European Respiratory Society statement on airway clearance techniques in adults with bronchiectasis

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Shareable abstract (@ERSpublications)
This ERS task force reviews the evidence for airway clearance techniques in bronchiectasis and suggests areas of further research https://bit.ly/3NaUauY

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Abstract

Airway clearance techniques (ACTs) are part of the main management strategy for patients with bronchiectasis. Despite being a priority for patients, accessibility, implementation and reporting of ACTs are variable in clinical settings and research studies. This European Respiratory Society statement summarises current knowledge about ACTs in adults with bronchiectasis and makes recommendations to improve the future evidence base. A task force of 14 experts and two patient representatives (10 countries) determined the scope of this statement through consensus and defined six questions. The questions were answered based on systematic searches of the literature. The statement provides a comprehensive review of the physiological rationale for ACTs in adults with bronchiectasis, and the mechanisms of action along with the advantages and disadvantages of each ACT. Evidence on ACTs in clinical practice indicates that the most frequently used techniques are active cycle of breathing techniques, positive expiratory pressure devices and gravity-assisted drainage, although there is limited evidence on the type of ACTs used in specific countries. A review of 30 randomised trials for the effectiveness of ACTs shows that these

interventions increase sputum clearance during or after treatment, reduce the impact of cough and the risk of exacerbations, and improve health-related quality of life. Furthermore, strategies for reducing the risk of bias in future studies are proposed. Finally, an exploration of patients' perceptions, barriers and enablers related to this treatment is also included to facilitate implementation and adherence to ACTs.

Introduction

Bronchiectasis is a chronic respiratory disease defined by abnormal and irreversible dilation of the bronchi [1, 2] with impaired mucociliary clearance. Common features include persistent cough with sputum production and recurrent acute exacerbations [2, 3]. Recurrent exacerbations contribute to progressive lung damage [4] and impaired health-related quality of life (HRQoL) [5–7], and they are linked to a worse prognosis [8].

Impaired mucociliary clearance is one of the main defects leading to bronchiectasis and disease progression [9, 10]. While some patients with bronchiectasis have an inherited cause of impaired mucociliary clearance, *e.g.* primary ciliary dyskinesia, in most cases the combined effects of chronic airway inflammation and infection lead to persistently impaired mucus clearance [10]. Enhancing or restoring mucus clearance from airways is, therefore, a key therapeutic strategy that aims to disrupt the pathogenic vortex of this disease.

The European Respiratory Society (ERS) guidelines for the management of people with bronchiectasis, as well as other national and international reference documents [2, 11–14], highlight airway clearance techniques (ACTs) as an essential strategy to control and address impaired mucociliary clearance and related symptoms [2, 15]. ACTs comprise a range of strategies to facilitate the mobilisation and expectoration of secretions. Nevertheless, access to this treatment is still suboptimal for people with bronchiectasis and clinical practice seems to be highly variable across countries [16, 17]. Preliminary international data suggest that clinicians' recommendations to perform ACTs are inconsistent [16, 17] and the overall global clinical practice is currently unknown. This may be related to the lack of knowledge about the beneficial effects of ACTs, namely, how to identify people who can benefit from them, and how to implement and ensure long-term adherence to this treatment. Thus, a statement summarising the current knowledge around this field is required.

The objectives of this ERS task force were first to describe the physiological rationale for prescribing ACTs in adults with bronchiectasis and to synthesise their main action mechanisms, highlighting their advantages and disadvantages. Second, the task force also reviewed the current global practice of ACTs and their short-term and long-term effects in this population, outlining suggestions to improve the future research on this topic. Finally, the patient experience, satisfaction and preference for ACTs, as well as the perceived enablers and barriers that may influence treatment adherence, were summarised [18].

Methods

Panel composition

The task force panel, which represented 10 countries, included 13 expert respiratory physiotherapists, two patient representatives and a respiratory physician with clinical and research expertise in bronchiectasis. Expert physiotherapists were selected by the task force chairs to ensure wide representation, *i.e.* inclusion of early career researchers and individuals from different countries, after an open invitation to all members of the ERS Group 9.02 – Physiotherapists. The patient representatives were suggested by the European Lung Foundation, with representation from one patient who is adherent to ACTs and one who is not. The patient representatives were included in the working teams, actively participating in the online meetings and providing input throughout the project, particularly on topics related to patients' feedback. The panel was supported by an experienced ERS methodologist.

All task force members signed a conflict-of-interest disclosure before project commencement according to ERS policies. Adherence to the ERS policy was monitored by the chairs throughout the project. Two external librarians (Sonya Di Giorgio and Karen Poole, King's College London) collaborated with the task force, running the search strategies and their updates.

The task force panel identified six main questions of clinical and research interest by discussion and consensus (table 1). The panel members formulated three working groups and addressed two questions each (supplement 1, table S1). Between June 2020 and June 2022, the task force panel met virtually six times and each working group held at least four additional teleconferences. Other communication and review of drafts was performed through email contact and manuscript collaboration on a secure cloud platform.

TABLE 1 Summary of the European Respiratory Society task force statement on ACTs in adults with bronchiectasis

Question	Statement summary
Question 1. What is the physiological rationale for the use of ACTs in adults with bronchiectasis?	• Sputum from people with bronchiectasis is abnormally hyper-concentrated (dehydrated) and mucin concentration is related to disease severity. This indicates that the level of mucus layer dehydration plays an important role in the pathophysiology of the disease. • The main physiological mechanism that promotes mucus clearance involves mechanical stress, such as fluid shear stresses, compressions or stretching, and osmotic shocks. ACTs which implement these mechanisms of action have the potential to enhance mucociliary clearance in bronchiectasis because they can potentially achieve a greater expiratory to inspiratory flow rate or direct volume of air behind lung regions that are obstructed by mucus accumulation.
Question 2. What is the physiological rationale of each one of the ACTs and what are the advantages and limitations of each technique?	• ACTs enhance sputum clearance by incorporating one or more of the following mechanism of actions: improvement of collateral ventilation and interdependence, increase of expiratory airflow velocity, reduction of the total airway cross-sectional ratio, use of gravity, change of airway pressures and generation of airway oscillations. Data specifically evaluating the above physiological principles in people with bronchiectasis are scarce. • The main advantages of specific ACTs are that they can be performed independently, they are feasible in different environments or can easily be implemented in a daily routine. • The main disadvantages of specific ACTs are the level of concentration and effort that is required to perform them, the need for cleaning and periodic replacement of devices, the noise or size of devices, difficulty of transport, the lack of biofeedback and the cost.
Question 3. Which are the ACTs that are clinically used in the management of adults with bronchiectasis and are there any patterns according to geographical location?	• There is limited evidence about the clinical use of ACTs in specific countries. Based on the available data (*i.e.* Australia, New Zealand, USA, Japan, UK), the active cycle of breathing technique is the most commonly used ACT in bronchiectasis. Positive expiratory pressure, oscillating positive expiratory pressure and techniques based on the effect of gravity are also commonly used. • Studies reporting on the clinical use of ACTs do not always adequately describe the responding population and sample. They also do not always clearly define ACTs. • Data on the use of ACTs in clinical practice are scarce and some data are likely to be out of date given the progress in bronchiectasis management in the past decade.
Question 4. What is the clinical evidence for the effectiveness of ACTs, in terms of function and disability (*e.g.* sputum expectoration), activity (*e.g.* physical activity) and participation (*e.g.* self-care), in adults with bronchiectasis?	• Although data on the effects of performing ACTs for periods over 6 or 12 months are limited, the findings demonstrate a reduction in the impact of cough, improvement in health-related quality of life and reduction in the risk of exacerbations. These findings support previously published clinical recommendations for the use of ACTs as part of bronchiectasis management in adults. However, no evidence exists about the optimal frequency or the number of sessions. • Randomised controlled trials have assessed a variety of ACTs, with oscillating positive expiratory pressure (mainly *via* Flutter and Acapella), gravity-assisted drainage and active cycle of breathing being the most commonly studied techniques. The existing literature does not demonstrate superiority of one technique over another but supports the use of ACTs. • Wet sputum weight or volume were the most commonly used outcome measures. ACTs increase the expectorated sputum during or following a single session of ACTs. Despite being frequently used in clinical practice, the interpretation of sputum changes is ambiguous. • To date, no studies have investigated the effect of ACTs on mortality or changes in disease severity using the bronchiectasis severity index or FACED. There are also no studies providing a health economics estimation for ACTs in bronchiectasis.

Continued

TABLE 1 Continued

Question	Statement summary
Question 5a. What are the experiences and perceived impact of ACTs on adults with bronchiectasis? **Question 5b. What are the perceived barriers to and enablers of ACTs in adults with bronchiectasis?**	• Patient experience was generally well rated for ACTs. Preference was mainly based on the independence of technique, patient satisfaction with symptom relief and perceived efficacy or difficulty. • Patient adherence to ACTs could be related to older age, good physical function, milder respiratory symptoms, less treatment burden and belief in treatment necessity. • Optimal engagement of patient and healthcare professionals, adequate motivation, time and resources were some of the enablers of and barriers to ACTs.
Question 6. In adults with bronchiectasis, how should studies for ACTs be conducted to reduce the risk of bias, facilitate comparison of findings, as well as conducting future meta-analyses?	• The risk of bias amongst the studies that assess ACTs is heterogeneous, but generally unclear. • For most studies, reporting was unclear for allocation concealment or there was selective reporting. • Blinding of the ACTs was also limited for patients and personnel, although this is often challenging due to the nature of the intervention. • Futures studies should be adequately powered, based on a sample size estimation of one or two primary outcome measures, which have well-explored psychometric properties. Blinding of outcome assessment and statistical analysis of the ACTs should be implemented to help minimise bias. Study reporting should be clear and follow the CONSORT reporting guidelines [19].

ACT: airway clearance technique.

Literature review

The task force panel designed the search strategies to address the six questions in collaboration with the librarians and the ERS methodologist. Systematic literature searches using MEDLINE (Ovid), Embase, AMED, CINAHL, Cochrane CENTRAL and PEDro databases were initially run in September 2020 and then updated in November 2021. Original research papers on ACTs in bronchiectasis were used for the sections on global clinical practice, effects of ACTs, research quality assessment and patient's feedback, barriers and enablers. For the physiological rationale of the use of ACTs in bronchiectasis and mechanisms of action, secondary articles, *i.e.* reviews, were also included. Articles in English were selected, except for Question 2, where the panel agreed to include studies in other languages (*e.g.* French, Spanish, Portuguese, Italian) to ensure the collection of information on ACTs that were not developed in the Anglosphere. The filters used for the search strategies were species (human) and age (⩾18 years), except for Question 1 and Question 2, where animal and *in vitro* studies were allowed.

The panel decided to assess techniques that were specifically developed to enhance airway clearance and improve the management of sputum-related symptoms; therefore, techniques with a different primary objective that have been explored as means of airway clearance, such as exercise, respiratory muscle training and noninvasive ventilation (NIV), were excluded from this statement. The panel also agreed not to consider cough manoeuvres as an individual ACT, because this is a physiological mechanism for sputum expectoration and in trials it is often used as a control treatment arm. Humidification, mucoactive agents and other medications were outside the scope of this task force, which focused on nonpharmacological approaches. Therefore, the aforementioned treatments were only reported if they were a comparative arm of an included study. The full search methodology for each question is available in supplement 2.

The sensitivity of all search strategies was checked before screening the results. Search strategies that lacked adequate sensitivity, *i.e.* Question 1 and Question 2, were re-designed twice (supplement 1). For each question, two independent reviewers screened the search results according to prespecified selection criteria. Disagreements were resolved by consensus between the two reviewers or consultation from a third reviewer. Data extraction was performed using prespecified spreadsheets and evidence obtained was assessed qualitatively. The quality of studies was assessed in Question 6 using the Cochrane tool for randomised trials risk of bias [20], given that the findings of this question aim to improve the methodological quality of future research in this topic.

Results

Question 1: What is the physiological rationale for the use of ACTs in adults with bronchiectasis?

Understanding the physiology of ACTs is fundamental to its application in clinical practice. Therefore, the task force initially sought to review studies examining the airway clearance impairment mainly in people with bronchiectasis, as well as studies investigating the physiological mechanisms of action to enhance mucus clearance.

Evidence overview

A total of 22 studies were identified, all meeting the inclusion criteria (supplement 1, figure S1 and table S2). Of these studies, nine studies were primary research [9, 21–28] and 13 were secondary research studies (one systematic review [29] and 12 narrative reviews [3, 30–40]). Data for 11 studies came from *in vitro* experiments [21, 22, 24–26, 32–34, 36, 38, 40] and three studies were experimental/clinical trials [21–23]. Six studies reported data from people with bronchiectasis [3, 9, 25, 27–29], five studies provided a mix of data from different respiratory diseases including bronchiectasis [24, 30, 35, 37, 39], seven studies outlined data from other respiratory diseases such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis [26, 32–34, 36, 38, 40] and one study involved healthy adults [23].

Impaired mucociliary clearance in people with bronchiectasis

Impaired mucociliary clearance in people with bronchiectasis is often demonstrated through productive cough, abnormally high presence of sputum or difficulty in sputum expectoration. Abnormalities in mucus production, ciliary function and biophysical and surface mucus properties directly contribute to a decreased mucus clearance rate compared to healthy people [34, 37, 40]. There are limited data about the function of the airway surface layer in bronchiectasis and the hypothesis that mucus layer dehydration impairs mucus transport is derived from other chronic respiratory diseases [26, 38, 40]. Still, considering that sputum samples from people with bronchiectasis are abnormally hyper-concentrated (dehydrated), this could be a possible explanation [9].

First, neutrophil elastase activity plays an important role in the pathogenesis and progression of bronchiectasis [27, 29]. Excessive neutrophil elastase activity within the inflamed airway has been reported to decrease ciliary beat frequency and directly stimulates mucin secretion [27, 29]. Mucin 5B appears to be the most predominant mucin in bronchiectasis [9]. Mucin 5AC and higher airway mucin levels are associated with increased disease severity [9, 27]. However, these findings are based on only a few studies in bronchiectasis [9, 27] and further research is needed to confirm them.

An excess of secreted mucins leads to mucus layer dehydration and generates an osmotic imbalance between the mucus layer and the periciliary layer. This phenomenon ultimately compresses the periciliary layer and ciliary system [33]. Consequently, ciliary beating is slowed down and mucus layer adhesion to the airway epithelial surface is facilitated (adhesivity is a surface property of the sputum, defined as the ability to bond to a solid surface [37]); therefore, mucus transport is reduced, which results in mucus accumulation [26, 40]. This perpetuates the pathogenesis of bronchiectasis, which has lately been described as a vicious vortex [3]. In fact, a hyper-concentrated mucus layer can lead to local epithelial hypoxia, which may limit the action of cystic fibrosis transmembrane conductance regulator channels and produce higher levels of dehydration in the airway surface layer [25]. Most ciliary dysfunction in bronchiectasis is due to the effects of chronic inflammation, but the genetic condition primary ciliary dyskinesia, caused by more than 50 recognised gene defects affecting the structure and function of motile cilia, is increasingly recognised [39].

Second, when respiratory muscle strength is preserved as in the case of bronchiectasis, mucus adhesivity appears to be the strongest factor determining cough effectiveness for airway clearance [34, 37]. This property is independent of mucus viscosity (the loss of energy from an object through a substance and thus the resistance to flow) and mucus elasticity (the recoil energy transmitted back to an object) [32, 37]. Greater adhesivity appears when there is high interfacial tension between the mucus layer and the airway epithelium and/or low mucus wettability (the surface energy at a solid-sputum–air interface) [34, 37]. The limited available data from *in vitro* experiments suggest that mucus transport *via* coughing is impaired in bronchiectasis [25].

Consequently, the rationale for the use of ACTs in bronchiectasis is based on improving the biophysical and surface properties of the mucus layer to enhance the clearance of inflammatory markers and to help modulate the pathogenic microorganism load in the airways. Thus, ACTs aim to break the pathogenic vortex and slow down disease progression.

Physiological mechanisms to enhance mucociliary clearance

Mechanical stress applied to the airways could stimulate hydration of the mucus layer and enhance airway clearance [24, 36]. During normal breathing, two mechanical stresses are generated during both respiratory phases of inspiration and expiration, and they are essential for the normal regulation of airway surface hydration: the airflow and the trans-airway pressure gradient [24]. Previous studies reported that fluid shear stress, compression or stretch and osmotic shock are the main physical mechanisms that stimulate airway surface hydration [24]. Additionally, an *in vitro* flow model suggests two conditions that promote airway clearance [21, 22, 30]: the peak expiratory flow rate should be greater than the peak inspiratory flow rate (rate difference >10%) for mucus to move proximally, and a peak expiratory flow rate of 30–60 $L \cdot min^{-1}$ is required to break the adhesive bonds generated between the mucus layer and the airway epithelial surface. Accordingly, airway clearance strategies are based on generating greater mechanical stress on the airways compared to normal breathing and the achievement of one of the above conditions may play an important role in improving airway clearance for people with bronchiectasis.

Achieving a sufficient volume of air behind the lung regions that are obstructed by mucus accumulation is another mechanism that may enhance mucus clearance [30]. Three different strategies have been described to achieve this: slow, deep inspirations to take advantage of the parenchymal interdependence and generate traction force to keep open or re-expand the smaller airways [31]; end-inspiratory breath-hold to reduce asynchronies in time constants between lung regions with different resistance or compliance constants [23]; and promotion of ventilation *via* collateral channels using adjacent lung units [30]. These mechanisms use the Pendelluft effect, which allows air to move into the lung units that are most obstructed by mucus accumulation [30].

In summary, evidence suggests that sputum-related symptoms result from increased mucus production, dehydration and impaired biophysical properties of mucus and reduced ciliary function due to primary and secondary ciliary dysfunction. The physiological mechanisms by which ACTs could enhance mucociliary clearance include improving the rate of mucus clearance by stimulating airway surface hydration, increasing the velocity of airflow and thus the air–mucus interaction, and facilitating a homogeneous distribution of ventilation. These mechanisms provide a physiological justification for the role of ACTs in bronchiectasis.

Question 1: Statements

- Sputum from people with bronchiectasis is abnormally hyper-concentrated (dehydrated) and mucin concentration is related to disease severity. This indicates that the level of mucus layer dehydration plays an important role in the pathophysiology of the disease.
- The main physiological mechanism that promotes mucus clearance involves mechanical stress, such as fluid shear stresses, compressions or stretching, and osmotic shocks. ACTs which implement these mechanisms of action have the potential to enhance mucociliary clearance in bronchiectasis, because they can potentially achieve a greater expiratory to inspiratory flow rate or direct a volume of air behind lung regions that are obstructed by mucus accumulation.

Question 1: Recommendations for research

- Investigate how biophysical and surface sputum properties such as viscoelasticity, adhesivity and cohesivity (defined as the tendency for a gel to remain attracted to itself [37]) change across the disease trajectory in relation to underlying aetiologies or with different endotypes or phenotypes in people with bronchiectasis.
- Investigate how biophysical and surface sputum properties influence the effectiveness of ACTs in people with bronchiectasis. Evaluate whether these sputum biomarkers could support the identification of good candidates/responders for specific ACTs in order to personalise airway clearance management.
- Explore whether the order or specific combination of the physiological mechanisms described above can improve mucus clearance, specifically in people with bronchiectasis according to their disease aetiology, endotype or phenotype. This may help in selecting the most suitable ACTs or combination of ACTs in clinical practice.

Question 2: What is the physiological rationale of each one of the ACTs and what are the advantages and limitations of each technique?

To answer this question, we searched for studies that examined or explained the physiological mechanism of mucociliary clearance for each ACT. Considering what could improve long-term adherence to ACTs, we also summarised the views of the panel about the key advantages and disadvantages of each technique, including the views of the patient representatives.

Evidence overview

A total of 30 studies were identified, all meeting the inclusion criteria (supplement 1, figure S2 and table S3). Of these studies, 18 were primary research papers, including 14 clinical trials, comprising one randomised controlled trial [41], nine crossover trials [42–50] and four quasi-experimental trials [51–54]. Five studies provided data from *in vitro* or animal experiments [21, 22, 36, 51, 53]. Only four studies reported data exclusively from people with bronchiectasis [50, 55–57], nine studies reported mixed data from various respiratory diseases (*e.g.* bronchiectasis, COPD and cystic fibrosis) [30, 46, 58–64], 10 studies included patients with other respiratory diseases [36, 41–45, 48, 49, 52, 65] and one study reported data from healthy adults [47].

The physiological rationale for each of the following ACTs was considered: forced expiration technique (FET), active cycle of breathing techniques (ACBT), manual percussions, manual vibrations or shaking, autogenic drainage, slow expiration with glottis opened in lateral posture (ELTGOL), gravity-assisted drainage (GAD) technique, positive expiratory pressure (PEP) devices, positive expiratory pressure devices with oscillation (O-PEP), high-frequency chest wall oscillation (HFCWO) and intrapulmonary percussive ventilation (IPV). These techniques appear to achieve one or several of the physiological principles proposed to enhance sputum clearance: improving collateral ventilation and interdependence, increasing expiratory airflow velocity, reducing the total airway cross-sectional ratio, use of gravity, changing airway pressures and producing airway oscillations. Specific data on frequencies and flow rates achieved through ACTs in other patient populations can be found in McIlwaine *et al.* [30].

The identified ACTs have a range of advantages. For instance, many ACTs can be used independently by the patient, and they are portable and easy to learn. Common disadvantages include the need for some level of concentration when performing the techniques, as well as the need for instructions or training to ensure optimal execution, especially when access to a specialist respiratory physiotherapist is limited. If the performance of ACTs includes the use of a device, the need for cleaning and periodic replacement, noise and/or transport difficulties are the main disadvantages associated with its use. Table S4 in supplement 1 presents the physiological rationale for the ACTs and table 2 their advantages and disadvantages from the respiratory physiotherapists' and patients' perspectives. Although some techniques may be combined with others, each technique was reported separately. Further information on the procedures for performing ACTs is available in online resources that include videos and illustrations [66–68].

Question 2: Statements

- The ACTs enhance sputum clearance by incorporating one or more of the following mechanism of actions: improving collateral ventilation and interdependence, increasing expiratory airflow velocity, reducing the total airway cross-sectional ratio, use of gravity, changing airway pressures and generating airway oscillations. Data specifically evaluating the above physiological principles in people with bronchiectasis are scarce.
- The main advantages of specific ACTs are that they can be performed independently, they are feasible in different environments or can easily be implemented in a daily routine.
- The main disadvantages of specific ACTs are the level of concentration and effort that is required to perform them, the need for cleaning and periodic replacement of devices, the noise or size of devices, difficulty of transport, the lack of biofeedback and the cost.

Question 2: Recommendations for research

- Assess if the physiological mechanisms described for each ACT work specifically in people with bronchiectasis and what are the related physiological actions (pressure, frequencies, flow rate, *etc*.) in this population.
- Establish whether the physiological effects of ACTs change depending on clinical status (*i.e.* clinical stability *versus* acute exacerbation) or disease severity (*i.e.* mild *versus* severe).
- Conduct studies that involve people with bronchiectasis in their design and incorporate strategies that enhance the advantages and mitigate the disadvantages of ACTs in clinical practice.

Question 3: Which are the ACTs that are clinically used in the management of adults with bronchiectasis and are there any patterns according to geographical location?

Despite ACTs being recommended in national and international guidelines, their clinical implementation across the globe is largely unknown. To identify the use of ACTs in the management of adults with bronchiectasis, we analysed surveys, audits and registries that recorded the clinical use of ACTs, alone or alongside other treatments. Potential location patterns were also assessed.

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TABLE 2 Advantages and disadvantages of each ACT

	FET	ACBT	Manual percussions	Manual vibrations or shaking	GAD	HFCWO	IPV	Autogenic drainage	ELTGOL	PEP	O-PEP
Advantages											
Can be performed independently	✓	✓	≈ (anterior lung regions)	≈ (anterior lung regions)	✓	✓		✓	✓	✓	✓
Can be combined with some other ACTs	✓ (*e.g.* GAD)	✓ (*e.g.* GAD)	✓ (*e.g.* GAD)	✓ (*e.g.* ACBT)	✓ (*e.g.* ACBT)	✓ (*e.g.* GAD)	✓ (*e.g.* GAD)	✓ (*e.g.* O-PEP)	✓ (*e.g.* O-PEP)	✓ (*e.g.* AD or ELTGOL)	✓ (*e.g.* AD or ELTGOL)
Easy to perform in different environments/easy to transport (*e.g.* when travelling)	✓	✓	✓	✓	✓	≈ (if using a portable HFCWO device)		✓	✓	✓	✓ (except TPEP)
Easy to teach (respiratory physiotherapist) and easy to learn how to perform (patients)	✓	✓				✓				✓	✓
Patient does not require concentration or effort			✓	✓	✓	✓	✓				
Technique can be applied passively, which can be appropriate when patients are too unwell to do independent techniques			✓	✓	✓	✓	✓				
Generate ventilatory support (*e.g.* recommended for exacerbations or in patients with more severe disease)							✓				
Patients may prefer this technique compared to other techniques								✓		✓	✓
Disadvantages											
Less commonly used as a standalone technique because a prolonged treatment time may be needed, especially when the goal is to enhance sputum clearance from peripheral airways	x			x	x						
Likelihood of airway dynamic collapse using low inspiratory lung volumes [58]	x	x									
Usually, assistance is required from a respiratory physiotherapist or another person (*e.g.* caregiver)			x	x			≈ (preferably used in clinical settings)				
It may be difficult for the respiratory physiotherapist or caregiver to perform long sessions while still achieving optimal performance			x	x					x (if it is assisted)		

Continued

TABLE 2 Continued

	FET	ACBT	Manual percussions	Manual vibrations or shaking	GAD	HFCWO	IPV	Autogenic drainage	ELTGOL	PEP	O-PEP
Patients may experience discomfort (especially those who are frail) or present adverse events (*e.g.* gastroesophageal reflux, shortness of breath, ventilation/perfusion mismatch, increased intracranial pressure), particularly in severe disease or during acute exacerbations			x	x	x (especially downward positions)	x			x (if side-lying position was not tolerated)		
Devices that are difficult to transport (size or weight) and require electrical source if a battery-operated device is not available						x	x				x (only TPEP)
Cost associated with the device (the price or because of the need to replace periodically)						x	x			x	x
Device does not provide feedback on whether it is used correctly or not (*e.g.* target pressure unless a manometer is used)						x	x			x (except TheraPEP)	x (except TPEP)
Noisy						x	x				x
Time required for cleaning and disinfection							x			x	x
Can take time to master the technique and requires concentration and effort compared to other techniques								x	x		

✓: advantages; x: disadvantages; ≈: yes, but with exceptions. ACT: airway clearance technique; ACBT: active cycle of breathing techniques; ELTGOL: slow expiration with glottis opened in lateral posture; FET: forced expiratory technique; GAD: gravity-assisted drainage; HFCWO: high-frequency chest wall oscillation; IPV: intrapulmonary percussive ventilation; O-PEP: oscillating positive expiratory pressure; PEP: positive expiratory pressure; TPEP: temporary positive expiratory pressure.

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Evidence overview

A total of 2934 studies were screened for eligibility and seven papers were included [69–75] (supplement 1, figure S3 and table S5). Five studies assessed the clinical use of ACTs *via* surveys [69–71, 73, 74], and two studies through audit [75] or registry data [72]. One registry recorded the ACTs during a clinically stable stage or exacerbation of the disease [72], and one survey only during exacerbations [74], while the other studies were conducted during a clinically stable stage or did not report this information. One study assessed ACTs during COVID-19 [73].

All surveys were administered to healthcare professionals [69–74], mainly physiotherapists (n=482) [69–71, 74]. In three studies that reported on survey response rates for healthcare centres and professionals, these ranged from 70% to 88% [69–71], while the response rate was only 0.5% in the survey that had the highest number of invited healthcare professionals (n=26 000) [74].

All studies assessed a variety of ACTs, apart from Santos *et al*. [71] that specifically assessed the use of different PEP devices. The ACTs were not always defined, but results were mainly presented as frequencies of use (figure 1). Based on six studies that compared a variety of ACTs, the most common routinely used ACT was the ACBT (range 48–91%). PEP or O-PEP (range 7–75%), techniques based on gravity such as GAD (range 8–76%) and modified GAD (range 10–55%), and techniques based on optimal positioning (range 35–84%) were also frequently reported. Other less-frequently used ACTs were manual percussion, deep breathing exercises, positions of ease (possibly for ease of breathlessness), manual and high-frequency vibrations, sustained maximum expiration, FET, autogenic drainage or other (figure 1 and supplement 1, figure S4).

Evidence for the clinical use of ACTs was mainly available from Australia, and ACBT with FET or directed cough were the most frequently selected choices [70, 73–75]. Owing to the limited data from other countries, it was not possible to identify additional geographical patterns.

Question 3: Statements

- There is limited evidence about the clinical use of ACTs in specific countries. Based on the available data (*i.e.* Australia, New Zealand, USA, Japan, UK), the ACBT is the most commonly used ACT in bronchiectasis. PEP, O-PEP and techniques based on the effect of gravity are also commonly used.
- Studies reporting on the clinical use of ACTs do not always adequately describe the responding population and sample. They also do not always clearly define ACTs.
- Data on the use of ACTs in clinical practice are scarce and some data are likely to be out of date given the progress in bronchiectasis management in the past decade.

Question 3: Recommendations for research

- Surveys, audits and clinical registries need to assess the ACTs that are currently used in clinical practice in different geographic areas and investigate potential variations.
- Surveys need to consistently report on the responder population and sample characteristics.
- Studies need to clearly and adequately define ACTs in line with the clinical practice of each country, so as to enable future comparisons.

Question 4: What is the clinical evidence for the effectiveness of ACTs, in terms of function and disability (e.g. sputum expectoration), activity (e.g. physical activity) and participation (e.g. self-care), in adults with bronchiectasis?

Clinical evidence for the effectiveness of ACTs is vital for the management of bronchiectasis. To identify this for adults with bronchiectasis, we analysed randomised clinical trials that assessed the effects of any ACT on the participant's function and disability, activity and participation. The comparative arm of the studies could be another ACT, a different type of treatment, placebo, sham intervention or no treatment.

Evidence overview

A total of 1936 studies were screened for eligibility and 30 papers were included (supplement 1, figure S5). All included studies were randomised; 10 had a parallel group design and 20 had a crossover design. They were mainly short-term studies with a range from 1 day to 4 weeks, while two studies had a duration of 3 months and 12 months each [76, 77]. Overall, there were 811 participants (57% female), with mean age of 58 years and mean forced expiratory volume in 1 s (FEV_1) of 59% predicted. Most studies included patients during a clinically stable condition (n=22), three during an acute exacerbation [78–80] and one

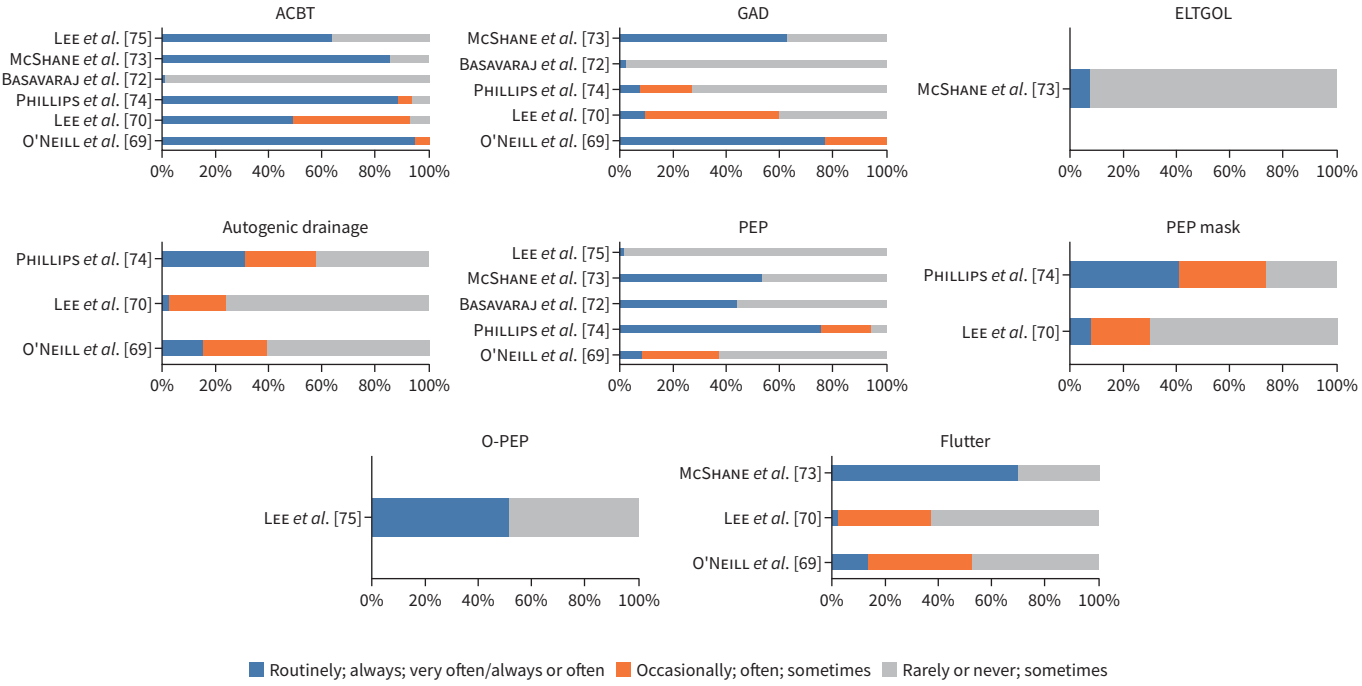

FIGURE 1 Clinical use of airway clearance techniques (ACTs). The graph presents the ACTs that were reported as the most routinely used. The terminology of the graphs follows the terminology of the original studies, *i.e.* PEP *versus* PEP mask and Flutter *versus* O-PEP. GAD was presented as postural drainage in the original studies. The study by Santos *et al.* [71] was not included in the graphs because it reported on the frequency of a specific type of ACT: PEP devices. Results of this study, presented as percentage of physiotherapists, were PEP mask 2%, PEP mouthpiece 32%, PEP bottle 72%, Flutter 36% and Acapella 46%. Percentages do not add up to 100% because the physiotherapists could choose all ACTs that apply. ACBT: active cycle of breathing techniques; ELTGOL: slow expiration with glottis opened in lateral posture; GAD: gravity-assisted drainage; O-PEP: oscillatory positive expiratory pressure; PEP: positive expiratory pressure.

study during both clinical stages [81], although this was not clearly reported in four studies [82–85]. Results are presented in table 3.

Most included studies were active comparator studies, with one ACT technique compared to another. Most studies investigated the effectiveness of O-PEP; specifically, Flutter (n=13), Acapella (n=7), Aerobika (n=1), RC-Cornet (n=2), Quake (n=1), temporary positive expiratory pressure (n=1), Lung Flute (n=1) and bubble PEP (n=2) were studied in different or the same trials. Studies also assessed GAD (n=13), ACBT (n=11), manual techniques (*i.e.* percussions/vibrations) (n=9), ELTGOL (n=4), autogenic drainage (n=4), PEP (n=2) and HFCWO (n=1). GAD and manual techniques were used alone or in combination with other ACTs, also referred to as conventional physiotherapy treatment. Most techniques were self-administered by the patients at the hospital, predominantly after training by a respiratory physiotherapist or another experienced healthcare professional. Alternatively, clinical supervision was provided in each session or selected ones.

The effectiveness of the techniques was assessed using function and disability outcomes, while there were limited trials that used activity and participation measures (table 3). Sputum volume or weight during or after treatment (n=30), patient-reported preference and comfort (n=16), dyspnoea (n=11) and HRQoL (n=7) were the most common outcome measures used, and most studies did not report on patients' adherence to treatment. Three studies included the number of coughs or presence of cough as one of their secondary outcomes [86–88] and only two studies used frequency of exacerbations or time to first exacerbation [76, 77]. There is no evidence about the optimal frequency or the number of sessions needed to ensure correct procedure of the ACTs. The studies that assessed ACT adverse events did not identify serious adverse effects that are related to ACTs.

Question 4: Statements

- Although data on the effects of performing ACTs for periods over 6 or 12 months are limited, the findings demonstrate a reduction in the impact of cough, improvement in HRQoL and reduction in the

TABLE 3 Effectiveness of ACTs

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Tsang *et al.* [79] 2003, Hong Kong	<4 weeks	RCT	Acute exacerbation	GAD+BC *vs* O-PEP (Flutter)+BC *vs* BC	Three daily (one supervised) from day 2 to day of discharge 15 min per session	Wet sputum weight (g) FVC (L) FEV_1 (L) PEF ($L \cdot min^{-1}$) S_{pO_2} (%) Heart rate (bpm) Hospitalisation length (days)	n=15 (47% F) Age (years): GAD+BC=67±15 O-PEP+BC=72±5 BC=74±6 FEV_1 (% pred): GAD+BC=48±24 O-PEP+BC=39±7 BC=36±11 Daily sputum (g): GAD+BC=47.5±23.2 O-PEP+BC=25.6±14.6 BC=26.2±20.3	There were no statistically significant differences between the GAD+BC, O-PEP+BC and BC.
Patterson *et al.* [89] 2004, UK	<4 weeks	RCX	Clinical stability	ACBT+GAD (2 positions) with vibrations *vs* IMT (80% of MIP)	Single session Maximum of 30 min	Wet sputum weight (g)[#] FVC (L; % pred) FEV_1 (L; % pred) PEF ($L \cdot min^{-1}$; % pred) S_{pO_2} (%)	n=20 (70% F) Age=54±14 years FEV_1=NR Daily sputum=NR (inclusion criteria→½ egg $cup \cdot day^{-1}$)	ACBT+GAD with vibration significantly improved sputum weight (during ACT intervention) when compared to IMT (6.3±6.6 g *vs* 4.0±4.3 g; MD 2.3 g; 95% CI 0.5–4.1 g; p=0.01).[#] ACBT+GAD with vibration significantly improved sputum weight (including session and 30 min post-intervention) when compared to IMT (9.0±7.8 g *vs* 6.5±6.8 g; MD 2.4 g; 95% CI 0.4–4.4 g; p=0.02).[#]
Patterson *et al.* [87] 2005, UK	<4 weeks	RCX	Clinical stability	ACBT+GAD (2 positions) with percussion/ vibrations *vs* O-PEP (Acapella)	Single session per technique Maximum of 30 min	Wet sputum weight (g)[#] FVC (L; % pred) FEV_1 (L; % pred) PEF ($L \cdot min^{-1}$; % pred) S_{pO_2} (%)	n=20 (65% F) Age=58±11 years FEV_1=64±22% pred Daily sputum=NR (inclusion criteria→½ egg $cup \cdot day^{-1}$)	No statistically significant differences were found.
Eaton *et al.* [90] 2007, New Zealand	<4 weeks	RCX	Clinical stability	ACBT *vs* ACBT+GAD *vs* O-PEP (Flutter)	Single session per technique Maximum of 30 min	Wet sputum weight (g)[#] Wet sputum volume (mL)[#] FEV_1 (% pred)[#] S_{pO_2} (%)[#] Borg scale dyspnoea (points)[#]	n=36 (67% F) Age=62±10 years FEV_1=57.8±19.8% pred Daily sputum=NR (inclusion criteria→chronic productive cough)	ACBT+GAD obtained significantly greater sputum quantity (during ACT intervention) when compared to the ACBT and O-PEP (O-PEP *vs* ACBT-GAD MD −5.6 ±8.2 g/ −5.1±8.8 mL; ACBT *vs* ACBT+GAD −5.9±9.6 g/−5.7±10.5 mL; p<0.01).[#] ACBT+GAD significantly obtained greater sputum quantity (including session and 30 min post-intervention) when compared to the ACBT and O-PEP (O-PEP *vs* ACBT-GAD MD −5.6±8.5 g/−4.9±8.2 mL; ACBT *vs* ACBT+GAD −5.6±9.2 g/ −5.3±9.9 mL; p<0.001).[#]

Continued

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Patterson *et al.* [78] 2007, UK	<4 weeks	RCT	Acute exacerbation	O-PEP (Acapella)+ GAD (2 positions) *vs* usual ACTs (ACBT, autogenic drainage, PEP, O-PEP-Flutter or no ACT)	Once (n=2) or twice (n=18) daily for 10–14 days (end day of antibiotics) O-PEP+GAD= 15±3 min Usual ACTs= 11±6 min	Wet sputum volume (mL)[#] FVC (L)/FEV_1 (L) VC (L) S_{pO_2} (%) Borg scale dyspnoea (points) 15-count breathlessness score (points)	n=20 (50% F) Age=61±11 years FEV_1=64.7±21.1% pred Daily sputum=NR	No statistically significant differences were found.
Syed *et al.* [91] 2009, India	<4 weeks	RCX	Clinical stability	ACBT+GAD *vs* GAD+ percussion and vibrations+BC	Single session Every 3 h while awake for 30 min	Wet sputum weight (g)[#] Wet sputum volume (NR) FVC (L) FEV_1 (L) FEV_1/FVC (L)[Unit]	n=35 (23% F) Age=45±11 years FEV_1 (% pred): ACBT+GAD=41±19 GAD+percussion and vibration+BC=43±20 Daily sputum=30–132 mL·day^{-1} Daily sputum >50 mL=11 participants Daily sputum ⩽50 mL=24 participants	A statistically significant difference in FEV_1/FVC values were observed between pre- and post-intervention in ACBT+GAD intervention (48.4±25.5% pred *vs* 56.1±27.9% pred; p<0.001). A statistically significant difference in FEV_1/FVC values were observed between pre- and post-intervention in GAD+percussion and vibration+BC intervention (49.1±23.9 *vs* 54.0±26.5; p=0.03).
Naraparaju *et al.* [82] 2010, India	<4 weeks	RCX	NR	O-PEP (Acapella) *vs* IMT (80% MIP)	Single session (NR)	Wet sputum volume (mL)	n=30 (67% F) Age=51±6 years FEV_1=44.5±16.2% pred Daily sputum=NR (inclusion criteria→chronic productive cough)	O-PEP (Acapella) significantly increased sputum volume (including session and 2 h post-intervention) when compared to IMT (80% MIP) (7.2±1.1 mL *vs* 6.5±1.1 mL; MD 0.7 mL; 95% CI 0.1–1.3 mL; p=0.014).
Shabari *et al.* [83] 2011, India	<4 weeks	RCX	NR	O-PEP (RC-Cornet) *vs* O-PEP (Acapella)	Single session Maximum of 20–30 min	Wet sputum volume (mL)[#]	n=40 (50% F) Age=52±16 years FEV_1=NR Daily sputum=NR (inclusion criteria→sputum expectoration >30 mL·day^{-1})	O-PEP (RC-Cornet) significantly increased sputum volume (including session and 2 h post-intervention) when compared to O-PEP (Acapella) (36.6±7.2 mL *vs* 34.6±9.0 mL; MD=1.9 mL; 95% CI NR; p=NR).[#]

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Tambascio *et al.* [92] 2011, Brazil	<4 weeks	RCX	Clinical stability	O-PEP (Flutter) *vs* PEP (modified Flutter)	Single session 4 weeks 30 min	Mucociliary transport (relative velocity) Sputum displacement using simulated cough machine (cm) Contact angle (°)	n=18 (72% F) Age=52±18 years FEV_1 (83–81% pred)=3 participants FEV_1 (77–62% pred)=9 participants FEV_1 (47–31% pred)=4 participants FEV_1 (29% pred)=1 participant Daily sputum=NR (inclusion criteria→not demonstrate a sufficient respiratory secretion quantity for the analysis)	O-PEP significantly increased sputum displacement from pre- to post-intervention (9.6±3.4 cm *vs* 12.4±10.5 cm; p<0.05). O-PEP significantly increased the contact angle from pre- to post-intervention (23.3 ±6.2° *vs* 29.4±5.7°; p<0.05).
Paneroni *et al.* [93] 2011, Italy	<4 weeks	RCX	Clinical stability	IPV *vs* GAD (3 positions) with percussion and vibration+FET	Single session 30 min	Wet sputum weight (g) Dry sputum weight (g) Wet sputum volume (mL) S_{pO_2} (%) Respiratory rate (cpm) Heart rate (bpm) Visual analogue scale dyspnoea (%)	n=22 (45% F) Age=64±9 years FEV_1=53±30% pred Daily sputum=NR (inclusion criteria→daily sputum volume >20 mL for at least 2 consecutive days)	IPV significantly increased respiratory rate when compared to GAD with percussion and vibration+FET (MD −1.6 cpm; 95% CI −3.2–−0.02 cpm; p=0.047). IPV significantly reduced dyspnoea from pre- to post-intervention (35±29% *vs* 23±20%; p=0.004).
Guimarães *et al.* [94] 2012, Brazil	<4 weeks	RCX	Clinical stability	O-PEP (Flutter) *vs* ELTGOL *vs* Control (no ACT)	Single session 15 min	Dry sputum weight (g)[#] FVC (L) FEV_1 (L) FEV_1/FVC (L) $FEF_{25–75\%}$ ($L·s^{-1}$) IC (L) VC (L) TLC (L) FRC (L) RV (L) RV/TLC (%) IC/TLC	n=10 (80% F) Age=56±18 years FEV_1=53±19% pred Daily sputum=NR (inclusion criteria→persistent productive cough)	ELTGOL significantly increased sputum weight (during ACT intervention) when compared to O-PEP and control period (median (min–max)): 0.4 g (2.6–0.1 g) *vs* 0.1 g (1.3–0.1 g) *vs* 0.1 g (0.6–0.0 g); p=NR.[#] ELTGOL and O-PEP significant decreased RV when compared to control period (−18.7 L (−71.5– −10.7 L) *vs* −29.6 L (−54.6– −8.9 L) *vs* 2.9 L (−8.0–35.1 L); p=NR), FRC −14.5 L (−55.6–3.6 L) *vs* −28.8 L (−52.0– −5.1 L) *vs* 4.3 L (−18.9–22.4 L); p=NR) and TLC (−9.7 L (−40.0– −1.9 L) *vs* −18.3 L (−42.8– −6.4 L) *vs* 4.6 L (−7.4–12.6 L); p=NR). O-PEP significant increased IC/TLC when compared with ELTGOL and control period (22.8 (−3.6–82.5) *vs* 17.9 (−10.2–57.8) *vs* 6.7 (−17.3–21.3); p=NR).

Continued

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Figueiredo *et al.* [95] 2012, Brazil	<4 weeks	RCX	Clinical stability	O-PEP (Flutter) *vs* sham O-PEP (sham Flutter)	Single session 15 min	Wet sputum volume (mL)# Impulse oscillometry: R5 ($kPa{\cdot}L^{-1}{\cdot}s^{-1}$) dR/dF ($kPa{\cdot}L^{-1}{\cdot}s^{-1}{\cdot}Hz^{-1}$) X5 ($kPa{\cdot}L^{-1}{\cdot}s^{-1}$) AX ($kPa{\cdot}L^{-1}{\cdot}s^{-1}{\cdot}Hz^{-1}$) f0 (Hz)	n=8 (50% F) Age±SEM=47±6 years FEV_1±SEM=65±6.8% pred Daily sputum ±SEM=47.8±7.1 mL	O-PEP significantly increased sputum volume (during ACT intervention) compared to sham O-PEP (28.0±5.4 mL *vs* 19.6±3.6 mL; 95% CI 3.4–13.4 mL; p<0.05). O-PEP (Flutter) significantly decreased R5 (MD −11.2 $kPa{\cdot}L^{-1}{\cdot}s^{-1}$; 95% CI −4.4– −18.2 $kPa{\cdot}L^{-1}{\cdot}s^{-1}$; p=NR), dR/dF (MD −20.8 $kPa{\cdot}L^{-1}{\cdot}s^{-1}{\cdot}Hz^{-1}$; 95% CI −32.4– −9.0 $kPa{\cdot}L^{-1}{\cdot}s^{-1}{\cdot}Hz^{-1}$; p=NR) and AX (MD −7.8 $kPa{\cdot}L^{-1}{\cdot}s^{-1}{\cdot}Hz^{-1}$; 95% CI −11.9– −3.7 $kPa{\cdot}L^{-1}{\cdot}s^{-1}{\cdot}Hz^{-1}$; p=NR) when compared to sham O-PEP.
Amit *et al.* [81] 2012, India	<4 weeks	RCX	Clinical stability (n=22) and acute exacerbation (n=13)	O-PEP (RC-Cornet) *vs* O-PEP (Quake)	Single session Maximum of 15 min	Wet sputum volume (mL)	n=35 (68% F) Age=52±14 years FEV_1=NR Daily sputum=NR (inclusion criteria→sputum expectoration of >20 $mL{\cdot}day^{-1}$)	O-PEP (Quake) significantly increased sputum volume (24 h post-intervention) when compared to O-PEP (RC-Cornet) (36.2±15.4 mL *vs* 33.8±12.4 mL; MD 2.4 mL; 95% CI 1.0–4.4 mL; p=0.021).

Continued

TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Nicolini *et al.* [96] 2013, Italy	<4 weeks	RCT	Clinical stability	HFCWO (the Vest) *vs* other ACTs including PEP bottle, PEP mask, ELTGOL, O-PEP (Acapella) *vs* no ACT (control)	Twice daily for 15 consecutive days 30 min for HFCWO 40 min for the other ACTs	BCSS (points)# CAT (points)# Sputum volume (mL) Haematology: White cells (10^3 cells) Red cells (10^6 cell) Neutrophils (%) Lymphocytes (%) C-reactive protein (NR) FVC (mL) FEV_1 (mL) FEV_1/FVC (mL) TLC (mL) RV (mL) MIP (cmH_2O) MEP (cmH_2O) P_{aO_2} (mmHg) P_{aCO_2} (mmHg) pH (NR) mMRC dyspnoea (points) Sputum cytology: TCCx (10^6 mg) Neutrophils (%) Lymphocytes (%) Eosinophils (%) Macrophages (%)	n=30 (70% F) Age (years): HFCWO=75±5 Other ACTs=74±4 No ACT=72±7 FEV_1=NR Daily sputum=NR (inclusion criteria→sputum expectoration ⩾20 mL·day^{-1} for ⩾3 consecutive days)	HFCWO and the group of other ACTs significantly increased sputum volume (during session and 1 h after intervention) (after values 52.0±16.9 mL *vs* 62.5±18.9 mL *vs* 77.0±10.6 mL; p=NR) and improved TCCx (7.225±1.186×10^6 mg *vs* 8.490.±2.771×10^6 mg *vs* 10 517±2514.9×10^6 mg; p=NR), neutrophils (59.9±10.1% *vs* 62.0±9.9% *vs* 78.1±6.8%; p=NR), lymphocytes (11.9±4.9% *vs* 13.5±3.9% *vs* 7.2±2.7%; p=NR), macrophages (35.6±15.2% *vs* 31.2.±7.5 *vs* 32.2±10.8; p=NR), MRC (MD −0.7±0.8 *vs* −0.5±1.1 *vs* 1.0±0.8; p=NR), BCSS (−2.7±1.8 *vs* −0.2±1.8 *vs* 3.1±1.4; p=NR), CAT (−8.0±4.0 *vs* −0.4±6.8 *vs* 9.9±3.6; p=NR), C-reactive protein (−1.0±0.8 *vs* −0.0±0.9 *vs* 1.3±1.1; p=NR) when compared to no ACT. HFCWO significantly improved sputum volume, neutrophils, macrophages, CAT, C-reactive protein, FVC (MD 192.1±80.9 mL *vs* 54.5±153.7 mL *vs* −37.0±35 mL; p=NR) and FEV_1 (135.5±93.4 mL *vs* −94.0±128.3 mL *vs* −21.0±30.7 mL; p=NR) when compared with other ACTs and no ACTs. HFCWO significantly improved white cells (MD −673.8±1093.6×10^3 cells *vs* 957.0±915.7×10^3 cells; p=NR), red cells 73.0±202.5×10^6 cells *vs* −82.0±62.3×10^6 cells; p=NR), TLC (−657.0±1088.9 mL *vs* 46.0±95.6 mL; p=NR), RV (−580.0±1118.1 mL *vs* 65.0±58.5 mL; p=NR), MIP (9.8±10.1 cmH_2O *vs* −4.1±2.5 cmH_2O; p=NR) and MEP (6.5±7.2 cmH_2O *vs* −8.3±3.9 cmH_2O; p=NR) when compared to no ACT.
Anand *et al.* [84] 2014, India	<4 weeks	RCT	NR	ACBT *vs* other ACTs (GAD, percussion, pressure-vibration, active bilateral respiratory exercises)	Single session 30 min	Wet sputum volume (mL) PEF (NR)	n=30 (NR) Age=NR FEV_1=NR Daily sputum=NR (inclusion criteria of 10–150 mL·day^{-1})	ACBT (192±62 *vs* 210±64) and other ACTs (192±44 *vs* 288±49) significantly improved PEF from pre- to post-treatment (p<0.001).
Semwal *et al.* [97] 2015, India	<4 weeks	RCX	Clinical stability	Autogenic drainage *vs* O-PEP (Acapella)	Single session 20–30 min	Wet sputum weight (g)# Wet sputum volume (mL) S_{pO_2} (%) Respiratory rate (cpm) PEF (mL) Modified Borg Scale dyspnoea (points)	n=30 (33% F) Age (male)=46±9 years Age (female)=49±10 years FEV_1=NR Daily sputum=NR (inclusion criteria→history of productive cough)	There were no statistically significant differences between autogenic drainage and O-PEP (Acapella).

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Ramos *et al*. [98] 2015, Brazil	<4 weeks	RCX	Clinical stability	GAD+FET (huffing) *vs* GAD+coughing *vs* GAD+ percussion+ coughing *vs* control (coughing)	Single session 2 periods of 20 min	Percentage of solids (dry/wet weight ratio (%)) Mucus viscosity (poise) Mucus elasticity (dynes·cm^{-1})	n=22 (73% F) Age=51 years (range 18–76 years) FEV_1=NR Daily sputum (mL): GAD+FET=27.4±8.6 GAD+percussion+ coughing=26.6±9.7 GAD+coughing=25.8±8.6 Coughing=24.9±10.7	The percentage of solids content at 60 min was significantly greater following GAD+ percussion+coughing compared to control (p=0.01). At 90 min, a significant increase was found in the percentage of solids content obtained following GAD+percussion+coughing (p=0.07) and GAD+FET (p=0.03) compared to control. At 90 min, a significant increase was found in the percentage of solids content obtained following GAD+percussion+coughing (p=0.01) and GAD+FET (p=0.04) compared to GAD+coughing. GAD+percussion+coughing obtained significantly greater sputum samples at 60 and 90 min compared to coughing (p=0.02 and p=0.01, respectively) and GAD+ coughing (p=0.04). GAD+coughing (p=0.01), GAD+percussion+ coughing (p=0.001 and GAD+FET (p=0.001) obtained significantly greater elastic sputum samples in comparison with coughing at 60 min, but only GAD+ percussion+coughing (p=0.001) and GAD+ FET (p=0.005) obtained significantly greater elastic sputum samples at 90 min.
Herrero-Cortina *et al*. [99] 2016 Spain	<4 weeks	RCX	Clinical stability	Autogenic drainage *vs* ELTGOL *vs* O-PEP (TPEP)	Three non-consecutive sessions in the same week 40 min	Wet sputum weight (g)[#] LCQ (points) FVC (L) FEV_1 (L) $FEF_{25-75\%}$ (L·s^{-1}) Patients feedback (Likert scale)	n=31 (71% F) Age=60±18 years FEV_1=63±23% pred Daily sputum: 21 mL (IQR 15.8–36.5 mL) 21.1 g (IQR 15.3–35.6 g)	Autogenic drainage and ELTGOL significantly increased sputum expectoration (during intervention) over O-PEP (median difference for autogenic drainage *vs* TPEP 3.1 g (95% CI 1.5–4.8 g); ELTGOL *vs* TPEP 3.6 g (95% CI 2.8–7.1 g)). Autogenic drainage, ELTGOL and TPEP significantly reduced the need for expectoration over 24 h after intervention compared to baseline assessment (median difference for autogenic drainage *vs* baseline 10.0 g (95% CI −15.0– −6.8 g); ELTGOL *vs* baseline −9.2 g (95% CI −14.2– −7.9 g); TPEP *vs* baseline −6.0 g (95% CI −12.0– −6.1 g)). Autogenic drainage (median difference 0.5, 95% CI 0.1–0.5), ELTGOL (0.9, 95% CI 0.5–2.1) and TPEP (0.4, 95% CI 0.1–1.2) significantly increased the total LCQ score from pre- to post-intervention.

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
AbdelHalim *et al.* [80] 2016, Egypt	<4 weeks	RCT	Acute exacerbation	ACBT+GAD *vs* other ACTs (GAD+ percussion+ breathing control)	Twice daily for 2 weeks 15–20 min	Wet sputum volume (mL) FVC (% pred) FEV_1 (% pred) FEV_1/FVC (NR) MMEF (% pred) LCQ (points) mMRC dyspnoea (points) P_{AO_2} (mmHg) P_{aO_2} (mmHg) P_{aCO_2} (mmHg) P_{A-aO_2} gradient	n=30 (33% F) Age=52±15 years FEV_1 (% pred): ACBT=57±14 Other ACTs=54±20 Daily sputum (mL): ACBT=43±9 Other ACTs=44±9	ACBT+GAD significantly improved dyspnoea (pre-intervention 2.9 *vs* post-intervention 1.6; p<0.001). Other ACTs significantly improved dyspnoea (pre-intervention 2.8 *vs* post-intervention 2.0; p<0.001). ACBT+GAD significantly increased FVC (pre-intervention 70.7% *vs* post-intervention 74.0%; p<0.001) and MMEF (pre-intervention 31.6% *vs* post-intervention 36.7%; p<0.001). Other ACTs significantly increased FEV_1 (pre-intervention 54.1% *vs* post-intervention 56.7%; p<0.04) and MMEF (pre-intervention 32.3% *vs* post-intervention 38.9%; p<0.001). ACBT+GAD significantly reduced P_{aCO_2} (pre-intervention 52.5 mmHg *vs* post-intervention 47.0 mmHg; p<0.001) increased P_{aO_2} (pre-intervention 73.0 mmHg *vs* post-intervention 80.8 mmHg; p<0.001) and P_{AO_2} (pre-intervention 84.0 mmHg *vs* post-intervention 90.9 mmHg; p<0.001). Other ACTs significantly reduced P_{aCO_2} (pre-intervention 55.9 mmHg *vs* post-intervention 49.7 mmHg; p=0.002), increased P_{aO_2} (pre-intervention 60.7 mmHg *vs* post-intervention 69.1 mmHg; p<0.001) and P_{AO_2} (pre-intervention 79.8 mmHg *vs* post-intervention 87.6 mmHg; p=0.002). ACBT+GAD presented significantly higher values of P_{aO_2} (80.9±13.0 mmHg *vs* 69.1±17.0 mmHg; p=0.043), total LCQ score (14±3 *vs* 12±4.2; p=0.019) and lower P_{A-aO_2} gradient (10.1±7.3 *vs* 18.5±10.0; p=0.014) and sputum volume (14.7±4.0 mL *vs* 19.0±5.7 mL; p=0.023) when compared with the other ACTs post-intervention.
Silva *et al.* [100] 2017, Australia	<4 weeks	RCX	Clinical stability	O-PEP (Lung Flute) *vs* O-PEP (Flutter)	Single session maximum of 30 min (+30 min rest)	Wet sputum weight (g)[#] Dry sputum weight (g)[#]	n=40 (73% F) Age=63±16 years FEV_1=66±30% pred Daily sputum=NR (inclusion criteria→productive of >25 mL·day^{-1})	O-PEP (Flutter) significantly increased wet sputum weight (during intervention) over O-PEP (Lung Flute) (5.1±6.3 g *vs* 3.7±3.4 g; MD 1.3 g; 95% CI 0.2–3.0 g; p=0.038). O-PEP (Lung Flute) significantly increased wet sputum weight (during 30 min post-intervention, not including session) over O-PEP (Flutter) (2.0±3.0 g *vs* 0.7±0.7 g; MD 1.3 g; 95% CI 0.5–2.2 g; p<0.001).

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
De Souza *et al.* [50] 2019, Brazil	<4 weeks	RCX	Clinical stability	O-PEP (Flutter) *vs* thoracic compression *vs* no ACTs (control)	Single session 30 min (+30 min rest)	Wet sputum weight (g) Dry sputum weight (g) Sputum adhesiveness (Lopez-Vidriero scale) Sputum purulence (Murray scale) Impulse oscillometry: R5 ($kPa{\cdot}L^{-1}{\cdot}s^{-1}$)# R20 ($kPa{\cdot}L^{-1}{\cdot}s^{-1}$) R5–R20 ($kPa{\cdot}L^{-1}{\cdot}s^{-1}$) X5 ($kPa{\cdot}L^{-1}{\cdot}s^{-1}$) AX ($kPa{\cdot}L^{-1}$) Fres (Hz) S_{pO_2} (%) mMRC dyspnoea (points)	n=20 (NR) Age=57±14 years FEV_1=60±0.28% pred Daily sputum=NR	O-PEP significantly increased wet (p=0.039) and dry (p=0.005) sputum compared to no ACTs (control). O-PEP significantly decreased total airway resistance (p=0.04), peripheral resistance (p=0.005) and reactance area (p=0.001) from pre- to post-treatment. Thoracic compression significantly decreased peripheral resistance (p=0.001) and reactance area (p=0.001) from pre- to post-treatment.
Santos *et al.* [86] 2020, Australia	<4 weeks	RCX	Clinical stability	ACBT *vs* O-PEP (bottle PEP) *vs* no ACT (control)	Single session 30 min (+60 min rest)	Wet sputum weight (g)# Dry sputum weight (g) FVC (L; % pred) FEV_1 (L; % pred) FEV_1/FVC (L; % pred) $MEF_{25-75\%}$ (L; % pred) ACT cycles (n) Coughs (n) Dyspnoea scale (0–10 points) Fatigue scale (0–5 points) S_{pO_2} (%) Heart rate (bpm) Treatment cycles	n=35 (68% F) Age=75±8 years FEV_1=72.0±20.0% pred Daily sputum=NR (inclusion criteria→daily sputum production)	ACBT and O-PEP significantly increased wet sputum weight during active intervention (ACBT *vs* no ACT MD 1.6 g, 95% CI 0.8–2.3 g; O-PEP *vs* no ACT MD 1.0 g, 95% CI 0.3–1.6 g) and during the total time of the session (30 min intervention+60 min rest) (ACBT *vs* no ACT MD 1.3 g, 95% CI 0.2–2.4 g; O-PEP *vs* no ACT MD 2.1 g, 95% CI 0.9–3.3 g).# ACBT and O-PEP significantly increased dry sputum weight during active intervention (ACBT *vs* no ACT MD 0.04 g, 95% CI 0.01–0.07 g; O-PEP *vs* no ACT MD 0.03 g, 95% CI 0.01–0.05 g) and during the total time of the session (30 min intervention+60 min rest) (ACBT *vs* no ACT MD 0.03 g, 95% CI 0.01–0.05 g; O-PEP *vs* no ACT MD 0.05 g, 95% CI 0.01–0.10 g) when compared to no ACT. ACBT significantly improved dyspnoea, S_{pO_2} and fatigue but increased heart rate (all p<0.005) compared to no ACT. O-PEP significantly increased FVC (%), heart rate, fatigue and improved dyspnoea and S_{pO_2} (all p<0.005) compared to no ACT. ACBT required significantly more treatment cycles when compared to O-PEP (MD −2.5; 95% CI −3.1– −2.0; p<0.05).

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
De Oliveira *et al.* [101] 2001, Brazil	⩾4 weeks	RCT	Clinical stability	GAD+manual percussion and/or vibration *vs* O-PEP (Flutter)	Twice a week for 4 weeks 60 min session (10 min of inhalation +20 min of ACT +30 min of rest)	Wet sputum weight (g) Dry sputum weight (g) PEF ($L \cdot min^{-1}$) Respiratory rate (cpm) S_{pO_2} (%) Heart rate (bpm)	n=10 (60% F) Age=59±14 years FEV_1=58±18% pred Daily sputum=NR	O-PEP significantly decreased oxygen saturation from pre-intervention to week 3 (95±2% *vs* 93±3%; p<0.05). Cardiac frequency also showed a statistically significant diminution in weeks 1 and 4 with O-PEP (77±9 bpm *vs* 72±7 bpm; 79±12 bpm *vs* 75±10 bpm; both p<0.05).
Thompson *et al.* [102] 2002, UK	⩾4 weeks	RCX	Clinical stability	ACBT *vs* O-PEP (Flutter)+FET Both groups could use GAD if necessary	Twice daily for 4 weeks Until there was no further sputum to expectorate (29 ±17 min for ACBT+FET *vs* 26 ±11 min for O-PEP+FET)	Wet sputum weight (g) PEF ($L \cdot min^{-1}$) FEV_1 (L) FVC (L) CRQ (points) Borg scale dyspnoea (points) Session length (min)	n=22 (64% F) Age (years): ACBT=68±16 O-PEP=59±8 FEV_1 (% pred): ACBT=70±42 O-PEP=67±38 Daily sputum=NR (inclusion criteria→productive bronchiectasis)	There was a statistically significant improvement in FEV_1 with the O-PEP[#], but this did not achieve a clinically meaningful change (data NR).
Murray *et al.* [77] 2009, UK	⩾4 weeks	RCX	Clinical stability	O-PEP (Acapella) *vs* no ACT	Twice daily for 3 months 20–30 min per session	LCQ (points)[#] Wet sputum volume (mL) FVC (L; % pred) FEV_1 (L; % pred) FEV_1/FVC (L; % pred) $FEF_{25-75\%}$ ($L \cdot s^{-1}$; % pred) MIP/MEP (cmH_2O; % pred) ISWT (m) Sputum bacterial load ($cfu \cdot mL^{-1}$) SGRQ (points) Exacerbations (n)	n=20 (40% F) Age=73 years (IQR 72–77) FEV_1=75.7% pred (IQR 48.3–98.1% pred) Daily sputum=5 mL (IQR 1.2–15 mL)	O-PEP significantly improved the total score of LCQ (median 1.3, IQR −0.2–3.2 *vs* median 0, IQR −1.5–0.5; p=0.002) compared to no ACT.[#] O-PEP significantly increased the 24-h sputum volume (median 2 mL, IQR 0–6 mL *vs* median −1 mL, IQR −5–0 mL; p=0.02), ISWT (40 m; 15–80 m *vs* 0 m; −10–20 m; p=0.001) and SGRQ score (7.8; −1.0–14.5 *vs* −0.7; −2.3–0.0; p=0.005) compared to no ACT.
Senthil *et al.* [85] 2015, India	⩾4 weeks	RCT	NR	ACBT *vs* ACBT +O-PEP (Acapella)	Once daily for 4 weeks 30 min	FVC (L) FEV_1 (L)	n=30 (NR) Age=55±3 years FEV_1=NR	FEV_1 significantly increased with ACBT (pre-intervention 2.31±0.42 L *vs* post-intervention 2.42±0.43 L; p=0.029) and ACBT+O-PEP (pre-intervention 2.33±0.73 L *vs* post-intervention 2.85±0.66 L; p=0.000). FVC significantly increased with ACBT+O-PEP (pre-intervention 3.22±0.67 L *vs* post-intervention 3.41±0.97 L; p=0.01).

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TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Tambascio *et al.* [103] 2017, Brazil	⩾4 weeks	RCX	Clinical stability	O-PEP (Flutter) *vs* Sham O-PEP (sham Flutter)	Once daily for 4 weeks 30 min	Sputum adhesiveness (points) Mucociliary transport (relative velocity) Sputum displacement (cm) Contact angle (°) Sputum purulence (Murray scale) Sputum cytology (n° inflammatory cells ($\times10^6$)/eosinophils (%)/neutrophils (%)/macrophages (%)/lymphocytes (%) Microbiology (bacterial isolation and colony-forming units)	n=17 (59% F) Age=55±14 years FEV_1=42±17% pred Daily sputum=NR (inclusion criteria→⩾0.5 mL of respiratory secretion)	O-PEP significantly increased sputum displacement (pre-intervention 9.9±3.1 cm *vs* post-intervention 14.0±5.7 cm; p=NR) and decreased sputum contact angle (pre-intervention 26.5±3.2° *vs* post-intervention 22.8±3.6°; p=NR).
Üzmezoglu *et al.* [88] 2018, Turkey	⩾4 weeks	RCT	Clinical stability	ACBT+GAD *vs* O-PEP (Flutter)	Twice daily for 4 weeks 15–20 min	Sputum production (four category changes) SF-36 (points) mMRC scale dyspnoea (points) Borg scale dyspnoea (points) FVC (% pred) FEV_1 (% pred) FEV_1/FVC (NR) PEF (% pred) Presence of cough, wheezing, fatigue and loss of appetite	n=40 (55% F) Age=54±11 years FEV_1=70.8±28.2% pred to 60.6±23.4% pred Daily sputum (ACBT)=14 participants (72%) Daily sputum (Flutter)=12 participants (60%)	O-PEP significantly improved SF-36 scores in general health (40.0±21.6 *vs* 35.6±27.9; p=0.048) and pain (86.7±17.8 *vs* 69.9±25.4; p=0.011) when compared to ACBT+GAD, post-intervention. O-PEP significantly improved SF-36 scores in pain (p=0.005) and physical state assessment (p=0.005) and dyspnoea (p=0.012 evaluated by mMRC; p=0.006 evaluated by Borg scale) from pre- to post-treatment. ACBT+GAD significantly improved dyspnoea (p=0.002 evaluated by mMRC) and reduced the number of patients presenting with cough (pre-treatment n=14; post-treatment n=4; p=0.002). O-PEP significantly reduced the number of patients presenting with fatigue (pre-treatment n=12; post-treatment n=4; p=0.021). ACBT+GAD (n=4; p=0.004) and O-PEP (n=5; p=0.003) significantly increased the number of patients with greater sputum production from baseline.

Continued

TABLE 3 Continued

Study	Intervention length	Study design	Clinical status	ACTs applied	Prescription of therapy per technique	Outcome measures (units)	Patient characteristics	Key findings
Muñoz *et al.* [76] 2018, Spain	⩾4 weeks	RCT	Clinical stability	ELTGOL *vs* upper limb stretches ("placebo" intervention)	Twice daily for 12 months 15 min if only one lung was affected or 30 min when both lungs were affected	Wet sputum volume (mL)# FEV_1 (L; % pred) 6-min walk test (m) SGRQ (points) LCQ (points) Exacerbations (n in 12 months) Time first exacerbation (days) Erythrocyte sedimentation rate (mm) Leukocytes ($\times 10^3 \cdot \mu L^{-1}$) Neutrophils (%) C-reactive protein ($mg \cdot dL^{-1}$) Fibrinogen ($mg \cdot dL^{-1}$)	n=44 (52% F) Age (years): ELTGOL=63±13 Upper limb stretches=64±8 FEV_1 (% pred): ELTGOL=58±23 Upper limb stretches= 65±28 Daily sputum (mL): ELTGOL=20 (IQR 15–40) Upper limb stretches=15 (IQR 15–20)	ELTGOL significantly increased sputum volume (obtained 24 h post-intervention) after the first session (median 17.5 mL; 95% CI 10.0–26.2 mL *vs* −5 mL; 95% CI −11.2–0.0 mL; p<0.001) and at month 12 (median 10.0 mL; 95% CI −5.0–25.0 mL *vs* 0.0 mL; 95% CI −10.0–3.7 mL; p=0.015) over upper limb stretches.# ELTGOL significantly improved the total LCQ score (−1.96; 95% CI 0.2–3.8 *vs* −2.0; 95% CI −2.8– −1.2; p<0.001), SGRQ (−6.8; 95% CI −15.1–1.5 *vs* 11.4; 6.9–15.9; p<0.001) and reduced the number of exacerbations (median −0.8; 95% CI −1.5– −0.1 *vs* 0.35; 95% CI −0.5–0.35; p=0.042) when compared to upper limb stretches.
Livnat *et al.* [104] 2021, Israel	⩾4 weeks	RCT	Clinical stability	O-PEP (Aerobika) *vs* autogenic drainage	Once daily for 4 weeks 15–20 min	Lung clearance index (points)# Sputum quantity (mL; self-reported) Sputum purulence scale (points) FEV_1 (% pred) Quality of Life Questionnaire-Bronchiectasis (points)	n=51 (64% F) Age (years): O-PEP=66±13 Autogenic drainage=67±13 FEV_1 (% pred): O-PEP=81±18 Autogenic drainage=96±18	Patients performing autogenic drainage reported a significantly higher sputum reduction than those using O-PEP (less sputum n=6 (24%) *vs* n=12 (52%); more sputum n=19 (76%) *vs* n=11 (48%); p=0.044). Autogenic drainage significantly increased social functioning score (pre-intervention median 50 (IQR 21–67) *vs* post-intervention 58 (IQR 37–76); p=0.04). Autogenic drainage significantly increased health perceptions score (pre-intervention 33 (IQR 25–58) *vs* post-intervention 42 (IQR 33–65); p=0.04).

Data are presented as mean±SD, unless otherwise stated. Studies have been classified according to the intervention length (<4 weeks or ⩾4 weeks). Table does not include patient preference, barriers and enablers, as these are presented in Question 5. ACBT: active cycle of breathing techniques; ACT: airway clearance technique; AX: integral of reactance between 5 Hz and resonant frequency; BC: breathing control; BCSS: Breathlessness, Cough and Sputum Scale; bpm: beats per min; CAT: COPD Assessment Test; cpm: cycles per min; CRQ: Chronic Respiratory Questionnaire; dR/dF: dependency of resistance as a function of oscillation frequency; ELTGOL: slow expiration with the glottis opened in the lateral posture; F: female; f0: resonant frequency; FEF: forced expiratory flow at 25–75% of forced vital capacity; FET: forced expiration technique; FEV_1: forced expiratory volume in 1 s; FRC: functional residual capacity; Fres: frequency response; FVC: forced vital capacity; GAD: gravity-assisted drainage; HFCWO: high-frequency chest wall oscillation; HS: hypertonic saline; IC: inspiratory capacity; IMT: inspiratory muscle training; IS: isotonic saline; ISWT: incremental shuttle walk test; LCQ: Leicester Cough Questionnaire; MD: mean difference; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; MMEF: maximal mid-expiratory flow; mMRC: modified Medical Research Council; NR: not reported; O-PEP: oscillatory positive expiratory pressure; P_{AO_2}: alveolar oxygen tension; P_{A-aO_2}: alveolar–arterial oxygen tension difference; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension; PEF: peak expiratory flow; PEP: positive expiratory pressure; QoL-B: Quality of Life Questionnaire-Bronchiectasis; R5: resistance at 5 Hz; RCT: randomised controlled trial; RCX: randomised crossover trial; RV: residual volume; SF36: 36-item Short Form Survey; SGRQ: St George Respiratory Questionnaire; S_{pO_2}: peripheral oxygen saturation; TCCx: total cell count; TLC: total lung capacity; TPEP: temporary positive expiratory pressure; VC: vital capacity; X5: reactance at 5 Hz. #: reported as primary outcomes in the study.

risk of exacerbations. These findings support previously published clinical recommendations for the use of ACTs as part of bronchiectasis management in adults [2, 11–14]. However, there is no evidence about the optimal frequency or number of ACT sessions.

- Randomised controlled trials have assessed a variety of ACTs, with O-PEP devices (mainly *via* Flutter and Acapella), GAD and ACBT being the most commonly studied techniques. The existing literature does not demonstrate superiority of one technique over another but supports the use of ACTs.
- Wet sputum weight or volume were the most commonly used outcome measures. The ACTs increase the expectorated sputum during or following a single session of ACTs. Despite being frequently used in clinical practice, the interpretation of sputum changes is ambiguous.
- To date, there are no studies that have investigated the effect of ACTs on mortality or changes in disease severity using the bronchiectasis severity index or FACED. There are also no studies providing a health economics estimation for ACTs in bronchiectasis.

Question 4: Recommendations for research

- Investigate the effectiveness of ACTs using large-scale and prospective randomised controlled trials, particularly during acute exacerbations.
- Assess the effect of ACTs in the long term, particularly in reducing exacerbations, hospitalisations, bronchiectasis disease severity and mortality. A follow-up of at least 6 months needs to be implemented in these studies.
- Assess the cost-effectiveness of ACTs based on direct and indirect costs, such as savings on medications and hospitalisation compared to therapist time and equipment expenses.
- Consider including patient adherence and disease-specific HRQoL questionnaires as a primary or secondary outcome in all clinical trials.
- Include alternative assessment tools and outcomes for the ACTs studies, such as impulse oscillometry for pulmonary function, lung clearance index for ventilation impairment, magnetic resonance or high-resolution computed tomography imaging and airway inflammatory markers or changes in airway microbiota.
- Identify the optimal frequency of ACTs and factors that enhance accessibility to physiotherapy, such as home techniques and telehealth.

Question 5a: What are the experiences and perceived impact of ACTs on adults with bronchiectasis?

Identifying patients' beliefs on the use of ACTs is essential for effective implementation in the long term, a necessary step to improve clinical outcomes in bronchiectasis. To support patient-reported strategies for optimising treatment implementation, we analysed crossover studies and parallel or crossover randomised controlled trials, which explored patients' perspective of ACTs and how this treatment impacts patients' daily life.

Evidence overview

A total of 22 studies met the inclusion criteria (supplement 1, figure S6); nine studies were included for examining participant experience and impact on symptoms [79, 82, 89–91, 93, 105–107], 17 studies examined preference for techniques or adherence [76, 78, 82, 83, 86, 87, 89, 90, 97, 99, 100, 102, 104, 105, 107–109] and one study explored participant satisfaction with ACTs [110]. Two studies were conducted in people experiencing an acute exacerbation [78, 79], while the remaining studies were in clinically stable individuals [82, 83, 86, 87, 89, 90, 93, 97, 99, 100, 102, 104, 105, 107] or the clinical state was unspecified [106, 108–110]. The instruments used to evaluate patient satisfaction and perceived experience were an adapted questionnaire that was validated in cystic fibrosis [110], visual analogue scales [91, 93, 107], Likert scales [79, 82, 86, 90, 106], tools developed by the authors [79, 82, 86, 90, 106] or the instrument was unspecified [89]. Adherence rates were measured by diary card recording [76, 104], while assessment of patients' preference was heterogeneous and included Likert scales and standard questionnaires [78, 82, 86, 87, 99, 100, 102, 108], visual analogue scales [97, 107] and asking the subject to indicate the preferred ACT [89, 90], or were not reported [105, 109].

There are mixed reports related to patient satisfaction, preference, experience related to symptoms and perceived impact of ACTs (table 4). Three studies focused on patient satisfaction after a single ACT session or following an unclear duration. A cross-sectional study [110] evaluated patient satisfaction for a mix of ACTs that did not require equipment (manual-assisted or self-administered) and O-PEP. Efficacy, convenience, comfort, satisfaction and cost-effectiveness were rated highly for all techniques. It was proposed that conventional chest physiotherapy (GAD, manual vibrations or percussions) may be easy to

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TABLE 4 Patient satisfaction, preference and perceptions of ACTs

Study authors	Study design	Patients (n)	Daily sputum quantity	ACTs applied	Prescription of therapy per technique	Tools applied to evaluate patient satisfaction, preference and perceptions	Key findings
Thompson *et al.* [102] 2002, UK	RCX	17	NR	ACBT-FET O-PEP (Flutter)+FET (Both groups could use GAD if necessary)	25–30 min, twice daily for 4 weeks	Investigator-derived questionnaire for patient preference	65% preferred O-PEP (Flutter), 18% preferred ACBT-GAD, 18% had no preference.
Tsang *et al.* [79] 2003, Hong Kong	RCT	15	NR	GAD+BC O-PEP (Flutter)+BC BC	15 min three times daily (one supervised) from day 2 to discharge	Likert scale (4-point scale) for ease of application of technique and effectiveness	No difference in ease of application between techniques. O-PEP (Flutter) perceived to be more effective than BC on each treatment day, but there was no difference between GAD and O-PEP (Flutter) on any treatment day.
Patterson *et al.* [89] 2004, UK	RCX	20	½ egg cup·day^{-1}	ACBT-GAD with vibrations IMT (80% of MIP)	Maximum of 30 min for a single session	Patient preference for each method and perceived effectiveness	20% of patients rated IMT more effective, 55% rated ACBT-GAD with vibrations more effective and 25% rated similar efficacy for both. 50% preferred IMT for home use and 50% preferred ACBT-GAD with vibrations.
Patterson *et al.* [87] 2005, UK	RCX	20	½ egg cup·day^{-1}	ACBT-GAD (2 positions) with manual percussion/ vibrations O-PEP (Acapella)	Maximum of 30 min (15 min in each position) once daily, single session per technique	Patient preference for each technique recorded using a standardised questionnaire	While a greater proportion of patients preferred Acapella (70%), this was not significant (MD 0.4, 95% CI −0.04–0.71).
Eaton *et al.* [90] 2007, New Zealand	RCX	37	NR	ACBT (seated position) ACBT-GAD O-PEP (Flutter)	Maximum of 30 min once daily, single session per technique	At final visit (conclusion of intervention), patients recorded their preferred clearance technique	ACBT-GAD was perceived as more useful in clearing secretions than ACBT (MD±SD 1.0±1.9). ACBT-GAD was associated with more discomfort (0.7±1.4) than ACBT, was more time-consuming than ACBT (1.3±1.4) and O-PEP (Flutter) (1.1±1.8) and harder to perform than O-PEP (Flutter). O-PEP (Flutter) interfered less with daily life compared to ACBT-GAD (1±1.6). All techniques were well accepted and tolerated. 44% preferred O-PEP (Flutter), 33% preferred ACBT-GAD, 22% preferred ACBT in seated position.

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TABLE 4 Continued

Study authors	Study design	Patients (n)	Daily sputum quantity	ACTs applied	Prescription of therapy per technique	Tools applied to evaluate patient satisfaction, preference and perceptions	Key findings
Patterson *et al.* [78] 2007, UK	RCT	20	NR	O-PEP (Acapella)+GAD (2 positions) Usual ACT (ACBT, autogenic drainage, PEP, Flutter or no ACT)	Maximum of 30 min once or twice daily for 10–14 days	Short questionnaire administered to those in the Acapella group determining preference of Acapella compared to their previous technique	35% preferred O-PEP (Acapella) to their usual ACT, 10% preferred their usual ACT, 5% reported no preference.
Syed *et al.* [91] 2009, India	RCX	35	NR	GAD+manual percussions/vibrations ACBT	Single occasion, every 3 h while awake for 30 min	VASs used to quantify the degree of comfort during each therapy session (anchor of uncomfortable and comfortable on a 10-cm line)	Greater comfort for ACBT.
Naraparaju *et al.* [82] 2010, India	RCX	30	>30 mL·day^{-1}	O-PEP (Acapella) IMT (80% of MIP)	Single occasion	Patient preference was recorded on an investigator-derived scale	O-PEP (Acapella) was more useful than IMT in clearing secretions (mean±SD 1.17±0.89 *vs* 0.67±1.03, p=0.03), but there was no difference in convenience, comfort or overall performance between techniques. Preference for clearing secretions was greater for O-PEP (Acapella).
Morgan *et al.* [109] 2011, Australia	RCX	12	NR	GAD O-PEP (Flutter)	Twice daily for 4 weeks	NR	Reported patient preference was greater for O-PEP (Flutter).
Paneroni *et al.* [93] 2011, Italy	RCX	22	>20 mL·day^{-1}	IPV GAD+manual percussions/vibrations with FET	30 min, single session	Patient subjective discomfort and sensation of phlegm encumbrance and dyspnoea measured with VASs (anchors of 0 to 100%)	Improvement in sensation of sputum encumbrance was similar between ACTs (p=0.48). Less discomfort with IPV compared to GAD (p=0.03).
Shabari *et al.* [83] 2011, India	RCX	40	>30 mL·day^{-1}	O-PEP (RC-Cornet) O-PEP (Acapella)	15–20 min, single session	Patient preference scale (5-point) for usefulness in clearing secretions, convenience, comfort and overall performance	RC-Cornet was preferred over Acapella on usefulness for clearing secretions, convenience, comfort and overall performance (p<0.05).
Vishteh *et al.* [105] 2011, Iran	CSS	29	NR	ACBT O-PEP (RC-Cornet)	Maximum of 30 min, single session	Seven questions for patient satisfaction	No difference in understanding the method, degree of time consumption, tediousness, need for additional training and overall satisfaction (p>0.05). Patients believed they can do physiotherapy with O-PEP (RC-Cornet) at home over ACBT and preferred this technique (25 *vs* 15, p=0.02).
Semwal *et al.* [97] 2015, India	RCX	30	NR	Autogenic drainage O-PEP (Acapella)	20–30 min, single session	VAS for patient preference	Higher preference for O-PEP (Acapella) *vs* autogenic drainage (mean VAS 6.87 *vs* 5.77).

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TABLE 4 Continued

Study authors	Study design	Patients (n)	Daily sputum quantity	ACTs applied	Prescription of therapy per technique	Tools applied to evaluate patient satisfaction, preference and perceptions	Key findings
Herrero-Cortina *et al.* [99] 2016, Spain	RCX	31	⩾15 mL·day^{-1}	Autogenic drainage (self-administered) ELTGOL (both lateral positions and respiratory physiotherapist assisted) O-PEP (TPEP, 1 cmH_2O pressure)	40 min daily for 3 non-consecutive days over 7 days	Likert questionnaire (self-administered) to indicate preference for technique at the end of each treatment arm	48.4% preferred autogenic drainage, 35.4% ELTGOL. Preference was attributed to increased sputum expectoration, independence and personal satisfaction with autogenic drainage.
Kamimura *et al.* [107] 2017, Japan	RCX	1	Expectoration of sputum >5 times·day^{-1}	O-PEP (Acapella) Tracheal vibration (at 80 Hz)	10 min twice daily for 4 weeks	Patient rating of device efficacy on a scale of 0–100, with preference for Acapella or tracheal vibration device using the VAS at opposite ends	Preference for tracheal vibration.
Silva *et al.* [100] 2017, Australia	RCX	40	25 mL·day^{-1}	O-PEP (Lung Flute) O-PEP (Flutter)	Maximum of 30 min, single session	Patient asked to state their preferred technique at final review	63% preferred Flutter, 10% preferred Lung Flute, 28% did not have a preference.
Nayak *et al.* [110] 2018, India	CSS	140	NR	GAD+manual percussions +vibrations, ACBT, FET, O-PEP (Flutter, Acapella, Quake, RC-Cornet)	NR	Questionnaire consisting of 21 questions including technique efficacy, convenience, comfort, satisfaction and cost-effectiveness	GAD+percussion+vibrations: efficacy 97%, convenience 95.7%, comfort 100%, satisfaction 95.7%, cost-effectiveness 93.7%. ACBT: efficacy 100%, convenience 100%, comfort 100%, satisfaction 100%, cost-effectiveness 100%. FET: efficacy 100%, convenience 100%, comfort 100%, satisfaction 100%, cost-effectiveness 95.8%. O-PEP: efficacy 100%, convenience 100%, comfort 100%, satisfaction 95.7%, cost-effectiveness 100%.
Muñoz *et al.* [76] 2018, Spain	RCT	44	⩾10 mL·day^{-1}	ELTGOL (affected lung in inferolateral position) +chest and abdominal compressions during expiration Repetitive upper limb stretches (biceps, triceps, deltoids, pectoralis major, latissimus dorsi)	15 min if one lung was affected or 30 min if both lungs were affected twice daily for 12 months	Adherence measured at each visit with a physiotherapist by diary card (good adherence=80% or more sessions were performed)	Adherence of ⩾80% was recorded for all participants in the ELTGOL group and 75% of the repetitive upper limb stretches.
Nicolini *et al.* [108] 2019, Italy	RCT	60	NR	HFCWO (SmartVest, 13–15 Hz with pressure 2–5 cmH_20) HFCWO (RespIn 11, focused pulse)	NR	Likert scale (5-point) to evaluate patient preference	Higher score for patient preference with RespIn 11.

Continued

TABLE 4 Continued

Study authors	Study design	Patients (n)	Daily sputum quantity	ACTs applied	Prescription of therapy per technique	Tools applied to evaluate patient satisfaction, preference and perceptions	Key findings
Santos *et al*. [86] 2020, Australia	RCX	35	Reported daily sputum	ACBT O-PEP (Bottle PEP) No therapy	30 min per technique, single session	Likert scales measuring patient perceptions of usefulness, ease of intervention in clearing secretions, ease of performing interventions, discomfort when performing interventions, if interventions were tiring, ease of understanding instructions and if perceived worthwhile to perform recorded 60 min post-intervention period Likert scale for which technique they preferred	ACBT was more useful in clearing secretions than O-PEP (Bottle PEP) (MD −0.6, 95% CI −0.9– −0.2). Both techniques were more useful, with greater ease of clearing secretions compared to control. Bottle PEP was easier to perform as an intervention compared to control (MD −0.3, 95% CI −0.6– −0.0). Both Bottle PEP and ACBT were more tiring compared to control, with Bottle PEP being more tiring than ACBT (MD 0.4, 95% CI 0.2–0.7). The instructions for all techniques were easy to understand, with similar levels of discomfort for all techniques. 47% preferred Bottle PEP therapy, 35% preferred ACBT, 18% reported no preference.
Barto *et al*. [106] 2020, USA	CSS	2596	NR	HFCWO (inCourage system, RespTech)	NR	Likert scale (5-point) for ratings of overall respiratory health and ability to clear secretions at baseline, 1, 3, 6, 12 months and at 6-month intervals thereafter	The proportion of patients who answered positively to the question "how would you rate your overall respiratory health" increased from 13.6% to 60.5% after 1 year (p<0.001). The proportion of patients who answered positively to the question "how would you rate your ability to clear your lungs?" increased from 13.9% to 76.6% after 1 year (p<0.001). Most improvement occurred within the first month and was sustained for 1 year.
Livnat *et al*. [104] 2021, Israel	RCT	55	NR	O-PEP (Aerobika) Autogenic drainage	15–20 min or until no further sputum was produced, daily for 4 weeks	Patient-reported adherence to therapy recorded daily by participants and reported weekly by telephone calls	Adherence to O-PEP was 88%, adherence to autogenic drainage was 87%.

ACBT: active cycle of breathing techniques; ACT: airway clearance technique; CSS: cross-sectional study; BC: breathing control; ELTGOL: slow expiration with the glottis opened in the lateral posture; FET: forced expiration techniques; GAD: gravity-assisted drainage; HFCWOL: high-frequency chest wall oscillation; IMT: inspiratory muscle training; IPV: intrapulmonary percussive ventilation; MD: mean difference; MIP: maximal inspiratory pressure; NR: not reported; O-PEP: oscillatory positive expiratory pressure; RCT: randomised controlled trial; RCX: randomised crossover trial; VAS: visual analogue scale.

learn, cost-effective and convenient for home use, but ACBT and O-PEP were highly rated due to the patient's active participation, independence, convenience and/or device portability.

Ten studies [76, 86, 87, 90, 97, 99, 102, 104, 105, 109] compared O-PEP (Acapella or Flutter) to a mix of ACTs that did not require equipment (ACBT with or without GAD and manual vibration or percussions, autogenic drainage and ELTGOL) or a control condition in individuals in a stable clinical state. A short-term study showed that most participants preferred autogenic drainage (49%) followed by ELTGOL (35%) [99]. In contrast, Semwal *et al.* [97] identified a lower preference for autogenic drainage over O-PEP (Acapella), which may be linked to the complexity of autogenic drainage. Eaton *et al.* [90] found that ACBT-GAD was considered more valuable at clearing sputum compared to ACBT, but was less preferable compared to O-PEP (Flutter). This finding was also demonstrated in three other studies, with their treatment ranging from single sessions to 4 weeks of ACBT-GAD or O-PEP (Acapella, Flutter or bottle PEP), with a greater preference for O-PEP [87, 102, 109]. In contrast, a recent study found O-PEP (bottle PEP) more useful for clearing secretions than ACBT (seated position) or no therapy, but still more tiring and with similar levels of discomfort to ACBT [86]. A different study [105] reported no difference in time consumption, tediousness or need for additional training between O-PEP (bottle PEP) and ACBT.

Two studies recruited people experiencing an acute exacerbation of bronchiectasis [78, 79]. GAD with breathing control, O-PEP (Flutter) with breathing control, and breathing control only were all perceived to be similar in ease of application. GAD and O-PEP were reported as equally effective and superior to breathing control for clearing secretions [79]. Patients in the same clinical state demonstrated a greater preference for O-PEP (Acapella) when it was newly introduced *versus* their usual ACT, with a proportion of patients still using the O-PEP device daily at 1 month follow-up [78].

Seven studies [82, 83, 89, 91, 93, 100, 106] compared a combination of techniques that were administered simultaneously (GAD, manual vibrations or percussions and/or ACBT) or equipment techniques (O-PEP, HFCWO, IPV). A preference for the RC-Cornet over Acapella, based on usefulness for clearing secretions, convenience, comfort and performance [83], and Flutter over the Lung Flute based on usefulness for clearing secretions, convenience, comfort and performance [100], was demonstrated in single studies. The Acapella was perceived to be more helpful in clearing secretions and a preferred technique compared to inspiratory muscle training [82], but ACBT-GAD was patient-reported as more effective compared to inspiratory muscle training, despite an equal patient preference for both techniques [89]. Moreover, both IPV and combination of GAD, FET or manual percussion and vibrations achieved patient-reported improvements in subjective perception of sputum expectoration [93]. Post-treatment discomfort was lower with IPV, which may be related to frequent position changes incorporated into GAD. Following a year of HFCWO use, there were improvements in subjective ratings of respiratory health and ability to clear secretions, compared to not using this treatment [106]. In the only comparison between techniques not requiring any equipment, Syed *et al.* [91] found greater comfort with ACBT with GAD compared to GAD with deep breathing and manual vibrations and percussions, which may influence compliance for the treatment.

Question 5b: What are the perceived barriers to and enablers of ACTs in adults with bronchiectasis?

A better understanding of the main factors influencing the routine use of ACTs from the perspectives of both people with bronchiectasis and healthcare professionals is crucial for designing strategies to overcome disease-specific problems and limitations arising from comorbidities and to enhance airway clearance self-management. It is also necessary for treatment adherence and the provision of patient-centred care. Therefore, a search strategy was conducted to identify studies exploring barriers and enablers of ACTs in adults with bronchiectasis.

Evidence overview

Five studies addressed barriers and/or enablers together with adherence to ACT in a mix of study designs, including cohort [111, 112] and qualitative studies [113–115] (supplement 1, figure S6). In all studies, participants were in a clinically stable state. A study for predictors of adherence measured the compliance to ACTs over a 12-month period [112]. A total of 41% of patients self-reported adherence to ACT. Those who were adherent to ACTs had a better Physical Function domain score on the Quality of Life-Bronchiectasis questionnaire (QoL-B) compared to those who were nonadherent (mean±SD: 42±28 *versus* 29±26, respectively) [112]. Higher adherence to ACT was associated with lower Treatment Burden domain score on QoL-B (regression coefficient (95% CI): −15.46 (−26.54 to −4.37)) and lower Respiratory Symptoms domain score on QoL-B (regression coefficient (95% CI): −10.77 (−21.45 to −0.09)) [112]. This cohort who reported using ACBT (53%) or O-PEP (Acapella) (61%) also completed a modified Beliefs about Medicine questionnaire specific to ACTs. In determining independent predictors of

adherence, those adherent to ACT (41%) were older (OR (95% CI): 2.94 (2.74–3.18)), based on a 10-year increase in age, and believed their ACT was necessary (OR (95% CI): 1.3 (1.1–1.53)). Those with fewer concerns about treatment were also more likely to be adherent to ACTs [111].

Three qualitative studies with patients and clinicians, including respiratory physicians, respiratory physiotherapists and nurses, described barriers and enablers to ACTs [113–115]. From the patient perspective, identified barriers were late referral to the multidisciplinary team, lack of engagement with a healthcare professional [114], lack of perceived health benefit, lack of motivation and time commitment required [113]. Enablers were working with a multidisciplinary team, which incorporates chronic disease management and support; recognition of the patient role in management and their substantial burden of disease; and a personalised approach to therapy [113, 114]. From the clinicians' perspective, barriers to management were availability of resources for ACTs, time and space restrictions, and funding. Enablers were working with the multidisciplinary team and using a chronic disease approach, as well as patient engagement [115].

Question 5: Statements

- Patient experience was generally well rated for ACTs. Preference was mainly based on the independence of technique, patient satisfaction with symptom relief and perceived efficacy or difficulty.
- Patient adherence to ACTs could be related to older age, good physical function, milder respiratory symptoms, less treatment burden and belief in treatment necessity.
- Optimal engagement of patient and healthcare professionals, adequate motivation, time and resources were some of the enablers of and barriers to ACTs.

Question 5: Recommendations for research

- Further investigate the barriers to and enablers of ACTs from the patients' and healthcare professionals' perspectives, and the factors that influence patient preference and adherence to treatment, in qualitative studies. Within this topic, examine the patients' perspectives upon changing techniques, through mixed-methods study designs.
- Investigate the barriers to and enablers of using ACTs in varying geographical locations and the underlying training and clinical experience of therapists that may be challenges to or facilitators of ACT therapy.
- Use standardised patient-reported outcome measures (PROMs) and patient-experience outcomes measures (PREMs), including patients' perceptions and preferences. To allow standardisation and comparison among studies, there are available disease-specific PROMs but there is a need to develop and validate PREMs in bronchiectasis.
- Conduct pragmatic trials, which consider the patients' preference, experience and satisfaction of ACT prescription in their design. For instance, trials investigating the effectiveness of two or more interventions could use stratified randomisation based on patient preferences, thus providing a more accurate reflection of real life.
- To facilitate clinical implementation and patient adherence, standardised tools that assess patient-related factors such as discomfort, fatigue, ease of performing ACTs, perceived impact of treatment effect and preference should be considered in ACT trials. Future studies need to embed patients', stakeholders' and public's perspectives in their design and delivery, through the patient and public involvement or study co-production.

Question 6: In adults with bronchiectasis, how should studies for ACTs be conducted to reduce the risk of bias, facilitate comparison of findings, as well as conducting future meta-analyses?

The methodological quality of studies impacts directly on the evidence that underpin clinical practice. Hence, identifying the most frequently used outcome measures, including those previously suggested as core outcomes [116], and reducing the biases in randomised trials for ACTs in bronchiectasis can lead to improvements in future studies and therefore clinical practice. To address this question, randomised trials for ACTs in bronchiectasis were analysed for risk of bias; this included all studies in Question 4. To additionally capture recently conducted work, studies that met the same criteria but were presented as conference abstracts were also included.

Evidence overview

In total, 34 randomised trials (30 full papers and four abstracts) were included (supplement 1, figure S7). The majority were crossover studies (n=21), conducted at a single centre (n=30) in European countries (n=13). A total of 915 patients with bronchiectasis were included. Gender was reported by 28 studies, with

females (n=445; 59%) being more represented than males (n=306; 41%). The mean age range was 39–75 years, while lung function (FEV_1) ranged from 29% to 96% predicted. Most studies included patients in a clinically stable condition (n=30), who had a productive cough or self-reported sputum expectoration; when reported, daily sputum volume ranged from 1.2 mL to 132 mL.

Sample size estimation was reported in 16 of the full-text studies (53%) (range 8–68 participants), with only three full-text studies including possible dropout rates (range 20–25%) in their sample size calculation. Primary end-points were clearly reported in 20 studies (59%), sputum quantity being the most frequent outcome measure used (wet sputum weight, n=8 (24%); dry sputum weight, n=2 (6%); wet sputum volume, n=7 (21%)). Sputum was collected during the ACTs intervention in seven studies (21%) and post-intervention in 10 studies (30%). Lung function, sputum quantity, HRQoL, symptoms (particularly breathlessness) and patients' feedback were other common outcomes (supplement 1, table S6).

The risk of bias of the included studies is presented in figure 2. Only one study had low risk of bias [76] and when considered across studies, none of the risk assessment domains were free of bias (supplement 1, table S7). The remaining 33 trials did not consistently report sufficient information to adequately assess risk of bias. For the domains of the Cochrane Risk of Bias Tool that could be assessed as high or low risk of bias (*i.e.* not unclear), there were six assessment domain scores that had a high risk of bias and 78 that had a low risk of bias.

On the risk of bias, allocation concealment, blinding and selective reporting were frequently classified as unclear (figure 2). Most studies failed to provide sufficient information about the method used to conceal the allocation sequence (selection bias) and most trials did not blind participants nor personnel (performance bias), although we need to acknowledge that the Cochrane tool was designed for placebo-controlled drug studies. Most studies combined objective and subjective (*e.g.* self-reported) outcome measures, which is a strong point. Nevertheless, data collection procedures for the subjective outcomes were often unclear. Selective reporting was classified as unclear risk of bias in most studies owing to insufficient information. Eight trials were included on a clinical trial registry and were classified as low risk because their results reported all primary outcomes and most secondary outcomes [76, 77, 94, 96, 99, 103, 104, 117].

Question 6: Statements

- The risk of bias amongst the studies that assess ACTs was heterogeneous, but generally unclear.
- For most studies, reporting was unclear for allocation concealment or there was selective reporting.
- Blinding of the ACTs was also limited for patients and personnel, although this is often challenging due to the nature of the intervention.
- Futures studies should be adequately powered, based on sample size estimation of one or two primary outcome measures, which have well-explored psychometrics properties. Blinding of outcome assessment and statistical analysis of the ACTs should be implemented to help minimise bias. Study reporting should be clear and following the CONSORT reporting guidelines [19].

Question 6: Recommendations for research

- Ensure that study reporting is clear and facilitates risk of bias assessment by following the CONSORT reporting guidelines. To reduce the risk of reporting bias, we recommend registering the studies in clinical trial registries or publishing their protocol in clinical journals, according to SPIRIT reporting guidelines [118].
- To minimise bias and maximise the validity of the results, trials should blind as many individuals as possible. Blinding of outcome assessment and statistical analysis of the ACTs is usually feasible and needs to be implemented. Where possible, studies should use blinding of the investigators who direct or supervise the treatment and/or the patients who perform ACTs. To achieve this last point, sham interventions, placebo-controlled designs for treatment-naive patients or cluster trials that include settings where ACTs are not part of standard care can be implemented.
- Studies should be adequately powered, based on sample size estimation of one or two primary outcome measures. Recruitment from multiple centres that can follow standardised procedures may be an optimal strategy.
- Future trials that use a core set of outcome measures, with well-explored psychometric properties according to COSMIN [119], could simplify future meta-analyses and support stronger conclusions. Current suggestions for core outcomes in bronchiectasis [116] together with exploration of core outcomes that are specific to physiotherapy [120] should be considered in future trials.

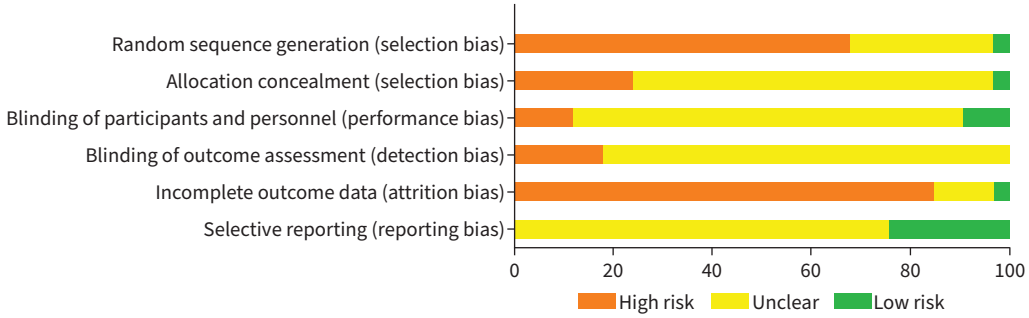

FIGURE 2 The Cochrane Collaboration's tool for assessing the risk of bias, based on reviewer's judgements for each risk of bias item and presented as percentages across all included studies (n=34).

Discussion

This task force statement panel included international experts, incorporating a wide geographical representation, and two patient representatives with bronchiectasis. Our patient representatives were invited to participate through the European Lung Foundation and were purposefully selected for their different behaviour regarding ACT treatment, *i.e.* one who was adherent to ACTs and the other who was not; thus, the statement had input from different perspectives. All statement questions were formulated with the aim of being clinically relevant, important and including the patients' perspective. Additionally, the statement results were based on systematic work.

Bronchiectasis is characterised by a dehydrated mucus layer, in part due to an abnormal increase in mucin secretion, which may play an important role in disease progression [9]. The impaired mucociliary clearance in this population has prompted the use of ACTs to enhance mucus clearance rate and reduce sputum-related symptoms. Clinical recommendations in adults with bronchiectasis consider ACTs an important strategy to disease self-management, although our understanding of their exact mechanisms of action is based on studies that are not specific to bronchiectasis.

Based on the physiology, effective ACTs are those that break the mucous layer by generating adequate mechanical stress in the airway [24] and those that move the mucus layer towards the proximal airways by enhancing peak expiratory flow [21, 22]. The ACTs that were explored in bronchiectasis by clinical trials appear to achieve these physiological principles (supplement 1, table S4), and they were effective in the short term in improving sputum expectoration, respiratory symptoms and HRQoL in patients with stable disease. Although the hydration or generation of an osmotic shock in the airways (as another mechanism of action for enhancing clearance) was outside of this task force, we need to consider the potential complementary role of hydration, humidification and mucoactive drugs in the efficacy of the ACTs [121, 122].

The ACTs that have been used in studies investigating efficacy in bronchiectasis varied. Most studies investigating the efficacy of ACTs were focused on O-PEP (table 3). It is unclear if this is due to heterogeneity of airway clearance clinical management across the world or reflects research availability. Findings suggest that ACBT and O-PEP devices are the most used ACTs in clinical practice. However, data come mainly from Australia, New Zealand, the UK and the USA; thus, these data may not reflect the clinical practice in other countries.

A 12-month long study for ACTs in bronchiectasis showed that performing ELTGOL twice daily can reduce the risk of exacerbations, improve HRQoL and reduce the impact of cough. In the short term, most ACTs in bronchiectasis enhance sputum removal, although no ACT has been shown to be more effective than another. Therefore, respiratory physiotherapists need to be aware of available ACTs and offer individual patients the opportunity to try more than one technique, considering their advantages and limitations (table 2). The choice of the most appropriate ACTs will be based on the patient's own experience and preference, including ease of performance, perceived efficacy in relieving symptoms and time consumption. When more robust evidence becomes available from pragmatic trials, clinical guidelines can inform the best approach to selecting the most appropriate ACTs for individuals with bronchiectasis.

Most studies examining the efficacy of ACTs had an unclear risk of bias in most categories and particularly in the performance, detection and reporting bias. In studies examining ACTs, blinding

participants and healthcare professionals in charge of the interventions may be challenging to establish and maintain over time. Different methods of blinding, such as use of sham interventions, blinding the assessors (masking) or recruiting previously treatment-naive patients could improve the quality of the evidence base.

EMBARC [18] and US registries [123] have previously identified important research priorities in bronchiectasis. Further studies of treatment efficacy in both a stable state and during an acute exacerbation and with larger sample sizes that include patients from different countries or regions should be conducted. Following other interventions in bronchiectasis, these studies should incorporate long-term follow-up, *i.e.* not less than 3 months for PROMs and not less than 6 months for exacerbations, hospitalisations or cost-effectiveness. Although sputum quantity is the most frequent outcome measure selected as the primary outcome in ACTs trials in bronchiectasis, its measurement properties are ambiguous [124]; thus, its interpretation is still unclear [125]. Future trials should incorporate more robust measures, such as exacerbation frequency, hospital admission and patient-reported outcomes, particularly validated disease-specific questionnaires that have a clear interpretation [126, 127]. Currently, disease-specific questionnaires are the QoL-B with 37 items and eight domain scores [128], the Bronchiectasis Health Questionnaire with 10 items and a total score [129] and the Bronchiectasis Impact Measure assessing eight domains with one item each [130]. A consensus on the essential outcomes in future trials, and a better definition, common terminology and consistent reporting in ACTs, will facilitate comparison between study findings. Importantly, the use of standardised assessments for patient preference and adherence, and patient and stakeholders' input into study design, will ensure a pragmatic approach.

Self-management and adherence are the cornerstone for the long-term management of any chronic disease, so it is crucial to identify the enablers of and barriers to using ACTs. When teaching ACTs, empowering the patient through clinical education on the benefits and limitations of the treatments, offering advice to reduce treatment burden, scheduling regular reviews and setting reminders could improve engagement and treatment adherence. This strategy also optimises the therapeutic relationship between the healthcare professionals and patients [114, 115].

This ERS statement was focused on techniques that were specifically developed to enhance mucus clearance and, based on our working definition for ACTs, techniques such as NIV or exercise were excluded. NIV is commonly evaluated in combination with other ACTs (*e.g.* FET, ACBT) in end-stage severe disease or during exacerbations [131, 132]; it has been shown to reduce breathlessness and respiratory rate, prevent airway dynamic collapse and maintain oxygenation [131, 132]. Exercise and its role in enhancing mucus clearance in bronchiectasis remains complex, because it usually does not exclude practicing ACTs. On the contrary, ACTs are often part of pulmonary rehabilitation, practically or as part of the education [133, 134]. Therefore, our ability to assess the role of exercise as an ACT is currently limited. Future work with a wider definition for ACTs and good control of potential confounders should investigate the role of NIV and exercise in airway clearance for bronchiectasis. Moreover, the role of other potential devices for ACTs in bronchiectasis, such as Simeox, Free Aspire Advanced, mechanical insufflation–exsufflation and intermittent positive pressure breathing, should also be evaluated in future studies.

Conclusion

The current evidence supports that ACTs are an effective treatment and have a crucial part in the usual care of adults with bronchiectasis. Accessibility to ACTs should be facilitated and ideally delivered by a specialist respiratory physiotherapist. However, there is limited evidence establishing the physiological effect of these techniques and current clinical practice based on geographical regions remains largely unclear. The use of data from large patient registries could help to better understand ACT practice globally. Randomised clinical trials indicate that ACTs increase the expectorated sputum, improve disease symptoms and HRQoL and reduce the risk of exacerbations, although they often have an unclear risk of bias or a poor description of their techniques. There is a great need for studies to investigate the role of ACTs during acute exacerbations of bronchiectasis and in the long term. Additionally, researchers can consider different settings, new modes of application and novel outcomes for future ACTs studies. Importantly, to achieve optimal care, study designs need to incorporate patient-centred outcomes and patient voice.

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