CHEST

Treating Cough Due to Non-CF and CF Bronchiectasis With Nonpharmacological Airway Clearance

CHEST Expert Panel Report

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BACKGROUND: In bronchiectasis due to cystic fibrosis (CF) and other causes, airway clearance is one of the mainstays of management. We conducted a systematic review on airway clearance by using non-pharmacological methods as recommended by international guidelines to develop recommendations or suggestions to update the 2006 CHEST guideline on cough.

METHODS: The systematic search for evidence examined the question, "*Is there evidence of clinically important treatment effects for non-pharmacological therapies in cough treatment for patients with bronchiectasis?*" Populations selected were all patients with bronchiectasis due to CF or non-CF bronchiectasis. The interventions explored were the non-pharmacological airway clearance therapies. The comparison populations included those receiving standard therapy and/or placebo. Clinically important outcomes that were explored were exacerbation rates, quality of life, hospitalizations, and mortality.

RESULTS: In both CF and non-CF bronchiectasis, there were systematic reviews and overviews of systematic reviews identified. Despite these findings, there were no large randomized controlled trials that explored the impact of airway clearance on exacerbation rates, quality of life, hospitalizations, or mortality.

CONCLUSIONS: Although the cough panel was not able to make recommendations, they have made consensus-based suggestions and provided direction for future studies to fill the gaps in knowledge.

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KEY WORDS: bronchiectasis; cough; cystic fibrosis; evidence-based medicine; guidelines

ABBREVIATIONS: ACBT = active cycle breathing technique; CCPT = conventional chest physiotherapy techniques; CF = cystic fibrosis; HFCWO = high-frequency chest wall oscillation; PEP = positive expiratory pressure; PICO = Population, Intervention, Comparator, Outcome

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Summary of Suggestions

1. For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that they be taught airway clearance techniques by professionals with advanced training in airway clearance techniques. (Ungraded Consensus-Based Statement)

2. For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that the frequency of airway clearance should be determined by disease severity and amount of secretions. (Ungraded Consensus-Based Statement)

3. For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that airway clearance techniques are individualized as there are many different techniques. (Ungraded Consensus-Based Statement)

Remarks: These suggestions are based on clinicians' expertise in managing non-CF and CF bronchiectasis because there is a lack of large and/or high quality randomized controlled trials.

The costs can vary depending on the modality of airway clearance used. In European studies, the least expensive method, the active cycle breathing technique (ACBT) with or without postural drainage is used first line.[1] Other methods are considered if there is inability to carry out ACBT with or without postural drainage or there is a clinical deterioration necessitating alternative airway clearance techniques.

In bronchiectasis due to cystic fibrosis (CF) and other causes, treatment of respiratory infections and airway clearance techniques are mainstays of management. The aims of airway clearance are to mobilize secretions from the airways and provide some control of cough. In clinical practice, there are a variety of techniques: active cycle breathing with or without the assistance of postural drainage; positive expiratory pressure (PEP); flutter-type devices; airway oscillation; respiratory muscle training; coached coughing; huffing; cough assist device (insufflation/exsufflation); assisted coughing (eg, quad coughing); functional electrical stimulation; high-frequency chest wall oscillators; and general exercise. The aims of treatment are to clear the airways of tenacious secretions, reduce cough and sputum production, improve functional and health status, and reduce the frequency and/or severity of exacerbations. The current expert panel report focuses on airway clearance as recommended by international guidelines.[1-5] We present evidence-based reviews for the key question developed on using non-pharmacological airway clearance techniques for the management of people with bronchiectasis, summary of the evidence, and the formulated suggestions based on these findings using CHEST's cough guidelines methods and framework.[6]

Methods

The methods of the CHEST Guideline Oversight Committee[6] were used to select the Expert Cough Panel Chair and the international panel of pediatric and adult experts in non CF-bronchiectasis and CF to synthesize the evidence and to develop the suggestions that are contained within this article. In addition to the quality of the evidence, the recommendation/suggestion grading also includes a strength of recommendation dimension, used for all CHEST Guidelines.[6] The strength of recommendation here is based on consideration of three factors: balance of benefits to harms, patient values and preferences, and resource considerations. Harms incorporate risks and burdens to the patients that can include convenience or lack of convenience, difficulty of administration, and invasiveness. These harms, in turn, affect patient preferences. The resource considerations go beyond economics and should also factor in time and other indirect costs. The authors of these suggestions have considered these parameters in determining the strength of the suggestions.

The findings of a systematic search for and evaluation of evidence were used to support the evidence-graded recommendations or suggestions. A highly structured consensus-based Delphi approach was used to provide expert advice on all guidance statements.[6] The total number of eligible voters for each guidance statement did not vary because none was recused from voting on any statements because of their potential conflicts of interest. Transparency of process was documented. Further details of the methods related to conflicts of interests and transparency for all CHEST guidelines have been published previously.[6]

Based on the evidence review and the Delphi methods described, the writing group developed guideline recommendations or suggestions. These then underwent review and voting by the full cough panel. For a recommendation or suggestion to be accepted, it had to be voted on by 75% of the eligible Cough Panelists and achieve ratings of strongly agree or agree by 80% of the voting panelists. Agreement was achieved by 85% to 90% of those voting in the current recommendations. No panelist was excluded from voting.

Key Question Development

A key clinical question was developed by using the PICO (Population, Intervention, Comparator, Outcome) format. The following question was addressed: *"Is there evidence of clinically important treatment effects for non-pharmacological therapies in cough treatment for patients with bronchiectasis?"*

Systematic Literature Search

A systematic literature search for individual studies was initially conducted by using the following databases: MEDLINE via

PubMed, EMBASE, and Scopus with date limitations from database inception through May 9, 2013, for non-pharmacological therapies for airway clearance. Thirty systematic reviews were identified in the Cochrane Library and 83 in PubMed. Additional searches for trials were conducted in the two databases, with 229 identified in PubMed and 319 in the Cochrane Library. The search was updated in February 2015, during which time separate searches were conducted for CF and for non-CF bronchiectasis in PubMed and the Cochrane Library. During this extended search, a total of 194 citations were retrieved for CF and 113 for non-CF bronchiectasis. To be certain that the most current versions of Cochrane reviews were used to inform the evidence, another search of the PubMed and Cochrane databases was performed on May 3, 2016. One update of an included Cochrane systematic review and five new systematic reviews were discovered while no newer primary studies were identified through this search (Fig 1).

Using dual review, four panelists independently reviewed the titles and abstracts of the search results to identify potentially relevant articles based on the inclusion and exclusion criteria. Discrepancies were resolved by discussion. Studies deemed eligible then underwent a second round of full-text screening for final inclusion. Important data from each included study were then extracted into structured evidence tables (e-Tables 1, 2). In each step, dual review and dual extraction were performed.

Quality Assessment

The identified systematic reviews were assessed for quality and risk of bias using the Documentation and Appraisal Tool For Systematic Reviews.[7]

Peer Review Process

The manuscript went through 2 rounds of review. During the first round, identified reviewers from the Guidelines Oversight Committee of the CHEST Organization reviewed the content and methods of the manuscript for consistency, accuracy, and completeness. The manuscript was revised after consideration by the panel of the feedback received from the Guidelines Oversight Committee reviewers and then submitted to the *CHEST* journal for review by a representative from the CHEST Board of Regents, one of the four CHEST Presidents, and journal-identified reviewers.

PICO Question Development

Initially, the key question was phrased as *"Is there evidence of clinically relevant treatment effects for non-pharmacological therapies in cough treatment for patients with diseases that affect airway clearance and ineffective cough?"* During the review process, the panel decided to substitute the word "important" for "relevant," eliminate the phrase "ineffective cough," and to focus on bronchiectasis. The initial search included the term ineffective cough; however, the subsequent searches did not.

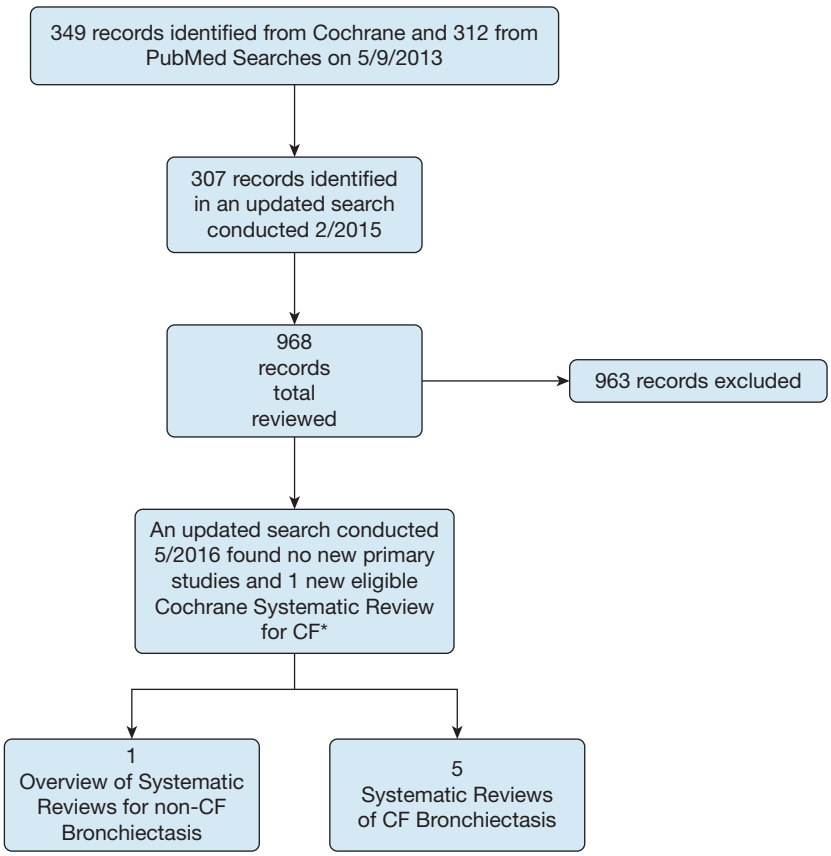

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart for non-pharmacological airway clearance treatment for children and adults with CF and non-CF bronchiectasis.* *An updated Cochrane systematic review (SR) for CF and an updated SR in the overview of SR for non-CF bronchiectasis were discovered during the May 2016 search and replaced the older versions. CF = cystic fibrosis.

The interventions included were the following non-pharmacological airway clearance therapies: PEP; vibrating vest; flutter-type devices; airway oscillation; conventional chest physiotherapy and postural drainage; respiratory muscle training; coached coughing (having patients start coughing at total lung capacity); huffing; cough assist device (insufflation/exsufflation); assisted coughing (quad coughing); functional electrical stimulation; and abdominal binders. The comparison populations were receiving standard therapy and/or placebo. Clinically important outcomes that were assessed were exacerbation rates, quality of life, hospitalizations, and mortality.

Results

Summary and Interpretation of the Evidence for Non-CF Bronchiectasis

After full-text review by panelists and the methodologist, no primary studies met all criteria described under the section "PICO Question Development." An updated search performed on May 3, 2016, after full-text review identified a good quality Cochrane overview of systematic reviews on the topic of pharmacological and non-pharmacological interventions for bronchiectasis.[8] Overviews of systematic reviews are a relatively new study design included in the *Cochrane Handbook for Systematic Reviews of Interventions*.[9] Overviews of Systematic Reviews compile evidence from multiple systematic reviews on an intervention into a single summary document. They are conducted following systematic and rigorous methods similar to systematic reviews but include systematic reviews rather than primary studies.

The overview identified nine eligible systematic reviews for the topic that included pharmacological therapies. Of these nine, only four examined non-pharmacological methods. One of the four was on singing and another compared nurse- vs doctor-led care. Two good quality systematic reviews examining the effectiveness of non-pharmacological airway clearance therapies remained. One of these reviews[10] evaluated an airway clearance technique that used a twice-daily oscillatory PEP device in one very small study of 20 adult subjects. This crossover study compared 3 months of treatment using an Acapella PEP device vs no chest physiotherapy in patients who admitted not practicing regular airway clearance.[11] In addition to being very small, the single study was assessed by the systematic review authors as having a high risk of bias. This leads to an overall assessment of very low quality for the finding of nonsignificant reduction in exacerbations. The review also evaluated quality of life but did not report CIs around the mean difference, and thus significance could not be assessed. Hospitalization and mortality were not assessed in this study. The updated search for Cochrane systematic reviews did discover an update of this systematic review in 2015. However, the updated systematic review did not identify any new primary studies that evaluated the clinically important outcomes we specified.

The second systematic review evaluated physical training using inspiratory muscle training compared with no or sham therapy. This review identified two eligible trials with a combined total of only 43 subjects.[12] The authors of the overview also described additional small studies not included in the systematic review by Bradley et al[12] in their evidence map. One, a small study in 32 patients, showed that the positive training benefits with pulmonary rehabilitation are maintained with adjunct of inspiratory muscle training.[13] A further study in 26 patients showed no quality of life improvement despite improved respiratory muscle strength.[14] The systematic review measured quality of life by using the Chronic Respiratory Disease Questionnaire.[15] The authors reported major deficiencies in the primary studies, including no description of randomization, no summary of findings, blinding was not possible, the subject groups differed at study start, and the total Jadad quality score was only 1 of 5. In summary, the two very small trials included in the second systematic review had high risk of bias. This summary leads to an overall assessment of very low quality and very low confidence in any findings. Therefore, no reliable evidence for non-pharmacological techniques to improve clinically important outcomes in non-CF bronchiectasis was identified.

Our findings are dissimilar to the most recent Cochrane review[10] on this subject since only one of the seven studies in the Cochrane review met all our inclusion criteria.

Discussion

There is a lack of large and/or high quality trials that address the clinically important outcomes of exacerbation rates, quality of life, hospitalizations, or mortality. The absence of high quality evidence does not imply that efforts to assist airway clearance be abandoned because it is a standard component of the management of bronchiectasis.

Summary and Interpretation of the Evidence for CF Bronchiectasis

Following the full-text review by panelists and the methodologist, no primary studies met all the criteria described under the section "PICO Question Development." Four Cochrane systematic reviews were identified. An updated search performed on May 3, 2016, after full-text review of the primary studies and specifically focusing on systematic reviews identified two updates of the Cochrane systematic reviews and three additional Cochrane systematic reviews on various non-pharmacological interventions for CF. Of those seven total systematic reviews identified, only five reported on the clinically important outcomes of mortality, hospitalizations, exacerbations, and quality of life, and these were of good quality.

The five systematic reviews examined the following interventions:

- PEP compared with Conventional Chest Physiotherapy Techniques (CCPT).
- PEP compared with oscillating devices.
- Various Forced Expiration Techniques (FET) and CCPT comparisons.
- Inspiratory muscle training (IMT) methods compared with each other, to no or sham methods.

A Cochrane review by Main et al[16] compared CCPT with other airway clearance techniques and examined some clinically important outcomes. One study of 61 subjects examined quality of life, two studies of 79 subjects examined number of hospital days, and two studies of 99 subjects examined number of admissions per year. For quality of life, one study was available as an abstract only, and thus the authors report unclear risk of bias and a low quality score (2 of 5 Jadad quality score). Data were not reported (only the overall finding of no difference between CCPT and PEP). For number of hospital days, one small study of 16 subjects comparing CCPT vs airway oscillating devices was available as an abstract only, and thus no quality assessment was performed. The range of values for the mean difference was broad, finding no significant difference. The study of 63 subjects comparing CCPT vs ACBT/FET did not report data. For number of admissions per year, one study of 36 subjects compared CCPT vs PEP, and the other study of 63 subjects compared CCPT vs ACBT/FET. Neither study found a significant difference between methods. The inability to evaluate whether any newer techniques are better than CCPT in CF is due to insufficient data.

A Cochrane review by McIlwaine et al[17] compared PEP vs oscillating devices and evaluated the outcome of exacerbations. Four studies were examined, and data were analyzed for two studies that were both rated as having low risk of bias by the reviewing authors. One study of 88 subjects over 1 year found a significant reduction in exacerbations for PEP compared with high-frequency chest wall oscillation (HFCWO) (RR = 0.73 [95% CI, 0.55-0.95]).[18] The mean number of pulmonary exacerbations were 1.14 for PEP vs 2.0 for HFCWO, and time to first pulmonary exacerbation was 220 days for PEP vs 115 days for HFCWO ($P = .02$). The study of PEP vs oscillating PEP included 41 subjects and found no significant difference.

A Cochrane review by McKoy et al[19] compared FET (ACBT) vs CCPT + FET for the outcome of exacerbations. One prospective study of 63 subjects over 3 years was included that suffered from unclear allocation concealment, and blinding was not possible. There was 6% loss to follow-up and no intention-to-treat analysis. There was no significant difference between treatments, with nine of 31 patients receiving FET and five of 30 receiving CCPT + FET experiencing exacerbations (RR = 1.64 [95% CI, 0.62-4.34]).

A Cochrane review by Morrison and Agnew[20] compared oscillatory devices vs PEP for the outcomes of quality of life, exacerbations, and number and days of hospitalizations. For quality of life that was assessed by using the Quality of Well-being Scale or the Chronic Respiratory Disease Questionnaire, there were two studies of 88 and 43 subjects that reported data. One study had an early dropout rate of nearly 20% and in the other, the groups differed at study start. There was no significant difference in quality of life between the groups. For exacerbations, one study of 88 subjects reported data. This study had an early dropout rate of nearly 20%. The study reported an increase in the requirement of antibiotics for exacerbations (OR = 4.10 [1.42-11.84]) for oscillation devices compared with PEP. This study is the same one reported in the review by McIlwaine et al[17] (described earlier). For number of hospitalizations, one study of 42 subjects found no significant difference between groups. For days of hospitalization, three studies of 86 total subjects comparing oscillation devices vs CCPT were all reported to suffer from high risk of bias. There were no significant differences between groups.

A Cochrane review by Houston et al[21] examined inspiratory muscle training as achieved by voluntary

isocapnic hyperpnea, resistive loading, or threshold loading compared with each other or with none or sham. Only two studies with a total of 180 adult subjects with CF were included. Both studies were poorly reported (one was only available as an abstract), and the authors rated the studies at high risk of bias. Quality of life was assessed, but no outcome data reported. The authors concluded that they did not find any evidence to suggest that the treatment was either beneficial or not, and they advised that practitioners evaluate on a case-by-case basis whether to use this therapy.

Although the systematic reviews were of good quality, most of the individual studies were not. All studies were small and were likely underpowered, and they provided insufficient data to identify differences between groups.

Only one primary study included in the five systematic reviews reported any significant differences between groups. This study, by McIlwaine et al,[18] compared HFCWO vs PEP in 88 analyzed subjects. It was reported as being at low risk of bias and found an increase in exacerbations in subjects using HFCWO compared with those using PEP.

In summary, there is insufficient evidence that any airway clearance technique is consistently more effective than any other for clinically important outcomes in CF bronchiectasis. The absence of high quality evidence does not imply that efforts to assist airway clearance be abandoned since it is a standard component of the management of CF.

Summary of Suggestions

1. For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that they be taught airway clearance techniques by professionals with advanced training in airway clearance techniques. (Ungraded Consensus-Based Statement)

2. For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that the frequency of airway clearance should be determined by disease severity and amount of secretions. (Ungraded Consensus-Based Statement)

3. For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that airway clearance techniques are individualized as there are many different techniques. (Ungraded Consensus-Based Statement)

Remarks: These suggestions are based on clinicians' expertise in managing non-CF and CF bronchiectasis because there is a lack of large and/or high quality randomized controlled trials.

The costs can vary depending on the modality of airway clearance used. In European studies, the least expensive method, the active cycle breathing technique (ACBT) with or without postural drainage is used first line.[1] Other methods are considered if there is inability to carry out ACBT with or without postural drainage or there is a clinical deterioration necessitating alternative airway clearance techniques.

Areas of Future Research

Airway clearance research in bronchiectasis due to CF or non-CF bronchiectasis has been underwhelming due to the lack of adequately powered randomized controlled trials. These trials are challenging as ideally the comparator arm would be no physiotherapy, making the studies challenging to blind and leading to ethical challenges, due to airway clearance being regarded as standard care. This has led to underpowered comparator studies of one technique vs another technique. Future studies assessing the optimum method, duration, and frequency for long-term (> 28 days) airway clearance with clinical important outcomes are needed as well as the optimum target group.

To advance the field, there are several potential research endeavors that should be undertaken. They are enumerated here:

1. To determine the clinically meaningful role of any non-pharmacological airway clearance modality, clinically important outcomes such as exacerbation rate, hospitalization rate, quality of life using an instrument validated in CF and/or bronchiectasis, or mortality should be targeted as primary outcomes in future studies.
2. Does regular daily airway clearance improve outcomes (eg, reduce the duration and frequency of exacerbations, improve quality of life) in children and adults with non-CF and CF bronchiectasis?
3. What is the optimum method for long-term (> 28 days) airway clearance in children and adults with non-CF and CF bronchiectasis that will lead to meaningful clinical outcomes?
4. What is the optimum duration and frequency for daily long-term (> 28 days) airway clearance in children and adults with non-CF and CF bronchiectasis that will lead to meaningful clinical outcomes?

5. What target group(s) among children and adults with CF and non-CF bronchiectasis will benefit in meaningful clinical outcomes from airway clearance considering severity of bronchiectasis, frequency of exacerbations, and comorbidities?

Conclusions

Since publication of the 2006 CHEST Cough Guidelines,[4] the effect of non-pharmacological airway clearance techniques on meaningful clinical outcomes in non-CF and CF bronchiectasis, such as rates of exacerbations, hospitalizations, quality of life, and mortality, is still not known. The systematic review portion of this article has identified gaps in our knowledge and areas for future research. Just as stated in the 2006 guidelines, a plea is again made that clinically important outcomes should be targeted as primary outcomes in future studies to determine the meaningful role of non-pharmacological airway clearance modalities.

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Endorsements: This guideline has been endorsed by the American College of Allergy, Asthma and Immunology (ACAAI) and Canadian Thoracic Society (CTS).

Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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