by the small number of included studies and participants, with one study contributing to each outcome.

Potential biases in the review process

This review was based on a published protocol (Lee 2015a). A broad search which incorporated handsearching of conference abstracts and trial registries was undertaken, with the inclusion of studies published only in the abstract form. Limited information was available from one paper (Altiay 2012), despite contacting the authors, with details only as reported in abstract form. Therefore, the ability to accurately assess the included data were limited. Two review authors independently extracted data and resolved disagreements via discussion. These two review authors independently rated the risk of bias.

Agreements and disagreements with other studies or reviews

The findings of this review are similar to a previously published review of the effects of oscillatory PEP therapy compared to other ACTs in individuals with stable bronchiectasis (Lee 2015). Oscillatory PEP therapy resulted in similar sputum expectoration as ACBT with GAD and, compared to other ACTs, had comparable impact on dynamic lung volumes, gas exchange, and breathlessness.

AUTHORS' CONCLUSIONS

Implications for practice

There appears to be similar benefits and effects of PEP therapy (oscillatory and non-oscillatory) to other ACTs in terms of HRQOL, sputum expectoration, lung function, and impact on symptoms. PEP therapy was not superior to any other ACT in the short and long term. The quality of the evidence however, was low, and therefore, these findings should be interpreted with caution. Additional information is required to establish the clinical value of PEP therapy compared to other ACTs on exacerbation rates and incidence of hospitalisation, both outcomes which influence disease progression in bronchiectasis. The effect of PEP therapy during an acute exacerbation of bronchiectasis requires further clarification.

Implications for research

The longer term effect of PEP therapy compared to other ACTs in people with bronchiectasis has not been established and larger scale studies are required to fully evaluate the effects of this therapy on HRQOL, symptoms, hospitalisation rates, and exacerbation frequency. Future trials should ensure that outcome assessors are blinded to the intervention and, in the case of cross-over trials, an adequate washout period between interventions is applied.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Altiay 2012

Methods	Randomised cross-over trial Study setting: Turkey Study duration: 4 weeks
Participants	36 adults (mean age not reported) with stable bronchiectasis
Interventions	Intervention 1: Active cycle of breathing technique, daily for 4 weeks Intervention 2: Oscillatory PEP therapy (Flutter), daily for 4 weeks
Outcomes	Symptoms of cough Borg dyspnoea score and Medical Research Council dyspnoea score Health-related quality of life: Short form-36 Spirometry (FEV_1 and FVC)
Notes	Study available in abstract form only; no further information available from authors despite requests No study sponsor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Unclear risk	Not specified

Antunes 2001

Methods	Randomised cross-over trial Study setting: medical department, Brazil Study duration: 4 weeks (1 week per therapy)
Participants	13 adults (mean age 59 years) with stable bronchiectasis, diagnosis confirmed by clinical history and radiological findings (chest x-ray and HRCT, number of lobes affected, and severity not reported), mean FEV_1 60% predicted
Interventions	Intervention 1: two treatment sessions in one week of oscillatory PEP therapy (Flutter) , performed in a seated position for 20 minutes, with coughing incorporated into the routine, followed by 30 minutes of rest Intervention 2: two treatment sessions in one week of conventional respiratory therapy, consisting of postural drainage with right and left lateral decubitus for 10 minutes on each side, with chest clapping and vibrocompression and coughing
Outcomes	Sputum volume (dry and wet weight) (g) during session Respiratory rate before and after treatment Expiratory flow rate (L/min) before and after treatment
Notes	No washout period between interventions Before control and intervention sessions, 10 minutes of inhalation bronchodilator therapy (ipratropium bromide and/or fenoterol) was administered No adverse events. No study sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated that participants are randomised, but mode of randomisation was unclear Quote "patients were randomly divided in two groups according to the technique..." Insufficient information was provided
Allocation concealment (selection bias)	Unclear risk	Comment: nothing is stated regarding concealment of allocation of participants to treatment order Insufficient information was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided Comment: Participants and therapist(s) were not likely to be blinded to group allocation. This may have influenced outcome measures of spirometry, respiratory rate, and sputum volume (dry weight)

Antunes 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided Comment: Outcome assessor(s) were not likely to be blinded to group allocation. As outcomes were objectively measured (spirometry, sputum dry weight, respiratory rate), it is likely they were resistant to issues with blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Thirteen patients took part in the study, 3 patients did not conclude the study...The results are from 10 patients that concluded the study" All data for participants who completed the study was provided
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all specified outcomes were reported
Other bias	Unclear risk	No washout period between interventions, which could have affected outcomes. Insufficient information provided

Eaton 2007

Methods	Randomised cross-over trial Study setting: physiotherapy department, New Zealand Study duration: 3 days
Participants	36 adults (mean age 62 years) with stable bronchiectasis with chronic productive cough, diagnosis confirmed by HRCT (number of lobes affected and severity not reported), mean FEV_1 57.8% predicted
Interventions	Intervention 1: one day of active cycle of breathing technique (ACBT), with thoracic expansion exercises, breathing control, and forced expiratory technique in seated position for maximum of 30 minutes Intervention 2: one day of ACBT as previously described, performed in gravity-assisted drainage position for maximum of 30 minutes Intervention 3: oscillatory PEP therapy (Flutter), no further details provided
Outcomes	Sputum wet weight (g) and volume (mL), collected during treatment and 30 minutes post treatment, with total volume and weight also recorded Borg dyspnoea score pre and post treatment Spirometry (FEV_1, FVC) Patient-reported tiredness, discomfort with technique (7-point Likert scale)
Notes	No washout period between interventions No adverse events reported No study sponsor

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "At each session one of the following standardised airway clearance techniques...was performed in random order determined by computer-generated randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "At each session, one of the following standardised airway clearance techniques...was performed in random order determined by computer-generated randomisation with concealed allocation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided Comment: Participants and therapist(s) were not likely to be blinded to group allocation. This may have influenced outcome measures of sputum volume and weight, dyspnoea, and participant-reported tiredness and discomfort
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided Comment: Outcome assessor(s) were not likely to be blinded to group allocation. This was unlikely to affect objective measures of gas exchange or spirometry, but could affect sputum volume and weight, dyspnoea scores, and participant-reported tiredness and discomfort
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: All participants completed the study, but data were not available for all reported outcomes
Selective reporting (reporting bias)	High risk	No report of spirometry measures or gas exchange included in results. Outcomes for Borg dyspnoea summarised in text All other measures outlined. No protocol was available.
Other bias	Unclear risk	No mention of washout period between interventions (consecutive days) and this may have influenced outcomes. Insufficient information provided

Guimaraes 2012

Methods	Randomised cross-over trial Study setting: medical department, Brazil Study duration: 24 days
Participants	10 adults (mean age 56 years) with stable bronchiectasis, with a persistent productive cough, diagnosis confirmed by HRCT (number of lobes affected and severity not reported), mean FEV_1 53% predicted
Interventions	Intervention 1: single session of oscillatory PEP therapy (Flutter), performed in a seated position for 15 minutes (breathing from total lung capacity until cough occurred), followed by 5 minutes coughing Intervention 2: single session of L-expiration Lente Totale Glotte Ouverte en Decubitus Lateral, with affected lung in the dependent position and the participant performing slow expirations with the glottis open from functional residual capacity to residual volume
Outcomes	Sputum dry weight (g) Spirometry (FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$) Static lung volumes (IC, VC, TLC, FRC, RV, RV/TLC, IC/TLC) All measurements were recorded immediately following completion of the intervention
Notes	1 week washout period between interventions Salbutamol and a series of 5 minutes of voluntary coughing were administered prior to commencing interventions No adverse events No study sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were submitted to the two interventions in a random order. Block randomisation sequences were created by a researcher not involved with recruitment, selection and assessments"
Allocation concealment (selection bias)	Low risk	Quote: "Sealed opaque envelopes containing patients' assignments were opened at the time of first treatment"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided. Comment: Participants and treating therapist(s) were not likely to be blinded to group allocation. This may have influenced outcome measures (spirometry, static lung volumes, and sputum dry weight)

Guimaraes 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided Comment: Outcome assessor(s) were not likely to be blinded to group allocation. As outcomes were objectively measured (spirometry, static lung volumes, and sputum dry weight), it is likely they were resistant to issues with blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All individuals tolerated and completed the steps in this study" Complete data were available for reported outcomes
Selective reporting (reporting bias)	Low risk	Protocol was available and all specified outcomes were reported
Other bias	Low risk	Adequate washout period was included. Quote: "Measurement of static lung volumes were conducted before the spirometry to avoid any residual effect of dynamic compression of the airways in the plethysmography results" Comment: Attempts were made to minimise the impact of multiple measures of lung function

Herrero-Cortina 2015

Methods	Randomised cross-over trial Study setting: tertiary hospital, Spain Study duration: one session per treatment, applied on non-consecutive days
Participants	31 adults (mean age 60 years) with stable bronchiectasis for previous 6 weeks, with mean daily sputum production > 15 ml, diagnosis confirmed by HRCT (number of lobes affected and severity not reported), mean FEV_1 63% predicted
Interventions	Intervention 1: single session of autogenic drainage, with breathing from lower lung volumes in the expiratory reserve volume through to higher lung volumes into the inspiratory reserve volume with an open glottis. Pauses were permitted between manoeuvres as necessary with spontaneous coughing. Total session time of 40 minutes, performed at same time of day Intervention 2: single session of L-expiration Lente Totale Glotte Ouverte en Decubitus Lateral, with the participant performing slow expirations with the glottis open from functional residual capacity to end expiratory reserve volume in both lateral positions. Pauses were permitted between manoeuvres as necessary with spontaneous coughing. Total session time of 40 minutes, performed at same time of day Intervention 3: single session of minimal PEP therapy, generating a pressure of 1 cmH_20 during breathing manoeuvres. Position used during this treatment was not stated. Pauses

	were permitted between manoeuvres as necessary with spontaneous coughing. Total session time of 40 minutes, performed at same time of day
Outcomes	Sputum wet weight (g) during treatment and over 24 hours following treatment Spirometry (FEV_1, FVC, $FEF_{25-75\%}$) Cough-related quality of life (Leicester Cough Questionnaire) Measurements for spirometry and cough-related quality of life were recorded immediately following intervention completion
Notes	1 week washout period between interventions No study sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Block randomisation was computer generated by an independent investigator"
Allocation concealment (selection bias)	Low risk	Quote: "The allocation was concealed" Comment: Although details of the allocation concealment method were not given, this was considered sufficient for low risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The same physiotherapist supervised/assisted each session to ensure treatment standardisation. Due to the nature of the intervention, neither participants nor physiotherapist were blinded to the intervention"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided Comment: Outcome assessor(s) were not likely to be blinded to group allocation. As some outcomes were objectively measured (spirometry, sputum wet weight), it is likely they were resistant to issues with blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two patients dropped out of the study due to acute low back pain and pulmonary exacerbation" Comment: data were available for all participants who completed the study
Selective reporting (reporting bias)	Low risk	Protocol was available and all specified outcomes were reported

Herrero-Cortina 2015 (*Continued*)

Other bias	Low risk	Quote: "There were no statistical differences in the total LCQ score and lung function between baseline of Session 1 and the end of the two washout periods, indicating no carryover effect" Comment: the washout period between interventions appeared to be adequate

Patterson 2005

Methods	Randomised cross-over trial Study setting: respiratory clinic, Northern Ireland Study duration: 2 days
Participants	20 adults (mean age 58 years) with stable bronchiectasis, productive of 1/2 egg cup of sputum per day, diagnosis confirmed by HRCT (number of lobes affected and severity not reported), mean FEV_1 64% predicted
Interventions	Intervention 1: Active cycle of breathing technique (ACBT) with thoracic expansion exercises, breathing control and forced expiration in two predetermined gravity-assisted drainage (GAD) positions with percussion and/or vibration. Treatment duration was either a maximum of 30 minutes (15 minutes per position), participant no longer expectorating sputum or participant was too fatigued to continue treatment Intervention 2: Oscillatory PEP therapy (Acapella) completed in two predetermined GAD positions. Treatment consisted of breathing control, 10 breaths through the Acapella, inhaling to 3/4 maximum breathing capacity, 2 to 3 second breath hold, active exhalation to functional residual capacity and cough or forced expiration in set cycle
Outcomes	Spirometry (FEV_1, FVC, PEF) pre and post treatment (10 minutes after completion) 15-count breathlessness score pre and post treatment (10 minutes after completion) Sputum weight (g) during treatment and 30 minutes post treatment
Notes	Prior to intervention, 1 day of 40 minutes training session was completed, to determine appropriate GAD position by auscultation, selection of correct Acapella device (green for participants able to sustain expiratory flow > 15 L/min for at least 3 seconds, blue for participants with an expiratory flow < 15 L/min), determination of the correct Acapella settings and training in ACBT and Acapella Each intervention was performed at the same time on 2 consecutive days. Short and/or long acting bronchodilators and steroids where applicable were administered 1 hour prior to treatment No washout period between interventions No study sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Patterson 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Treatment order was determined by a concealed computerised randomisation procedure"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment order was determined by a concealed computerised randomisation procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The same physiotherapist administered all treatment sessions Comment: It is likely that neither participants or treating therapist(s) were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "an independent assessor conducted pre and post treatment...measures of spirometric lung function, pulse oximetry and 15-count breathlessness score It is not clear if the independent assessor was blinded to treatment order. It is likely that some outcome measures were resistant to issues with blinding (spirometry, SpO_2) , but other measures (dyspnoea score) may not have been resistant
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All twenty patients...completed the study" Not all outcomes were provided
Selective reporting (reporting bias)	Unclear risk	Outcome related to breathlessness score was not provided. All other outcomes were provided
Other bias	High risk	Comment: treatments were performed on consecutive days, which allowed for no washout period

Semwal 2015

Methods	Randomised cross-over trial Study setting: respiratory or medicine clinic, India Study duration: 1 day
Participants	30 adults (mean age of males 46 years, mean age of females 49 years) with stable bronchiectasis, with history of productive cough, diagnosis not confirmed by HRCT, mean FEV_1 not reported)

Semwal 2015 (*Continued*)

Interventions	Intervention 1: Autogenic drainage. Participant seated and instructed to breathe at different lung volumes starting from low lung volumes, with a series of 10 to 20 breaths at low volumes until secretions were audible on auscultation. Participants then instructed to breathe at tidal volumes for a further 10 to 12 breaths, then breathe at vital capacity followed by cough. Treatment duration was 20 to 30 minutes Intervention 2: Oscillatory PEP therapy (Acapella) completed in unspecified position. Treatment consisted of 10 to 12 breaths through the Acapella, with a 2 to 3 second breath hold and exhalation. Cough or huff was performed every 10 breaths. Treatment duration was 20 to 30 minutes depending on participant requirements
Outcomes	PEF, immediately post and 10 minutes after treatment Borg score for breathlessness, immediately post and 10 minutes after treatment Sputum wet weight (g), immediately post and 10 minutes after treatment
Notes	Washout period of 3 hours between techniques No study sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: Title of paper indicated randomised cross-over trial. No information provided on nature of randomisation process
Allocation concealment (selection bias)	Low risk	Quote: "The patients were recruited for ether the chest physiotherapy technique Acapella or Autogenic Drainage via concealed envelope method" Comment: While limited detail was provided, the use of concealed envelopes indicated a low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided Comment: Participants and treating therapist(s) were not likely to be blinded to group allocation. This may have influenced outcome measures (spirometry, breathlessness, SpO_2, and sputum wet weight).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided Comment: Outcome assessor(s) were not likely to be blinded to group allocation. As outcomes were objectively measured (spirometry, breathlessness, SpO_2, and sputum wet weight), it is likely they were resistant to issues with blinding

Semwal 2015 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The total of thirty completed the study". Comment: Data were available for all 30 participants for each arm of the study
Selective reporting (reporting bias)	Low risk	Although no protocol was available, all outcomes were reported
Other bias	High risk	Comment: Treatments were performed within three hours of each other, which was a limited washout period for this type of intervention

Thompson 2002

Methods	Randomised cross-over trial Study setting: United Kingdom Study duration: 8 weeks
Participants	22 adults (median age ranging from 59 to 68 years), with stable bronchiectasis and diagnosis confirmed by HRCT (number of lobes affected and severity not reported), with median FEV_1 ranging from 0.67 to 0.70 L
Interventions	Intervention 1: Active cycle of breathing technique (ACBT) in a gravity-assisted drainage (GAD) positioning, performed twice daily at home until no further sputum was expectorated. GAD was used as necessary throughout Intervention 2: Oscillatory PEP therapy (Flutter), with the device tilted until maximum vibrations were felt within the chest to loosen the secretions with forced expiratory technique, performed twice daily at home until no further sputum was expectorated
Outcomes	Sputum weight (g) daily Spirometry (PEFR, FEV_1, FVC) pre and post intervention Dyspnoea score (Borg scale) pre and post intervention Health-related quality of life (Chronic Respiratory Questionnaire) at baseline and post 4 weeks intervention
Notes	Report of nausea in one participant when using the Flutter, no other adverse events reported No report of washout period between interventions Study sponsor: Frenchay Respiratory Research Fund

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "ACBT and the Flutter were each used unassisted at home for 4 weeks in a

Thompson 2002 (*Continued*)

		randomised crossover design" Comment: nothing was stated beyond the fact that the study was randomised Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Comment: Nothing was stated regarding concealment of assignment of participants to treatment order Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Before the ACBT arm each patient had a refresher session with the physiotherapist", "Before the Flutter arm they were instructed to tilt the device until maximum vibrations were felt within the chest" Comment: It was likely that neither participants or treating therapist(s) were blinded to the intervention, which may have affected outcome measures of (spirometry, sputum weight, dyspnoea and HRQOL scores)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Patients recorded the daily weight of sputum produced, PEFR and breathlessness scores" Comment: As participants were unlikely to be blinded to the intervention and were collecting some outcome measures, this may have affected these outcomes measures. It was not stated that personnel were blinded to other outcomes of spirometry and HRQOL scores, which may have affected these outcome measures
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Five of the 22 patients recruited to the study were withdrawn" Complete data were available for reported outcomes
Selective reporting (reporting bias)	Low risk	Although no protocol was available, all specified outcomes were reported
Other bias	Unclear risk	No washout period between intervention, which may have had impact on findings. Insufficient information provided

Tsang 2003

Methods	Randomised controlled trial Study setting: Hong Kong Study duration: from day 2 of admission until day of discharge (mean ranging from 6. 2 to 7.2 days)
Participants	15 adults (mean age ranging from 67 to 74 years), with acute exacerbation of bronchiectasis (presenting with symptoms of persistent cough and sputum production), diagnosis of bronchiectasis stated only as being of at least 1 year in duration, mean FEV_1 ranging from 36.1 to 48.5% predicted
Interventions	Intervention 1: two gravity-assisted drainage (GAD) positions, with position choice based on chest radiographs and auscultation. Breathing control every 3 minutes consisting of 5 slow, deep inspiratory breaths followed by relaxed expiration and a voluntary cough and normal relaxed breathing, repeated for 15 minutes Intervention 2: Oscillatory PEP therapy (Flutter) in a seated position. Angle of inclination set for maximal resonance of the chest wall. Cycle consisted of every 3 minutes, 5 deep breaths, expired through the Flutter, followed by a voluntary cough and breathing control, repeated for 15 minutes Each intervention was to be completed 3 times daily (one supervised, two unsupervised) , with coughing as necessary to expectorate sputum
Outcomes	Spirometry (FEV_1, FVC, PEFR) pre and post intervention on days 2, 4, and day of discharge Sputum wet weight (g) during 15 minutes intervention, 15 minutes post intervention and at 24 hours post intervention on days 2, 4 and day of discharge
Notes	No reports of adverse events No study sponsor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients recruited were randomised into...groups by drawing lots" Comment: nothing was stated beyond use of this method, it was not clear if this was sufficiently robust Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	Comment: Nothing was stated regarding concealment of assignment of participants Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "All protocols were carried out once per day, under the supervision of the same physiotherapist" Comment: This suggested that treating therapist(s) was not blinded to group

		allocation. Participants may also have been unblinded to group allocation which may have influenced selected outcomes of spirometry and sputum weight
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided Comment: Outcome assessor(s) were not likely to be blinded to group allocation. As outcomes were objectively measured (spirometry, static lung volumes, and sputum dry weight), it is likely they were resistant to issues with blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for all participants. Complete data were available for most outcomes
Selective reporting (reporting bias)	Low risk	Although no protocol was available, all specified outcomes were reported
Other bias	Unclear risk	No evidence of other bias

ACBT - active cycle of breathing technique; cmH2o - centimetres of water pressure; FEV_1 - forced expiratory volume in one second; $FEF_{25–75\%}$ - forced expiratory ratio in 25-75% of expiration; FVC - forced vital capacity; FRC - functional residual capacity; g - grams; GAD - gravity-assisted drainage; HRCT - high resolution computed tomography; IC - inspiratory capacity; IC/TLC - ratio of inspiratory capacity over total lung capacity; L - litres; LCQ - Leicester Cough Questionnaire; L/min - litres per minute; mL - millilitres; PEP - positive expiratory pressure; PEF - peak expiratory flow
PEFR - peak expiratory flow rate; RV - residual volume; RV/TLC - ratio of residual volume over total lung capacity; SpO_2 - percutaneous oxygen saturation; TLC - total lung capacity; VC - vital capacity.

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

Study	Reason for exclusion
Ambrosino 1995	Mixed disease sample, data for bronchiectasis not available (via correspondence with study author)
Amit 2012	Two types of PEP therapy compared
Andrejak 2013	No use of PEP therapy
Barbagallo 2012	No use of PEP therapy
Cecins 1999	No use of PEP therapy

(*Continued*)

Cegla 1993	Mixed disease sample, data for bronchiectasis not available (via correspondence with study authors)
Chakrovorty 2011	No inclusion of individuals with bronchiectasis
Conway 1992	No use of PEP therapy
Feng 1998	No comparison group
Figueiredo 2012	No comparison group (non-PEP ACT)
Furumoto 2008	No use of PEP therapy
Gastaldi 2011	No comparison group (non-PEP ACT)
Gokdemir 2013	No use of PEP therapy
Goldman 2004	No use of PEP therapy
Jao 2010	No use of PEP therapy
Kaminska 1988	Not randomised
Kubal 2013	Not randomised
Kurz 1997	No comparison group (non-PEP ACT)
Landau 1973	No use of PEP therapy
Lavery 2011	No use of PEP therapy
Maa 2007	No use of PEP therapy
Mandal 2012	No comparison group (non-PEP ACT)
Marques 2012	No use of PEP therapy
Messens 1973	No use of PEP therapy
Morgan 1999	Mixed disease group with data for individuals with bronchiectasis unable to be extracted
Murray 2009	No comparison group (non-PEP ACT)
Naraparaju 2010	No comparison group (non-PEP ACT)
NCT00452114	No use of PEP therapy
Newall 2005	No use of PEP therapy

(*Continued*)

Nicolini 2013	Data for PEP group (from mix of airway clearance techniques) not able to be extracted
Osadnik 2014	No inclusion of individuals with bronchiectasis
Patterson 2004	No use of PEP therapy
Patterson 2007	Data for usual airway clearance group (mix of techniques) not able to be individually extracted per technique
Pryor 1979	No use of PEP therapy
Punithavathi 2014	No use of PEP therapy
Richmond 2016	No comparison group
Santamaria 1998	No comparison group (non-PEP ACT)
Senthill 2015	PEP therapy combined with another technique
Shabari 2011	No comparison group (non-PEP ACT)
Silva 2015	Comparison of two types of oscillatory PEP therapy
Su 2012	Positive pressure therapy not meeting the definition applied in this review
Sunderram 2000	No use of PEP therapy
Svenningsen 2014	No comparison group (non-PEP ACT)
Syed 2009	No PEP therapy included
Tambascio 2011	Comparison of Oscillatory PEP therapy and PEP therapy
Tambascio 2014	No use of PEP therapy
Valente 2004	No comparison group (non-PEP ACT)
Venturelli 2012	Mixed disease sample, data for bronchiectasis not available (via correspondence with study author)
Vishteh 2011	Not randomised

Characteristics of studies awaiting assessment *[ordered by study ID]*

Fazzi 2010

Methods	Randomised cross-over trial
Participants	20 participants with stable bronchiectasis
Interventions	T-PEP (1 cmH_20) vs PEP therapy (mask) (20 cmH_20)
Outcomes	Distribution of ventilation (radioaerosol measurements)
Notes	Identified in 2015 search. Further information required to confirm appropriateness

NCT03013452

Methods	Randomised controlled trial
Participants	Individuals with bronchiectasis (confirmed by HRCT, sputum production most days of the year, stable chronic therapy in the last 4 weeks, FEV_1 = 70% predicted, aged 18 to 80 years)
Interventions	Autogenic drainage daily for 15 minutes each day, for 1 month vs Aerobika oPEP device daily for 15 minutes each day for 1 month
Outcomes	Lung clearance index, Total score on Quality of Life - Bronchiectasis, Score on respiratory domain on Quality of Life - Bronchiectasis, FEV_1, FVC
Notes	Identified in 2017 search. Further information required to confirm appropriateness

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

ACTRN12614001233617

Trial name or title	Does the bubble-positive expiratory pressure (PEP) device improve secretion clearance compared to the active cycle of breathing technique (ACBT) or no intervention (control) in people with non-cystic fibrosis bronchiectasis?
Methods	Randomised controlled trial
Participants	Diagnosis of bronchiectasis confirmed by HRCT, daily sputum production, ability to perform airway clearance technique
Interventions	Bubble-positive expiratory pressure (PEP) device (10-20 cm H_2O) vs Active cycle of breathing technique (ACBT)
Outcomes	Sputum weight, acceptability and perceived benefit of Bubble PEP therapy
Starting date	05/01/2015

ACTRN12614001233617 (*Continued*)

Contact information	mary.santos@sesiahs.health.nsw.gov.au
Notes	Identified in 2015 search. Further information required to confirm appropriateness

NCT01929356

Trial name or title	Chest Physiotherapy and Lung Function in Primary Ciliary Dyskinesia
Methods	
Participants	Diagnosis of primary ciliary dyskinesia, aged 6- 60 years
Interventions	Chest physiotherapy with PEP (positive expiratory pressure) device
Outcomes	FEV_1, Lung clearance index, multiple breath washout
Starting date	October 2013
Contact information	
Notes	Identified in 2015 search. Further information required to confirm appropriateness

NCT02324855

Trial name or title	Long-term Airway Clearance Therapy in Non-cystic Fibrosis Bronchiectasis
Methods	Randomised controlled trial
Participants	Chronic sputum production, two confirmed exacerbations in previous year, ability to understand and perform airway clearance therapy, clinically stable
Interventions	Usual medical care vs usual medical care and oscillatory PEP therapy
Outcomes	Leicester cough questionnaire, Quality of life - Bronchiectasis, exacerbation frequency, lung function, exercise capacity, inflammatory markers
Starting date	October 2015
Contact information	
Notes	Identified in 2015 search. Further information required to confirm appropriateness

NCT02411981

Trial name or title	Effects of Chest Physiotherapy (CPT) on Lung Clearance Index (LCI) in Non Cystic Fibrosis (CF) Bronchiectasis
Methods	
Participants	Diagnosis of non-cystic fibrosis bronchiectasis, clinically stable
Interventions	Autogenic drainage
Outcomes	Lung clearance index, FEV_1, $FEV_{25–75}$%, sputum weight
Starting date	April 2013
Contact information	
Notes	Identified in 2015 search. Further information required to confirm appropriateness

NCT02509637

Trial name or title	Acute Effects of a Flutter Device and Chest Wall Compression on Respiratory System Impedance in Bronchiectasis Patients
Methods	Randomsed controlled trial
Participants	Diagnosis of bronchiectasis (by HRCT and confirmed clinically), aged 30 to 80 years
Interventions	Oscillatory PEP therapy (Flutter) vs Chest compression intervention
Outcomes	Respiratory system impedance, difficulty in expectorating sputum, dry and wet weight of sputum, oxygen saturation, dyspnoea, acceptability and tolerance, adhesiveness of expectorated sputum
Starting date	August 2015
Contact information	
Notes	Identified in 2016 search. Further information required to confirm appropriateness

NCT02906826

Trial name or title	Adherence to Airway Clearance. Novel Approaches to Improving Adherence
Methods	
Participants	Diagnosis of bronchiectasis, confirmed by HRCT or chest radiograph, aged 6 to 12 years, previous use of PEP therapy, clinically stable, willingness to adhere to treatment
Interventions	No monitoring of adherence vs monitoring of adherence of use of PEP therapy

NCT02906826 (*Continued*)

Outcomes	Rate of adherence to prescribed therapy, FEV_1
Starting date	August 2016
Contact information	mmcilwaine@cw.bc.ca
Notes	Identified in 2017 search. Further information required to confirm appropriateness

DATA AND ANALYSES

Comparison 1. Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRQ Dyspnoea score	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 CRQ Fatigue score	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 CRQ Mastery score	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4 CRQ Emotional function score	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5 CRQ Total score	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 2. Oscillatory PEP therapy vs ACBT with GAD (single session)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sputum weight (g)	2		Std. Mean Difference (Random, 95% CI)	Totals not selected
2 Sputum volume (ml)	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
3 Fatigue	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
4 Discomfort	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 3. Oscillatory PEP therapy vs ACBT (single session)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sputum weight (g)	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
2 Sputum volume (ml)	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
3 Fatigue	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
4 Discomfort	1		Std. Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 4. Oscillatory PEP vs GAD during acute exacerbation

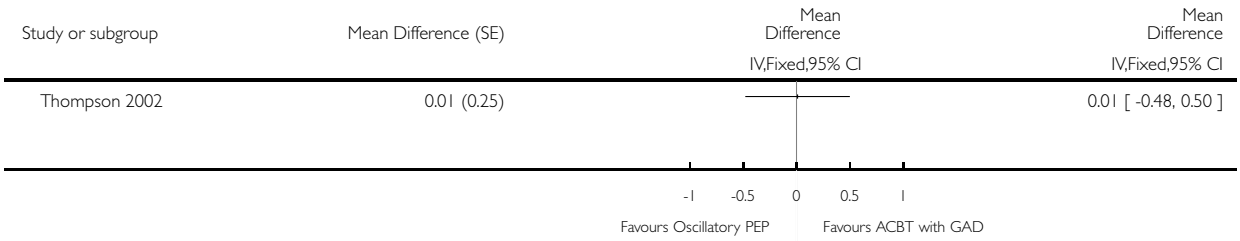
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sputum weight (over 24 hours) Day 2 of admission	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Sputum weight (over 24 hours) Day 4 of admission	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Sputum weight (over 24 hours) Day of Discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 FEV1 (Day 2 of admission)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 FEV1 (Day 4 of admission)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 FEV1 (Day of Discharge)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 FVC (Day 2 of admission)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 FVC (Day 4 of admission)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 FVC (Day of Discharge)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 PEFR (Day 2 of admission)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 PEFR (Day 4 of admission)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 PEFR (Day of Discharge)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks), Outcome 1 CRQ Dyspnoea score.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks)

Outcome: 1 CRQ Dyspnoea score

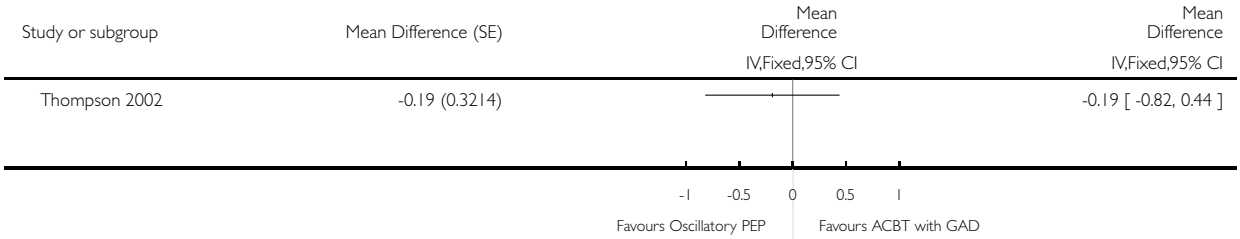


Analysis 1.2. Comparison 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks), Outcome 2 CRQ Fatigue score.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks)

Outcome: 2 CRQ Fatigue score

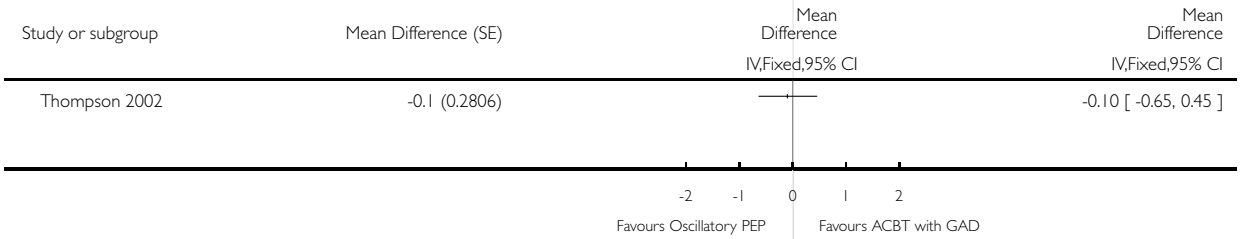


Analysis 1.3. Comparison 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks), Outcome 3 CRQ Mastery score.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks)

Outcome: 3 CRQ Mastery score

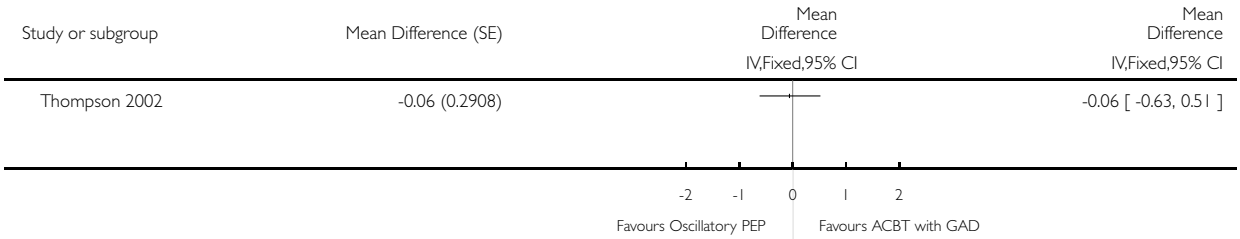


Analysis 1.4. Comparison 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks), Outcome 4 CRQ Emotional function score.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks)

Outcome: 4 CRQ Emotional function score

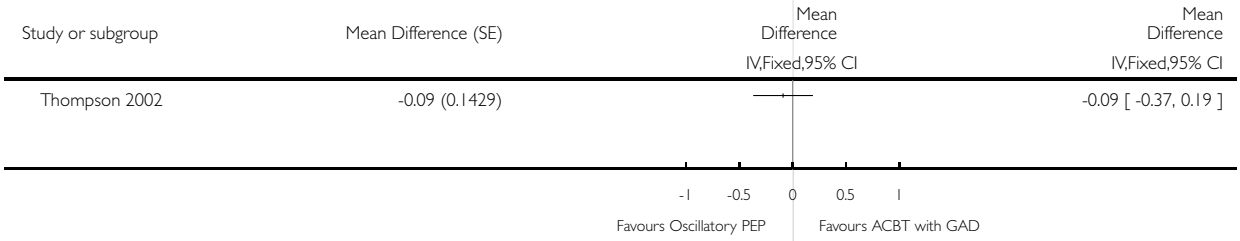


Analysis 1.5. Comparison 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks), Outcome 5 CRQ Total score.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 1 Oscillatory PEP therapy (Flutter) vs ACBT with GAD (4 weeks)

Outcome: 5 CRQ Total score

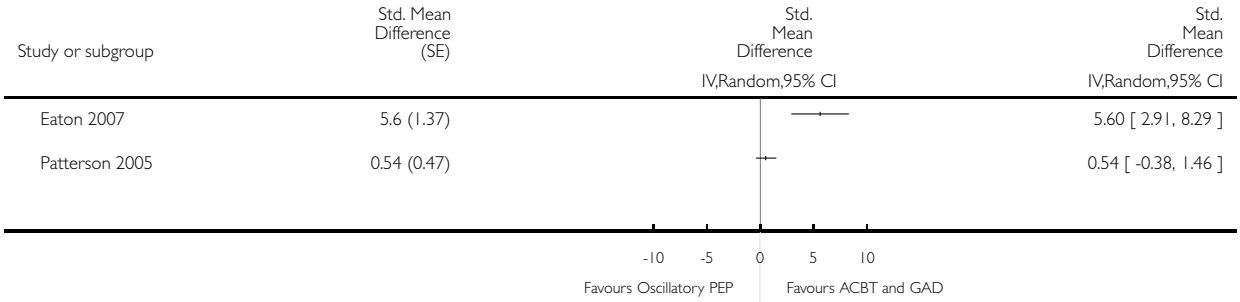


Analysis 2.1. Comparison 2 Oscillatory PEP therapy vs ACBT with GAD (single session), Outcome 1 Sputum weight (g).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 2 Oscillatory PEP therapy vs ACBT with GAD (single session)

Outcome: 1 Sputum weight (g)

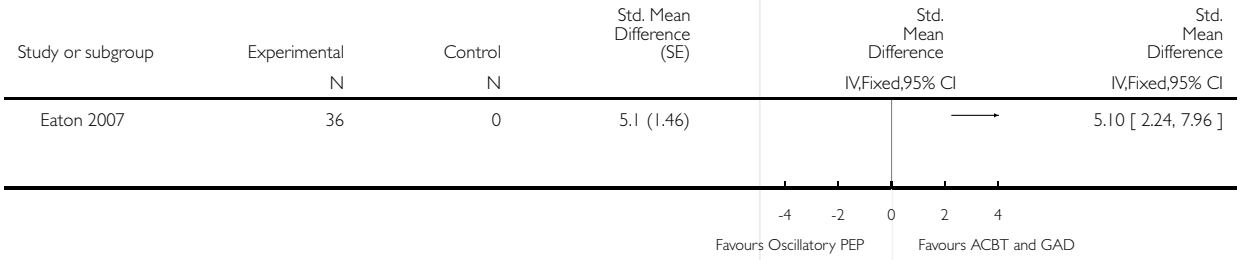


Analysis 2.2. Comparison 2 Oscillatory PEP therapy vs ACBT with GAD (single session), Outcome 2 Sputum volume (ml).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 2 Oscillatory PEP therapy vs ACBT with GAD (single session)

Outcome: 2 Sputum volume (ml)

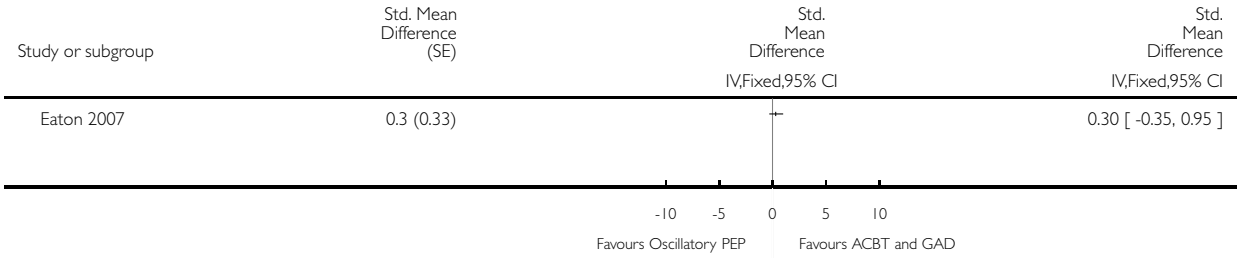


Analysis 2.3. Comparison 2 Oscillatory PEP therapy vs ACBT with GAD (single session), Outcome 3 Fatigue.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 2 Oscillatory PEP therapy vs ACBT with GAD (single session)

Outcome: 3 Fatigue

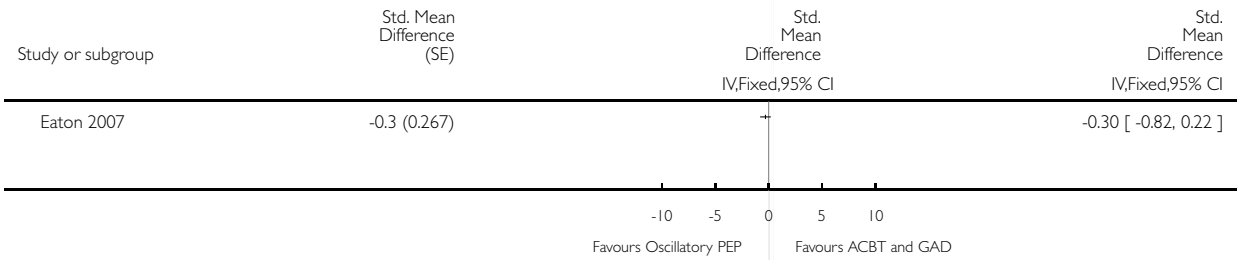


Analysis 2.4. Comparison 2 Oscillatory PEP therapy vs ACBT with GAD (single session), Outcome 4 Discomfort.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 2 Oscillatory PEP therapy vs ACBT with GAD (single session)

Outcome: 4 Discomfort

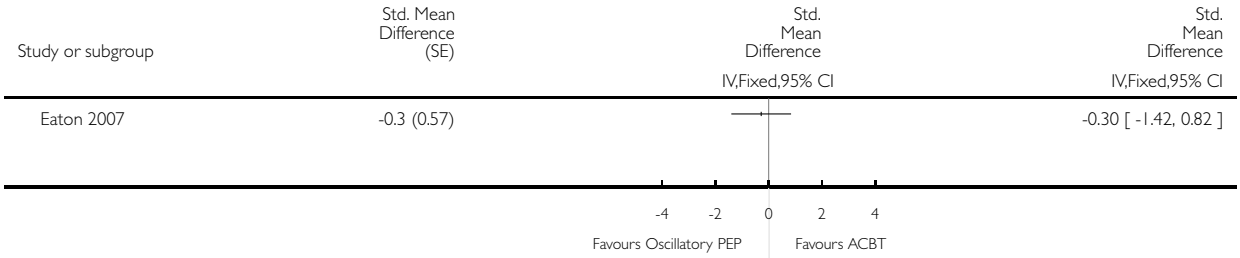


Analysis 3.1. Comparison 3 Oscillatory PEP therapy vs ACBT (single session), Outcome 1 Sputum weight (g).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 3 Oscillatory PEP therapy vs ACBT (single session)

Outcome: 1 Sputum weight (g)

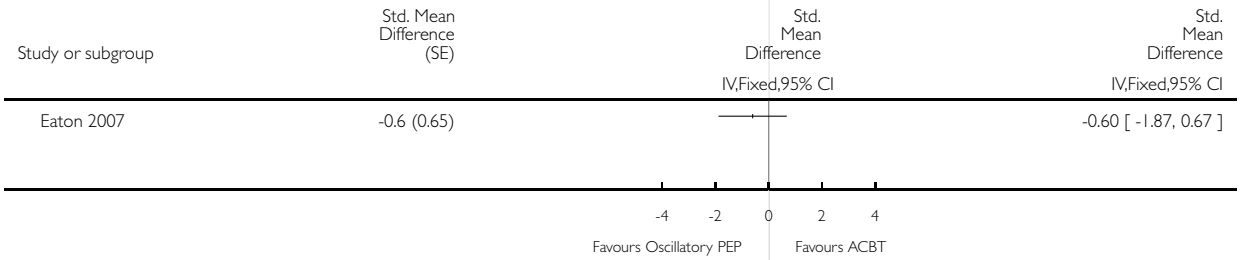


Analysis 3.2. Comparison 3 Oscillatory PEP therapy vs ACBT (single session), Outcome 2 Sputum volume (ml).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 3 Oscillatory PEP therapy vs ACBT (single session)

Outcome: 2 Sputum volume (ml)

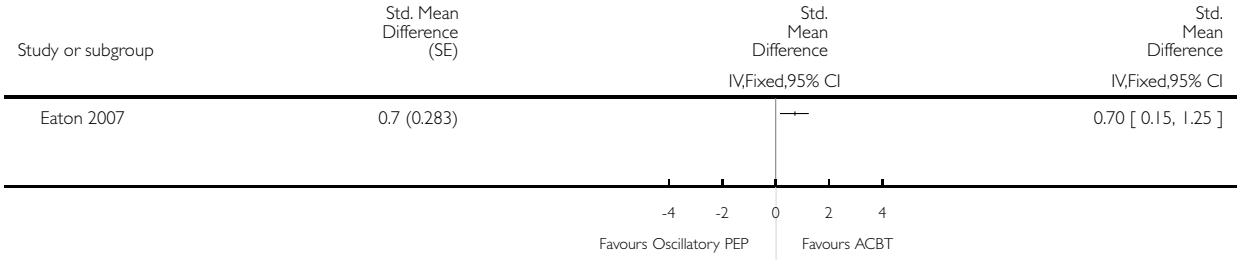


Analysis 3.3. Comparison 3 Oscillatory PEP therapy vs ACBT (single session), Outcome 3 Fatigue.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 3 Oscillatory PEP therapy vs ACBT (single session)

Outcome: 3 Fatigue

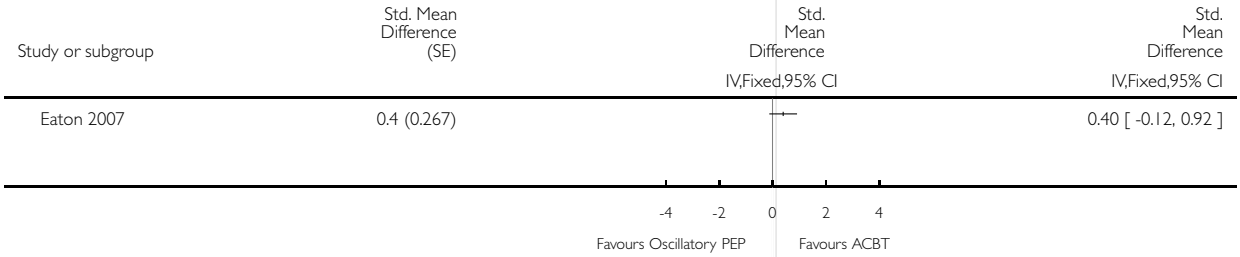


Analysis 3.4. Comparison 3 Oscillatory PEP therapy vs ACBT (single session), Outcome 4 Discomfort.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 3 Oscillatory PEP therapy vs ACBT (single session)

Outcome: 4 Discomfort



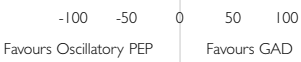
Analysis 4.1. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 1 Sputum weight (over 24 hours) Day 2 of admission.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 1 Sputum weight (over 24 hours) Day 2 of admission

Study or subgroup	Experimental N	Mean(SD)[g]	Control N	Mean(SD)[g]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Tsang 2003	5	45.34 (26.48)	5	25.48 (17.47)		19.86 [-7.95, 47.67]



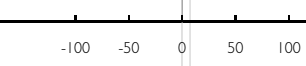
Analysis 4.2. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 2 Sputum weight (over 24 hours) Day 4 of admission.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 2 Sputum weight (over 24 hours) Day 4 of admission

Study or subgroup	Experimental N	Mean(SD)[g]	Control N	Mean(SD)[g]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Tsang 2003	5	36.35 (35.67)	5	13.89 (12.64)		22.46 [-10.71, 55.63]



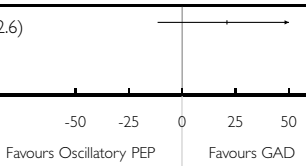
Analysis 4.3. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 3 Sputum weight (over 24 hours) Day of Discharge.

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 3 Sputum weight (over 24 hours) Day of Discharge

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[g]	N	Mean(SD)[g]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	34.99 (34.65)	5	13.96 (12.6)		21.03 [-11.29, 53.35]



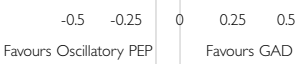
Analysis 4.4. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 4 FEV1 (Day 2 of admission).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 4 FEV1 (Day 2 of admission)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	0.76 (0.47)	5	0.64 (0.16)		0.12 [-0.32, 0.56]



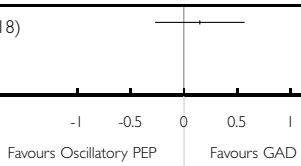
Analysis 4.5. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 5 FEV1 (Day 4 of admission).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 5 FEV1 (Day 4 of admission)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	0.79 (0.44)	5	0.64 (0.18)		0.15 [-0.27, 0.57]



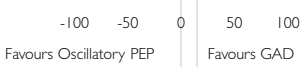
Analysis 4.6. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 6 FEV1 (Day of Discharge).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 6 FEV1 (Day of Discharge)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	1.19 (68)	5	1.07 (0.28)		0.12 [-59.48, 59.72]



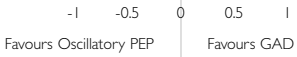
Analysis 4.7. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 7 FVC (Day 2 of admission).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 7 FVC (Day 2 of admission)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	0.92 (0.42)	5	1.14 (0.52)		-0.22 [-0.81, 0.37]



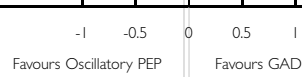
Analysis 4.8. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 8 FVC (Day 4 of admission).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 8 FVC (Day 4 of admission)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	1.26 (0.72)	5	1.06 (0.29)		0.20 [-0.48, 0.88]



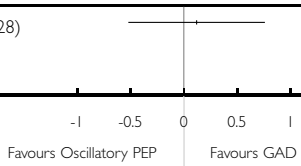
Analysis 4.9. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 9 FVC (Day of Discharge).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 9 FVC (Day of Discharge)

Study or subgroup	Experimental N	Mean(SD)[L]	Control N	Mean(SD)[L]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Tsang 2003	5	1.19 (0.68)	5	1.07 (0.28)		0.12 [-0.52, 0.76]



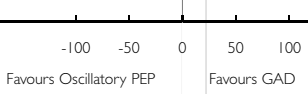
Analysis 4.10. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 10 PEFR (Day 2 of admission).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 10 PEFR (Day 2 of admission)

Study or subgroup	Experimental N	Mean(SD)[L]	Control N	Mean(SD)[L]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Tsang 2003	5	136 (70.17)	5	113.8 (35.59)		22.20 [-46.76, 91.16]



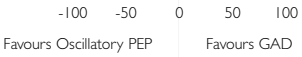
Analysis 4.11. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 11 PEFR (Day 4 of admission).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 11 PEFR (Day 4 of admission)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	131.4 (54.38)	5	108.8 (47.5)		22.60 [-40.69, 85.89]



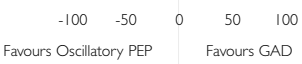
Analysis 4.12. Comparison 4 Oscillatory PEP vs GAD during acute exacerbation, Outcome 12 PEFR (Day of Discharge).

Review: Positive expiratory pressure therapy versus other airway clearance techniques for bronchiectasis

Comparison: 4 Oscillatory PEP vs GAD during acute exacerbation

Outcome: 12 PEFR (Day of Discharge)

Study or subgroup	Experimental		Control		Mean Difference	Mean Difference
	N	Mean(SD)[L]	N	Mean(SD)[L]	IV,Fixed,95% CI	IV,Fixed,95% CI
Tsang 2003	5	141.2 (49.65)	5	118 (51.59)		23.20 [-39.56, 85.96]



ADDITIONAL TABLES

Table 1. Individual study outcomes for HRQOL

Study name	Number of participants	Comparison	Results
Thompson 2002	17	Oscillatory PEP therapy vs ACBT with GAD	**Disease-specific QOL** Dyspnoea domain: MD 0.01 (95% CI -0.48 to 0.50) Fatigue domain: MD -0.19 (95% CI -0.82 to 0.45) Emotional function domain: MD -0.06 (95% CI -0.63 to 0.52) Mastery domain: MD -0.10 (95% CI -0.65 to 0.46)
Altiay 2012	36	Oscillatory PEP therapy vs ACBT (daily for 4 weeks)	Improved general health on SF-36 (P = 0.048) with PEP therapy
Herrero-Cortina 2015	31	Minimal PEP therapy vs AD Minimal PEP therapy vs ELTGOL	**Cough-related quality of life (LCQ)** median 0.4 (95% CI 0.1 to 1.2) vs 0.5 (95% CI 0.1 to 0.5) median 0.4 (95% CI 0.5 to 2.1) vs 0.9 (95% CI 0.1 to 1.2)

ACBT - active cycle of breathing technique; AD - autogenic drainage; CI - confidence interval; ELTGOL - L'expiration Lente Totale Glotte Ouverte en Decubitus Lateral; LCQ - Leicester cough questionnaire; MD - mean difference; PEP - positive expiratory pressure; QOL - quality of life; SF-36 - short form 36.

Table 2. Individual study outcomes for sputum yield

Study	Number of participants	Comparison	Results
Antunes 2001	10	Oscillatory PEP therapy (Flutter) vs ELTGOL	dry weight (MD 0.28 g (SD 0.28) vs 0.16 g (0.06)), P > 0.05 wet weight (MD 7.2 g (SD 2.3) vs 6.3 g (0.7)), P > 0.05
Thompson 2002	17	Oscillatory PEP therapy (Flutter) vs ACBT with GAD	median difference 7.64 g, P = 0.77
Tsang 2003	10	Oscillatory PEP therapy (Flutter) vs GAD	Day 2: MD 19.86 g (95% CI -7.95 to 47.67) Day 4: MD 22.46 g (95% CI -10.71 to 55.63) Day of discharge: MD 21.03 g (95% CI -11.29 to 53.35)

Table 2. Individual study outcomes for sputum yield (*Continued*)

Patterson 2005	20	Oscillatory PEP therapy (Acapella) vs ACBT with GAD	MD 0.54 g (95% CI -0.39 to 1.46)
Eaton 2007	36	Oscillatory PEP therapy (Flutter) vs ACBT Oscillatory PEP therapy (Flutter) vs ACBT with GAD	MD 0.3 g (95% CI -1.42 to 0.82) MD -5.6 g (95% CI -10.1 to -1.0)
Guimaraes 2012	10	Oscillatory PEP therapy (Flutter) vs ELTGOL	median 0.15 g (minimum to maximum 0.05 to 0.13 g) vs 0.38 g (0.06 to 2.63 g)
Herrero-Cortina 2015	31	Minimal PEP therapy vs AD Minimum PEP therapy vs ELTGOL	median difference 3.1 g (95% CI 1.5 to 4.8 g) median difference 3.6 g (95% CI 2.8 to 7.1 g)
Semwal 2015	30	Oscillatory PEP therapy vs AD	mean 15.8 g (SD 5.7) vs 16.2 g (7.9)

ACBT - active cycle of breathing technique; AD - autogenic drainage; CI - confidence interval; ELTGOL - L'expiration Lente Totale Glotte Ouverte en Decubitus Lateral; g - grams; GAD - gravity assisted drainage; MD - mean difference; PEP - positive expiratory pressure; SD - standard deviation.

Table 3. Individual study outcomes for lung function

Study	Number of participants	Comparison	Results
Antunes 2001	10	Oscillatory PEP therapy (Flutter) vs ELTGOL	Day 1 PEFR: mean 405 L/min (SD 157) vs 439 L/min (175) Day 2 PEFR: 434 L/min(150) vs 417 L/min (134) Day 3 PEFR: 428 L/min(166) vs 419 L/min (157) Day 4 PEFR: 456 L/min(159) vs 462 L/min (185)
Thompson 2002	17	Oscillatory PEP therapy (Flutter) vs ACBT with GAD	PEFR morning: median difference -2.5 L/min, P = 0.38) PEFR evening: median difference -2.72 L/min (95% CI -6.95 to 1.52), P = 0.30
Tsang 2003	10	Oscillatory PEP therapy (Flutter) vs GAD	Day 2 FEV_1: MD 0.12 L (95% -0.32 to 0.56) Day 4 FEV_1: MD 0.15 L (95% CI -0.27 to 0.57)

Table 3. Individual study outcomes for lung function (*Continued*)

			Day of discharge FEV_1: (MD 0.12 L (95% CI -0.52 to 0.76) Day 2 FVC: MD -0.22 L (95% CI -0.81 to 0.37) Day 4 FVC: MD 0.2 L (95% CI -0.48 to 0.88) Day of discharge: FVC MD 0.12 L (95% CI -0.52 to 0.76) Day 2 PEFR: MD 22.2 L/min (95% CI -48.88 to 93.28) Day 4 PEFR: MD 22.6 L/min (95% CI -40.69 to 85.89) Day of discharge PEFR: MD 23.2 L/min (95% CI -39.56 to 85.96)
Patterson 2005	20	Oscillatory PEP therapy (Acapella) vs ACBT with GAD	FEV_1: mean (SD) 65 (22) % predicted vs 65 (22) FVC: 81 (20) % predicted vs 81 (20) PEF: 68 (19) L/min vs 70 (18)
Altiay 2012	36	Oscillatory PEP therapy (Flutter) vs ACBT	No difference between techniques, MD NR
Guimaraes 2012	10	Oscillatory PEP therapy (Flutter) vs ELTGOL	FEV_1: median 1.6 L (minimum to maximum -6.8 to 21.4) vs 2.2 L (-20.2 to 20.9) FVC: median 2.44 L (minimum to maximum -3.9 to 8.1) vs 0.96 L (-11.8 to 22.1) FEV_1/FVC: median 0.7 L (minimum to maximum -11.3 to 19.6) vs 0.0 L (-8.6 to 10.6) FEF_{25-75}: median 4.5 L (minimum to maximum -21.4 to 160.0) vs 6.0 (-90.51 to 236) Change in IC: median 3.5 L (minimum to maximum 28.5 to 33.8) vs 2.7 (-15.7 to 27.7) Change in TLC: median -18.3 L (minimum to maximum -42.4 to -6.4) vs 9.7 (-40.0 to -1.9) Change in FRC: median -25.8 L (minimum to maximum -52.0 to -5.1) vs -14.5 L (-55.7 to -3.6) Change in RV (median -29.6 L (minimum to maximum -54.7 to -8.9) vs -18.7 L (-71.9 to -10.7) Change in RV/TLC ratio (median -5.

Table 3. Individual study outcomes for lung function (*Continued*)

			2 L (minimum to maximum -22.8 to 27.6) vs -8.5 L (-25.5 to 113.0)
Herrero-Cortina 2015	31	Minimal PEP therapy vs ELTGOL	FEV_1, FVC, FEF_{25-75} remain unchanged between techniques, MD NR, P > 0.05
Semwal 2015	30	Oscillatory PEP therapy (Acapella) vs AD	PEFR: mean 176.1 L/min (SD 72.6) vs 179.1 (72.6), P = 0.87

ACBT - active cycle of breathing technique; AD - autogenic drainage; ELTGOL - L'expiration Lente Totale Glotte Ouverte en Decubitus Lateral; FEF 25-75 - forced expiratory flow at 25 to 75% of forced vital capacity; FEV_1 - forced expiratory volume in one second; FRC - functional residual capacity; FVC - forced vital capacity; GAD - gravity assisted drainage; IC - inspiratory capacity; L - litres; L/min - litres per minute; MD - mean difference; NR - not reported; PEFR - peak expiratory flow rate; PEP - positive expiratory pressure; RV - residual volume; SD - standard deviation; TLC - total lung capacity.

Table 4. Individual study outcomes for symptoms

Study	Number of participants	Comparison	Results
Thompson 2002	17	Oscillatory PEP therapy (Flutter) vs ACBT with GAD	Borg dyspnoea scale morning: MD 0.13 (95% CI -0.078 to 0.34), P = 0.36 Borg dyspnoea scale evening: median difference -0.04, P > 0.99
Patterson 2005	20	Oscillatory PEP therapy (Acapella) vs ACBT with GAD	15-count breathlessness score: MD NR
Eaton 2007	36	Oscillatory PEP therapy (Flutter) vs ACBT with GAD Oscillatory PEP therapy (Flutter) vs ACBT	Fatigue: MD -0.3 points (95% CI -0.35 to 0.95) Discomfort: MD -0.3 points (95% CI -0.82 to 0.22) Fatigue: MD 0.7 points (95% CI 0.15 to 1.25) Discomfort: MD 0.40 points (95% CI -0.12 to 0.92)
Altiay 2012	36	Oscillatory PEP therapy (Flutter) vs ACBT	Borg and Medical Research Council scores: no difference between techniques, MD NR
Semwal 2015	30	Oscillatory PEP therapy (Acapella) vs AD	mean 1.8 (SD 1.1) vs 1.8 (1.2), P = 1.00

ACBT - active cycle of breathing technique; AD - autogenic drainage; CI - confidence interval; GAD - gravity assisted drainage; MD - mean difference; NR - not reported; PEP - positive expiratory pressure.

APPENDICES

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

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 Positive-Pressure Respiration Explode All
#6 positive* NEAR expirat*
#7 PEP:ti,ab
#8 Hi-PEP:ti,ab
#9 *PEP:ti,ab
#10 VRP1
#11 flutter*
#12 acapella*
#13 cornet*
#14 quake*
#15 resistance* NEAR breath*
#16 desitin*
#17 scandipharm*
#18 flute*

#19 *oscillat*
#20 high* NEAR pressur*
#21 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 #4 and #21
[Note: In line #1, MISC1 denotes field in which the reference has been coded for condition, in this case, bronchiectasis]

Appendix 3. Search terms used in PEDro database

'bronchiectasis',
'Kartegener*'
'Agammaglobulinaemia'.

CONTRIBUTIONS OF AUTHORS

Initiated the protocol: AL

Developed the protocol: AL, AB, and AH.

Undertook literature search and retrieved papers: AL

Screened retrieved papers against eligibility criteria: AL and AB.

Appraised quality of papers: AL and AB.

Extracted data: AL and AB.

Wrote to study authors for additional information: AL.

Entered data into RevMan: AL.

Performed analysis: AL.

Wrote review: AL, reviewed manuscript: AB and AH.

Served as guarantor of the review: AL.

DECLARATIONS OF INTEREST

AL: none known.

AB: none known.

AH: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The term non-cystic fibrosis bronchiectasis has been altered to bronchiectasis, to align with recent recommendations.