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Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis (Review)

McIlwaine M, Button B, Dwan K

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TABLE OF CONTENTS

[Intervention Review]

Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis

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ABSTRACT

Background

Chest physiotherapy is widely prescribed to assist the clearance of airway secretions in people with cystic fibrosis. Positive expiratory pressure (PEP) devices provide back pressure to the airways during expiration. This may improve clearance by building up gas behind mucus via collateral ventilation and by temporarily increasing functional residual capacity. Given the widespread use of PEP devices, there is a need to determine the evidence for their effect. This is an update of a previously published review.

Objectives

To determine the effectiveness and acceptability of PEP devices compared to other forms of physiotherapy as a means of improving mucus clearance and other outcomes in people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising of references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. The electronic database CINAHL was also searched from 1982 to 2013.

Most recent search of the Group's Cystic Fibrosis Trial Register: 02 December 2014.

Selection criteria

Randomised controlled studies in which PEP was compared with any other form of physiotherapy in people with cystic fibrosis. This included, postural drainage and percussion, active cycle of breathing techniques, oscillating PEP devices, thoracic oscillating devices, bilevel positive airway pressure (BiPaP) and exercise. Studies also had to include one or more of the following outcomes: change in forced expiratory volume in one second; number of respiratory exacerbations; a direct measure of mucus clearance; weight of expectorated secretions; other pulmonary function parameters; a measure of exercise tolerance; ventilation scans; cost of intervention; and adherence to treatment.

Data collection and analysis

Three authors independently applied the inclusion and exclusion criteria to publications and assessed the risk of bias of the included studies.

Main results

A total of 26 studies (involving 733 participants) were included in the review. Eighteen studies involving 296 participants were cross-over in design. Data were not published in sufficient detail in most of these studies to perform any meta-analysis. These studies compared PEP to active cycle of breathing techniques (ACBT), autogenic drainage (AD), oral oscillating PEP devices, high frequency chest wall oscillation (HFCWO) and Bi level PEP devices (BiPaP) and exercise.

Forced expiratory volume in one second was the review's primary outcome and the most frequently reported outcome in the studies. Single interventions or series of treatments that continued for up to three months demonstrated no significant difference in effect between PEP and other methods of airway clearance on this outcome. However, long-term studies had equivocal or conflicting results regarding the effect on this outcome. A second primary outcome was the number of respiratory exacerbations. There was a lower exacerbation rate in participants using PEP compared to other techniques when used with a mask for at least one year. Participant preference was reported in 10 studies; and in all studies with an intervention period of at least one month, this was in favour of PEP. The results for the remaining outcome measures were not examined or reported in sufficient detail to provide any high-level evidence. The only reported adverse event was in a study where infants performing either PEP or postural drainage with percussion experienced some gastro-oesophageal reflux. This was more severe in the postural drainage with percussion group. Many studies had a risk of bias as they did not report how the randomisation sequence was either generated or concealed. Most studies reported the number of dropouts and also reported on all planned outcome measures.

Authors' conclusions

Following meta-analyses of the effects of PEP versus other airway clearance techniques on lung function and patient preference, this Cochrane review demonstrated that there was a significant reduction in pulmonary exacerbations in people using PEP compared to those using HFCWO in the study where exacerbation rate was a primary outcome measure. It is important to note, however, that there may be individual preferences with respect to airway clearance techniques and that each patient needs to be considered individually for the selection of their optimal treatment regimen in the short and long term, throughout life, as circumstances including developmental stages, pulmonary symptoms and lung function change over time. This also applies as conditions vary between baseline function and pulmonary exacerbations.

However, meta-analysis in this Cochrane review has shown a significant reduction in pulmonary exacerbations in people using PEP in the few studies where exacerbation rate was a primary outcome measure.

PLAIN LANGUAGE SUMMARY

Using positive expiratory pressure physiotherapy to clear the airways of people with cystic fibrosis

Review question

We reviewed the evidence on the effect of positive expiratory pressure (PEP) physiotherapy to clear the airways of people with cystic fibrosis.

Background

Cystic fibrosis affects approximately one in 3000 Caucasians and causes frequent infection, as the airways get blocked with mucus. Chest physiotherapy is often used to try to clear the mucus out of the lungs. We wanted to discover whether using a PEP device, which is one form of chest physiotherapy, was better or worse than other other forms of chest physiotherapy for clearing the mucus out of the lungs in people with cystic fibrosis. A PEP device provides positive pressure behind the mucus to try to push it out of the lungs. This is an update of a previously published review.

Search date

The evidence is current to 02 December 2014**.**

Study characteristics

The review includes 26 studies with 733 people with cystic fibrosis ranging from six to 47 years of age and with mild to severe lung disease. The studies compared PEP to other methods of chest physiotherapy with length of treatment varying from a single physiotherapy session to two years of treatment.

Key results

In general, the efficacy of PEP is similar to other methods of chest physiotherapy such as postural drainage with percussion, active cycle of breathing techniques, autogenic drainage, oscillatory PEP devices such as the flutter and acapella, thoracic oscillating devices such as the 'Vest', and BiPaP which is a type of PEP system delivering both positive inspiratory and expiratory pressure. We found no difference in lung function; the amount of mucus cleared from the airways or its related effects on the health of people with cystic fibrosis between PEP and other forms of chest physiotherapy. However, there was a decrease in the rate of flare ups of respiratory symptoms in people

using PEP compared to other forms of physiotherapy such as a vibrating PEP device or a vibrating vest. There was some evidence that people with cystic fibrosis may prefer PEP to other chest physiotherapy methods. There was no evidence of PEP causing harm, except in a study with infants, where infants performing either PEP or percussion performed in various positions which use gravity to help drain secretions, experienced some gastro-oesophageal reflux (regurgitation of food). This was more severe in the group using postural drainage with percussion.

In 10 of the 26 studies, the effects of PEP were only studied during a single treatment. The results from these studies are very limited as they could not report on the number of respiratory infections and lung function did not change with just one treatment. Two studies, each lasting one year, compared PEP to postural drainage and percussion; in the study with children, PEP improved their lung function, while in the adult study, lung function declined slightly with both PEP and postural drainage and percussion. Also the method of performing PEP was different in the two age groups.

In conclusion, although PEP seems to have an advantage in reducing flare ups (based on the combined results of a few studies), different physiotherapy techniques and devices may be more or less effective at varying times and in different individuals during baseline function and chest flare ups. Each person should talk to their clinician to help choose which method of airway clearance is best for them and which they will adhere to, so as to provide the best quality of life and long-term outcomes.

Quality of the evidence

Some studies were of low quality. These studies highlight the difficulty in comparing studies using PEP compared to other forms of chest physiotherapy. Factors such as age and severity of lung disease in the participants may affect the results as well as the method of performing each treatment.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a relatively common, inherited, life-limiting disorder. The genetic defect causes abnormal mucus secretion in the airways, potentially leading to airway obstruction and mucus plugging (Zach 1990). This predisposes the airways to infection and inflammation, which in turn promote further mucus secretion. Persistent infection and inflammation within the lungs are the major contributory factors to airway damage and the progressive loss of respiratory function (Cantin 1995; Konstan 1997).

Description of the intervention

Treatment methods which improve mucus clearance are considered essential in optimising respiratory status and reducing the progression of lung disease. A variety of methods are used, some physical, e.g. airway clearance techniques, and some chemical, e.g. inhaled medications.

Airway clearance techniques (also referred to as chest physiotherapy) are widely prescribed to assist the clearance of airway mucus and usually commenced as soon as the diagnosis of CF is made. Traditionally, airway clearance consisted of postural drainage (gravity-assisted drainage positions) combined with percussion and vibration (performed by an assistant such as a physiotherapist or relative), and forced expirations (huffing and coughing). Some protocols included deep breathing exercises. This form of airway clearance is time-consuming and sometimes uncomfortable. It also requires assistance, which may have an adverse effect on adherence. Recently, several self-administered alternatives that are able to be used in upright sitting positions have been developed. Among these are a range of positive expiratory pressure (PEP) devices, which provide a back pressure to the airways during expiration.The most common method of using PEP was defined by the Danes and is known as the, "PEP technique" (Falk 1984). It consists of breathing through a flow-dependant PEP device attached to a face mask with a closed system creating a PEP of between 10 to 20 cm H_20 for 12 to 15 breaths. The PEP mask is then removed from the individual's face and he or she then performs two to three huffing manoeuvres (also known as a forced expiration). For the purposes of this paper we have included studies using pressures between 8 to 20 cm H_2O. Another method of using PEP devices is defined by Oberwaldner in Austria and is known as, "High Pressure PEP" (Hi-PEP). In Hi-PEP, the expiratory pressure may be reach 40 to 100 cm H_20. Hi-PEP also incorporates forced expiratory manoeuvres through the PEP device, which generates higher pressures and may stimulate coughing through the mask (Oberwaldner 1986).

How the intervention might work

A theory is that PEP devices are able to improve clearance by increasing gas pressure behind mucus via collateral ventilation and a temporary increase in functional residual capacity (FRC). The FRC level is gradually increased over the 12 to 15 breaths. The forced expiratory manoeuvres then assist the movement of mucus from the peripheral airways centrally to where they can be expectorated (Andersen 1979; Groth 1985). It has also been hypothesised that Hi-PEP may stabilise airways by splinting them open during expiration, which may facilitate airway clearance (Oberwaldner 1986).

Why it is important to do this review

A Cochrane systematic review comparing any form of chest physiotherapy with no chest physiotherapy found evidence to demonstrate the benefit of chest physiotherapy for increasing mucus transport, but did not find evidence for any long-term outcomes (Warnock 2013). Several narrative reviews have compared different types of chest physiotherapy, including PEP, with conflicting conclusions (McIlwaine 1996; Prasad 1993; Prasad 2000; Williams 1994; Zach 1987). This review will examine the effect and acceptability of PEP compared to other techniques used for secretion clearance.

The most effective technique for secretion clearance during an infective exacerbation of CF may differ from that which is most effective for maintenance therapy. The PEP technique is also used in combination with various other interventions (e.g. pharmacological therapies, other physical therapy techniques, or a modification to the PEP technique.). It is therefore important to establish the effect of PEP in each stage of CF lung disease with and without co-interventions. This review is an update of previously published versions of the Cochrane review (Elkins 2004; Elkins 2006).

OBJECTIVES

To determine the effect of PEP on the clearance of airway secretions compared to other airway clearance techniques in people with CF and test the following hypotheses:

1. PEP improves outcomes for people with CF more than other airway clearance techniques;
2. PEP is more acceptable to people with CF than other airway clearance techniques.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled studies.This included both parallel and cross-over designs. Blinding was not a determinate for inclusion since participants could not be blinded as to which technique they were performing. Eligible studies included both individual and cluster randomised designs.

Types of participants

People with CF, of any age, diagnosed on the basis of clinical criteria and sweat testing or genotype analysis, with any degree of disease severity. People with CF, post-lung transplant, were excluded.

Types of interventions

In the existing literature, variation occurs in the application of each individual airway clearance technique. For example; when using PEP as an airway clearance technique, some people perform 12 breaths through the device, whereas others perform 15 breaths. This may be followed by two or three forced expiratory manoeuvres. As separate analyses of variations within each technique would render this review unmanageable, it has been necessary to group these variations within broad definitions of the established treatment modalities.

One of the interventions used in the studies will be required to meet one of the two following descriptions.

1. PEP mask, or mouthpiece as described by the authors, with or without additional techniques. Originally, PEP was defined as breathing with a positive expiratory pressure of 10 to 20 cm H_2O (Falk 1984).
2. High pressure PEP (Hi-PEP) mask therapy as described by the authors, with or without additional techniques. Hi-PEP includes a full forced expiration against a fixed mechanical resistance which usually generates pressures ranging from 40 to 100 cm H_2O (Oberwaldner 1986).

At least one comparator intervention used in the studies will be required to meet one of the following descriptions.

1. Postural drainage with percussion and vibration (PDPV) - in other reviews this has been described as conventional chest physiotherapy (CCPT).
2. Active cycle of breathing techniques (ACBT) - this comprises relaxation or breathing control, forced expiration technique (FET), thoracic expansion exercises and may include postural drainage or percussion.
3. Autogenic drainage (AD) - this breathing technique uses high expiratory flow rates at varying lung volumes to enhance mucous clearance while avoiding airway closure.
4. Oral oscillatory devices - include flutter, cornet, acapella and intrapulmonary percussive ventilation. The flutter, cornet and acapella devices produce an oral oscillatory PEP effect within the airways. Intrapulmonary percussive ventilation provides continuous oscillation of the air pressure in the airways via the mouth.
5. Thoracic oscillating devices - these include Thairapy Vest®, InCourage system, Smart vest, and the Hiyak Oscillator which provide external chest wall oscillation.
6. BiPaP - a bilevel PEP system which delivers both inspiratory and expiratory positive pressure.
7. Exercise - prescribed for the purpose of airway clearance either independently or as an adjunct to other techniques.

Types of outcome measures

Primary outcomes

1. Forced expiratory volume at one second (FEV_1) (change in FEV_1 between baseline and post-intervention; litre and per cent (%) predicted values are both stated wherever possible)
2. Number of respiratory exacerbations between baseline and post-intervention (respiratory exacerbations must have been defined either by symptoms or by initiation of antibiotics for respiratory symptoms after medical assessment)
3. Direct measures of mucus clearance (mucus transport rate or mucociliary clearance rate as assessed by radioactive tracer)

Secondary outcomes

1. Expectorated secretions, dry or wet weight, or volume (an increase in the amount of expectorated secretions as a short-term (less than seven days) effect of the intervention is considered as beneficial; in long-term studies this outcome variable will not be included)
2. Other pulmonary parameters (post-intervention change from baseline)
   a. forced vital capacity (FVC)
   b. forced expiratory flow 25-75% (FEF_{25-75})
   c. total lung capacity (TLC)
   d. residual volume (RV)
   e. functional residual capacity (FRC)
3. Exercise tolerance (subjective exercise tolerance, or objective measures such as six-minute walk test)
4. Well-being (quality of life scales such as the CF Quality of Life scale, or ability to participate in activities of daily living using instruments such as the HAES (Habitual Activity Estimation Scale)
5. Blood oxygen levels (measured by arterial blood gas, pulse oximetry or transcutaneous oximetry)
6. Lung clearance index (LCI)
7. Ventilation scanning (radiological or nuclear medicine imaging)
8. Cost of intervention (equipment and duration)
9. Adherence to treatment or participant preference (may be determined either as the nominated technique of choice by the participant at the conclusion of the study, or by a comparison of technique acceptability (e.g. visual analogue scales))
10. Adverse effects (such as pneumothorax, hemoptysis, deaths or other adverse changes in condition from baseline)

Search methods for identification of studies

Electronic searches

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the terms: positive expiratory pressure

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis.* Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module

We performed an additional search of the electronic database CINAHL from 1982 to 2013. For the full search strategy, please see the appropriate additional table (Appendix 1).

Date of the most recent search of the Cystic Fibrosis Trials Register: 02 December 2014.

Searching other resources

The review authors contacted manufacturers of PEP devices regarding any additional studies. The authors contacted other centres where studies on PEP were being undertaken. Authors of included studies were contacted to see if they knew of any unpublished studies. References of included studies were also checked for any further relevant studies.

Data collection and analysis

Selection of studies

Three authors independently reviewed all citations and abstracts identified by the search to determine which papers should be included. The authors resolved disagreements by discussion and consensus.

Data extraction and management

Three authors independently extracted data for each of the outcome measures listed above. Where studies were published in insufficient detail, the review authors contacted the study authors with a request to provide the required data. The authors used the Cochrane Collaboration software (Review Manager) to compile and analyse the data (Review Manager 2014).

For all included studies, the authors recorded the following details where possible: criteria for diagnosis of CF; methods of participant selection; and baseline characteristics of the active and placebo groups including age, sex, genotype and lung function.

Assessment of risk of bias in included studies

Three authors independently assessed the risk of bias using text from study reports to make judgements of high, low or unclear risk for six features of a study (Higgins 2003). These include: random sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other types of bias. The authors resolved any disagreements through discussion. The review authors used both published data and additional data obtained from study authors in determining whether criteria were met.

Measures of treatment effect

For continuous outcomes, the review authors recorded either the mean change from baseline for each group or mean post-treatment or intervention values and the standard deviation (SD) for each group. The authors combined data using the mean difference (MD) and 95% confidence intervals (CIs).

In the case of binary outcomes, the authors combined the data from the studies using risk ratios (RR) and 95% CIs.

Unit of analysis issues

None of the included studies were cluster randomised.

Elbourne discusses methods for meta-analysing cross-over studies (Elbourne 2002). These methods rely on the data that are reported within the primary paper. The authors have adopted a method within this review which uses the data from the first period only, ignoring any data from the second period that was available if a carryover effect was identified. If the authors did not identify a carryover effect and the papers reported data sufficiently, then the review authors planned to use the methods stated by Elbourne (Elbourne 2002).

When a study included multiple interventions, the review authors included each in the relevant comparison, as specified in the data synthesis section below.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors collected data on the number of participants with each outcome event by allocated treated group irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded for treatment or follow up.

The authors contacted the primary investigators of the included studies for any additional data they thought were missing.

Assessment of heterogeneity

If the authors had been able to include adequate numbers of studies, they would have looked for heterogeneity between studies. The authors planned to assess this visually in the forest plots and using the I^2 statistic which describes the percentage of total variation across studies that are due to heterogeneity rather than chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that the authors planned to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) (Higgins 2003). They will also consider the Chi^2 test with a P value less than 0.10 indicating significant heterogeneity, although the authors will be cautious with interpretation due to the low power of this test.

Assessment of reporting biases

The authors planned to construct a funnel plot if there were sufficient studies (i.e. 10) to assess publication bias. If the funnel plot is asymmetrical then they will consider other reasons as well as publication bias, i.e. heterogeneity, small study effects and outcome reporting bias.

The authors planned to assess outcome reporting bias in the risk of bias section, by comparing protocols, if available, to the study reports, or comparing the methods section to the results section with knowledge of the clinical area.

Data synthesis

The authors have analysed the data using a fixed-effect model. If, in the future, they are able to include more studies and they identify a moderate or high degree of heterogeneity, as defined above, they will use a random-effects model in the data analysis.

Different interventions were analysed separately. In this update, the comparisons include:

- PEP compared with postural drainage, percussion and vibration;
- PEP compared with oscillating PEP;
- PEP compared with high frequency chest wall oscillation (HFCWO).

The authors analysed studies in which the intervention consists of a single treatment separately from those studies in which a course of treatments is used. Within the latter group, the authors analysed studies of up to seven days treatment separately from studies of longer duration. The authors grouped outcome data from longer-term studies (more than seven days) into those measured at one, three, six, 12 months, and annually thereafter. If studies recorded outcome data at other time periods, then the authors considered examining these as well.

Subgroup analysis and investigation of heterogeneity

To investigate any heterogeneity identified, the authors planned to perform separate subgroup analyses based on the following factors: a PEP level of 8 to 20 cm H_2O; a PEP level of over 20 cm H_2O as used in Hi-PEP; disease state (exacerbation versus stable); use of co-interventions (positioning, other airway clearance techniques); age (paediatric, adolescent, adult); gender; and disease severity (FEV_1% predicted greater than 90%, 70% to 90%, 40% to 69%, less than 40%).

Sensitivity analysis

The authors planned to test the robustness of their results by performing sensitivity analyses such as excluding studies that were at high risk of bias for blinding and using the random-effects model if they detected a moderate or high degree of heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Studies awaiting classification.

Results of the search

The search retrieved 100 citations which represented 61 studies. No extra studies were identified with the CINAHL search or through contacting manufacturers of PEP devices.

A total of 26 studies involving 733 participants met the inclusion criteria; 19 were published as full articles (Braggion 1995; Darbee 2004; Darbee 2005; Fainardi 2011; Falk 1984; Hofmeyr 1986; Lagerkvist 2006; Lannefors 1992; McIlwaine 1997; McIlwaine 2001; McIlwaine 2013; Mortensen 1991; Newbold 2005; Pfleger 1992; Pryor 2010; Steen 1991; Tyrrell 1986; van Asperen 1987; van Winden 1998). Seven studies were published in abstract form only (Costantini 2001; Darbee 1990; Falk 1993; Gaskin 1998; Kofler 1998; McIlwaine 1991; Tannenbaum 2005).

A total of 29 studies are listed as excluded.

Six studies are awaiting assessment as they have been published in abstract form only; the study design or outcome data have been reported in insufficient detail to determine whether the inclusion criteria have been met (Elkins 2005; Parreira 2008; Kofler 1994; Rodriguez 2013; West 2010; Wong 2000).

Included studies

Additional data were obtained from the authors of nine of the studies (Costantini 2001; Darbee 1990; Gaskin 1998; Kofler 1998; McIlwaine 1991; McIlwaine 1997; McIlwaine 2001; Tyrrell 1986; van Asperen 1987).

Trial design

Among the 26 included studies, 733 participants were involved, with sample sizes in individual studies ranging from five (Darbee 2004) to 107 participants (McIlwaine 2013). Ten of these studies had more than two treatment arms (i.e. more than one comparator to PEP).

Ten were single treatment studies (Darbee 2005; Darbee 2004; Fainardi 2011; Falk 1984; Falk 1993; Kofler 1998; Lagerkvist 2006; Lannefors 1992; Mortensen 1991; Pfleger 1992). In two studies the duration of each treatment arm was less than seven days (Braggion 1995; Hofmeyr 1986). In the remaining 14 studies, the duration of each treatment arm ranged from two weeks to two years (Costantini 2001; Darbee 1990; Gaskin 1998; McIlwaine 1997; McIlwaine 1991; McIlwaine 2001; McIlwaine 2013; Newbold 2005; Pryor 2010; Tannenbaum 2005; Steen 1991; Tyrrell 1986; van Asperen 1987; van Winden 1998).

Eighteen of the included studies, involving 296 participants, were cross-over studies. The four studies conducted in participants experiencing a respiratory exacerbation all used a cross-over design with a duration of one or two days in each arm (Braggion 1995; Darbee 2005; Fainardi 2011; Hofmeyr 1986). Data from the end of the first period were obtained for three of the 18 cross-over studies (Darbee 1990; Tyrrell 1986; van Asperen 1987), but could not be obtained for the remaining 15 studies, although analysis was made on all available data (Braggion 1995; Darbee 2004; Darbee 2005; Fainardi 2011; Falk 1984; Falk 1993; Hofmeyr 1986; Kofler 1998; Lagerkvist 2006; Lannefors 1992; McIlwaine 1991; Mortensen 1991; Pfleger 1992; Steen 1991; van Winden 1998). Six studies had a washout period between techniques which ranged from two days to eight weeks (Darbee 2004; Lagerkvist 2006; Lannefors 1992; McIlwaine 1991; Mortensen 1991; van Winden 1998).

One study was a multicentre study involving nine CF centres in Canada (McIlwaine 2013).

Participants

One study was conducted exclusively with infants under four months of age (Costantini 2001). Eight studies were conducted exclusively with children between the ages of six years and 18 years of age (Lagerkvist 2006; McIlwaine 1991; McIlwaine 1997; McIlwaine 2001; Tannenbaum 2005; Tyrrell 1986; van Asperen 1987; van Winden 1998). Four studies were conducted exclusively in adults (Darbee 1990; Fainardi 2011; Newbold 2005; Pryor 2010). Twelve studies combined paediatric and adult participants; only one of these provided data for any age subgroup independently (Gaskin 1998). One study did not report the age of the participants (Falk 1993).

The gender of the participants was reported in 21 of the included studies involving 660 participants (Braggion 1995; Costantini 2001; Darbee 1990; Darbee 2004; Fainardi 2011; Falk 1984; Gaskin 1998; Hofmeyr 1986; Kofler 1998; Lagerkvist 2006; Lannefors 1992; McIlwaine 1997; McIlwaine 2001; McIlwaine 2013; Mortensen 1991; Newbold 2005; Pfleger 1992; Tannenbaum 2005; Tyrrell 1986; Pryor 2010; van Winden 1998). One had an even gender ratio (Braggion 1995), but most had more male than female participants, resulting in an overall male: female ratio of 3:2.

Four cross-over studies were conducted in participants experiencing a respiratory exacerbation with a duration of one or two days in each arm; hence they provide limited evidence for the effect of PEP for treatment of an exacerbation (Braggion 1995; Darbee 2005; Fainardi 2011; Hofmeyr 1986). Three studies did not report any measure of disease severity of the included participants. A total of 23 studies reported the FEV_1% predicted values of participants at baseline. In two of these studies, FEV_1 values were only in the moderate to severe range (less than 70% predicted) (Darbee 2004; Falk 1984). The remaining 21 studies included participants with a wide range of lung function impairment, most

commonly from severe to normal (less than 40% to greater than 90% predicted). Those studies reporting Shwachman scores as a measure of disease severity also included participants with a wide range of scores.

Interventions

In two of the included studies, the intervention included a full forced expiration against a fixed mechanical resistance at pressures greater than 20 cm H_2O and thus met the definition of Hi-PEP (Darbee 2004; Pfleger 1992).

Eight studies (n = 207) compared PEP with postural drainage, percussion and vibration (PDPV) (Braggion 1995; Costantini 2001; Darbee 1990; Falk 1984; Gaskin 1998; McIlwaine 1997; Tyrrell 1986; van Asperen 1987). Six studies (n = 224) compared PEP with oscillating PEP (flutter and cornet) (Lagerkvist 2006; McIlwaine 2001; Newbold 2005; Pryor 2010; Darbee 2005; van Winden 1998). Fours studies (n = 174) compared PEP with high frequency chest wall oscillation (Braggion 1995; Darbee 2005; Fainardi 2011; McIlwaine 2013). In nine cross-over studies, PEP was compared to a variety of different airway clearance techniques.

Outcome measures

Individual outcomes are reported for each PEP comparison, with FEV_1 being reported in 24 studies. One of the two studies who did not report FEV_1 used $FEV_{0.75}$ (Tyrrell 1986) and the second study was on infants (Costantini 2001). Lung clearance index was used in two studies (Darbee 2005; Tannenbaum 2005). More details on the reported outcomes can be found in the characteristics tables (Characteristics of included studies).

Excluded studies

A total of 27 studies were excluded from the review.

Three studies did not compare PEP to a physical airway clearance technique (Aquino 2006; Falk 1988; Laube 2000) and in a further six studies, neither of the interventions was PEP (Aquino 2012; Kraemer 1996; Liedtke 1996; Oermann 2001; Patel 2013; Roos 1987). Eight studies were excluded as the PEP technique used did not meet the definition of PEP for this review; two used underwater tubing (Balestri 2004; Battistini 2001), two used a flow-independant PEP device (Padman 1999; van der Schans 1991), three did not include huffing (McCarren 2006; Placidi 2001; Sanchez Riera 1999) and one was positive end-expiratory pressure and not PEP (Dosman 2003). In five studies, PEP versus other airway clearance techniques was not the randomised intervention (Borka 2012; Fitzgerald 2001; Marks 1998; Orlik 2000; Znotina 2000). Two studies did not report any data in their published papers for outcomes of interest in this review (Castle 1994; Gotz 1995). Two studies recruited participants not eligible for this review; one study was performed on post-transplant individuals (Munro 2007) and one on people with chronic bronchitis (van Hengstum 1987). One study compared the timing of dornase alfa in relation to PEP therapy (Fitzgerald 2005).

Studies awaiting classification

Eight studies are currently awaiting classification and will be fully assessed at the next update of the review (Elkins 2005; Grzincich 2008; Kofler 1994; Parreira 2008; Rodriguez 2013; Tonnesen 1982; West 2010; Wong 2000).

Risk of bias in included studies

Allocation

Sequence generation

Three studies described the randomisation procedure (Fainardi 2011; McIlwaine 2013; Pryor 2010) and were considered to have a low risk of bias. In the remaining 23 studies, the participants were described as being randomly allocated to groups (in those that were cross-over in design, to treatment order), but no further details were provided; these studies were therefore at an unclear risk of bias.

Allocation concealment

In three studies the allocation was concealed (i.e., the person who determined if a participant was eligible for inclusion in the study was unaware, when this decision was made, to which group the participant would be allocated) and these three studies were therefore deemed at low risk of bias (McIlwaine 2001; McIlwaine 2013; Newbold 2005). None of the remaining 23 studies discussed the method of allocation concealment and thus were deemed to have an unclear risk of bias.

Blinding

Due to the nature of the therapy, the participants in each of the studies were aware of which group they had been allocated to. All studies were therefore at a high risk of bias. Also, after randomisation occurred, the person applying the therapy knew which group the participants were allocated to.

In eight of the studies the person assessing at least one outcome measure did not know which group the participants had been allocated to and they were therefore deemed to be at a low risk of bias (Fainardi 2011; Falk 1984; McIlwaine 1997; McIlwaine 2001; McIlwaine 2013; Mortensen 1991; Newbold 2005; Pryor 2010). For self-reported outcomes (e.g., visual analogue scale, pain diary), the assessor is only considered to be blinded if the participant was blinded. No other study reported on who was blinded and are judged to have an unclear risk of bias.

Incomplete outcome data

In 19 studies, the measures of at least one key outcome at one time point were obtained from more than 85% of the participants initially allocated to groups (Darbee 1990; Darbee 2005; Fainardi 2011; Falk 1984; Gaskin 1998; Hofmeyr 1986; Kofler 1998; Lagerkvist 2006; Lannefors 1992; McIlwaine 1991; McIlwaine 1997; McIlwaine 2013; Mortensen 1991; Newbold 2005; Pfleger 1992; Steen 1991; Pryor 2010; Tannenbaum 2005; van Winden 1998).

In five studies, all participants, for whom outcome measures were available, received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention-to-treat" (Falk 1984; Gaskin 1998; Lagerkvist 2006; McIlwaine 2013; Pryor 2010). This criterion is satisfied (even if there is no mention of analysis by intention-to-treat) if the report explicitly states that all participants received treatment or control conditions as allocated. Intention-to-treat analysis was explicitly mentioned in two studies (McIlwaine 2013; Pryor 2010); however, 13 participants in the Pryor study withdrew as they did not like the intervention they had been randomised to; it is unclear if these participants were included in the intention-to-treat group (Pryor 2010). In the 2013 McIlwaine

study, 16 participants withdrew after randomisation but prior to initiation of study therapy regimens, these participants were not included in the intention-to-treat analysis (McIlwaine 2013). In the 2001 McIlwaine study, three participants dropped out from the PEP group due to non-compliance while five participants dropped out from the flutter group as they believed that the flutter was ineffective in clearing their secretions (McIlwaine 2001). It is unclear whether these participants were included in the analysis. In the Tyrrell study, three out of 19 participants were excluded due to non-adherence (Tyrrell 1986). The risk of bias is low in the first two studies (McIlwaine 2013; Pryor 2010) and unclear in the last two studies (McIlwaine 2001; Tyrrell 1986).

Selective reporting

The results of between-group statistical comparisons are reported for all outcomes in 11 studies (Darbee 2004; Darbee 2005; Fainardi 2011; Falk 1984; Falk 1993; Lagerkvist 2006; McIlwaine 2001; McIlwaine 2013; Mortensen 1991; Newbold 2005; van Winden 1998). The results of between-group statistical comparisons are reported for at least one key outcome in 13 studies (Darbee 1990; Gaskin 1998; Hofmeyr 1986; Kofler 1998; Lannefors 1992; McIlwaine 1991; McIlwaine 1997; Pfleger 1992; Pryor 2010; Tannenbaum 2005; Steen 1991; Tyrrell 1986; van Asperen 1987). Two studies did not report any between group statistical comparisons (Braggion 1995; Costantini 2001).

In 25 studies the following are provided, either:
(a) point measures and measures of variability for at least one continuous outcome; or
(b) the number of participants in each category for at least one categorical outcome; or
both (a) and (b) (Costantini 2001; Darbee 1990; Darbee 2004; Darbee 2005; Fainardi 2011; Falk 1984; Falk 1993; Gaskin 1998; Hofmeyr 1986; Kofler 1998; Lagerkvist 2006; Lannefors 1992; McIlwaine 1991; McIlwaine 1997; McIlwaine 2001; McIlwaine 2013; Mortensen 1991; Newbold 2005; Pfleger 1992; Pryor 2010; Steen 1991; Tannenbaum 2005; Tyrrell 1986; van Asperen 1987;van Winden 1998). The risk of bias for these studies is low. In one study neither (a) or (b) were provided (Braggion 1995). In this study the risk of bias was assessed as high.

Other potential sources of bias

In one study, no information was provided regarding similarities at baseline (unclear risk of bias) (Costantini 2001). In the remaining 25 studies, the groups were similar at baseline regarding the most important prognostic indicators (i.e. based on at least one measure of the severity of CF and one outcome measure at baseline, the groups' outcomes would not be expected to differ by a clinically significant amount), which indicates a low risk of bias.

There were 18 studies of cross-over design which has the potential to increase the risk of bias. Eight studies were of one or two days in duration, with no washout period, which may be a potential source of bias (Braggion 1995; Darbee 2005; Fainardi 2011; Falk 1984; Falk 1993; Hofmeyr 1986; Kofler 1998; Pfleger 1992). Cross-over studies of longer duration have a higher risk of bias and in these 10 studies, there were three which lasted one month and had no washout period between techniques (Steen 1991; Tyrrell 1986; van Asperen 1987).

There are relatively few meetings for reporting research about CF; however, it is possible that some studies may have been published or presented as abstracts at physiotherapy conferences that do not appear on online searches.

Effects of interventions

PEP compared with postural drainage, percussion and vibration (PDPV)

Eight studies included in this review (n = 207) make comparisons of PEP versus conventional physiotherapy (PDPV) for CF (Braggion 1995; Costantini 2001; Darbee 1990; Falk 1984; Gaskin 1998; McIlwaine 1997; Tyrrell 1986; van Asperen 1987). These comparisons are also made by the Cochrane review 'Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis' (Main 2005).

Primary outcomes

1. Forced expiratory volume at one second (FEV_1)

Five studies measured FEV_1 (Braggion 1995; Darbee 1990; Gaskin 1998; McIlwaine 1997; van Asperen 1987) (Analysis 1.1).

a. Short-term (up to seven days)

One study measured FEV_1 after four treatments of PEP, postural drainage with undefined chest physiotherapy techniques, or flutter over two days and found no significant differences in FEV_1 (Braggion 1995). This was a cross-over study from which data from the end of the first randomisation arm could not be obtained.

b. Long-term studies (more than seven days)

Four studies measured FEV_1 after a series of treatments over more than seven days (Darbee 1990; Gaskin 1998; McIlwaine 1997; van Asperen 1987) (Analysis 1.1). Results are reported as change in % predicted for FEV_1. No significant differences in FEV_1 were demonstrated after one month of PEP or PDPV, MD 0.60% predicted (95% CI -6.33 to 7.53) (van Asperen 1987), or after three months of PEP or PDPV, MD -0.50% predicted (95% CI -3.68 to 2.68) (Darbee 1990).

Two studies lasted at least one year (Gaskin 1998; McIlwaine 1997). In the one year study of children and adolescents, FEV_1 improved by a mean of 5.98% predicted for the PEP group, while in the PDPV group it deteriorated by 2.28% predicted, this was a significant difference favouring PEP, MD 8.26 (95% CI 0.76 to 15.76) (McIlwaine 1997). However, in a two-year study, predominately in adults, no significant difference in the rates of decline in FEV_1 were reported between the PEP group and the PDPV group, with mean annual declines of 2.76% predicted and 2.11% predicted, respectively, MD -0.65 (95% CI -3.25 to 1.95) (Gaskin 1998).

One cross-over study reported participants being withdrawn due to exacerbations, although these are not well-defined (van Asperen 1987). It is also unclear which treatments the participants were randomised to at the time of departure.

2. Number of respiratory exacerbations between baseline and post-intervention

No studies reported on this outcome.

3. Direct measures of mucus clearance

One study measured radio-labelled aerosol clearance after a single treatment of PEP and found no significant difference in clearance

between PEP and PDPV (Darbee 1990). This was a cross-over study from which data from the end of the first randomisation arm could not be obtained so no data have been entered into the review.

Secondary outcomes

1. Expectorated secretions, dry or wet weight, or volume

Three cross-over studies reported measures of expectorated sputum (Braggion 1995; Falk 1984; van Asperen 1987).

a. Single treatment

One study found that wet weight of sputum during and for 50 minutes after PEP (whether in sitting or PD positions) was greater than that induced by PDPV or pursed lip breathing (Falk 1984), this is presented in an additional table (Table 1).

b. Short-term (up to seven days)

No significant difference in expectorated secretions was identified between the treatment groups, measured by sputum volume (van Asperen 1987). No significant difference in wet or dry weight of sputum was identified between PEP and PDPV or HFCC and no further data were available (Braggion 1995).

c. Long-term (more than seven days)

As outlined in the Types of outcome measures section, this review does not examine this outcome where it is measured after more than seven days of treatment.

2. Other pulmonary parameters

a. forced vital capacity (FVC)

Six studies measured FVC (Darbee 1990; Falk 1984; Gaskin 1998; McIlwaine 1997; Tyrrell 1986; van Asperen 1987) (Analysis 1.2; Analysis 1.3).

i. Single treatment

One study measured FVC after a single treatment (Tyrrell 1986;). After a single treatment with PEP or PDPV, no significant difference in FVC was demonstrated, MD 1.90 (95% CI -4.96 to 8.76) (Tyrrell 1986).

ii. Short-term (up to seven days)

After two days of twice-daily treatment, FVC significantly increased in a group performing PEP in sitting and significantly decreased in a group performing PDPV (Falk 1984). This is presented in an additional table (Table 2).

iii. Long-term (more than seven days)

Five studies measured FVC after a series of treatments over more than seven days (Darbee 1990; Gaskin 1998; McIlwaine 1997; Tyrrell 1986; van Asperen 1987). After one month of twice-daily treatments with PEP or PDPV, no significant difference in FVC was found in adolescents (Tyrrell 1986), or in children and adolescents (van Asperen 1987). Meta-analysis of these two studies indicated a significant difference in favour of PDPV, MD -4.18 (95% CI -12.92 to 4.56) (Tyrrell 1986; van Asperen 1987) (Analysis 1.2). Results are reported as change in % predicted for FVC. No significant difference in FVC was demonstrated after three months of PEP or PDPV, MD 2.09 (95% CI -5.46 to 9.64) (Darbee 1990).

At the end of a one-year study, mean FVC for the PEP group increased by 6.57% predicted, and mean FVC for the PDPV group decreased by approximately 2.17% predicted; this was a significant difference favouring PEP, MD 8.74 (95% CI 1.44 to 16.04) (McIlwaine 1997). In a two-year study, no significant difference in the rates of decline in FVC were reported between the PEP group and the PDPV group, with mean annual declines of 2.54% predicted and 0.97% predicted, respectively, MD -1.57 (95% CI -4.33 to 1.19) (Gaskin 1998).

b. Forced expiratory flow 25-75%

Three studies reported results for FEF_{25-75} (Darbee 1990; McIlwaine 1997; van Asperen 1987).

i. Single treatment

No studies reported at this time-point.

ii. Short-term (up to seven days)

No studies reported at this time-point.

iii. Long-term (more than seven days)

Three studies measured FEF_{25-75} after a series of treatments over more than seven days (Darbee 1990; McIlwaine 1997; van Asperen 1987) (Analysis 1.3). No significant differences in FEF_{25-75} were demonstrated after two weeks of treatment with either PEP or flutter (van Winden 1998). No significant differences in FEF_{25-75} were demonstrated after one month of PEP or PDPV, MD -6.20 (95% CI -14.41 to 2.01) (van Asperen 1987). No significant difference in FEF_{25-75} was demonstrated after three months of PEP or PDPV, MD -3.08 (95% CI -7.87 to 1.71) (Darbee 1990).

At the end of a one-year study, mean FEF_{25-75} for the PEP group increased by 3.32% predicted; mean FEF_{25-75} for the PDPV group decreased by approximately 0.24% predicted. This equates to a MD for this study of 3.56 (95% CI -6.18 to 13.30) (McIlwaine 1997).

c. Total lung capacity

One study measured TLC (Darbee 1990). No statistically significant difference in TLC was demonstrated after three months of PEP or PDPV, MD -3.38 (95% CI -13.67 to 6.91) (Darbee 1990) (Analysis 1.4).

d. Residual volume

No studies reported on this outcome.

3. Exercise tolerance

One study conducted exercise testing using cycle ergometry, but reported no data for this outcome measure (Gaskin 1998).

4. Well-being

One study reported well-being as an outcome measure and used the quality of well-being (QWB) scale (Gaskin 1998). In the two-year, parallel study of PEP versus PDPV, neither group demonstrated a significant change in QWB scores, which was similar at baseline and no further data were available (Gaskin 1998).

5. Blood oxygen levels

Two studies measured blood oxygen levels (Costantini 2001; Falk 1984).

a. Single treatment

No studies reported at this time-point.

b. Short term (up to seven days)

In a study comparing four treatments once each over two days, the mean gain in SpO_2 35 minutes after treatment was significantly higher for PEP in sitting than for PEP in postural drainage (PD) positions, for pursed lip breathing, or for PDPV. Please note, the treatment durations were unequal in this study (Falk 1984). This is presented in an additional table (Table 3).

c. Long-term (more than seven days)

One study measured SpO_2 after a series of treatments over more than seven days (Costantini 2001). In a one-year study of infants, oxygen saturation values in the PEP group are described as "higher than the PDPV group in every evaluation (98.1% versus 96.7%, P = 0.049)". Participants were evaluated at 0, 6 and 12 months in this study, so it is unclear to which evaluation the data refer. The data have not been entered in Data and analyses as no measures of variability were available (Costantini 2001).

6. Lung clearance index (LCI)

No studies reported on this outcome.

7. Ventilation scanning

Four studies reported on this outcome (Costantini 2001; Gaskin 1998; McIlwaine 1997; McIlwaine 2001) (Analysis 1.5; Analysis 1.6)

In a year-long study of infants, an increase in radiologic bronchial markings was less common in the PEP group than the PDPV group, RR 0.88 (95% CI 0.69 to 1.12) (Costantini 2001) (Analysis 1.5). In the same study, hyperinflation was assessed, but only data for the PDPV group are reported for this outcome. A one-year study of PEP versus PDPV measured Brasfield chest radiograph score, and reported identical results for the two groups, MD 0.00 (95% CI -1.20 to 1.20) (McIlwaine 1997) (Analysis 1.6). A two-year study of PEP versus PDPV also measured Brasfield chest radiograph score, but reported no data for this outcome measure (Gaskin 1998).

In a one-year study of PEP versus flutter, a blinded radiologist evaluated changes in chest radiographs. The groups were not significantly different, although no data were published to support this (McIlwaine 2001).

8. Cost of intervention

No studies reported on this outcome.

9. Adherence to treatment and participant preference

One study monitored adherence with PEP versus PDPV over one year (McIlwaine 1997). Adherence was 96% in the PEP group and 92% in the PDPV group (McIlwaine 1997), this is presented in an additional table and no SDs were reported (Table 4).

Five studies reported on technique acceptability or participant preference (Braggion 1995; Costantini 2001; Darbee 1990; Falk 1984; McIlwaine 1997).

a. Single treatment

One study measured participant preference after a single treatment (Falk 1984). The preferred treatment for 11 of 14 participants was PEP in sitting when compared to PEP in PD positions, PDPV, or pursed lip breathing. It was reported that "even though all participants had received postural drainage and percussion as an integral part of treatment, they did not hesitate to accept (PEP in sitting), which was easier, less time-consuming and could be used when needed" (Falk 1984).

b. Short-term (up to seven days)

One study involving 16 participants measured participant preference after a short-term treatment course. A two-day course of four treatments with PEP was compared with the same regimen of PD with undefined chest physiotherapy techniques, or flutter. Three-point rating scales (criteria unspecified) of effectiveness and tolerance were recorded after each arm, with no significant differences between interventions and no further data were available (Braggion 1995).

c. Long-term (more than seven days)

Three studies measured participant preference after a treatment course of greater than seven days duration (Costantini 2001; Darbee 1990; McIlwaine 1997). In the long-term, cross-over study PEP was the treatment of choice when compared to PDPV, "patients... preferred PEP mask for convenience, independence and ease of use, as determined by a standardized written questionnaire" (not described) (Darbee 1990).

Participant preference also favoured PEP in two one-year parallel studies (Costantini 2001; McIlwaine 1997). In the study of PEP versus PDPV, participant preference was only recorded in the PEP group, as all participants were PEP-naive prior to starting the study; and all 18 participants in the PEP group nominated the PEP intervention as their preferred airway clearance modality (McIlwaine 1997). Although it was not stated how participant preference was determined, the conclusion from the study of PEP versus PDPV in infants was that the parents and infants preferred PEP (Costantini 2001). Data from these studies could not be obtained in sufficient detail for inclusion in the graphs.

10. Adverse effects

Two studies with 66 participants reported adverse events as an outcome measure (Costantini 2001; McIlwaine 1997). In a year-long study of PEP versus conventional PDPV in children and adolescents, no adverse events were reported by either group (McIlwaine 1997). In a one-year study of infants, side effects were described as rare. Although gastro-oesophageal reflux was reported more commonly in the PEP group than the PDPV group, risk ratio (RR) 1.07 (95%CI 0.37 to 3.11), those in the PEP group described their reflux as mild. Reflux severe enough to cause withdrawal from the study was also examined, with all three cases occurring in the PDPV group, RR 0.12 (95% CI 0.01 to 2.18) (Costantini 2001).

PEP compared with oscillating PEP (flutter and cornet)

This comparison was made in six studies (n = 224) (Lagerkvist 2006; McIlwaine 2001; Newbold 2005; Pryor 2010; Tannenbaum 2005; van Winden 1998). However, the Pryor study had five treatment arms and three are included here (PEP, and two types of oscillating PEP (flutter and cornet)) (Pryor 2010).

Primary outcomes

1. Forced expiratory volume at one second (FEV_1)

All six studies measured FEV_1 (Lagerkvist 2006; McIlwaine 2001; Pryor 2010; Newbold 2005; Tannenbaum 2005; van Winden 1998) (Analysis 2.1).

a. Single treatment

Two studies found no significant difference in FEV_1 after PEP compared to the flutter after a single treatment (Lagerkvist 2006; van Winden 1998). The two studies were cross-over studies from which data from the end of the first randomisation arm could not be obtained.

b. Short-term (up to seven days)

No studies considered this outcome in the short term.

c. Long-term studies (more than seven days)

Five studies measured FEV_1 after a series of treatments over more than seven days (McIlwaine 2001; Newbold 2005; Pryor 2010; Tannenbaum 2005; van Winden 1998). No significant differences in FEV_1 were demonstrated after two weeks of treatment with either PEP or flutter (van Winden 1998). This was a cross-over study from which data from the end of the first randomisation arm could not be obtained.

Four studies lasted at least one year. In a one-year study in children and adolescents, FEV_1 declined by a mean of 1.24% predicted in the PEP group, while in the flutter group it deteriorated by 10.95%, MD 9.71 (95% CI -2.12 to 21.54) (McIlwaine 2001) (Analysis 2.1). However, in a 13-month study in adults, the annual decline in FEV_1 was 4.2% predicted in the PEP group and 2% predicted in the flutter group, MD -2.20 (95% CI -7.07 to 2.67) (Newbold 2005) (Analysis 2.1). No reported significant difference was found in FEV_1 between PEP and flutter with a decline over a one-year period of 0.15 L with PEP and 0.03 L with flutter (change data were not reported) (Pryor 2010). Another one-year study reported a decrease in FEV_1 of 1.9% in the PEP group and an increase of 1.3% in the cornet group, MD -3.20 (95% CI -15.29 to 8.89) (Tannenbaum 2005). There was no significant difference between groups when the two studies were combined, MD -2.34 (95% CI -6.86 to 2.18) (Analysis 2.1).

2. Number of respiratory exacerbations between baseline and post-intervention

Two parallel studies reported the number of respiratory exacerbations severe enough to require either intravenous (IV) antibiotics or hospitalisation (McIlwaine 2001; Newbold 2005) (Analysis 2.2).

In a one-year study with 20 participants per group, respiratory exacerbations severe enough to require hospitalisation occurred five times in the PEP group and 18 times in the flutter group. A Wilcoxon rank sum test indicated this difference was statistically significant favouring PEP (P = 0.03) but the number of hospitalisations per individual is not reported, so these data do not appear in our analysis (McIlwaine 2001). Similarly, a 13-month study with 21 participants per group found respiratory exacerbations severe enough to require hospitalisation occurred six times in the PEP group and 14 times in the flutter group (Newbold 2005). This represented a mean of 0.3 hospitalisations per participant in the PEP group and 0.7 hospitalisations per participant in the flutter group, MD -0.40 (95% CI -0.92 to 0.12). This is the only study entered in the graphs for this section (Analysis 2.2).

One parallel study of one year, reported the number of respiratory exacerbations requiring either oral or IV antibiotics as the primary outcome (Tannenbaum 2005). There were eight respiratory exacerbations reported in 14 participants in the PEP group (mean 0.57) and six respiratory exacerbations in 10 participants in the cornet group (mean 0.6) which was not significantly different. It is unclear if these participants required IV only or IV or oral antibiotics.

3. Direct measures of mucus clearance

No studies reported on this outcome.

Secondary outcomes

1. Expectorated secretions, dry or wet weight, or volume

No studies reported this outcome.

2. Other pulmonary parameters

a. forced vital capacity (FVC)

Five studies measured FVC (Lagerkvist 2006; McIlwaine 2001; Newbold 2005; Pryor 2010; van Winden 1998) (Analysis 2.3; Analysis 2.4).

i. Single treatment

Two cross-over studies measured FVC after a single treatment, but data from the end of the first randomisation arm could not be obtained (Lagerkvist 2006; van Winden 1998). No significant difference in FVC was demonstrated after one treatment with either PEP or flutter (Lagerkvist 2006; van Winden 1998).

ii. Short-term (up to seven days)

No studies reported at this time-point.

iii. Long-term (more than seven days)

Four studies measured FVC after a series of treatments over more than seven days (McIlwaine 2001; Newbold 2005; Pryor 2010; van Winden 1998).

No significant difference in FVC was demonstrated after two weeks of treatment with PEP or flutter (as above, no data available from first arm) (van Winden 1998). Over one year, a decrease in mean FVC was reported with flutter of 8.62% predicted, while in the PEP group mean FVC increased 0.06% predicted, but this was not significant, MD 8.68 (95% CI -0.54 to 17.90) (McIlwaine 2001). In a 13-month study, the annual decline in FVC was 4.7% predicted in the PEP group and 3% predicted in the flutter group, MD -1.70 (95% CI -6.27 to 2.87) (Newbold 2005) (Analysis 2.3).

In another one-year study comparing PEP to flutter, no significant difference between techniques were found although the study did not report the actual data (Pryor 2010).

b. Forced expiratory flow 25-75%

Three studies reported results for FEF_{25-75} (McIlwaine 2001; Newbold 2005; van Winden 1998) (Analysis 2.4).

i. Single treatment

No significant difference in FEF_{25-75} was noted after one treatment with PEP or flutter (van Winden 1998). This study was a cross-over study from which data from the first randomisation arm could not be obtained.

ii. Short-term (up to seven days)

No studies reported at this time-point.

iii. Long-term (more than seven days)

Two studies measured FEF_{25-75} after a series of treatments over more than seven days (McIlwaine 2001; Newbold 2005; van Winden 1998). No significant differences in FEF_{25-75} were demonstrated after two weeks of treatment with either PEP or flutter (as above, no data available from first arm) (van Winden 1998).

In a one-year study in children and adolescents, FEF_{25-75} declined by a mean of 3.58% predicted in the PEP group, while in the flutter group it deteriorated by 8.87% predicted; however, the difference was not significant, MD 5.29 (95% CI -7.84 to 18.42) (McIlwaine 2001). In a 13-month study, annual decline in FEF_{25-75} was 3.1% predicted in the PEP group and 2% predicted in the flutter group, MD -1.10 (95% CI -6.50 to 4.30) (Newbold 2005) (Analysis 2.4).

c. Total lung capacity

One cross-over study measured TLC (as above, no data available from first arm) (van Winden 1998). No significant changes in TLC occurred both after one treatment and after two weeks of treatment with PEP and flutter (van Winden 1998).

d. Residual Volume

No studies reported this.

3. Exercise tolerance

One study conducted exercise testing and used the modified shuttle test and reported no significant difference in outcome (P = 0.52) between PEP, AD, ACBT, cornet and flutter over a one-year period (Pryor 2010).

4. Well-being

Two studies reported well-being as an outcome measure (Tannenbaum 2005; Pryor 2010). There was no significant change from baseline in either group on the QWB scale; no data are available as this study was only published in abstract form (Tannenbaum 2005).

Pryor found no significant differences in the physical domain among the five groups (P = 0.99) or the mental domain (P = 0.27) using Short Form -36; and no significant differences among the five groups in the dyspnoea domain (P = 0.7), fatigue (P = 0.85), emotion (P = 0.39) or mastery (P = 0.82) using the Chronic Respiratory Questionnaire (Pryor 2010).

5. Blood oxygen levels

Two studies measured blood oxygen levels (Lagerkvist 2006; van Winden 1998).

a. Single treatment

In one cross-over study, with no data available for the first arm, both transcutaneous oxygen levels (P_{to2}) and carbon dioxide levels (P_{tco2}) were measured. The immediate results after a single treatment of flutter showed higher P_{to2} (P = 0.05) and lower P_{tco2} (P < 0.0001) compared to PEP, but at steady state after treatment all differences had disappeared (Lagerkvist 2006).

b. Short term (up to seven days)

No studies reported at this time-point.

c. Long-term (more than seven days)

One cross-over study, with no data available for the first arm, measured SpO_2 after a series of treatments over more than seven days (van Winden 1998). In this two-week study, there was no difference in SPO_2 between flutter and PEP measured before, during and after treatment.

6. Lung clearance index (LCI)

One study used multiple, breath inert gas washout to examine lung clearance (Tannenbaum 2005). They reported no significant difference in LCI between PEP and cornet over a one-year period, MD 0.80 (95% CI -1.36 to 2.96) (Analysis 2.5).

7. Ventilation scanning

In a one-year study of PEP versus flutter, a blinded radiologist evaluated changes in chest radiographs. The groups were not significantly different, although no data were published to support this (McIlwaine 2001).

8. Cost of intervention

No studies reported on this outcome.

9. Adherence to treatment and participant preference

One study monitored adherence with a series of treatments over one year (McIlwaine 2001).

a. Single treatment

No studies reported at this time-point.

b. Short-term (up to seven days)

No studies reported at this time-point.

c. Long-term (more than seven days)

In the one-year study of PEP versus flutter, two participants were withdrawn from the PEP group due to non-compliance, RR 5.00 (95% CI 0.26 to 98.00) (Analysis 2.6). While no participants were withdrawn from the flutter group for non-compliance, five dropped out due to a perceived lack of treatment efficacy with flutter, and a further two were withdrawn due to clinical deterioration. Overall, adherence was reported as 95.6% for the PEP group and 93.8% for the flutter group (McIlwaine 2001). This is presented in an additional table (Table 5).

Participants preferred PEP in the one-year parallel study of PEP versus flutter which reported "discontinuation due to lack of perceived effectiveness in clearing their secretions" (McIlwaine 2001). Of 40 participants, five discontinued for this reason, all from the flutter group; however, there was no significant difference

between treatment groups, RR 0.09 (95% CI 0.01 to 1.54) (McIlwaine 2001) (Analysis 2.7).

PEP compared with high frequency chest wall oscillation (HFCWO)

This comparison was made in four studies (n = 174) (Braggion 1995; Darbee 2005; Fainardi 2011; McIlwaine 2013).

Primary outcomes

1. Forced expiratory volume at one second (FEV_1)

Four studies measured FEV_1 (Braggion 1995; Darbee 2005; Fainardi 2011; McIlwaine 2013) (Analysis 3.1; Analysis 3.2).

a. Single treatment

Two studies measured FEV_1 after a single treatment (Darbee 2005; Fainardi 2011). There was no significant difference in FEV_1 after PEP compared to HFCWO (Darbee 2005; Fainardi 2011). The Fainardi study was a cross-over study from which data from the end of the first randomisation arm could not be obtained.

b. Short-term (up to seven days)

One cross-over study, with no data available for the first arm, measured FEV_1 after four treatments of PEP, postural drainage with undefined airway clearance techniques, or flutter over two days and found no significant differences in FEV_1 (Braggion 1995).

c. Long-term studies (more than seven days)

One study measured FEV_1 after a series of treatments over more than seven days (McIlwaine 2013). In the only one-year study comparing PEP to HFCWO, FEV_1 increased by a mean of 0.22 L with PEP and 0.23 L with HFCWO (McIlwaine 2013). Data were provided at each study visit and the change in FEV_1 % predicted over one year was not significantly different between the two groups, MD -3.59 (95% CI -9.29 to 2.11) (Analysis 3.1).

2. Number of respiratory exacerbations between baseline and post-intervention

One parallel study with 107 participants which ran for one year, reported the number of respiratory exacerbations requiring either oral or IV antibiotics as the primary outcome (McIlwaine 2013). In 43 participants performing PEP, 26 had 49 respiratory exacerbations compared with 96 respiratory exacerbations in 40 of the 48 participants performing HFCWO, which showed a statistically significant difference in favour of PEP, RR 0.73 (95% CI 0.55to 0.95) (Analysis 3.2). This study by McIlwaine also reported that respiratory exacerbations, which were severe enough to require either IV antibiotics or hospitalisation, occurred six times in the PEP group (six participants) and 19 times in the HFCWO group (13 participants). This represented a mean of 0.12 respiratory exacerbations requiring IV antibiotics per participant in the PEP group and a mean of 0.4 respiratory exacerbations requiring IV antibiotics per participant in the HFCWO group (McIlwaine 2013).

3. Direct measures of mucus clearance

No study reported on this outcome.

Secondary outcomes

1. Expectorated secretions, dry or wet weight, or volume

Two cross-over studies., with no data available for the first arms, reported measures of expectorated sputum (Braggion 1995; Fainardi 2011).

a. Single treatment

One study measured expectorated secretions after a single treatment (Fainardi 2011). Wet weight of sputum was not significantly different after single treatments of PEP and HFCWO (Fainardi 2011).

b. Short-term (up to seven days)

No significant difference in wet or dry weight of sputum was identified between PEP and PDPV or HFCC (Braggion 1995).

c. Long-term (more than seven days)

As outlined in the Data extraction and management section, this review does not examine this outcome where it is measured after more than seven days of treatment.

2. Other pulmonary parameters

a. Forced vital capacity (FVC)

Three studies measured FVC (Darbee 2005; Fainardi 2011; McIlwaine 2013) (Analysis 3.3).

i. Single treatment

Two cross-over studies, with no data available for the first arms, measured FVC after a single treatment (Darbee 2005; Fainardi 2011). Both PEP and HFCWO significantly improved FVC during an acute exacerbation, but there was no significant difference between either treatment (Darbee 2005). A second study comparing PEP to HFCWO over a single treatment also showed no significant difference (Fainardi 2011).

ii. Short-term (up to seven days)

No study reported at this time-point.

iii. Long-term (more than seven days)

One study measured FVC after a series of treatments over more than seven days (McIlwaine 2013). No significant difference in FVC was demonstrated at the end of a one-year study comparing PEP to HFCWO (McIlwaine 2013). The PEP group increased by mean 0.3 L and HFCWO by mean 0.35 L. Data were provided at each study visit and the change in FVC % predicted over one year was not significantly different between the two groups, MD -5.00 (95% CI -10.30 to 0.30) (Analysis 3.3).

b. Forced expiratory flow 25-75%

Three studies measured FEF_{25-75} (Darbee 2005; Fainardi 2011; McIlwaine 2013).

i. Single treatment

Two cross-over studies, with no data available for the first arms, measured FEF_{25-75} after a single treatment (Darbee 2005; Fainardi 2011). There was no significant difference between treatments (Darbee 2005). A second study comparing PEP to HFCWO over a

single treatment also showed no significant difference (Fainardi 2011).

ii. Short-term (up to seven days)

No study reported at this time-point.

iii. Long-term (more than seven days)

One study measured FEF_{25-75} after a series of treatments over more than seven days (McIlwaine 2013). No significant difference in FEF_{25-75} was demonstrated at the end of a one year study comparing PEP to HFCWO (McIlwaine 2013). The PEP group increased by mean 0.27 L and HFCWO by mean 0.19 L. Data were provided at each study visit and the change in FEF_{25-75} % predicted over one year was not significantly different between the two groups, MD -0.34 (95% CI -12.54 to 11.86) (Analysis 3.4).

c. Total lung capacity

No study reported this outcome.

d. Residual volume

No study reported this outcome.

3. Exercise tolerance

No study reported this outcome.

4. Well-being

No study reported this outcome.

5. Blood oxygen levels

Two studies measured blood oxygen levels (Fainardi 2011, Darbee 2005). HFCWO was associated with a significant decrease in Spo_2 during treatment whereas the PEP technique produced significant increases in Spo_2 during treatment and is presented as a figure in the trial report.

a. Single treatment

During a single treatment of HFCC compared to HFCC, there was a small but significant decrease in SpO_2 values after PEP treatment (98% ± 1% versus 97% ± 1.2%; P < 0.001), but not after HFCC (97% ± 1.6% versus 97% ± 1.2%) (Fainardi 2011).

b. Short term (up to seven days)

No study reported at this time-point.

c. Long-term (more than seven days)

No study reported at this time-point.

6. Lung clearance index (LCI)

One cross-over study, for which data were not available for the first arm, reported the results of lung clearance using a single-breath inert gas test which examines distribution of ventilation (Darbee 2005). This study compared PEP to HFCWO and showed an improvement in ventilation distribution and gas mixing with both treatments which was not significantly different between both techniques (Darbee 2005).

7. Ventilation scanning

No study reported this outcome.

8. Cost of intervention

One study discussed costs of devices (PEP device at GBP 50 versus a HFCWO device at GBP 7000), but no further information was provided (McIlwaine 2013).

9. Adherence to treatment and participant preference

In a one-year study comparing PEP to HFCWO, adherence was measured by participants keeping a daily diary and reported on monthly phone calls, at 96% in both groups (McIlwaine 2013).

Two studies reported on technique acceptability or participant preference (Braggion 1995; Fainardi 2011).

a. Single treatment

One study measured participant preference after a single treatment (Fainardi 2011). In this group of 36 participants comparing PEP to HFCWO,18 preferred PEP, three preferred HFCWO and 13 had no preference.

b. Short-term (up to seven days)

One study involving 16 participants measured participant preference after a short-term treatment course. A two-day course of four treatments with PEP was compared with the same regimen of PD with undefined chest physiotherapy techniques, or flutter. Three-point rating scales (criteria unspecified) of effectiveness and tolerance were recorded after each arm, with no significant differences between interventions (Braggion 1995) and no further data were available.

c. Long-term (more than seven days)

No studies reported at this time-point.

PEP compared with a variety of different airway clearance techniques

Nine cross-over studies compared PEP with different airway clearance techniques (n = 136) (Darbee 2004; Falk 1993; Hofmeyr 1986; Kofler 1998; Lannefors 1992; McIlwaine 1991; Mortensen 1991; Pfleger 1992; Steen 1991). Darbee compared two types of PEP (Darbee 2004). Three studies compared PEP to ACBT (Falk 1993; Hofmeyr 1986; Mortensen 1991). As these studies were all cross-over in design, limited data are available as data from the end of the first randomisation arm could not be obtained.

Primary outcomes

1. Forced expiratory volume at one second (FEV_1)

Seven studies measured FEV_1 (Darbee 2004; Falk 1993; Hofmeyr 1986; Kofler 1998; McIlwaine 1991; Pfleger 1992; Steen 1991).

a. Single treatment

Four studies measured FEV_1 after a single treatment (Darbee 2004; Falk 1993; Kofler 1998; Pfleger 1992). There was no significant difference in FEV_1 after PEP compared to the forced expiratory technique (FET) (Falk 1993), non-invasive bilevel ventilatory support (nBVS) (Kofler 1998), or > 20 cm H_2O PEP (Darbee 2004). One study found that FEV_1 was significantly lower after a treatment of AD followed by Hi-PEP, compared to AD alone (Pfleger 1992). This is presented in an additional table (Table 6).

b. Short-term (up to seven days)

One study measured FEV_1 after four treatments of PEP in sitting, PEP in postural drainage positions, or breathing exercises in postural drainage positions on a single day and found no significant differences in FEV_1 (Hofmeyr 1986).

c. Long-term studies (more than seven days)

Two studies measured FEV_1 after a series of treatments over more than seven days (McIlwaine 1991; Steen 1991). No significant differences in FEV_1 were demonstrated after one month of PEP, PEP followed by PDPV, PDPV, or PEP + FET (Steen 1991) or after two months of PEP, AD, or PDP (McIlwaine 1991).

2. Number of respiratory exacerbations between baseline and post-intervention

Two cross-over studies reported participants being withdrawn due to exacerbations, although these are not well-defined (Pfleger 1992; Steen 1991). It is also unclear which treatments the participants were randomised to at the time of departure from any of these studies.

3. Direct measures of mucus clearance

Three studies measured radio-labelled aerosol clearance after a single treatment of PEP (Falk 1993; Lannefors 1992; Mortensen 1991). Please note, all were cross-over studies from which data from the end of the first randomisation arm could not be obtained so no data have been entered in the Data and analyses. Radioisotope retention two hours after a 20-minute treatment of PEP and FET was significantly less than for FET alone (Falk 1993), this is presented in an additional table (Table 7). No significant difference in clearance was identified between PEP plus FET and PD plus FET (Lannefors 1992; Mortensen 1991) or exercise plus FET (Lannefors 1992).

Secondary outcomes

1. Expectorated secretions, dry or wet weight, or volume

Four cross-over studies reported measures of expectorated sputum (Darbee 2004; Hofmeyr 1986; McIlwaine 1991; Mortensen 1991; Pfleger 1992).

a. Single treatment

Four studies measured expectorated secretions after a single treatment (Darbee 2004; Hofmeyr 1986; Mortensen 1991; Pfleger 1992). One study found wet weight of sputum was significantly greater during PD with FET and breathing exercises compared to PEP and FET in sitting ($P < 0.001$) or PEP and FET in PD positions ($P < 0.025$) (Hofmeyr 1986). This is presented in an additional table (Table 8). However, wet weight of sputum expectorated during and for 120 minutes after treatment demonstrated no significant difference between PEP and PD (Mortensen 1991). Dry weight of sputum was not significantly different after single treatments of PEP and > 20 cm H_2O PEP (Darbee 2004). One study demonstrated Hi-PEP produced significantly more sputum than either AD ($P < 0.001$) or AD then Hi-PEP ($P < 0.001$) (Pfleger 1992). This is presented in an additional table (Table 9).

b. Short-term (up to seven days)

When wet weight of sputum was measured during and for 30 minutes after treatment, breathing exercises in postural drainage positions induced significantly greater sputum expectoration than PEP in postural drainage positions. The latter in turn produced significantly more expectorate than PEP in sitting (Hofmeyr 1986). This is presented in an additional table (Table 8).

c. Long-term (more than seven days)

As outlined above in the Types of outcome measures section, this review does not examine this outcome where it is measured after more than seven days of treatment.

2. Other pulmonary parameters

a. forced vital capacity (FVC)

FVC was measured in five studies (Darbee 2004; Kofler 1998; McIlwaine 1991; Pfleger 1992; Steen 1991).

i. Single treatment

Three studies measured FVC after a single treatment (Darbee 2004; Kofler 1998; Pfleger 1992). No significant difference in FVC was demonstrated with a single treatment of PEP versus > 20 cm H_2O PEP (Darbee 2004). No significant difference in FVC was noted after one treatment with PEP or nBVS (Kofler 1998). These were cross-over studies from which data from the end of the first randomisation arm could not be obtained. One study found that FVC was significantly lower after a treatment of AD followed by Hi-PEP, compared to AD alone (Pfleger 1992). This is presented in an additional table (Table 10).

ii. Short-term (up to seven days)

No studies reported at this time-point.

iii. Long-term (more than seven days)

Two studies measured FVC after a series of treatments over more than seven days (McIlwaine 1991; Steen 1991). Data from one study were not able to be included in the meta-analysis, but the paper reported no significant differences in FVC were demonstrated after one month of PEP, PEP followed by PDPV, PDPV, and PEP + FET (Steen 1991). A cross-over study comparing two months of PEP, PDPV or AD also showed no significant differences in FVC (McIlwaine 1991).

b. Forced expiratory flow 25-75%

Five studies reported results for FEF_{25-75} (Darbee 2004; Kofler 1998; McIlwaine 1991; Mortensen 1991; Steen 1991).

i. Single treatment

No significant difference in FEF_{25-75} was noted after one treatment with PEP or nBVS (Kofler 1998) or after one treatment with PEP or > 20 cm H_2O PEP (Darbee 2004). These were cross-over studies from which data from the end of the first randomisation arm could not be obtained.

ii. Short-term (up to seven days)

No studies reported at this time-point.

iii. Long-term (more than seven days)

Two studies measured FEF_{25-75} after a series of treatments over more than seven days (Mortensen 1991; Steen 1991). No significant differences in FEF_{25-75} were demonstrated after one month of PEP, PEP followed by PDPV, PDPV, and PEP + FET (Steen 1991). A

study comparing two months of PEP, PDP or AD also showed no significant differences in FEF_{25-75} (McIlwaine 1991).

c. Total lung capacity

No studies reported on this outcome.

d. Residual volume

The change in residual volume from baseline was not significantly different after a single treatment of PEP or > 20 cm H_2O PEP (Darbee 2004).

3. Exercise tolerance

No studies reported on this outcome.

4. Well-being

No studies reported on this outcome.

5. Blood oxygen levels

Three studies measured blood oxygen levels (Darbee 2004; Hofmeyr 1986; Kofler 1998).

a. Single treatment

Two studies were single treatments. The improvement in SpO_2 during a single nBVS treatment was statistically significantly greater than with one treatment with PEP (Kofler 1998), this is presented in an additional table (Table 11). The change in SpO_2 was not significantly different after a single treatment of PEP versus > 20 cm H_2O PEP (Darbee 2004).

b. Short term (up to seven days)

There were no significant mid- or post-treatment differences between four treatments of breathing exercises with forced expirations in postural drainage positions, PEP in postural drainage positions, and PEP in sitting in a single day (Hofmeyr 1986).

c. Long-term (more than seven days)

No studies reported on this outcome.

6. Lung clearance index (LCI)

One study reported the results of lung clearance using a single-breath inert gas test which examines distribution of ventilation (Darbee 2004). This study reported worsening of the distribution of ventilation following PEP and high pressure PEP compared to control (Darbee 2004); however, in this study gas mixing improved suggesting that PEP opened up previously closed partially obstructed airways.

7. Ventilation scanning

No studies reported on this outcome.

8. Cost of intervention

No studies reported on this outcome.

9. Adherence to treatment and participant preference

Three studies reported on technique acceptability or participant preference (Kofler 1998; McIlwaine 1991; Steen 1991).

a. Single treatment

One study measured participant preference after a single treatment (Kofler 1998). When compared to nBVS, 60% of participants preferred nBVS, 25% preferred PEP, and 15% had no preference (Kofler 1998).

b. Short-term (up to seven days)

No studies reported at this time-point.

c. Long-term (more than seven days)

Two studies measured participant preference after a treatment course of greater than seven days duration (McIlwaine 1991; Steen 1991). The cross-over study comparing two months of PEP, conventional PDPV, and AD recorded five subjective measures which may influence participant preference: treatment duration; treatment comfort; flexibility of treatment times; control in performing own treatment; and how interruptive treatment was to daily living. It was reported that PEP had a significantly shorter treatment time than PDPV or AD; also, PEP was rated significantly better than PDPV and not significantly different to AD on each of the other four measures (McIlwaine 1991). Standard deviations were not available for these outcomes and mean data are presented in an additional table (Table 12). In another long-term, cross-over study, PEP was the treatment of choice (Steen 1991). A total of 23 of 24 participants chose PEP in combination with FET in preference to PEP alone, PDPV and FET, or five minutes of PEP followed by PDPV and FET as their long-term airway clearance physiotherapy (Steen 1991). Data from these studies could not be obtained in sufficient detail for inclusion in the graphs.

Subgroup analyses

None of the intended subgroup analyses were possible due to small numbers of studies or insufficient detail to allow the separation of subgroup data within any study. One study provided subgroup analysis based on age, which did not conform to the age groups for subgroup analysis defined in the protocol for this review. The data for the subgroup used are presented as an additional table (Table 13).

Sensitivity analyses

None of the intended sensitivity analyses were possible due to small numbers of studies included in each comparison.

DISCUSSION

Summary of main results

A total of 26 studies involving 733 participants with cystic fibrosis (CF) (infants, children, adolescents and adults) met the review's inclusion criteria. Sample sizes in individual studies ranged from five to 107 participants; 19 studies were reported in full articles and seven were published in abstract form only.

There was a wide range of therapies to which positive expiratory pressure (PEP) was compared. The duration of the intervention period varied from single treatments to two years. These factors together with the frequent use and poor reporting of cross-over design, the small number of studies, and the limited information provided by some authors restricted the number of meta-analyses that could be performed.

A one-year study in children and adolescents reported a significantly reduced rate of hospital admission with PEP as opposed to flutter (McIlwaine 2001). A similar study in adults showed similar results (Newbold 2005). A large (107 participants) well-designed one-year multicentre randomised controlled trial comparing PEP with high frequency chest wall oscillation (HFCWO) found that the PEP group experienced significantly fewer pulmonary exacerbations requiring oral, inhaled or intravenous (IV) antibiotics during the 12 months and a longer time to the first pulmonary exacerbation compared to the HFCWO group (McIlwaine 2013).

The measurement of lung function forced expiratory volume at one second (FEV_1) is important in CF because of its correlation with survival and quality of life (Liou 2001). Six studies did not report FEV_1 as an outcome measure. Four of these studies examined mucus clearance using a radio-labelled isotope (Darbee 1990; Falk 1993; Lannefors 1992; Mortensen 1991). One study measured $FEV_{0.75}$ (Tyrrell 1986), and another study was on infants where FEV_1 could not be measured (Costantini 2001). Five studies measured FEV_1 and compared PEP with postural drainage with percussion and vibration (PDPV); one was a study of less than seven days and four studies lasted more than seven days. Two studies lasted at least one year. In a 12-month study in children with CF, FEV_1 increased in the PEP group and decreased in the PDPV group with the difference recorded being statistically significant (McIlwaine 1997). However, in a two-year study (predominantly in adults) comparing PEP with PDPV, there was no difference in the rates of decline in FEV_1. Both groups experienced rates of annual decline greater than 2% (Gaskin 1998). When PEP was compared with oscillating PEP using the flutter there were six studies that measured FEV_1. Two short-term studies (less than seven days) found no difference between techniques. Five studies measured FEV_1 after a series of treatments over more than seven days. No differences were seen between these techniques in the two-week study and there were mixed results in the four studies lasting one year. In one study of children and adolescents, FEV_1 declined more in the flutter group than the PEP group (McIlwaine 2001); while in a 13-month study in adults both groups declined similarly (Newbold 2005). No significant difference was found in two further one-year studies comparing these and other techniques including active cycle of breathing techniques (ACBT), autogenic drainage (AD) and oscillating PEP using the cornet device (Tannenbaum 2005; Pryor 2010).

A small number of studies found significant differences in expectorated sputum measures when other types of chest physiotherapy were compared to PEP in single treatment and short-term studies up to seven days (Falk 1984; Hofmeyr 1986) or Hi-PEP (Pfleger 1992). However, these measures may be confounded by expectorated saliva, swallowed secretions and regurgitated contents and are generally regarded as less useful outcomes than measurement of mucociliary clearance. One cross-over study measured radio-labelled aerosol clearance after a single treatment of PEP versus PDPV; no significant difference in clearance was found (Darbee 1990).

Many other outcomes did not show a significant difference between PEP and other compared therapies. In the year-long study in infants, blinded examination of chest radiographs showed no significant difference in the incidence of increased bronchial markings between the PEP and PDPV groups (Costantini 2001). When compared to flutter in children and adolescents, similar results occurred in FEF_{25-75} and total lung capacity (TLC) (McIlwaine 2001).

It was recorded that there were no adverse events in the PEP group or in the PDPV group in the year long study of 40 children (McIlwaine 1997). Nor were adverse events recorded in the PEP or the flutter groups in the year-long study of 40 children (McIlwaine 2001). In a year-long study of 26 infants, which was published in abstract form only, there was no statistically significant difference in the incidence of reflux between the PEP and PDPV groups; gastro-oesophageal reflux severe enough to cause withdrawal from the study occurred in three participants in the PDPV group and in no participants in the PEP group (Costantini 2001).

In the majority of studies included in this Cochrane review, there were no significant differences in outcomes when PEP was compared to other techniques. However, three long-term trials undertaken in Canada using PEP have found that outcomes in the PEP group were significantly better than PDPV in children and adolescents (McIlwaine 1997), oscillating PEP using the flutter (McIlwaine 2001) and HFCWO in a multicentre trial across all age groups (McIlwaine 2013). These studies provide evidence that PEP may be more effective in limiting exacerbations and potentially preserving lung function in the longer term. Of note, these three studies all employed PEP via the mask set-up.

In the study comparing PEP with HFCWO, treatment time was significantly shorter in the PEP group (McIlwaine 2013). Limited evidence was identified in support of the hypothesis that PEP is more acceptable to people with CF than other forms of airway clearance therapy. In studies with an intervention period of at least one month, any measures of participant preference were in favour of PEP. The tools used to record patient preference were generally not well-described or validated.

There were a large number of cross-over studies in the sample included in the review. Elbourne discusses methods for meta-analysing cross-over studies which rely on the data that are reported within the primary papers (Elbourne 2002). The method that has been adopted within this review uses the data from the first period only, ignoring any data from the second period that was available if a carryover effect was identified. In this review 3 studies of one month duration were identified as having no washout period and thus may have had a carryover effect (Steen 1991; Tyrrell 1986; van Asperen 1987). A limitation of this study was that data from the first period of cross-over studies was only available in three out of the 18 cross over studies.

Overall completeness and applicability of evidence

There is a large body of evidence to support the use of PEP as a stand-alone airway clearance technique in CF. Numerous studies found PEP to be equal to other compared techniques, however, a few long-term studies suggest that PEP may be superior to other techniques. In these studies PEP was administered using a facemask in order to obtain a seal during the cycles of PEP which resulted in a temporary increase in functional residual capacity (FRC) during the cycles; this in turn allowed air to accumulate behind secretions and move them proximally. Where PEP was found to be superior to other techniques, the way in which it was applied may have contributed to these superior findings. Thus the

applicability of the evidence is highly based on these studies which have demonstrated fewer exacerbations and decreased need for treatment with antibiotics.

Quality of the evidence

The quality of the evidence varied between studies carried out over a few days to well-designed year-long randomised controlled trials. Small sample sizes and drop outs in some studies were likely to have impacted on the precision of the results and the quality of the evidence. As stated below, cross-over designs are not really appropriate for CF studies and results from studies of this design are likely to be of low quality. Blinding of participants and researchers in these studies is not possible, however, blinded assessors have been utilised in a number of the studies increases the quality of the evidence and reduced the risk of biased results. Some unclear information regarding methodology (randomisation sequences and allocation concealments) increased the risk of bias.

Potential biases in the review process

The search process was rigorous and undertaken according to the Cochrane Collaboration's recommendations. It is possible that studies have been undertaken that have not been identified with this online review process or that omissions have inadvertently occurred in the search of conference publications because they have not emerged using the recommended search process. Three authors were involved in the selection of studies to be included in the review and disagreements were resolved by discussion and consensus. When a study that included one of the authors of this report was being considered for inclusion, the author recused themselves from the selection process in relation to that article.

AUTHORS' CONCLUSIONS

Implications for practice

There was some evidence to recommend PEP as a more acceptable intervention long term than other forms of physiotherapy for people with CF. However, the evidence that PEP was preferred over other techniques came from studies which were generally of low quality.

The evidence suggests that all techniques and devices described in this Cochrane review have a place in the clinical treatment of people with cystic fibrosis. The use of PEP via a mask should be high on the list for trial by individuals, especially if they experience a higher than usual or higher than expected exacerbation rate.

Implications for research

The abstract format frequently prevents evaluation of the scientific methodology of a study. Abstracts should be structured to contain essential information about methods and results. The large proportion of studies which were published only as abstracts highlights the need for full publication of studies in this area.

Cross-over studies are not a good design for clinical studies in CF due to the unstable nature of the disease (Southern 2003). They are potentially influenced by carry-over effects. More parallel, randomised clinical studies comparing PEP with other airway clearance modalities are needed. These studies should be adequately powered and a multicentre approach may facilitate this. Such studies should, in particular, examine the influence of PEP and other therapies on FEV_1 and quality of life. Other important areas, which have not been assessed or reported in detail, include survival, exercise tolerance, and cost.

Twelve studies with 188 participants were conducted using short-term interventions on stable participants, which may be of little value given the nature of CF-lung disease, a chronic course with acute exacerbations. Future studies should be planned to reflect clinical practice by focusing on short-term interventions during an exacerbation or long-term studies on initially stable patients.

The studies in this review frequently found no significant difference in efficacy between treatments. Future studies should include validated measures of participant preference, including treatment time (potential barriers to adherence) as this may help to determine a suitable treatment when measures of efficacy are equivocal. Similarly, cost and adverse effect outcome data would assist consumers in decision-making.

Further studies are required to broaden the knowledge of the effects of different techniques on different aspects of the pathophysiology of CF. As CF is a long-term disease, research that spans at least 12 months tends to be more useful in determining the best evidence-based practice. Sputum rheology differs between individuals with CF and between different organisms and combinations of organisms in CF. Research to determine the best technique for situations where sputum is thin and liquid versus thick and viscous may be a new frontier for more targeted research and application of the different techniques in different patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Braggion 1995

Methods	RCT. Cross-over design. Each treatment given twice daily for 2 days.
Participants	CF confirmed by sweat test. 16 participants (8 male); mean age 20.3 years; mean FEV_1 52.5, range 32% - 98% predicted; mean Schwachman score 65.1, range 45 - 87 points. Entry to study at time of hospital treatment of an acute pulmonary exacerbation.
Interventions	4 interventions: No washout period between interventions 1. PEP treatment - participants breathed through a Medipep, (Nuova Tecnomedica) mask with a steady PEP of 10 - 20 cm H_2O; 2. PDPV - 6 positions based on recent chest radiography for each participant; 3. HFCC - using ThAIRapy Bronchial Drainage System, chest compression in sitting at frequencies of 6, 8, 14, 15, 18 and 19 Hz were performed for 6 treatment sessions; 4. Control - resting in sitting, spontaneous coughing allowed. Each treatment lasted 50 minutes: six 5-minute periods of the specific treatment, each followed by a 3-minute period of the FET.
Outcomes	FEV_1, FVC, and FEF_{25-75} were measured before and 30 minutes after each treatment. Expectorated sputum wet and dry weights during and for 30 minutes after each treatment were also measured. Technique acceptability was assessed using a 3-point rating of effectiveness completed by the participant, and a 3-point rating of tolerance, completed by the participant and also by the physiotherapist.
Notes	No statement on withdrawals or dropouts. Participants were familiar with PDPV and PEP interventions. All were introduced to HFCC on the day before their first use. The participant's usual airway clearance regimen was used for 2 days between the 2nd and 3rd treatment periods. This was a published paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further details provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participant and the physiotherapist providing the therapy were not blinded, no information provided regarding other assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals or dropouts. Outcome data were recorded.
Selective reporting (reporting bias)	High risk	All outcome data were only reported as no significant difference.
Other bias	High risk	No washout period between interventions, potential risk for carry-over effect.

Costantini 2001

Methods	RCT. Parallel design. Treatment for 1 year.
Participants	CF identified by newborn screening within the 2nd month of life and confirmed on sweat test and genotyping 26 participants (14 male); aged under 4 months.
Interventions	2 interventions: 13 participants each group 1. PEP treatment - applied via a mask; 2. PDPV. Each treatment was performed for 30 minutes, twice daily. The airway clearance intervention was applied by the carer(s), who received a 2-week training period in either PEP or PDPV. Participants were followed as outpatients for 1 year.
Outcomes	The number of courses of total and intravenous antibiotic treatment were recorded, although it is not stated whether these were prescribed in response to a respiratory exacerbation. Possible adverse effects were monitored. Oxygen saturation, chest radiographs, and growth were assessed. No method of radiograph assessment is mentioned. Measurements were conducted at 0, 6 and 12 months.
Notes	3 participants in the PDPV group withdrew from the study. These were among 4 participants in this group who developed gastro-oesophageal reflux. The 3 who withdrew did so "for the severity of their symptoms and were not evaluated". Published as abstract only, no further information obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participant and the person providing the therapy were not blinded, no information provided regarding other assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants in the PDPV group withdrew from the study. These were among 4 participants in this group who developed gastro-oesophageal reflux. The 3 who withdrew did so "for the severity of their symptoms and were not evaluated". All outcome measures were reported.
Selective reporting (reporting bias)	High risk	Not all outcome measures were reported in full. No statistics were provided for any outcomes, only percentages and mean measurements were reported.
Other bias	Unclear risk	Unclear whether groups were similar at baseline.

Darbee 1990

Methods	RCT.

Darbee 1990 *(Continued)*

	Cross-over design. Each treatment given 2 - 3 times daily for 3 months.
Participants	CF confirmed by sweat test. 13 participants (7 male); mean age 25.7 years, range 18 - 34 years are reported in the abstract. Results from 20 participants were presented at conference. Data on 20 participants was shared with authors. Outcome data for 20 participants were used in the outcome analysis.
Interventions	2 interventions: No washout period between interventions 1. PEP treatment - participants exhaled through a mask for 8 - 10 breaths, then exhaled to a low lung volume through the mask which usually stimulated a cough; this was repeated 5 - 6 times; 2. PDPV - percussion was applied for 3 minutes over all segments, participants breathed deeply several times at each minute, 3 vibrations followed with exhalation through an open mouth, without force, until productive coughing occurred. Participants were instructed to treat until clear, 2 - 3 times per day.
Outcomes	2 measures of mucociliary clearance were repeated after each 3-month treatment arm: the time taken for half the radiolabeled sputum in the whole lung to clear (T1/2-W) and the same in the peripheral region (T1/2-P). Convenience, independence and ease of use was determined with a standardised written questionnaire (not described).
Notes	No statement on withdrawals or dropouts. Participants reported that they got clearer faster with PEP. Published as Abstract only, further information obtained from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further details provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participant and the person providing the therapy were not blinded, no information provided regarding other assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals or dropouts. All outcome measure were reported
Selective reporting (reporting bias)	Low risk	All outcome measures were reported in full.
Other bias	High risk	No washout period between each 3 month period of interventions, potential risk for carry-over effect. Groups similar at baseline regarding the most important prognostic indicators.

Darbee 2004

Methods	RCT. Cross-over design.

Darbee 2004 *(Continued)*

	Each treatment given once.
Participants	CFconfirmed by sweat test; stable (not defined) and not hospitalised during the previous month for management of an exacerbation. 6 participants (3 female), mean age 18 years, range 13 years to 22 years; mean FEV1 52, range 35 - 68% predicted.
Interventions	2 interventions: each interventions was separated by a 5 day washout period 1. PEP treatment - pressure 10 - 20 cm H_2O, participants breathed through a mask with an expiratory resistor between 10 - 20 cm H_2O for 8 - 10 breaths, followed by coughing; this was repeated 6 times; 2. High pressure PEP using a resistor at which FVC with PEP exceeded FVC with no PEP - participants were instructed to perform 8 - 10 slightly lager tidal volume breaths through the PEP device followed by an inspiration to TLC and a forced expiration into the mask; 6 cycles were performed. Each intervention was applied on a different day (order randomised). A 3rd intervention was a "control", Participants sat for 20 minutes and outcome measures were performed pre and post this time period. This was performed on Day 1 by all participants and was not randomised
Outcomes	FEV_1, FEF_{25-75}, RV, SVC, dry weight of sputum, and SpO_2 were recorded before, after, and 45 minutes after each intervention session. Distribution of ventilation and gas mixing were also measured by lung clearance examining the phase 111 slope.
Notes	1 participant's data were excluded when it was determined that there was a pulmonary exacerbation. Published paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information was provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participant and the person providing the therapy were not blinded, no information provided regarding other assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant's data were excluded when it was determined that there was a pulmonary exacerbation. All outcome measures were reported under results.
Selective reporting (reporting bias)	Low risk	Outcome measures are reported in full.
Other bias	Low risk	5 day washout period between each intervention thus low risk of carry over effect. Groups similar at baseline regarding the most important prognostic indicators.

Darbee 2005

Methods	RCT.

Darbee 2005 *(Continued)*

	Cross-over design. Each treatment given once.
Participants	CF confirmed by sweat test; hospitalised with a pulmonary exacerbation. 15 participants 8 males, 7 females, mean (SD) age 17.5 (4.2) years, BMI 18.3 (2).
Interventions	2 Interventions: No washout period between interventions PEP using pressures between 10 - 20 cm H_2O via facemask for 8 breaths followed by huffing and coughing; this was repeated for 8 - 10 cycles. HFCWO, pressure 5, frequency 10 H_z for 15 minutes, then 15 H_z for next 15 minutes; 6 cycles of 5 minutes with a pause for huffing and coughing in between each cycle.
Outcomes	Lung clearance using nitrogen washout measuring Phase III N_2 slope, index values. PFT measurements of FVC and FEV_1, and pulse oximetry.
Notes	Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were assigned treatment order by numbering 1 - 15 at study entrance. Coin toss was used to allocate whether odd numbered participants received treatment first, thus all odd numbered participants received the same treatment allocation.
Allocation concealment (selection bias)	High risk	All odd numbered participant were pre-allocated order of treatment intervention.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study does not mention blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no reported dropouts. All outcomes tested are reported in the results.
Selective reporting (reporting bias)	Low risk	The outcomes are reported fully reported for all participants pre- and post-treatment.
Other bias	High risk	No washout period between interventions, thus potential risk for carryover effect. Groups are similar at baseline based on one prognostic factor.

Fainardi 2011

Methods	RCT. Cross-over, single treatment.
Participants	36 participants, confirmed diagnosis of CF. Age > 18 years, mean (SD) 26 (6.5) years. 14 males, 20 females. Mild to moderate lung function impairment.

Fainardi 2011 *(Continued)*

	Incusion criteria included in hospital for a pulmonary exacerbation.
Interventions	2 Interventions: One day washout period between interventions. PEP using pressures between 10 - 20 cm H_2O, consisted of cycles of 15 breathes through PEP mask interspersed with huffing, number of cycles was individualised. HFCC also known as HFCWO used Hillrom Vest Model 4, with pressure 6 - 10 and frequency between 15 - 20 H_z. Huffing and coughing was interspersed throughout HFCC.
Outcomes	PFTs measuring FVC, FEV_1 and FEF_{25-75} % predicted measured pre and post, pulse oxygen saturation (SpO_2%), sputum weight.
Notes	34 participants completed the study, 2 participants withdrew due to discomfort of HFCC device. Published Paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were assigned to either intervention by numbering consecutively: odd numbers got control intervention first. Even numbers got PEP intervention first. There was no random allocation to intervention.
Allocation concealment (selection bias)	High risk	Thee was no apparent concealment as it was a consecutive numbering sequence.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participant and the person providing the therapy were not blinded - Unclear risk. Outcome assessors were blinded - low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes in study design are reported.
Selective reporting (reporting bias)	Low risk	2 participants withdrew due to discomfort of HFCC device. All outcomes are reported in full.
Other bias	Unclear risk	Only one day washout period between interventions. More outcomes were reported than documented in study design.

Falk 1984

Methods	RCT. Cross-over design. Each treatment given once.
Participants	CF diagnosis, chronic pseudomonas infection, and expectoration of greater than 1.5 g/hr of sputum. 14 participants (10 male); mean age 18 years, range 14 - 30 years; mean FEV_1 34, range 15 - 55% predicted. Participants were excluded during or immediately after anti-pseudomonas treatment or a change in routine medication.
Interventions	4 interventions:One day washout period between interventions

Falk 1984 *(Continued)*

	1. PEP treatment in sitting (PEPs) - pressure 17 cm H_2O using an Astra Meditec PEP mask; seated participants exhaled 6 - 12 times, followed by forced expirations with the glottis open and coughing as needed, this was repeated for 20 minutes; 2. PEP treatment in postural drainage positions (PEPpd) - participants performed the same breathing regimen for 4 - 5 minutes in each of 7 postural drainage positions, this intervention lasted 35 minutes; 3. Postural drainage, percussion and vibration (PDPV) - during the same postural drainage regimen, participants received manual percussion, followed by 3 deep breaths with vibration, and FET. This intervention lasted 35 minutes; 4. Pursed lip breathing in sitting (PLBs) - seated participants inhaled slowly and exhaled through pursed lips 5 - 8 times, followed by FET, this intervention lasted 20 minutes. The 4 interventions were randomised over 2 days: 1 each morning and 1 each afternoon, with an interval of at least 5 hours.
Outcomes	FEV_1 and FVC were measured before and 50 minutes after each intervention session. Wet weight of expectorated sputum during and until 50 minutes after each intervention session. Transcutaneous pO_2 was measured during the intervention and for 50 minutes after each intervention. Technique efficiency and acceptability were assessed using a questionnaire completed by the participant, although details of the questionnaire are not provided.
Notes	No withdrawals nor dropouts. The authors state that 7 participants were studied during admission for their usual anti-pseudomonas treatment and the other 7 at least 1 month after treatment. This appears inconsistent with the exclusion criteria; see 'Participants'. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and person providing the therapy were not blinded - unclear risk Outcome assessors were blinded - low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals nor dropouts. Data for at least 1 key outcome analysed by 'intention-to-treat'.
Selective reporting (reporting bias)	Low risk	Outcome measures were reported in full.
Other bias	Unclear risk	Only one day washout period between interventions. Groups similar at baseline regarding the most important prognostic indicators.

Falk 1993

Methods	RCT. Cross-over design. Each treatment given once.

Falk 1993 *(Continued)*

Participants	CF diagnosis. 12 participants.
Interventions	3 interventions: One day washout period between interventions 1. FET; 2. Combined intervention of PEP with FET (PEP+FET). This is a combined i; 3. Control (not defined). Each intervention was applied for 20 minutes on 1 of 3 consecutive days.
Outcomes	Retention of radiolabeled secretions in the lung was recorded at 0.5, 1, 2, and 24 hours after the start of the intervention. (The 24-hour value was used as a measure of the radioaerosol deposition.) Wet weight of sputum expectorated for the half hour during which the intervention was applied, and for the subsequent 1.5 hours was measured. The number of huffs and coughs during the half hour during which the intervention was applied, and for the subsequent 1.5 hours were counted.
Notes	No statement on withdrawals or dropouts. Published as abstract only, no further information obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals or dropouts.All outcome measure were reported.
Selective reporting (reporting bias)	Low risk	Outcome measures were reported in full.
Other bias	Unclear risk	Only one day washout period between interventions. Groups similar at baseline regarding the most important prognostic indicators.

Gaskin 1998

Methods	RCT. Parallel design. Treatment for 2 years.
Participants	CF diagnosed by Toronto CF Clinics (criteria not stated); FEV_1 > 40% predicted. 66 participants (34 males); mean age 21.6 years, range 11 - 45 years; mean FEV_1 70.2% predicted (PEP group) and 65.3% predicted (PDPV group).
Interventions	2 interventions: 33 participants were randomised to each intervention. 1. PEP treatment - participants exhaled through the Astra Meditec PEP mask;

Gaskin 1998 *(Continued)*

	2. Postural drainage and percussion (PDPV) - not described beyond "conventional postural drainage and percussion". The daily regimen for use of the devices is not described.
Outcomes	FEV_1, FVC, QWBS, a cycle ergometer exercise test, and the Brasfield chest radiograph score. All were recorded at 3-monthly intervals. The participants also kept adherence and exercise diaries.
Notes	5 participants withdrew from the study, but none were lost to follow up. 4 from the PDPV group withdrew soon after randomisation and 1 from the PEP group moved away, but returned to the clinic. No reason is provided for the withdrawals. Published as Abstract only, further information obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants withdrew from the study, but none were lost to follow up. 4 from the PDPV group withdrew soon after randomisation and 1 from the PEP group moved away, but returned to the clinic. No reason is provided for the withdrawals. Data for at least 1 key outcome analysed by 'intention-to-treat'.
Selective reporting (reporting bias)	Unclear risk	Statistical analysis was only reported for 1 outcome measure (FEV_1).
Other bias	Low risk	Groups similar at baseline regarding the most important prognostic indicators.

Hofmeyr 1986

Methods	RCT. Cross-over design. Each treatment given 4 times daily for 1 day.
Participants	CF confirmed by positive sweat test, malabsorption, and chronic lung infection. 18 participants (12 male); mean age 22.5 years, range 13 - 37 years; mean FEV_1 1.3, range 0.45 - 3.25 litres; and FVC was 2.5, range 1.1 - 5.1 litres. All participants were studied close to the end of an admission to hospital with an exacerbation of their lung infection.
Interventions	3 interventions: No washout period between interventions 1. PEP treatment in sitting (PEP) - pressure 12 - 17 cm H_2O using an Astra Meditec PEP mouthpiece; seated participants exhaled 6 times through the mouthpiece, followed by relaxed breathing, 1 - 2

Hofmeyr 1986 *(Continued)*

	forced expirations (huffs) from mid to low lung volume, relaxed breathing, and a huff or cough from high lung volume if secretions reached the upper airways; 2. PEP in postural drainage (PEPpd) - the same breathing regimen was performed in (usually) 2 postural drainage positions chosen before the start of the study as the most appropriate from (undescribed) clinical assessment; 3. Breathing exercises in postural drainage positions (BEpd) - consisting of 4 deep inspirations with relaxed expiration, breathing control and the FET which included 1 - 2 forced expirations (huffing) from mid to low lung volume, followed by breathing control then forced expirations or a cough from high lung volumes. In each intervention, the respiratory manoeuvres described above were continued in cycles until the participant and physiotherapist felt that forced expiration and coughing no longer resulted in expectoration. 4 treatment sessions were performed per day.
Outcomes	FEV_1 and FVC were measured before and 30 minutes after each intervention session. Wet weight of sputum expectorated during and for 30 minutes after the intervention session was measured. SpO_2 was recorded before, during, and for 30 minutes after each intervention session.
Notes	There were no withdrawals or dropouts. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals or dropouts. All outcome measures are reported.
Selective reporting (reporting bias)	High risk	Statistiicial outcome measures are provided for wet weight of sputum expectorated during and for 30 minutes and SpO_2 but not for FEV_1 and FVC.
Other bias	High risk	No washout period between interventions, thus there is a potential for a carryover effect. Groups similar at baseline regarding the most important prognostic indicators.

Kofler 1998

Methods	RCT. Cross-over design. Each treatment given once.
Participants	CF diagnosed by CF Clinic at Children's Hospital, Rome.

Kofler 1998 *(Continued)*

	20 participants (11 males); mean age 15.25, range 6 - 23 years; mean (SD) Schwachman score 80.8 (15.3) points.
Interventions	2 interventions: One day washout period between interventions 1. PEP treatment - followed the Danish protocol of breathing through a PEP mask against a PEP of 10 - 20 cm H_2O pressure, followed by a pause, 2 - 3 huffs and coughing; no further information was provided; 2. BiPAP - while sitting participants breathed against 11cm H_2O inspiratory positive pressure and 9 cm H_2O expiratory positive pressure applied via a mask attached to a Puritan Bennett 335, followed by a pause, 2 - 3 huffs and coughing. Single treatments of 15 minutes were applied on 2 consecutive days. All participants were using PEP as their airway clearance therapy prior to the study. This was stopped the day before the study commenced.
Outcomes	FEV_1, FVC and FEF_{25-75} were measured at the beginning, at the end, 15 min after and 30 min after each session. Oxygen saturation and heart rate were continuously monitored throughout this time via pulseoximetry. Following the 2 sessions, participant preference was recorded.
Notes	No statement on withdrawals or dropouts. All participants were performing PEP prior to the study. PEP was applied "according to the Danish protocol" (not defined). Published as abstract only, no further information obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals or dropouts. All outcome measures are reported.
Selective reporting (reporting bias)	Unclear risk	FEV_1, FVC and FEF_{25-75} were only reported as no significant difference between groups.
Other bias	Unclear risk	Only one day washout period between interventions. Groups similar at baseline regarding the most important prognostic indicators.

Lagerkvist 2006

Methods	RCT. Cross-over design. Single treatment.

Lagerkvist 2006 *(Continued)*

Participants	15 CF patients, 6 females, 9 males, age 6.9 to 1.5 years. CF confirmed by sweat test.
Interventions	2 interventions:Eight week washout period between interventions 1. PEPusing Astra Tech system with mouthpiece pressures 10 - 20cm H_2O - participant breathed through the device for 2 minutes followed by huffing; this was repeated 4 times; 2. Oscillating PEP using the flutter - participants were instructed to inhale deeply then exhale quickly through the device and repeat for 1 minute followed by huffing; this was repeated 4 times.
Outcomes	PFTs consisting of FVC, FEV_1, MEF_{50} and MEF_{25} all of 5 predicted. P_{t02}, P_{tco2}.
Notes	Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of how the participants were randomised.
Allocation concealment (selection bias)	Unclear risk	No mention of how the allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes in study design are reported.
Selective reporting (reporting bias)	Low risk	All outcomes are reported in full.
Other bias	Low risk	Good washout period, thus low risk of carry over effect. Groups similar at baseline regarding the most important prognostic indicators. No dropouts.

Lannefors 1992

Methods	RCT. Cross-over design. Each treatment given once.
Participants	CF with daily sputum production. 9 participants (6 male); mean age 25, range 12 - 36 years; mean FEV_1 51, range 20 - 78% predicted; mean Schwachman score 66, range 39 - 94 points.
Interventions	3 interventions: 1 to 5 day washout period between interventions. 1. PEP treatment - performed in a sitting position using a PEP mask and positive expiratory pressures 15 - 20 cm H_2O;

Lannefors 1992 *(Continued)*

	2. PD - participants alternated between deep and relaxed breaths while lying on the left side, rotated slightly backward towards supine, 15 degrees head down tilt, (PD position for postural drainage from right middle lobe) and sat up to cough; no percussion or vibrations were performed; 3. Physical exercise - physical exercise was performed on a cycle ergometer at 80% of the participant's peak work capacity (as assessed on their most recent annual maximal exercise test). Each 20-minute intervention session consisted of three 3-minute periods of performing the intervention, each followed by a 3-minute pause, during which a standard number of forced expirations from mid-lung volume and relaxed breaths were performed.
Outcomes	Mucus clearance was measured by delivering a radioaerosol (99mTc-labelled colloidal albumin) to the airways and measuring the distribution of radiolabeled secretions in the lung fields. Anterior and posterior planar gamma camera images of the thorax were collected for 2 minutes at baseline, after 15 minutes rest in sitting, after the 20-minute intervention, and after another 15 minutes rest in sitting. Clearance was calculated as a reduction in count rate between successive images. Whole lung clearance was calculated. In addition, the planar images were divided into a central 'hilar' region and peripheral region, and clearance from these regions was calculated.
Notes	No withdrawals or dropouts. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.
Selective reporting (reporting bias)	High risk	Not all outcome measures were reported with statistical analysis.
Other bias	Low risk	1 - 5 day washout period between interventions, thus low risk of carry over effect. Groups similar at baseline regarding the most important prognostic indicators.

McIlwaine 1991

Methods	RCT. Cross-over design. Treatment for 2 months.
Participants	CF diagnosis. 18 participants, aged 6 - 18 years of age.
Interventions	3 interventions each performed twice a day: One month washout period between interventions

McIlwaine 1991 *(Continued)*

	1. PEP treatment using the Astra Meditech mask - participants performed 15 breaths through the mask with a PEP between 10 - 20 cms H_20; this was followed by 2 - 3 huffs from a mid to high lung volume followed by a cough and cycle was repeated 6 times; 2. PDP - participants performed PD using 6 positions in the morning and 5 positions in the evening; in each position their chest wall was percussed for 3 minutes, this was followed by huffing and coughing; 3. AD - performed in a sitting position and participants were instructed to exhale to residual volume then perform TV manoeuvres at this level while adjusting the velocity of their expiratory airflow until they felt secretions moving; they then progressed to TV breathing at mid-lung volumes and then to high-lung volumes where they would cough up any secretions. Number of cycles was individualised to each participant, but each treatment session lasted between 20 - 30 minutes.
Outcomes	FEV_1, FVC, and FEF_{25-75} were measured at the start and end of each 2-month treatment period. Sputum weight weighed after one treatment session per week. Other measures included reported treatment duration, treatment comfort, requirement for assistance with treatment, flexibility of treatment times, control in performing own treatment, and how interruptive treatment was to daily living.
Notes	Published as Abstract only, further information obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and person providing the therapy were not blinded - unclear risk. Outcome assessors were blinded low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Unclear risk	Results reported for all outcome measures but not in full.
Other bias	Low risk	one month washout period between each intervention, thus low risk of carry over effect. Groups similar at baseline regarding the most important prognostic indicators Author of the study is one of this review's authors, thus to eliminate bias, the study was assessed by the other two independent authors of this paper and by the previous authors.

McIlwaine 1997

Methods	RCT. Parallel design. Treatment for 1 year.
Participants	CF confirmed by sweat test. 40 participants (22 male); age range 6 - 17 years; mean age 10.40 years (PEP group) and 9.75 years (PDPV group); mean FEV_1 80.47, range 37 - 115% predicted.

McIlwaine 1997 *(Continued)*

	Participants were excluded if their condition was not stable as judged by clinical evaluation, chest radiograph and pulmonary function. Also, no participant entered the study within 1 month of discharge from hospital or use of IV antibiotics or other intensive therapy for an exacerbation.
Interventions	2 interventions: 20 participants were randomised to each group. 1. PEP treatment - pressure 10 - 20 cm H_2O using an Astra Meditec PEP mask; seated participants breathed 15 times through the mask, followed by 2 - 3 forced expirations, cough and relaxed breathing, this was repeated 6 times over a 20-minute session; 2. PDP - performed forced expirations and vigorous coughing in 5 - 6 positions, 3 - 5 minutes of percussion, 2 - 4 minutes of expiratory vibrations; these sessions lasted 30 minutes. Both interventions were performed twice daily.
Outcomes	FEV_1, FVC, and FEF_{25-75} were measured at 3-month intervals. Clinical assessments using Shwachman and Huang scores. Chest radiographs were performed at the start and end of the 1 year period and measured using the Brasfield scoring system. Compliance was measured via daily record keeping, with those compliant with less than 85% of the twice-daily sessions over a 1-month period being withdrawn from the study. Adverse events and participant preference were assessed via questionnaire.
Notes	2 dropouts from each arm, due to non-compliance (< 85% of twice-daily sessions performed) or non-attendance at clinic. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised. Participants were first matched as pairs based on age, sex and FEV_1. Participants within each pair were randomly assigned by computer to either group.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and person providing the therapy were not blinded - unclear risk. Outcome assessors were blinded - low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts from each arm, due to non-compliance (< 85% of twice-daily sessions performed) or non-attendance at clinic. Intention to treat approach used.
Selective reporting (reporting bias)	Unclear risk	Not all outcome measures are reported with full statistical analysis.
Other bias	Low risk	Participants were matched as pairs at baseline, thus groups were similar at baseline regarding the most important prognostic indicators. Author of the study is one of this review's author's, thus to eliminate bias, the study was assessed by the other two independent authors of this paper and by the previous authors.

McIlwaine 2001

Methods	RCT. Parallel design.

McIlwaine 2001 *(Continued)*

	Treatment for 1 year.
Participants	CF confirmed by sweat test. 40 participants (24 male); age range 7 - 17 years; FEV_1 range 47 - 107% predicted; Schwachman score range 54 - 98 points. Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, or if they were not stable on clinical evaluation, chest radiograph or pulmonary function.
Interventions	2 interventions:20 participants were randomised to each group. 1. PEP treatment - participants inhaled and exhaled through the Astra Meditec PEP mask in sitting; the resistor which produced 10 to 20 cm H_2O pressure during mid-expiration was used. Over approximately 2 minutes, 15 tidal breaths with slightly active expiration were performed. Participants then removed the mask, performed 2 or 3 forced expirations, and coughed, followed by 1 - 2 minutes of relaxed breathing. This sequence was repeated 6 times and these 20-minute sessions were repeated twice daily; 2. Oscillating PEP - participants exhaled through the flutter device which was angled to maximise the sensation of vibration in the chest. In sitting, participants inhaled deeply through the nose, followed by a breath hold for 2 - 3 seconds, and exhaled through the device slightly into the expiratory reserve volume. After 10 - 15 breaths, participants huffed through the device, increasing the TV and speed of exhalation to precipitate coughing and expectoration. This sequence was repeated "until clear" and not for less than 15 minutes per session, twice daily. The daily regimen for use of the devices is not described.
Outcomes	FEV_1, FVC, and FEF_{25-75} and clinical assessment using Shwachman and Huang scores were measured at the beginning and at 3-monthly intervals throughout the study. Number of hospitalizations for pulmonary exacerbations were recorded throughout the study Compliance with the interventions was recorded daily by the participants. A monthly questionnaire recorded physical activity, general well-being, cough, sputum production, subjective impression of the therapy, and adverse events. Chest radiographs were evaluated by a blinded radiologist at the beginning and end of the study.
Notes	3 participants were withdrawn due to non-compliance (< 85% of twice-daily sessions performed over 1 month) in the PEP group. 5 participants dropped out from the flutter group stating that subjectively the flutter did not appear to clear their secretions. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised. Randomised using a computer-generated block of numbers.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and person providing the therapy were not blinded - unclear risk. Outcome assessors were blinded - low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants were withdrawn due to non-compliance (< 85% of twice-daily sessions performed over 1 month) in the PEP group. 5 participants dropped out from the flutter group stating that subjectively the flutter did not appear to clear their secretions, they also had a clinically significant deterioration in pulmonary function. intention to treat approach used.

McIlwaine 2001 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcome measures are reported in full.
Other bias	Low risk	Both groups were reported to be similar at baseline regarding the most important prognostic indicators. Author of the study is one of the authors on this review, thus to eliminate bias, the study was assessed by the other two independent authors of this paper and by the previous authors.

McIlwaine 2013

Methods	Multi-centre RCT. Parallel design. Treatment for 1 year.
Participants	CF confirmed by sweat test or genotyping. 107 participants from 12 CF centres (57 males); age range 6 - 47 years; FEV_1 over 40% predicted. Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, or if they were not stable on clinical evaluation, chest radiograph or pulmonary function. On entering the study, participants performed a 2-month washout period before being allocated to an intervention.
Interventions	2 interventions: 51 participants were randomised to PEP and 56 to HFCWO. 1. PEP - using a mask with pressures 10 - 20 cms H_20, participants breathed through the device for 15 breaths followed by 2 -3 huffs and a cough; this was repeated for 6 cycles; 2. HFCWO - using the InCourage^{TM} system; 6 sets of 5-minute cycles were performed with frequencies between 6 - 15 Hz, this was interspersed with huffing and coughing.
Outcomes	Number of pulmonary exacerbations and time to first exacerbation. PFTs measuring FVC, FEV_1 and $FEF_{25-75\%}$ in absolute change. Quality of life using the Cystic Fibrosis Questionnaire and patient satisfaction visual analogue scale.
Notes	There were 16 drop-outs during the washout period before participants commenced one of the two interventions being studied. These were not included in the results. A further 3 dropped out during the intervention period. These were included in analysis with intention to treat analysis. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised was by an independent statistician using a computer-generated randomisation table. Participants were matched for age, sex and pseudomonas status. The statistician also attempted to block patients within each centre to control for any treatment differences between centres.
Allocation concealment (selection bias)	Low risk	The randomisation was performed by an independent statistician who provided the randomisation to the centre after the participant had enrolled in the study.

McIlwaine 2013 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and person providing the therapy were not blinded - unclear risk. Outcome assessors were blinded - low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes in study design are reported.Dropouts prior to commencement of interventions being studies were not included in analysis. 3 dropouts during the intervention period were included in analysis with intention to treat approach.
Selective reporting (reporting bias)	Low risk	All outcomes in study design are reported. PFTs results were provided by the author.
Other bias	Low risk	Author of the study is one of this review's authors, thus to eliminate bias, the study was assessed by the other two independent authors of this paper.

Mortensen 1991

Methods	RCT. Cross-over design. Each treatment given once.
Participants	CF diagnosis and chronic pseudomonas infection. 10 participants (6 male); mean age was 20 years, range 15 - 26 years; mean FEV_1 38.5, range 26 - 101% predicted. Participants entered the study in the last 2 weeks of regular hospital admission for intravenous anti-pseudomonas treatment.
Interventions	3 interventions: 2 day washout period between interventions 1. PEP treatment - pressure 10 - 20 cm H_2O using a mask; seated participants breathed TV breathing with slightly active expirations through the system for 1 minute, followed by 1 - 2 forced expirations from mid to low lung volume, relaxed breathing and cough; this breathing regimen was repeated for 20 min; 2. Breathing exercises in postural drainage positions (BEpd) - participants breathed deeply 4 times followed by relaxed breathing for 10 minutes in each of right and left side lying with 20 degrees head down tilt; this was again followed by 1 - 2 forced expirations from mid to low lung volume, relaxed breathing and cough. The same number of huffs and coughs performed with the first treatment were matched with the subsequent active intervention. 3. Control - 20 minutes of resting in sitting with spontaneous coughing allowed.
Outcomes	Mucus clearance was measured directly by delivering a radioaerosol (99mTc-labelled albumin colloid) to the airways and then measuring the distribution of radiolabeled secretions within the lung fields. Posterior planar gamma camera images of the thorax were collected as single 5-minute exposures every 30 minutes for 3 hours. Clearance was calculated as a reduction in count rate between successive images. Whole lung clearance was calculated. In addition, the planar images were divided into central, mid and peripheral regions, and upper, mid and basal regions. Clearance from these regions was calculated. Wet weight of sputum expectorated during the initial 30-minute (intervention) period and for the remainder of the 3-hour clearance measurement period was measured. Sputum weight pre and post and 3 hours post and 99mTc-labelled sputum measured post.
Notes	No statement on withdrawals or dropouts. Published paper.

Risk of bias

Mortensen 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information was provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals or dropouts.
Selective reporting (reporting bias)	Low risk	All outcome measures are fully reported.
Other bias	Low risk	Two day washout period between each intervention, thus low risk of carry over effect. Groups similar at baseline using FEV_1 as the most important prognostic indicators.

Newbold 2005

Methods	RCT. Parallel design. Treatment for 13 months.
Participants	CF diagnosed by St Michael's Hospital CF Clinic, Toronto. 42 participants (24 male). PEP Group: 21 participants (15 male); mean age 28, SD 8.1 years; mean FEV_1 2.5, SD 1.2 litres; mean FEV_1 66, SD 19.9% predicted. Flutter Group: 21 participants (9 male); mean (SD) age 31 (8.7) years; mean (SD) FEV_1 2.2 (0.7) litres; mean (SD) FEV_1 69(18.5) % predicted. Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, had changed their medication within the past month, or did not have a daily cough or daily sputum.
Interventions	2 interventions: 21 participants were randomised to each group. 1. PEP treatment - pressure 10 - 20 cm H_2O using an Astra Meditec PEP mask; seated participants breathed 10 - 15 times through the mask, followed by huffing, coughing and relaxed breathing, this was repeated 5 - 6 times, over a 20-minute session, twice daily; 2. Oscillating PEP - participants exhaled through the flutter device (Axcan Scandipharm) which was angled to maximise the sensation of vibration in the chest. In sitting, participants inhaled deeply through the nose, followed by a breath hold for 2 - 3 seconds, and exhalation through the device. After 5 - 10 breaths, participants increased the TV and speed of exhalation through the device, to precipitate coughing and expectoration. This sequence was repeated "until clear" or for approximately 20 minutes, twice daily.
Outcomes	Slope of change in FEV_1, FVC, and FEF_{25-75} (absolute and % predicted). Number of hospitalisations. Adherence.
Notes	1 participant was withdrawn when he stopped attending the CF clinic.

Newbold 2005 *(Continued)*

	Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random numbers table and block randomisation were used to ensure that groups would be of equal size.
Allocation concealment (selection bias)	Low risk	Allocation was sealed in opaque envelopes by an independent assistant. The envelopes were open in sequence after a participant was enrolled.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and person providing the therapy were not blinded - unclear risk. Outcome assessors were blinded - low risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant was withdrawn when he stopped attending the CF clinic.
Selective reporting (reporting bias)	Low risk	Results are reported for all outcome measures.
Other bias	Low risk	Groups similar at baseline regarding the most important prognostic indicators.

Pfleger 1992

Methods	RCT. Cross-over design. Each treatment given once.
Participants	CF confirmed by repeat sweat tests, and sputum production of > 20 ml per day. 15 participants (9 female, 1 unspecified); mean age 16 years, range 9.8 - 22.4 years; mean Schwachman score 62.2, range 26 - 90 points. Participants were excluded if unstable at the time of investigation (criteria unspecified). 6 months before the study, each participant was trained in the 2 self-administered techniques (PEP and AD).
Interventions	5 interventions: One day washout period between each intervention. 1. Hi-PEP intervention - expiratory resistance chosen to increase the FVC to the greatest extent when performed through the PEP mask; participants inhale and exhale 8 - 10 times followed by a forced expiratory manoeuvre, all through the mask; 2. AD - participants breathed at low lung volumes with progressive increases in the lung volume at which breathing was performed in response to evidence of secretion transport; coughing and forced expiratory manoeuvres were avoided; 3. Hi-PEP for the first half of the session, followed by AD; 4. AD for the first half of the session, followed by Hi-PEP; 5. Control - spontaneous coughing only. Each intervention session was equal to the time taken for the individual participant to clear their lungs using AD, as judged from pre-study experience.
Outcomes	FEV_1, FVC, RV, and TLC were measured at all PFT measurement points. Wet weight of expectorated sputum during the complete (both halves) intervention period was also measured.
Notes	1 withdrawal due to development of an acute respiratory viral infection during the study.

Pfleger 1992 *(Continued)*

	Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawal due to development of an acute respiratory viral infection during the study.
Selective reporting (reporting bias)	High risk	Not all outcome measure results are reported in full.
Other bias	Unclear risk	Only one day washout period between each intervention. Groups similar at baseline regarding the most important prognostic indicators.

Pryor 2010

Methods	RCT. Parallel design. Treatment period: 12 months.
Participants	75 participants were enrolled into the study. Age range 17 - 63 years, 47 males, 28 females CF Diagnosed by sweat test. Inclusion criteria FEV_1 over 25% predicted. Enrolled when stable.
Interventions	5 interventions all performed in a sitting position. Number of treatments per day and length of treatment was individualised to each participant. 15 participants randomised to each group. 1. Active cycle of breathing techniques 2. AD 3. PEP 4. Oscillating PEP using the flutter 5. Oscillating PEP using the RC cornet
Outcomes	Primary outcome was FEV_1. Other PFT outcomes were FVC, MEF 25 and RV BMI, modified shuttle test, chronic respiratory questionnaire, short form 36 and number of course of IV antibiotics were also measured.

Pryor 2010 *(Continued)*

Notes	10 participants lost to follow up. Data reported on 65 using intention to treat. 53 participants completed the study. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computerised and used a random number sequence, stratified by FEV_1 and sputum volume.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and person providing the therapy were not blinded - unclear risk. Outcome assessors were blinded - low risk
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants requiring IV antibiotics is listed under outcome measures but was not reported as could not be analysed due to small numbers and the scattered nature of the data.
Selective reporting (reporting bias)	Unclear risk	Only the results of the primary outcome FEV_1 were reported in full. All the other outcome measures were reported only as no significant difference.
Other bias	Unclear risk	13 participants withdrew as they did not like the regimen they had been randomised to. Unsure if these participants were included in intention to treat or lost to follow up.

Steen 1991

Methods	RCT. Cross-over design. Each treatment given for 1 month.
Participants	CF confirmed by sweat tests. 28 participants (gender unspecified); mean age 14 years, range 8 - 21 years; mean FEV_1 68, range 15 - 114% predicted; mean Schwachman score 65, range 33 - 91 points.
Interventions	4 interventions: No washout period between each intervention 1. PEP treatment - pressure 10 - 15 cm H_2O; seated participants exhaled 10 - 15 times through an Astra or Vitapep mask, followed by forced expiration and cough, if required. This cycle was then repeated; 2. PEP & FET intervention - the following was added to the above technique, 1 or 2 forced expirations with an open glottis from mid-lung volume to low-lung volume followed by a period of relaxed diaphragmatic breathing (FET); 3. PDPV & FET intervention - participants received percussion in PD positions, with FET; 4. PEP-PDPV & FET intervention - participants performed PEP (position not defined) for 5 minutes, followed by PDPV & FET. Frequency and duration of treatment sessions was not specified. There was no washout period between months.
Outcomes	FEV_1 and FVC were measured at the start and finish of each month. At the end of each month, the wet weight of expectorated sputum over a 2-hour period which included a treatment with that month's in-

Steen 1991 *(Continued)*

	tervention was measured. At the end of the study period, participants nominated which intervention they would use as ongoing airway clearance physiotherapy.
Notes	2 withdrawals (1 death, 1 non-compliance) and 2 dropouts (1 pneumothorax, 1 subjective lack of effect). A fifth intervention, FET alone, was undertaken by a subset of 5 participants. This treatment was performed after the 4 randomly-assigned interventions and therefore does not form part of the randomised study. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 withdrawals (1 death, 1 non-compliance) and 2 dropouts (1 pneumothorax, 1 subjective lack of effect).
Selective reporting (reporting bias)	High risk	Not all outcomes were reported in full.
Other bias	High risk	There was no washout period between months, thus there is a potential for a carryover effect.

Tannenbaum 2005

Methods	RCT. Parallel design. Treatment period of 12 months.
Participants	30 children with CF, age range 6 - 15 years, 20 females.
Interventions	2 interventions: 15 participants were randomised to each group. 1. PEP (no further data provided); 2. Oscillating PEP provided by the RC cornet (no further data provided).
Outcomes	QWBS FEV_1, pulmonary exacerbations, LCI.
Notes	Information was provided from 3 abstracts, no further information obtained.

Tannenbaum 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified by age, sex and FEV_1 How randomisation was generated was not recorded.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts are reported, one from each group. One found the cornet ineffective and difficult to clean. The other preferred a previously used device. Used Intention to treat approach.
Selective reporting (reporting bias)	Unclear risk	Not all outcome measures results were provided in full. QWBS was reported as no significant changes over the year.
Other bias	Low risk	Groups were similar at baseline regarding the most important prognostic indicators.

Tyrrell 1986

Methods	RCT. Cross-over design. Each treatment given for 1 month.
Participants	CF diagnosed by the Nottingham City Hospital Cystic Fibrosis Clinic. 19 participants (after withdrawals, 9 females and 7 males); mean age 13 years, range 10 - 18 years; mean Schwachman score 62, range 47 - 85 points.
Interventions	2 interventions:There was no washout period between each treatment period. 1. PEP treatment - pressure 10 - 15 cm H_2O; seated participants exhaled 10 times through an Astra mask, followed by "forced expiratory coughing"; 2. PDP - participants received percussion and performed coughing in PD positions. Treatment was performed for 20 minutes, twice daily.
Outcomes	FEV 0.75, FVC, PEFR were recorded before, 20 minutes after, and 90 minutes after a single supervised treatment at the beginning of the randomisation month. Wet weight of sputum expectorated during the therapy was also measured. The same measures were repeated over a single treatment at the end of the randomisation month. In addition, during each treatment month, diary card records were kept regarding the following symptoms: sleep, cough, wheeze, activity, sputum production. (Details of the scoring system for these symptoms are not provided.) Although not listed as a formal outcome measures, antibiotic use and participant preference are also discussed in the results section.
Notes	3 withdrawals due to non-adherence. Those children who showed airway reversibility with salbutamol were asked to use it before treatment throughout the whole study. Published paper.

Tyrrell 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 withdrawals due to non-adherence.
Selective reporting (reporting bias)	High risk	Not all outcomes were reported in full.
Other bias	High risk	There was no washout period between each treatment period, thus there is a potential for a carryover effect.

van Asperen 1987

Methods	RCT. Cross-over design. Each treatment given for 4 weeks.
Participants	CF diagnosed by Camperdown or Westmead Hospitals, and daily sputum production. 13 participants (gender unspecified); age range 7 - 18 years. No change in treatment in the 2 months prior to commencing the study.
Interventions	2 interventions:There was no washout period between each treatment period. 1. PEP treatment - pressure 10 - 15 cm H_2O; participants inhaled and exhaled 10 - 15 times through an Astra mask (position unspecified), followed by forced expiration and coughing; 2. PDP - participants received manual percussion to all areas in PD positions, followed by forced expiration and coughing. The PEP intervention was continued for 20 minutes. PDP lasted "at least 20 minutes". Each intervention treatment was administered twice daily for 4 weeks. There was no washout period.
Outcomes	FEV_1 and FVC were measured before and 1 hour after the first treatment of each randomisation period. Volume of expectorated sputum was measured over 1 hour which commenced with the first treatment of the randomisation period.
Notes	2 withdrawals due to infective exacerbations and 1 dropout. Published paper.

Risk of bias

Bias	Authors' judgement	Support for judgement

van Asperen 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further details provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals due to infective exacerbations and one dropout.
Selective reporting (reporting bias)	High risk	Not all outcomes were reported in full.
Other bias	High risk	Groups similar at baseline regarding the most important prognostic indicators. There was no washout period between each treatment period, thus there is a potential for a carryover effect.

van Winden 1998

Methods	RCT. Cross-over design. Each treatment given for 2 weeks.
Participants	CF confirmed by sweat tests or DNA mutation analysis. 22 participants (12 male); median age 12 years, range 7 - 17 years; median FEV_1 82, range 55 - 129% predicted. Participants were excluded if they had been clinically unstable during the 2 weeks prior to entering the study, according to PEFR and symptoms scores (criteria not specified).
Interventions	2 interventions:There was a one week washout period between each treatment period. 1. PEP treatment - pressure 8 - 12 cm H_2O; seated participants breathed through an Astra Meditec PEP mask 15 times, followed by 3 huffs and coughing, this sequence was repeated 5 times; 2. Oscillating PEP (flutter) - participants inhaled deeply, held their breath for 2 - 3 seconds, then exhaled through the VarioRaw flutter device 15 times, following which the participant again huffed 3 times and coughed. This sequence was also repeated 5 times. The flutter was tilted upwards or downwards a few degrees from horizontal until the maximum vibration sensation was obtained. Each intervention was performed twice per day for 2 weeks, preceded by a 1-week washout period. During the washout weeks, all participants performed "routine physiotherapy" with huff and cough manoeuvres.
Outcomes	FEV_1, FVC, and TLC were measured before the initial, 1-week washout period. These measures were repeated on the first day of each of the 2 treatment periods, before and 30 minutes after the first session of therapy. At the end of the 2-week treatment periods, these measures were again taken 30 minutes after physiotherapy. Oxygen saturation via pulse oximetry was measured before during and after the first and last treatments of each 2-week period.
Notes	No withdrawals or dropouts. One week washout period between treatments. Published paper.

van Winden 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.
Selective reporting (reporting bias)	Low risk	All outcomes are reported in full.
Other bias	Low risk	There was a one week washout period between each treatment period, thus there is low risk of any carry over effect. Groups similar at baseline regarding the most important prognostic indicators.There was a one week washout period between treatments.

AD: autogenic drainage
BMI: body mass index
CE: cycle ergometry
CF: cystic fibrosis
FEV 0.75: forced expiratory volume in 0.75 sec
FEF_{25-75}: forced expiratory flow 25-75%
FET: forced expiratory technique
FEV_1: forced expiratory volume at one second
FRC: functional residual capacity
FVC: forced vital capacity
HFCC: high frequency chest compression
HFCWO: High frequency chest wall oscillation
Hi-PEP: High-pressure PEP
IV: intravenous
LCI: lung clearance index
PD: postural drainage
PDP: postural drainage with percussion
PDPV: postural drainage with percussion and vibration
PEP: positive expiratory pressure
PEFR: peak expiratory flow rate
PFT: pulmonary function test
pO2: blood test measuring oxygen in the blood
P_{tco2}: transcutaneously measured carbon dioxide tension
P_{t02}: transcutaneous oxygen tension
QWBS: quality of life using the quality of life well-being scaleRCT: randomised controlled trial
RV: residual volume
SD: standard deviation
SpO2: saturation of haemoglobin with oxygen using pulse oximetry
TLC: total lung capacity
TV: tidal volume
nBVS: non-invasive bilevel ventilatory support

SVC: slow vital capacity
W/kg: watt per kilogram

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

Study	Reason for exclusion
Aquino 2006	The intervention, to which PEP was compared, was not a physical airway clearance therapy.
Aquino 2012	Neither of the interventions were PEP.
Balestri 2004	Used a different type of PEP system (underwater tubing) which did not meet the PEP criteria for this review.
Battistini 2001	Used a different type of PEP system (underwater tubing) which did not meet the PEP criteria for this review.
Borka 2012	Study was not randomised.
Castle 1994	No outcome data were reported.
Dosman 2003	Used a different type of PEP system (positive end expiratory pressure) which did not meet the PEP criteria for this review.
Falk 1988	The intervention, to which PEP was compared, was not a physical airway clearance therapy.
Fitzgerald 2001	PEP versus other airway clearance was not the randomised comparison made in this study.
Fitzgerald 2005	The timing of dornase alfa was being compared in relation to PEP therapy. This is not study of the efficacy of PEP compared to another airway clearance technique.
Gotz 1995	No data were reported for the outcomes of interest.
Kraemer 1996	Neither of the interventions were PEP.
Laube 2000	The intervention to which PEP was compared was not a physical airway clearance therapy.
Liedtke 1996	Neither of the interventions were PEP.
Marks 1998	The use of PEP versus the other physical airway clearance therapy (flutter) was not the randomised comparison made in this study.
McCarren 2006	Study used PEP breathing, but not the PEP technique as defined in this review.
Munro 2007	Study was performed on post-transplant patients.
Oermann 2001	Neither of the interventions being compared was PEP.
Orlik 2000	The use of PEP versus the other physical airway clearance therapies was not the factor which was random in this study.
Padman 1999	Used a different type of PEP system (Vitalsigns flow independent system) which did not meet the PEP criteria for this review.
Patel 2013	Neither of the interventions being compared was PEP.
Placidi 2001	Study used PEP breathing, but not the PEP technique as defined in this review.

Study	Reason for exclusion
Roos 1987	Niether of the interventions were PEP.
Sanchez Riera 1999	PEP technique did not include huffing and was performed in a postural drainage position.
van der Schans 1991	Used a different type of PEP system (Vitalsigns flow independent system) which did not meet the PEP criteria for this review.
van Hengstum 1987	The study was performed in participants with chronic bronchitis.
Znotina 2000	The use of PEP versus the other physical airway clearance therapy (oscillating PEP) was not the factor which was randomised in this study.

PEP: positive expiratory pressure

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

Elkins 2005

Methods	Randomised, cross-over trial.
Participants	12 participants with CF aged 16 to 34 years.
Interventions	PEP compared to oscillating PEP, PDPV and ACBT.
Outcomes	Mucociliary clearance.
Notes	Results have not been published.

Grzincich 2008

Methods	Randomised trial, participants randomised to receive either HFCWO or PEP during the first 3 days of hospitalisation for an exacerbation.
Participants	23 participants. 12 female, mean age 25 years.
Interventions	Use of HFCWO at setting of 20 Hz for 30 minutes compared with 30 minutes of PEP; this occurred during the first 3 days of treatment.
Outcomes	FEV_1, FVC and FEF_{25-75} were assessed pre and 30 minutes post intervention. Sputum volume was collected after each intervention.
Notes	Abstract only, full paper not published as yet.

Kofler 1994

Methods	Randomised, cross-over trial.
Participants	33 children (19 boys, 14 girls) with CF, mean (SD) age 11 (3.9) years. 23 completed.

Kofler 1994 *(Continued)*

Interventions	ACBT compared to PEP mask in addition to conventional CF therapy. 4 months treatment A then changed to other treatment for a further 4 months.
Outcomes	FVC, FEV_1, MEEF, questionnaire re acceptability of techniques. Outcomes measured before and after each treatment period.
Notes	Abstract only.

Parreira 2008

Methods	RCT.
Participants	13 participants with CF mean (SD) age 18 (3) years.
Interventions	Flutter® compared to EPAP.
Outcomes	Short-term lung function changes.
Notes	Abstract only.

Rodriguez 2013

Methods	RCT.
Participants	20 participants with CF.
Interventions	PEP mask compared to NIV with Bilevel-PAP.
Outcomes	Lung function test, 6-minute walk test, blood gases, sputum culture, blood samples.
Notes	Abstract only.

Tonnesen 1982

Methods	Randomised, cross-over.
Participants	14 participants with CF, age range 12 - 29 years, mean age 15.9 years, chronic infection with *Pseudomonas aeruginosa*.
Interventions	PEP compared to conventional physiotherapy, 4 days
Outcomes	FVC, FEV_1, RV, FRC, TLC, PF, bacteriology (*Pseudomonas aeruginosa, Staphylococcal aureus, E. coli*)
Notes	Paper in Danish, needs full translation.

West 2010

Methods	RCT.
Participants	23 participants with CF.
Interventions	PEP mask compared to Acapella.
Outcomes	Change in lung function and exercise performance, total sputum production, patient satisfaction.
Notes	Published as Paper, unable to get hold of Paper at time of publishing.

Wong 2000

Methods	RCT.
Participants	17 participants with CF and suspected GER, mean age 12.6 years, 4 did not complete study.
Interventions	Oesophageal pH monitoring for 48 hours, in this time 2 sessions of PDP and 2 sessions of PEP in an upright position.
Outcomes	Reflux episodes per hour, fractional reflux time, cough.
Notes	Abstract only, waiting for further information.

ACBT: active cycle of breathing technique
CF: cystic fibrosis
EPAP: expiratory positive airway pressure
GER: gastroesophageal reflux
NIV: non-invasive ventilation
PAP: positive airway pressure
PEP: positive expiratory pressure
PDP: postural drainage and percussion
RCT: randomised controlled trial

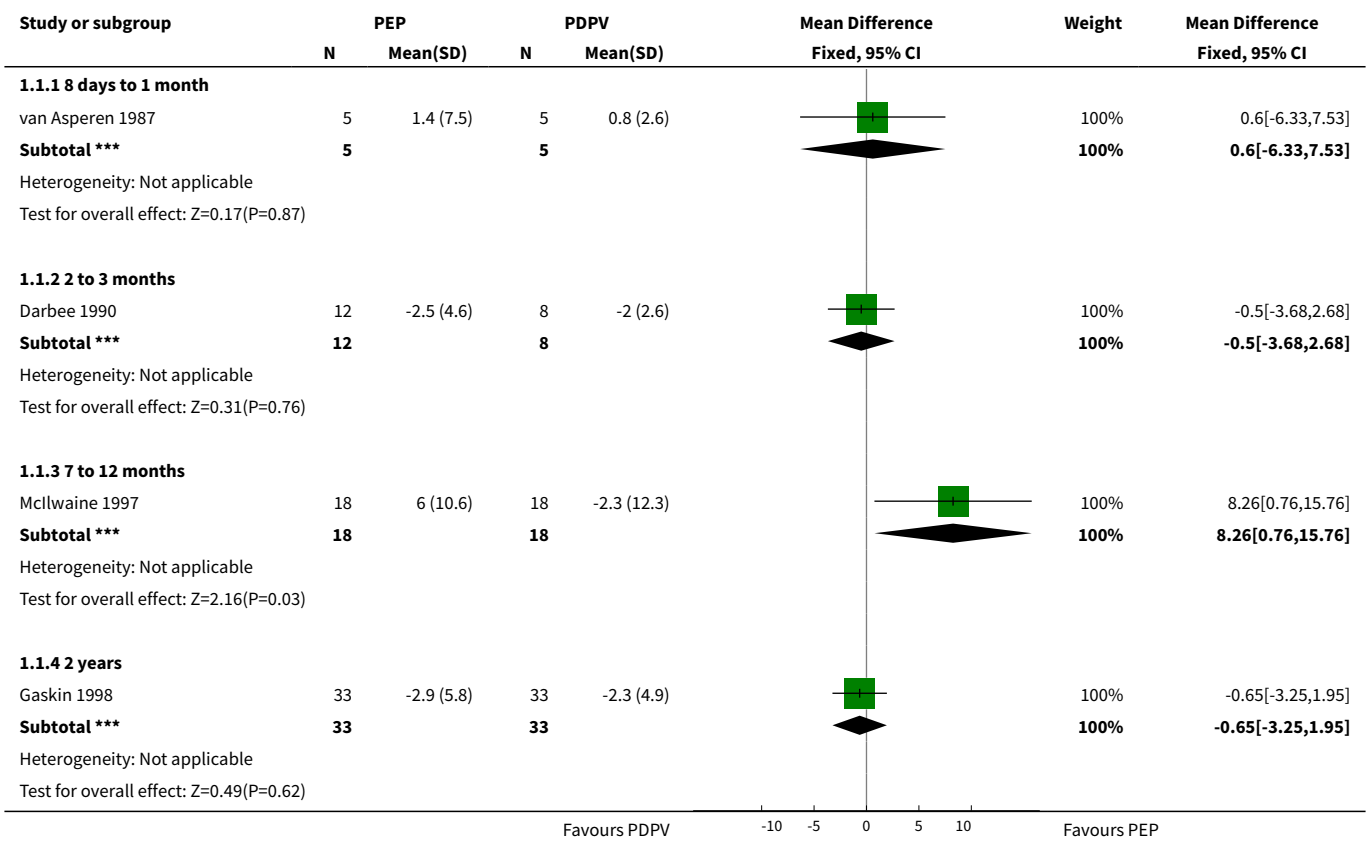
DATA AND ANALYSES

Comparison 1. PEP compared with postural drainage, percussion & vibration

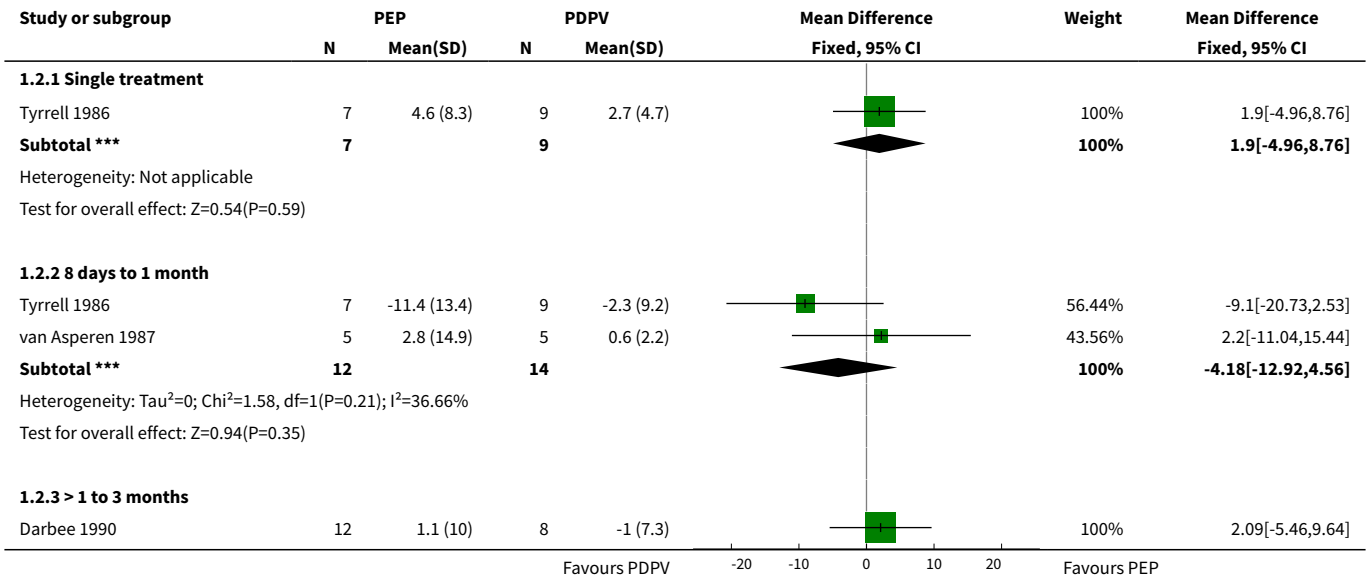
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Forced expiratory volume in 1 second (FEV_1)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 8 days to 1 month	1	10	Mean Difference (IV, Fixed, 95% CI)	0.60 [-6.33, 7.53]
1.2 2 to 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-3.68, 2.68]

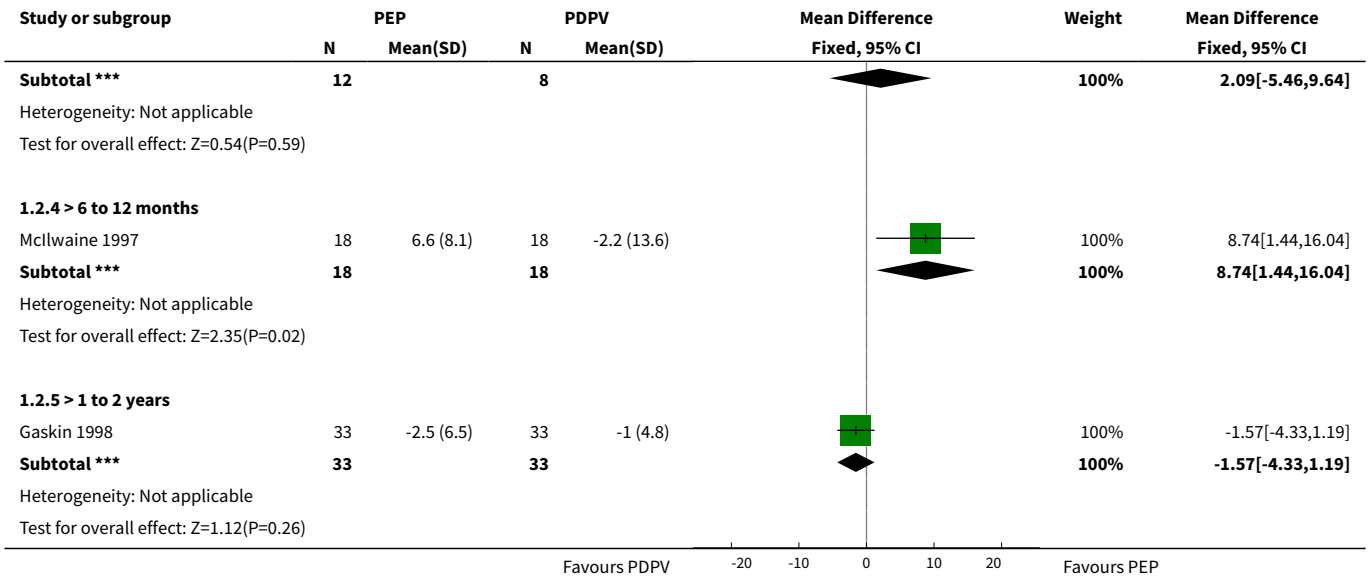
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.3 7 to 12 months	1	36	Mean Difference (IV, Fixed, 95% CI)	8.26 [0.76, 15.76]
1.4 2 years	1	66	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-3.25, 1.95]
2 Forced vital capacity (FVC)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Single treatment	1	16	Mean Difference (IV, Fixed, 95% CI)	1.90 [-4.96, 8.76]
2.2 8 days to 1 month	2	26	Mean Difference (IV, Fixed, 95% CI)	-4.18 [-12.92, 4.56]
2.3 > 1 to 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	2.09 [-5.46, 9.64]
2.4 > 6 to 12 months	1	36	Mean Difference (IV, Fixed, 95% CI)	8.74 [1.44, 16.04]
2.5 > 1 to 2 years	1	66	Mean Difference (IV, Fixed, 95% CI)	-1.57 [-4.33, 1.19]
3 Forced expiratory flow 25 - 75% (FEF 25-75)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 8 days to 1 month	1	10	Mean Difference (IV, Fixed, 95% CI)	-6.2 [-14.41, 2.01]
3.2 > 1 to 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-3.08 [-7.87, 1.71]
3.3 > 6 to 12 months	1	36	Mean Difference (IV, Fixed, 95% CI)	3.56 [-6.18, 13.30]
4 Total lung capacity (TLC)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 >1 to 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-3.38 [-13.67, 6.91]
5 Radiological imaging: increased bronchial markings	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 > 6 to 12 months	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.12]
6 Radiological imaging: change in Brasfield score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 > 6 to 12 months	1	36	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.20, 1.20]

Analysis 1.1. Comparison 1 PEP compared with postural drainage, percussion & vibration, Outcome 1 Forced expiratory volume in 1 second (FEV_1).

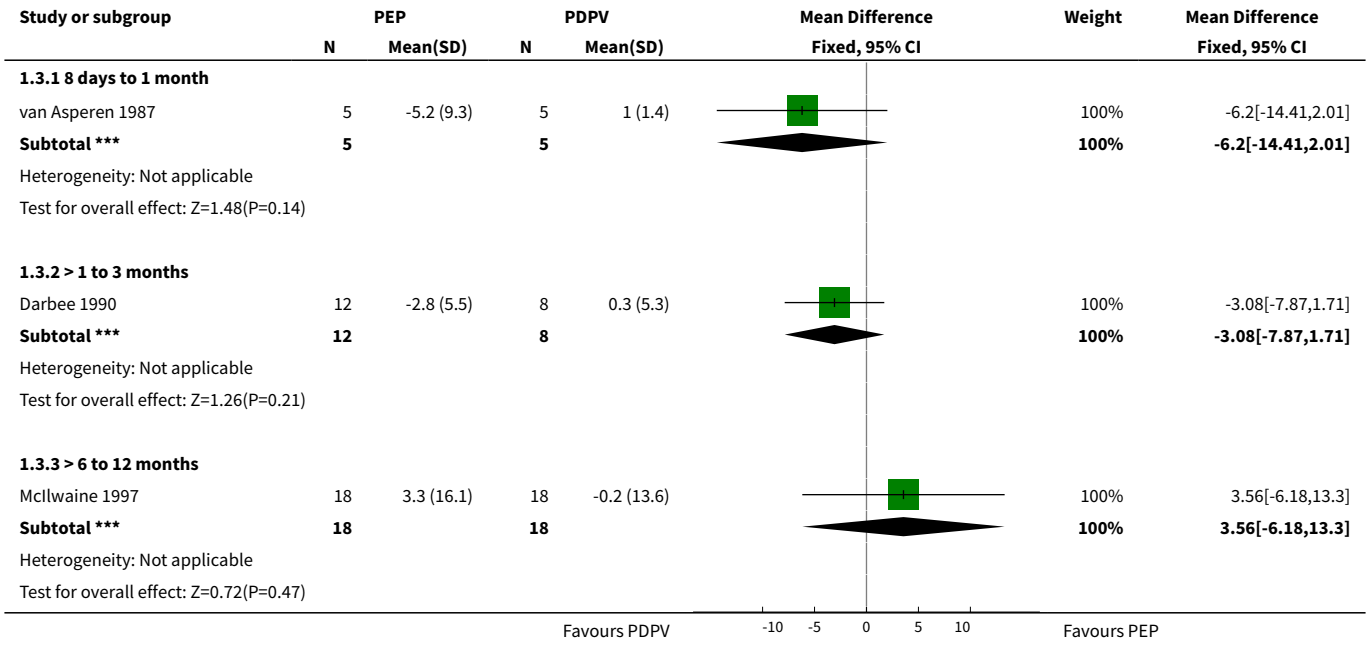


Analysis 1.2. Comparison 1 PEP compared with postural drainage, percussion & vibration, Outcome 2 Forced vital capacity (FVC).

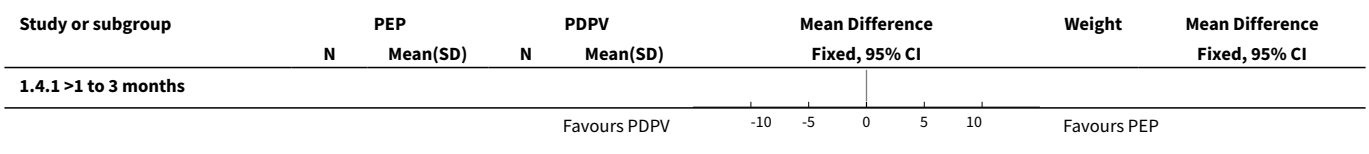


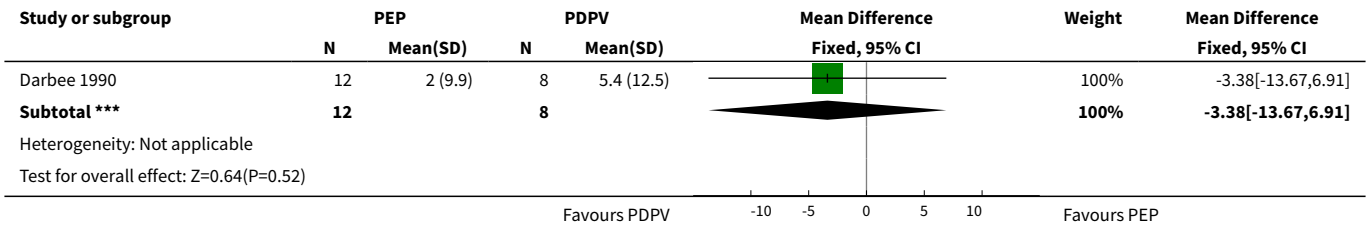


Analysis 1.3. Comparison 1 PEP compared with postural drainage, percussion & vibration, Outcome 3 Forced expiratory flow 25 - 75% (FEF 25-75).

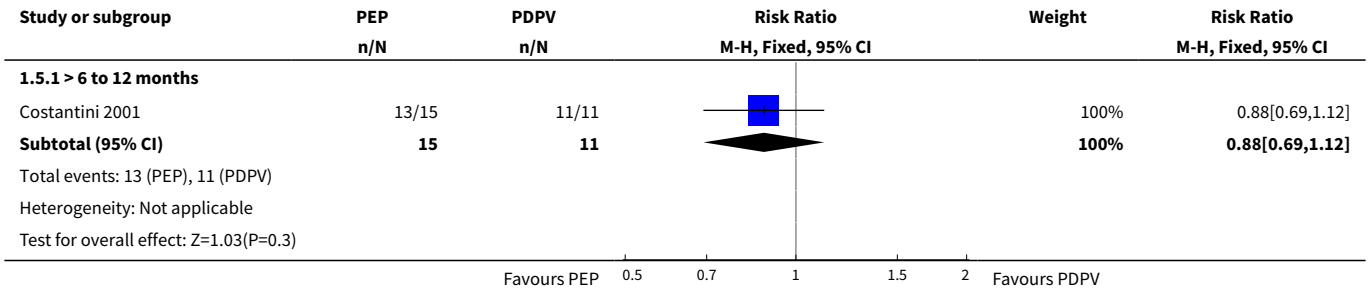


Analysis 1.4. Comparison 1 PEP compared with postural drainage, percussion & vibration, Outcome 4 Total lung capacity (TLC).

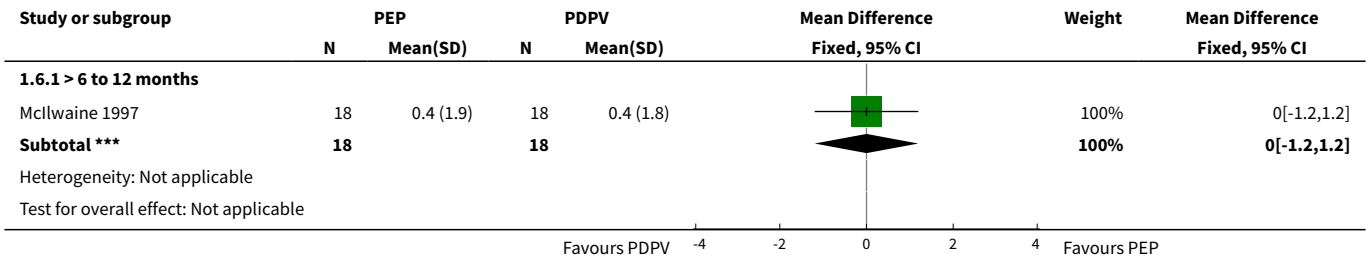




Analysis 1.5. Comparison 1 PEP compared with postural drainage, percussion & vibration, Outcome 5 Radiological imaging: increased bronchial markings.



Analysis 1.6. Comparison 1 PEP compared with postural drainage, percussion & vibration, Outcome 6 Radiological imaging: change in Brasfield score.



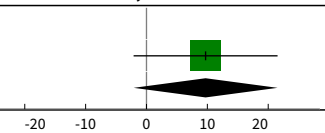
Comparison 2. PEP compared with oscillating PEP (Flutter and Cornet))

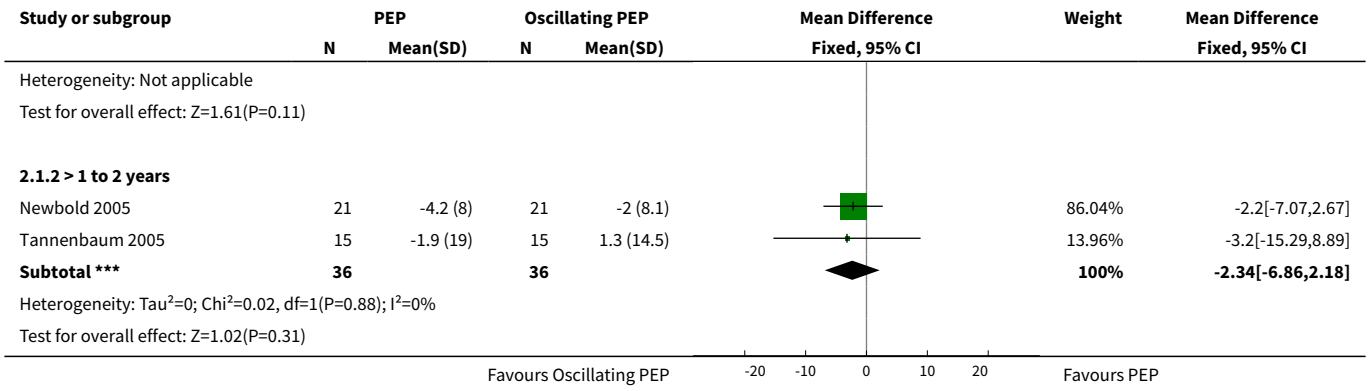
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Forced expiratory volume in 1 second (FEV_1)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 > 6 to 12 months	1	30	Mean Difference (IV, Fixed, 95% CI)	9.71 [-2.12, 21.54]
1.2 > 1 to 2 years	2	72	Mean Difference (IV, Fixed, 95% CI)	-2.34 [-6.86, 2.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Hospitalisations for respiratory exacerbation (number per participant)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 > 1 to 2 years	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.92, 0.12]
3 Forced vital capacity (FVC)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 > 6 to 12 months	1	30	Mean Difference (IV, Fixed, 95% CI)	8.68 [-0.54, 17.90]
3.2 > 1 to 2 years	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-6.27, 2.87]
4 Forced expiratory flow 25 - 75% (FEF 25-75)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 > 6 to 12 months	1	30	Mean Difference (IV, Fixed, 95% CI)	5.29 [-7.84, 18.42]
4.2 > 1 to 2 years	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-6.50, 4.30]
5 Lung Clearance Index	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 1 year	1	30	Mean Difference (IV, Fixed, 95% CI)	0.8 [-1.36, 2.96]
6 Adherence: at least 85% of prescribed treatments performed	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 > 6 to 12 months	1	40	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 98.00]
7 Participant preference: self-withdrawal due to lack of perceived effectiveness	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 > 6 to 12 months	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.54]

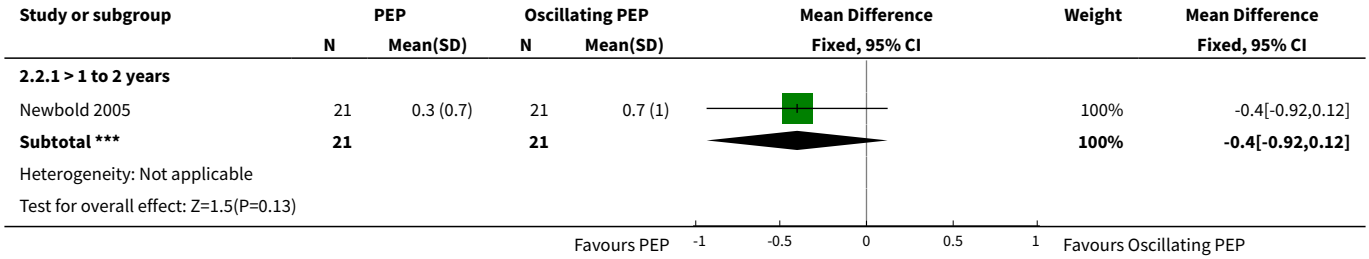
Analysis 2.1. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 1 Forced expiratory volume in 1 second (FEV_1).

Study or subgroup	PEP N	PEP Mean(SD)	Oscillating PEP N	Oscillating PEP Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 > 6 to 12 months							
McIlwaine 2001	17	-1.2 (9.9)	13	-10.9 (20)		100%	9.71[-2.12,21.54]
Subtotal ***	**17**		**13**			**100%**	**9.71[-2.12,21.54]**

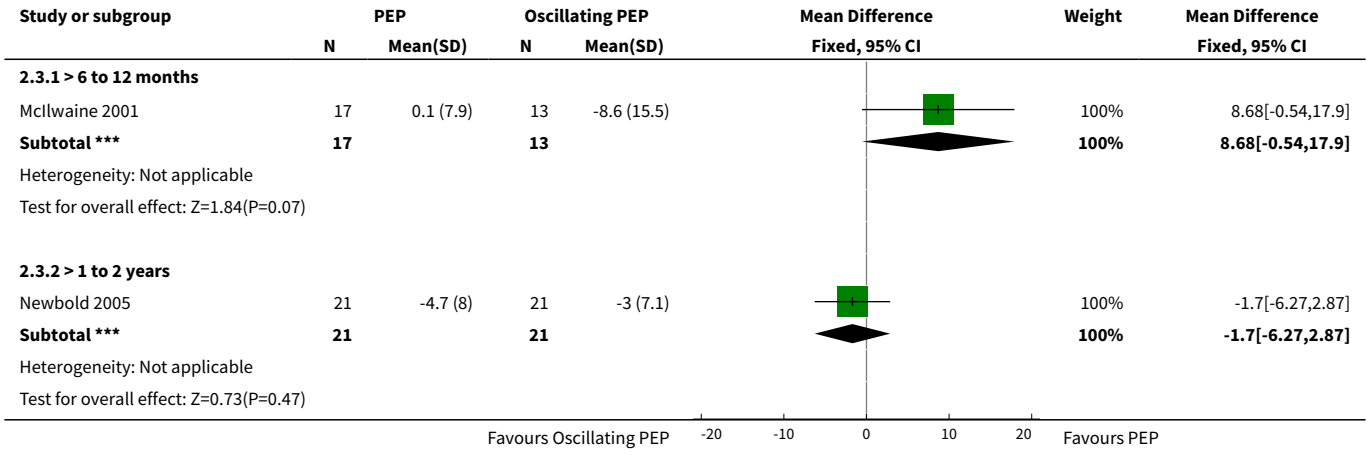




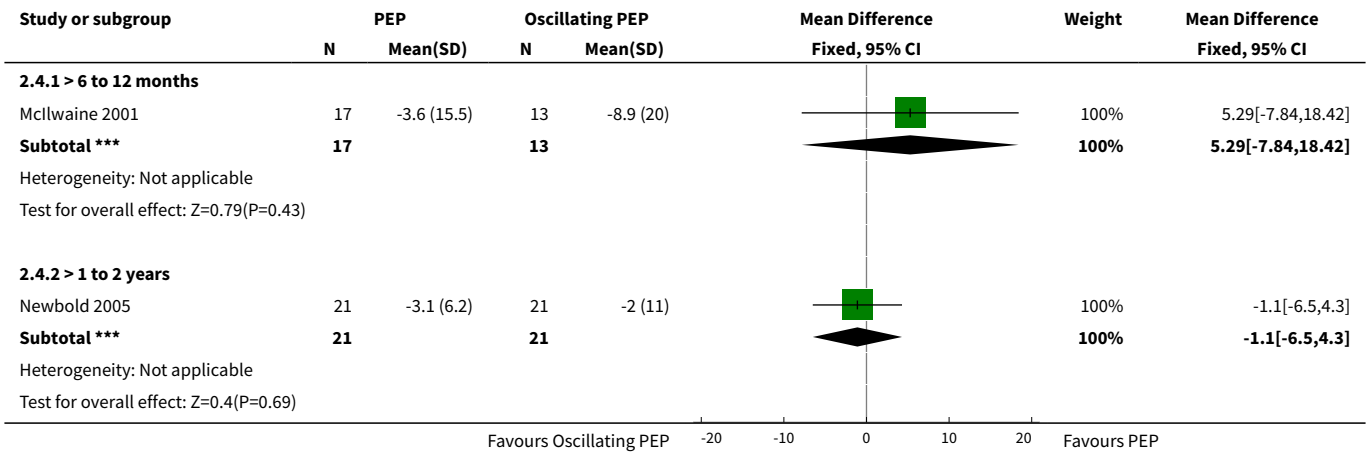
Analysis 2.2. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 2 Hospitalisations for respiratory exacerbation (number per participant).



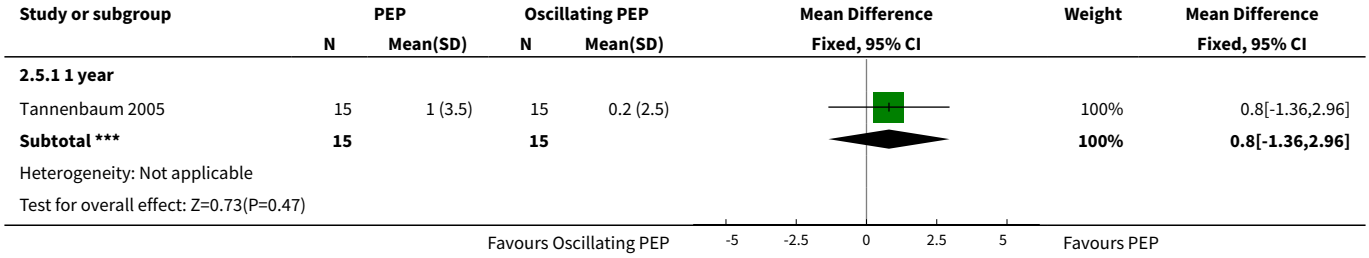
Analysis 2.3. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 3 Forced vital capacity (FVC).



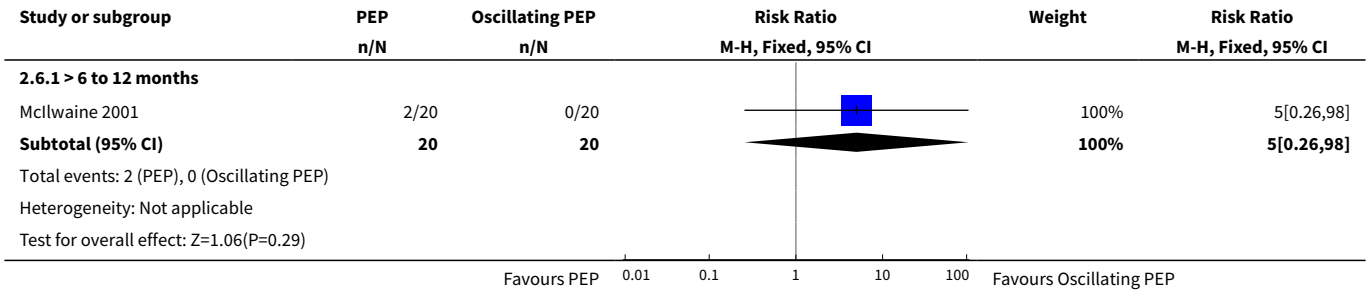
Analysis 2.4. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 4 Forced expiratory flow 25 - 75% (FEF 25-75).



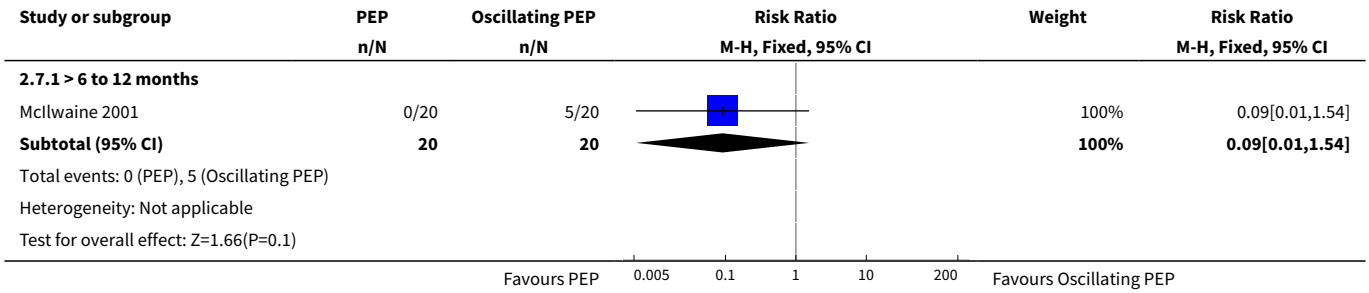
Analysis 2.5. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 5 Lung Clearance Index.



Analysis 2.6. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 6 Adherence: at least 85% of prescribed treatments performed.



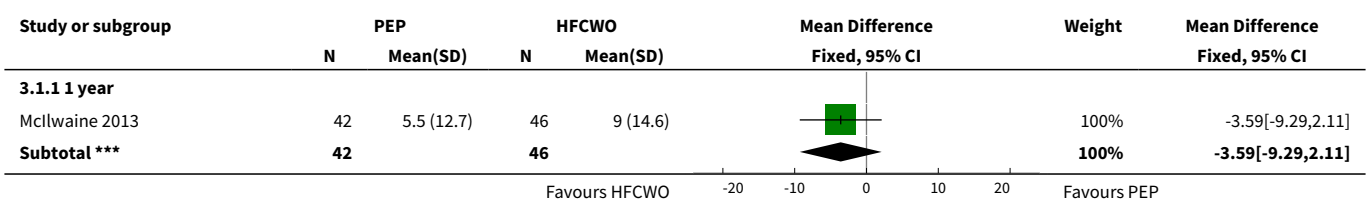
Analysis 2.7. Comparison 2 PEP compared with oscillating PEP (Flutter and Cornet)), Outcome 7 Participant preference: self-withdrawal due to lack of perceived effectiveness.

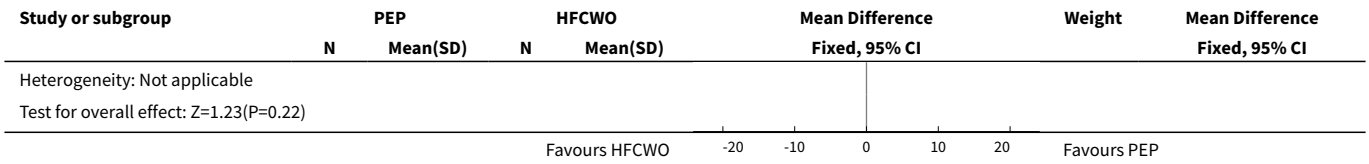


Comparison 3. PEP compared with high frequency chest wall oscillation (HFCWO)

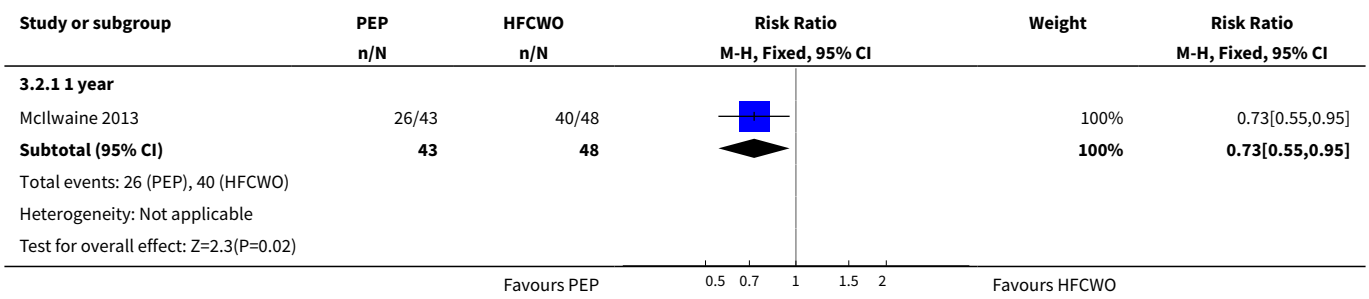
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Forced expiratory volume in 1 second (FEV_1)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 1 year	1	88	Mean Difference (IV, Fixed, 95% CI)	-3.59 [-9.29, 2.11]
2 Participants experiencing a respiratory exacerbation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 1 year	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.95]
3 Forced vital capacity (FVC)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 1 year	1	88	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-10.30, 0.30]
4 Forced expiratory flow 25 - 75% (FEF 25-75)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 1 year	1	88	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-12.54, 11.86]

Analysis 3.1. Comparison 3 PEP compared with high frequency chest wall oscillation (HFCWO), Outcome 1 Forced expiratory volume in 1 second (FEV_1).

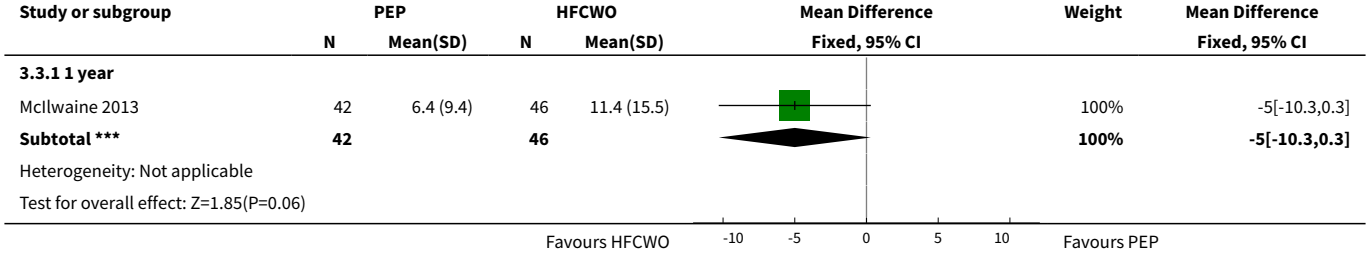




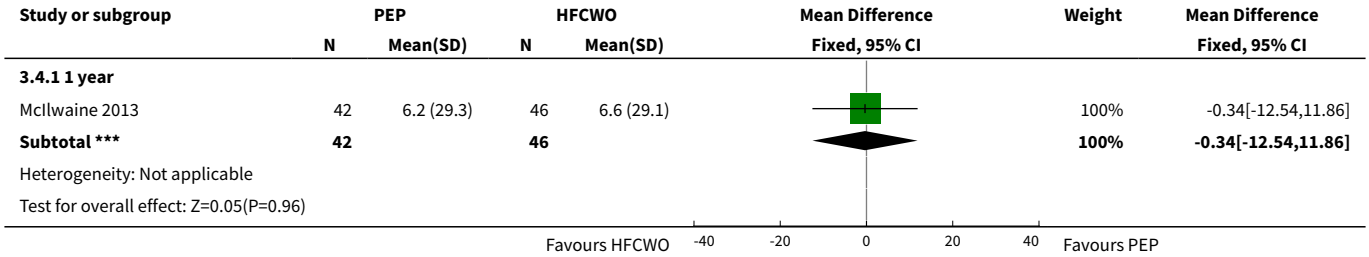
Analysis 3.2. Comparison 3 PEP compared with high frequency chest wall oscillation (HFCWO), Outcome 2 Participants experiencing a respiratory exacerbation.



Analysis 3.3. Comparison 3 PEP compared with high frequency chest wall oscillation (HFCWO), Outcome 3 Forced vital capacity (FVC).



Analysis 3.4. Comparison 3 PEP compared with high frequency chest wall oscillation (HFCWO), Outcome 4 Forced expiratory flow 25 - 75% (FEF 25-75).



ADDITIONAL TABLES

Table 1. Wet weight of sputum during and 50 minutes after treatment (Falk 1984)

Treatment	Mean (range) weight	P value
PEP in sitting	21.6 (12.5 - 53.5) g	P < 0.01
PEP in PD positions	17.4 (5.8 - 50.7) g	P < 0.01
Pursed Lip Breathing	15.0 (5.4 - 44.9) g	P < 0.01
PDPV	10.0 (1.9 - 51.1) g	P < 0.01

PD: postural drainage
PDPV: postural drainage, percussion and vibration
PEP: positive expiratory pressure

Table 2. FVC change after four treatments (Falk 1984)

Treatment	Mean (range) change	P value
PEP in sitting	+6.6 (0 - 11) %	P < 0.01
PDPV	- 4.7 (0 - 7.9) %	P < 0.01
PEP in PD positions	not stated	
Pursed Lip Breathing	not stated	
	NB It is unclear whether these percentages refer to absolute percentage change or change in % predicted.	

FVC: forced vital capacity
PDPV: postural drainage, percussion and vibration
PEP: positive expiratory pressure

Table 3. Oxygenation change by 35 minutes after treatment (Falk 1984)

Treatment	Mean (1-3 quartile)	Mean Rx duration *	P value
PEP in sitting	14.4 (4.6 - 27.4) %	20 min	P < 0.01
PEP in pd	3.2 (0 - 15.4) %	39 min	
PLB	2.4 (-8.0 - 11.3) %	21 min	
PDPV	4.3 (-9.4 - 12.1) %	37 min	
NB Treatment durations unequal			

PD: postural drainage
PDPV: postural drainage, percussion and ventilation
PEP: positive expiratory pressure
PLB: pursed lip breathing
Rx: treatment

Table 4. Adherence at one year (McIlwaine 1997)

Treatment	Adherence
PEP	92% (SD not stated)
PDPV	96% (SD not stated)

PDPV: postural drainage, percussion and ventilation
PEP: positive expiratory pressure
SD: standard deviation

Table 5. Adherence at one year (McIlwaine 2001)

Treatment	Adherence
PEP	95.6% (SD not stated)
Flutter	93.8% (SD not stated)

PEP: positive expiratory pressure
SD: standard deviation

Table 6. FEV1 after single treatment (Pfleger 1992)

Treatment	Mean (SD) FEV1	P value
Hi-PEP	54 (20) % predicted	$P < 0.05$
AD	56 (19) % predicted	NS
Hi-PEP then AD	55 (18) % predicted	$P < 0.02$
AD then Hi-PEP	54 (19) % predicted	NS

AD: autogenic drainage
NS: non significant
PEP: positive expiratory pressure

Table 7. Percentage of radioaerosol retention (Falk 1993)

Treatment	Mean (SD) at 0.5 hr	Mean (SD) at 1.0 hr	Mean (SD) at 2.0 hr
PEP + FET	92.4 (5.0) %	90.1 (4.8) %	86.9 (5.1) %
FET	92.7 (5.3) %	90.8 (5.4) %	89.9 (6.4) %

FET: forced expiration technique
PEP: positive expiratory pressure
SD: standard deviation

Table 8. Wet weight of sputum during and for 30 minutes after treatment (Hofmeyer 1986)

Treatment	Mean (range) weight

Table 8. Wet weight of sputum during and for 30 minutes after treatment (Hofmeyer 1986) *(Continued)*

BE in PD positions	79.8 (30.7 - 219.8) g
PEP in PD positions	70.6 (24.7 - 256.8) g
PEP in sitting	66.1 (15.3 - 189.4) g

BE: breathing exercises
PD: postural drainage
PEP: postive expiratory pressure

Table 9. Wet weight of sputum during treatment (Pfleger 1992)

Treatment	Mean (SD) weight
Hi-PEP	50 (29) g
AD	35 (25) g
Hi-PEP then AD	44 (29) g
AD then Hi-PEP	39 (23) g
	NB Data measured from graph

AD: autogenic drainage
PEP: positive expiratory pressure
SD: standard deviation

Table 10. FVC after single treatment (Pfleger 1992)

Treatment	Mean (SD) FVC	P value
Hi-PEP	73 (20) % predicted	P < 0.01
AD	74 (19) % predicted	P < 0.05
Hi-PEP then AD	73 (20) % predicted	P < 0.01
AD then Hi-PEP	71 (21) % predicted	NS

AD: autogenic drainage
FVC: forced vital capacity
NS: non significant
PEP: positive expiratory pressure
SD: standard deviation

Table 11. Oxygenation change during treatment (Kofler 1998)

Treatment	Mean (SD) Chg SpO2	P value
PEP	0.04 (1.28) %	P = 0.036
nBVS	1.2 (2.12) %	P = 0.036

PEP: positive expiratory pressure
nBVS: non-invasive bilevel ventilatory support
SD: standard deviation
SpO2: percentage of oxygen saturation in blood

Table 12. Measures of technique acceptability (McIlwaine 1991)

Treatment	Mean Duration of Rx	Comfort Score	Flexibility Score	In Control of Own Rx	Disruption Score
PEP	21	75	73	89	33
AD	25	84	73	87	35
PDPV	27	49	42	62	63
		0 = very uncomfortable	0 = very rigid	0 = no control	0 = Rx not interruptive
		100 = very comfortable	100 = very flexible	100 = full control	100 = Rx very interruptive

AD: autogenic drainage
PDPV: postural drainage, percussion and vibration
PEP: positive expiratory pressure
Rx: treatment

Table 13. FEV1 change over two years in participants under 19 years of age (Gaskin 1998)

Treatment	FEV1 change
PEP	-1.58% predicted per year (SD not stated)
PDPV	-1.65% predicted per year (SD not stated)

PDPV: postural drainage, percussion and ventilation
PEP: positive expiratory pressure
SD: standard deviation

APPENDICES

Appendix 1. Search strategy CINAHL

1982 to 2001
#1. Positive expiratory pressure OR PEP OR High pressure PEP
#2. Cystic fibrosis OR CF OR Mucoviscidosis
#3. #1 AND #2

WHAT'S NEW

Date	Event	Description
20 May 2015	New citation required and conclusions have changed	The conclusions of this review have been amended due to the inclusion of new studies and the exclusion of previously included studies.
20 May 2015	New search has been performed	A search of the Group's Cystic Fibrosis Trials register identified potentially eligible trials. Six newly identified studies met the inclusion criteria (Darbee 2005; Fainardi 2011; Lagerkvist 2006; McIlwaine 2013; Pryor 2010; Tannenbaum 2005). A further eight were excluded after assessment (Aquino 2006; Borka 2012; Fitzgerald 2005; McCarren 2006; Munro 2007; Patel 2013; Placidi 2001; Sanchez Riera 1999). A total of six studies are awaiting assessment (Elkins 2005; Kofler 1994; Parreira 2008; Rodriguez 2013; West 2010; Wong 2000). Five studies that were included in the previous publication of this paper have been excluded (Balestri 2004; Battistini 2001; Padman 1999; Placidi 2001; van der Schans 1991). Two used an underwater positive expiratory pressure (PEP) technique, two used a flow-independent PEP system and the fifth one, which had been published previously only as an abstract, has now been published as a full paper and revealed that the technique studied was not the PEP technique. A new review team has updated the review which was originally Pubilshed by Mark Elkins, Alice Jones and Cees van der Schans.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 1, 2004

Date	Event	Description
12 November 2008	Amended	Converted to new review format.
22 February 2006	Amended	Cees van der Schans has stepped down as co-author on this review as from February 2006.
22 February 2006	New search has been performed	Five studies have been added to the list of included studies in this update (Balestri 2004; Battistini 2001; Darbee 2004; Newbold 2005; Placidi 2001). Five studies have been added to the list of excluded studies (Castle 1994; Dosman 2003; Fitzgerald 2001; Oermann 2001; Orlik 2000).

CONTRIBUTIONS OF AUTHORS

Maggie McIlwaine, Brenda Button and Kerry Dwan updated the review which was originally drafted by Mark Elkins, Alice Jones and Cees van der Schans.

Maggie McIlwaine and Brenda Button independently assessed studies for inclusion in the updates of this review from 2014; Kerry Dwan and Brenda Button independently assessed the studies which were authored by McIlwaine. All review authors contributed to data extraction

and updated the text and analyses in this review. Maggie McIlwaine wrote the text of this version with contributions from Brenda Button; the original text was written by Mark Elkins, with contributions from Alice Jones.

Maggie McIlwaine acts as guarantor of the review.

DECLARATIONS OF INTEREST

Maggie McIlwaine is the Principal Investigator for four of the included studies. These studies were independently assessed by the other review authors.

Brenda Button declares no potential conflict of interest.

Kerry Dwan declares no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was based on the previous review of 2006. A new team undertook the 2014 review and we amended the primary outcomes to include direct measures of mucus clearance. The number of respiratory exacerbations was kept as a primary outcome, however the number of days of intravenous antibiotic use was removed. This was because, between 2006 and 2014, respiratory exacerbations had further been defined to include both oral and IV antibiotics. Well-being, adverse effects, exercise tolerance and patient preference were moved to secondary outcomes as none of the studies reviewed had reported any of them as a primary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Chest Wall Oscillation; Cystic Fibrosis [complications] [*therapy]; Drainage, Postural; Forced Expiratory Volume; Mucociliary Clearance; Mucus [*metabolism]; Positive-Pressure Respiration [instrumentation] [*methods]; Randomized Controlled Trials as Topic; Vital Capacity

MeSH check words

Humans