




Measuring airway clearance outcomes in bronchiectasis: a review

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For airway clearance research in bronchiectasis, sputum volume, lung function, dyspnoea and health-related and cough-related quality of life are currently the most common clinical and patient-reported measures of airway clearance treatment efficacy. <https://bit.ly/2KXRdg8>

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ABSTRACT While airway clearance techniques (ACTs) are recommended for individuals with bronchiectasis, many trials have demonstrated inconsistent benefits or failed to reach their primary outcome. This review determined the most common clinical and patient-reported outcome measures used to evaluate the efficacy of ACTs in bronchiectasis. A literature search of five databases using relevant keywords and filtering for studies published in English, up until the end of August 2019, was completed. Studies included randomised controlled trials, using crossover or any other trial design, and abstracts. Studies were included where the control was placebo, no intervention, standard care, usual care or an active comparator. Adults with bronchiectasis not related to cystic fibrosis were included. Extracted data comprised study authors, design, duration, intervention, outcome measures and results. The search identified 27 published studies and one abstract. The most common clinical outcome measures were sputum volume (n=23), lung function (n=17) and pulse oximetry (n=9). The most common patient-reported outcomes were health-related quality of life (measured with St George's Respiratory Questionnaire, n=4), cough-related quality of life (measured with Leicester Cough Questionnaire, n=4) and dyspnoea (measured with Borg/modified Borg scale, n=8). Sputum volume, lung function, dyspnoea and health- and cough-related quality of life appear to be the most common clinical and patient-reported measures of airway clearance treatment efficacy.

Introduction

Bronchiectasis is a chronic and progressive lung disease associated with cough, sputum and respiratory infection [1]. It is a highly heterogeneous disease of varied aetiology, coexisting conditions and overlap syndromes [2–4]. Chronic airway infection with pathogenic bacteria is common [5]. Individuals differ in terms of disease severity, exacerbation frequency and prognosis [6, 7]. Recent years have seen increasing worldwide prevalence of bronchiectasis [8–11], increased economic burden [12–14] and increased interest in clinical trials [15–19]. The objectives of treatment are to improve symptoms and quality of life, prevent respiratory exacerbations and slow disease progression [20, 21]. International guidelines highlight the paucity of evidence-based treatment options available for individuals with bronchiectasis [1, 20].

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Currently, most therapies are based on low to moderate quality evidence, with many clinical trials failing to reach their primary end-point or outcome, or producing inconsistent findings [5, 19, 20, 22, 23].

In contrast, many therapies have demonstrated clinical utility in cystic fibrosis (CF) and COPD [24, 25] with researchers extrapolating these therapies and outcome measures to bronchiectasis [26]. However, the failure of some therapies to show benefits in bronchiectasis, notably recombinant human deoxyribonuclease [27], suggests this approach may be misleading. Despite a lack of high-quality evidence, current international guidelines [1, 20, 28, 29] for the management of bronchiectasis recommend strategies that minimise airway damage by reducing inflammation and infection and improving airway clearance [28, 30].

Most individuals with bronchiectasis produce sputum daily and airway clearance is regarded as a mainstay of therapy [20, 31, 32]. Airway clearance techniques (ACTs) are applied by respiratory clinicians to facilitate secretion removal [33–36]. International guidelines [1, 20, 28] recommend ACTs be personalised to the individual with bronchiectasis to improve outcomes. Although ACTs have been extensively studied in other chronic lung diseases, our understanding of ACT usage remains limited in individuals with bronchiectasis. The purpose of this narrative review is to identify and discuss the most common clinical and patient-reported outcome measures used to evaluate the efficacy of ACTs in bronchiectasis.

Literature search strategy

A narrative review was conducted on the reporting of airway clearance studies in adults with bronchiectasis. The Cochrane, PubMed, PEDro, EMBASE and MEDLINE databases were searched using the keywords “bronchiectasis”, “non-cystic fibrosis bronchiectasis”, “airway clearance”, “airway clearance techniques”, “airway clearance devices”, “physiotherapy”, “chest physiotherapy” and “positive expiratory pressure devices”, and filtered for studies published in English, up until the end of August 2019. The review included randomised controlled trials, using crossover or any other trial design, and abstracts. Only studies examining subjects aged >18 years with bronchiectasis not related to CF were included. The interventions involved an airway clearance technique or device. Studies were included in which the control was placebo, no intervention, standard care, usual care or an active comparator. Trials specifically testing pharmacotherapies, diet or exercise were excluded, as the objective of the review was to determine outcomes specifically for airway clearance trials. The principal author extracted the studies and data. Extracted data comprised study authors, design, duration, intervention, outcome measures and results. Any issues raised with study inclusion criteria were resolved by discussion with the research team. The search identified 27 published studies and one abstract that were included in this narrative review.

Clinical outcome measures

Sputum

The purpose of an ACT is to supplement the body’s mucociliary clearance system and facilitate sputum removal [33, 34], with guidelines [1, 20, 25, 28, 29, 37–39] recommending individuals with chronic productive cough or difficulty expectorating sputum be taught ACTs. The rationale by which ACTs improve sputum clearance includes changes in lung volumes, pressures and flows, the use of gravity, and the application of compressive or vibratory forces [36, 40].

Sputum volume

Sputum volume has been assessed in airway clearance studies using different methods including sputum wet weight [41–44], dry weight [42], the volume collected during and/or immediately following an intervention [35, 41–46] or the volume collected in a 24-h period post-intervention [35, 41, 43]. Studies of airway clearance in bronchiectasis report variations in results on sputum volume. Most studies document an increase in sputum volume with use of ACTs [35, 43, 45, 46] but some report inconsistent findings between different studies depending on when sputum volume was measured [35, 42, 43], while other studies found no benefit on sputum volume with different ACT interventions [41, 42, 44]. These variations may be due to different study populations, variations in ACTs applied and the sputum measurement time-periods. The longer term effect of regular ACTs is relatively unknown, with only one study conducted over 12 months. This study reported that sputum volume during interventions with expiration with an open glottis in the lateral posture (ELTGOL), and 24 h later, was higher in the ELTGOL group than in the placebo group, both at the beginning and end of the study [35].

While the measurement of sputum volume and weight would appear to be straightforward or simple, there are well-documented limitations with the collection and characterisation of sputum including the compliance required when collecting sputum weight over specific time-periods [30, 47, 48]. Limitations associated with the use of sputum weight include day-to-day variability, within day variability and swallowing of secretions [42]. Variables such as hydration, diet, weather and saliva contamination can also affect sputum weight [47] and the process of obtaining dry sputum weight from wet sputum weight has

not been standardised [42]. Airway clearance sessions or antibiotic use may increase sputum weight or volume in the short term, but actually reduce sputum weight or volume over the long term as inflammation reduces [47]. Furthermore, none of these studies discussed data on sputum volume variability as an outcome measure or the minimal clinically important difference required for sputum volume. Despite these limitations, 23 out of the 28 reviewed studies used sputum volume as an outcome measure (table 1).

Sputum inflammatory analysis

Bronchiectasis is characterised by neutrophilic inflammation [67] but only two of the 28 reviewed studies included a sputum cytology measure [45, 52] such as neutrophils, lymphocytes, macrophages, eosinophils and total cell count (table 1). NICOLINI *et al.* [45] reported no changes in sputum total cell counts measured after use of high frequency chest wall oscillation (HFCWO) or conventional chest physiotherapy (including positive expiratory pressure (PEP) bottle, PEP mask, ELTGOL and oscillatory PEP) twice daily for 15 days. However, a reduction in neutrophil percentage and an increase in macrophage percentage were observed in the HFCWO group. TAMBASCIO *et al.* [52] reported no differences in total number of cells, eosinophils, neutrophils, macrophages and lymphocytes between 4 weeks' daily use of an oscillating PEP device, the Flutter, and the comparator group (Flutter generating PEP only, without the inner ball). However, when only the Flutter group was evaluated, there was a decrease in the total number of inflammatory cells. Both studies identify the therapeutic potential of ACTs in improving some sputum inflammatory markers in individuals with stable bronchiectasis.

Sputum microbiology

The predominance of *Pseudomonas aeruginosa* in sputum has been shown to increase exacerbations [68, 69] and hospitalisation [69], impair health-related quality of life (HRQoL) [69, 70] and lung function [68], and increase disease severity [70, 71] and mortality [69]. The impact of ACTs on both qualitative and quantitative bacteriology has been used to assess response to ACTs, with four of the 28 reviewed studies documenting a measure of sputum microbiology. Using quantitative bacteriology, TAMBASCIO *et al.* [52] reported *Pseudomonas aeruginosa* as the most common detected bacteria but found no difference in the total number of colony-forming units pre- and post-4 weeks' daily use of the Flutter or control. MURRAY *et al.* [30] also found no differences in sputum bacterial load when using an oscillating PEP device, the Acapella Choice, twice daily for 3 months compared with no ACT in individuals with stable bronchiectasis. Using qualitative bacteriology, MUNOZ *et al.* [35] reported *Pseudomonas aeruginosa* and *Haemophilus influenzae* to be the two most common pathogens but did not report differences in pathogen number after 12 months of ACT. In a 2-week study by ABDELHALIM [46], the authors reported they tested sputum culture and sensitivity; however, the results of these measures were not documented.

Sputum: other

Several studies included measures of sputum colour [35], purulence [35, 52], adhesiveness [52], mucociliary transport [34, 52], viscoelasticity [62] or change in sputum characteristics [62] pre- and post-ACT interventions. While changes were documented the results were inconsistent. Moreover, the methods of reporting these characteristics appear nonstandardised and difficult to replicate, making the application of these results problematic.

Respiratory exacerbations

Minimising respiratory exacerbations is a key aim in bronchiectasis management [1] and a major topic for pharmacological research in this disease [72]. Until recently there was no consensus-based definition for a respiratory exacerbation in bronchiectasis research [73]. Subsequently, a systematic review of pharmacotherapeutic trial end-points for individuals with bronchiectasis identified many variations in protocol-defined respiratory exacerbations, methods of analyses and durations of follow-up [47]. Unlike pharmacotherapeutic trials, in which the most frequently used end-point was exacerbation frequency, there has only been one study on airway clearance that has used exacerbation frequency and time to first exacerbation as an outcome measure. MUNOZ *et al.* [35] conducted the first and longest randomised placebo-controlled trial in airway clearance in bronchiectasis and found twice daily airway clearance (ELTGOL) over 12 months was associated with fewer exacerbations compared with placebo ($p=0.042$). However, the time to first exacerbation was not different between the groups. It is of interest to note that the definition of respiratory exacerbation used in this study does not meet the current consensus definition of a respiratory exacerbation recommended for use in bronchiectasis research. The current definition includes a deterioration in three or more symptoms including cough, sputum (volume, consistency, purulence), breathlessness, exercise tolerance, fatigue, malaise, haemoptysis, and a clinician must determine a change in treatment is required [73]. Now that there is a clearer definition for respiratory exacerbation, it

TABLE 1 Airway clearance studies in bronchiectasis

First author [ref.]	Design	Duration	Subjects (n)	Intervention	Outcome measures
MUNOZ [35]	Randomised controlled trial	1 year	44	ELTGOL Placebo (stretches)	Sputum: volume, purulence, colour, microbiology Respiratory function testing: FEV ₁ HRQoL: SGRQ Cough-related QoL: LCQ Dyspnoea: mMRC Exercise capacity: 6MWT Exacerbations: frequency, time to first exacerbation Systemic inflammation: venous blood Adherence: self-report diary Adverse events: SpO ₂ , Borg scale for dyspnoea
ARIF [49]	Randomised controlled trial	4 weeks	60	Antibiotics Chest PT Antibiotics and chest PT	Sputum: quantity Respiratory function testing: PEF Dyspnoea: Modified Borg scale Pulse oximetry: SpO ₂ Other: auscultation
TSANG [41]	Randomised controlled trial	<1 week	15 (acute exacerbation)	PD + breathing + cough Flutter + breathing + cough Breathing + cough	Sputum: wet weight Respiratory function testing: FVC, FEV ₁ , PEF Patient perception: Likert scale (ease and effectiveness of ACT)
HERALA [50]	Randomised controlled trial	Unclear	15	Thoracic compression Bubble PEP	Transcutaneous partial pressure of carbon dioxide
NICOLINI [45]	Randomised controlled trial	15 days	37	HFCWO Conventional chest PT Control (medical therapy)	Sputum: volume, cell count [#] Respiratory function testing: FEV ₁ , FVC, TLC, RV, MIP, MEP HRQoL: CAT Cough-related QoL: breathing, cough and sputum scale Dyspnoea: mMRC Gas exchange: PaO ₂ , PaCO ₂ Systemic inflammation: C-reactive protein
DE SOUZA [51]	Randomised crossover	10 days	40	Flutter Thoracic compression with deep breathing Control (tidal volume breathing)	Sputum: wet and dry weight, adhesiveness, purulence Respiratory function testing: impulse oscillometry Dyspnoea: MRC Patient perception: Likert scales (acceptability, tolerance, difficulty of expectorating sputum) Pulse oximetry: SpO ₂ , heart rate
SILVA [42]	Randomised crossover	<2 weeks	40	Flutter Lung flute	Sputum: wet and dry weight Patient perception: Likert scale (acceptance, tolerability of ACT)
TAMBASCIO [52]	Randomised crossover	10 weeks	17	Flutter Flutter (PEP only)	Sputum: adhesiveness, purulence, mucociliary transport, displacement in simulated cough machine, contact angle measurement, inflammatory analysis, microbiology

Continued

TABLE 1 Continued

First author [ref.]	Design	Duration	Subjects (n)	Intervention	Outcome measures
HERRERO-CORTINA [43]	Randomised crossover	5 weeks	31	AD ELTGOL Temporary PEP (Uniko)	Sputum: wet weight Respiratory function testing: FEV ₁ , FEV ₁ % pred, FVC, FVC % pred, FEF _{25-75%} Cough-related QoL: LCQ Pulse oximetry: SpO ₂ , heart rate Patient perception: Likert scale (preference for ACT) Adverse events: pulse oximetry, heart rate
SEMVAL [44]	Randomised crossover	1 day	30	ADA Acapella	Sputum: volume, wet weight Respiratory function testing: PEF Dyspnoea: Modified Borg Pulse oximetry: SpO ₂ Other: Respiratory rate Patient perception: VAS (comfort of ACT)
SVENNINGSEN [53]	Randomised crossover	6 weeks	29 (15 COPD, 14 bronchiectasis)	Aerobika Usual care	Respiratory function testing: FEV ₁ % pred, FVC % pred, FEV ₁ /FVC HRQoL: SGRQ Exercise capacity: 6MWT Patient perception: patient evaluation questionnaire (cough frequency, dyspnoea, ease in bringing up sputum)
FIGUEIREDO [33]	Randomised crossover	9 days	8	Flutter Flutter sham	Sputum: volume Respiratory function testing: Impulse oscillometry (FOT)
GUIMARÃES [54]	Randomised crossover	24 days	10	ELTGOL Flutter Control (sitting)	Sputum: dry weight Respiratory function testing: FVC, FEV ₁ , FEV ₁ /FVC, FEF _{25-75%} , IC, VC, TLC, RV
TAMBASCIO [34]	Randomised crossover	9 weeks	18	Flutter Flutter (PEP only)	Sputum: mucociliary relative transport velocity, displacement in a simulated cough machine and contact angle measurement
MURRAY [30]	Randomised crossover	7 months	20	Acapella Choice No chest PT	Sputum: 24 h sputum volume, microbiology Respiratory function testing: FEV ₁ , FVC, FEF _{25-75%} , MIP, MEP HRQoL: SGRQ Cough-related QoL: LCQ Exercise capacity: incremental shuttle walk test Adherence: diary Adverse events: diary (haemoptysis, increased use of short-acting bronchodilator)
SYED [55]	Randomised crossover	<2 days	35	ACBT with PD Conventional chest PT (percussion, vibrations, PD, coughing, breathing)	Sputum: wet weight Respiratory function testing: FVC, FEV ₁ , FEV ₁ /FVC Patient perception: VAS (comfort of ACT)

Continued

TABLE 1 Continued

First author [ref.]	Design	Duration	Subjects (n)	Intervention	Outcome measures
PATTERSON [56]	Randomised crossover	10–12 days	20 (acute exacerbation)	Acapella DM or DH with PD Usual ACT (ACBT, PEP, huffs, nil)	Sputum: volume/weight Respiratory function testing: FEV ₁ , FEV ₁ % pred, FVC, VC, PEF Dyspnoea: Borg scale, 15-count breathlessness score Pulse oximetry: SpO ₂ Patient symptoms: Interview-Based Questionnaire Patient adherence: diary and weekly phone calls Patient perception: preference
PATTERSON [57]	Randomised crossover	2 days	20	Acapella DH and DM with PD ACBT (including percusion, vibrations and PD)	Sputum: weight Respiratory function testing: FEV ₁ , FEV ₁ % pred, FVC, FVC % pred, PEF, PEF % pred Dyspnoea: 15 count breathlessness score Pulse oximetry: SpO ₂ Patient perception: questionnaire (preference) Other: number of coughs
THOMPSON [58]	Randomised crossover	4 weeks	17	ACBT Flutter	Sputum: weight Respiratory function testing: PEF HRQoL: Chronic Respiratory Disease Questionnaire Dyspnoea: Borg scale duration of airway clearance session Patient perception: preference
ANTUNES [59]	Randomised crossover	8 weeks	13	Conventional chest PT (percussion with vibrations, PD) Flutter	Sputum: wet and dry weight Respiratory function testing: FVC, FEV ₁ , PEF Pulse oximetry: SpO ₂ , heart rate Other: respiratory rate
SUTTON [60]	Randomised crossover	4 days	8	PD + FET Control (sitting) with nebulised saline and nebulised terbutaline	Sputum: wet weight Respiratory function testing: FEV ₁ , FVC Other: radio aerosol clearance
UZMEZOGLU [61]	Randomised comparative	4 weeks	40	Flutter ACBT with PD	Sputum: change in sputum production Respiratory function testing: FEV ₁ % pred, FVC % pred, FEV ₁ /FVC, PEF % predicated HRQoL: SF-36 Dyspnoea: Modified Borg, MRC Patient symptoms: questionnaire
ABDELHALIM [46]	Randomised comparative	2 weeks	30 (acute exacerbation)	ACBT + PD Conventional PT (PD + diaphragmatic breathing + percussion)	Sputum: wet volume, microbiology Respiratory function testing: FEV ₁ , FVC, MMEF, FEV ₁ /FVC QoL: LCQ Dyspnoea: mMRC Gas exchange: PaO ₂ , PaCO ₂ , P _{A→O₂} Adverse events: not defined

Continued

TABLE 1 Continued

First author [ref.]	Design	Duration	Subjects (n)	Intervention	Outcome measures
RAMOS [62]	Randomised comparative	4 days	22	PD + coughing PD + percussion + coughing PD + huff Control (coughing)	Sputum: wet and dry weight, viscoelasticity
EATON [63]	Prospective randomised comparative	7 days	37	Flutter ACBT ACBT + PD	Sputum: wet weight, volume Respiratory function testing: FEV ₁ % pred, FVC % pred Dyspnoea: Borg scale Pulse oximetry: SpO ₂ Patient perception: Likert scales (acceptability and tolerability, preference)
SVENNINGSEN [64]	Randomised comparative	3 weeks	30	Aerobika Health control	Respiratory function testing: FEV ₁ , FVC, D _{LCO_{sb}} Exercise capacity: 6MWT HRQoL: SGRQ Imaging: CT, MRI Patient perceptions: patient evaluation questionnaire
D'ABROSCA [65]	Retrospective cohort study	Minimum 10 days of ACT (4-year data collection period)	162 (97 COPD, 65 bronchiectasis)	Temporary PEP (Uniko) PEP (mask) during a pulmonary rehabilitation programme	Respiratory function testing: FEV ₁ , FEV PaO ₂ % pred, FVC, FVC % pred, FEV ₁ /FVC, FEF _{25-75%} , FEF _{50%} Gas exchange: PaO ₂
GRILLO [66]	Prospective Cohort study	~2 weeks	90 (32 stable, 32 exacerbation, 26 control)	Usual ACT (type of ACT not defined): stable Usual ACT (type of ACT not defined): exacerbation Healthy control	Respiratory function testing: LCI, FEV ₁ , transfer factor for CO, CO transfer coefficient

ELTGOL: slow expiration with the glottis open in lateral posture; FEV₁: forced expiratory volume in 1 s; HRQoL: health-related quality of life; SGRQ: St George's Respiratory Questionnaire; QoL: quality of life; LCQ: Leicester Cough Questionnaire; mMRC: modified Medical Research Council Questionnaire; 6MWT: 6-min walk test; SpO₂: oxygen saturation measured by pulse oximetry; PT: physiotherapy; PEF: peak expiratory flow; PD: postural drainage; FVC: forced vital capacity; ACT: airway clearance technique; PEP: positive expiratory pressure; HFVCO: high frequency chest wall oscillation; TLC: total lung capacity; RV: residual volume; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; CAT: COPD assessment tool; PaO₂: arterial oxygen tension; PaCO₂: arterial carbon dioxide tension; MRC: Medical Research Council Scale; AD: autogenic drainage; FEF_{25-75%}: forced expiratory flow at 25–75% of FVC; VAS: Visual Analogue Scale; FOT: forced oscillatory technique; IC: inspiratory capacity; VC: vital capacity; ACBT: active cycle of breathing technique; DM: <definition>; DH: <definition>; FET: forced expiratory technique; SF-36: Short Form 36; MMEF: maximal mid-expiratory flow; P_{A-aO₂}: alveolar–arterial oxygen tension difference; D_{LCO_{sb}}: single breath diffusing capacity of the lung for carbon monoxide; CT: computed tomography; MRI: magnetic resonance imaging; LCI: lung clearance index. #cell count (white blood cells, red blood cells, neutrophils and lymphocytes).

is important that future trials include this outcome for a range of ACTs, as well as having longer follow-up periods (>12 months) to evaluate exacerbation frequency.

Lung function

Measures of lung function, particularly forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC), are frequently used as markers of pharmacotherapy treatment efficacy in bronchiectasis [16, 17], CF [74] and COPD [75]. Provided studies follow guidelines [76–78], the measurement of lung volumes may be reliable enough to assess lung function pre- and post-ACT interventions. However, numerous

studies in individuals with bronchiectasis have demonstrated lung function is poorly responsive to pharmacotherapy [17, 23, 79, 80]. From the 28 reviewed studies on airway clearance, 23 had at least one outcome measure related to lung function. Only one of these 23 studies, a randomised controlled trial by NICOLINI *et al.* [45], reported a significant improvement in FEV₁ and FVC after using conventional chest physiotherapy or HFCWO twice daily for 15 days, but the authors stated the improvement was unlikely to be of clinical significance.

Other measures of lung function, such as peak expiratory flow, mid-expiratory flow (forced expiratory flow at 25–75% FVC and maximal mid-expiratory flow), total lung capacity and residual volume, have also been used as outcome measures in 17 out of 28 airway clearance studies but with most reporting no improvements [30, 41, 43–46, 54, 56–59, 61, 65]. Therefore, to date, lung function does not appear to be a useful outcome measure for treatment efficacy in bronchiectasis airway clearance studies with durations less than 12 months. It has been suggested that lung function may be more beneficial for monitoring potential adverse treatment effects rather than to assess treatment efficacy [21, 27].

Respiratory muscle strength

Respiratory muscle strength has also been studied in individuals with bronchiectasis through the measurement of maximal inspiratory and expiratory pressure (MIP and MEP, respectively) [81]. Two of the 28 reviewed studies [30, 45] used MIPs and MEPs as outcome measures with conflicting results. NICOLINI *et al.* [45] reported a benefit in MIP and MEP with HFCWO for 15 days compared with control; however, a randomised crossover trial by MURRAY *et al.* [30] reported no improvement in MIP or MEP with twice daily use of the Acapella Choice compared with no chest physiotherapy over 3 months.

Lung clearance index

More recently, assessment of peripheral airway function as a measure of disease severity has been explored in CF [82–84] and asthma [85]. The lung clearance index (LCI) is derived from the multiple breath inert gas washout technique and is a measure of airway ventilation heterogeneity [83]. In chronic lung diseases, factors that may contribute to ventilation heterogeneity include sputum retention, airway inflammation and airway wall remodelling, and hence increase washout time [21]. The LCI has been shown to be a valid, reliable and responsive measure in CF [86] and more sensitive to airway damage than spirometry in CF [82]. Some limitations to using LCI include the purchase of expensive equipment, technology required to measure LCI and time and training of staff to administer [82, 87]. Studies investigating the role of LCI in bronchiectasis are very limited. ROWAN *et al.* [88] found LCI a repeatable and sensitive indicator of radiological changes in bronchiectasis [88] and GONEM *et al.* [89] found the LCI may have potential as a marker of disease severity in bronchiectasis. To date, one study has used the LCI as an outcome measure for airway clearance in bronchiectasis [66]. LCI was repeatable but unresponsive to two single airway clearance interventions; however, the type of ACT was not defined [66]. While the LCI may be a promising outcome measure that examines the important ventilatory heterogeneity, further robust studies examining its efficacy across a range of ACTs and in longer term studies in bronchiectasis are warranted.

Impulse oscillometry/forced oscillatory technique

Conventional methods of lung function testing provide measurements obtained during specific respiratory manoeuvres of the subject [90]. In contrast, the impulse oscillometry/forced oscillatory technique (FOT) is a noninvasive method of evaluating respiratory mechanics [91] using an interface device that allows its application by means of impulse oscillometry. FOT employs small amplitude pressure oscillations superimposed on normal tidal breathing to describe the resistive and reactive properties of the respiratory system [92] and has the advantage over conventional pulmonary assessment methods in that it is not patient effort dependent [91]. FOT is a reliable measure in the assessment of bronchial responsiveness [93] and has been used to classify disease severity in COPD and asthma [91, 94], and assess lung function in CF [92]. Literature evaluating FOT in adults with bronchiectasis is very limited. GUAN *et al.* [95] reported that FOT parameters readily discriminated individuals with bronchiectasis from healthy subjects, but were not superior to the diagnostic performance of spirometry. In a more recent study by the same authors, they concluded that FOT and peripheral airway spirometry parameters have similar diagnostic value in reflecting peripheral airway disorders, and correlate with high-resolution computed tomography (HRCT) scores and the bronchiectasis severity index [96]. In terms of using FOT as an outcome measure in airway clearance in bronchiectasis, a small randomised crossover study by FIGUEIREDO *et al.* [33] found that a single intervention of the Flutter diminished total and peripheral airway resistance in adults with bronchiectasis. Similarly, a recent study by DE SOUZA [51] found that the Flutter was effective for secretion removal and decreasing total and peripheral respiratory system resistance, and thoracic compression had comparable positive effects on reducing peripheral resistance.

Systemic inflammatory analysis

A very limited number of studies have explored the impact of ACTs on haematological measurements in bronchiectasis. Only two of the 28 reviewed studies collected serum inflammatory markers. MUNOZ *et al.* [35] included total leukocyte and neutrophil count, C-reactive protein, erythrocyte sedimentation rate and fibrinogen, and NICOLINI *et al.* [45] included C-reactive protein. MUNOZ *et al.* [35] reported no differences in systemic inflammatory markers with airway clearance over 12 months, whereas NICOLINI *et al.* [45] reported a reduction in C-reactive protein after using HFCWO twice daily for 15 days compared with conventional chest physiotherapy. The correlation between airway inflammation and systemic inflammation is relatively poor [97] and systemic inflammatory markers may have a minimal role in evaluating responses to ACTs in stable disease. Instead, these markers may have more of a role during acute respiratory exacerbations that are typically associated with a systemic inflammatory response, although further studies are required to determine this [21].

Exercise capacity

Exercise capacity is an important reflection of respiratory-related function and the 6-min walk test (6MWT) and incremental shuttle walk test (ISWT) are valid and reliable field tests in bronchiectasis [98–100]. Of the 28 reviewed studies, three used the 6MWT [35, 54, 65] as a measure of exercise capacity and one study used the ISWT [30] in stable bronchiectasis. MURRAY *et al.* [30] reported an improvement in ISWT distance following 3 months of twice daily use of Acapella Choice. The authors postulated that with greater sputum clearance and cough control, exercise capacity may also improve. Unlike MURRAY *et al.* [30], MUNOZ *et al.* [35], SVENNINGSEN *et al.* [53] and SVENNINGSEN *et al.* [64] did not observe any improvement in the 6MWT. Comparisons between the studies are difficult due to the different exercise tests and study populations. It may be necessary to combine an ACT with a specific exercise-based programme to improve exercise capacity, given that the main objective of ACTs is secretion expectoration [35, 101].

Imaging/radiology

HRCT is the gold standard in diagnosis of bronchiectasis [102], but no studies have used HRCT as an outcome measure in ACT research in bronchiectasis. Only one of the 28 reviewed studies used magnetic resonance imaging (MRI) as an outcome. In this small study by SVENNINGSEN *et al.* [64], approximately half of the participants had evidence of ventilation improvements on MRI after 3 weeks of daily use of an oscillating PEP device, the Aerobika. Given the very limited evidence available to date, the role of imaging/radiology as a clinical outcome measure in airway clearance studies is difficult to evaluate and requires further investigation. Limitations such as cost and radiation exposure may also provide reasons for the lack of imaging/radiology outcomes used in airway clearance studies.

Pulse oximetry

Pulse oximetry is a simple noninvasive approximation of arterial oxygenation and heart rate [103]. Nine of the 28 reviewed studies included an outcome measure of pulse oximetry. No studies documented whether a finger or forehead probe was used. No studies showed a difference in resting oxygen saturation or heart rate pre- or post-ACTs. It is most likely that pulse oximetry has been used as an outcome to assess safety rather than efficacy of ACTs [51].

Gas exchange

Measures of arterial gas exchange including arterial carbon dioxide tension (P_{aCO_2}), arterial oxygen tension (P_{aO_2}) and venous transcutaneous carbon dioxide tension (P_{tcCO_2}) were used as outcome measures in four of the 28 reviewed studies. A small study by HERALA *et al.* [50] evaluated changes in P_{tcCO_2} and reported both thoracic compression and a PEP device (Bubble PEP) temporarily reduced P_{tcCO_2} . Results varied for other studies with NICOLINI *et al.* [45] finding no differences with ACT on P_{aO_2} and P_{aCO_2} . ABDELHALIM *et al.* [46] and D'ABROSCA *et al.* [65], however, reported improvements in P_{aO_2} before and after ACTs. These authors suggested this may be due to ACTs improving alveolar ventilation and optimising ventilation/perfusion matching and therefore improving gas exchange.

Patient-reported outcome measures

HRQoL

Improving HRQoL is a major goal of management of individuals with bronchiectasis [21]. HRQoL questionnaires in chronic respiratory diseases consist of questions about physical and psychological morbidity and allow clinicians to quantify the effect of the disease on an individual's daily life [21]. Most health-related questionnaires have been minimally validated for use in bronchiectasis and only two, the Bronchiectasis Health Questionnaire (BHQ) and Quality of Life – Bronchiectasis (QOL-B), have been specifically designed for use in this patient population [104, 105].

BHQ

The BHQ is the most recently developed and validated HRQoL questionnaire for use in bronchiectasis [104]. It is a brief evaluation of 10 items and one single domain including aspects of daily life, sputum and infection [104]. To date, there have been no studies published on bronchiectasis pharmacotherapy or airway clearance research that have used this tool.

QOL-B

The QOL-B consists of 37 items and eight scales including respiratory symptoms, physical, role, emotional and social functioning, vitality, health perceptions and treatment burden [105]. Although designed and validated for use in bronchiectasis [105], no studies have used it in airway clearance research. The questionnaire has been used in pharmacology clinical trials [5, 22] and one qualitative study by DUDGEON *et al.* [106] investigating patient preference for quality of life tools in bronchiectasis.

St George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) was developed for use in COPD and is a 50-item self-administered questionnaire assessing the domains of symptoms, activity and impact [107]. It has been validated for use by one study in bronchiectasis [108]. It is the most common HRQoL questionnaire used in airway clearance research in bronchiectasis with four out of the 28 reviewed studies using it. In a small, randomised crossover study by MURRAY *et al.* [30], twice daily use of the Acapella Choice compared with no chest physiotherapy over 3 months improved HRQoL (measured using SGRQ). Similarly, a longer term study by MUNOZ *et al.* [35] reported an improvement in SGRQ total score when using ELTGOL compared with placebo. Two short-term studies by SVENNINGSEN and co-workers [53, 64] reported varying results on SGRQ. In a mixed cohort of COPD and bronchiectasis, 3 weeks of daily Aerobika use improved quality of life (measured using SGRQ) [53]. A study by the same group with a single cohort of individuals with bronchiectasis, however, found no improvements in SGRQ with 3 weeks of daily Aerobika use [64]. Comparing the results of these two studies is not possible because the study by SVENNINGSEN *et al.* [53] is a published abstract with limited methodological detail and the results from participants with either COPD or bronchiectasis were pooled, which may have impacted study results.

Short Form-36

The Short Form-36 (SF-36) is a generic 36-item questionnaire with eight subscales including physical function, social function, role limitations for physical problems and emotional problems, mental health, vitality, health perception and health transition [109]. It has been validated for use in individuals with COPD [110], interstitial lung disease [111] and asthma [112] but not for individuals with bronchiectasis. Of the 28 studies reviewed, only one used this questionnaire to evaluate airway clearance in individuals with bronchiectasis. UZMEZOGLU *et al.* [61] reported an improvement in the physical sub-scale of SF-36 score after twice daily use of either the Flutter or active cycle of breathing technique (ACBT) for 4 weeks.

Chronic Respiratory Disease Questionnaire

The Chronic Respiratory Disease Questionnaire (CRDQ) consists of 20 items and assesses the domains of dyspnoea, fatigue, emotional function and mastery [113]. It was originally developed for use in COPD and has been validated in both COPD [114] and mild to moderate bronchiectasis [115]. The small study by THOMPSON *et al.* [58] used the CRDQ and reported no health impact for individuals with bronchiectasis who completed 4 weeks of daily ACBT or Flutter.

COPD assessment tool

The COPD assessment tool (CAT) was developed for use in COPD and consists of eight items assessing the global impact of cough, sputum, dyspnoea, and chest tightness on health status [116]. It has been validated for use in individuals with COPD [116] and bronchiectasis [117]. One randomised controlled trial by NICOLINI *et al.* [45] reported improvements in CAT scores when using HFCWO and conventional chest physiotherapy compared with controls with bronchiectasis.

Cough-related quality of life

The Leicester Cough Questionnaire (LCQ) was developed to evaluate quality of life in individuals with chronic cough. It contains 19 items with three domains (physical, psychological and social) and has been validated for use in bronchiectasis [118]. It is one of the most common quality of life measures, with four out of the 28 reviewed studies utilising it. MUNOZ *et al.* [35] reported that twice daily ELTGOL over 1 year improved cough impact (measured using LCQ). In a randomised crossover study of 1 week duration by Herrero-CORTINA *et al.* [43], LCQ scores improved with use of autogenic drainage, ELTGOL or temporary PEP, although this improvement was not clinically significant. ABDELHALIM *et al.* [46] reported improvement in the physical domain and total score of the LCQ after using either ACBT or conventional chest physiotherapy twice daily

for 14 days during a respiratory exacerbation. Furthermore, MURRAY *et al.* [30] found that with 3 months of twice daily use of Acapella Choice, there was improvement in all domains and total LCQ score.

Dyspnoea

Medical Research Council scale for dyspnoea

The Medical Research Council scale for dyspnoea (MRC) is a five-point scale (graded from 1 to 5) which establishes functional impairment due to dyspnoea attributable to respiratory disease [119]. It has been used in studies in COPD [120], asthma [121] and idiopathic pulmonary fibrosis [122]. The MRC was used in two out of the 28 reviewed studies.

A study by UZMEZOGLU *et al.* [61] demonstrated reduced MRC scores with daily use of the Flutter, causing a greater improvement in the perception of dyspnoea than when using ACBT. Alternately, a randomised crossover study by DE SOUZA *et al.* [51] found no reduction in MRC score with use of either the Flutter, thoracic compression or control.

The modified MRC breathlessness scale (mMRC) is similar to the original MRC but uses a five-point scale from 0 to 4 [123]. The three reviewed studies that used the mMRC produced differing results. NICOLINI *et al.* [45] found HFCWO compared with conventional chest physiotherapy produced an improvement in mMRC scores when used twice daily for 15 days. ABDELHALIM *et al.* [46] also reported improvement in mMRC scores before and after the use of both ACBT and twice daily conventional physiotherapy for 14 days during a respiratory exacerbation. A longer duration study by MUNOZ *et al.* [35], however, found no differences in mMRC scores after 1 year of daily ELTGOL. The differences in results on dyspnoea are most likely to be attributed to methodological differences between the studies. Furthermore, it is of interest to mention that the Bronchiectasis Severity Index, a valid tool using a combination of clinical, radiological and microbiologic features to predict morbidity and mortality in bronchiectasis, includes the mMRC as one of its components [6].

15-count breathlessness score

The 15-count breathlessness score is determined by asking the subject to take a large inspiration then count to 15. The number of breaths that the subject requires to reach a count of 15 is the score. It has been validated for use in children with CF [124] but not in bronchiectasis. Two of the reviewed studies by PATTERSON and co-workers used this tool as an outcome measure [56, 57]. PATTERSON *et al.* [56] reported no differences between pre- and post-treatment dyspnoea for Acapella or usual airway clearance method during a 2 week mild respiratory exacerbation. Another randomised crossover study by PATTERSON *et al.* [57] studied the Acapella DH, DM or ACBT and reported no differences in dyspnoea.

Borg scale

The Borg scale is a 15-point subjective scoring system with ratings from 6 to 20 of perceived exertion while performing a particular activity [125]. Four of the 28 reviewed studies used the Borg scale but to assess different factors. MUNOZ *et al.* [35] monitored for any adverse effects of ELTGOL. The other three studies used the Borg scale to monitor perception of dyspnoea pre- and post-ACT interventions. PATTERSON *et al.* [56] found no differences in dyspnoea with the Acapella or usual airway clearance method for 14 days. EATON *et al.* [63] also found no differences pre- and post-ACTs with the Flutter, ACBT or ACBT with postural drainage over 1 week. A small 4 week randomised crossover study by THOMPSON *et al.* [58] also found no change in Borg score after individual physiotherapy sessions with either the Flutter or ACBT.

The modified Borg is similar to the original version but is a 12-point scoring system with ratings ranging from 0 to 10 [126]. Four of the 28 reviewed studies used the modified Borg to assess dyspnoea, with varying results. ARIF *et al.* [49] reported that the combined effect of antibiotic therapy and chest physiotherapy produced an improvement on the modified Borg score of subjects compared with antibiotics or chest physiotherapy alone. UZMEZOGLU *et al.* [61] also reported a reduction in the perception of dyspnoea with daily use of the Flutter and ACBT for 4 weeks compared with study commencement. In contrast, a randomised crossover study by SEMWAL *et al.* [44] documented no differences between modified Borg dyspnoea scores pre- and post-intervention with a single session of autogenic drainage or Acapella for 20–30 min.

Patient-reported symptoms/perceptions/adherence

To assist in the prescription of ACTs for individuals with bronchiectasis, it is essential to determine patient perspectives and beliefs about airway clearance and factors affecting adherence. International guidelines [1] recommend that clinicians consider patient preference and adherence when prescribing ACTs, with this recommendation based on expert consensus. Recent data from the European

Bronchiectasis Data Registry report only half of data registrants performed regular airway clearance [127]. There have only been a limited number of studies investigating symptom burden [106] and adherence [128–130] in individuals with bronchiectasis, all with varying study objectives and methodologies. A study by SPINOY *et al.* [131] used the LCQ to objectively evaluate cough frequency. The authors found that cough was a common and significant symptom in patients with bronchiectasis, and that sputum, exacerbations and age, but not lung function, were independent predictors of cough frequency [131].

Several studies in bronchiectasis airway clearance research have included an objective measure of patient perception documented by subjects on a Likert scale or questionnaire. These questions explored the perceived effectiveness or ease of use of ACTs [41], acceptance or tolerability of ACTs [42, 57, 63], perceived comfort [44, 55] and symptoms such as cough [57, 61]. The most common question asked is patient preference for an ACT; however, this was only asked in four studies [43, 56, 58, 63]. In some studies [58, 61, 63], patient-reported perceptions have been asked in addition to HRQoL questionnaires.

Only three of the 28 reviewed studies reported a measure of subject adherence to ACTs, each using a self-report diary card. A randomised crossover study by MURRAY *et al.* [30] monitored adherence with the Acapella Choice; however, the authors did not document any details about subject adherence. MUNOZ *et al.* [35] measured adherence to ELTGOL and control over 1 year with adherence rates of 80% and 75%, respectively. PATTERSON *et al.* [56] evaluated patient adherence during a mild respiratory exacerbation with the Acapella DM/DH with postural drainage and usual airway clearance. The diary card recorded duration of airway clearance sessions, sputum volume produced during airway clearance sessions and dyspnoea. In terms of adherence, the authors reported that subjects completed the diary card daily, but authors did not report definite adherence rates.

Adverse events

Only four of the 28 reviewed studies commented on any adverse events or side-effects during the studies. MUNOZ *et al.* [35] monitored for complications using a diary card and by observing changes in oxygen saturation measured by pulse oximetry and the Borg scale. Herrero-CORTINA *et al.* [43] monitored changes in oxygen saturation measured by pulse oximetry and heart rate. MURRAY *et al.* [30] monitored adverse events, specifically the presence of haemoptysis or increased use of bronchodilator therapy. ABDELHALIM *et al.* [46] also monitored adverse events but the authors did not describe their definition of such an event. There were no adverse events reported in any of the four studies.

Discussion

The aim of this narrative review is to determine and discuss the most common clinical and patient-reported outcome measures used to evaluate the efficacy of ACTs in bronchiectasis. Given that several recent large-scale pharmacological trials have failed to achieve consistently significant results [5, 19, 22], a re-evaluation of the outcome measures used in bronchiectasis is timely. International guidelines over the past decade have also emphasised the need for high-quality evidence to support ACTs in bronchiectasis [1, 20, 29, 132]. A recent editorial has issued a “call for action” for increased awareness and research into ACTs in bronchiectasis and the need for establishing clinically important outcomes [133]. The European Respiratory Society guidelines also confirmed the nine most important Patient/problem, Intervention, Comparison, Outcome (PICO) topics agreed between clinicians and patients, with respiratory physiotherapy considered one of the most important [20]. Therefore, it is essential to reach consensus for the most clinical and patient-reported outcome measures for airway clearance to guide development of future studies.

Our review has demonstrated that there is indeed a large range of outcome measures; however, some are clearly used in more trials than others. The most common clinical outcomes used include measures of sputum volume, lung function and pulse oximetry. Even though these are the most frequently used outcomes in trials to date, they are not without their limitations. As the objective of ACTs is to improve sputum clearance, it is not surprising that a large proportion of studies used sputum volume as an outcome. Although there are limitations to using sputum volumes, the perception of the individual with bronchiectasis about sputum is very important to assess. The optimal method for obtaining sputum volume requires further investigation to determine what is most reliable and repeatable. Studies are also required to identify sputum cytology measures and evaluate microbiology during studies of airway clearance, particularly during respiratory exacerbations. What is interesting is that many studies used lung function, namely spirometry, to assess efficacy of ACTs despite the sensitivity of spirometry being a questionable measure of short- to medium-term treatment efficacy in airway clearance studies [35, 46]. Further studies are needed to assess the impact of lung function in relation to patient health status and the relevance of different measurements of lung function in assessing response to ACTs. Adequately powered studies that include clinical outcome measures for small airway function, such as FOT or LCI, may be more clinically useful or sensitive to assessing treatment response.

The most common patient-reported outcomes included HRQoL, cough-related quality of life and dyspnoea. HRQoL can be significantly impaired in individuals with bronchiectasis [105, 106, 134] and, therefore, it is important to assess this patient-reported outcome especially due to the long-term treatment burden associated with ACTs. There are also differences in approaches to measuring quality of life in airway clearance studies and limited information has been published about minimal clinically important differences in these measures. It is interesting to observe that no airway clearance studies included the QOL-B, despite it being designed for and validated in bronchiectasis. Furthermore, a qualitative study by DUDGEON *et al.* [106] compared four different quality of life measures in bronchiectasis and reported that QOL-B was the preferred measure compared with the CAT, LCQ and SGRQ. The QOL-B and BHQ are relatively new outcome measures and may be the reason why they are yet to be used in airway clearance research.

The LCQ was the only measure used to investigate cough-related quality of life. The most common measure of dyspnoea was the Borg or modified Borg scale, but there is some confusion in the interpretation of the results of these studies as the authors did not describe the way patients assessed dyspnoea. It is not clear which anchor points or terminology was used, or whether these scales scored dyspnoea exclusively or rate of perceived exertion. It is therefore important that future studies use standardised versions of scales that are specifically validated to quantify dyspnoea intensity. It is reasonable that cough-related quality of life and dyspnoea were assessed in studies as they are some of the main symptoms of bronchiectasis. This is also supported by HALL *et al.* [135] who evaluated the impact of a specialist respiratory physiotherapy clinic on health and cough-related quality of life. Patients attended two clinic visits 4 to 6 weeks apart for individualised physiotherapy sessions (involving ACTs, exercise and use of adjunctive inhalation therapies) and reported improvements in the CAT and LCQ scores.

Other important factors to consider are patient preference and adherence to ACTs. As international guidelines recommend that clinicians consider these factors when prescribing ACTs [1], the fact few studies included these as outcomes is concerning. Future studies should include these outcomes, as well as potential recommendations regarding the minimum criteria for adherence to airway clearance and offer strategies to help maximise adherence.

Much like the literature examining therapeutic options in this population, the current evidence base for ACTs in bronchiectasis remains ambiguous due to variations in study aims, methodologies and outcome measures. Research challenges include the personalisation of ACTs, study blinding and placebo effects. Study designs including active comparators, clusters based on endotypes or phenotypes, or stepped-wedge implementation trials are alternative approaches that require consideration for future studies [133]. Adding to the confusion, there is currently no validated respiratory exacerbation prediction tool and there have been varying definitions of respiratory exacerbations in airway clearance studies [46, 59]. Factors such as disease heterogeneity, varying disease aetiology, ranging disease severity, coexisting conditions and overlap syndromes have made comparison of studies difficult. The methodological quality of the literature is variable with differences in risk of study bias, time frames and characterisation or definition of outcome measures. Most of the studies reviewed are crossover trials (n=16), with one placebo-controlled trial, and many randomised studies (n=26). Perhaps the most important and potentially significant limitation is that nearly all studies are short term. As bronchiectasis is a chronic and progressive disease, it is pivotal that studies investigating the efficacy of regular ACTs be conducted in long-term (>12 month) studies. The longer term trials by MUNOZ *et al.* [35] and MURRAY *et al.* [30] provide important results in this way regarding the effect of ACTs over 12 and 7 months, respectively.

HRQoL measures specifically designed and validated for individuals with bronchiectasis, such as the BHQ and QOL-B, should be examined further in studies along with cough-related quality of life and patient-reported symptoms. Treatment decisions and airway clearance prescription by clinicians should consider the potential beneficial effects of the ACT, supporting evidence for the ACT, current treatment burden and risk for adverse events [20]. It is essential that an integrated and personalised approach be applied when prescribing ACTs that includes patient preference, sputum quality, exacerbation history, quality of life, disease severity and underlying aetiology, as these factors may effect long-term outcomes [20]. Given the current state of knowledge, further studies are needed to investigate the optimum method of ACT, duration and frequency. Assessment of clinical and patient-reported outcome measures over the long term in varying severities of bronchiectasis are required, as well as evaluating the effects of ACTs in individuals undergoing a respiratory exacerbation.

Summary

This review has identified and discussed the most common clinical and patient-reported outcome measures used to assess efficacy of ACTs in bronchiectasis. While there is large heterogeneity in the studies published to date, the most common clinical outcome measures are sputum volume, lung function

and pulse oximetry. The most common patient-reported outcome measures are health and cough-related quality of life and dyspnoea. There is an urgent need for guidance to standardise and implement the most important clinical and patient-reported outcome measures in long-term studies to increase the likelihood of demonstrating significant benefits and to guide personalised prescription of ACTs in bronchiectasis.

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