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Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis

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ABSTRACT

This paper aims to provide physiological rationale for airway clearance, mucoactive therapy and pulmonary rehabilitation (PR) (or exercise interventions) in bronchiectasis. There is increasing emphasis on the role of airway clearance techniques (ACT) in the management of bronchiectasis. No single ACT has currently shown superior effect over another. Given the large range of different techniques available, consideration of the physiological effects underpinning a technique including expiratory flow, ventilation and oscillation, is essential to effectively personalize ACT. Key clinical trials of mucoactives in bronchiectasis are underway and will provide clarity on the role of these agents in the management of patients with bronchiectasis. Prescription of mucoactive therapies should be done in conjunction with ACT and therefore the mechanism of action of mucoactive drugs and their timing with ACT should be taken into consideration. PR and/or exercise training are recommended in all current bronchiectasis guidelines. There is a clear physiological rationale that muscle weakness and physical inactivity may play a role in disease progression as well as impacting health-related quality of life, frequency of pulmonary exacerbations and ability to mobilize sputum. However, there are residual unanswered questions surrounding the delivery and accessibility to PR. This review summarizes the physiological principles and supporting evidence for airway clearance, mucoactive medication and PR, which are key components in the management of bronchiectasis.

Key words: airway clearance, bronchiectasis, mucoactives, pulmonary rehabilitation.

INTRODUCTION

Chronic cough, sputum production as well as decreased exercise capacity and inactivity are some of the main clinical manifestations reported in patients with bronchiectasis.[1–3] These symptoms worsen during exacerbations and impact negatively on health-related quality of life (HRQoL).[4] This paper summarizes the physiological rationale for airway clearance including mucoactive therapy as well as pulmonary rehabilitation (PR) (or exercise interventions) in bronchiectasis.

AIRWAY CLEARANCE IN BRONCHIECTASIS

Airway clearance techniques (ACT) are non-pharmacological strategies to improve symptoms and HRQoL and reduce exacerbation frequency.[5,6] Short-term goals are to provide more effective sputum clearance that improves ventilation and reduces cough impact and breathlessness. Longer term goals are reducing further airway damage by halting the vicious cycle of bacterial colonization and subsequent inflammation, reducing the number of pulmonary exacerbations and hospitalizations and improving HRQoL.[7–9]

Published guidelines agree that ACT are a key component in the management of bronchiectasis and that all patients with bronchiectasis should be taught ACT by a respiratory physiotherapist. ACT which can be performed independently are recommended in these guidelines.[7,9] Patients with a chronic productive cough or difficulty expectorating sputum may benefit from regular twice daily ACT as recommended in current guidelines.[9] In addition, the physiotherapist can discuss step up and step down ACT in managing exacerbations.[9] In practice, ACT remain significantly underutilized. Data from the European Bronchiectasis Data Registry (EMBARC) report that only 45% of data registrants perform an ACT regularly.[10] Furthermore, airway clearance has very low rates of adherence.[11]

ACT rely on two overriding physiological principles. First, a mechanism to allow air to move behind the obstruction and ventilate the regions distally and second, modulation of expiratory airflow to propel secretions proximally up the airways. in vitro flow models suggest two conditions that improve airway clearance: (i) the peak expiratory flow rate should be greater than the peak

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inspiratory flow rate (at least 10%) for mucus to move proximally; (ii) and a peak expiratory flow rate of 30–60 L/min is required to break the adhesive bonds generated between the mucus layer and the airway epithelial surface.[12] Both are essential for enhancing mucus clearance.

Recommendations and the evidence to support the use of ACT are based on a limited number of clinical trials, many of which are single treatment studies. Two Cochrane reviews have summarized data from 16 randomized controlled trials (RCT) (13 of which were crossover design) concluding that airway clearance is safe and may account for improvements in sputum expectoration, some measures of lung function, symptoms and HRQoL.[5,6] One of the reviews concluded that positive expiratory pressure (PEP) was as effective as other ACT.[5]

Considering studies with interventions longer than single treatments, Patterson *et al.* demonstrated that there was no difference in lung function and sputum weight with active cycle of breathing techniques (ACBT) versus Acapella (Smiths Medical International, Hythe, UK) (oscillating PEP device) over a 10–14 day treatment period in 20 stable patients.[13] In 17 patients, Thompson *et al.* reported that there was no significant difference between ACBT and the Flutter (oscillating PEP device) after a 4-week treatment period, in any of the outcomes used (HRQoL, lung function and sputum).[14] Over three treatment sessions, the techniques of autogenic drainage (AD) and ELTGOL (an active technique where the subject carries out slow expiration with the glottis open in a lateral decubitus position) have been compared to a control group of 31 patients performing temporary PEP in a study by Herrero-Cortina *et al.* Both AD and ELTGOL resulted in significantly greater sputum compared to the control group.[15] Munoz *et al.* compared the ELTGOL technique to placebo exercises twice daily (b.d.) in 44 patients over a 1-year period and reported fewer exacerbations, reduced cough impact and improved HRQoL in the ELTGOL group.[16]

In terms of the supporting evidence for oscillating PEP, Murray *et al.* compared Acapella to no treatment in 20 stable adult bronchiectasis patients over a 3-month period.[17] There was no change in pulmonary exacerbation frequency or pulmonary function. There was significant increases in HRQoL, sputum volume and exercise capacity for patients performing Acapella compared to the control. Tambascio *et al.* compared Flutter to control (flutter-sham) in 17 stable adult bronchiectasis patients over a 4-week period and reported an improvement in sputum transport and a reduction in inflammatory cells in respiratory secretions using Flutter.[18] In a very small study (n=15) comparing Flutter+breathing and coughing (BC), postural drainage+BC and BC alone in patients during hospitalisation for an exacerbation (mean duration 5-7 days), Tsang et al reported no difference in sputum weight or lung function, although Flutter was perceived by patients to be the most effective in clearing secretions.[19]

These studies with interventions longer than a single treatment demonstrate some proof of concept on the effectiveness of ACT in bronchiectasis and support the general consensus that currently no one ACT is superior in terms of clinical outcomes.[6]

Selection of ACT should be targeted according to the patient's individual characteristics, that is personalized to that patient.[20,21] McIlwaine *et al.* highlighted that key to personalizing ACT is considering the physiological principles underpinning the technique. ACT rely on two main physiological premises: the ability to ventilate behind obstructed regions of the lung and the capacity to achieve the minimum expiratory airflow bias necessary to mobilize secretions. The authors advocate that understanding how each ACT incorporates these proposed physiological effects could inform clinical decision-making and drive personalization of ACT, for example, use of a forced expiration may need to be adapted to a patient with collapsible airways.[20] We now describe how a range of additional techniques utilize the physiological principles of ventilation and expiratory airflow (Table 1). These additional techniques have been used in studies of bronchiectasis and/or reported by the manufacturers to be of benefit in bronchiectasis for airway clearance. Albeit, many of these techniques have not been subject to clinical trials. Table 1 provides a description of the technique and how they perform considering these key physiological principles (Table 1).

For children with bronchiectasis, the principles of ACT in current practice follow what has been described in adults, given the paucity of research which exists.[36] Questions remain around how airway clearance relates to key clinical outcomes in bronchiectasis in both adults and children.[6,36] Crucially, there is no strong evidence to inform choice, frequency or duration of ACT in bronchiectasis. Tailoring of ACT to the individual patient is recommended across the age range[19,37] and physiotherapists must consider how to optimally personalize ACT. Tailoring includes physiology, symptoms, evidence base and patient factors as well as age-related factors when treating children which include levels of understanding, maturity and the parent–child relationship, all of which may influence adherence to ACT. There are recognized challenges performing traditional, longer term RCT of ACT due to the huge challenge of blinding and random allocation of such treatments as well as the influence of patient preference. Exploration of different study designs has been suggested in cystic fibrosis (CF).[38] In bronchiectasis, future research using novel designs and long-term observational data from large data sets as well as the exploration of delivering ACT personalization will both contribute to the current evidence base and support the delivery of personalized ACT.

MUCOACTIVE THERAPY IN BRONCHIECTASIS

Mucoactive therapy should be considered if ACT are not effective.[9] ACT should be coordinated with mucoactive medications to ensure the overall effect is optimized.

Mucoactive drugs potentially increase the ability to expectorate sputum and/or decrease mucous hypersecretion.[39] They can broadly be characterized into several major groups based on their potential mechanism of action:

Table 1 Physiological effects of ACT

	Ventilation				Expiratory airflow		
Technique title and description	Interdependence	CV	Breath hold	Huffing	PEFR/ PIFR > 1.1	PEFR > 30–60 L/ min	Oscillation
ACBT[†]	Thoracic expansion exercises utilize interdependence	Thoracic expansion exercises utilize CV	Sometimes used with this technique if hypoventilating	Uses forced expirations at different levels	Yes Ratio = 2.8	Average 302 L/ min with huffing	No
Autogenic drainage[†]	No	Yes with breath hold	Uses 3 s breath hold with each breath	No	Yes, emphasis is on slow inspiration and increased velocity on expiration	40–70 L/min. Depends on level of breathing and degree of airway obstruction	No
ELTGOL **E**fficacité de **l**'expiration lente **t**otale **g**lotte **o**uverte en décubitus **l**atéral/ slow expiration with the glottis opened in the lateral posture[‡15,16]	No Tidal breathing during inspiration	No Tidal breathing during inspiration	No	No	Yes Emphasis is on slow, prolonged expiration from functional residual capacity to residual volume	Yes Airflow may be increased with the application of slow abdominal and thoracic compression during expiration	No
PEP devices							
PEP mask (Astra Tech AB, Molndal, Sweden)[†]	No	As PEP is maintained within the airways during 12–15 breaths, use of CV is maximized	Not necessary as PEP is maintained within the airways during 12–15 breaths	Used at the end of each cycle of 12–15 breaths	No Ratio = 0.47	No Average 26 L/ min	No
Oscillating PEP devices							
Oscillating PEP with Flutter (VarioRaw, Aubonnie, Switzerland)[†22]	Oscillations between 3 and 5 Hz may play a role, but frequency used in Flutter is >5 Hz	Yes with breath hold	Uses 3 s breath hold with each breath	Used at the end of each cycle of 8–10 breaths	Ratio = 1.15	Average 68 L/ min.	2–32 Hz Most often uses 6–26 Hz

Table 1 Continued

Technique title and description	Ventilation				Expiratory airflow		
	Interdependence	CV	Breath hold	Huffing	PEFR/ PIFR > 1.1	PEFR > 30–60 L/ min	Oscillation
Oscillating PEP with Acapella (Smiths Medical International, Hythe, UK)[†22]	Oscillations between 3 and 5 Hz may play a role, but frequency used in Acapella is >5 Hz	As a PEP (10.31–19.41 cm H_2O) is maintained within the airways during 12–15 breaths, use of CV is maximized	Not necessary	Used at the end of each cycle of 12–15 breaths	No Ratio = 0.64	Average 35.4 L/ min	10–18 Hz
Oscillating PEP with Aerobika Trudell Medical UK Limited, Hampshire, UK.[†23–25]	Oscillations between 3 and 5 Hz may play a role, but frequency used in Aerobika is >5 Hz Thoracic expansion exercises utilize interdependence	Thoracic expansion exercises utilize CV As a PEP (5–20 cm H_2O) is maintained within the airways during 10–20 breaths, use of CV is maximized	Uses 2–3 s breath hold with each breath	Used at the end of each cycle of 10–20 breaths	Yes Ratio > 1.1.	PEFR can range from 15 to 40 L/ min depending on breath volume and resistance settings	9–20 Hz (depending on resistance settings and PEFR)
Oscillating PEP with Shaker (HaB International Ltd. Warwickshire, UK)[‡26,27]	Oscillations between 3 and 5 Hz may play a role, but frequency used in shaker is >5 Hz Thoracic expansion exercises utilize interdependence	Thoracic expansion exercises utilize CV As a PEP of 11.48–16.88 cm H_2O maintained within the airways, use of CV is maximized	No	Used at the end of each cycle of 8–10 breaths	Emphasis is on slow inspiration and increased velocity on expiration	5–32 L/min depending on breath volume and angle of device	10–28.5 Hz (depending on angle of device)
Oscillating PEP with REVITIVE Aerosure Medic (Actegy Limited, Bracknell, UK)[‡28]	Oscillations between 3 and 5 Hz may play a role, but frequency used in REVITIVE Aerosure Medic is >5 Hz	As a PEP of 4–25 cm H_2O is maintained within the airways during 15–20 breaths, the use of CV is maximized	No	Used at the end of each cycle of 15–20 breaths	No	Unknown	15 Hz with non-Inspiratory Muscle Training (IMT) mode 25 Hz with IMT mode

Table 1 Continued

Technique title and description	Ventilation: Interdependence	Ventilation: CV	Ventilation: Breath hold	Ventilation: Huffing	Expiratory airflow: PEFR/ PIFR > 1.1	Expiratory airflow: PEFR > 30–60 L/ min	Expiratory airflow: Oscillation
Oscillating PEP with RC-Cornet device or RC-cornet PLUS device (R. Cegla GmbH & Co. KG, Montabaur Germany)[†] [29–32]	Oscillations between 3 and 5 Hz may play a role, but frequency used in RC-Cornet is >5 Hz Thoracic expansion exercises utilize interdependence	Thoracic expansion exercises utilize CV As a PEP of 10–28 cm H_2O is maintained within the airways, the use of CV is maximized	No	Used at the end of each cycle of 10 breaths	No	RC-Cornet device: 90–177 L/min RC-Cornet PLUS device: Setting 1 resistance 37.2–149 L/min Setting 2 resistance 43.2–236 L/min	RC-Cornet device: 8–160 Hz (depending on resistance settings) RC-Cornet PLUS device 12–14 Hz
Oscillating PEP with lung flute (Medical Acoustics, LLC, Bowmansville, NY, USA)[‡33]	No Tidal breathing during treatment Oscillations between 3 and 5 Hz may play a role, but frequency used in Lung flute is >5 Hz	No. A PEP of 2.5 cm H_2O is maintained in the airways during a single breath Tidal breathing during treatment	No	Used at the end of five sets of two blows	Emphasis is on expiratory flow rate higher than inspiratory flow rate	Minimal flow rate required 128.4 L/ min	16–25 Hz
Percussion devices Vibralung Acoustical Percussor (intrapulmonary acoustical airway clearance) (when used independently with no active component) VibraLung, Inc. (Colorado, USA)[‡34]	Tidal breathing during treatment but oscillations between 3 and 5 Hz may play a role	When using the PEP resistor, a PEP in the airways 4–20 cm H_2O therefore CV can be maximized	No	No	No	No	Frequency range 5–1200 Hz depending on setting

Table 1 Continued

	Ventilation				Expiratory airflow		
Technique title and description	Interdependence	CV	Breath hold	Huffing	PEFR/ PIFR > 1.1	PEFR > 30–60 L/ min	Oscillation
Frequencer (acoustic sound waves) (when used independently with no active component) Dymedso (Montreal (QC) Canada)[‡35]	No Tidal breathing during treatment Oscillations between 3 and 5 Hz may play a role, but frequency used in Frequencer is >5 Hz	No	No	No	No	No	20–65 Hz
HFCWO devices							
HFCWO (The Vest® System, Hill-Rom, Minnesota, USA) (inCourage®, RespirTech, MN, USA) (Smart Vest®, New Prague, MN, USA) and (AffloVest®, Austin, TX, USA).[§]	Oscillations between 3 and 5 Hz may play a role, but frequency used in HFCWO is >5 Hz	No	No	Interspersed with HFCWO	Yes, expiratory flow rate is much higher than inspiratory flow rate	Average 120 L/ min	5–25 Hz

Reproduced from McIlwaine *et al.*,[19] with permission. Grey sections denote content from the original paper. Manufacturer details now provided.

[†]Further description of how this technique works and the application of the technique is available at http://bronchiectasis.com.au/physiotherapy

[‡]See references for a further description of how this technique works and the application of the technique.

[§]Further description of how this technique works and the application of the technique is available at https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance/High-Frequency-Chest-Wall-Oscillation/

ACBT, active cycle of breathing technique; ACT, airway clearance technique; CV, collateral ventilation; HFCWO, high-frequency chest wall oscillation; IMT, inspiratory muscle training; PEFR, peak expiratory flow rate; PEP, positive expiratory pressure; PIFR, peak expiratory flow rate.

- Expectorants: drugs that induce discharge or expulsion of mucous from the respiratory tract. Typically, this requires coughing action to loosen and bring up the mucous from the lungs or upper respiratory tract. Examples include hypertonic saline (HTS) and guaifenesin.
- Mucoregulators: drugs that regulate mucous secretion or interfere with the DNA/F-actin network. Examples include carbocisteine and anticholinergic agents.
- Mucolytics: drugs that decrease mucous viscosity. Examples include N-acetylcysteine, erdosteine and DNase.
- Mucokinetics: drugs that increase mucociliary clearance by acting on the cilia. Also referred to as cough clearance promoters. Examples include bronchodilators and surfactants.[39]

The ERS guidelines[7] summarize the findings of three systematic reviews that have comprehensively examined the current evidence for mucoactives.[40–42] None of the mucoactive agents significantly reduced the number of exacerbations, and the exacerbation rate was higher in the recombinant human DNase (rhDNase) group compared with placebo.[43] The Wilkinson *et al.*'s systematic review focused on the evidence for bromhexine and DNase. Due to methodological differences in studies, a meta-analysis could not be performed.[41] One trial with 88 participants showed that high doses of bromhexine with antibiotics significantly eased difficulty in expectoration and sputum production days compared to placebo; however, the quality of the evidence was rated as low.[44] In a single small, blinded but not placebo-controlled trial of older (>55 years) participants with stable bronchiectasis and mucus hypersecretion, erdosteine combined with physiotherapy over a 15-day period significantly improved spirometry and sputum purulence more effectively compared with physiotherapy alone.[45] Further long-term trials are needed to fully understand if these mucoactives are beneficial in bronchiectasis. The remaining two studies in this review (with a combined total of 410 participants) compared rhDNase versus placebo.[43,46] The larger and longer of these studies showed a significant negative effect on forced expiratory volume in 1 s (FEV_1) and an increase in exacerbations.[43] Based on this evidence, synthesis of proprietary patented mucolytics such as DNase, the ERS and BTS guidelines recommend that DNase should not be offered to patients with bronchiectasis. Similarly, for oral carbocisteine, the evidence base in bronchiectasis is poor and there is insufficient evidence to recommend.[7,9]

With regard to mannitol, current systematic reviews[40,42] as well as studies subsequent to the reviews[47] provide insufficient evidence to draw firm conclusions on its effect. Bilton *et al.* found that inhaled mannitol at 400 mg b.d. for 12 months in patients with non-CF bronchiectasis did not reduce exacerbation rates, thus supporting the findings in the Hart *et al.*'s review.[47]

The Hart *et al.*'s systematic review concluded that inhaled HTS had no significant benefit over isotonic saline (IS).[40] This review highlighted that there was only one long-term (1 year) randomized parallel group study exploring the efficacy of HTS (6%) versus placebo in bronchiectasis and the study demonstrated that there was no difference between treatment and placebo in hospital admissions.[48] The findings in this study contrasts to other respiratory conditions where the evidence base for HTS is stronger[49] as well as the more positive results seen in other single intervention/crossover studies exploring the use of HTS in bronchiectasis.[50,51] There may be a number of issues that contributed to the findings in the Nicolson *et al.*'s study, including the different methodologies used for the collection of exacerbation data.[52] Both groups experienced benefit, which may be linked to the frequent medical review obtained by participating in the study and the potential for increased self-awareness related to the disease process. A third potential contributing factor is that IS is not a true placebo in this context and may have benefits by increasing airway hydration, with further benefit possibly conferred by the respiratory manoeuvres that participants were instructed to undertake during nebulization. The Nicolson *et al.*'s trial may also have been underpowered based on exacerbation from recent trials (RESPIRE trials).[53,54] In this trial, as well as many of the current trials on mucoactives, the inclusion criteria may not have been specific enough to recruit patients to which mucoactives should be targeted and this is an important consideration for future trials. These issues contribute to uncertainty regarding whether the 'no effect' observed by Nicolson *et al.* was due to study design or a true lack of effect of HTS.[52]

In a recent double-blind randomized crossover trial in patients with bronchiectasis and chronic sputum, three solutions (7% HTS; 0.1% hyaluronic acid (HA) + 7% HTS; and 0.9% IS) were compared.[50] It was hypothesized that HA would mitigate bronchospasm caused by HTS. Participants inhaled each solution across four consecutive sessions separated by a 7-day washout period. Both HTS and HA + HTS promoted greater sputum weight during sessions than IS, with HA + HTS being associated with less side effects. The 24-h sputum volumes were higher for IS than for HTS. This study highlights that HTS has short-term efficacy likely linked to HTS immediate effects on airway surface liquid volume biophysical sputum properties and stimulation of cough.[50]

In children, whilst 7% HTS is likely the most commonly used clinically and is probably safe and effective, there is no RCT evidence to support the use of mucolytics.[37]

Many of the trials exploring inhaled mucoactives incorporated a drug response assessment (DRA) (formally known as a challenge test or a bronchoconstriction trial) to exclude hyper-responsiveness to airway pharmacotherapy and/or the need for using bronchodilators prior to mucoactive therapies. Some studies have used a bronchodilator with all patients prior to HTS inhalation. Whilst a short-acting bronchodilator should be considered prior to HTS inhalation (especially in patients who exhibit some bronchoconstriction on DRA), there is no evidence to support this if the patient passed the DRA and this could be an additional burden to treatment. If the patient normally uses a short-acting bronchodilator, then it is reasonable to take this prior to HTS inhalation to minimize bronchoconstriction. The Association of Chartered Physiotherapists in

CF have published a comprehensive standard operating procedure (SOP) for DRA directed at patients with CF upon a new nebulized or inhaled medication (e.g. inhaled antibiotic, anti-fungal or mucolytic drug). These SOP are recommended for use in CF but have broad applicability for inhaled medications in other respiratory diseases including bronchiectasis.[55] For mannitol, a specific DRA template should be used.

Prescription of mucoactive therapies should be done in conjunction with ACT and therefore it is important that the mechanism of action of mucoactive drugs and their timing with ACT are taken into consideration. For example, HTS has a short-term/immediate effect,[56] therefore ACT should be done immediately after HTS inhalation. All trials of HTS have delivered HTS immediately prior to ACT. If adherence to treatment is a major barrier, consider delivering HTS during ACT if technology allows. In fact, considering the devices described in Table 1, six can facilitate nebulization during ACT, that is, PEP mask, Acapella, Aerobika, RC-Cornet PLUS, Vibralung and Frequencer. The type of nebulizer can impact the time required to nebulize the mucoactive drug.[57] Although traditional jet nebulizers are still in use (e.g. Pari LC jet nebulizer (PARI Respiratory Equipment, Inc. Midlothian, VA, Canada) or equivalent), the use of 'intelligent nebulisers' (I-neb (Actelion Pharmaceuticals US, Inc)/eFlow (PARI GmbH, Starnberg GERMANY) devices) may be preferred by patients because they are more portable and can reduce nebulization times.

There are two active clinical trials exploring the efficacy of commonly used mucoactives (HTS and carbocisteine) in bronchiectasis. The results of these trials are likely to have an important impact on future practice, not least because of the differential cost of these mucoactive medications.[58,59] Data from the British Thoracic Society (BTS) audit[60] and, more recently, a European database[61] indicate that HTS (7%) and carbocisteine are the two mucoactive agents used in bronchiectasis by up to 20% of patients. Despite current guidelines indicating there is insufficient evidence to recommend their use, it is probable that the stronger evidence base for carbocisteine and HTS in other respiratory conditions[62] justifies the current audit data which suggest that carbocisteine and HTS are the most commonly used mucoactives in bronchiectasis.[61] These trials will be key to ascertaining the role of these agents in the management of patients. If ineffective, then up to 20% of patients are on ineffective treatments; if they are effective, then up to 80% of patients currently do not have access to effective treatments. Until these definitive trials are completed, a pragmatic approach is to consider stopping the use of mucoactives in patients if there is no benefit after a 4-week trial.

PR IN BRONCHIECTASIS

All of the current guidelines and clinical reviews in bronchiectasis recommend incorporating PR and/or exercise training (ET) into treatment protocols.[7,9,63–65] PR and ET programmes exist in many parts of the world but the content and duration of the programmes vary. In general, PR incorporates several exercise modalities (treadmill walking, cycle ergometry, weight lifting and arm ergometry) and patient education. ET programmes are comprised of the exercise modalities without an educational component. PR and ET programmes are generally aimed at improving both upper limb and lower limb endurance and are tailored to the needs of the individual patient. The exercise is supervised by trained staff; depending upon the location of the programme, these staff may include exercise physiologists, respiratory care practitioners, physiotherapists and nurses. Patients participating in PR or ET are generally monitored with oximetry and occasionally cardiac monitoring. The location of these programmes vary: some are incorporated into hospital-based physical medicine and rehabilitation medicine facilities; others are free standing and may even be in a community centre or in an outpatient physiotherapy department. Home-based programmes have also been developed. The duration of the programs vary: in the United States, these programmes are generally comprised of an initial intensive phase which includes 36 1-hour sessions over 12 weeks followed by a self-guided maintenance phase. In other parts of the world, the patients may receive shorter or longer periods of supervision.[66] Almost all programmes obtain a baseline patient assessment of exercise capacity and HRQoL and then measure those parameters again at the end of the rehabilitation period. Incorporation of disease-specific education as well as general respiratory health and overall wellness training (including nutrition education and psychosocial support) varies. A challenge in many parts of the world is that PR programmes are primarily aimed at patients with chronic obstructive pulmonary disease (COPD); patients with bronchiectasis also need additional focused training in airway clearance modalities and other disease-specific education.[67]

A recent systematic review confirmed the short-term benefits that patients achieve from participating in supervised PR and ET, but noted that sustaining benefit is challenging.[68] The physiological rationale for PR and ET in bronchiectasis is that muscle weakness and physical inactivity may play a role in disease progression as well as impact HRQoL, frequency of infectious exacerbations and ability to mobilize secretions.[69] One observational study of 41 patients with bronchiectasis showed that 36 sessions of PR significantly improved forced vital capacity and residual volume measurements.[70] A retrospective study of 95 patients from two tertiary institutions in Australia where subjects received 6–8 weeks of PR demonstrated improvement in 6-min walk distance and HRQoL measured by the Chronic Respiratory Disease Questionnaire.[71] An Italian cohort of 108 bronchiectasis subjects who enrolled in a 3-week PR programme showed similar results. Multivariate analysis revealed that male gender, baseline FEV_1/vital capacity less than 70% and greater than two exacerbations in the previous year were independent predictors of PR efficacy.[72] A prospective randomized trial carried out in Scotland compared PR and chest physiotherapy versus chest physiotherapy alone in 30 patients with bronchiectasis: the PR/physiotherapy group showed significant improvement over the control group in walking distance and HRQoL measures.[73] Another randomized study carried out in Australia

comparing ET with airway clearance training to standard care also showed improvement in exercise capacity, dyspnoea and fatigue as well as fewer exacerbations over 12 months.[74] All of these programmes included lower and upper limb exercises and strengthening exercises and were tailored to the individual patient's capabilities. In children, exercise (especially endurance exercise) is helpful and some experts have also suggested that singing may have a salutatory effect in children.[36,37]

Although the evidence base and anecdotal experience suggest that PR or ET is beneficial for patients with bronchiectasis, there are residual unanswered questions. Indeed, exercise as an ACT is an unanswered question in this patient group. Further research questions include the timing of referral for PR; it is unclear at what stage of disease patients might get the most benefit. In addition, there are potential risks associated with PR and ET in the bronchiectasis population including the potential for unrecognized cardiac comorbidities, exercise induced hypoxaemia and haemoptysis.[69] Many patients with bronchiectasis are elderly and frail with orthopaedic risks.[75] Finally, the potential for spread of infectious respiratory pathogens from patient to patient is a concern in this population although there is currently no evidence that cross infection occurs in the group setting.[9] More study is needed on home-based PR[76] and tele-rehabilitation programmes.[77] Finally, access to rehabilitation programmes is a problem worldwide and ways to maintain benefit must also be further evaluated.

SUMMARY

Airway clearance, mucoactive medication and PR are key components in the management of bronchiectasis. The stepwise approach to the management of bronchiectasis in line with disease severity is advocated in a key review with the inclusion of airway clearance and PR for patients at all stages of disease severity and the escalation of therapy and inclusion of mucoactive medication in patients with persistent symptoms or exacerbations despite standard care.[78] There are few RCT assessing treatments in children with bronchiectasis. Future research is needed to drive personalization of ACT, inform clinical decision-making on mucoactive medication and improve accessibility to PR in children and adults.

Disclosure statement

A.E.O. has acted as paid scientific consultant to Electromed Inc.

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Abbreviations: ACBT, active cycle of breathing technique; ACT, airway clearance technique; AD, autogenic drainage; CF, cystic fibrosis; CV, collateral ventilation; DRA, drug response assessment; ERS, xxxx xxxx; ET, exercise training; FEV_1, forced expiratory volume in 1 s; HA, hyaluronic acid; HFCWO, high-frequency chest wall oscillation; HRQoL, health-related quality of life; HTS, hypertonic saline; IMT, xxxx xxxx; IS, isotonic saline; PEFR, xxxx xxxx; PEP, positive expiratory pressure; PR, pulmonary rehabilitation; RCT, randomized controlled trial; rhDNase, recombinant human DNase; SOP, standard operating procedure.

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