Supplementary material - 1

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

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Table S1. Professional background and working groups of the European Respiratory Society (ERS) Task Force panel.

Members	Speciality	Country	Working group
Beatriz Herrero-Cortina	Respiratory Physiotherapist, Co-chair	Spain	Questions 1 and 2
Annemarie Lee	Respiratory Physiotherapist	Australia	Questions 5 and 6
Ana Oliveira	Respiratory Physiotherapist	Portugal	Questions 3 and 4
Brenda O´Neill	Respiratory Physiotherapist	UK	Questions 1 and 2
Cristina Jàcome	Respiratory Physiotherapist	Portugal	Questions 5 and 6
Simone Dal Corso	Respiratory Physiotherapist	Brazil	Questions 5 and 6
William Poncin	Respiratory Physiotherapist	Belgium	Questions 1 and 2
Gerard Muñoz	Respiratory Physiotherapist	Spain	Questions 3 and 4
Deniz Inal-Ince	Respiratory Physiotherapist	Turkey	Questions 5 and 6
Victoria Alcaraz-Serrano	Respiratory Physiotherapist	Spain	Questions 1 and 2
Gregory Reychler	Respiratory Physiotherapist	Belgium	Questions 3 and 4
Angela Bellofiore	Respiratory Physiotherapist	Italy	Questions 1 and 2
Annette Posthumus	European Lung Foundation representative	Netherlands	Questions 1 and 2
Patient Representative	European Lung Foundation representative	Israel	Questions 5 and 6
James Chalmers	Respiratory Physician	UK	Questions 3 and 4
Arietta Spinou	Respiratory Physiotherapist, Co-chair	UK	Questions 3 and 4

UK, United Kingdom.

Selection criteria for the studies

Types of studies

For a representative overview of the use of airway clearance techniques (ACTs) in bronchiectasis, a wide variety of studies were considered in our general search: clinical trials (randomised controlled trials, randomised crossover trials; quasi-experimental trials); observational studies (cross-sectional, case-control and cohort studies) and qualitative studies. However, only randomised controlled trials and randomised crossover trials were included to explore the Question 4 (clinical effectiveness) and Question 5 (risk of bias and facilitate comparison between findings). Secondary studies i.e., narrative and systematic reviews, were only included in Question 1 and Question 2. This was due to the topic addressed (physiological /pathophysiological rationale), which is commonly updated using reviews and the difficulty in finding relevant original articles (failed sensitive analysis) despite re-designing the search strategy twice. More detailed information on the specific criteria used for selecting studies for each Question is available in supplementary material 2.

Participants

Our generic selection criteria were adults (≥18 years) with a diagnosis of bronchiectasis using high-resolution computed tomography and clinical symptoms without any restriction based on disease severity, daily sputum expectoration and/or clinical status (e.g., stable or exacerbation). Overlap syndromes (e.g., bronchiectasis with chronic obstructive pulmonary disease, COPD, or bronchiectasis with asthma) were included, but people with cystic fibrosis were excluded. Data from studies recruiting with different respiratory diseases (e.g., bronchiectasis and COPD) were only included if it was possible to separately extract data from people with bronchiectasis.

Specifically for the physiological/pathophysiological Questions 1 and 2, the selection criteria were extended to in vitro and animal model studies, due to the limited information on this topic in bronchiectasis. The panel also agreed to extend the population to muco-obstructive respiratory diseases (e.g., cystic fibrosis, COPD, etc.) and to healthy people for Questions 1 and 2. Additional information in methodology is available in supplementary material 2.

Intervention

Airway clearance techniques were defined as all manual or instrumental techniques and devices that were developed with the main purpose to enhance mucus clearance and manage sputum. We considered single and combined interventions, irrespective of the treatment duration (short and long-term) and based on HERMES (harmonised education in respiratory medicine for European specialists) physiotherapy curriculum [1].

As the panel agreed to focus only on the interventions specifically developed primarily to increase sputum clearance and improve the management of sputum-related symptoms; therefore, techniques with a different primary objective, such as exercise, respiratory muscle training, education of ACTs in a rehabilitation programme and non-invasive ventilation were excluded from this statement. The current evidence on exercise as a potential therapy option to enhance airway clearance is mostly based on pulmonary rehabilitation trials, where ACTs are considered an active component of the programme or an educational approach [2, 3]. Therefore, the ability to identify the effect of the ACTs undertaken by participants in addition to the exercise training (combination of aerobic and resistance training) is not currently possible. Furthermore, the measurements used in these trials do not specifically focus on sputum-related outcomes[2-4] and it is hard to comment on its use as an ACT. Moreover, ACTs may be part of the usual care of patients with bronchiectasis participating in pulmonary rehabilitation/exercise trials (similar to patients with cystic fibrosis). In these studies, since

it is unusual to consider the use of ACTs as an exclusion criterion for the trial, there is a great risk of confounding and bias.

On the other hand, most of the evidence of the role of NIV as an ACT comes from patients with cystic fibrosis, especially, in end-stage severe disease or during exacerbations. The use of NIV helps to reduce patient fatigue and respiratory rate, avoid airway dynamic collapse, and maintain oxygenation during airway clearance sessions. In fact, it is common to evaluate the effect of NIV in combination with other ACTs (e.g., forced expiratory technique, active cycle of breathing technique)[5, 6]. Therefore, the panel agreed that NIV is used as support for the ACTs and is considered more often an adjuvant to ACTs rather than an ACT in itself. Thus, the definition of ACTs we agreed on in our methods resulted in excluding NIV from our work. Finally, other airway clearance methods such as humidification, muco-active agents, other drugs and invasive methods were also outside the scope of this task force.

Search methods

The databases Medline (Ovid), EMBASE, Scopus, AMED, CINAHL, Cochrane CENTRAL and PEDro were used to identify studies. Only articles in English were selected from their inception in these databases. For Question 2, articles in other languages (e.g., French, Spanish, Portuguese, Italian) were allowed to ensure the collection of information on ACTs not developed in Anglo-Saxon countries. These studies were analysed by members of the panel who are native speakers of that language. First literature searches were conducted in November 2020 and an update search was conducted at the end of November 2021. Panel agreed to use the reference lists of all full text articles included in Question 4 for identification of potential reports for Questions 1 and 2 after search strategies failed to find relevant original articles (failed the sensitivity analysis).

Additional information about methodology applied

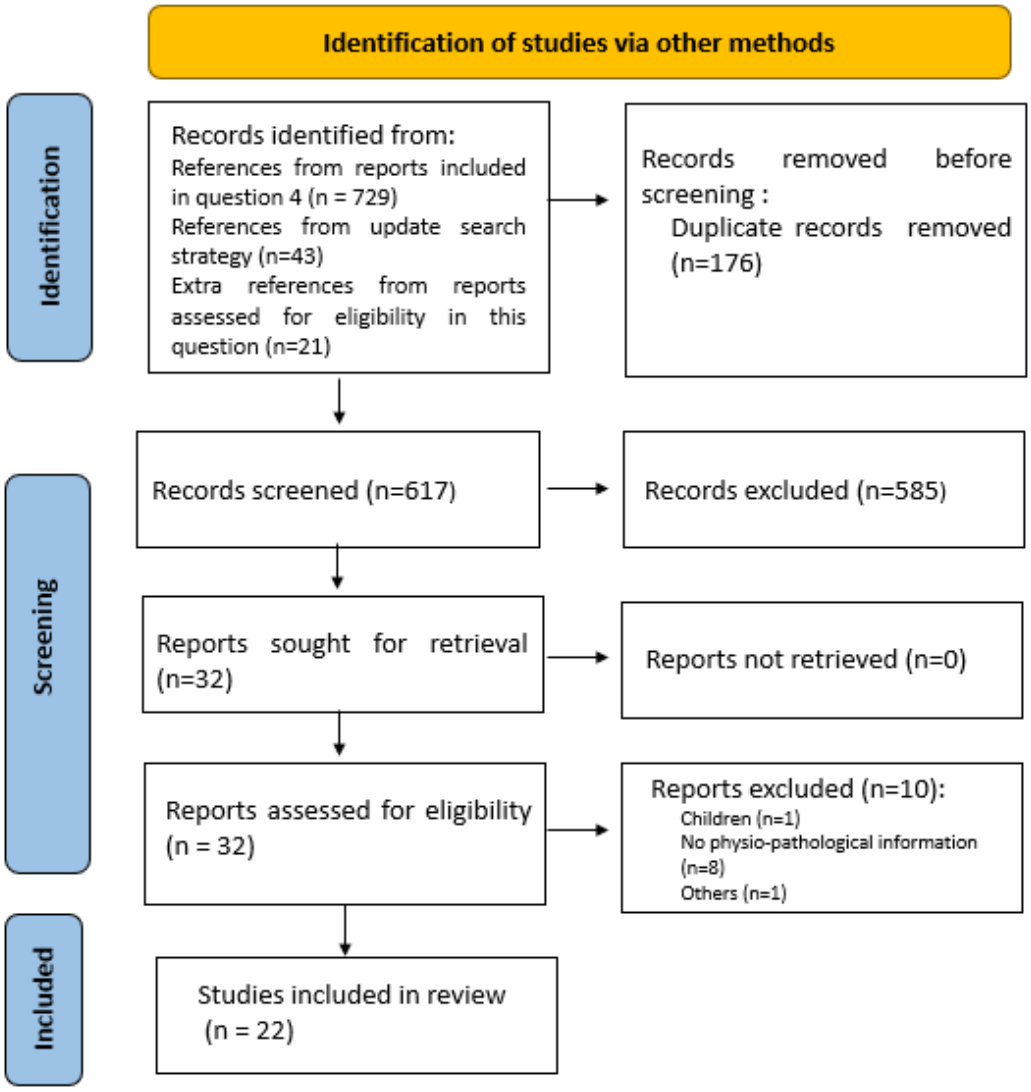


Figure S1. Literature search flow diagram for Question 1 - *What is the physiological rationale for the use for ACTs in adults with bronchiectasis?*

Table S2. Summary of the main features of studies included for Question 1 - *What is the physiological rationale for the use for ACTs in adults with bronchiectasis?*

First author, year, country	Publication type	Study design	Human / animal / in vitro / others	Population / origin of samples	Topic	Relevant findings related to this question
Mead et al.[7] 1970, USA	Secondary	Narrative review	Mathematical models	N/A	Airway physiology (interdependence / collateral ventilation)	The main function of the mechanical interdependence seems to be to promote a homogeneous air opening. The interdependence of air-space distension influences the size of air spaces, the static and dynamic stability of air spaces, the dryness of air spaces, the forces distending airways and blood vessels within lungs, and the distribution of pulmonary oedema.
Kim et al.[8] 1986, USA	Primary	Experimental	In vitro	Sputum samples with similar rheological properties than healthy and people with respiratory diseases	Airway clearance	Mucus transport by two-phase gas-liquid flow mechanism depends on the airway surface liquid layer thickness and rheological properties of fluid.
Kim et al.[9] 1987, USA	Primary	Experimental	In vitro	Sputum samples with similar rheological properties than healthy and people with respiratory diseases	Airway clearance	Effective mucus clearance can be achieved by two-phase gas-liquid flow mechanism in patients with excessive bronchial secretions with biased tidal breathing favouring the expiratory flow and that the clearance can be further promoted by changing rheological properties of mucus.
Crawford et al.[10] 1989, Australia	Primary	RXT	Human	Healthy people	Airway physiology (ventilation distribution)	The main factor of ventilation distribution below closing capacity is the inhomogeneous closure of airways subtending regions in the lung periphery that are close together.
Girod et al.[11] 1992, France	Secondary	Narrative review	In vitro	Chronic bronchitis Cystic fibrosis	Biophysical properties of mucus/sputum	Airway mucus needs appropriate rheological (viscoelasticity and spinnability) and physical surface (adhesiveness, wettability) properties

						for the protection, hydration and lubrication of the underlying airway epithelium.
Randell et al.[12] 2006, USA	Secondary	Narrative review	In vitro / human	Cystic fibrosis, CODP	Airway clearance	Summary of the structure and function of airway clearance system, its regulation and how genetic or acquired disease impacts on its functionality.
Button et al.[13] 2008, USA	Primary	CSS	In vitro / human	Bronchiectasis, Cystic fibrosis, Chronic bronchitis	Airway clearance	Airway mechanical stress stimulates mucus clearance via increases in rates of ATP release into the luminal compartment, resulting in increases in ASL hydration.
Rubin et al.[14] 2010, USA	Secondary	Narrative review	Human	Cystic fibrosis, Chronic bronchitis	Cough clearance / biophysical properties of mucus	The greatest determinant of cough transportability is not viscoelasticity but tenacity, which is the product of adhesivity and cohesivity. Treatments for ineffective cough should consider the interaction between biophysical properties and cough mechanism.
Rubin et al.[15] 2010, USA	Secondary	Narrative review	In vitro / human	Bronchiectasis, Cystic fibrosis, Chronic bronchitis PCD	Airway clearance	Summary of the composition and structure of mucus and phlegm, the mucin secretion and how is the function of the mucus clearance system. Therapies to improve mucus clearance were also described.
Tambascio et al.[16] 2013, Brazil	Primary	CSS	In vitro / human	Bronchiectasis	Biophysical properties of mucus / sputum	Respiratory secretions in individuals with bronchiectasis have poor transport properties, which manifest as reduced mucociliary transport, reduced mucus transport by cough, and higher contact angle. These features were more accentuated in the purulent samples.
Button et al.[17] 2013, USA	Secondary	Narrative review	In vitro / human	Cystic fibrosis	Airway clearance / Action mechanism of ACTs	The application of mechanical stress on airway epithelia promotes changes in ion transport and increases ASL hydration. ACTs used in CF are described based on their mechanism of action.
Rubin et al.[18] 2014, USA	Secondary	Narrative review	Human	Bronchiectasis, Cystic fibrosis, Chronic bronchitis Lung cancer, Allergy Asthma, Fucosidosis, Plastic bronchitis	Biophysical properties of mucus / sputum	Mucus production and biophysical properties of sputum change with the progression of the airway diseases. Thus, sputum samples may be a good biomarker to identify the severity of airway diseases.

Anderson et al.[19] 2015, USA	Primary	CSS	In vitro / human	Chronic bronchitis	Airway clearance	Alterations in the outcomes related to mucus concentration (e.g., extracellular nucleotide / nucleoside-dependent, airway hydration and mucin secretion rates) may slow mucociliary clearance and contribute to disease pathogenesis and loss of lung function in chronic bronchitis.
Sibila et al.[20] 2015, UK	Primary	CSS	Human	Bronchiectasis	Airway infection	Airway mucin (MUC2) levels were higher in bronchiectasis patients colonised with PPM compared with those without airway colonisation, especially in patients with P. aeruginosa. These findings suggest that airway-secreted mucins levels may play a role in the pathogenesis of airway infection in bronchiectasis
Button et al.[21] 2016, USA	Secondary	Narrative review	In vitro / human	Chronic bronchitis Cystic fibrosis	Airway clearance	In health, the osmotic modulus/ pressure of the PCL exceeds that of the mucus layer, resulting in efficient, low-friction movement of mucus. In disease, through multiple mechanisms, the osmotic pressure of the mucus begins to exceed basal PCL values, resulting in compression of the cilia and slowing of mucus transport. Mucus hyperconcentration (mucin overproduction and/or abnormal regulation of ion/water transport), may be a simple method to diagnose chronic bronchitis, monitor its progression, and serve as a biomarker for development of new therapies.
Bennett et al.[22] 2016, USA	Secondary	Narrative review	In vitro / human	Chronic bronchitis Cystic fibrosis	Airway clearance	There is growing evidence that chronic bronchitis and cystic fibrosis may have parallels in disease pathogenesis as well, including cystic fibrosis transmembrane conductance regulator dysfunction, mucus dehydration, and defective mucociliary clearance.

Chalmers et al.[23] 2017, UK	Primary	CSS	Human	Bronchiectasis	Airway inflammation	Sputum neutrophil elastase activity is a biomarker of disease severity and future risk in adults with bronchiectasis.
Mcllwaine et al.[24] 2017, Canada	Secondary	Narrative review	Human	Chronic suppurative lung diseases (including bronchiectasis)	Airway clearance	Description on how to provide a personalised approach to selecting the most appropriate ACT for each patient. It is based on a synthesis of the physiological evidence that supports the modulation of ventilation and expiratory airflow as a means of assisting airway clearance.
Gramegna et al.[25] 2017, Italy	Secondary	Systematic review	Human	Bronchiectasis	Airway inflammation	Sputum neutrophil elastase is useful as an inflammatory marker both in stable state bronchiectasis and during exacerbations and local or systemic antibiotic treatment. Neutrophil elastase has also been associated with risk of exacerbation, time to next exacerbation and all-cause mortality.
Flume et al.[26] 2018, UK	Secondary	Narrative review	Human	Bronchiectasis	Pathophysiology	Description of the pathophysiology of bronchiectasis and an in-depth understanding of the endotypes and clinical phenotypes of this disease.
Contarini et al.[27] 2018, UK / Italy	Secondary	Narrative review	Human	PCD Bronchiectasis	Pathophysiology	Primary ciliary dyskinesia (PCD) is a genetic cause of bronchiectasis in which failure of motile cilia leads to poor mucociliary clearance. This study summarises the current literature describing why, when and how to investigate PCD in adult patients with bronchiectasis.
Ramsey et al.[28] 2020, USA	Primary	CSS	Human	Bronchiectasis	Airway clearance	Bronchiectasis sputum exhibited increased percent solids, total and individual (MUC5B and MUC5AC) mucin concentrations, osmotic pressure and elastic and viscous moduli compared with healthy sputum. Hyperconcentrated airway mucus likely contributes to disease pathophysiology in bronchiectasis.

ASL, airway surface layer; CF, cystic fibrosis; PCD, primary ciliary dyskinesia; PCL, periciliary layer; PPM, potentially pathogenic microorganisms; ACT, airway clearance techniques; CSS, cross-sectional; RXT, randomised crossover trial; NA= not applied

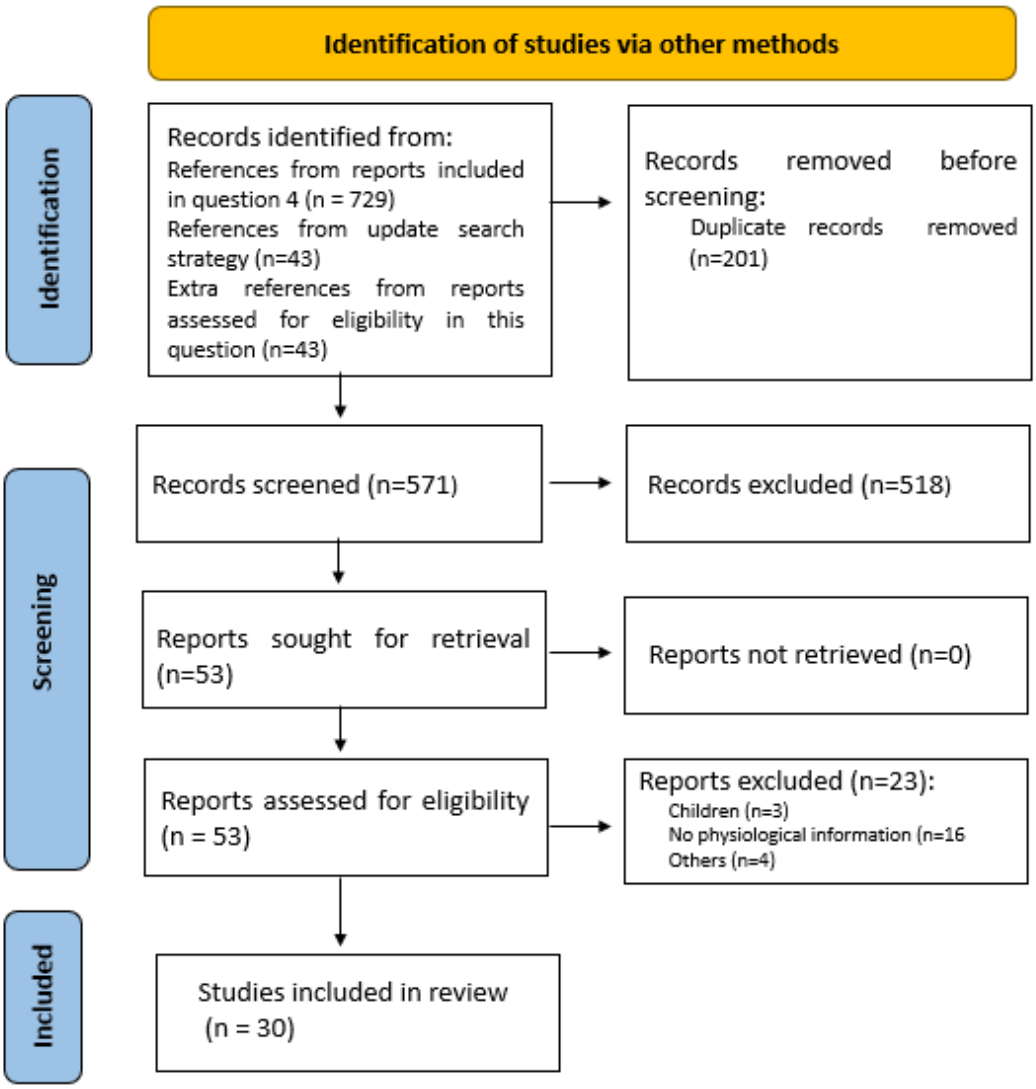


Figure S2. Literature search flow diagram for Question 2 - *What is the physiological rationale of each one of the ACTs and what are the advantages and limitations of each technique?*

Table S3. Summary of the main features of studies included for Question 2 - *What is the physiological rationale of each one of the ACTs and what are the advantages and limitations of each technique?*

First author, year, country	Publication type	Study design	Human / animal / in vitro / others	Population / Origin of samples	Topic	Relevant findings related to this question
Mead et al.[29] 1967, USA	Primary	Cross-sectional	Mathematical models	N/A	Airway physiology (equal pressure points)	Equal pressure points refer to the points where the pressure at the inner wall of the airways is equal to the pleural pressure. During forced expirations, there are points within airways that equal pleural pressure, and the pressure drop from alveoli to these points approximates the static recoil pressure of the lungs. The resistance of these segments has a frictional component which increases as lung volume decreases and an accelerative component which decreases as lung volume decreases.
Pryor et al.[30] 1979, UK	Primary	RXT	Human	Cystic fibrosis	ACTs	During a forced expiratory manoeuvre, there are forces tending to collapse or compress the airways downstream (towards the mouth) of the equal pressure point. This dynamic compression is an essential part of the mechanism of a huff or cough, which is therefore effective only at the compression points (choke points) downstream of the equal pressure point. These choke points move upstream (towards the alveoli) as the lung volume decreases. The FET + GAD cleared more sputum in less time than manual percussion applied by a physiotherapist + GAD in people with cystic fibrosis.
Kim et al.[8] 1986, USA	Primary	Experimental	In vitro	Sputum samples with similar rheologic properties than healthy and people with	Airway clearance	Mucus transport by two-phase gas-liquid flow mechanism depends on the airway surface liquid layer thickness and rheological properties of fluid.

				respiratory diseases		
Kim et al.[9] 1987, USA	Primary	Experimental	In vitro	Sputum samples with similar rheological properties than healthy and people with respiratory diseases	Airway clearance	Effective mucus clearance can be achieved by two-phase gas-liquid flow mechanism in patients with excessive bronchial secretions with flow-bias tidal breathing favouring the expiratory flow and that the clearance can be further promoted by changing rheological properties of mucus.
Postiaux et al.[31] 1990, France	Primary	RXT	Human	COPD	ACTs	It is described how to perform the ELTGOL technique and showed that ELTGOL technique enhances greater mucus clearance than control period in lateral position (especially in the dependent lung) using scintigraphy.
Lannefors et al.[32] 1992, Sweden	Primary	RXT	Human	Cystic fibrosis	ACTs	No difference in mucus clearance using scintigraphy was observed between GAD, PEP and exercise in people with cystic fibrosis. Surprisingly, GAD in the left position promoted greater mucus clearance in the dependent lung (left) than in the right lung.
App et al.[33] 1998, Canada	Primary	RXT	Human	Cystic fibrosis	ACTs	Oscillations applied using an O-PEP device (Flutter) are capable of decreasing mucus viscoelasticity in patients with cystic fibrosis.
van der Schans et al.[34] 1999, Netherlands	Secondary	Narrative review	Human	Bronchiectasis COPD Cystic fibrosis Asthma	ACTs	Description the mechanism of actions of various ACTs and outcome measures to assess the effects of ACTs combined data from different respiratory diseases.
Pryor et al.[35]1999, UK	Secondary	Narrative review	Human	Bronchiectasis Cystic fibrosis Asthma	ACTs	Description of how to perform each technique and its physiological principles.
Cecins et al.[36] 1999, Australia	Primary	RXT	Human	Bronchiectasis Cystic fibrosis PCD	ACTs	No difference was observed in sputum expectorated between ACBT in gravity-assisted drainage positions with or without a head-down tilt. However, breathlessness was higher following the technique in head-down tilt. Patients preferred the ACBT without a head-down tilt.

Wong et al.[37]2003, Singapore	Primary	Quasi-experimental	Animal model	N/A	ACTs	Manual clapping, vibration, and shaking applied by physiotherapists increase expired tidal volume but not peak expiratory flow rate in an animal model. No significant hemodynamic effects were observed during the manoeuvres. The rates achieved during vibrations and shaking are related to physiotherapists' characteristics, particularly clinical experience.
Dosman et al.[38] 2005, Canada	Secondary	Narrative review	Human	Various respiratory diseases	ACTs	Description the history, mechanism of actions and global effectiveness of HFCWO
McCarren et al.[39] 2006, Australia	Primary	RXT	Human	Healthy people	ACTs	During manual vibration the chest behaves as a highly linear system. Changes in intrapleural pressure occurring during vibration appear to be the sum of changes in pressure due to lung recoil and the compressive and oscillatory components of the technique, which suggests that all three components are required to optimise expiratory flow.
McCarren et al.[40] 2006, Australia	Primary	RXT	Human	Cystic fibrosis	ACTs	Peak expiratory flow rate of manual vibration was greater than Flutter (O-PEP), manual percussion, Acapella (O-PEP) and PEP. Vibrations generate lower oscillations of the airflow than Acapella and Flutter (both O-PEP), but similar to manual percussion.
Agostini et al.[41] 2007, UK	Secondary	Narrative review	Human	Cystic fibrosis Chronic bronchitis	ACTs	Description of the technique (based on previous report from J. Chevallier), offering explanations about how the technique works to enhance sputum clearance and evidence supporting its use
Martins et al.[42] 2012, Brazil	Primary	RXT	Human	COPD	ACTs	ELTGOL significantly increased mucus clearance in the peripheral area of the infralateral lung in patients with stable chronic bronchitis, most of whom had mild to moderate COPD.
Riffard et al.[43] 2012, France	Secondary	Narrative review	N/A	N/A	ACTs	Description of the device (IPV), its action mechanism to improve ventilation and enhance sputum clearance and how to set it according to your target treatment.

Button et al.[17] 2013, USA	Secondary	Narrative review	In vitro / human	Cystic fibrosis	Airway clearance / Action mechanism of ACTs	The application of mechanical stress on airway epithelia promotes changes in ion transport and increases ASL hydration. ACTs used in CF are described based on their mechanism of action.
Testa et al.[44] 2015, Italy	Primary	Quasi-experimental	Human	COPD	ACTs	Short-term combination of IPV and various techniques (ELTGOL, PEP mask, PEP bottle, FET and cough) improves PO_2, SpO_2 and perceived dyspnea than the other techniques in patients with COPD and productive cough.
Lanza et al.[45] 2015, Brazil	Primary	Cross-sectional	Human	Bronchiectasis	ACTs	ELTGOL mobilised more than 80% of expiratory reserve volume in subjects with moderate airway obstruction; there is no difference in ERV exhaled during the technique applied by a physiotherapist or by the subject.
Fagevik-Olsen et al.[46] 2015, Sweden	Secondary	Narrative review	Human	Bronchiectasis Cystic fibrosis COPD Asthma	ACTs	Description of the purpose, performance, clinical application, and underlying physiology of PEP when it is used to increase lung volumes, decrease hyperinflation or improve airway clearance.
Terry et al.[47] 2016, USA	Secondary	Narrative review	Human	Various respiratory diseases	Airway physiology (interdependence / collateral ventilation)	Description of the anatomical pathways of collateral ventilation, their physiology and relationship to disease states, their modulatory effects on gas exchange, treatment considerations, and their effect on diagnostic procedures.
Mcllwaine et al.[24] 2017, Canada	Secondary	Narrative review	Human	Chronic suppurative lung diseases (including bronchiectasis)	Airway clearance	Description on how to provide a personalised approach to selecting the most appropriate ACT for each patient. It is based on a synthesis of the physiological evidence that supports the modulation of ventilation and expiratory airflow as a means of assisting airway clearance.
Lee et al.[48] 2017, Australia	Secondary	Systematic Review	Human	Bronchiectasis	ACTs	Systematic review providing extensive information about physiological rationale for PEP devices, especially explained how the intervention might work
Taher et al.[49] 2018, USA	Primary	Quasi-experimental	Human	Healthy subjects COPD	Airway physiology (interdependence / collateral ventilation)	Chest wall strapping induces breathing at low lung volumes but also increases parenchymal elastic recoil. Chest wall strapping increases

						expiratory airflow in normal subjects as well as subjects with mild to moderate COPD.
Nicolini et al.[50] 2018, Italy	Primary	RCT	Human	COPD	ACTs	HFCWO and IPV improved daily life activities and lung function in patients with severe COPD. IPV demonstrated a significantly greater effectiveness in improving some pulmonary function tests linked to the small bronchial airways obstruction and respiratory muscle strength and scores on health status assessment scales as well as a reduction of sputum inflammatory cells compared with HFCWO.
Wong et al.[51] 2018, New Zealand	Secondary	Narrative review	Human	Bronchiectasis	ACTs	In the ELTGOL technique, the volume of the dependent lung is reduced by placing the patient in the lateral decubitus position and by limiting breathing to expiratory reserve volume. This reduces the total cross-sectional area of the peripheral airways where mucus is primarily produced. Since maximum airflow velocity is inversely proportional to airway diameter, the velocity of airflow in the peripheral airways is increased. Airway patency is maintained by increasing intraluminal pressure via slow expiration through an open glottis. Overall, this results in greater clearance of mucus from the peripheral airways.
Reychler G. et al.[52] 2018, Belgium	Secondary	Systematic Review	Human	Bronchiectasis Cystic fibrosis COPD Asthma	ACTs	The main findings showed that IPV improves gas exchange during exacerbation and could reduce the hospital length of stay for patients with COPD. In subjects with cystic fibrosis, neither lung function nor other parameters were improved. IPV is poorly studied in bronchiectasis (only one study was included).
de Souza et al.[53] 2019, Brazil	Primary	RXT	Human	Bronchiectasis	ACTs	The oscillatory PEP technique was effective for the removal of secretions and in decreasing total and peripheral respiratory system resistance, thoracic compression had comparable positive effects on the peripheral resistance

Demchuck et al.[54] 2021, USA	Primary	Quasi-experimental	In vitro	N/A	ACTs	PEP devices behaved similarly, with increased pressure with increased flow (flow resistors) or flow independence (threshold resistors). There was much greater variation in the performance of the O-PEP devices. A higher oscillation index indicates better mechanical performance characteristics.

RXT, randomised crossover trial; RCT, randomised controlled trial; FET, forced expiration technique; GAD, gravity-assisted drainage; PEP, positive expiratory pressure; O-PEP, oscillations positive expiratory pressure; ACTs, airway clearance techniques; HFCWO, high frequency chest wall oscillations; COPD, chronic obstructive pulmonary disease; IPV, intrapulmonary percussive ventilation; PCD, primary ciliary dyskinesia; NA= not applied

Table S4. Description and physiological rationale of each airway clearance technique (ACT).

Airway clearance techniques not requiring devices	
Forced Expiration Technique (FET)	
Description	*Mechanisms of action*
Consists of forced expirations through the mouth while maintaining an open glottis (huffs). Huffing or FET from low lung volumes moves secretions downstream (towards the mouth) from more peripheral airways. Huffing or FET from mid and high lung volumes clears secretions from the central airways	▪ The underlying principle is based on the equal pressure point, i.e., the point at which pressure in the airways is equal to pressure outside the airways (pleural pressure) [29, 30]. ▪ Lung volumes are voluntarily altered, depending on the depth of inspiration and this can facilitate movement of the equal pressure point. ▪ FET displaces the position of the equal pressure point to a more distal or proximal airway position. ▪ Additionally, high expiratory flows are generated during the FET, which helps create shearing forces to move mucus through the airways [34]

Active Cycle of Breathing Techniques (ACBT)	
Description	*Mechanisms of action*
The ACBT has 3 key components: breathing control (relaxed breathing at tidal volume), thoracic expansion exercises (deep breathing above tidal volume towards full inspiration) and FET (Please see above section on FET). Thoracic expansion exercises can include a breath hold at the end of full inspiration; a sniff at the end of full inspiration can also be added to further promote increase in lung volumes. When thoracic expansion exercises are facilitated by a respiratory physiotherapist, the physiotherapist can place their hands over the patient's lower and lateral rib cage; however, the ACBT is effective with or without any assistance [30, 35].	▪ Relaxed rhythmical breathing helps control the respiratory rate and respiratory effort during breathing control. ▪ Thoracic expansion exercises generate a greater trans-airway pressure gradient than in normal breathing [29] enhancing lung volumes via interdependence and collateral ventilation and allowing a decrease in airway resistance to facilitate some air entry behind airway mucus. Collateral ventilation in the lungs is proposed to occur via the alveolar pores of Kohn, inter-bronchiolar channels of Martin and bronchoalveolar channels of Lambert [17, 47]. ▪ Same mechanisms described for FET in the above section.
Manual percussions	
Description	*Mechanisms of action*
Rhythmical external oscillations that are applied manually on the chest wall by the physiotherapist.	▪ Transmitting the external oscillation to the airways, with the intention to reduce the adhesivity of the mucus layer, change mucus viscoelastic properties and detach mucus from the bronchial wall (decrease adhesivity). ▪ This effect seems to be dependent on the frequency of oscillations transmitted to the thorax and adequate frequency may be difficult to achieve [34]. Therefore, the manual application of the percussion manoeuvre by the respiratory physiotherapist does not necessarily achieve the optimal frequencies for airway clearance and could be ineffective [37]

Manual vibrations or shaking (compression and external oscillation)	
Mechanisms of action The respiratory physiotherapist / caregiver places their hands over an area of the rib cage/thoracic cavity and apply pressure to the rib cage/thorax as the patient exhales. In addition to the pressure created by the compression, oscillations may be created by the respiratory physiotherapist using their hands to create small undulating movements. [37, 39, 53].	*Mechanisms of action* ▪ It is anticipated that the mechanical effect created by the pressure and oscillations is transmitted through the ribs into the lungs and airways to loosen and move airway mucus. ▪ There is a resultant increase in intrapulmonary pressure as well as expiratory flow rate and expired tidal volume, which contribute to loosening airway mucus [37, 39, 53]. ▪ Slow thoracic compressions may reduce peripheral respiratory system resistance [53]. ▪ Vibrations have been shown to increase peak expiratory flow rates in patients with cystic fibrosis and produce oscillations with frequencies which can enhance mucus transport [40]. ▪ Oscillations may alter sputum viscoelastic properties further helping clearance [24]. McCarren et al. [39] have shown that there is a strong linear relationship between the force applied to the chest wall by the respiratory physiotherapists' hands, the chest wall displacement, the intrapleural pressure, and the expiratory flow rate during vibrations [39]. ▪ Additionally, the impact of compression and oscillation combined together is greater than each technique alone [39].
Gravity-Assisted Drainage (GAD) technique	
Description The patient is positioned with the relevant lung segment in a semi vertical position (as able), so that the bronchopulmonary segment with excess of airway mucus is positioned higher than the central airway.	*Mechanisms of action* ▪ These positions theoretically promote flow of airway mucus from distal to proximal airways, using the effects of gravity. ▪ The angle of the drainage position, length of time spent in the position as well as the size and resistance in the airway can all impact on the effectiveness of GAD positions [36]. ▪ Gravity is believed to be the main physiological effect for enhancing mucus clearance with this technique, but interestingly greater mucus clearance rates have been observed in dependent lung areas compared to

	non-dependent lung areas [32, 42]. Thus, the reduction of airway cross-sectional area in dependent lung regions may play a more important role in improving mucus clearance than gravity.
Autogenic Drainage	
Description	*Mechanisms of actions*
Patients start breathing repeatedly using low lung volumes in the expiratory reserve volume, with slow and short inspirations, and with active but gentle expiratory phases ("stage 1 or loosening phase"). During this breathing pattern, patients need to keep the glottis opened and a breath-hold may be included after the inspiratory phases. The technique progresses by encouraging patients to breath progressively using high lung volumes into the inspiratory reserve volume and shorten the expiratory phase ("stage 2 and 3 or collect and move up phase) [41]	▪ During the first phase of the technique, a reduction of the cross-sectional area of the airways is attempt [41], and therefore, the lineal air velocity increases, particularly in the peripheral and medium airways, to produce an effective shearing stress on the mucus layer obstructing the bronchial lumen [51]. ▪ Patients need to keep the glottis open during expiratory phases which increases the intrapleural pressure [41]. ▪ The breath-hold included after the inspiratory phases promotes collateral ventilation and air movement behind the obstructed lung regions [24]. This physiological effect is emphasised during the second and third phases of the technique, when the patient breathes progressively using high lung volumes towards the inspiratory phase [41]. In order to avoid dynamic compression during the technique, it is recommended to modulate expiratory effort and coughing is restrained until the mucus has built up into the proximal airways, particularly in patients with reduced elastic recoil [41].
Slow expiration with glottis opened in lateral posture (ELTGOL)	
Description	*Mechanisms of action*
The patient lies in lateral decubitus position with the affected lung in the dependent position. If both lungs are affected, the patient will perform the technique in both lateral decubitus. The patient's breathing pattern during the technique involves active slow expirations from functional residual	▪ Mucus clearance is enhanced by increasing the airflow velocity in the medial and peripheral airways, while the airway cross-section in the dependent lung is reduced [56] [51] [31]. ▪ The patient's breathing pattern during the active slow expirations with the glottis opened [45] also facilitates a reduction of the cross-sectional ratio of the airways while maintaining the airway patency; thus, enhancing the air-gas interaction without dynamic compression [31, 51].

capacity to the end of the expiratory reserve volume with the glottis opened [45]. The technique may be assisted by a respiratory physiotherapist / caregiver by placing their hands on the upper rib cage and infra-umbilical region [45]	▪ The volume of air exhaled seems to be similar regardless if the technique is performed independently or with assistance [45]

Airway clearance techniques requiring devices

Positive expiratory pressure (PEP) devices (*PEP mask, PiPEP, Threshold PEP, TheraPEP, Resistex, etc.)*	
Description Positive expiratory pressure (PEP) therapy involves the use of a device. During PEP therapy, the patient exhales through a mouthpiece or mask against a mild resistance (positive pressure), which is provided by a flow resistor, threshold resistor or an external flow source during expiration [54].	*Mechanisms of action* ▪ A mild resistance (positive pressure), generally between 10 and 20 cmH_2O, is usually the target expiratory pressure to achieve with the use of these devices [48] ▪ The increase in pressure is transmitted to airways, creating back pressure which splints open the airways during exhalation, preventing premature airway closure and reducing gas trapping [46]. ▪ PEP therapy may promote collateral ventilation, and therefore hypothetically improve the delivery of air behind the mucus and facilitate airway clearance.
Oscillating positive expiratory pressure (O-PEP) devices *(Acapella, Flutter, Aerobika, VibraPEP, ShurClear, PocketPEP, RC Cornet, TurboForte, Shaker, Quake, Bottle PEP, Flute, Uniko TPEP, etc.)*	
Description Oscillating positive expiratory pressure (O-PEP) devices are used through a mouthpiece and provide short interruptions during expiration, with the aim to generate positive oscillatory airway pressure and flow waveforms [54].	*Mechanisms of action* ▪ Although the mechanisms of action for the generation of the oscillations is different between the O-PEP devices, the generation of these oscillations or interruptions induce shear forces on the mucus layer and, mechanically reduce the viscoelasticity of airway mucus; thus, enhance mucociliary clearance and ciliary beat [33]. ▪ Same mechanisms described for PEP devices in the above section.

High-Frequency Chest Wall Oscillation (HFCWO)	
Description	*Mechanisms of action*
It is a self-administered technique delivered by a pneumatic vest or band placed around the chest. A high-output compressor or a battery generates a background pressure, which inflates the vest and compresses the patient's chest. A superimposed frequency of air pressure then oscillates with a sinusoidal or triangular waveform [38]	▪ External oscillation is a physical mechanism to stimulate the mucus layer hydration and reduce the interfacial tension between the mucus layer and the airway epithelium (adhesivity), change the viscoelastic properties of mucus, and increase the ciliary beating [38] Alternative methods of compression applied (e.g., chest strapping) have been shown to reduce the pulmonary compliance and increase the lung elastic recoil [49]. Both principles seem to reduce airway resistance (particularly in the smaller airways) and increase expiratory airflow, which facilitates mucus clearance proximally through the two-phase gas-liquid mechanism (airflow bias) [8, 9].
Intrapulmonary Percussive Ventilation (IPV)	
Description	*Mechanisms of actions*
It is an instrumental ACT designed to provide internal thoracic percussion by intermittent high-frequency positive pressure burst of gas [44].	▪ The rapid variation and the high amplitude of the pressure peaks lead to oscillation effects on the airways [43], which enhance mucus clearance, reduce its adhesivity and cohesivity and improve the viscoelastic properties of mucus. ▪ Moreover, the asymmetric flow pattern allows the expiratory flow to be greater than the inspiratory flow, and therefore, improves mucus clearance as well [8, 9, 52] . A positive end expiratory pressure (PEEP) is an effect also described in the IPPV that allows recruitment of poorly ventilated lung zones and improves distribution of ventilation [43, 50].

Techniques were classified according to whether they require the use of a device or not. FET, forced expiratory technique; ACBT, active cycle of breathing techniques; GAD, gravity-assisted drainage; HFCWO, high-frequency chest wall oscillation; IPV, intrapulmonary percussive ventilation; PEEP, positive end expiratory pressure; O-PEP, oscillating positive expiratory pressure; ELTGOL, slow expiration with glottis opened in lateral posture; PEP, positive expiratory pressure; TPEP, temporary positive expiratory pressure. Note: This table does not include the potential contraindications of ACTs and clinicians should check those before using any ACT. Contraindications could include undrained pneumothorax, bullae, shock or severe hemodynamic instability, haemoptysis or active pulmonary haemorrhage, acute bronchospasm (relative contraindication), etc.

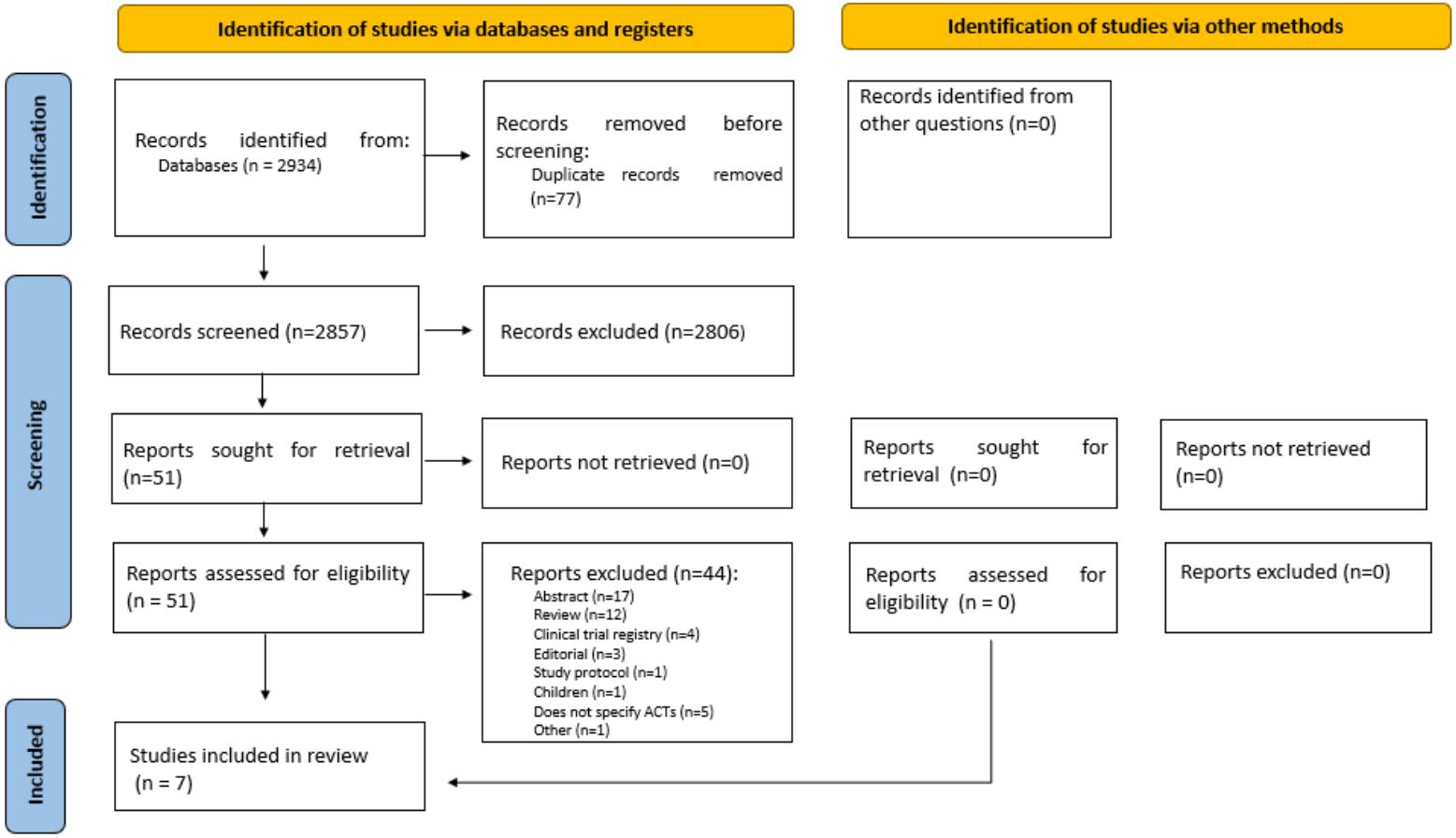


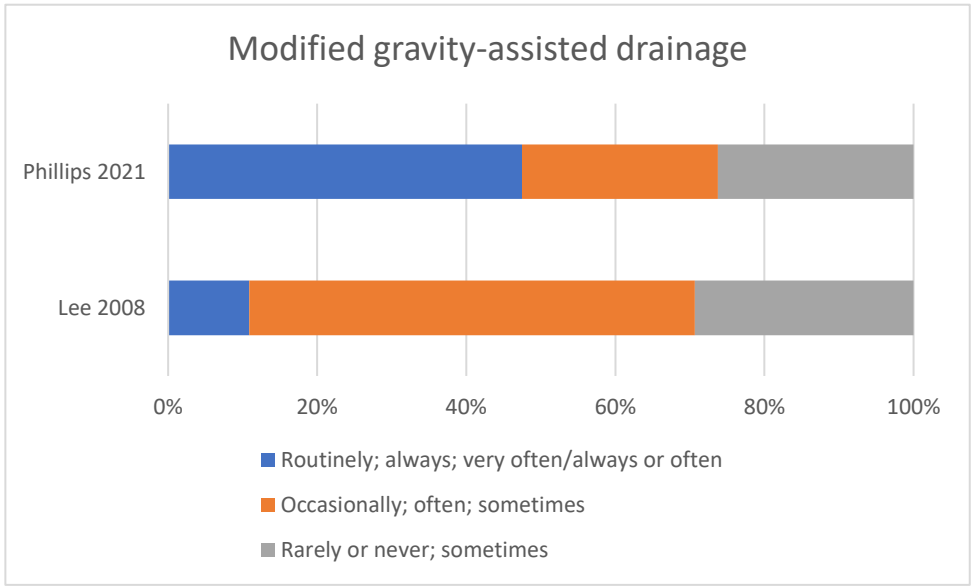
Figure S3 Literature search flow diagram for Question 3 - *Which are the ACTs that are used in the management of adults with bronchiectasis and are there any patterns according to geographical location?*

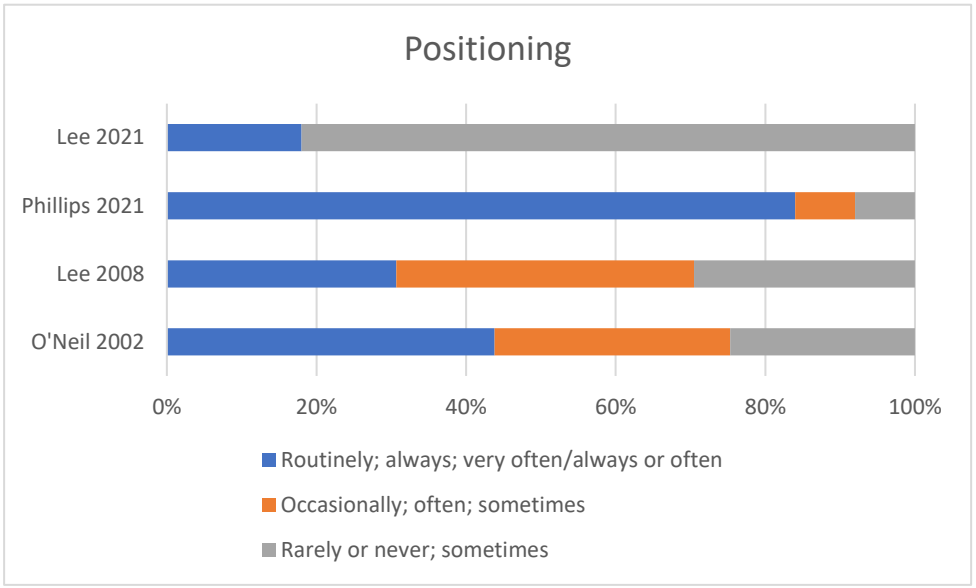
Table S5. Summary of the main features of studies included in Question 3 - *Which are the ACTs that are used in the management of adults with bronchiectasis and are there any patterns according to geographical location?*

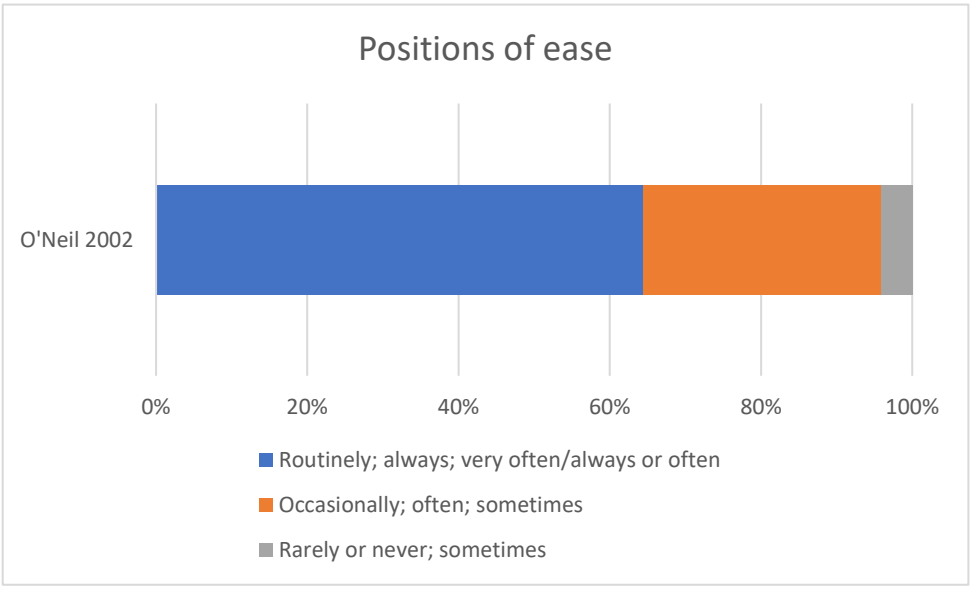
First Author, year	Country	Study start - end date	Data collection	Study design	Sites response rate	HCP response rate	Nº of participants and response rate	Years' experience	Areas of work	Location (urban *vs.* rural)	Responders	Clinical stage of disease
O'Neill et al.[55] 2002	UK	NR	Survey (NR)	Cross-sectional	82%	82%	n=82 (82%)	NR	NR	NR	Physiotherapists	NR
Lee et al.[56] 2008	Australia and New Zealand	NR	Survey (mail)	Cross-sectional	85%	85%	n=102 (85%)	10 (2-42)	Inpatients (93%) and outpatients (70%)	Public/private (6%); tertiary (65%); large major city (1%); large regional/rural (16%)	Cardiorespiratory physiotherapists	NR
Santos et al.[57] 2016	Australia	July 2012 - May 2013	Survey (mail)	Cross-sectional	88%	70%	n=169 (55%)	<1 2%; 1-5 37%; 6-10 24%; >10 28%	Surgical 54%; General medicine 49%; Intensive care/high-dependency unit 43%; Respiratory 43%; Outpatients 36%; Orthopedics 33%; Rehabilitation 20%; Gerontology	Tertiary/ teaching hospitals 47%; rural hospitals 33%; generalist hospitals 9%, private hospitals 6%, specialist hospitals 4%	Physiotherapists	NR

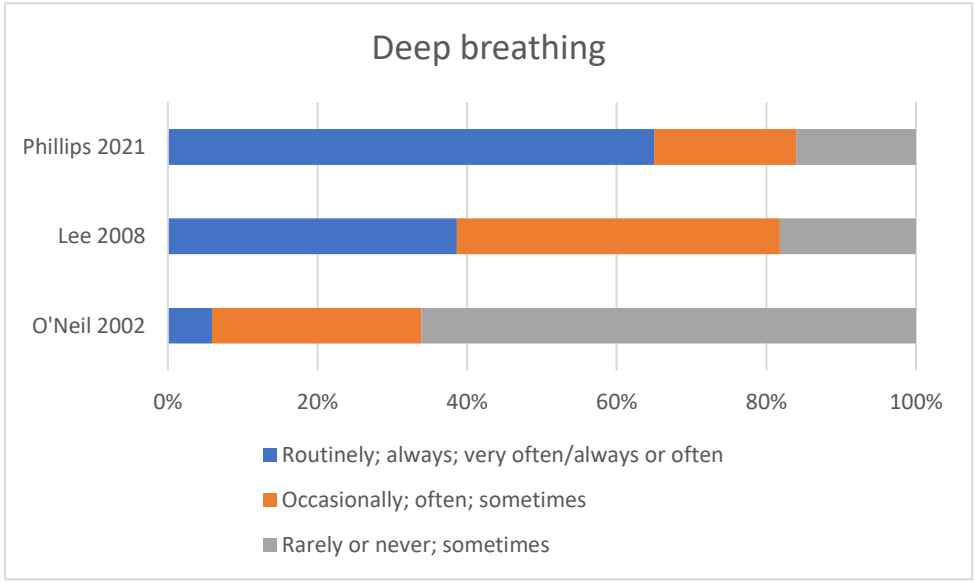
									18%; Community 15%; Neurology 14%; Oncology 13%; Cardiology 11%; Palliative care 11%; Pediatrics 7%; Others 4%			
Basavaraj et al.[58] 2020	USA	2008 - 2019	Registry	Retrospe ctive	NR	NR	n= 535 NR	NR	NR	NR	Patients	Stable + exacerbation
McShane et al.[59] 2020	Japan	April 2020 - NR	Survey (email)	Cross-sectional	NR	NR	n=51	NR	inpatients, outpatients and home settings	NR	Medical doctors (86.8%) Other (13.2%)	NR
Phillips et al.[60] 2021	Australia and New Zealand	August 2016 - April 2017	Survey (online)	Cross-sectional	NR	0.5%	n=130 (0.24%)	<5 28%; 6-10 17%; 11-15 16%; 16-20 13%; >21 16%	inpatients and outpatients	NR	Physiotherap ists	Exacerbation
Lee et al.[61] 2021	Australia	June 2018 - June 2019	Audit	Cross-sectional	NR	NR	n=54	NR	NR	NR	NR	NR

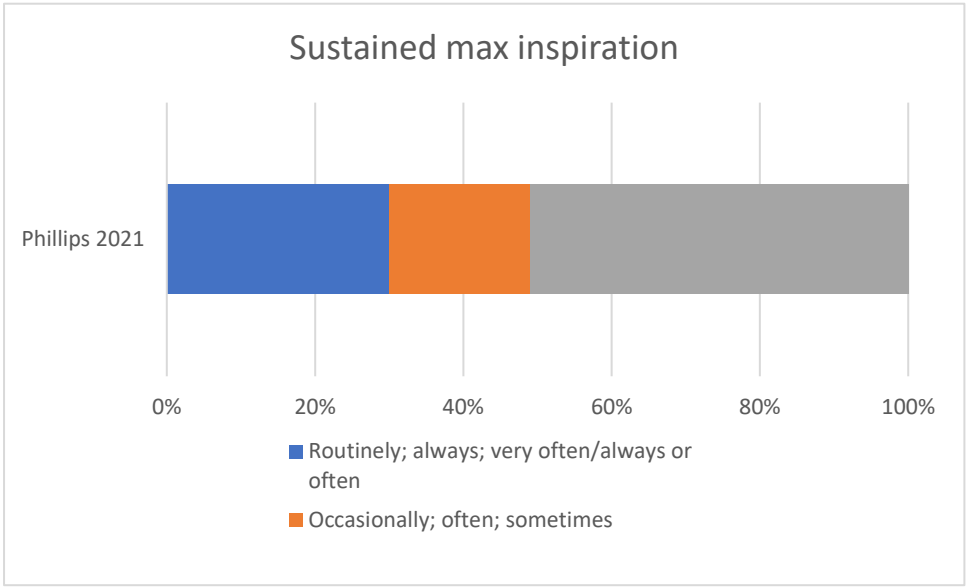
NR, not reported.

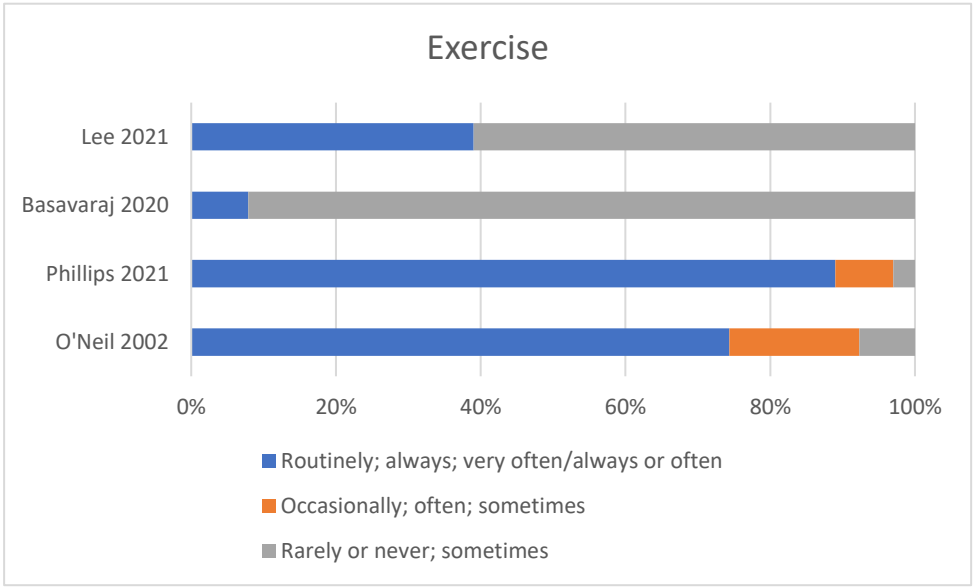

Modified gravity-assisted drainage
Phillips 2021
Lee 2008
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes

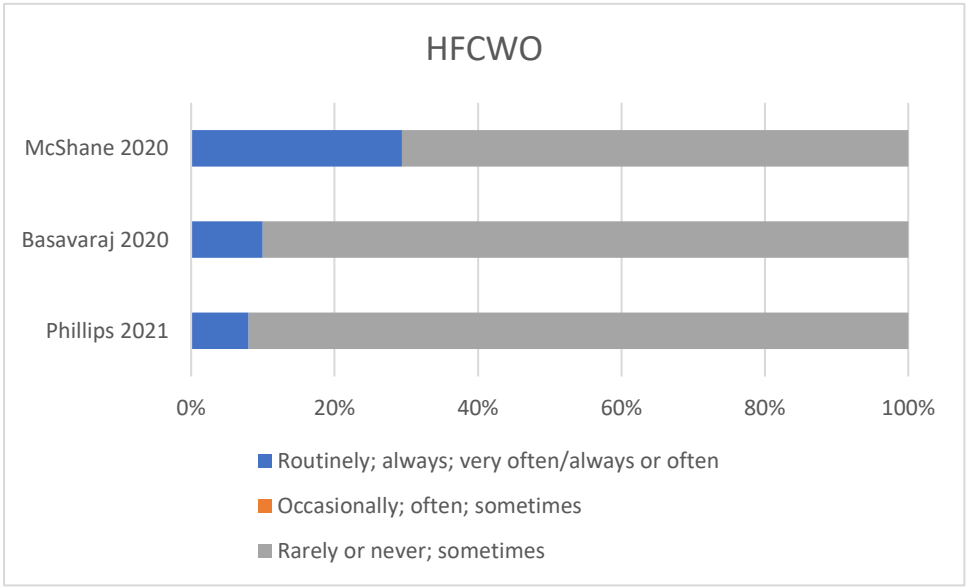

Positioning
Lee 2021
Phillips 2021
Lee 2008
O'Neil 2002
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes

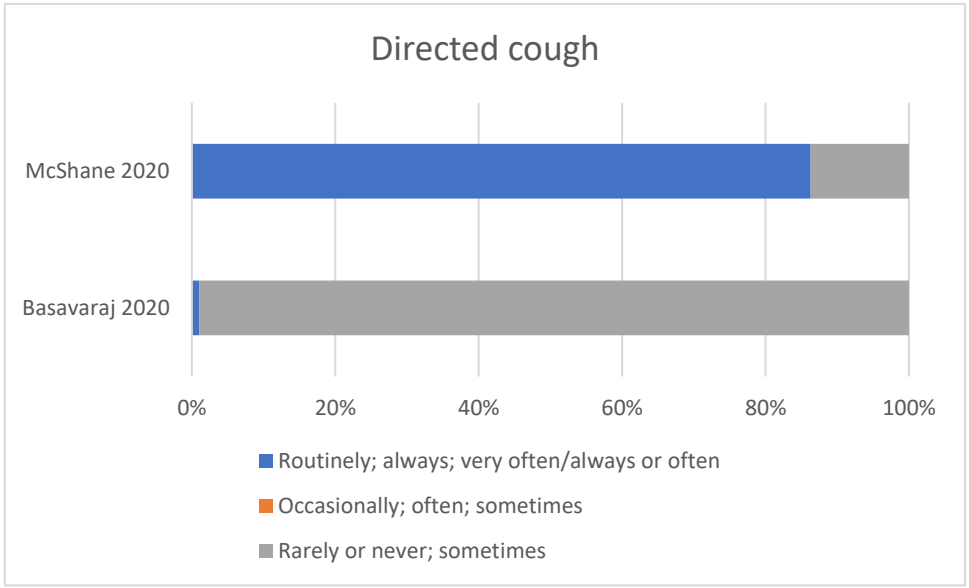

Positions of ease
O'Neil 2002
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes

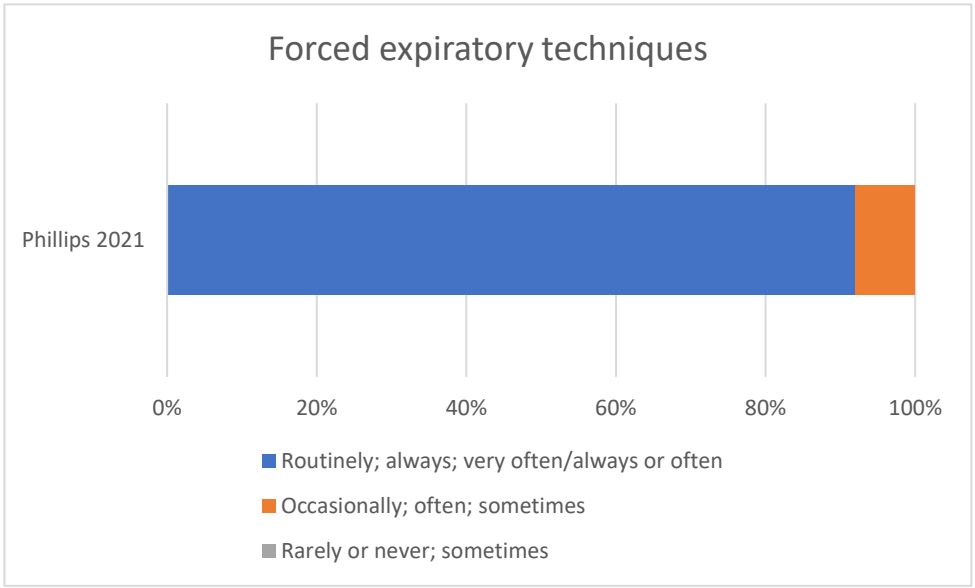

Deep breathing
Phillips 2021
Lee 2008
O'Neil 2002
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes

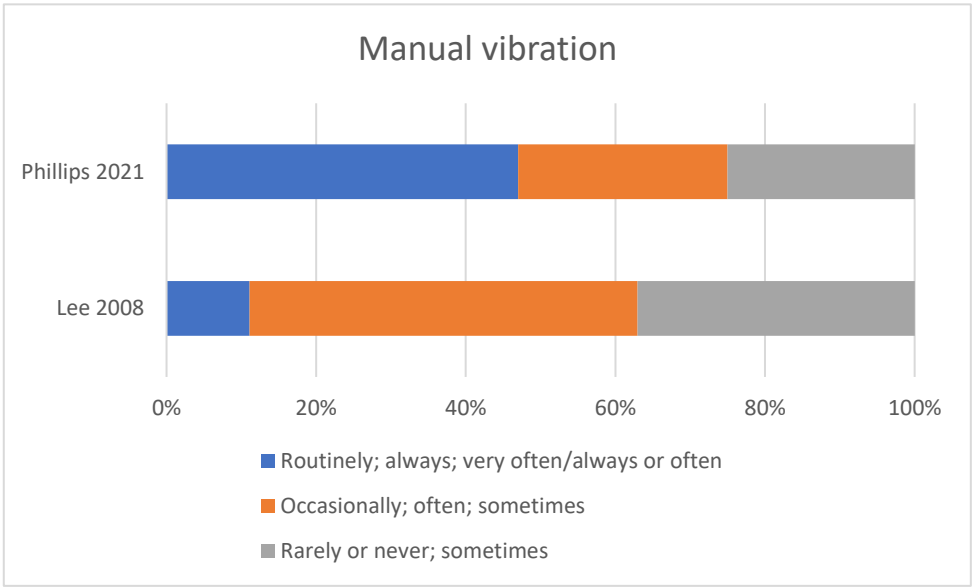

Sustained max inspiration
Phillips 2021
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes


Exercise
Lee 2021
Basavaraj 2020
Phillips 2021
O'Neil 2002
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes


HFCWO
McShane 2020
Basavaraj 2020
Phillips 2021
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes


Directed cough
McShane 2020
Basavaraj 2020
0%
20%
40%
60%
80%
100%
Routinely; always; very often/always or often
Occasionally; often; sometimes
Rarely or never; sometimes





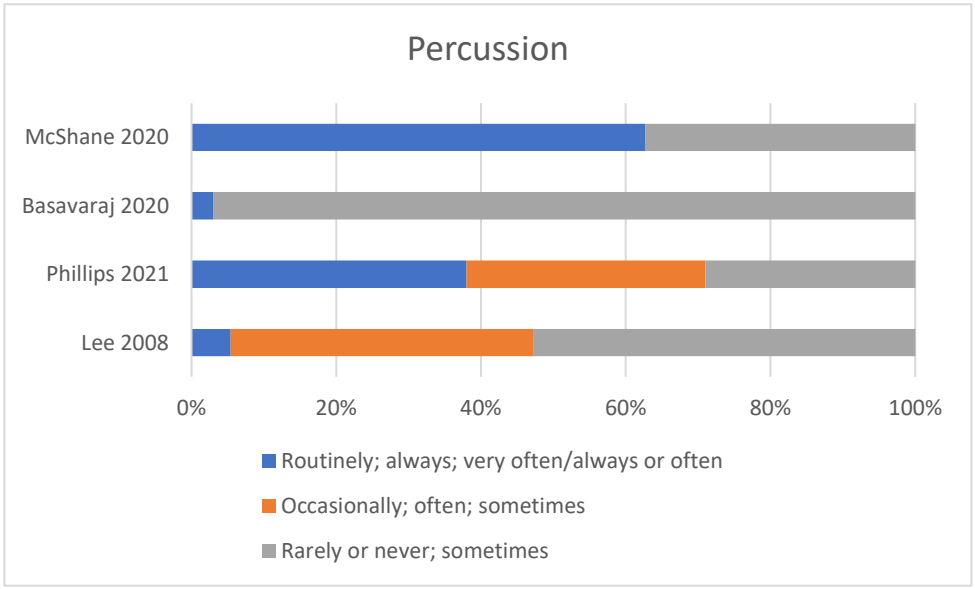


Figure S4. Question 3 - Which are the ACTs that are used in the management of adults with bronchiectasis and are there any patterns according to geographical location? Clinical use of airway clearance techniques (ACTs) which were reported as used less frequently compared to other ACTs. The terminology of the graphs follows the terminology of the original studies. Modified gravity-assisted drainage was presented as modified postural drainage in the original studies. HFCWO, high-frequency chest wall oscillation.

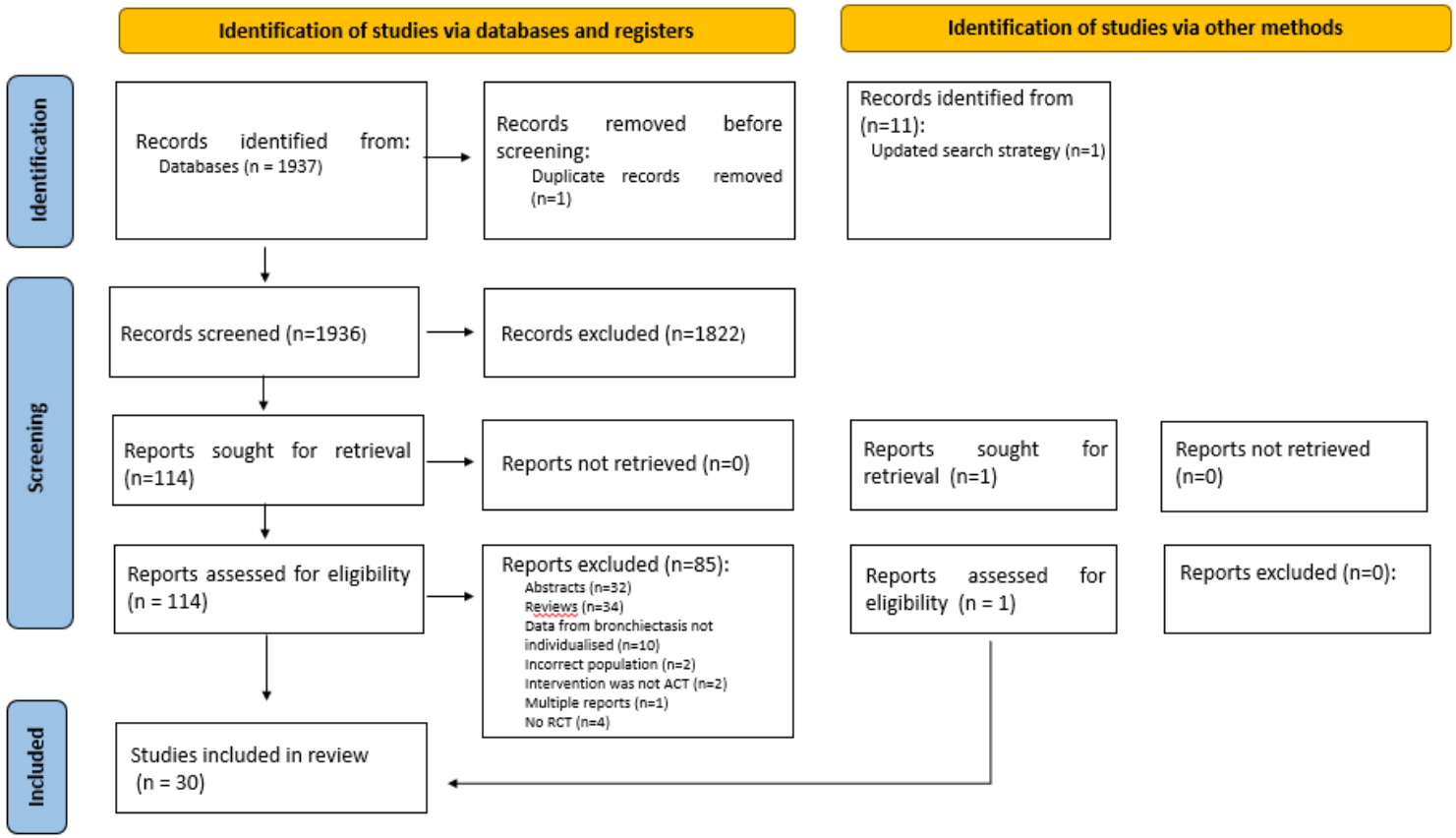


Figure S5. Literature search flow diagram for Question 4 - *What is the clinical evidence for the effectiveness of ACTs, in terms of function and disability (e.g., sputum expectoration), activity (e.g., physical activity) and participation (e.g., self-care), in adults with bronchiectasis?*

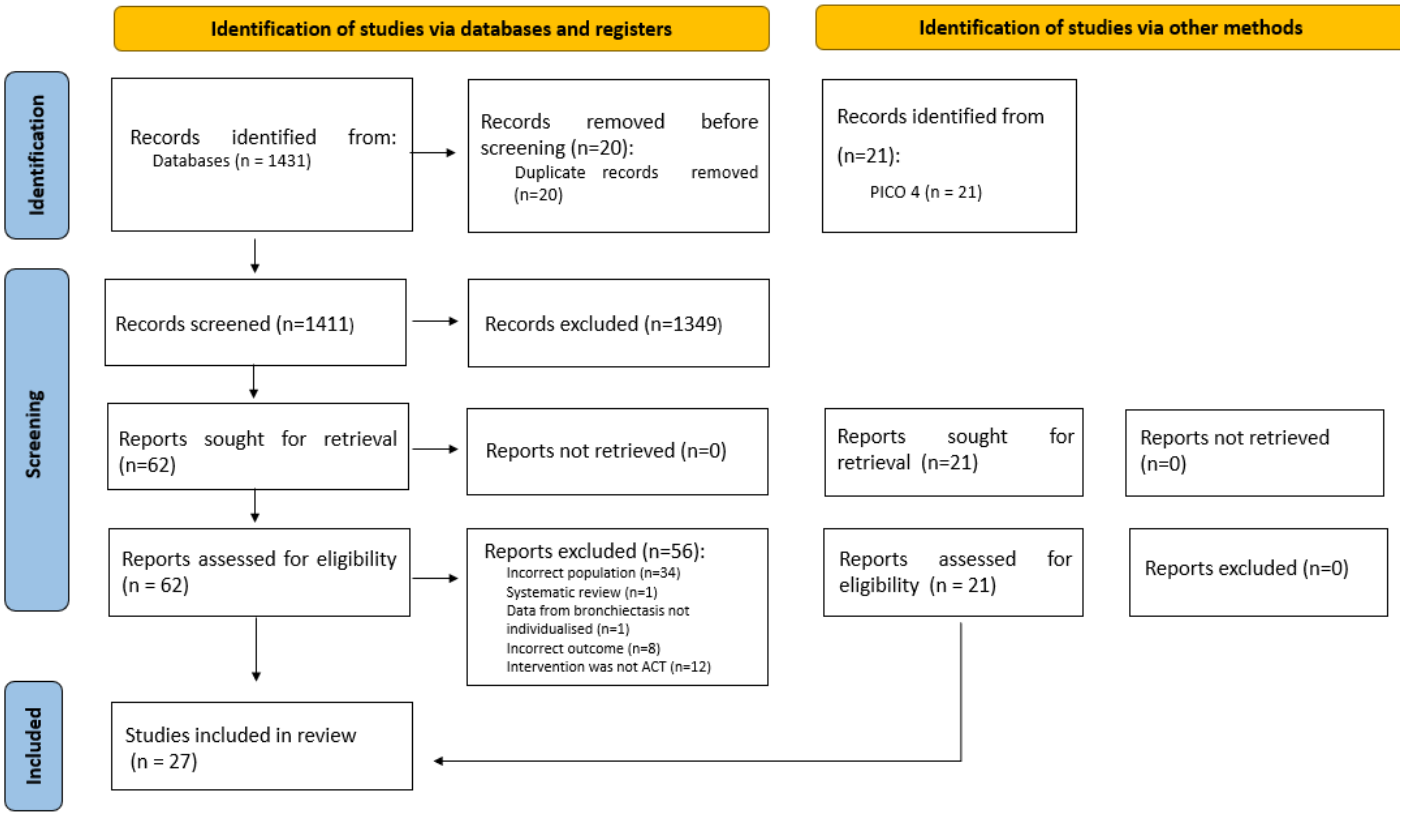


Figure S6. Literature search flow diagram for Question 5 - *a. What are the experiences and perceived impact of ACTs on adults with bronchiectasis? b. What are the perceived barriers to and enablers of ACTs in adults with bronchiectasis?* One search strategy was conducted for both questions.

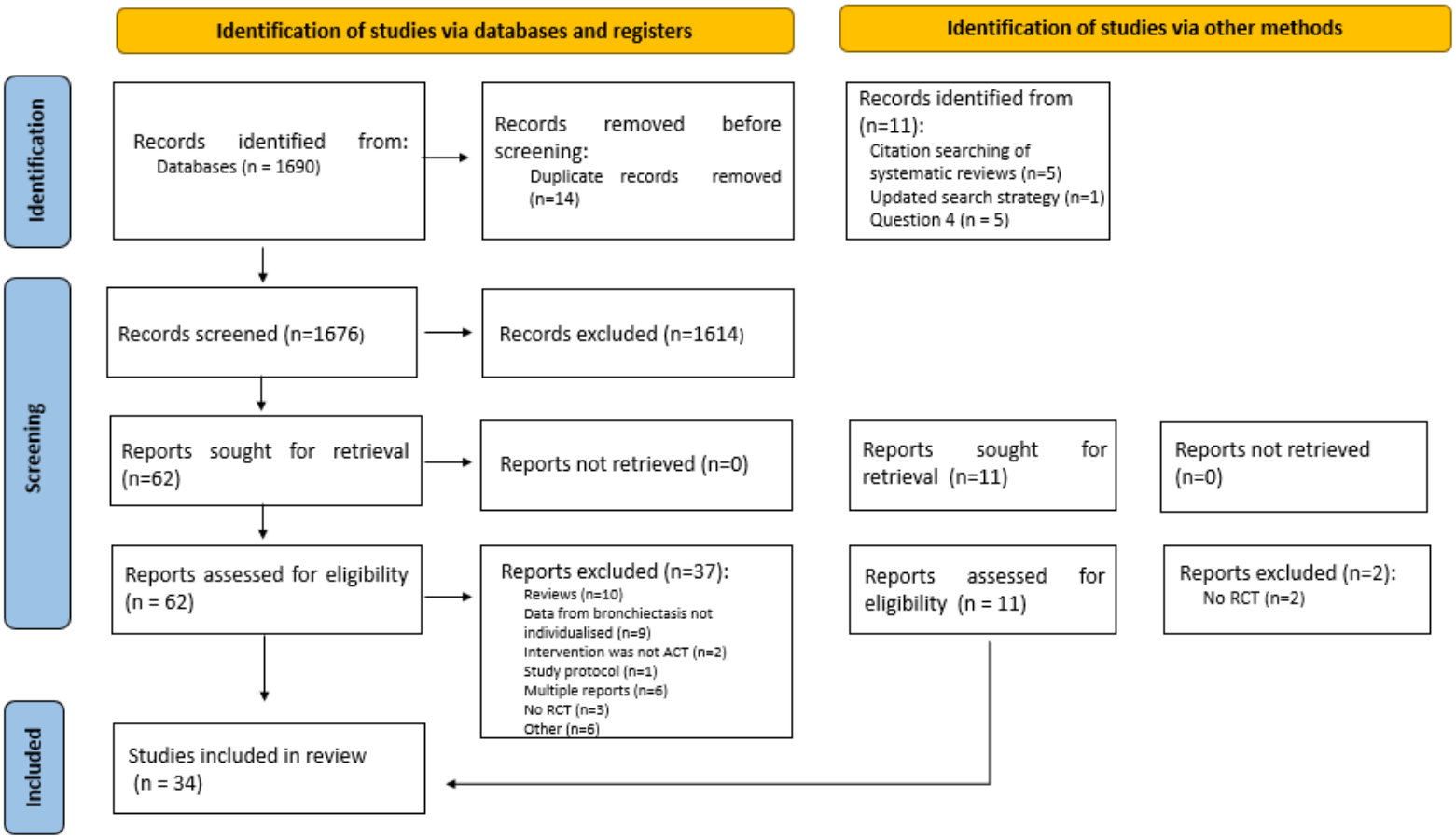


Figure S7. Literature search flow diagram for Question 6 - *In adults with bronchiectasis, how should studies for ACTs be conducted to reduce the risk of bias, facilitate comparison of findings, as well as conducting future meta-analyses?*

Table S6. Description of the outcome measures used in the included studies for 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?*.

Outcome measures	Timeframe	Nº of studies that used this outcome measure as primary endpoint	Nº of studies that used this outcome measure to estimate the sample size #	Nº of studies that used this outcome measure as secondary endpoint or not specified
Sputum quantity				
Wet sputum weight	During intervention	4 (12%)	3 (10%)	5 (15%)
	≤4h-after intervention	4 (12%)	4 (13%)	9 (26%)
	24-h after intervention	0	0	3 (9%)
Dry sputum weight	During intervention	2 (6%)	2 (6%)	4 (12%)
	≤4h-after intervention	0	0	5 (15%)
	24-h after intervention	0	0	0
Wet sputum volume	During intervention	1 (3%)	1 (3%)	12 (35%)
	≤4h-after intervention	4 (12%)	0	3 (9%)
	24-h after intervention	2 (6%)	1 (3%)	2 (6%)
Self-reported sputum quantity (Likert scale, VAS, etc.)	During intervention	0	0	0
	≤4h-after intervention	0	0	0
	24-h after intervention	0	0	1 (3%)
Sputum colour	Pre / Post intervention	0	0	2 (6%)
Sputum properties				
Percentage of solids	Pre / Post intervention	0	0	1 (3%)

Mucociliary transport (relative velocity)	Pre / Post intervention	0	0	2 (6%)
Displacement	Pre / Post intervention	1 (3%)	1 (3%)	1 (3%)
Contact angle	Pre / Post intervention	0	0	1 (3%)
Adhesiveness	Pre / Post intervention	0	0	2 (6%)
Viscosity	Pre / Post intervention	0	0	1 (3%)
Elasticity	Pre / Post intervention	0	0	1 (3%)
Self-reported sputum characteristics	Pre / Post intervention	0	0	1 (3%)
Sputum cytology	Pre / Post intervention	0	0	2 (6%)
Microbiology (bacterial isolation, colony-forming units)	Pre / Post intervention	0	0	2 (6%)
Lung function				
FEV_1, FVC, FEF_{25-75}%, PEF	Pre / Post intervention	1 (3%)	0	20 (59%)
TLC, IC, VC, RV, FRC	Pre / Post intervention	0	0	4 (12%)
LCI	Pre / Post intervention	1 (3%)	1 (3%)	0
Oscillometry	Pre / Post intervention	1 (3%)	1 (3%)	1 (3%)
HRQoL				
LCQ	Pre / Post intervention	2 (6%)	1 (3%)	5 (15%)
QoL-B	Pre / Post intervention	0	0	2 (6%)
SGRQ	Pre / Post intervention	0	0	2 (6%)
CRQ	Pre / Post intervention	0	0	1 (3%)
CAT	Pre / Post intervention	0	0	1 (3%)
BHQ	Pre / Post intervention	0	0	1 (3%)
SF36	Pre / Post intervention	0	0	1 (3%)

Nº exacerbations	Follow-up period	1 (3%)	0	3 (10%)
Time to first exacerbations	Follow-up period	0	0	2 (6%)
Nº hospitalisations	Follow-up period	0	0	1 (3%)
Hospitalisation length	During intervention	0	0	1 (3%)
Exercise capacity				
6MWT	Pre / Post intervention	0	0	2 (6%)
ISWT	Pre / Post intervention	0	0	1 (3%)
Respiratory muscle (MIP/MEP)	Pre / Post intervention	0	0	2 (6%)
Respiratory sounds	Pre / Post intervention	1 (3%)	0	0
Nº of coughs	During intervention	0	0	1 (3%)
Symptoms				
Breathlessness	Pre / Post intervention	1 (3%)	0	8 (23%)
BCSS	Pre / Post intervention			
Other self-reported symptoms (e.g., fatigue, pain, etc)	Pre / Post intervention	0	0	4 (12%)
ABG	Pre / Post intervention	0	0	3 (10%)
Biochemistry and haematology	Pre / Post intervention	0	0	3 (10%)
Vital signs (HR, SpO2, RR)	Pre / Post intervention	1 (3%)	0	9 (26%)
Session length	During intervention	0	0	2 (6%)
Patients´feedback	After the intervention	0	0	18 (53%)

VAS, visual analogical scale; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; $FEF_{25-75\%}$,forced expiratory flow between 25-75% of vital capacity; PEF, peak expiratory flow; TLC, total lung capacity; IC, inspiratory capacity; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; LCI, lung clearance index; LCQ, Leicester cough questionnaire; QoL-B, quality of life of bronchiectasis; SGRQ, Saint George respiratory questionnaire; CRQ, chronic respiratory disease questionnaire: CAT, COPD assessment test; BHQ, bronchiectasis health questionnaire; SF36, 36 item short form survey; 6MWT, six minute walk test; ISWT, incremental shuttle walk test; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; BCSS, breathlessness, cough and sputum scale; ABG, arterial blood gas; HR, heart rate; SpO2, oxygen saturation; RR, respiratory rate. # As sample size estimation is not usually included in abstracts, only full text manuscripts were included in this analysis (n=30).

Table S7. Risk of bias of the studies included in 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?*

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Morgan et al.[62] 1999, Australia ¥	?	?	?	?	?	?
De Oliveira et al.[63] 2001, Brazil	?	?	?	?	+	?
Thompson et al.[64] 2002, UK	?	?	?	?	+	?
Tsang et al.[65] 2003, Hong Kong	+	?	+	?	-	?
Patterson et al.[66] 2004, UK	+	?	?	?	+	?
Patterson et al.[67] 2005, UK	+	?	?	+	+	?
Eaton et al.[68] 2007, New Zealand	+	+	?	?	+	?
Patterson et al.[69] 2007, UK	+	?	?	?	+	?
Murray et al.[70] 2009, UK	+	?	?	?	+	+
Syed et al.[71] 2009, India	-	?	?	?	+	?
Naraparaju et al.[72] 2010, India	+	?	?	?	+	?

Shabari et al.[73] 2011, India	?	?	?	?	+	?
Tambascio et al.[74] 2011, Brazil	+	?	?	?	+	?
Paneroni et al.[75] 2011, Italy	+	?	?	?	+	?
Guimarães et al.[76] 2012, Brazil	+	+	?	?	+	+
Figueiredo et al.[77] 2012, Brazil	+	+	?	+	+	?
Amit et al.[78] 2012, India	+	-	?	?	+	?
Nicolini et al.[79] 2013, Italy	+	?	?	?	+	+
Anand et al.[80] 2014, India	?	?	?	?	?	?
Senthil et al.[81] 2015, India	?	?	?	?	?	?
Semwal et al.[82] 2015, India	?	?	?	?	+	?
Ramos et al.[83] 2015, Brazil	+	?	?	?	?	?
Herrero-Cortina et al.[84] 2016, Spain	+	?	+	?	+	+
AbdelHalim et al.[85] 2016, Egypt	?	?	?	?	+	?
Silva et al.[86] 2017, Australia	+	+	-	?	+	?
Tambascio et al.[87] 2017, Brazil	+	?	?	?	+	+

Üzmezoğlu et al.[88] 2018, Turkey	+	?	?	?	+	?
Muñoz et al.[89] 2018, Spain	+	+	+	+	+	+
Herrero-Cortina et al.[90] 2018, Spain ¥	?	+	+	+	+	?
Herrero-Cortina et al.[91] 2019, Spain ¥	?	?	?	?	+	?
de Souza et at.[53] 2019, Brazil	+	?	-	?	+	?
Santos et al.[92] 2020, Australia	+	+	-	+	+	?
Nicolini et al.[93] 2020, Italy ¥	+	+	?	?	+	+
Livnat et al.[94] 2021, Israel	+	?	?	+	+	+

+ low risk of bias; ? unclear risk of bias; - high risk of bias. Only randomised trials were included in the analysis. Multiple reports from the same study were also excluded. ¥ Abstracts.
Scoring based on the reviewer's judgement for each risk of bias category.

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