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Airway clearance techniques for chronic obstructive pulmonary disease (Review)

Osadnik CR, McDonald CF, Jones AP, Holland AE

Osadnik CR, McDonald CF, Jones AP, Holland AE.
Airway clearance techniques for chronic obstructive pulmonary disease.
Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD008328.
DOI: 10.1002/14651858.CD008328.pub2.

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[Intervention Review]

Airway clearance techniques for chronic obstructive pulmonary disease

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 3, 2012.

Citation: Osadnik CR, McDonald CF, Jones AP, Holland AE. Airway clearance techniques for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD008328. DOI: 10.1002/14651858.CD008328.pub2.

ABSTRACT

Background

Cough and sputum production are common in chronic obstructive pulmonary disease (COPD) and are associated with adverse clinical outcomes. Airway clearance techniques (ACTs) aim to remove sputum from the lungs, however evidence of their efficacy during acute exacerbations of COPD (AECOPD) or stable disease is unclear.

Objectives

To assess the safety and efficacy of ACTs for individuals with AECOPD and stable COPD.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials from inception to October 2011, and PEDro in October 2009.

Selection criteria

We included randomised parallel trials and randomised cross-over trials which compared an ACT to no treatment, cough or sham ACT in participants with investigator-defined COPD, emphysema or chronic bronchitis.

Data collection and analysis

Two review authors independently conducted data extraction and assessed the risk of bias. We analysed data from studies of AECOPD separately from stable COPD, and classified the effects of ACTs as 'immediate' (less than 24 hours), 'short-term' (24 hours to eight weeks) or 'long-term' (greater than eight weeks). One subgroup analysis compared the effects of ACTs that use positive expiratory pressure (PEP) to those that do not.

Main results

Twenty-eight studies on 907 participants were included in the review. Study sample size was generally small (range 5 to 96 people) and overall quality was generally poor due to inadequate blinding and allocation procedures. Meta-analyses were limited by heterogeneity of outcome measurement and inadequate reporting of data.

In people experiencing AECOPD, ACT use was associated with small but significant short-term reductions in the need for increased ventilatory assistance (odds ratio (OR) 0.21, 95% confidence interval (CI) 0.05 to 0.85; data from four studies on 171 people), the duration of ventilatory assistance (mean difference (MD) -2.05 days, 95% CI -2.60 to -1.51; mean duration for control groups seven days; data from two studies on 54 people) and hospital length of stay (MD -0.75 days, 95% CI -1.38 to -0.11; mean duration for control groups nine days; one study on 35 people). Data from a limited number of studies revealed no significant long-term benefits of ACTs on the number of exacerbations or

hospitalisations, nor any short-term beneficial effect on health-related quality of life (HRQoL) as measured by the St. George's Respiratory Questionnaire (SGRQ) total score (MD -2.30, 95% CI -11.80 to 7.20; one study on 59 people).

In people with stable COPD, data from single studies revealed no significant short-term benefit of ACTs on the number of people with exacerbations (OR 3.21, 95% CI 0.12 to 85.20; one study on 30 people), significant short-term improvements in HRQoL as measured by the SGRQ total score (MD -6.10, 95% CI -8.93 to -3.27; one study on 15 people) and a reduced long-term need for respiratory-related hospitalisation (OR 0.27, 95% CI 0.08 to 0.95; one study on 35 participants).

The magnitude of effect of PEP-based ACTs on the need for increased ventilatory assistance and hospital length of stay was greater than for non-PEP ACTs, however we found no statistically significant subgroup differences. There was one report of vomiting during treatment with postural drainage and head-down tilt.

Authors' conclusions

Evidence from this review indicates that airway clearance techniques are safe for individuals with COPD and confer small beneficial effects on some clinical outcomes. Consideration may be given to the use of airway clearance techniques for patients with COPD in both acute and stable disease, however current studies suggest that the benefits achieved may be small.

PLAIN LANGUAGE SUMMARY

Airway clearance techniques for chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is an umbrella term for chronic lung conditions characterised by airflow obstruction that cannot be fully reversed, such as emphysema and chronic bronchitis. Individuals with COPD often experience breathlessness, cough and sputum which may worsen during acute flare-ups. Airway clearance techniques (ACTs) are techniques that aim to clear sputum from the lungs. The usefulness of ACTs for individuals with acute flare-ups of COPD or stable COPD has been difficult to ascertain.

This review comprised 28 studies of 907 participants, with the quality of evidence being generally poor. Performing ACTs during an acute flare-up of COPD reduced the likelihood of needing mechanical assistance to breathe, as well as the length of time for which it was required. Time spent in hospital was slightly reduced, but there was little evidence to suggest any benefit on future flare-ups or health-related quality of life. Performing ACTs during stable COPD did not appear to affect flare-ups or hospitalisations, however it may improve health-related quality of life.

Techniques which involve breathing out against a positive expiratory pressure resistance may provide greater benefits than other types of ACTs. The lack of adverse events observed in this review suggests that ACTs are safe for individuals with COPD.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Airway clearance techniques for individuals with an exacerbation of COPD

ACTs for individuals with an AECOPD

Patient or population: individuals with an exacerbation of COPD
Settings: hospital (inpatient ward or emergency department)
Intervention: airway clearance techniques (ACTs)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ACTs				
Need for increased ventilatory assistance (invasive or non-invasive)	**Study population**		**OR 0.21** (0.05 to 0.85)	171 (4 studies)	⊕⊕⊝⊝ **low** [1,2]	
	112 per 1000	**26 per 1000** (6 to 97)				
	Medium-risk population					
	67 per 1000	**15 per 1000** (4 to 58)				
Duration of ventilatory assistance days	7 days[3]	The mean duration of ventilatory assistance in the intervention groups was **2.05 lower** (2.6 to 1.51 lower)		54 (2 studies)	⊕⊕⊝⊝ **low** [1,2]	
Length of hospital stay days	9 days[3]	The mean length of hospital stay in the intervention groups was **0.75 lower** (1.38 to 0.11 lower)		171 (3 studies)	⊕⊕⊝⊝ **low** [1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ACT: airway clearance technique; **AECOPD:** acute exacerbation of chronic obstructive pulmonary disease; **CI:** Confidence interval; **OR:** Odds ratio

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

Very low quality: We are very uncertain about the estimate.

[1] (-1 limitations) Some significant risks of bias across included studies.
[2] (-1 imprecision) Small sample sizes across included studies +/- wide confidence intervals.
[3] Mean duration in control arm of trials.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a disabling respiratory condition defined by airflow obstruction which is not fully reversible (Rabe 2007). It is a major source of global mortality and healthcare burden and has a rising prevalence (World Health Organization 2008). Individuals with COPD are characterised by symptoms such as chronic and progressive dyspnoea, cough and sputum production (Rabe 2007). Chronic cough and sputum production are independently associated with more frequent exacerbations and increased risk of hospitalisation (Burgel 2009) as well as being independent predictors of premature COPD-related death (Ekberg-Aronsson 2005; Lange 1990; Prescott 1995). Removal of sputum from the airways may therefore be a beneficial goal of therapy.

Description of the intervention

Airway clearance techniques (ACTs) are techniques performed by the external application of forces to clear pulmonary secretions from the lungs (Holland 2006). There are many types of ACTs used in clinical practice, including 'conventional' therapy (e.g. postural drainage, percussion, vibration), breathing exercises (e.g. active cycle of breathing technique, autogenic drainage), hand-held positive expiratory pressure (PEP) devices (e.g. mask, mouthpiece or oscillatory PEP) and mechanical devices that are applied externally to the chest wall (e.g. high-frequency chest wall oscillation). Most ACTs involve a degree of active respiratory effort, however some can be applied passively (e.g. postural drainage).

How the intervention might work

Airway clearance techniques may affect sputum transport via manipulation of lung volumes, gas flow, pulmonary pressures and compressive forces. A combination of these factors exerts shearing forces onto sputum at the air-liquid interface, and the resulting energy transfer shifts secretions towards the mouth. This mechanism is known as two-phase gas-liquid flow and is considered essential for sputum clearance in individuals with mucociliary dysfunction (Kim 1987). There is some evidence supporting beneficial effects of ACTs on mucus clearance (Bateman 1979; Martins 2007; Olseni 1994), sputum volume (Ambrosino 1995; Bellone 2000) and dyspnoea (Cegla 1993; Kodric 2009) in people with COPD. Whether such benefits lead to fewer exacerbations or reduced hospitalisation remains unclear.

Why it is important to do this review

Confusion surrounds the clinical utility of ACTs in individuals with COPD and there are variable outcomes documented in the literature. For example, postural drainage with percussion has been associated with increased (Clarke 1973), decreased (Campbell 1975) and unchanged (May 1979; Mohsenifar 1985; Newton 1978a) lung function measures in individuals with chronic bronchitis. This may reflect the heterogeneous nature of both participants and interventions. Response to treatment may differ with the pathophysiological variation between stable and acute disease. Acute exacerbations of COPD (AECOPD) are defined by acute, excessive increases in dyspnoea, cough and/or sputum, and are often associated with bacterial infection, neutrophilic inflammation and specific immune responses (Rabe 2007). Such factors may affect breathing patterns, sputum transport, lung volumes and airflow limitation. Airway clearance techniques which apply PEP to the airways may cause different effects to those that do not, due to changes in lung volumes such as functional residual capacity (Garrard 1978) and prevention of early airway closure during expiration (Oberwaldner 1986).

This review was conducted to summarise the results of the literature evaluating the safety and efficacy of ACTs in people with AECOPD and stable COPD and to determine the effects of ACTs on exacerbation rate, hospitalisation and health-related quality of life (HRQoL). This review is one of two separate updates of a previous Cochrane review that investigated the effects of bronchopulmonary hygiene physical therapy in people with COPD and bronchiectasis (Jones 1998).

OBJECTIVES

Primary

To determine whether ACTs have beneficial effects on exacerbations, hospitalisation and HRQoL in people with AECOPD and stable COPD.

Secondary

To assess whether:

- airway clearance techniques are effective in both individuals with AECOPD and stable COPD;
- airway clearance techniques are safe for individuals with AECOPD and stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) and randomised cross-over trials (RXTs) were eligible for inclusion in the review.

Types of participants

Participants must have had a diagnosis of COPD, emphysema or chronic bronchitis according to the investigators' definition. We considered participants to have had AECOPD if they had an exacerbation of symptoms (dyspnoea, cough or sputum) requiring medical treatment, whether or not they were admitted to hospital. We considered participants to have had stable COPD if they were free from an exacerbation requiring medical treatment for a period of four weeks (Burgel 2009), or as defined by the investigators. We analysed studies involving participants with AECOPD separately from studies involving participants with stable COPD.

We excluded studies if participants had bronchiectasis or asthma (baseline FEV_1 > 15% reversibility in more than 50% of participants) that did not co-exist with COPD, or if they had cystic fibrosis or breathed via an artificial airway. No exclusions were made on the basis of disease severity, age, gender or smoking history.

Types of interventions

Intervention

We considered any techniques applied with the primary purpose of clearing sputum from the airways. This included but was not

restricted to 'conventional' techniques, breathing exercises, and PEP or mechanical devices, but excluded suctioning and breathing strategies for purposes of relaxation (e.g. relaxed controlled breathing) or respiratory muscle strengthening (e.g. inspiratory/expiratory muscle training).

Control

This comprised either no intervention, sham intervention or coughing alone.

Where multiple ACTs were investigated in a single study, we only included data from independent comparisons of each ACT to the control condition. We did not include studies which compared one ACT to another ACT only.

Types of outcome measures

Primary outcomes

1. Rate of, or time to, AECOPD, defined according to the investigators' definition.
2. Respiratory-related hospitalisations and resource utilisation:
   a. For AECOPD this included: the need for increased ventilatory assistance (invasive or non-invasive ventilation), duration of ventilatory assistance, intensive care unit (ICU) and hospital length of stay (LOS), time to re-admission and number of hospital admissions and hospital days.
   b. For stable COPD this included: time to hospitalisation and number of hospital admissions and hospital days.
3. Health-related quality of life, measured by either generic or disease-specific instruments.

Secondary outcomes

1. Pulmonary function (e.g. FEV_1, FVC, FEV_1/FVC%, $FEF_{25-75\%}$, TLC, FRC).
2. Gas exchange (e.g. SpO_2, PaO_2, $PaCO_2$).
3. Symptoms (e.g. dyspnoea, cough).
4. Sputum clearance and expectoration (e.g. mucociliary transport, sputum weight, sputum volume).
5. Exercise tolerance (e.g. six-minute walk distance, shuttle test).
6. Antibiotic use.
7. Mortality (all-cause).
8. Participant withdrawal.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (Appendix 1). We searched records in the CAGR coded as 'COPD' using the following terms:

physiotherap* or "physical therap*" or "bronchopulmonary hygiene" or "tracheobronchial clearance" or "airway* clearance" or "chest clearance" or "lung clearance" or "sputum clearance" or "mucus clearance" or "active cycle" or ACBT or "deep breath*" or DBE or "thoracic expansion" or TEE or "sustained maximal inspirat*" or SMI or "breathing exercise*" or "postural drainage" or "gravity assisted drainage" or "gravity-assisted drainage" or "autogenic drainage" or GAD or CCPT or ELTGOL or FET or "forced expiratory technique" or huff* or *PEP or PEEP or "resistance breath*" or "positive expiratory pressure" or "hi-PEP" or "bubble-PEP" or "bottle-PEP" or "oscillat*-PEP" or "mouthpiece-PEP" or "pari-PEP" or VRP1 or Flutter or desitin or cornet or acapella or scandipharm or percuss* or vibrat* or vest or HFCWO or OHFO or "chest wall oscillat*" or "oral oscillat*" or "thoracic oscillat*".

We searched the PEDro database using the following terms:

COPD or COAD or "chronic obstructive pulmonary disease" or "chronic obstructive airways disease" or "chronic obstructive lung disease" or emphysema or "chronic bronchitis".

We searched databases from inception to October 2009 (PEDro) and October 2011 (CAGR). There was no restriction on the language of publication.

Searching other resources

We handsearched reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and experts in the field to identify other published and unpublished studies where possible.

Data collection and analysis

Selection of studies

Two review authors independently coded studies identified in the literature searches for relevance by examining titles, abstract and keywords fields as follows:

1. INCLUDE: study met all review criteria;
2. UNCLEAR: study appeared to meet some review criteria but insufficient information available to categorically determine relevance; or
3. EXCLUDE: study clearly did not meet review criteria.

Two review authors (CO, AH) used a full-text copy of studies in categories INCLUDE and UNCLEAR to decide on study inclusion. We resolved disagreements by consensus and kept a full record of decisions for calculation of simple agreement and a kappa statistic.

Data extraction and management

Two review authors independently extracted data (CO, AH) using a prepared checklist. We compared the generated data and resolved any discrepancies by consensus. One review author (CO) entered data into RevMan 5 with random checks on accuracy. We contacted authors of included studies to verify the extracted data for their study and to provide details of missing data where possible.

Assessment of risk of bias in included studies

Two review authors (CO, AH) conducted a 'Risk of bias' assessment in accordance with recommendations outlined in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008). We assessed the risk of bias for each study against six potential sources of bias (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). We graded bias as either a low, high or unclear risk with discrepancies resolved by consensus. We summarised results in a 'Risk of bias' table.

Measures of treatment effect

We summarised findings of all included studies in descriptive tables. For continuous variables, were recorded mean change from baseline or mean post-intervention values and standard deviations. We calculated weighted mean difference (MD; same metric scales) or standardised mean difference (SMD; differing metric scales) and 95% confidence intervals (CI) for pooled analyses.

Unit of analysis issues

We analysed exacerbations and hospitalisations as either dichotomous (yes/no) or ratio (e.g. rate, frequency) data and the need for increased ventilatory assistance as dichotomous data. We analysed scores from instruments measuring HRQoL and symptoms as continuous or ordinal data. For studies which compared multiple ACTs to a control condition, we combined data from ACTs of the same subgroup classification (PEP or non-PEP ACTs) using the formulae in Table 7.7.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Where ACTs were of different subgroup classification (e.g. a PEP and non-PEP ACT), we divided control group data evenly. Where an ACT was compared to more than one suitable control condition (e.g. rest and cough), we selected data from the most passive intervention for analysis. We analysed quantitative data from cross-over trials using the generic inverse variance method in RevMan 5. We converted any data reported as kPa to mmHg.

Dealing with missing data

We contacted authors of studies with missing data and asked them to provide data if able. We performed intention-to-treat (ITT) analyses where possible.

Assessment of heterogeneity

We investigated the statistical variability of treatment effects due to heterogeneity using the I^2 statistic. We defined significance as I^2 values greater than 60%, in accordance with recommendations proposed by Deeks 2008.

Assessment of reporting biases

We examined data for publication bias via visual inspection of funnel plots, where indicated.

Data synthesis

We analysed data from studies of AECOPD separately from data from studies of stable COPD, and sub-classified them according to duration of post-intervention follow-up, as follows: 'immediate' (less than 24 hours); 'short-term' (24 hours to eight weeks); and 'long-term' (greater than eight weeks). We used eight weeks to distinguish between short-term and long-term due to its reported significance as an indicator of a 'high-risk' period for re-exacerbations (Hurst 2009). Where studies reported repeated-measures data within one time category, we only used the earliest ('immediate') or latest ('short-term' or 'long-term') data for quantitative analysis. Within each patient group, we pooled data that were both clinically and statistically homogeneous using a fixed-effect model. We pooled data that were clinically homogeneous but statistically heterogeneous using a random-effects model. We did not pool data that were clinically heterogeneous. We generated 'Summary of findings' tables for the three primary outcomes.

Subgroup analysis and investigation of heterogeneity

We conducted one subgroup analysis, specified *a priori*, to identify any potential influence on pooled results:

- Positive expiratory pressure devices: ACTs that use PEP (PEP-based ACTs) may have different physiological effects and outcomes compared to those that do not (non-PEP-based ACTs). This simple classification did not allow for statistical investigation of any potential differences between type of PEP device (oscillatory or non-oscillatory) or interface (mask or mouthpiece).

Sensitivity analysis

We performed a sensitivity analysis to analyse the effects of allocation concealment, assessor blinding and use of ITT analysis on results.

RESULTS

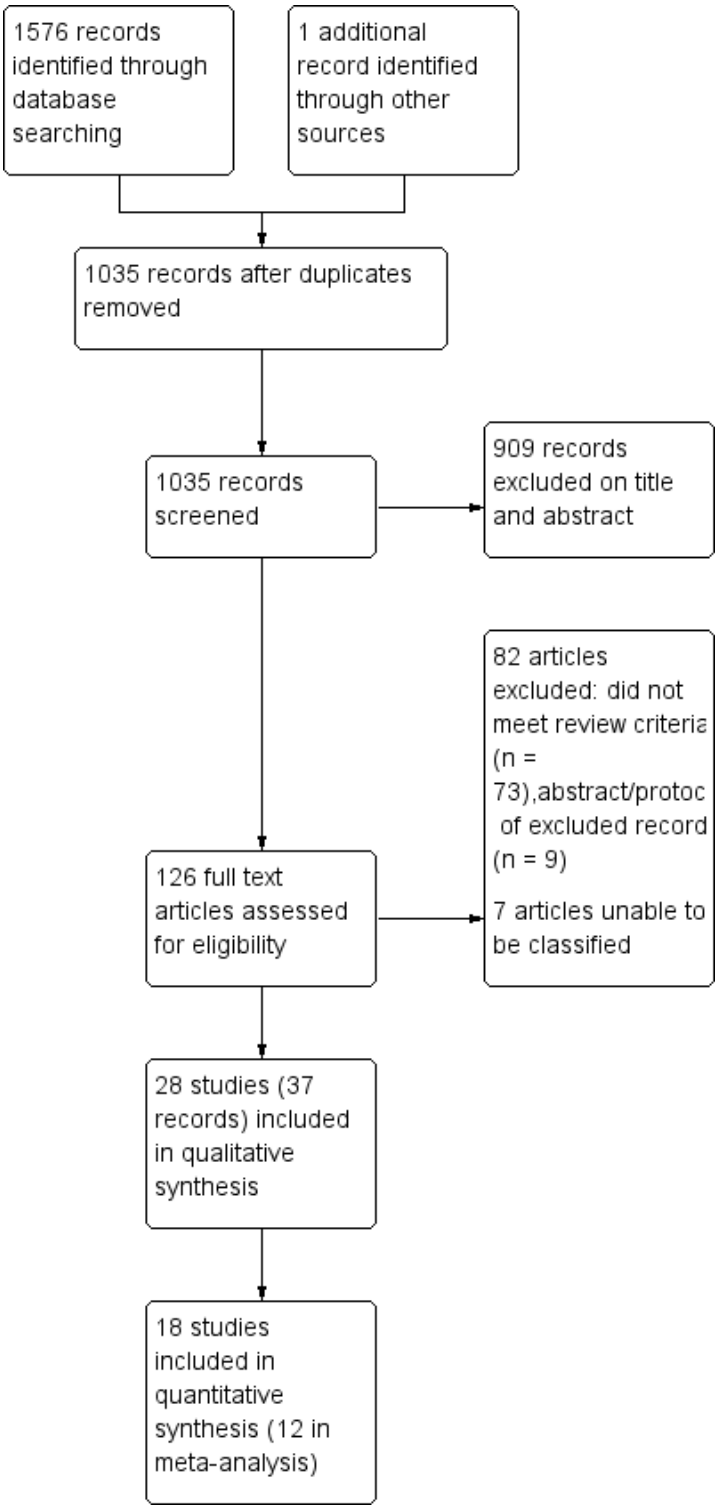
Description of studies

Refer to Characteristics of included studies, Characteristics of excluded studies and Characteristics of studies awaiting classification for complete details of studies which were included, excluded or awaiting classification.

Results of the search

The initial search was conducted in 2009 and yielded 382 (Cochrane database) and 655 (PEDro) records respectively (81 common to both) after discarding duplicates. Repeat searches of the Cochrane database in 2010 and 2011 yielded an additional 78 records and one was additionally identified via handsearching (total 1035 records). We excluded 909 on title and abstract and assessed 126 for eligibility via full text. We made attempts to contact authors of 17 (of 51) records rated 'unclear' to determine accurately their suitability for inclusion in the review, with 10 responses. We excluded 73 studies (82 records) as they clearly did not meet the review criteria. Seven could not be classified due to insufficient available detail. Twenty-eight studies (37 records) were appropriate for inclusion in the review (Figure 1). Agreement between the two independent assessors was excellent (kappa = 0.96).

Figure 1. Study flow diagram.



Included studies

Refer to Characteristics of included studies, Table 1 and Table 2.

Study

This review comprised 13 randomised controlled trials (RCT) on 629 participants and 15 randomised cross-over trials (RXT) on 278 participants. Four studies were only available in abstract form (Hasani 1995; Martins 2006; Martins 2007; Rasmussen 2001).

Population

All studies defined participants as having COPD or chronic bronchitis (n = 18,10 respectively), using clinical-only (n = 2,7),

spirometric-only (n = 1,0), combined clinical and spirometric (n = 9,3) or unspecified (n = 5,1) definitions. Nine studies (seven RCTs) investigated participants during AECOPD and 19 studies (six RCTs) during stable disease. The sample size of included studies varied from 5 to 96 participants with mean age ranging from 54 to 72 years and FEV_1 from 29 to 58 per cent predicted, indicating moderate to very severe disease severity (Rabe 2007).

Setting

Most studies were based in Europe, Canada or Brazil. They were conducted over a wide-ranging period (1964 to 2009), with six studies published prior to 1980 and 13 since 2000.

Intervention

Interventions during AECOPDs were usually applied for a short duration (e.g. single session or treatment until hospital discharge). Outcomes were seldom measured beyond hospital discharge, with the exception of two studies (Kodric 2009; Newton 1978) which conducted six and three-month follow-up respectively. Three studies investigated PEP-based ACTs during an AECOPD, with therapeutic pressures ranging from 10 to 25 cm H_2O. A mask interface was used by Bellone 2002 for non-oscillatory PEP and by Vargas 2005 for oscillatory PEP, and mouthpiece oscillatory PEP was used by Haidl 2002 (Table 1).

Studies in stable COPD evaluated the effect of interventions of a more varied duration (e.g. single session or home therapy for weeks to years). Long-term follow-up after the intervention was uncommon, with only three studies collecting data beyond eight weeks (Cegla 2002; Christensen 1990; Weiner 1996). Twelve studies investigated PEP-based ACTs and eight studies investigated non-PEP-based ACTs during stable COPD. One cross-over trial (van Hengstum 1988) compared the effects of both a PEP and non-PEP-based ACT to a suitable control. Mouthpiece oscillatory PEP (n = 6 studies) was more commonly used than mask-based non-oscillatory PEP (n = 4 studies). One study (Rasmussen 2001) provided inadequate detail to identify whether mouthpiece or mask PEP was performed (Table 2).

The most common control conditions were 'standard care', cough or resting. Sham therapy was utilised in eight studies of stable COPD (Christensen 1990; Christensen 1991; Christensen 1991a; May 1979; Rasmussen 2001; Weiner 1996; Wolkove 2002; Wolkove 2004); all studies except one used inactive PEP devices as sham interventions such as a Flutter with the steel ball removed or a PEP setting of 0 cm H_2O.

It was not always possible to pool data from studies due to heterogenous study designs (e.g. RCTs and RXTs), co-interventions (ACTs combined with bronchodilator therapy) and outcomes (e.g. quantification of symptoms using validated scales or investigator-created diaries).

Excluded studies

The most common reasons for exclusion were inappropriate control (n = 34), intervention not an ACT (n = 23) and lack of randomisation (n = 8). Many excluded studies compared different ACTs to each other without a suitable control or combined ACTs with other therapy (e.g. pulmonary rehabilitation), which made it impossible to identify the effects of the ACTs only. Reasons for exclusion are provided in Characteristics of excluded studies.

Risk of bias in included studies

There was considerable variation in risk of bias across the included studies. Some judgements were limited by inadequate reporting which made determining the true quality of the study design difficult. Refer to Characteristics of included studies or full details of the risk of bias across all studies and to Figure 2 and Figure 3 for a summary of our judgements on the potential risks of bias across studies.

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

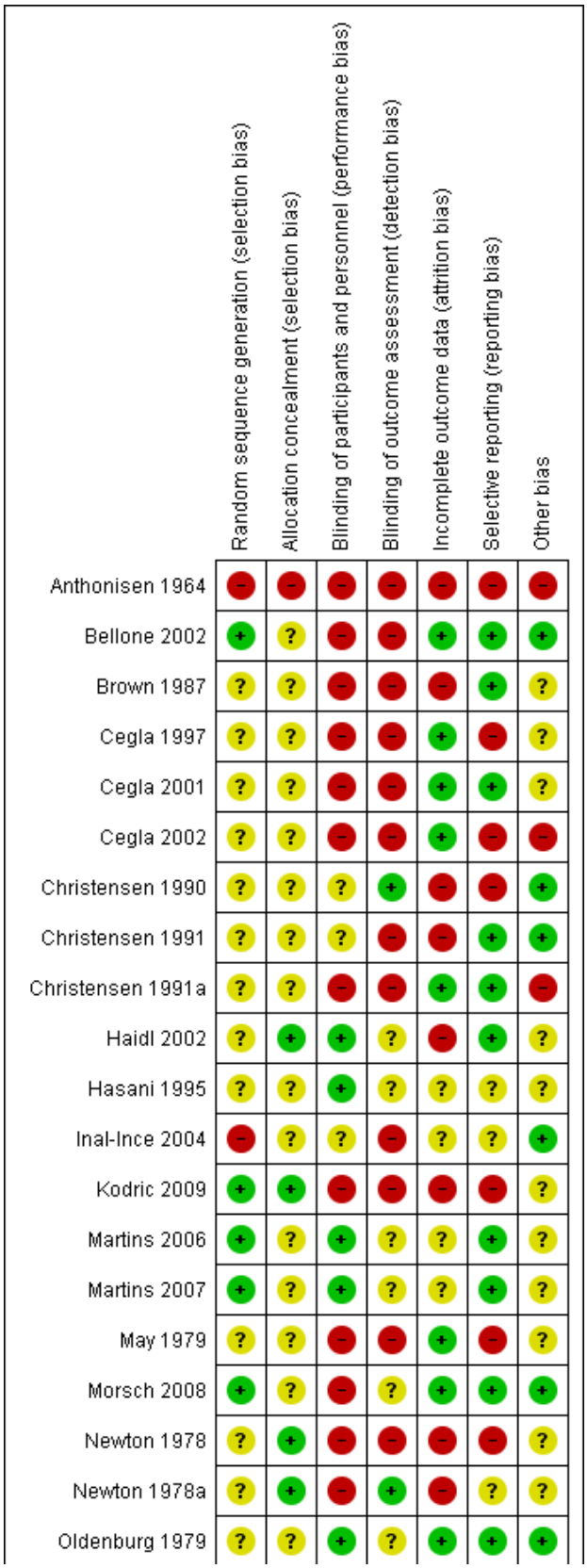


Figure 2. (Continued)

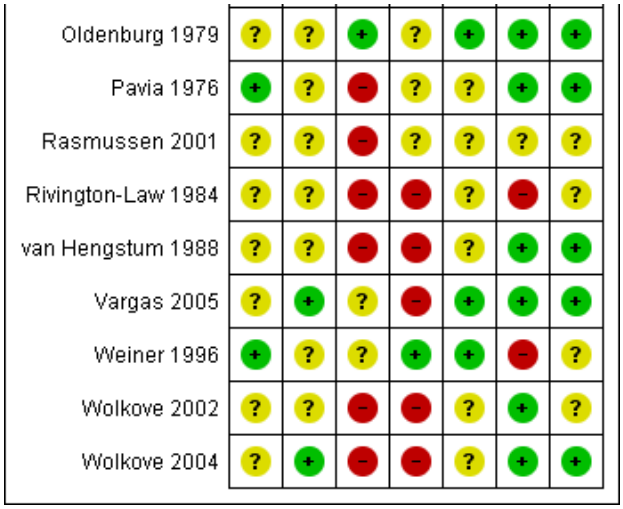
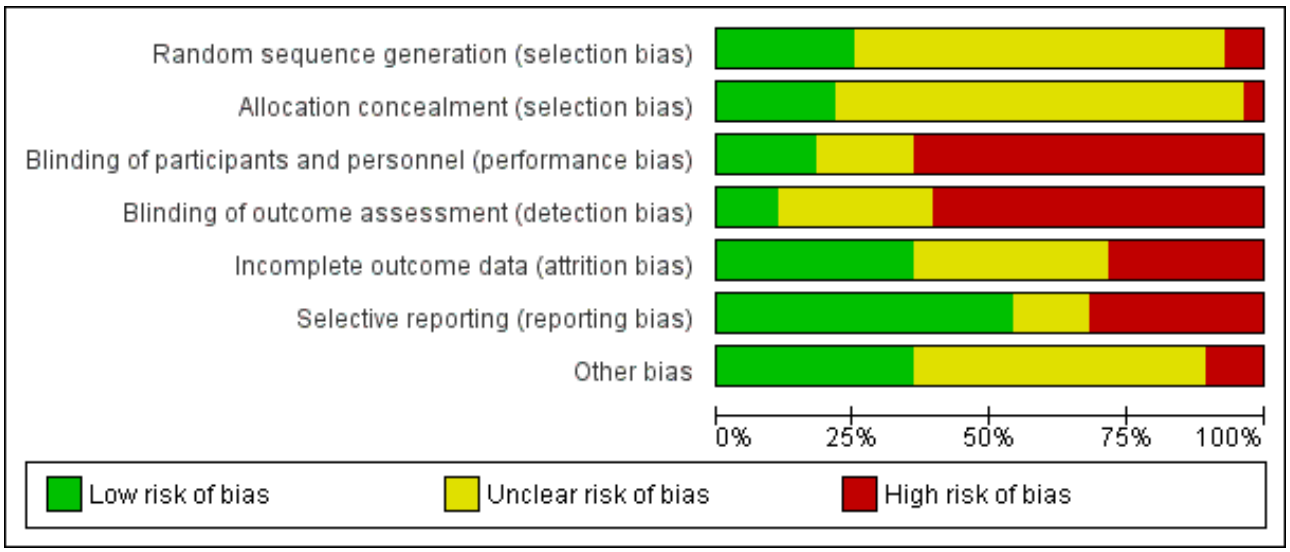


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Six studies reported sufficient detail to confirm adequate allocation concealment (Haidl 2002; Kodric 2009; Newton 1978; Newton 1978a; Vargas 2005; Wolkove 2004), whilst one was at high risk of bias (Anthonisen 1964) and the remainder were unclear. We judged seven studies to be at low risk of bias due to random sequence generation (Bellone 2002; Kodric 2009; Martins 2006; Martins 2007; Morsch 2008; Pavia 1976; Weiner 1996). Only one study (Kodric 2009) had both adequate allocation concealment and random sequence generation.

Blinding

Many studies rated poorly on this item. We rated 18 of the 28 included studies a high risk of bias due to inadequate blinding of participants. Eight studies attempted to blind participants to knowledge of the intervention via use of a sham ACT (Christensen 1990; Christensen 1991; Christensen 1991a; May 1979; Rasmussen 2001; Weiner 1996; Wolkove 2002; Wolkove 2004), however this did not guarantee that certain outcomes would be unaffected. The risk of bias for all cross-over trials was rated 'high' for this item unless outcomes were unlikely to have been affected by knowledge of the intervention (e.g. radiological measures of mucociliary clearance or number of hospitalisations). We rated randomised controlled trials without a sham control 'high' for this item if outcomes were likely to be affected by knowledge of group allocation as there is a high chance that participants could identify whether they received treatment or no treatment. We rated 17 of the 28 included studies a high risk of bias due to inadequate blinding of study personnel.

Incomplete outcome data

We rated eight studies at high risk of bias due to incomplete outcome data (Anthonisen 1964; Brown 1987; Christensen 1990; Christensen 1991; Haidl 2002; Kodric 2009; Newton 1978; Newton 1978a), mainly due to loss of data during testing procedures

(e.g. inadequate radioaerosol particle deposition to measure mucociliary clearance) or incomplete data at long-term follow-up. We rated 10 studies a low risk of bias for this item (Bellone 2002; Cegla 1997; Cegla 2001; Cegla 2002; Christensen 1991a; May 1979; Morsch 2008; Oldenburg 1979; Vargas 2005; Weiner 1996) and rated 10 unclear, often due to uncertainty of the completeness of data or unclear reasons for excluding participants. It was not possible to analyse study data via ITT, usually due to inadequate written detail supplied in the article.

Selective reporting

Studies generally rated well on this item. Most studies documented findings for all pre-specified outcomes, however data were not always reported in a format suitable for meta-analysis. Nine studies failed to report findings for all pre-specified outcomes (Anthonisen 1964; Cegla 1997; Cegla 2002; Christensen 1990; Kodric 2009; May 1979; Newton 1978; Rivington-Law 1984; Weiner 1996). We conducted no searches of clinical trials registers when formulating judgements for this item as most studies were conducted prior to registration requirements.

Other potential sources of bias

There was no evidence of cross-over trials utilising inappropriate (e.g. unpaired) statistical analyses. Most cross-over trials incorporated adequate washout periods (e.g. ≥ 24 hours), however one study (Brown 1987) assessed the effect of an ACT or control treatment on lung function and oxygen saturation during an AECOPD on two consecutive days. No investigation of treatment order effects was undertaken and results may possibly have been influenced by the rapid improvement in health that can occur during an AECOPD. Anthonisen 1964 described instances of participants crossing from the control group to the treatment group due to ethical concerns around denial of treatment, and participants being recruited to the same study more than once. We rated Cegla 2002 a high risk of bias due to three participants being excluded to create equal group numbers, and rated Christensen 1991a a high risk of bias as data from the initial three study days were excluded due to concerns regarding carry-over effects.

Effects of interventions

See: **Summary of findings for the main comparison** Airway clearance techniques for individuals with an exacerbation of COPD

We were able to include data from 18 studies in quantitative synthesis (meta-analysis) (Bellone 2002; Brown 1987; Cegla 1997; Cegla 2002; Christensen 1990; Christensen 1991; Haidl 2002; Inal-Ince 2004; Kodric 2009; May 1979; Morsch 2008; Newton 1978; Oldenburg 1979; Pavia 1976; Vargas 2005; Weiner 1996; Wolkove 2002; Wolkove 2004) and these are discussed together with qualitative or narrative data from the remaining 10 studies (Anthonisen 1964; Cegla 2001; Christensen 1991a; Hasani 1995; Martins 2006; Martins 2007; Newton 1978a; Rasmussen 2001; Rivington-Law 1984; van Hengstum 1988).

Acute exacerbations of chronic obstructive pulmonary disease (COPD)

Primary outcome: exacerbations and hospitalisations

Very few studies evaluated the impact of treating patients with airway clearance techniques (ACTs) during acute exacerbations of COPD (AECOPD) on future exacerbations and hospitalisations. Long-term data at three months (Newton 1978) and six months (Kodric 2009) follow-up from two studies involving 101 participants each showed no significant difference between (non-positive expiratory pressure (PEP)) treatment and control groups, however data could not be pooled due to differing metrics (Analysis 1.1; Analysis 1.2). The effect of treatment appeared divergent across studies, with findings from Kodric 2009 slightly favouring the treatment group. Neither study showed a statistically significant difference in the need for hospitalisation (due to respiratory causes). Kodric 2009 also reported no long-term significant differences between groups in the time to exacerbation or hospitalisation. No data were available to assess the impact of ACTs on the total number of AECOPDs or hospital days.

Primary outcome: hospital resource utilisation (ventilatory assistance)

Few studies reported data for the impact of ACTs on ventilatory assistance. Short-term data from four studies (Bellone 2002; Inal-Ince 2004; Newton 1978; Vargas 2005) (two PEP, two non-PEP ACTs) involving 171 participants revealed a significantly lower need for increased ventilatory assistance (invasive or non-invasive ventilation) in favour of ACTs (odds ratio (OR) 0.21, 95% confidence interval (CI) 0.05 to 0.85; $I^2 = 0\%$; Analysis 1.5; Figure 4). This benefit was greater for PEP-based ACTs than non-PEP ACTs, however the difference between these subgroups was not statistically significant ($Chi^2 = 1.04$, P = 0.31). Short-term data from two studies (Bellone 2002; Inal-Ince 2004) of 54 participants showed a significantly shorter duration of ventilatory assistance favouring those who performed ACTs (mean difference (MD) -2.05 days, 95% CI -2.60 to -1.51; $I^2 = 0\%$; Analysis 1.6; Figure 5).

Figure 4. Forest plot of comparison: 1 Acute COPD: ACTs vs no ACTs (control), outcome: 1.5 Need for increased ventilatory assistance (invasive or non-invasive).

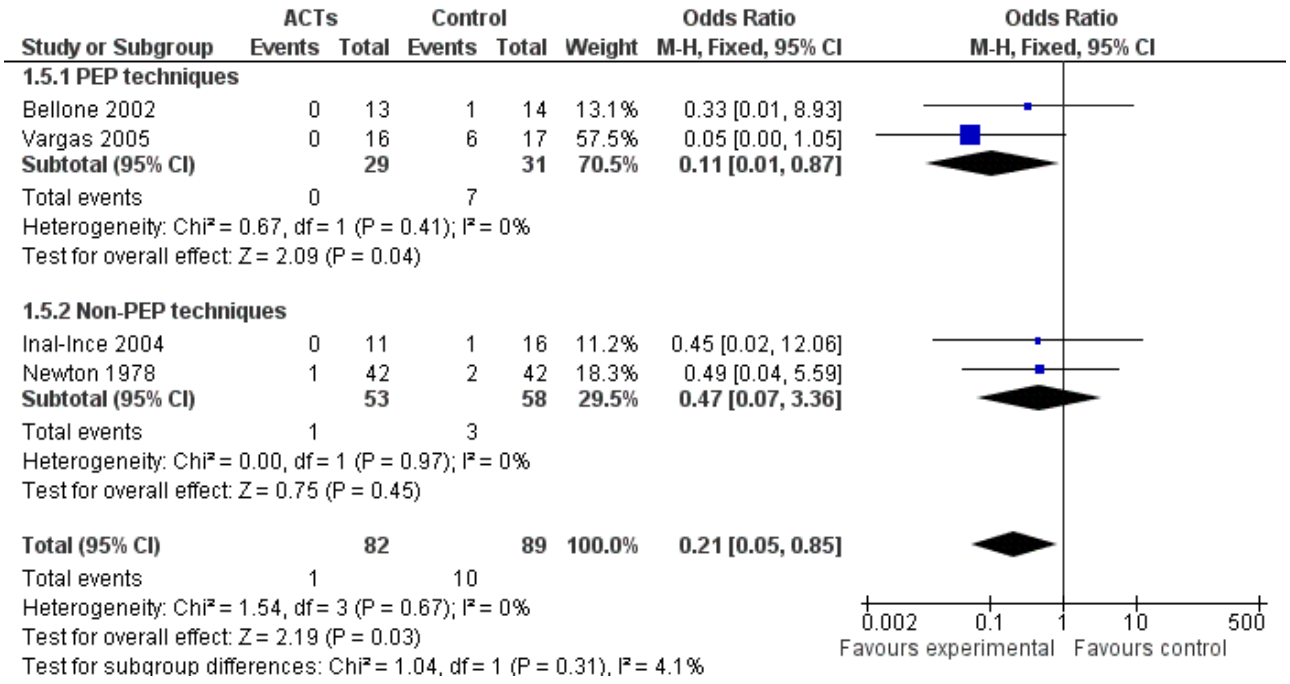
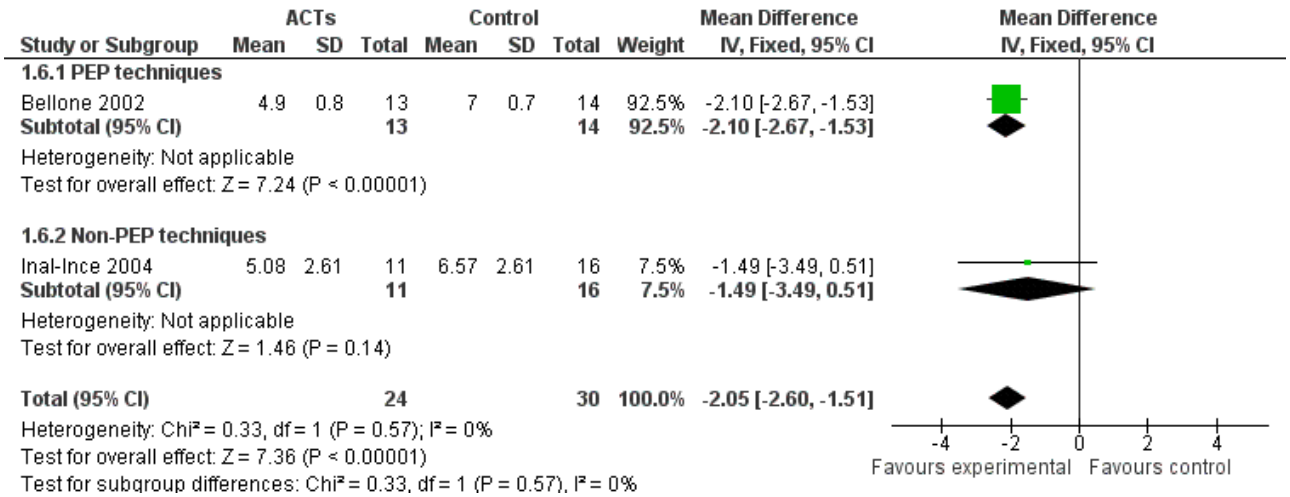


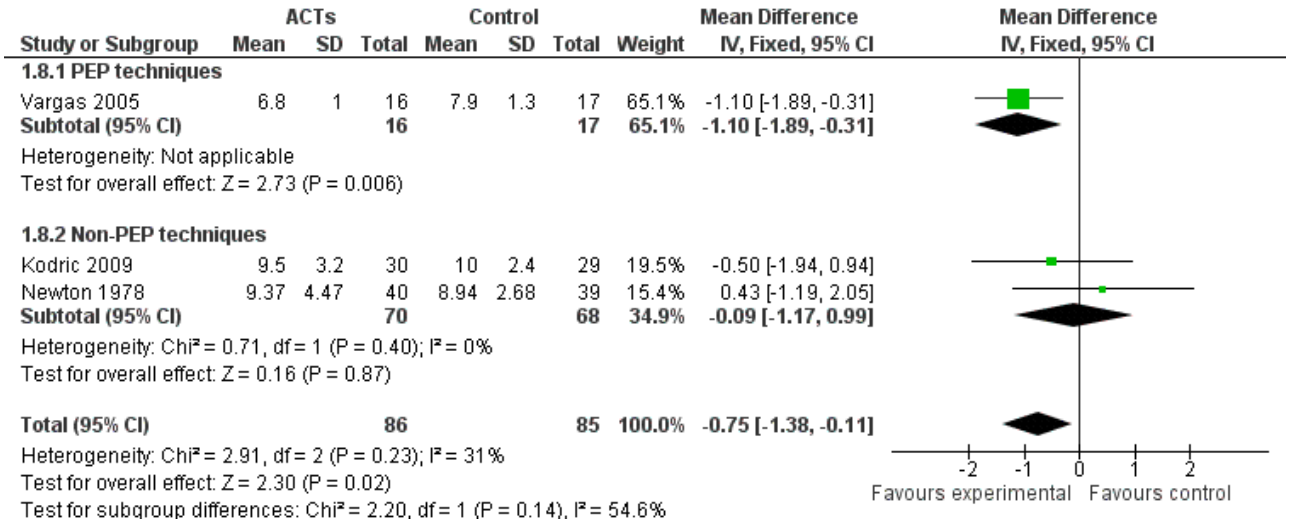
Figure 5. Forest plot of comparison: 1 Acute COPD: ACTs vs no ACTs (control), outcome: 1.6 Duration of ventilatory assistance (days).



Primary outcome: hospital resource utilisation (length of stay)

Four studies comprising a total of 198 participants reported short-term data for length of hospital stay. Inal-Ince 2004 found no significant difference between groups in the duration of stay in the intensive care unit (ICU) (MD 0.64 days, 95% CI -3.16 to 4.44; Analysis 1.7), whereas analysis of short-term data from three studies (Kodric 2009; Newton 1978; Vargas 2005) of 171 participants revealed a modest but significant reduction in the duration of hospital stay in favour of ACTs (MD -0.75 days, 95% CI -1.38 to -0.11; I^2 = 31%; Analysis 1.8; Figure 6). A statistically significant effect was evident for PEP-based ACTs that was not present for non-PEP ACTs, however no significant subgroup difference existed between PEP and non-PEP ACTs.

Figure 6. Forest plot of comparison: 1 Acute COPD: ACTs vs no ACTs (control), outcome: 1.8 Length of hospital stay (days).



Primary outcome: health-related quality of life (HRQoL)

One study (Kodric 2009) of 59 participants revealed no significant difference between groups at discharge or one month follow-up in HRQoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) total score (MD -2.30, 95% CI -11.80 to 7.20; Analysis 1.9). No long-term data were available.

Secondary outcome: pulmonary function

Several studies investigated measures of lung function either immediately following treatment or shortly afterwards. Only short-term data from three studies involving 106 participants were suitable for meta-analysis, from which no significant between-group differences were found for forced expiratory volume in one second (FEV_1) (Bellone 2002; Newton 1978) (MD 0.02 L, 95% CI -0.16 to 0.20; Analysis 1.10), vital capacity (VC) (Newton 1978) (MD -0.12 L, 95% CI -0.49 to 0.25; Analysis 1.11) or FEV_1/forced vital capacity (FVC) (Bellone 2002; Kodric 2009) (MD 4.33%, 95% CI -1.99 to 10.64; Analysis 1.12). Similar findings for FEV_1 and VC were apparent immediately following treatment in studies without appropriate data for meta-analysis (Brown 1987; Newton 1978a). Kodric 2009 reported significant within-group improvements in FEV_1 (% predicted) in ACT and control groups during the course of a hospital stay, however no significant differences existed between groups. Newton 1978a also showed a significant, short-lasting (< 40 minutes) increase in functional residual capacity (FRC) and airway conductance (Gaw) after (non-PEP) ACTs. No long-term data were available for any variable.

Secondary outcome: gas exchange

Three studies reported gas exchange data that were suitable for quantitative analysis. One study of 26 participants (Bellone 2002) found no significant short-term difference between ACT and control groups for pH (MD 0.02, 95% CI -0.98 to 1.02; Analysis 1.13). Data from two studies of 106 participants (Kodric 2009; Newton 1978) showed no significant difference between groups for PaO_2 (MD -0.66 mmHg, 95% CI -5.02 to 3.71; I^2 = 0%; Analysis 1.14) or $PaCO_2$ (MD -1.10 mmHg, 95% CI -5.56 to 3.37; I^2 = 0%; Analysis 1.15; n = 105) and no significant subgroup difference between PEP and non-PEP ACTs. Anthonisen 1964 reported no significant difference between groups for $PaCO_2$ in 30 participants with 'obvious respiratory insufficiency' (SpO_2 < 80%, $PaCO_2$ > 45 mmHg), however data were could not be pooled for meta-analysis. A study of 59 participants (Kodric 2009) found no significant difference between groups in SpO_2 at discharge (MD 1.00%, 95% CI -0.61 to 2.61; Analysis 1.16). Anthonisen 1964, Brown 1987 and Newton 1978a each found no significant difference in SpO_2 between ACT and control groups either immediately following treatment or in the short-term, however data were not suitable for pooling for quantitative analysis. Brown 1987 reported SpO_2 levels 30 minutes after a non-PEP ACT to be significantly higher than after the control condition (93.2% and 92.5% respectively) in a subset of participants who received supplemental oxygen, however this likely *post hoc* finding was acknowledged by the authors as being of little clinical relevance. Despite finding no significant difference in SpO_2 between groups at hospital discharge, Kodric 2009 did report small but significant improvements in SpO_2 from admission in both the control and non-PEP ACT groups (2.5% and 3% increase respectively). No long-term data were available for analysis.

Secondary outcome: symptoms

Short-term data from one study (Kodric 2009) of 59 participants showed a significantly greater improvement in self reported breathlessness (Borg scale) in favour of a non-PEP ACT (MD -1.30 points, 95% CI -2.14 to -0.46; Analysis 1.17). The mean difference exceeded the minimum clinically important difference (MCID) of one point (Borg 1982; Solway 2002). No immediate or long-term data were available for analysis.

Secondary outcome: sputum clearance

Significantly greater clearance of sputum (weight) immediately following an ACT was reported in one study (Bellone 2002) of 27 participants (MD 4.90 g, 95% CI 2.41 to 7.39; Analysis 1.18) and in another (sputum volume) (Brown 1987) of 24 participants (MD 1.40 mL, 95% CI 0.15 to 2.65; Analysis 1.19). Whilst data from these two studies could not be pooled due to differing metrics, the magnitude

of difference between groups appeared larger in the PEP-based study (Bellone 2002).

Meta-analysis of short-term (24-hour) data from two studies (Kodric 2009; Newton 1978) of 138 participants revealed no significant differences in sputum volume between groups (MD 0.04 mL, 95% CI -3.73 to 3.80; Analysis 1.20). This was consistent with findings from Anthonisen 1964 and Brown 1987. No long-term data were available for meta-analysis.

Two studies investigated the effects of ACTs on mucociliary clearance using radioaerosol imaging (Haidl 2002; Hasani 1995). Haidl 2002 reported no significant improvements in particle deposition (penetration index) in 14 participants immediately following completion of a PEP-based ACT, whilst Hasani 1995 reported significantly greater regional (inner) clearance in eight participants immediately following completion of a non-PEP-based ACT (FET/huff) compared to resting. In the latter study, however, significant regional (inner and outer) benefits were also reported immediately following coughing compared to resting, without direct comparison between the two techniques.

Secondary outcome: exercise tolerance

No suitable data were available for analysis. Short-term measures of a one-minute walk test were made by Newton 1978, however data for differences between groups were not reported.

Secondary outcome: antibiotic use

No data were available for analysis.

Secondary outcome: mortality (all-cause)

Short-term data from four studies (Bellone 2002; Inal-Ince 2004; Newton 1978; Vargas 2005) of 161 participants revealed no significant difference in mortality between groups (OR 0.72, 95% CI 0.14 to 3.80; Analysis 1.21). Both Vargas 2005 and Inal-Ince 2004 reported no deaths in either group. Similar long-term findings were apparent from analysis of data from two studies (Kodric 2009; Newton 1978) of 107 participants (OR 0.82, 95% CI 0.26 to 2.63; Analysis 1.22).

Secondary outcome: participant withdrawal

No significant differences between ACT or control groups were apparent in the rate of participant withdrawal following treatment, either immediately (Haidl 2002) (OR 3.46, 95% CI 0.12 to 100.51; Analysis 1.23), in the short-term (Bellone 2002; Kodric 2009; Newton 1978; Vargas 2005) (OR 0.55, 95% CI 0.11 to 2.69; Analysis 1.24) or long-term (Kodric 2009; Newton 1978) (OR 0.87, 95% CI 0.39 to 1.94; Analysis 1.25).

Stable COPD

Primary outcome: exacerbations and hospitalisations

Very few studies investigated the effect of ACTs on exacerbations or hospitalisations. One PEP-based study (Christensen 1991) of 30 participants investigated the short-term effect of ACTs on the number of AECOPDs, finding no significant differences between groups at four weeks (OR 3.21, 95% CI 0.12 to 85.20; Analysis 2.1). One PEP-based study (Cegla 2002) of 50 participants investigated the effect of ACTs on respiratory-related hospital admissions, with long-term data revealing a significantly lower need for hospitalisation in favour of the ACT group (OR 0.27, 95% CI 0.08 to 0.95; Analysis 2.2). No difference was evident, however, in the total number of days hospitalised during the study period. Christensen 1990 reported no long-term differences between groups in the number of exacerbations, need for hospitalisation or total number of hospitalised days in a study of 60 participants.

Primary outcome: HRQoL

Only one study (Wolkove 2004) of 15 participants investigated the effect of a PEP-based ACT on HRQoL, with short-term data revealing significantly lower (better) SGRQ (St. George's Respiratory Questionnaire) total scores following one week of daily ACTs compared to a sham intervention (MD -6.10, 95% CI -8.93 to -3.27; Analysis 2.4). The mean difference exceeds the MCID of four points (Jones 1991).

Secondary outcome: pulmonary function

Pulmonary function was evaluated in 13 studies, however only three trials involving 141 participants (Cegla 1997; Christensen 1991; Wolkove 2002) provided suitable data for meta-analysis. The effects of ACTs were generally small and inconsistent across trials. Quantitative analysis of data from one study (Wolkove 2002) of 23 participants showed a significantly greater increase in FEV_1 (MD 0.04 L, 95% CI 0.00 to 0.07; Analysis 2.5) in favour of a PEP-based ACT immediately following treatment, but no significant difference in VC (MD -0.12 L, 95% CI -0.49 to 0.25; Analysis 2.7). Meta-analysis of short-term data from two studies (Cegla 1997; Christensen 1991) of 118 participants showed no significant differences in the effect of a control or PEP-based ACT on FEV_1 (MD -0.04 L, 95% CI -0.35 to 0.28; Analysis 2.6) or VC (MD -0.05 L, 95% CI -0.43 to 0.33 L; Analysis 2.8).

Similar findings (not included in the meta-analysis) were reported immediately following treatment for FEV_1 in one study (Cegla 2001), and for VC in four studies (May 1979; Oldenburg 1979; Rivington-Law 1984; van Hengstum 1988). Wolkove 2004 reported no significant difference in FEV_1 or VC either immediately following a single session of a PEP-based ACT or sham ACT combined with bronchodilator therapy or following one week of daily therapy, however significantly greater improvements favouring the PEP-based ACT were apparent in both outcomes 30 to 120 minutes after treatment on the first occasion and after 60 to 120 minutes at one week. In contrast to the findings of the meta-analysis were reports of no significant differences between groups immediately following treatment in FEV_1 in four individual studies (Christensen 1991a; May 1979; Oldenburg 1979; van Hengstum 1988), and a significantly greater (130 mL) increase in VC following a PEP-based ACT in one study (Cegla 2001). No long-term data were suitable for meta-analysis, however three studies (Cegla 2002; Christensen 1990; Weiner 1996) of 117 participants each found no significant difference between groups in FEV_1, and two (Christensen 1990; Weiner 1996) found no significant difference in VC. Cegla 2002 (n = 50) reported a significantly greater decline in VC (% predicted) in the control group, however the magnitude of the difference was not quantified. No data of FEV_1/FVC (%) were available for analysis.

Other reported measures of lung function included forced expiratory flow (May 1979; van Hengstum 1988), residual volume and FRC (Cegla 2001; Rivington-Law 1984). No immediate significant differences were found for any of these outcomes, however Cegla 2002 reported greater long-term reductions in FRC (% predicted) in individuals who performed ACTs. Four studies

investigated measures of airway resistance and conductance (sGaw, Raw, Re). Cegla 2001 reported a greater reduction (0.08 kPa/L/s) in airway resistance favouring the use of a PEP-based ACT and Cegla 2002 reported similar findings however the magnitude of the difference was not quantified. Cegla 1997 found no significant difference between PEP and control groups in airway resistance (0.29 versus 0.31 kPa/L/s), whilst van Hengstum 1988 found no significant difference in specific airway conductance following a PEP-based ACT, a non-PEP-based ACT or resting (0.64 versus 0.69 versus 0.61 kPa/L/s).

Secondary outcome: gas exchange

Several studies reported the effects of ACTs on gas exchange, however results were mixed. Appropriate data for quantitative analysis were only available from two studies (Cegla 1997; Wolkove 2002). One study (Cegla 1997) of 90 participants revealed no short-term differences between ACT and control groups at day seven for PaO_2 (MD -1.50 mmHg, 95% CI -7.18 to 4.18; Analysis 2.9) or $PaCO_2$ (MD -1.20 mmHg, 95% CI -3.08 to 0.68; Analysis 2.10). Another study (Wolkove 2002) of 23 participants showed no significant differences between groups in SpO_2 (MD 0.50%, 95% CI -0.14 to 1.14; Analysis 2.11) immediately following treatment. Similar findings from other studies (not included in the quantitative analysis) included no significant difference between groups in PaO_2 immediately after treatment (May 1979) or in the long term (up to six months) (Christensen 1990; Weiner 1996), and no significant long-term difference between groups at three months for $PaCO_2$ (Weiner 1996). Christensen 1990 detected a statistically significant improvement in $PaCO_2$ at six months in participants who performed sham PEP therapy, but acknowledged the magnitude of change (-0.03 kPa or ~ -0.2 mmHg) was clinically unimportant. Whilst no appropriate short-term or long-term SpO_2 data were available for meta-analysis, one cross-over trial of 15 participants (Wolkove 2004) reported no significant difference in SpO_2 following one week of daily treatment with either a PEP-based ACT or sham ACT. There was, however, significantly less desaturation on exertion (6MWT) following the PEP-based ACT. The authors proposed this may have been due to an enhanced response to bronchodilator therapy, which was administered immediately following either treatment. Contrasting these findings, Rivington-Law 1984 reported a small but statistically significant 2% decrease in SpO_2 following a non-PEP ACT (deep breathing exercises), however this did not appear to differ significantly from the control intervention and was both short-lasting (< 15 minutes) and described as clinically unimportant by the authors. There were no reports of findings relating to pH.

Secondary outcome: symptoms

Several studies investigated the impact of ACTs on respiratory symptoms, however most utilised unique, self reported symptom scales. This restricted the ability to pool data from multiple studies. Suitable data for quantitative analysis were only available from one study (Wolkove 2002), which utilised the Borg scale of perceived breathlessness. In this study of 23 participants, Borg scores were significantly lower immediately following a PEP-based ACT plus inhaled bronchodilator therapy than after a sham ACT plus inhaled bronchodilator therapy (MD -0.30 points, 95% CI -0.53 to -0.07; Analysis 2.12), however the mean difference was less than the MCID of one point (Borg 1982; Solway 2002). In contrast, a similar study of 15 participants by the same authors (Wolkove 2004) found no significant difference in Borg scores immediately following a single treatment of a PEP-based ACT plus inhaled bronchodilator therapy or sham ACT plus inhaled bronchodilator therapy, nor any significant short-term difference following one week of either intervention. There was, however, significantly less of an increase in breathlessness on exertion (6MWT) following one week of the PEP-based ACT. Results from other studies which evaluated the effect of ACTs on breathlessness using alternative measures (e.g. visual analogue scale or other scales) were mixed. No significant short-term differences between groups were found in one study of 28 participants (Christensen 1991), whereas significant long-term improvements favouring a PEP-based ACT were found in another (Weiner 1996). Christensen 1990 reported no long-term differences between groups in breathlessness when walking on level ground in a randomised controlled trial (RCT) of 47 participants, but significantly less breathlessness when walking on a staircase in favour of those who performed a sham ACT compared to a PEP-based ACT.

No significant benefits of ACT use were reported on cough frequency immediately after treatment (Pavia 1976), but they were reported in the short term (Christensen 1991; Christensen 1991a) and long term (Weiner 1996). Two studies reported greater benefits favouring ACT use on self reported sputum characteristics in the short term (Christensen 1991) and long term (Weiner 1996), with the latter study also finding significantly greater self reported general well-being in favour of performing a PEP-based ACT. Results from Christensen 1990 contrasted these findings, revealing no significant long-term difference between groups in sputum characteristics and significantly greater improvement in cough in participants who performed a sham ACT compared to those who performed a PEP-based ACT at six months. Poor treatment compliance in the ACT group was discounted as a cause of these findings as patients were asked at monthly clinical visits about usage of the mask and the technique was controlled several times.

Secondary outcome: sputum clearance

Two studies (May 1979; Morsch 2008) of 55 participants reported quantitative data of the effects of ACTs on sputum clearance, however they could not be pooled due to differing metrics. May 1979 (n = 35) reported significantly greater sputum volume immediately following a non-PEP ACT compared to a passive sham treatment (MD 4.10 mL, 95% CI 1.16 to 7.04; Analysis 2.14), whereas Morsch 2008 (n = 20) found no immediate significant difference in sputum weight between a PEP-based ACT or control group (MD 0.65 g, 95% CI -0.86 to 2.16; Analysis 2.13). By contrast, significantly greater sputum weight immediately following two ACTs compared to a control was reported by van Hengstum 1988, with the non-PEP ACT (FET) yielding significantly greater amounts than the PEP-based ACT. Rasmussen 2001 investigated the effect of four days of twice daily ACTs and found no significant differences between the average weight of sputum expectorated within one hour of performing either sham PEP (0 cm H_2O) or 5, 12.5 or 20 cm H_2O PEP, however a significant benefit favouring therapeutic PEP became apparent when sham therapy was compared to participants' preferred PEP pressure setting.

The effect of ACTs on (whole lung) mucociliary clearance, measured via radioaerosol imaging, were evaluated immediately following treatment in seven studies. Two studies (Oldenburg 1979; Pavia 1976) provided suitable data for meta-analysis which revealed no significant difference in retention (% of initial uptake) of radioaerosol particles between a non-PEP ACT (postural drainage)

and control intervention (resting) (MD 1.20%, 95% CI -2.79 to 5.19; Analysis 2.15). In the study by Oldenburg 1979, despite the lack of improvement following postural drainage, significant benefits were identified following both physical exercise (cycle ergometry) and cough compared to resting, with coughing achieving the greatest effect. Similar effects were also detected in regional (peripheral) lung areas. Three other studies (Martins 2006; Martins 2007; van Hengstum 1988) reported significantly enhanced mucociliary clearance immediately following one PEP and two non-PEP ACTs compared to a control intervention (resting), with van Hengstum 1988 reporting sustained effects for up to two hours. In this study, subsequent analysis using a region of interest technique attributed the observed benefit to clearance from inner (proximal) lung regions, and the effects of the non-PEP ACT (comprising postural drainage, breathing exercises, huffing and coughing) were found to be significantly greater than PEP mask therapy (46% versus 70% particle retention, respectively).

Secondary outcome: exercise tolerance

Short-term data from two PEP-based studies (Wolkove 2002; Wolkove 2004) of 38 participants showed ACT use was associated with significantly greater exercise tolerance as measured by the six-minute walk distance (6MWD) than a sham ACT (MD 12.93 m, 95% CI 5.98 to 19.89; Analysis 2.16). Long-term data from one study (Weiner 1996) showed significantly greater exercise tolerance as measured by the 12-minute walk distance (12MWD) in patients who performed a PEP-based ACT compared with those who did not (MD 111.00 m, 95% CI 66.46 to 155.54; Analysis 2.17). The significant difference in 6MWD between groups reported by Wolkove 2004 was only evident after one week of daily treatment, and not immediately following a single treatment (6MWD approximately 190 m after both ACT or sham ACT).

Secondary outcome: antibiotic use

Data were available for quantitative analysis from two out of three studies (Cegla 2002; Christensen 1990; Christensen 1991) which investigated the effect of PEP-based ACTs on the need for antibiotics. Short-term data from one study (Christensen 1991) of 28 participants showed no significant difference in the need for antibiotics between groups at four weeks (OR 0.31, 95% CI 0.01 to 8.29; Analysis 2.18), whereas long-term data from another study (Cegla 2002) of 50 participants showed a significant reduction in the need for antibiotics favouring ACTs (OR 0.05, 95% CI 0.01 to 0.39; Analysis 2.19) at two years. In contrast, Christensen 1990 described no significant long-term differences between groups at six months in a study of 47 participants, however they did not report any data.

Secondary outcome: mortality (all-cause)

No data were available for analysis.

Secondary outcome: participant withdrawal

Data relating to participant withdrawal were not commonly reported. From the few studies which supplied adequate data for quantitative analysis, no significant short-term (Cegla 1997; Christensen 1991) (OR 1.00, 95% CI 0.06 to 17.62; Analysis 2.20) or long-term (Christensen 1990) (OR 0.55, 95% CI 0.16 to 1.93; Analysis 2.21) differences between groups were found.

Safety

There were very few reports of adverse events. Studies which clearly reported no negative effects from ACTs included Christensen 1990; Christensen 1991; Christensen 1991a; Morsch 2008 and Rivington-Law 1984. The only study to report a clinically important adverse event was May 1979, where one participant vomited and two others felt uncomfortable during a sequence of postural drainage positions incorporating a head-down tilt. Meta-analysis revealed no significant effect of ACTs during an AECOPD on mortality in the short term (OR 0.72, 95% CI 0.14 to 3.80; Analysis 1.21) or long term (OR 0.82, 95% CI 0.26 to 2.63; Analysis 1.22), however this outcome is likely to be underpowered.

Sensitivity analyses

We re-analysed data using only those studies deemed to have adequate allocation concealment, assessor blinding, complete data or evidence of ITT analysis. Studies which met these criteria are shown in Table 3. No study satisfied all criteria.

Removal of studies with inadequate or unclear allocation concealment did not affect findings from the meta-analysis for the need for increased ventilatory assistance, hospital length of stay (LOS) or exercise tolerance (stable COPD), but resulted in a loss of significance for the duration of ventilatory assistance and sputum weight (acute COPD).

Removal of studies with inadequate assessor blinding resulted in the loss of all data for quantitative analysis except participant withdrawal (AECOPD and stable COPD) and exercise tolerance (stable COPD; 12MWD; n = 1).

In AECOPD, removal of studies with incomplete data or no evidence of ITT analysis did not affect the significance of findings for the need for increased ventilatory assistance or hospital LOS, however no data were available for quantitative analysis for any other outcome. In stable COPD, data were no longer available for quantitative analysis for all primary outcomes except the need for respiratory hospitalisation (n = 1) and participant withdrawal (short-term), without changing the findings. The following secondary outcomes additionally remained with unchanged findings:

- immediate: sputum weight, sputum volume, mucociliary clearance;
- short-term: FEV_1, VC, PaO_2, $PaCO_2$;
- long-term: exercise tolerance (12MWD), need for antibiotics.

DISCUSSION

This review sought to determine whether airway clearance techniques (ACTs) are effective for individuals with chronic obstructive pulmonary disease (COPD). Results from 28 studies of 907 participants were mixed. There is evidence associating ACT use with a reduced need for and duration of increased ventilatory (invasive or non-invasive) assistance during an acute exacerbation of COPD (AECOPD) and a small reduction in hospital length of stay (Summary of findings for the main comparison); outcomes that are meaningful to patients and healthcare providers. However the evidence to support the clinical impact of ACTs across a broader range of outcomes in both acute and stable disease is weak. The small magnitude of treatment effects, uncertain risks of bias of included studies, and small number of studies using clinically meaningful outcomes (Bellone 2002; Cegla 2002; Christensen 1991;

Inal-Ince 2004; Kodric 2009; Newton 1978; Vargas 2005; Wolkove 2002) significantly limits the potential impact of the review findings for individuals and healthcare policy-makers.

The ability to pool data for meta-analyses was limited by heterogeneity of outcome measurement and inadequate reporting from cross-over studies. The small number of pooled studies meant that investigation of publication bias via funnel plots was not possible for any meta-analysis. The limited data from outcomes suitable for subgroup analysis tended to favour positive expiratory pressure (PEP)-based ACTs over non-PEP ACTs. Positive pressure during expiration is thought to be well suited to the pathological mechanics of COPD lungs due to its potential to shift the intrapulmonary equal pressure point proximally (i.e. towards the mouth) to prevent dynamic airway compression, increase ventilation via collateral channels, enhance expiratory flow and clear secretions (Fagevik Olsen 2009; Holland 2006). The precise mechanisms by which this may occur are not clear. Further investigation of PEP-based ACTs for people with COPD may be warranted.

The primary outcomes selected for this review, particularly exacerbations and health-related quality of life (HRQoL), are important to both patients and healthcare providers, however these were seldom measured in the included studies. We identified a heavy reliance on 'traditional' outcomes such as pulmonary function, sputum clearance and gas exchange (n = 18, 16, 13 studies respectively) with widely varying results. Whilst such outcomes may provide important physiological or mechanical information to explain how ACTs work, the review findings highlight their limitation as surrogate markers of ACT effectiveness. In order to prevent future issues relating to study heterogeneity, we recommend the ongoing use of clinically meaningful outcomes such as those used in this review.

Some favourable findings associated with ACT use (e.g. the need for increased ventilatory assistance and hospital length of stay (LOS)) appeared notably influenced by strong positive data from a single French study (Vargas 2005) which utilised intrapulmonary percussive ventilation (IPV). Whilst IPV is a device for airway clearance, it is dissimilar to other ACTs in that it is applied via a gas flow which maintains a positive pressure throughout both expiration and inspiration. This could arguably be considered a variant of non-invasive ventilation, however was classified as a form of PEP for the purpose of subgroup analysis. As the effects of IPV may differ from other ACTs and the equipment is unlikely to be easily accessed by therapists of many countries, further research in this area appears warranted.

Sham ACTs were considered suitable controls for this review despite their known inadequacies (van der Schans 2000). A sham or alternative intervention minimises the likelihood that participants in a true 'no intervention' control group will receive less therapist contact time, however its success as a sham treatment is reliant upon complete naivety to ACTs due to observable differences between active and passive interventions, particularly in cross-over trials. For this reason, we rated the risk of bias for participant blinding as 'unclear' or 'high', even where a sham ACT was used. This reflects the difficulty in achieving a true placebo treatment for physical interventions. This review did not include findings from studies which compared the effect of an ACT to another ACT only. This was intended to simplify the interpretation of the literature and establish whether ACTs should have a role in treatment of people with COPD. The classification of ACTs as either PEP-based or non-PEP-based further facilitated this process and does not imply uniform effectiveness of all techniques for all individuals.

Unlike conditions such as cystic fibrosis, where airway clearance has been described as one of 'the cornerstones of treatment' (Yankaskas 2004) and true control conditions may not be considered ethically appropriate (van der Schans 2000), a similar role for ACTs in COPD has not yet been established. This review suggests there may be small clinical benefits from the use of ACTs, particularly in AECOPD, and indicates that further research using clinically meaningful outcomes may be warranted. Given that conclusive benefits for ACT use in COPD have not been demonstrated here, the use of 'no-treatment' control groups for future research of ACTs in COPD is justified.

Summary of main results

In individuals with an AECOPD, ACT use is associated with a reduced need for, and duration of, ventilatory assistance as well as a small reduction in length of hospital stay. No effect of ACTs on future exacerbations or hospitalisations was evident. Small improvements in breathlessness and sputum clearance also appear possible. In individuals with stable COPD, evidence from single studies suggests ACT use may reduce the need for hospital admission and improve HRQoL, however more data are needed to confirm this. Improvements in sputum clearance, exercise tolerance and the need for antibiotics may also be achieved but confirmation of this requires further research. We did not find convincing evidence of other benefits of ACTs in acute or stable COPD. The use of ACTs during an AECOPD appears clinically justifiable, however their impact during stable disease appears limited.

Overall completeness and applicability of evidence

Findings from this review can be translated into practice immediately, however the impact may not be large. The aims of prescribing ACTs should be carefully considered and their clinical efficacy critically appraised. Concerns about the safety of ACTs are not well supported by evidence in this review.

Quality of the evidence

The quality of the original studies included in this review is difficult to ascertain accurately. Study samples were generally small and the risk of bias was mostly high or unclear, in part due to inadequate reporting. Where data were available for quantitative analysis for the primary outcomes (Summary of findings for the main comparison), the quality of the evidence was poor. Further research is therefore very likely to have an important impact on the confidence of the estimate of effect for these outcomes and is likely to change the estimate.

Potential biases in the review process

Our attempts to contact authors of studies rated 'unclear' to determine their suitability for inclusion in the review may have introduced selection bias favouring those with whom correspondence was established. This may also have affected some judgements of the risk of bias for those studies.

Agreements and disagreements with other studies or reviews

The significant benefits of ACTs found in this review did not appear in the earlier Cochrane review on bronchopulmonary hygiene physical therapy for COPD and bronchiectasis (Jones 1998).This is most likely due to differences in the population, intervention, key outcomes and methodology (e.g. search strategy). The significant pooled effect of ACTs on hospital length of stay appears unique to this review, however other findings such as the reduced need for and duration of increased ventilatory assistance, the lack of benefit of ACTs on pulmonary function and gas exchange and the positive effect of PEP on sputum clearance appears consistent with other previous systematic reviews (Fagevik Olsen 2009; Hill 2009; Tang 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from this review indicates airway clearance techniques (ACTs) are safe for individuals with chronic obstructive pulmonary disease (COPD) but of limited clinical value. Consideration should be given to use of ACTs in patients with acute exacerbations of COPD (AECOPD), however the impact of ACTs on clinically relevant outcomes for patients with stable disease remains unclear.

Implications for research

This review highlights the need for ongoing research into the efficacy of ACTs in COPD. In order to derive clear evidence of treatment effectiveness there is an urgent need for consensus in the choice of outcomes, such as a preference towards those classified as 'primary' in this review, and higher quality of reporting. More research in the area of AECOPD is important due to the high associated healthcare costs and resource utilisation, however the lack of randomised controlled trials in stable COPD is also of concern. Given the significant heterogeneity of disease severity, symptoms and functional impairment that is characteristic of COPD, it is possible that certain individuals may derive greater benefit from ACTs than others. In addition, the impact of co-existing bronchiectasis which has been reported in 50% to 58% of individuals with COPD (Martinez-Garcia 2011; Patel 2004) has not been fully explored and was beyond the scope of this review.

ACKNOWLEDGEMENTS

The authors would like to thank Susan Hansen for her assistance with the development of the search strategy.

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CHARACTERISTICS OF STUDIES

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

Anthonisen 1964

Methods	Quasi-randomised controlled trial (2 x parallel groups)
	Study setting: 2 medical departments, Denmark (1961 to 1963)
	Study duration: until hospital discharge

Anthonisen 1964 *(Continued)*

Participants	69 participants (mean age 59.3) with an acute exacerbation of chronic bronchitis (defined as a cough for ≥ 6 months plus acute deterioration with raised temperature and muco-purulent sputum) randomised. 63 participants completed.
Interventions	Control: 'conventional treatment' (antibiotics and bed-rest +/- digitalis, theophylline, diuretics, expectorants, oxygen as required) Intervention: same as control + additional daily lung physiotherapy (expansion exercises, tapotement or vibrations and postural drainage) for 10 days
Outcomes	Days to regain a normal temperature, 24/24 sputum volume, ABGs, ECG, CXR
Notes	Some participants represented more than once (e.g. multiple admissions throughout study duration), including across both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote (from article): "...those admitted on even dates received daily lung physiotherapy, whilst those admitted on off dates did not..." Comment: inadequate sequence generation
Allocation concealment (selection bias)	High risk	Likely inadequate given method of sequence generation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants and therapists not likely to have been blind to group allocation. May have affected sputum volume.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcomes assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected sputum volume.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 patients excluded due to incomplete investigations. Some ABG data missing. Unclear whether all other outcome data complete - frequently reported as number of observations.
Selective reporting (reporting bias)	High risk	2 outcomes not reported (ECG, CXR)
Other bias	High risk	Data contamination likely. Quote: "Very occasionally it was found advisable for psychological reasons to give lung physiotherapy to patients who...should not have received it; these patients have been included in the treatment group".

Bellone 2002

Methods	Randomised controlled trial (2 x parallel groups) Setting: 1 respiratory ICU, Italy Study duration: until discharge from respiratory ICU

Bellone 2002 *(Continued)*

Participants	30 participants (17 M, 13 F, mean age 64.5 +/- 7.8) with an acute exacerbation of COPD (ATS criteria) with hypersecretion and acute hypercapnic respiratory failure requiring NIV randomised. 27 participants completed. Mean FEV_1 0.89 +/- 0.32 L.
Interventions	Control: standardised medical care (bronchodilators, steroids, antibiotics, oxygen, BiPAP) and assisted coughing (tracheal stimulation) Intervention: standardised medical care + PEP mask therapy (with supplemental oxygen). PEP therapy comprised 5 to 7 cycles of 2 minutes tidal breathing through mask (10 to 15 cm H_2O) followed by assisted coughing and 2 minutes undisturbed breathing Dosage: 30 to 40 minutes per session, 3 times/day for 3 days
Outcomes	Primary: sputum volume (g) Secondary: time to wean from NIV, incidence of treatment 'failure' (mortality or need for intubation), SpO_2, ABGs, FEV_1, FEV_1/FVC
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed using a computer programme (Statsoft)..."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants and treating therapist not likely to have been blind to group allocation. May have affected sputum volume, FEV_1 and FEV_1/FVC.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcome assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected sputum volume, FEV_1 and FEV_1/FVC.
Incomplete outcome data (attrition bias) All outcomes	Low risk	$PaCO_2$ and pH data from one participant was omitted due to intubation
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Brown 1987

Methods	Randomised cross-over trial (2 x study arms) Setting: 1 hospital, Canada Study duration: 2 days

Brown 1987 *(Continued)*

Participants	28 participants with COPD (undefined), chronic productive cough (≥ 30 ml in 24/24) and an acute exacerbation or episode of pneumonia were randomised. 24 (14 M, 7 F, mean age 66.5 +/- 11.5) completed study. Mean FEV_1 33.4 +/- 17.5% predicted
Interventions	Control: forward lean sitting with head on pillow (duration unspecified) Intervention: control + mechanical vibration (pad), applied via firm pressure and moved every 30 secs + spontaneous coughing Dose: 15 minutes per affected bronchopulmonary segment (if CXR changes) or dependent lung regions (no CXR changes)
Outcomes	FEV_1, FVC, SpO_2, sputum volume
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each patient was randomly assigned to..." Comment: inadequate detail provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants and therapists not likely to have been blind to group allocation. May have affected primary outcomes (sputum volume, FEV_1, FVC).
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcomes assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected primary outcomes (sputum volume, FEV_1, FVC).
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants excluded from data analysis due to worsening of symptoms (group allocation not stated)
Selective reporting (reporting bias)	Low risk	Data reported for all outcomes
Other bias	Unclear risk	Adequate (24/24) washout period; appropriate (paired) statistical analysis employed; no evidence of testing for period and order effects; detail lacking regarding potential co-intervention of additional therapy (which included regular physiotherapy)

Cegla 1997

Methods	Randomised controlled trial (3 x parallel groups) Study setting: 1 outpatient pulmonary clinic (Germany) Study duration: 7 days

Cegla 1997 *(Continued)*

Participants	90 participants (61 M, 29 F, mean age 56.0 +/- 10.4) with (presumed stable) COPD (undefined), tracheobronchial instability (check-valve in flow-volume curve and trapped air in body plethysmography resistance loop), productive of sputum and < 65 years randomised and completed. Mean FEV_1 1.74 +/- 0.8L.
Interventions	Control: 'standard medical therapy' (steroids, theophylline, bronchodilators +/- short-term oxygen) Intervention 1): 'standard medical therapy' plus Cornet. Dose: 5 minutes, 4 times/day for 7 days. First session (only) supervised. Intervention 2): 'standard medical therapy' plus Flutter. Dose: 5 minutes, 4 times/day for 7 days. First session (only) supervised.
Outcomes	VC, RV, FEV_1, R_{aw}, S_{Gaw}, PEFR, $PaCO_2$, PaO_2, pH, VAS scale for cough sputum and dyspnoea
Notes	Study written in German. Data from both interventions combined for inclusion in quantitative analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (translated): "Patients were assigned to 3 groups randomly" Comment: unclear whether adequate
Allocation concealment (selection bias)	Unclear risk	No information provided Comment: unclear whether adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants and treating therapist not likely to have been blind to group allocation. May have affected primary (FEV_1, VC) and secondary (PEFR, symptom-change) outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcomes assessors not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected primary (FEV_1, VC) and secondary (PEFR, symptom-change) outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available for reported outcomes
Selective reporting (reporting bias)	High risk	Data not available for pH, PEFR, SGaw
Other bias	Unclear risk	Full English translation not available

Cegla 2001

Methods	Randomised cross-over trial (2 x study arms) Setting: Pulmonary Research Institute, Germany Study duration: 2 days

Cegla 2001 *(Continued)*

Participants	35 participants (25 M, 10 F, mean age 65.0 +/- 10.0) with stable COPD (undefined) and tracheobronchial instability* randomised and completed. All were non-smokers in the last 5 years. Mean FEV_1 1.15 +/- 0.4 L (47.1 +/- 15.8% predicted).
Interventions	Control: inhalation of 2 puffs salbutamol via autohaler followed by 750 µg ipratropium bromide in 3 ml 0.9% NaCl nebulised via Pari Inhaler Boy and LC-plus atomiser (25 minutes post-salbutamol). Normal exhalation through Pari. Intervention: same as control, except exhalation via Cornet (position 1). Estimated pressure 20 +/- 5 cm H_2O during oscillations.
Outcomes	FEV_1, VC, RV, R_{aw}
Notes	*Refer Cegla 1997 for definition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants not likely to have been blind to group allocation. May have affected primary outcomes (FEV_1, VC).
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcomes assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected primary outcomes (FEV_1, VC).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available for reported outcomes
Selective reporting (reporting bias)	Low risk	Data reported for all outcomes
Other bias	Unclear risk	Washout period (24/24) adequate; no evidence of investigation for period and order effects; paired (non-parametric) statistical analysis employed

Cegla 2002

Methods	Randomised controlled trial (2 x parallel groups) Setting: Pulmonary Research Institute, Germany Study duration: 2 years

Cegla 2002 *(Continued)*

Participants	81 participants with stable severe COPD, check-valve in flow-volume curve and trapped air in body plethysmography resistance loop* randomised. 50 completed (38 M,12 F; mean age 63.4 +/- 9.2). Mean post-bronchodilator FEV_1 1.27 +/- 0.43 L (41 +/- 12% predicted).
Interventions	Control: drug therapy (theophylline, salmeterol, Atrovent, glucocorticosteroids) Intervention: drug therapy + Cornet. Dose: used in the start position for ≥ 5mins, 3 times/day plus whenever they noticed mucus or dyspnoea.
Outcomes	FEV_1, VC, R_{aw}, lung volumes, ABG, SpO_2, hospitalisations (due to AECOPD), no. of hospital days, need for antibiotics
Notes	*Presumed definition of tracheobronchial instability, based on similar research by same author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Insufficient information provided Comment: participants not likely to have been blind to group allocation. May have influenced FEV_1, VC and reporting of antibiotic use.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information provided Comment: outcomes assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have influenced FEV_1, VC.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear available for all initial and follow-up assessment outcomes
Selective reporting (reporting bias)	High risk	Data only reported for 50/81 participants; data not reported for ABG or SpO_2
Other bias	High risk	Unclear why 3 participants were randomly excluded to make 2 even groups (n = 25)

Christensen 1990

Methods	Randomised controlled trial (2 x parallel groups) Setting: 1 x outpatient chest-clinic, Denmark Study duration: 6 months

Christensen 1990 *(Continued)*

Participants	60 participants with stable severe COPD (FEV_1 < 40% predicted; FEV_1/FVC < 0.7; < 20% reversibility; Medical Research Council (MRC) definition of chronic bronchitis) and chronic mucus hypersecretion randomised. 47 completed (21 M, 26 F, median age 64). Median FEV_1 0.97L.
Interventions	Control: PEP mask (with incorporated PEEP valve, set at 0 cm H_2O*) therapy. Dose: ≥ 15 minutes, 3 times/day Intervention: same as control, but PEEP valve set at 10 cm H_2O*
Outcomes	FEV_1, FVC, a questionnaire of smoking habits, dyspnoea, cough and sputum, no. AECOPDs, no. days bedridden, no. days hospitalised, antibiotic and other medication use, VAS for dyspnoea, cough, sputum and exercise tolerance, PaO_2, $PaCO_2$, and global assessment of treatment
Notes	*The addition of the PEEP valve was noted to add 1.5cm H_2O to each setup

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomised..." Comment: insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The patients were randomised double-blindly..." Comment: participants may not have been blind to group allocation despite 'sham' control. May have affected FEV_1, FVC and questionnaire or VAS scale-based outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients were randomised double-blindly..." Comment: outcomes assessor(s) presumed to have been blind to group allocation. Unlikely to have affected outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Complete data reported for only 47/60 participants. Reasons for withdrawal (5 in intervention group, 8 in control group) reported as being unrelated to the trial. No ITT analysis evident.
Selective reporting (reporting bias)	High risk	Quote: "Although we had data from the monthly visits, we decided to make the statistical analysis between the first and last visit in order to avoid repeated statistical testing" Comment: some data available for months 1 to 5 for FEV_1. Inadequate data reporting.
Other bias	Low risk	

Christensen 1991

Methods	Randomised controlled trial (2 x parallel groups) Setting: 1 x hospital, Denmark

Christensen 1991 *(Continued)*

	Study duration: 4 weeks
Participants	30 participants with stable chronic bronchitis (MRC definition) randomised. Included smokers, ex-smokers and non-smokers. 28 completed (mean age 64, range 58 to 73). Mean FEV_1 2.1 L (range 1.1 to 3.3), mean FEV_1/FVC 0.71 (range 0.48 to 0.81).
Interventions	Control: usual oral bronchodilators + 2 puffs (0.5 mg) terbutaline via spacer connected to a PEP mask (0 cm H_2O). Dose: 10 tidal breaths, twice/day for 4 weeks. Intervention: same as control, except PEP of 10 to 20 cm H_2O
Outcomes	Daily diary of symptoms (cough and dyspnoea each rated 1 to 3; sputum rated 1 to 9), side effects, bronchodilator use, PEFR (via Mini-Wright Peak flow meter); FEV_1, FVC
Notes	3 non-smokers (1 in intervention group; 2 in control group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to treatment..." Comment: insufficient information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "In this kind of trial it is not possible to make a double-blind design..." Comment: participants may not have been blind to group allocation despite 'sham' control. May have affected all outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "In this kind of trial it is not possible to make a double-blind design..." Comment: outcomes assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected FEV_1 and FVC outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants (1 from each group) withdrew due to respiratory illness in the first week, not included in baseline data; data missing for PEFR outcome; no evidence of ITT analysis
Selective reporting (reporting bias)	Low risk	Data from all outcomes reported
Other bias	Low risk	

Christensen 1991a

Methods	Randomised cross-over trial (3 x study arms). Setting: 1 x outpatient clinic, Denmark. Study duration: 3 x 2 week periods.

Christensen 1991a *(Continued)*

Participants	10 participants (7 M, 3 F; mean age 54.4+/- 16.6) with stable COPD (not clearly defined) and daily cough, expectoration and dyspnoea, requiring daily bronchodilators randomised and completed. Mean FEV_1 1.07+/- 0.54L (34.7+/- 15.3% predicted).
Interventions	Control: inhalation of 2 ml 5 mg nebulised terbutaline via PARI-Inhaler-boy connected to a PEP mask (0 cm H_2O). Dose: tidal breathing until end of nebuliser (8 to 10 minutes), 3 times/day for 2 weeks. Additional terbutaline was allowed when needed. Intervention 1: same as control except 10 to 15 cm H_2O Intervention 2*: same as intervention 1 except placebo medication
Outcomes	Daily diary of symptoms (cough, mucus and dyspnoea; each rated 1 to 3), side effects, bronchodilator use, PEFR (via Mini-Wright Peak flow meter); FEV_1, FVC
Notes	*Intervention 2 not considered in this review Washout period unclear (presumably consecutive days)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was double-blind with respect to the inhaled medication, but open concerning PEP, because the expiratory resistance could be felt" Comment: may have affected all outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was double-blind with respect to the inhaled medication, but open concerning PEP, because the expiratory resistance could be felt" Comment: outcomes assessor(s) not likely to have been blind to intervention (presumably the same therapist that prescribed the intervention). May have affected spirometry outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available for all outcomes
Selective reporting (reporting bias)	Low risk	Complete data reported for all outcomes
Other bias	High risk	Washout period unclear (presumably consecutive days), however data from the first 3 days of each study arm were excluded due to concerns of carry-over. Suitable paired statistical analysis methods used.

Haidl 2002

Methods	Randomised controlled trial (2 x parallel groups) Study setting: 1 hospital, Germany

Haidl 2002 *(Continued)*

	Study duration: 1 day
Participants	14 patients with (acute) COPD (FEV_1 < 60% predicted + peripheral flow limitation (FIV_1/FEV_1 > 1.5, MEF_{50} < 35% target)) and suspected pulmonary embolus or lung volume reduction surgery workup randomised. 13 completed (10 M, 3 F, mean age 65.9 +/- 6.8). Mean FEV_1 1.2 +/- 0.5L (38.6 +/- 16.7% predicted).
Interventions	Control: inhalation of radioaerosol (1 breath) + 5 breaths with normal exhalation Intervention: same as control except 5 breaths with exhalation via the RC-Cornet (position 1)
Outcomes	Regional (proximal and peripheral) scintigraphic measurement of aerosol particle deposition (penetration index)
Notes	Article written in German. Randomisation confirmed via correspondence with author. Data not suitable for meta-analysis (not a measure of whole lung clearance).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (correspondence with author): "[participants were] randomly allocated by a sealed list (ABBA etc.)" Comment: inadequate detail
Allocation concealment (selection bias)	Low risk	Quote (correspondence with author): "randomly allocated by a sealed list (ABBA etc.)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Insufficient information provided Comment: participants may not have been blind to intervention. Not likely to have affected primary outcome.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided Comment: outcome assessor(s) not likely to have been blind to intervention. Unclear whether may have affected primary outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant excluded from the intervention group after randomisation
Selective reporting (reporting bias)	Low risk	Data from all outcomes reported
Other bias	Unclear risk	Full English translation not available

Hasani 1995

Methods	Randomised cross-over trial (3 x study arms) Setting: 1 x thoracic medicine department, United Kingdom Study duration: 1 day

Hasani 1995 *(Continued)*

Participants	24 participants: 8 with asthma, 8 with bronchiectasis, 8 (5 M, 3 F; mean age 69 +/- 8.5) with stable chronic bronchitis* (not clearly defined) randomised and completed. Mean FEV_1 41 +/- 9% predicted
Interventions	Control: resting Intervention 1: 6 coughs/min x 5 cycles with 1 min rests between cycles Intervention 2: 6 FETs/min x 5 cycles with 1 min rests between cycles
Outcomes	Regional (inner and outer) lung clearance (radioaerosol deposition) via penetration index
Notes	*Only data from participants with chronic bronchitis were included in review/meta-analysis. Abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No information provided Comment: participants not likely to have been blind to intervention. Not likely to have affected outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided Comment: outcomes assessor(s) not likely to have been blind to intervention. Unclear whether may have affected outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information available
Selective reporting (reporting bias)	Unclear risk	Insufficient information available
Other bias	Unclear risk	Insufficient information available

Inal-Ince 2004

Methods	Quasi-randomised controlled trial (2 x parallel groups) Study setting: 1 medical ICU, Turkey (2000 to 2002) Study duration: until discharge from ICU
Participants	35 participants with acute hypercapnic respiratory failure requiring ICU and NIV randomised. 34 (12 M, 22 F) completed (27 with COPD, undefined, mean age 66.5 +/- 9.4).
Interventions	Control: usual ICU care + NIV (≤ continuous first 24/24, then progressive wean according to study protocol)

Inal-Ince 2004 *(Continued)*

	Treatment: same as control + ACBT (2 cycles of 4 to 6 RCBs, 3 to 4 thoracic expansion exercises +/- percussion and vibration with FET, 4 to 6 RCBs, 2 to 3 huffs) in upright positions, once/day supervised (only), total time 15 to 30mins
Outcomes	Primary: time (hours) from onset to cessation of NIV Secondary: change in acute physiology score and ABGs, total number of days requiring NIV, ICU LOS, need for intubation, mortality
Notes	Limited data available for COPD-only participants, obtained via correspondence with author. Intervention group (COPD subset) underpowered to detect primary outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "patients were allocated randomly, using file numbers" Comment: inadequate sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: participants and treating therapists not likely to have been blind to group allocation. May have affected outcomes measured pre/post treatment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcomes assessors not blind to group allocation. May have affected outcomes measured pre/post treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "One patient from the control group refused treatment 1.5 days after admission" Comment: reported data not inclusive of this participant (unclear if COPD)
Selective reporting (reporting bias)	Unclear risk	Comment: complete ABG data not available for COPD participants (after correspondence with author)
Other bias	Low risk	

Kodric 2009

Methods	Randomised controlled trial (2 x parallel groups) Study setting: 1 hospital, Italy (2002) Study duration: 6 months
Participants	59 (41 M, 18 F; mean age 70.2 +/- 8.4) patients with an acute exacerbation of COPD (GOLD) randomised and completed up to 1 month. 22 completed 6-month follow-up. Mean FEV_1 54.0 +/- 23.2% predicted.
Interventions	Control: 'standard medical therapy' (steroids, bronchodilators, antibiotics according to GOLD guidelines) Intervention: 'standard medical therapy' + ELTGOL (slow expiration with glottis open in the lateral position) for 30 to 40 minutes/session, twice/day for 7 days

Kodric 2009 *(Continued)*

Outcomes	Primary: 24/24 sputum volume Secondary: hospital LOS, AECOPDs, hospitalisations, dyspnoea severity, HRQoL (SGRQ), FEV_1, FEV_1/FVC
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from report): "patients were randomly assigned to two groups" Quote (from correspondence): "patients were randomised using a computer-generated (Excel) list of random numbers"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information provided. Patients not likely to have been blind to group allocation. May have influenced FEV_1, FEV_1/FVC and self reported outcomes (e.g. Borg, MRC, SGRQ)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment (from correspondence): outcomes assessors were not blind to group allocation. May have influenced FEV_1, FEV_1/FVC, sputum collection, and some self reported outcomes (e.g. MRC, SGRQ), but unlikely to have affected LOS, hospitalisations and AECOPDs data.
Incomplete outcome data (attrition bias) All outcomes	High risk	Complete data at discharge, however only reported from 22/59 patients at 6 months. No ITT analysis.
Selective reporting (reporting bias)	High risk	Methods state measurements included ABGs, sputum volumes at 1 hour after treatment and daily until discharge. No ABG results reported; baseline sputum volume only reportedly compared to 1 other day.
Other bias	Unclear risk	Unclear if patients in both groups were comparable at baseline in all outcomes

Martins 2006

Methods	Randomised cross-over trial (2 x study arms) Setting: 1 x physiotherapy/nuclear medicine department, Brazil Study duration: 1 week
Participants	5 participants with mild-moderate stable (≥ 3 weeks) COPD (GOLD criteria) and daily excessive sputum expectoration (MRC chronic bronchitis definition) randomised and completed
Interventions	Control: rest for 20 minutes (instructed to swallow secretions). Spontaneous coughing (only) allowed. Intervention: ELTGOL for 20 minutes. Dose: 10 x slow, deep expirations followed by 2 minutes rest x 3 sets in the right lateral position. Participants were instructed to swallow secretions. Spontaneous coughing (only) allowed.
Outcomes	Quantity stomach scintillation as measured by static scintigraphy

Martins 2006 *(Continued)*

Notes	Abstract only. 1-week washout between cross-over arms. Study details obtained via correspondence with author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Correspondence with author: "...were referred to intervention or control procedure in a random allocation (MatLab, The MathWorks Inc, Natick, MA, USA)"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Inadequate information provided Comment: participants not likely to have been blind to intervention. Not likely to have affected outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information provided Comment: outcome assessor(s) not likely to have been blind to intervention. Unclear whether may have affected outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inadequate information provided
Selective reporting (reporting bias)	Low risk	Data reported for stated outcomes
Other bias	Unclear risk	Inadequate information provided

Martins 2007

Methods	Randomised cross-over trial (2 x study arms) Setting: 1 x physiotherapy/nuclear medicine department, Brazil Study duration: 1 week
Participants	12 participants (age range 45 to 75) with mild-moderate stable (≥ 3 weeks) COPD (GOLD criteria) and daily excessive sputum expectoration (MRC chronic bronchitis definition) randomised and completed
Interventions	Control: rest for 20 minutes. Spontaneous coughing (only) allowed. Intervention: ELTGOL for 20 minutes. Dose: 10 x slow, deep expirations followed by 2 minutes rest x 3 sets in the right lateral position. Spontaneous coughing (only) allowed.
Outcomes	Scintigraphic measurement of percentage (%) retention radioaerosol in right lung
Notes	Abstract only. 1-week washout between cross-over arms. Study details obtained via correspondence with author.

Risk of bias

Bias	Authors' judgement	Support for judgement

Martins 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Correspondence with author: "...were referred to intervention or control procedure in a random allocation (MatLab, The MathWorks Inc, Natick, MA, USA)"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Inadequate information provided Comment: participants not likely to have been blind to intervention. Not likely to have affected outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information provided Comment: outcome assessor(s) not likely to have been blind to group allocation. Unsure if this may have affected outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inadequate information provided
Selective reporting (reporting bias)	Low risk	Data reported for stated outcomes
Other bias	Unclear risk	Inadequate information provided

May 1979

Methods	Randomised cross-over trial (2 study arms, with a third subset only) Setting: 1 x hospital, Canada Study duration: 2 days
Participants	35 participants (29 M, 6 F; mean age 59) with stable chronic bronchitis (MRC definition), history of chronic productive cough and obstructive defect on spirometry randomised and completed. Median FEV_1 1.44 L.
Interventions	Control: 30 minutes chest heat lamp therapy (10 minutes heat in side-lying, 10 minutes rest supine no heat, 10 minutes heat side-lying alternate side) Intervention 1: 90 secs manual percussion followed by vibrations, assisted coughing and a brief rest, applied in 7 different postural drainage positions (with head tilt), covering each lobe Intervention 2 (subset of participants only): directed, unassisted coughing every 5 minutes for 30 minutes
Outcomes	Perceived improvement, adverse reactions, vital signs, sputum volume, ABGs (including A-a O_2 difference), spirometry (FEV_1, FVC, PEF, FEF_{50}, FEF_{75})
Notes	Group headings ("heat lamp" and "percussion and drainage") for results data in table 1 appear erroneously labelled in reverse (according to text description)

Risk of bias

Bias	Authors' judgement	Support for judgement

May 1979 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Every patient received both methods of treatment, one on each of two consecutive mornings in random sequence" Comment: inadequate detail provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants not likely to have been blind to group allocation. May have affected perceived improvement, (subjective) adverse reactions or sputum volume.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcome assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected measurement of vital signs or spirometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available all for all reported outcomes
Selective reporting (reporting bias)	High risk	No data reported for vital signs
Other bias	Unclear risk	Reasons for why the first 11 participants (only) received a third intervention not stated

Morsch 2008

Methods	Randomised controlled trial (4 x parallel groups total, 2 for participants with COPD) Setting: 1 x outpatient pulmonology clinic, Brazil Study duration: 1 day
Participants	32 participants with asthma and 20 participants (2 M, 18 F; mean age 64.9 +/- 6.8) with stable stage III COPD (GOLD criteria) randomised and (all COPD participants) completed. Mean FEV_1 1.4 +/- 0.5 L.
Interventions	Control: 7 minutes induced sputum (9 ml 3% hypertonic saline) via ultrasonic nebuliser. If non-productive, the procedure was repeated with 0.9% saline until adequate expectoration was achieved. Intervention: same as control + Flutter (in upright sitting). Dose: 5 minutes of calm, prolonged exhalations through Flutter (horizontal alignment) followed by vigorous coughing. If non-productive, 10 x FETs at 30-sec intervals (incorporating relaxed breathing), followed by vigorous coughing were performed.
Outcomes	Sputum weight (following processing), total cell counts (×10^6/mL), cell viability (%), time to obtain sputum, SpO_2, HR
Notes	
Risk of bias	

Morsch 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In this clinical trial, the patients were assigned, by random drawing, to one of the two procedures" Comment: inadequate information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Insufficient information provided Comment: participants not likely to have been blind to group allocation. May have affected sputum expectoration.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The material was processed by an experienced laboratory technician, who was blinded to the protocol performed to obtain sputum samples" Comment: cell count and viability data not likely to be affected. As the therapist responsible for collecting the sputum sample not likely to have been blind to group allocation, may have affected time to obtain sample and sputum volume.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available for all outcomes for COPD participants
Selective reporting (reporting bias)	Low risk	All outcomes reported, however limited data available for SpO_2 and HR
Other bias	Low risk	

Newton 1978

Methods	Randomised (stratified) controlled trial (2 x parallel groups) Study setting: 1 hospital, United Kingdom Study duration: 3 months
Participants	96 patients with an acute exacerbation of chronic bronchitis (MRC definition), aged > 45 years randomised. 79 (63 M,16 F; mean age 67.5) completed at discharge and (presumably) 3 months. Mean FEV_1 0.7 +/- 0.3L.
Interventions	Control: 'standard medical management' (antibiotics, bronchodilators, diuretics, oxygen via FiO_2 0.24 Ventimask) Intervention: 'standard medical management' + physiotherapy (10 to 15 minutes breathing exercises + chest vibration and percussion in different postures + postural drainage, if tolerated, 3 times/day) + IPPV with saline nebulisation (15 minutes, 3 times/day)
Outcomes	Temperature, weight, eating score (0 to 3), sleep score (0 to 3), MRC scale, Neuroticism Score Questionnaire (NSQ), 1-minute walk distance (1MWD), spirometry, 24-hour sputum volume (over 3 days), ABGs, LOS, chest infections, hospitalisations, mortality
Notes	

Newton 1978 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (from report): "We then randomly allocated patients" Comment: insufficient information, unable to contact author
Allocation concealment (selection bias)	Low risk	Quote (from report): "randomly allocated patients...using prearranged sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants not likely to have been blind to group allocation. May have affected survey scores, 1MWD and sputum volume.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcome assessor(s) not likely to have been blind to group allocation (presumably the same therapist that prescribed the intervention). May have affected 1MWD, spirometry and sputum volume.
Incomplete outcome data (attrition bias) All outcomes	High risk	23 recruited patients were omitted after randomisation without ITT analysis. Unclear how many participants completed 3-month follow-up (presumed 79).
Selective reporting (reporting bias)	High risk	Data not reported for MRC, sleep or eating scores and temperature
Other bias	Unclear risk	Long term follow-up not specified a priori; 'chest infection' outcome not defined

Newton 1978a

Methods	Randomised cross-over trial (2 x parallel groups*) Setting: 1 x hospital, United Kingdom Study duration: 1 day
Participants	42 participants with an acute exacerbation (increased cough, breathlessness or sputum for > 24/24) of chronic bronchitis (MRC criteria), FEV_1/FVC < 50% and < 15% reversibility randomised. 33 completed. Mean FEV_1 1.0 +/- 0.4 L.
Interventions	Control: 30 minutes rest followed by 15 minutes of breathing exercises, vibrations and percussions in different positions (unspecified) plus postural drainage (if tolerated) Intervention: 15 minutes of breathing exercises, vibrations and percussions in different positions (unspecified) plus postural drainage (if tolerated), followed by 30 minutes rest
Outcomes	FEV_1, VC, FRC, S_{Gaw}, G_{aw}
Notes	*2 separate groups, however response to treatment determined by pooling data from both groups. Data available pre and post-rest, but unsuitable for meta-analysis.

Risk of bias

Newton 1978a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to two groups..." Comment: inadequate information provided
Allocation concealment (selection bias)	Low risk	Quote: "The patients were randomly allocated to two groups by a physiotherapist drawing a card from a sealed envelope" Comment: adequate procedure
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not likely to have been blind to intervention. May have affected FEV_1 and VC.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The operator of the body plethysmograph (body box) did not know to which group the patient was allocated" Comment: adequate information provided for relevant outcomes. Presumably applies to FEV_1 and VC.
Incomplete outcome data (attrition bias) All outcomes	High risk	9 participants excluded (presumably after randomisation) due to inability to perform test procedures. No ITT analysis evident.
Selective reporting (reporting bias)	Unclear risk	Data unable to be used for meta-analysis due to pooling across groups for some outcomes. Data reported for all outcomes.
Other bias	Unclear risk	Unclear why ABGs were performed on a subset of participants only. Mean and SD data reported for FRC, G_{aw} and S_{Gaw} despite non-parametric analysis.

Oldenburg 1979

Methods	Randomised cross-over trial (4 x study arms) Setting: 1 x hospital clinic, Canada Study duration: 5 x 1 day (over up to 10 days)
Participants	8 participants (7 M, 1 F; mean age 62.1 +/- 4.4) with stable (simple and obstructive) chronic bronchitis (MRC definition), capable of exercising at 70% to 75% predicted HR_{max} and avoiding coughing during test procedures randomised and completed. Mean FEV_1 1.6 +/- 0.7 L (58.4 +/- 21.2% predicted).
Interventions	All interventions (including control) took place following 30 minutes upright rest (between 0.5 to 1.16 hours) Control: upright resting Intervention 1: 5 x 4 minutes cycle ergometry at 70% to 75% predicted HR_{max} intensity, interspersed with 4-min rests Intervention 2: 5 x 6 minutes postural drainage in the left lateral decubitus position (15° head-down tilt), interspersed with 1-min rests Intervention 3: coughing once/minute for 5 minutes, interspersed with 3-min rests

Oldenburg 1979 *(Continued)*

Outcomes	Total and outer zone radioaerosol deposition and % retention (clearance)
Notes	Error in original text (postural drainage 1.2 hour total lung % mean/SD data miscalculated, table 2 column 4). Washout period 1 day. Intervention 3 not included in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The order of the experiments was randomised" Comment: insufficient information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Insufficient information provided Participants not likely to have been blind to intervention. Unlikely to have affected primary outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided Comment: outcome assessor(s) not likely to have been blind to intervention. Unclear whether may have affected primary outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available for all outcomes
Selective reporting (reporting bias)	Low risk	Data reported for all outcomes
Other bias	Low risk	Appropriate (paired) statistical analyses employed; adequate washout period (separate days)

Pavia 1976

Methods	Randomised cross-over trial (2 x study arms) Setting: hospital chest clinic, United Kingdom Study duration: unclear
Participants	10 participants (9 M, 1 F; mean age 65.3 +/- 5.9) with stable chronic bronchitis (productive cough, shortness of breath and difficulty expectoration phlegm) randomised and completed. Mean FEV_1 1.5 +/- 0.9 L.
Interventions	Control: 1 hour of rest in 45° reclined position (over 80 minutes). Vibration pad positioned between patient's back and couch (inactive). Intervention: same as control, except mechanical vibration delivered via pad (active). Amplitude 2 mm; frequency (mean) 41 Hz; intensity determined by the onset of tremulous speech.
Outcomes	Rate (per min) radioaerosol clearance and sputum volume

Pavia 1976 *(Continued)*

Notes	1 participant (female) was a non-smoker. Washout period unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The order...was determined by random numbers, subject to the proviso that half of the subjects had the control first" Comment: sufficient information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants not likely to have been blind to intervention. May have affected sputum volume outcome.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided Comment: outcome assessor(s) not likely to have been blind to intervention. Unclear whether may have affected primary outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant had inadequate inhalation of aerosol particles during control run. Unclear whether may have affected outcome data.
Selective reporting (reporting bias)	Low risk	Data reported for all outcomes
Other bias	Low risk	

Rasmussen 2001

Methods	Randomised cross-over trial (4 x cross-over arms) Setting: 1 x hospital, Denmark Study duration: 4 x 4 days
Participants	25 participants (12 M, 13 F; mean age 66.6) with stable COPD (undefined) randomised and completed. Mean FEV_1/FVC 46.8%.
Interventions	Control: self administered PEP-valve therapy (0 cm H_2O), twice/day for 4 days Intervention 1: same as control except 5 cm H_2O Intervention 2: same as control except 12.5 cm H_2O Intervention 3: same as control except 20 cm H_2O
Outcomes	1/24 sputum wet-weight, patient preference.
Notes	Abstract only. Washout period unclear. No usable data for analysis.

Rasmussen 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not likely to have been blind to intervention despite 'sham' control. May have affected primary outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided
Other bias	Unclear risk	Washout period unclear

Rivington-Law 1984

Methods	Randomised cross-over trial (2 x study arms) Setting: Canada Study duration: 3 consecutive days (including 1 rest day)
Participants	14 participants with stable chronic bronchitis (ATS definition), crackles on ausculation and skinfold calliper thickness < 60 mm over 4 sites (to exclude obesity) randomised. 12 (11 M, 1 F; mean age 66, range 48 to 80) completed. Mean FEV_1 0.9 +/- 0.4 (35.9 +/- 13.5% predicted).
Interventions	Control: 15 minutes rest with therapist hands on chest followed by 15 minutes of no intervention (30° supine position) Intervention 1: same as control except first 15 minutes followed by 15 minutes of deep breathing Intervention 2: same as control except first 15 minutes followed by 15 minutes of deep breathing + manual chest wall vibrations (every 3rd exhalation, moderate intensity)
Outcomes	FEV_1, VC, FRC, RV, ERV, SpO_2
Notes	Lung volumes measured in 30 degrees supine position

Risk of bias

Bias	Authors' judgement	Support for judgement

Rivington-Law 1984 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "A crossover design was used to randomize the treatment modalities" Comment: inadequate information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants not likely to have been blind to intervention. May have affected FEV_1, VC.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcomes assessor(s) not likely to have been blind to intervention (presumably the same therapist that prescribed the intervention). May have affected FEV_1, VC and SpO_2 outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Complete data presumed to be available for all outcomes (not explicitly stated)
Selective reporting (reporting bias)	High risk	Reported data unsuitable for meta-analysis. Outcomes described only as 'spirometry' and 'lung volumes' in methods, but reported as individual measures in results.
Other bias	Unclear risk	Unclear which groups the 2 excluded participants were from; adequate washout period (consecutive days); outcomes measured following 15 minutes rest used as baseline due to significant changes from first measurement

van Hengstum 1988

Methods	Randomised cross-over trial (3 x study arms) Setting: 1 x hospital, The Netherlands Study duration: ≥ 12 days (inadequate information available)
Participants	8 participants (7 M, 1 F; mean age 63, range 48 to 73) with (presumed stable) chronic bronchitis (MRC definition) randomised and completed. Mean FEV_1 1.79 +/- 0.65L (56 +/- 21% predicted).
Interventions	Control: rest with spontaneous coughing (only) Intervention 1: PEP-mask therapy in forward lean sitting (elbows resting on table) position. Dose: 10 to 15 cm H_2O for 2 minutes, followed by abdominal breathing and 2 maximal huffs and coughs x 5 cycles (total duration approx. 20 minutes). Intervention 2: 6 positions of postural drainage (4 in a 15° head-down tilt position, 2 upright) with diaphragmatic breathing, thoracic expansion exercises, diaphragmatic breathing, 2 huffs (with chest compression) interspersed with relaxed diaphragmatic breathing and coughs (total duration approx. 30mins)
Outcomes	Immediate and 24/24 lung radioaerosol particle deposition, whole lung clearance, regional (inner, intermediate, peripheral) lung clearance, sputum weight, FEV_1, FVC, S_{Gaw}, FEF_{25-75}

van Hengstum 1988 *(Continued)*

Notes	Data enabling comparison between each intervention to control available, but unsuitable for meta-analysis as no significance values stated; washout period 2 days between study arms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The sequence of the measurements in each patient was determined at random" Comment: inadequate information available
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided Comment: participants not likely to have been blind to intervention. May have affected sputum volume, FEV_1, FVC outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided Comment: outcomes assessor(s) not likely to have been blind to intervention (presumably the same therapist that prescribed the intervention). Unclear whether may have affected radioaerosol clearance. May have affected FEV_1, FVC.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data appears complete (n = 8) for stated outcomes. Unclear why additional measurements made for only 4/8 participants at 7 hours.
Selective reporting (reporting bias)	Low risk	Data available for all outcomes
Other bias	Low risk	Adequate washout period between study arms; paired statistical analysis employed

Vargas 2005

Methods	Randomised controlled trial (2 x parallel groups) Study setting: 1 ICU, France Study duration: until discharge
Participants	33 participants (mean age 69.7 +/- 5.5) with an acute exacerbation of COPD (ATS criteria) admitted to ICU randomised and completed. Mean FEV_1 38.5 +/- 7.5% predicted
Interventions	Control: 'standardised medical care' (oxygen, bronchodilators, corticosteroids, antibiotics) Intervention: 'standardised medical care' + intrapulmonary percussive ventilation via face-mask (peak pressure 20 cm H_20, percussion frequency 250/minute, I:E 1:2.5, delivered with nebulised 0.9% NaCl and supplemental oxygen). Dosage: 30 minutes per session, twice/day.
Outcomes	Primary: 'therapy success' (avoidance of clinical deterioration, including need for NIV)

Vargas 2005 *(Continued)*

	Secondary: hospital LOS, ABGs, RR, mucus clearance (subjective)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (from article): "Patients were randomly assigned to receive..." Comment: inadequate information available
Allocation concealment (selection bias)	Low risk	Quote (from article): "Random assignments were made with sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and treating physiotherapist (unblinded) may not have been blind to group allocation Comment: may have affected (subjective) mucus clearance
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unclear if the outcome assessor was the unblinded treating physiotherapist or whether involved in participants' care. May have affected decisions of need for NIV, timing of AGBs, RR and subjective measures of mucus clearance.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data reported at discharge
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported at discharge
Other bias	Low risk	

Weiner 1996

Methods	Randomised controlled trial (2 x parallel groups) Setting: 1 x medical centre, Israel Study duration: 3 months
Participants	20 participants (13 M, 7 F; mean age 63.3 +/- 9.5) with stable COPD (not clearly defined) and bronchial hypersecretion (> 30 ml) randomised and completed. Mean FEV_1 35 +/- 8.5% predicted
Interventions	Intervention: Flutter (from TLC + 1 to 2-sec breath hold to RV) x 10 breaths followed by 30-sec rest x 4 to 8 sets (approx. 10 minutes), daily for 3 months Control: same as intervention except steel ball removed
Outcomes	Primary: FEV_1, FVC, exercise tolerance (12MWT) Secondary: ABGs, maximum voluntary ventilation, Borg
Notes	Article published in Hebrew. Randomisation confirmed via correspondence with author.

Risk of bias

Weiner 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomly allocated to the treatment or control group via random number generator" (source: correspondence with author)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants may not have been blind to group allocation despite 'sham' control. May have affected primary outcomes and Borg.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor (doctor) was blinded to the group that participants belonged to during all assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data reported for all outcomes
Selective reporting (reporting bias)	High risk	Data reported for all outcomes, but not all suitable for meta-analysis
Other bias	Unclear risk	Full English translation not available

Wolkove 2002

Methods	Randomised cross-over trial (2 x study arms) Study setting: 1 x hospital, Canada Study duration: 3 separate days
Participants	23 participants (10 M, 13 F; mean age 71.7 +/- 6.3) with clinically stable, severe COPD (clinical history, FEV_1 < 50% predicted, FEV_1/FVC < 65%) randomised and completed. Mean FEV_1 0.74 +/- 0.28 L (34.5 +/- 12.7% predicted).
Interventions	Intervention: 10 minutes Flutter (used in the position which generated the best 'flutter' sensation within the chest) followed by 4 puffs Combivent via MDI and spacer Control: same as intervention except 10 minutes sham Flutter (steel ball removed)
Outcomes	FEV_1, FVC, 6MWD, Borg, HR, SpO_2
Notes	Washout period unclear (separate days)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "On 2 subsequent days, in random order..." Comment: insufficient information provided

Wolkove 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided. Participants not likely to have been blind to intervention, despite 'sham' control. May have affected FEV_1, FVC, Borg and 6MWD outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided. Outcomes assessor(s) not likely to have been blind to intervention (presumably the same therapist that prescribed the intervention). May have affected FEV_1, FVC, Borg and 6MWD outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported for all outcomes (presumed to be complete, not explicitly stated)
Selective reporting (reporting bias)	Low risk	Data reported for all outcomes
Other bias	Unclear risk	Appropriate (paired) statistical analysis employed; appropriate washout period; no evidence of investigation for period and order effects

Wolkove 2004

Methods	Randomised cross-over trial (2 x study arms) Setting: 1 x outpatient clinic, Canada Study duration: 22 days
Participants	15 participants (9 M, 6 F; age 71 +/- 10 years) with a clinical diagnosis of (≥ 2 months stable) COPD, ≥ 10 pack-year smoking history and FEV_1/FVC ≤ 0.7 L randomised and completed. Mean FEV_1 0.75 +/- 0.26 L (29 +/- 9% predicted).
Interventions	Intervention: 10 minutes Flutter (used in the position which generated the best 'flutter' sensation within the chest), 4 times/day prior to usual bronchodilator therapy (administered via spacer) for 1 week Control: same as intervention (self selected mouth position) except steel ball removed from Flutter (sham Flutter)
Outcomes	FEV_1, FVC, 6MWD, HR, Borg and SpO_2 pre/post-6MWT
Notes	1-week washout period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Quote: "...randomised through sealed ordered envelopes"

Wolkove 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided. Participants not likely to have been blind to intervention despite 'sham' control. May have affected FEV_1, FVC, SGRQ, Borg and 6MWD outcomes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided. Outcome assessor(s) not likely to have been blind to intervention (presumably the same therapist that prescribed the intervention). May have affected FEV_1, FVC and 6MWD outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported for all outcomes (presumed to be complete, not explicitly stated)
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Comment: adequate washout period; paired statistical analysis employed

1MWD = one-minute walk distance; 6MWT = 6 minute walk test; 6MWD = six-minute walk distance; ABGs = arterial blood gases; A-a O_2 difference = alveolar/arterial oxygen difference; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; ATS = American Thoracic Society; BiPAP = bi-level positive airway pressure; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; ECG = electrocardiograph; ELTGOL = expiration with the glottis open in the lateral posture; ERV = expiratory reserve volume; F = female; FET = forced expiratory technique; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in one second; FIV_1 = forced inspiratory volume in the first second; FRC = functional residual capacity; FVC = forced vital capacity; GOLD = Global initiative for Chronic Obstructive Lung Disease; H_2O = water; HR = heart rate; HR_{max} = maximum heart rate; HRQoL = health-related quality of life; ICU = intensive care unit; I:E = inspiratory to expiratory time ratio; IPPV = intermittent positive pressure ventilation; ITT = intention-to-treat; LOS = length of stay; M = male; MDI =metered-dose inhaler; MEF = maximal expiratory flow; MRC = medical research council; NaCl = sodium chloride; NIV = non-invasive ventilation; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial pressure of oxygen; PEEP = positive end-expiratory pressure; PEFR = peak expiratory flow rate; PEP = positive expiratory pressure; pH = power of hydrogen; R_{aw} = airway resistance; RCB = relaxed controlled breathing; RR = respiratory rate; RV = residual volume; SD = standard deviation; S_{Gaw} = specific airway conductance; SGRQ = St. George's Respiratory Questionnaire; SpO_2 = arterial oxyhaemoglobin saturation; TLC = total lung capacity; VAS = visual analogue scale; VC = vital capacity.

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

Study	Reason for exclusion
Ambrosino 1981	Not an ACT
Ambrosino 1995	No appropriate control
Anonymous 2001	Not a randomised trial
Antonaglia 2006	No appropriate control
Babu 2010	No appropriate control
Badr 2002	Not a randomised trial
Barat 1975	Participants breathing via an artificial airway
Bateman 1981	Mixed disease sample, unable to contact author for COPD data
Bellone 1997	No appropriate control

Study	Reason for exclusion
Bellone 2000a	No appropriate control
Boye 1994	No appropriate control
Butcher 2007	Not an ACT
Cai 2003	Not an ACT
Campbell 1955	Not an ACT
Cegla 1993	Mixed disease population, unable to contact author to obtain COPD data
Chahal 2008	No appropriate control (via correspondence with author)
Chahal 2008a	No appropriate control (via correspondence with author)
Christensen 1990b	No appropriate control
Christensen 1991c	No appropriate control
Conkic 1972	Not a randomised trial
Craven 1974	Not COPD, no appropriate control
Cross 2010	No appropriate control
de Mello 2009	Participants breathing via an artificial airway
della Torre 1990	No appropriate control
Diette 2004	No relevant outcomes reported, unable to contact author
Elkins 2001	No appropriate control, no relevant outcomes
Elkins 2001a	No appropriate control, no relevant outcomes
Esteve 1996	Not an ACT
Falk 1981	Not an ACT
Gallon 1991	Not COPD
George 1985	Not an ACT
Gervasini 1983	Not an ACT
Guell 2000	Not an ACT
Hasani 1994	Mixed disease population, unable to contact author for COPD data
He 1988	Not an ACT
Herala 1995	No appropriate control
Ho 2000	No appropriate control

Study	Reason for exclusion
Kaminska 1988	Not COPD
Krishnan 2009	Mixed disease population (> 50% participants asthma), unable to obtain COPD-only data from correspondence with author
Kurabayashi 1998	Not an ACT, no appropriate control
Kurabayashi 2000	Not an ACT, no appropriate control
Lewczuk 1998	Not an ACT
Marcq 1975	No randomisation, mixed disease population, unable to contact author
Marcq 1981	Not COPD, inappropriate (combination) therapy
Marrara 2008	No appropriate control
McCarroll 2005	No appropriate control
McNeill 1955	Not an ACT
Mohsenifar 1985	No appropriate control
Moiz 2006	No appropriate control
Muzembo 2001	Not a randomised trial
Nakayama 1998	Not an ACT
Nava 2006	No appropriate control
Nosworthy 1992	No appropriate control
Olseni 1994	No appropriate control
Padkao 2010	Not an ACT
Petersen 1967	Not an ACT
Salhi 2011	Not an ACT
Saski 2005	Not a randomised trial, no appropriate control
Saunders 1965	Inappropriate (combination) therapy
Savci 2000	No appropriate control
Sergi 1990	No appropriate control
Shen 2008	Not an ACT
Skaria 2008	No appropriate control
Soler 2006	Not an ACT

Study	Reason for exclusion
Su 2007	No appropriate control
Sutton 1983	Not COPD
Szczegielniak 2006	No appropriate control
Thomas 1988	Not a randomised trial, not an ACT
Toshima 1990	Inappropriate (combined) therapy, no appropriate control
van der Schans 1986	Not a randomised trial, no appropriate control
Wollmer 1985	No appropriate control
Xu 2000	Not an ACT
Zakerimoghadam 2006	Not an ACT

ACT: airway clearance technique; COPD: chronic obstructive pulmonary disease

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

Cegla 2000b

Methods	Cross-over trial Setting: insufficient information available Study duration: insufficient information available
Participants	10 participants with COPD
Interventions	Intervention: inhalation of Sultanol (salbutamol) and Atrovent (ipratropium bromide) via Pari-Boy with expiration through RC-Cornet Control: same as intervention but normal expiration
Outcomes	Conductance (body plethysmography)
Notes	Unclear whether intervention order randomised. Article written in German.

Chakravorty 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Identified by 2011 search. Requires further information to confirm appropriateness.

Diette 2009

Methods	2 x parallel-group trial Setting: United States of America Study duration: 12 weeks
Participants	50 participants (32 M, 18 F, mean age 63) with (presumably stable) doctor diagnosed COPD, FEV_1/FVC ≤ 0.7, ≥ 20 pack-years tobacco, aged ≥ 45 years, daily mucus production and ≥ 1 AECOPD in the last 6 months
Interventions	Intervention: high-frequency chest wall oscillation (HFCWO). Dosage: 30 minutes/day for 12 weeks. Control: sham HFCWO (undefined)
Outcomes	Primary: rate of AECOPD Secondary: treatment adherence, quality of life, self reported sputum frequency and severity, FEV_1, exercise tolerance (6MWT)
Notes	Unclear whether randomised. Relevance of reported outcomes unclear. Abstract only.

Esquinas 2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	Identified by 2011 search. Requires further information to confirm appropriateness.

Long 2001

Methods	Insufficient information available
Participants	Insufficient information available
Interventions	Insufficient information available
Outcomes	Insufficient information available
Notes	Clinical trial register only

Qu 2009 Jul

Methods	

Qu 2009 Jul *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Identified by 2011 search. Requires further information to confirm appropriateness.

Timbury 2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	Identified by 2011 search. Requires further information to confirm appropriateness.

6MWT: six-minute walk test; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity

DATA AND ANALYSES

Comparison 1. Acute COPD: ACTs vs no ACTs (control)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of AECOPDs (long-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Number of AECOPDs (long-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Non-PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Need for respiratory hospital admission (long-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Need for respiratory hospital admission (long-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

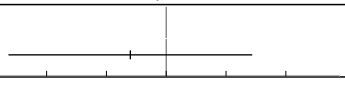
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 Non-PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Need for increased ventilatory assistance (invasive or non-invasive)	4	171	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.85]
5.1 PEP techniques	2	60	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.87]
5.2 Non-PEP techniques	2	111	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.36]
6 Duration of ventilatory assistance (days)	2	54	Mean Difference (IV, Fixed, 95% CI)	-2.05 [-2.60, -1.51]
6.1 PEP techniques	1	27	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-2.67, -1.53]
6.2 Non-PEP techniques	1	27	Mean Difference (IV, Fixed, 95% CI)	-1.49 [-3.49, 0.51]
7 Length of ICU stay (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Length of hospital stay (days)	3	171	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.38, -0.11]
8.1 PEP techniques	1	33	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.89, -0.31]
8.2 Non-PEP techniques	2	138	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-1.17, 0.99]
9 QOL - SGRQ total (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 FEV1 (L) (short-term)	2	106	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.16, 0.20]
10.1 PEP techniques	1	27	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.17, 0.32]
10.2 Non-PEP techniques	1	79	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.32, 0.22]
11 VC (L) (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 FEV1/FVC (%) (short-term)	2	86	Mean Difference (IV, Fixed, 95% CI)	4.33 [-1.99, 10.64]
12.1 PEP techniques	1	27	Mean Difference (IV, Fixed, 95% CI)	1.0 [-11.37, 13.37]
12.2 Non-PEP techniques	1	59	Mean Difference (IV, Fixed, 95% CI)	5.5 [-1.85, 12.85]
13 Gas exchange: pH (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Gas exchange: PaO2 (mmHg) (short-term)	2	106	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-5.02, 3.71]
14.1 PEP techniques	1	27	Mean Difference (IV, Fixed, 95% CI)	0.80 [-6.86, 8.46]
14.2 Non-PEP techniques	1	79	Mean Difference (IV, Fixed, 95% CI)	-1.36 [-6.67, 3.95]
15 Gas exchange: PaCO2 (mmHg) (short-term)	2	105	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-5.56, 3.37]
15.1 PEP techniques	1	26	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-17.83, 10.23]
15.2 Non-PEP techniques	1	79	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-5.50, 3.92]
16 Gas exchange: SpO2 (%) (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Breathlessness - Borg scale (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Non-PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Sputum weight, g (immediate)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
19 Sputum volume, ml (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
19.1 Non-PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Sputum volume, ml (24/24) (short-term)	2	138	Mean Difference (IV, Fixed, 95% CI)	0.04 [-3.73, 3.80]
20.1 Non-PEP techniques	2	138	Mean Difference (IV, Fixed, 95% CI)	0.04 [-3.73, 3.80]
21 Mortality (short-term)	4	171	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.14, 3.80]
21.1 PEP techniques	2	60	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.93]
21.2 Non-PEP techniques	2	111	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
22 Mortality (long-term)	2	107	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.26, 2.63]
22.1 Non-PEP techniques	2	107	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.26, 2.63]
23 Participant withdrawal (immediate)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
23.1 PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Participant withdrawal (short-term)	4	203	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.11, 2.69]
24.1 PEP techniques	2	60	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.93]
24.2 Non-PEP techniques	2	143	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.10, 4.10]
25 Participant withdrawal (long-term)	2	143	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.39, 1.94]
25.1 Non-PEP techniques	2	143	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.39, 1.94]

Analysis 1.1. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 1 Number of AECOPDs (long-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.1.1 Non-PEP techniques						
Kodric 2009	11	2.8 (3)	11	3.4 (1.7)		-0.6[-2.64,1.44]

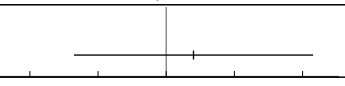


Analysis 1.2. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 2 Number of AECOPDs (long-term).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Non-PEP techniques				
Newton 1978	11/40	8/39		1.47[0.52,4.17]

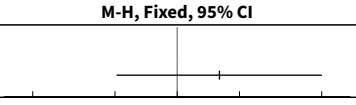
Analysis 1.3. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 3 Need for respiratory hospital admission (long-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 Non-PEP techniques						
Kodric 2009	11	1.9 (2.5)	11	1.5 (1.6)		0.4[-1.35,2.15]



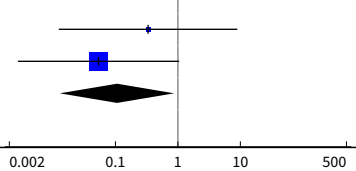
Analysis 1.4. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 4 Need for respiratory hospital admission (long-term).

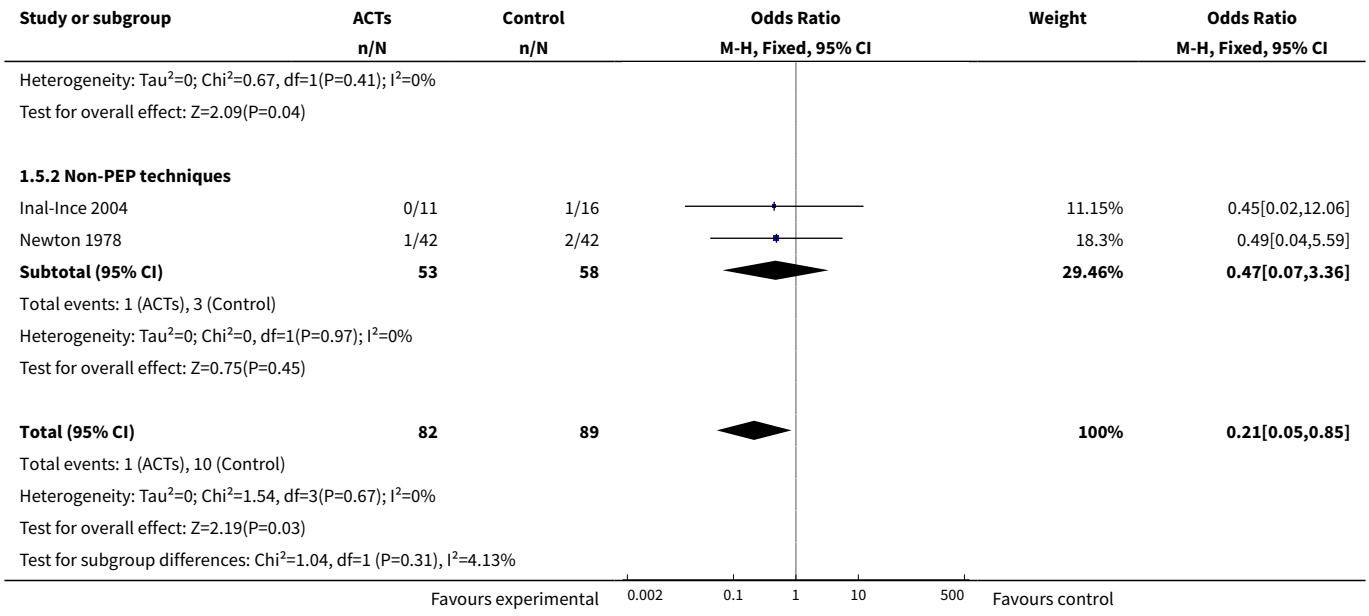
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Non-PEP techniques				
Newton 1978	9/40	6/39		1.6[0.51,5.01]



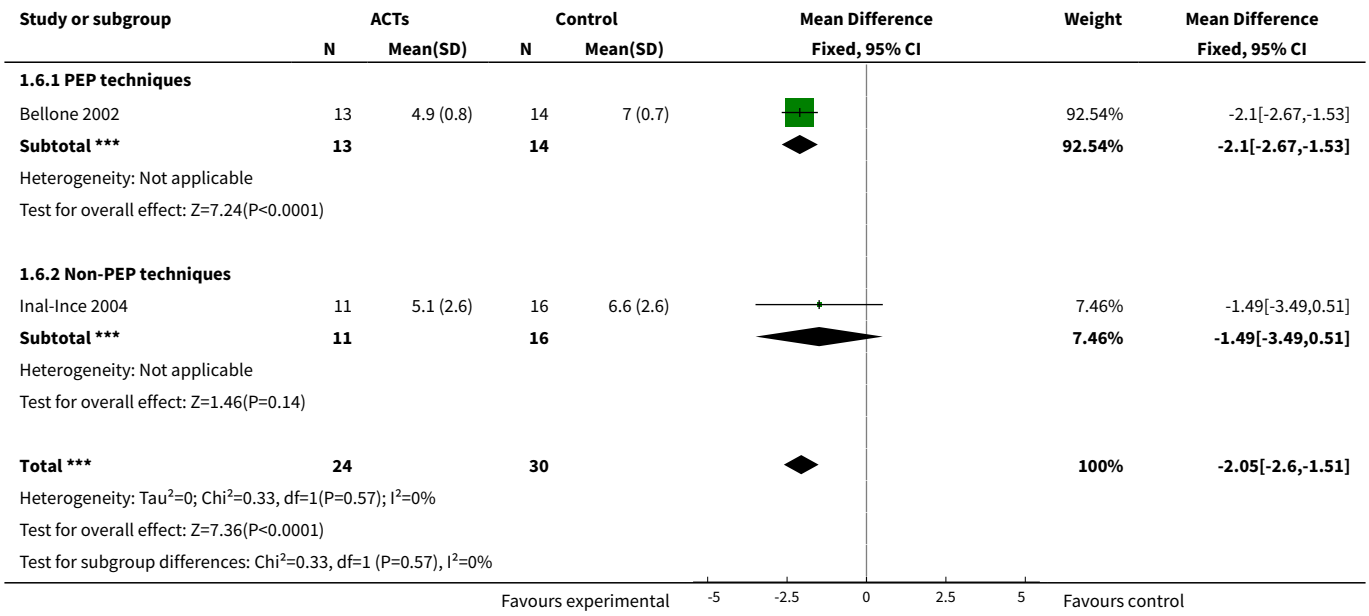
Analysis 1.5. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 5 Need for increased ventilatory assistance (invasive or non-invasive).

Study or subgroup	ACTs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 PEP techniques					
Bellone 2002	0/13	1/14		13.09%	0.33[0.01,8.93]
Vargas 2005	0/16	6/17		57.45%	0.05[0,1.05]
Subtotal (95% CI)	**29**	**31**		**70.54%**	**0.11[0.01,0.87]**
Total events: 0 (ACTs), 7 (Control)					

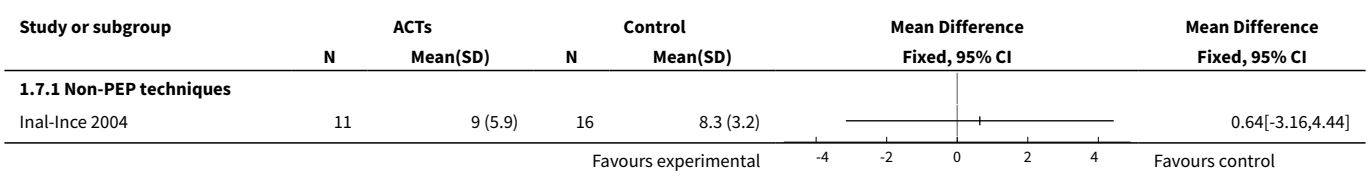




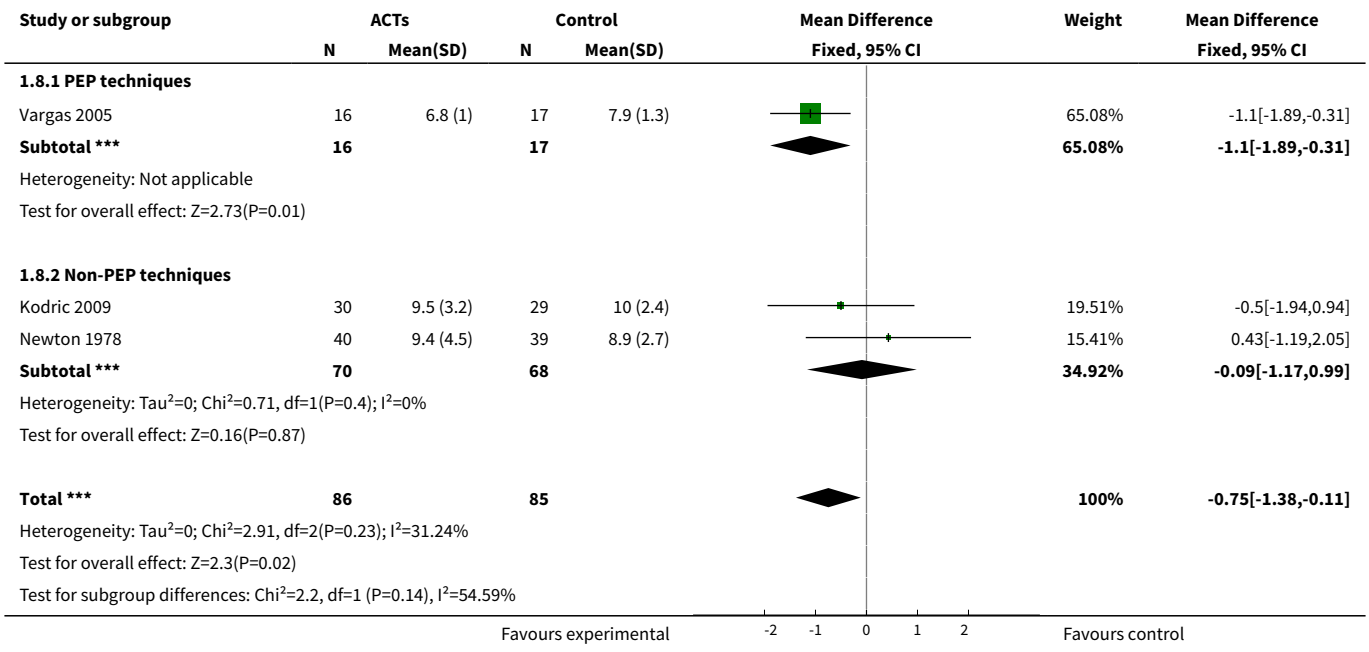
Analysis 1.6. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 6 Duration of ventilatory assistance (days).



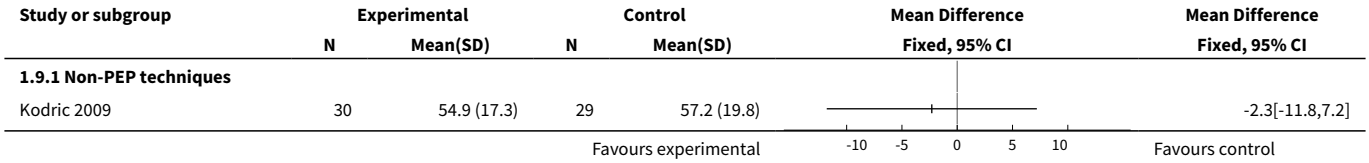
Analysis 1.7. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 7 Length of ICU stay (days).



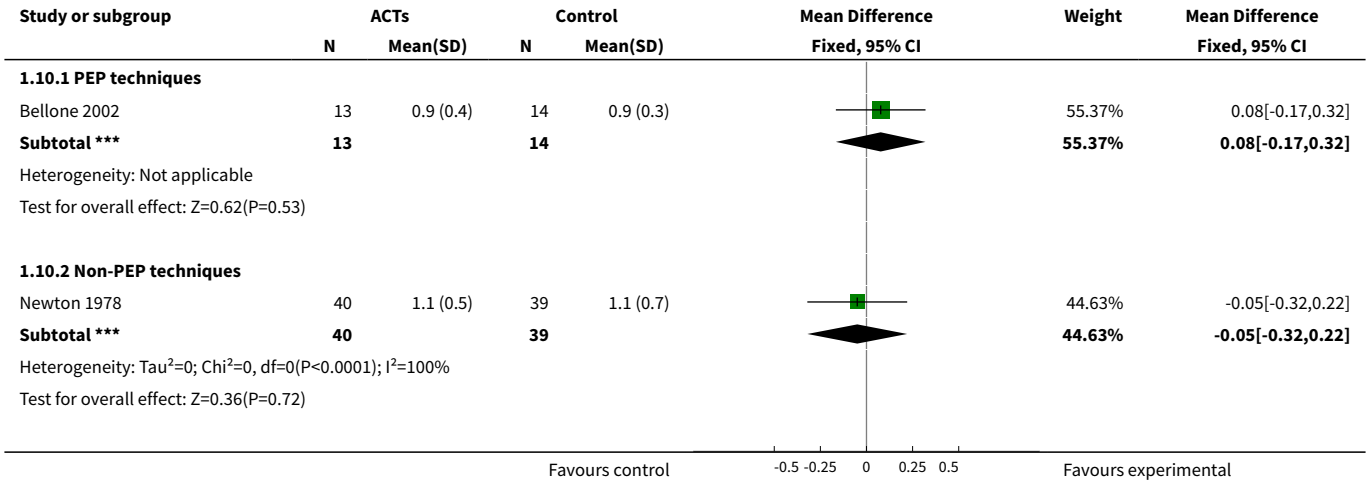
Analysis 1.8. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 8 Length of hospital stay (days).

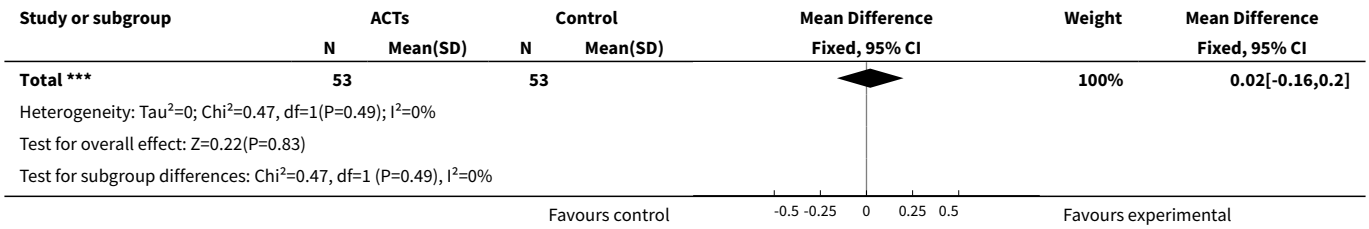


Analysis 1.9. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 9 QOL - SGRQ total (short-term).

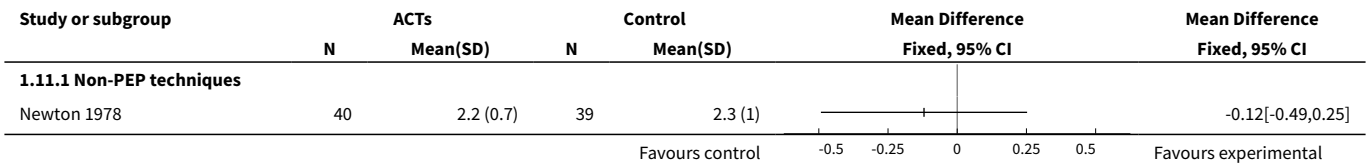


Analysis 1.10. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 10 FEV1 (L) (short-term).

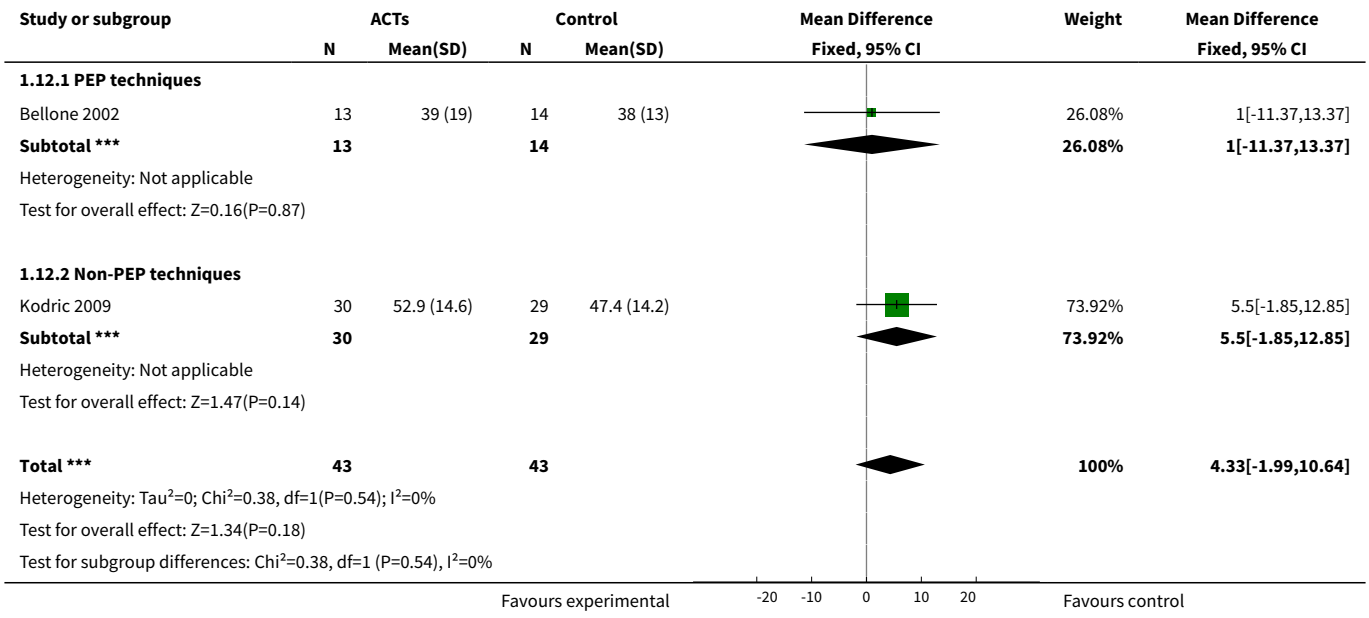




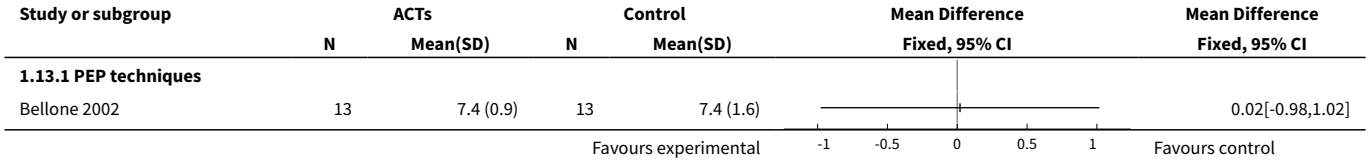
Analysis 1.11. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 11 VC (L) (short-term).



Analysis 1.12. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 12 FEV1/FVC (%) (short-term).

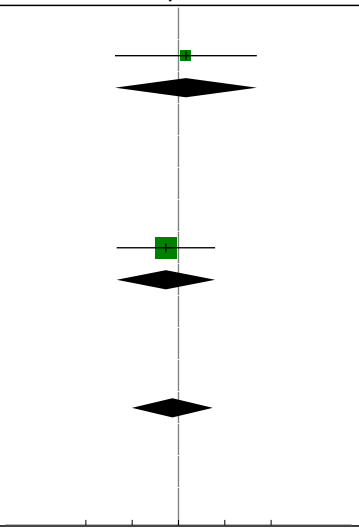


Analysis 1.13. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 13 Gas exchange: pH (short-term).



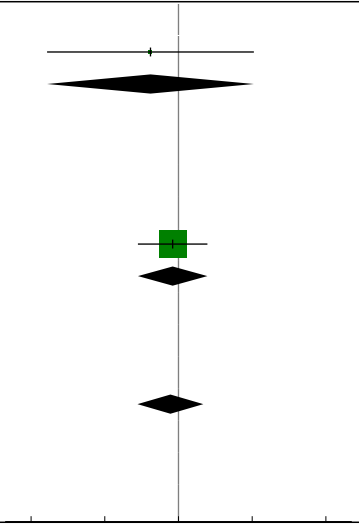
Analysis 1.14. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 14 Gas exchange: PaO2 (mmHg) (short-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.14.1 PEP techniques							
Bellone 2002	13	51.8 (9.8)	14	51 (10.5)		32.51%	0.8[-6.86,8.46]
Subtotal ***	**13**		**14**			**32.51%**	**0.8[-6.86,8.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.2(P=0.84)							
1.14.2 Non-PEP techniques							
Newton 1978	40	63.8 (9.9)	39	65.1 (13.8)		67.49%	-1.36[-6.67,3.95]
Subtotal ***	**40**		**39**			**67.49%**	**-1.36[-6.67,3.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.5(P=0.62)							
Total ***	**53**		**53**			**100%**	**-0.66[-5.02,3.71]**
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%							
Test for overall effect: Z=0.3(P=0.77)							
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.65), I^2=0%							



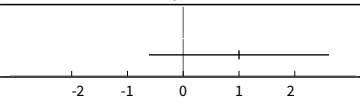
Analysis 1.15. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 15 Gas exchange: PaCO2 (mmHg) (short-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.15.1 PEP techniques							
Bellone 2002	13	51 (21)	13	54.8 (15)		10.15%	-3.8[-17.83,10.23]
Subtotal ***	**13**		**13**			**10.15%**	**-3.8[-17.83,10.23]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.53(P=0.6)							
1.15.2 Non-PEP techniques							
Newton 1978	40	41.9 (11.1)	39	42.7 (10.2)		89.85%	-0.79[-5.5,3.92]
Subtotal ***	**40**		**39**			**89.85%**	**-0.79[-5.5,3.92]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.33(P=0.74)							
Total ***	**53**		**52**			**100%**	**-1.1[-5.56,3.37]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%							
Test for overall effect: Z=0.48(P=0.63)							
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%							



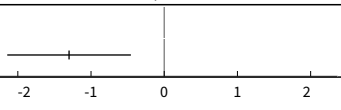
Analysis 1.16. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 16 Gas exchange: SpO2 (%) (short-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.16.1 Non-PEP techniques						
Kodric 2009	30	93.1 (2.9)	29	92.1 (3.4)		1[-0.61,2.61]



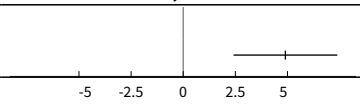
Analysis 1.17. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 17 Breathlessness - Borg scale (short-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.17.1 Non-PEP techniques						
Kodric 2009	30	3 (1.8)	29	4.3 (1.5)		-1.3[-2.14,-0.46]



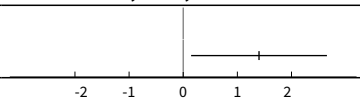
Analysis 1.18. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 18 Sputum weight, g (immediate).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.18.1 PEP techniques						
Bellone 2002	13	9.6 (3.9)	14	4.7 (2.5)		4.9[2.41,7.39]



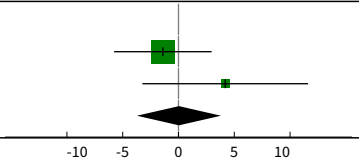
Analysis 1.19. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 19 Sputum volume, ml (immediate).

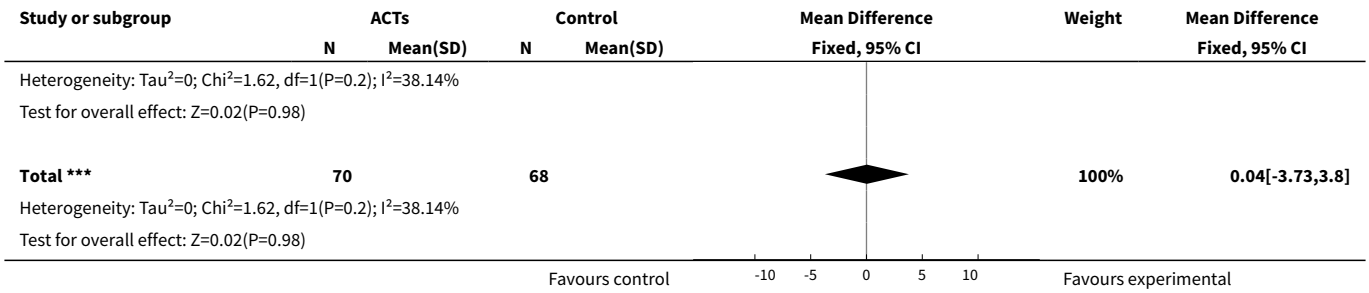
Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.19.1 Non-PEP techniques					
Brown 1987	0	0	1.4 (0.64)		1.4[0.15,2.65]



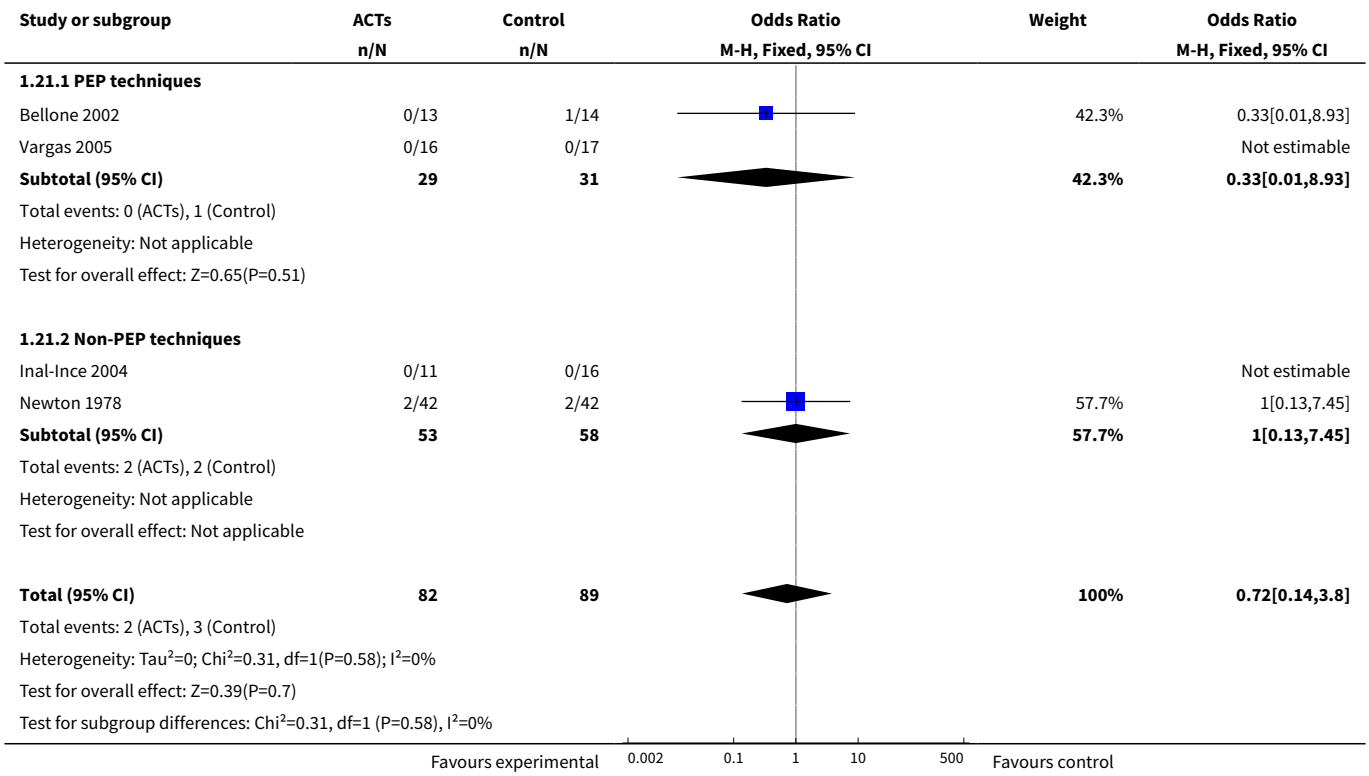
Analysis 1.20. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 20 Sputum volume, ml (24/24) (short-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.20.1 Non-PEP techniques							
Kodric 2009	30	6.8 (7.6)	29	8.2 (9.4)		74.28%	-1.4[-5.77,2.97]
Newton 1978	40	18.9 (16.3)	39	14.7 (17.3)		25.72%	4.19[-3.24,11.62]
Subtotal ***	**70**		**68**			**100%**	**0.04[-3.73,3.8]**

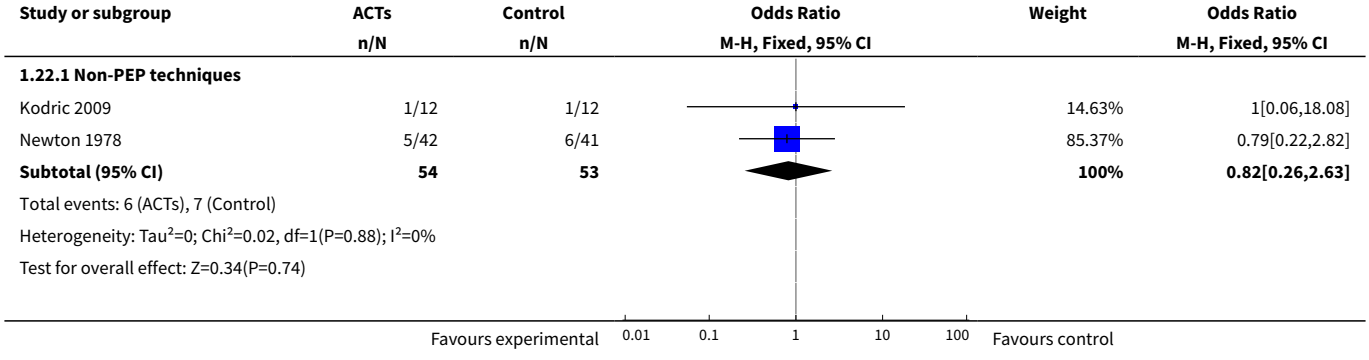


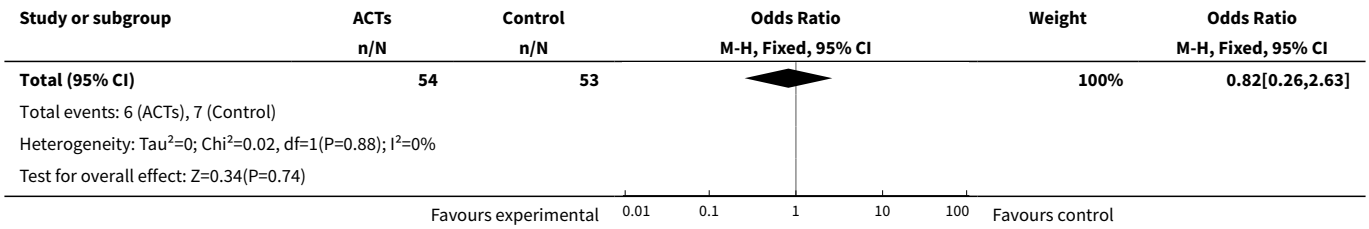


Analysis 1.21. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 21 Mortality (short-term).

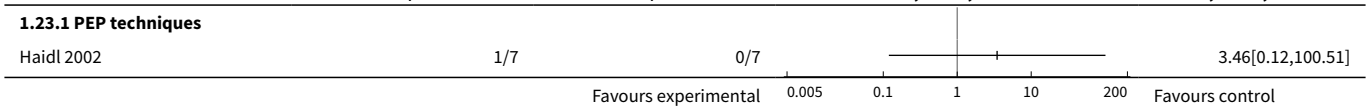


Analysis 1.22. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 22 Mortality (long-term).

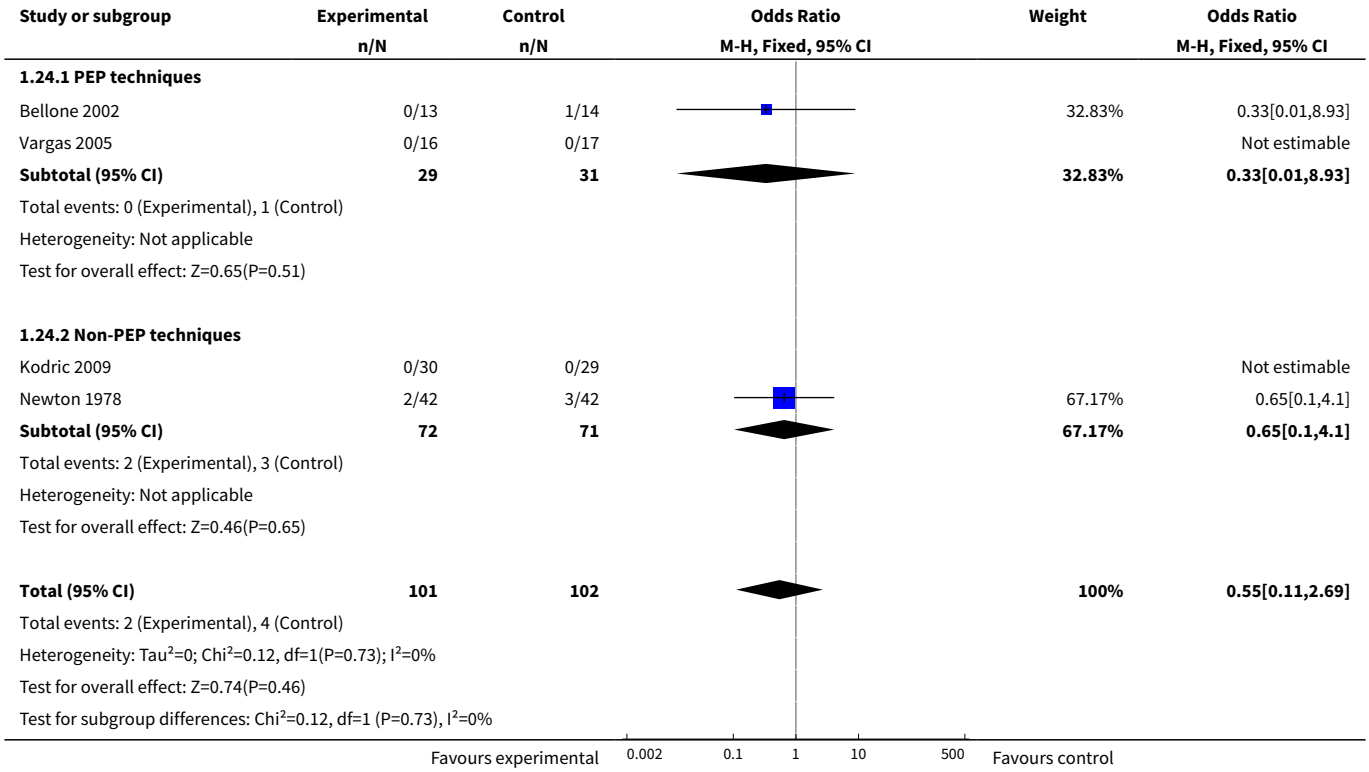




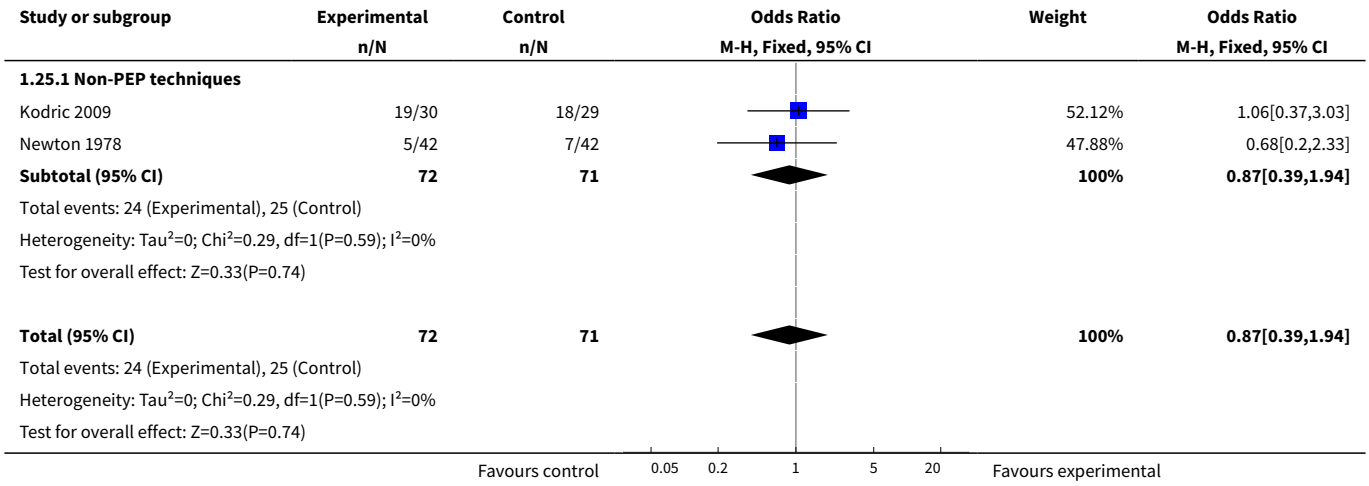
Analysis 1.23. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 23 Participant withdrawal (immediate).



Analysis 1.24. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 24 Participant withdrawal (short-term).



Analysis 1.25. Comparison 1 Acute COPD: ACTs vs no ACTs (control), Outcome 25 Participant withdrawal (long-term).



Comparison 2. Stable COPD: ACTs vs no ACTs (control)

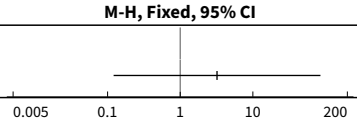
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of AECOPDs (short-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Need for respiratory hospital admission (long-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Total number of days hospitalised (long-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 QOL - SGRQ total (short-term)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4.1 PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
5 FEV1 (L) (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5.1 PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 FEV1 (L) (short-term)	2	118	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.35, 0.28]
6.1 PEP techniques	2	118	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.35, 0.28]
7 VC (L) (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
7.1 PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
8 VC (L) (short-term)	2	118	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.43, 0.33]
8.1 PEP techniques	2	118	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.43, 0.33]
9 Gas exchange: PaO2 (mmHg) (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Gas exchange: PaCO2 (mmHg) (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Gas exchange: SpO2 (%) (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
11.1 PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Breathlessness, Borg scale (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
12.1 PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Sputum weight, g (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
13.1 PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Sputum volume, ml (immediate)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
14.1 Non-PEP techniques	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Mucociliary clearance, scintigraphy (% retention)	2		Mean Difference (Fixed, 95% CI)	1.20 [-2.79, 5.19]
15.1 Non-PEP techniques	2		Mean Difference (Fixed, 95% CI)	1.20 [-2.79, 5.19]
16 Exercise tolerance, 6MWD (m) (short-term)	2		Mean Difference (Fixed, 95% CI)	12.93 [5.98, 19.89]
16.1 PEP techniques	2		Mean Difference (Fixed, 95% CI)	12.93 [5.98, 19.89]
17 Exercise tolerance, 12MWD (m) (long-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 PEP techniques	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Need for antibiotics (short-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Need for antibiotics (long-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
19.1 PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Participant withdrawal (short-term)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1 PEP techniques	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Participant withdrawal (long-term)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
21.1 PEP techniques	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

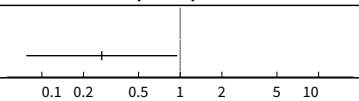
Analysis 2.1. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 1 Number of AECOPDs (short-term).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.1.1 PEP techniques				
Christensen 1991	1/15	0/15		3.21[0.12,85.2]



Analysis 2.2. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 2 Need for respiratory hospital admission (long-term).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.2.1 PEP techniques				
Cegla 2002	5/25	12/25		0.27[0.08,0.95]

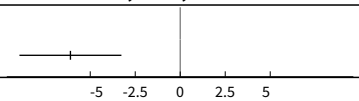


Analysis 2.3. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 3 Total number of days hospitalised (long-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.3.1 PEP techniques						
Cegla 2002	25	16.2 (6.3)	25	18.3 (4.7)		-2.1[-5.18,0.98]

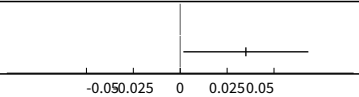
Analysis 2.4. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 4 QOL - SGRQ total (short-term).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
2.4.1 PEP techniques					
Wolkove 2004	0	0	-6.1 (1.445)		-6.1[-8.93,-3.27]



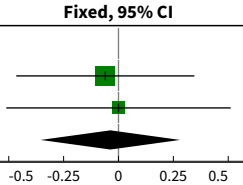
Analysis 2.5. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 5 FEV1 (L) (immediate).

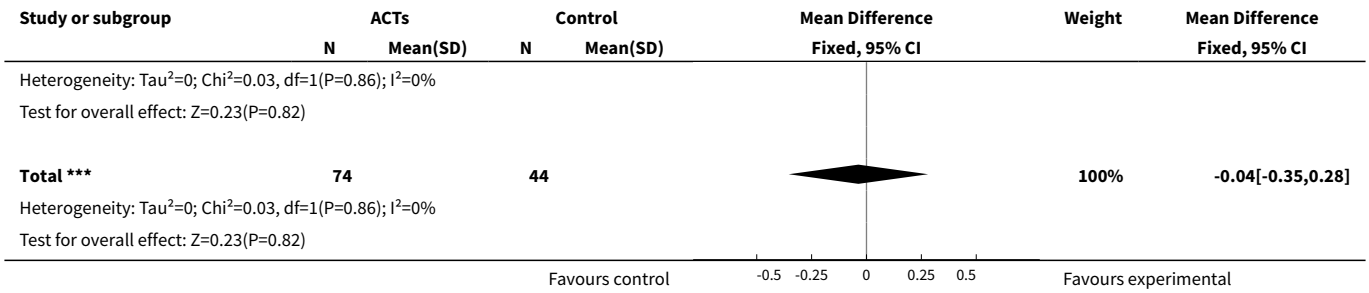
Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
2.5.1 PEP techniques					
Wolkove 2002	0	0	0 (0.017)		0.04[0,0.07]



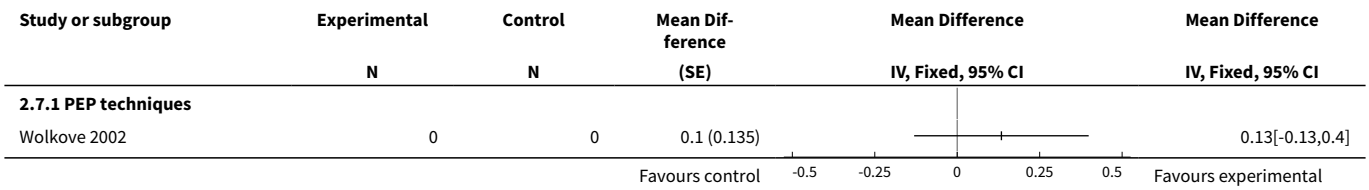
Analysis 2.6. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 6 FEV1 (L) (short-term).

Study or subgroup	ACTs N	ACTs Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.6.1 PEP techniques							
Cegla 1997	60	1.7 (0.8)	30	1.8 (1)		61.35%	-0.06[-0.47,0.35]
Christensen 1991	14	1.9 (0.7)	14	1.9 (0.7)		38.65%	0[-0.51,0.51]
Subtotal * **	**74**		**44**			**100%**	**-0.04[-0.35,0.28]**

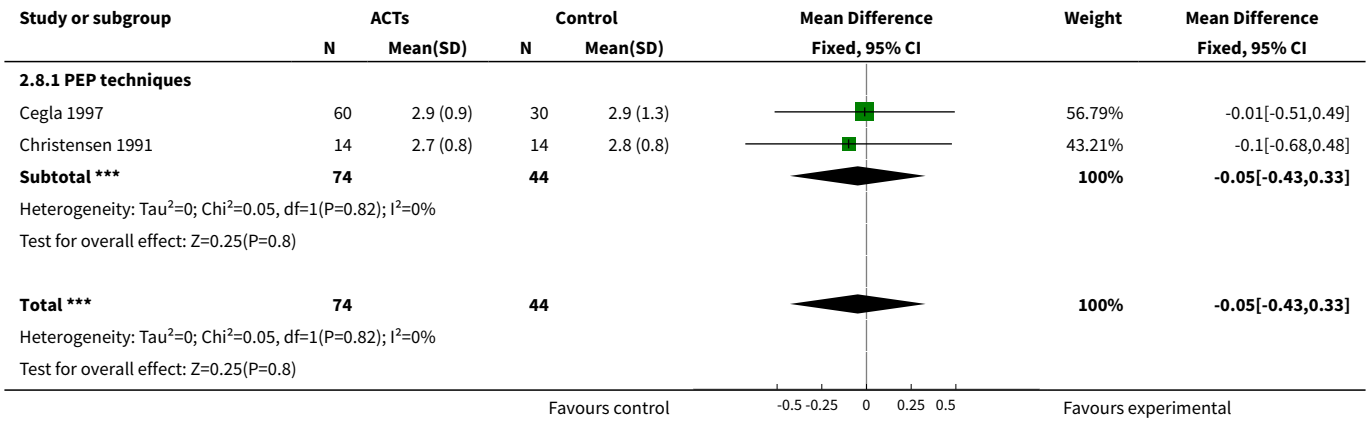




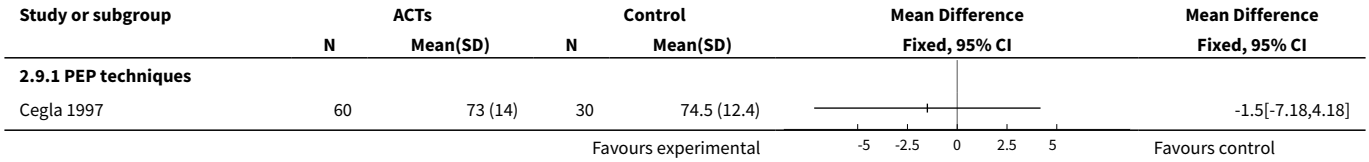
Analysis 2.7. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 7 VC (L) (immediate).



Analysis 2.8. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 8 VC (L) (short-term).

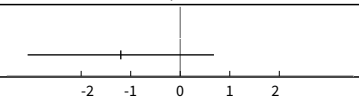


Analysis 2.9. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 9 Gas exchange: PaO2 (mmHg) (short-term).



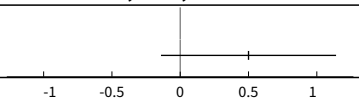
Analysis 2.10. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 10 Gas exchange: PaCO2 (mmHg) (short-term).

Study or subgroup	ACTs		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
2.10.1 PEP techniques						
Cegla 1997	60	36.4 (4.9)	30	37.6 (3.9)		-1.2[-3.08,0.68]



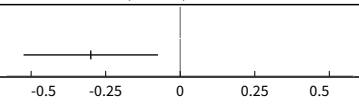
Analysis 2.11. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 11 Gas exchange: SpO2 (%) (immediate).

Study or subgroup	Experimental	Control	Mean Difference	Mean Difference	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.11.1 PEP techniques					
Wolkove 2002	0	0	0.5 (0.327)		0.5[-0.14,1.14]



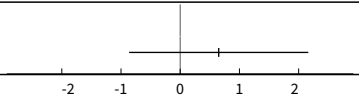
Analysis 2.12. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 12 Breathlessness, Borg scale (immediate).

Study or subgroup	Experimental	Control	Mean Difference	Mean Difference	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.12.1 PEP techniques					
Wolkove 2002	0	0	-0.3 (0.115)		-0.3[-0.53,-0.07]



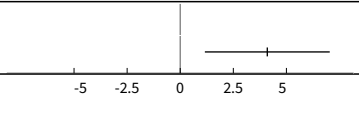
Analysis 2.13. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 13 Sputum weight, g (immediate).

Study or subgroup	Experimental	Control	Mean Difference	Mean Difference	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.13.1 PEP techniques					
Morsch 2008	0	0	0.7 (0.772)		0.65[-0.86,2.16]



Analysis 2.14. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 14 Sputum volume, ml (immediate).

Study or subgroup	Experimental	Control	Mean Difference	Mean Difference	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.14.1 Non-PEP techniques					
May 1979	0	0	4.1 (1.5)		4.1[1.16,7.04]

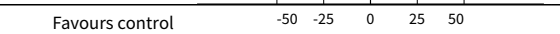


Analysis 2.15. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 15 Mucociliary clearance, scintigraphy (% retention).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.15.1 Non-PEP techniques						
Oldenburg 1979	0	0	0.9 (2.142)		90.2%	0.86[-3.34,5.06]
Pavia 1976	0	0	4.3 (6.5)		9.8%	4.29[-8.45,17.03]
Subtotal (95% CI)					**100%**	**1.2[-2.79,5.19]**
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%						
Test for overall effect: Z=0.59(P=0.56)						
Total (95% CI)					**100%**	**1.2[-2.79,5.19]**
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%						
Test for overall effect: Z=0.59(P=0.56)						

Analysis 2.16. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 16 Exercise tolerance, 6MWD (m) (short-term).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.16.1 PEP techniques						
Wolkove 2002	0	0	12 (3.598)		97.26%	12[4.95,19.05]
Wolkove 2004	0	0	46 (21.447)		2.74%	46[3.96,88.04]
Subtotal (95% CI)					**100%**	**12.93[5.98,19.89]**
Heterogeneity: Tau^2=0; Chi^2=2.44, df=1(P=0.12); I^2=59.09%						
Test for overall effect: Z=3.64(P=0)						
Total (95% CI)					**100%**	**12.93[5.98,19.89]**
Heterogeneity: Tau^2=0; Chi^2=2.44, df=1(P=0.12); I^2=59.09%						
Test for overall effect: Z=3.64(P=0)						

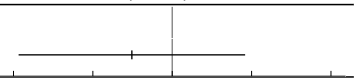


Analysis 2.17. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 17 Exercise tolerance, 12MWD (m) (long-term).

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.17.1 PEP techniques						
Weiner 1996	10	649 (46.5)	10	538 (54.8)		111[66.46,155.54]

Analysis 2.18. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 18 Need for antibiotics (short-term).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.18.1 PEP techniques				
Christensen 1991	0/14	1/14		0.31[0.01,8.29]



Analysis 2.19. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 19 Need for antibiotics (long-term).

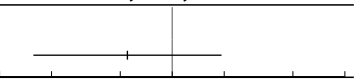
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.19.1 PEP techniques				
Cegla 2002	13/25	24/25		0.05[0.01,0.39]

Analysis 2.20. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 20 Participant withdrawal (short-term).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.20.1 PEP techniques				
Cegla 1997	0/60	0/30		Not estimable
Christensen 1991	1/15	1/15		1[0.06,17.62]

Analysis 2.21. Comparison 2 Stable COPD: ACTs vs no ACTs (control), Outcome 21 Participant withdrawal (long-term).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.21.1 PEP techniques				
Christensen 1990	5/30	8/30		0.55[0.16,1.93]



ADDITIONAL TABLES

Table 1. Comparison of interventions (AECOPD)

Study	Design	Intervention	Intensity	Session duration, frequency	Total therapy duration	Max. follow-up
Anthonisen 1964	RCT	Non-PEP (CCPT)	Unclear	Unclear, od	10 days	D/C from hospital

Table 1. Comparison of interventions (AECOPD) *(Continued)*

Bellone 2002	RCT	PEP (mask)	10 to 15 cm H_2O	30 to 40 minutes, tds	3 days	D/C from RICU
Brown 1987	RXT	Non-PEP (CCPT)	'Firm pressure'	15 minutes/affected segment	Single session	24/24
Haidl 2002	RCT	PEP (Cornet)	Position 1	5 breaths	Single session	Immediate
Inal-Ince 2004	RCT	Non-PEP (breathing exs)	N/A	15 to 30 minutes, od	Until D/C from ICU	D/C from ICU
Kodric 2009	RCT	Non-PEP (breathing exs)	N/A	30 to 40 minutes, bd	7 days	6 months
Newton 1978	RCT	Non-PEP (CCPT + IPPV)	Unclear	10 to 15 minutes, tds + 15 minutes IPPV, tds	Unclear	3 months
Newton 1978a	RXT	Non-PEP (breathing exs + CCPT)	Unclear	15 minutes	Single session	Immediate
Vargas 2005	RCT	PEP (IPV via mask)	Peak pressure 20 +/- 5 cm H_2O, percussion frequency 250 +/- 50/min, I:E 1:2.5	30 minutes, bd	Until spontaneous RR < 25/min and pH > 7.38 for 24/24 (mean 3 +/- 1 days)	D/C from hospital

RCT: randomised controlled trial; RXT: randomised cross-over trial; od: once/day; bd: twice/day; tds: three times/day; exs: exercises; RR: respiratory rate; D/C: discharge; CCPT: conventional chest physiotherapy (postural drainage, percussion, vibration); IPV: intrapulmonary percussive ventilation; PEP: positive expiratory pressure.

Table 2. Comparison of interventions (stable COPD)

Study	Design	Intervention	Intensity	Session duration, frequency	Total therapy duration	Max. follow-up
Cegla 1997	RCT	PEP (Cornet, Flutter)	Unclear	5 minutes, qid	7 days	Short-term (end of 7 days)
Cegla 2001	RXT	PEP (Cornet)	Position 1 (estimated pressure 20 +/- 5 cm H_2O)	Duration of nebulisation	Single session	Immediate (25 minutes)
Cegla 2002	RCT	PEP (Cornet)	Start position	≥ 5 minutes, tds + prn (if mucus or dyspnoea)	2 years	Long-term (end of 2 years)
Christensen 1990	RCT	PEP (mask with PEEP valve)	10 cm H_2O	≥ 15 minutes, tds	6 months	Long-term (end of 6 months)
Christensen 1991	RCT	PEP (mask)	10 to 20 cm H_2O	10 breaths, bd	4 weeks	Short-term (end of 4 weeks)

Table 2. Comparison of interventions (stable COPD) *(Continued)*

Christensen 1991a	RXT	PEP (mask)	10 to 15 cm H_2O	8 to 10 minutes, tds	2 weeks	Short-term (end of 2 weeks)
Hasani 1995	RXT	Non-PEP (FET)	N/A	9 minutes	Single session	Immediate
Martins 2006	RXT	Non-PEP (ELTGOL)	N/A	20 minutes	Single session	Immediate (20 minutes)
Martins 2007	RXT	Non-PEP (ELTGOL)	N/A	20 minutes	Single session	Immediate (120 minutes)
May 1979	RXT	Non-PEP (CCPT)	Unclear	Unclear	Single session	Immediate (120 minutes)
Morsch 2008	RCT	PEP (Flutter +/- FET)	Horizontal position, 0.8 to 25 cm H_2O	5 minutes	Single session	Immediate
Oldenburg 1979	RXT	Non-PEP (CCPT); Non-PEP (physical exercise)	N/A (CCPT); 70% to 75% predicted HRmax (physical exercise)	30 minutes (CCPT); 20 minutes (physical exercise)	Single session (CCPT); Single session (physical exercise)	Immediate (2.5 hours)
Pavia 1976	RXT	Non-PEP (mechanical vibration)	Onset of tremulous speech; amp 2 mm; frequency 41Hz	60 minutes	Single session	Immediate (5 hours)
Rasmussen 2001	RXT	PEP (valve)	5 to 20 cm H_2O	Unclear, bd	4 days	Immediate (1 hour)
Rivington-Law 1984	RXT	Non-PEP (breathing exs); Non-PEP (breathing exs + CCPT)	N/A (breathing exs); 'Moderate' (≤ 20 mmHg) intensity (breathing exs + CCPT)	15 minutes	Single session	Immediate (15 minutes)
van Hengstum 1988	RXT	PEP (mask); Non-PEP (breathing exs + CCPT)	10 to 15 cm H_2O (PEP); N/A (breathing exs + CCPT)	20 minutes (PEP); 30 minutes (breathing exs + CCPT)	Single session	Short-term (24/24)
Weiner 1996	RCT	PEP (Flutter)	Unclear	10 minutes, od	3 months	Long-term (end of 3 months)
Wolkove 2002	RXT	PEP (Flutter)	Position which generated the best chest 'flutter' sensation	10 minutes	Single session	Immediate (120 minutes)
Wolkove 2004	RXT	PEP (Flutter)	Position which generated the best chest 'flutter' sensation	10 minutes, qid	1 week	Short-term (end of 1 week)

RCT: randomised controlled trial; RXT: randomised cross-over trial; od: once/day; bd: two times/day; tds: three times/day; qid: four times/day; prn: as needed; exs: exercises; CCPT: conventional chest physiotherapy (postural drainage, percussion, vibration); ELTGOL: expiration with the glottis open in the lateral posture; PEP: positive expiratory pressure.

Table 3. Studies which met sensitivity analysis requirements

Adequate allocation concealment	Adequate assessor blinding	Complete data or evidence of ITT analysis
Haidl 2002	Christensen 1990	Cegla 1997
Kodric 2009	Newton 1978a	Cegla 2001
Newton 1978	Weiner 1996	Cegla 2002
Newton 1978a		Christensen 1991a
Vargas 2005		May 1979
Wolkove 2004		Morsch 2008
		Oldenburg 1979
		Vargas 2005
		Weiner 1996

Study must have been rated as 'low risk of bias' for relevant item to be included in sensitivity analysis. ITT: intention-to-treat.

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*T he Cochrane Library*)	Quarterly
PSYCINFO (Ovid)	Monthly
CINAHL (Ebsco)	Monthly
AMED (Ebsco)	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

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

CONTRIBUTIONS OF AUTHORS

Christian Osadnik: initiation and writing of protocol and manuscript, data extraction and analysis.

Christine McDonald: protocol development and review, manuscript review.

Arthur Jones: author of original review, manuscript review.

Anne Holland: protocol development and review, manuscript review, data extraction.

DECLARATIONS OF INTEREST

CO, CM and AH are conducting a study which may be included in future updates of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Canada Research Chairs Program, Ottawa, ON, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added measures of exercise tolerance and antibiotic use as secondary outcomes. We performed no analyses using a random-effects model due to an absence of significant statistical heterogeneity. We calculated no standardised mean differences as no data of differing metric scales were combined. We reported outcome data suitable for quantitative analysis but expressed as different types (e.g. dichotomous and ratio) separately and did not pool.

NOTES

This review superseeds a previous Cochrane review on bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis (Jones 1998) which is no longer being updated.

INDEX TERMS

Medical Subject Headings (MeSH)

Disease Progression; Length of Stay; Pulmonary Disease, Chronic Obstructive [physiopathology] [*therapy]; Randomized Controlled Trials as Topic; Respiratory Therapy [*methods]; Sputum [*metabolism]

MeSH check words

Humans