Special Articles

Cystic Fibrosis Pulmonary Guidelines: Airway Clearance Therapies

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Cystic fibrosis (CF) is a genetic disease characterized by dehydration of airway surface liquid and impaired mucociliary clearance. As a result, there is difficulty clearing pathogens from the lung, and patients experience chronic pulmonary infections and inflammation. Clearance of airway secretions has been a primary therapy for those with CF, and a variety of airway clearance therapies (ACTs) have been developed. Because ACTs are intrusive and require considerable time and effort, it is important that appropriate techniques are recommended on the basis of available evidence of efficacy and safety. Therefore, the Cystic Fibrosis Foundation established a committee to examine the clinical evidence for each therapy and provide guidance for their use. A systematic review was commissioned, which identified 7 unique reviews and 13 additional controlled trials that addressed one or more of the comparisons of interest and were deemed eligible for inclusion. Recommendations for use of the ACTs were made, balancing the quality of evidence and the potential harms and benefits. The committee determined that, although there is a paucity of controlled trials that assess the long-term effects of ACTs, the evidence quality overall for their use in CF is fair and the benefit is moderate. The committee recommends airway clearance be performed on a regular basis in all patients. There are no ACTs demonstrated to be superior to others, so the prescription of ACTs should be individualized. Aerobic exercise is recommended as an adjunctive therapy for airway clearance and for its additional benefits to overall health. *Key words: cystic fibrosis, airway clearance, exercise, autogenic drainage, active cycle of breathing, PEP, oscillating PEP, high frequency chest wall compression, guidelines, systematic review.* [Respir Care 2009;54(4): 522–537. © 2009 Daedalus Enterprises]

Introduction

Cystic fibrosis (CF) is a complex disorder affecting many organs, although 85% of the mortality is a result of lung disease.[1] The pathophysiology of CF lung disease begins early in life with abnormal airway surface fluid resulting in impaired mucociliary clearance and consequent obstruction of the small airways by mucus.[2] Chronic infection of the airways and an exaggerated inflammatory response further obstruct the airways with bacteria as well as cellular debris from the lysis of large numbers of neutrophils.[3–6] The rapid degradation of these cells and release of their intracellular contents, including neutrophil-derived deoxyribonucleic acid (DNA) and filamentous actin (F-actin), further increase the viscosity and adhesivity of the airway secretions.[7,8] The secretions present in the CF airways contain pathogenic bacteria and inflammatory cytokines that perpetuate the injury to the airways by recruiting new inflammatory cells. It is intuitive that to maintain lung health, individuals with CF should clear their airways of these secretions in order to relieve the obstruction of the airways, as well as reduce infection and inflammation. These individuals become dependent upon cough and other techniques to clear their airways of the thick sputum. Airway clearance therapies (ACTs) have thus long been considered the most fundamental tool in the management of CF airway disease.

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To provide guidance to the clinician who must choose from an ever-expanding arsenal of treatments for chronic CF lung disease, the CF Foundation established the Pulmonary Therapies Committee. This document represents the committee's recommendations, based on available evidence, for the use of ACTs intended to maintain lung health.

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Methods

Assessment of Evidence

A preliminary meeting of the Pulmonary Therapies Committee (Appendix) was held in November 2006 to initiate the process of identifying and prioritizing therapies to be covered in these guidelines. Only those ACTs believed to be used with regularity in patients and for which there would be peer-reviewed literature were selected for consideration (Table 1).

The committee members developed and refined a series of Questions related to ACTs. For each therapy, the committee asked (1) What is the efficacy of the therapy compared with no therapy? and (2) What is the efficacy of the therapy compared with the other therapies under review? Outcomes that were considered included sputum production, lung function, arterial oxygen saturation, exercise tolerance, exacerbations, adverse events, mortality, quality of life measures, and patient preferences.

A systematic review was commissioned from Johns Hopkins University. Because of the breadth of the questions to be addressed, existing systematic reviews were considered.[9] The existing systematic reviews were identified via a search of *The Cochrane Library*, PubMed, and the Cumulative Index of Nursing and Allied Health Literature. The relevant systematic reviews were used to identify primary studies conducted up to the date of the most recent search in the reviews. A new search was also carried out to identify relevant primary studies not included in existing systematic reviews (ie, completed since the last date of searching performed for the relevant systematic reviews). Searches of PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CINAHL), PsycInfo, and the Cochrane Central Register of Controlled Trials (CENTRAL) were performed for studies published between 1999 and our completion date in April 2007. Reference lists of eligible primary studies were also scanned.

Process of Drafting Recommendations

Members of the committee were provided with summaries of relevant existing systematic review(s) and a qualitative synthesis of identified studies that were not included in the existing systematic reviews. Subcommittees were formed to review the evidence for each specific treatment. Their assessment of the evidence and draft statements were presented to the full committee at a guideline development meeting in September 2007. Recommenda-

Table 1. Airway Clearance Techniques

Technique	Method
Percussion and postural drainage (P&PD)*	Postural drainage, percussion, and vibration of the chest
Positive expiratory pressure (PEP)[86,87]	Expiratory breathing against pressure at 10–25 cm H_2O to raise functional residual capacity or re-inflate collapsed lung Resistor at 10–25 cm H_2O to retard expiratory airflow and prevent complete exhalation; or Expiration against a device that generates pressure of 40–100 cm H_2O (high-pressure PEP)
Active-cycle-of-breathing technique (ACBT)[58,88,89]	1. Thoracic expansion exercises 2. Controlled breathing to aerate alveoli and distal airways, move mucus to proximal airways 3. Forced expiratory technique to clear secretions
Autogenic drainage (AD)[90]	Tidal breathing (controlled expiratory flow) at: 1. Low lung volumes to unstick mucus in peripheral airways 2. Mid-lung volumes to collect mucus in middle airways 3. High lung volumes to expel mucus from central airways
Oscillatory PEP (OPEP)	Devices include: Intermittently interrupt expiratory flow Causes air to vibrate
High-frequency chest compression (HFCC)[91]	Pulses of pressure through inflatable compressive vest to vibrate airways, which increases airflow at low lung volume to increase mobilization of sputum
Exercise	Regular vigorous activity designed to improve physical, heart, and/or muscle strength Aerobic training (eg, cycling, running) for a set time at target intensity Anaerobic training (eg, weight or resistance training, sprinting) for short time at high intensity

* There is very poor consensus on the definition of percussion and postural drainage; although it may be argued that it requires the use of hands or devices to generate percussion or vibration, this is not universally accepted.

Table 2. What the Recommendation Grades Mean, and Suggestions For Practice

Grade	Definition	Suggestions for Practice
A	The committee recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The committee recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The committee recommends against routinely providing the service. There may be considerations that support providing the service to an individual patient. There is moderate or high certainty that the net benefit is small.	Offer/provide this service only if other considerations support offering or providing the service to an individual patient.
D	The committee recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read clinical considerations section of the recommendations. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

(Adapted from Reference 92.)

tions were made using the United States Preventive Services Task Force (USPSTF) grading scheme,[10] which provides a mechanism to weigh the quality of evidence and the potential harms and benefits in determining recommendations (Table 2).

A draft of the recommendations was presented at the 2007 North American Cystic Fibrosis Conference; additionally, the committee solicited commentary from the CF community, which includes physicians, nurses, physical therapists, and respiratory therapists, among others. This input was considered by the committee in development of these recommendations.

Results

Systematic Review

(i) Existing Systematic Reviews

We identified 41 unique citations in our search for existing systematic reviews (Fig. 1). Thirty-four articles were

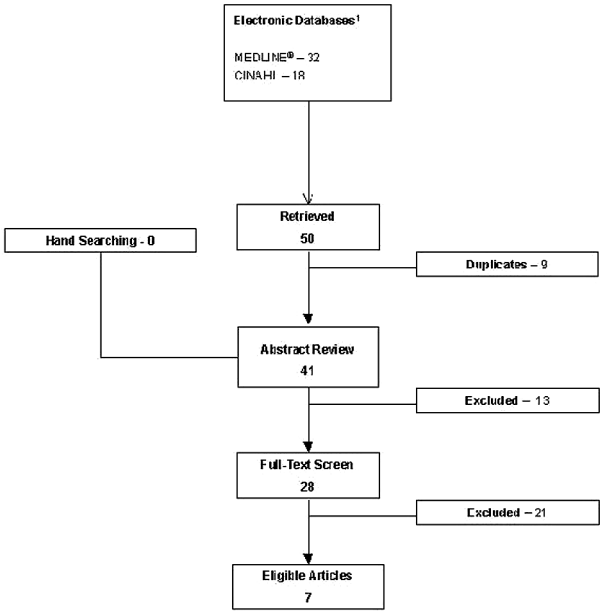

Fig. 1. Literature search for systematic reviews. MEDLINE was accessed via PubMed. CINAHL = Cumulative Index to Nursing and Allied Health Literature.

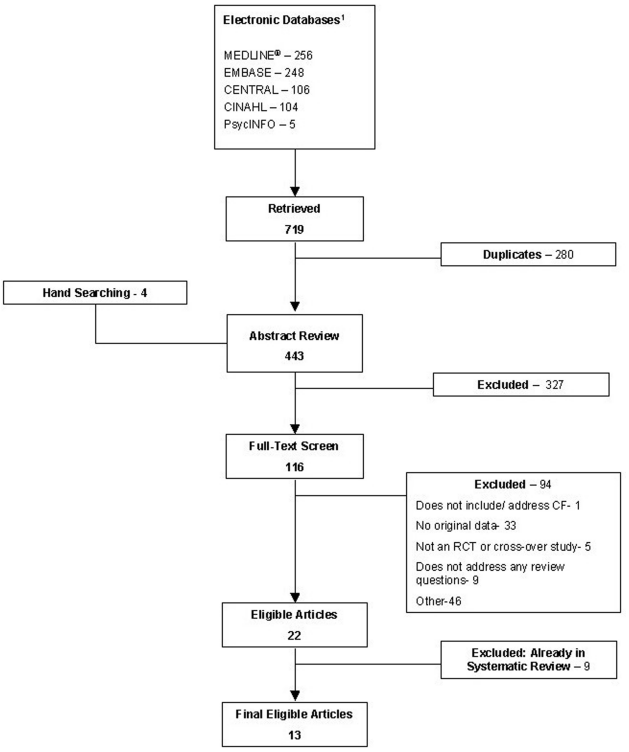

Fig. 2. Literature search for original research. MEDLINE was accessed via PubMed. EMBASE = Excerpta Medica database. CENTRAL = Cochrane CENTRAL Register of Controlled Trials. CINAHL = Cumulative Index to Nursing and Allied Health Literature. PsycInfo = Psychological Literature database.

omitted, primarily because the articles did not address one of the study Questions or did not describe a review. The American College of Chest Physicians Clinical Practice Guidelines on ACTs[11] was identified in our search, but it included conditions other than CF and was therefore excluded. Seven reviews were thus identified, of which 5 were Cochrane reviews. Four reviews addressed percussion and postural drainage (P&PD),[12-15] 2 reviews addressed positive expiratory pressure (PEP),[15,16] and 2 addressed physical training.[17,18] Elkins and co-workers[16] were the only reviewers to address high pressure PEP (hPEP), while Hess[15] was the only reviewer to address any oscillating PEP devices (OPEP), high frequency chest compression (HFCC), autogenic drainage (AD), or the active cycle of breathing technique (ACBT).

(ii) Systematic Reviews of Original Research

Our search for studies published since the completion of existing systematic reviews identified a total of 443 unique citations (Fig. 2). All but 13 of the studies were omitted, primarily because they did not address a review Question (n = 263), did not report a clinical trial (n = 94), or did not contain original data (n = 100). Five of the included studies assessed P&PD,[19-22] 2 studies assessed PEP,[23,24] 4 assessed OPEP,[21,22,25,26] 6 assessed HFCC,[19,20,22,24,25,27] 3 assessed physical or exercise training,[28-30] and 3 assessed ACBT.[26,27] No additional studies were identified addressing hPEP or AD.

Assessment of Evidence

For each question the results are discussed by the various end points under consideration.

Question: What Is the Efficacy of Any ACT Compared with No Therapy?

Perhaps because airway clearance has been considered a vital part of CF care for decades, few studies exist that compare an ACT with no intervention at all. Most studies that attempted this comparison utilized directed coughing or postural drainage (PD) as the control, although in some studies, directed cough was considered a forced expiration technique (FET), and PD was considered a form of P&PD. In this review, the committee considered PD equivalent to "no therapy," and directed cough equivalent to FET.

Sputum Production

The studies that assessed ACT-induced increases in sputum production examined the effects of P&PD or PEP (Table 3) on amount of sputum expectorated. The committee chose to look solely at actual sputum production. Although we recognize that sputum weight has not been validated as a clinically useful outcome measure, clini-

Table 3. Comparison of Airway Clearance Therapies* to No Therapy

	P&PD	PEP	Aerobic Exercise	Anaerobic Exercise
Sputum production	4 trials[31-34], $n = 70$ Favored P&PD	1 trial[23], $n = 17$ Favored positive expiratory pressure	ND	ND
Lung function	4 trials, $n = 48$ 2 favored P&PD[35,36] 2 no difference[37,38]	1 trial[23], $n = 17$ 2 trials[40,41]†, $n = 28$ No difference[4]	4 trials, $n = 168$ 2 short-term no difference[42,45] 2 long-term favored exercise[43,44]	4 trials, $n = 108$ 1 favored exercise[45] 3 no difference[28,29,46]
S_{aO_2}	ND	1 trial[23], $n = 17$ No difference	1 trial[45], $n = 44$ No difference	1 trial[45], $n = 44$ No difference
Exercise tolerance	ND	ND	2 trials, $n = 109$ 1 short-term favored exercise[45] 1 long-term no difference[44]	2 trials, $n = 64$ 1 short-term no difference[45] 1 long-term favored exercise[46]
Exacerbations	ND	ND	1 trial[44], $n = 65$ No difference	ND
Adverse events	ND	ND	ND	ND
Mortality	ND	ND	ND	ND
QOL	ND	ND	2 trials[44,45]‡, $n = 131$ Favored exercise	3 trials, $n = 115$ 2 no difference[45,46] 1 favored exercise[29]
Preferences	ND	ND	2 trials[30,44]§, $n = 89$ Good adherence	1 trial[46]§, $n = 20$ Good adherence

* There are no data for the active cycle of breathing, high-frequency chest compression, high-frequency PEP (positive expiratory pressure), oscillating PEP, or autogenic drainage techniques.
† Compared to postural drainage alone.
‡ The trial by Selvadurai et al[45] compared the effects of aerobic exercise ($n = 22$), anaerobic exercise ($n = 22$), and no exercise ($n = 22$); the sample number here includes all 66 patients.
§ The authors reported adherence to program.
P&PD = percussion and postural drainage
PEP = positive expiratory pressure
ND = no data reported
S_{aO_2} = arterial oxygen saturation
QOL = quality of life

cians commonly use sputum production in their patient assessment, and patients commonly consider sputum productions in their own assessment of the efficacy of ACT. The committee elected to exclude mucus clearance measured by radiotracer as an outcome measure because there were limited data and the relevance to clinical outcomes was unclear.

P&PD: There were 4 trials ($n = 70$) assessing the effects of P&PD compared with no therapy. Three of the trials consisted of only one treatment[31-33]; one study lasted for 4 treatments.[34] All of the trials demonstrated more sputum production with P&PD compared to no therapy.

PEP: Our search for effects on sputum production revealed only one trial that met our inclusion criteria. The trial, in 17 hospitalized patients, demonstrated greater sputum production after PEP therapy compared with no therapy (wet weight 15.78 g vs 13.78 g, $P < .05$, no difference in dry weights).[23]

Lung Function

The studies that assessed ACT-induced changes in lung function included trials of P&PD, PEP, and exercise (see Table 3).

P&PD: There were 4 trials ($n = 48$) comparing the effects of P&PD to no therapy. Differences in forced expiratory volume in the first second (FEV_1) percent of predicted ranged between −0.8% and 8.8%, which was statistically significant in favor of P&PD in 2 studies: a single-treatment ($n = 9$) before-after trial reported a difference of 8.8% (95% confidence interval [CI] 3.5 to 14%),[35] and a 3-week crossover trial ($n = 10$) reported a 7.1% difference (95% CI 2.5 to 11.7%).[36] The other 2 trials that compared P&PD with no therapy showed no difference between the 2 groups; these included a single-treatment crossover trial ($n = 9$)[37] and a 2-week randomized trial ($n = 20$).[38] A long-term study (3 years, $n = 63$) compared P&PD with FET and demonstrated a lower rate of decline in one mea-

sure of pulmonary function ($FEF_{25\%-75\%}$) in the P&PD group[39]; however, it is not clear that this represents a comparison with no therapy.

PEP: Our search identified 3 studies ($n = 45$) that assessed the effects on lung function of PEP compared with no therapy. One short-term (2 d) trial ($n = 17$) showed no difference.[23] Two studies ($n = 28$), consisting of either 4 treatments or 4 weeks of therapy, compared PEP with postural drainage alone; again, no differences in lung function were noted.[40,41]

Exercise: We identified 4 studies ($n = 168$) of aerobic exercise compared with no therapy that examined effects on lung function.[42-45] In the 2 short-term studies (ie, during hospitalization, $n = 61$) no differences were seen in lung function between the 2 groups.[42,45] However, a 1-year study ($n = 42$)[43] demonstrated greater improvement in forced vital capacity (FVC) in the exercise group (weighted mean difference [WMD] 213.0 mL, 95% CI 3.0 to 423 mL), though there was no difference in FEV_1. In addition, a 3-year study ($n = 65$)[44] noted a greater rate of decline of FVC in the control group than in the exercise group; there was a similar, but not significant, trend for FEV_1.

There were 2 studies ($n = 64$) examining lung function effects of anaerobic exercise compared with no therapy. One in-patient study (average duration 18.7 d, $n = 44$) demonstrated a significant improvement in FEV_1 (% predicted) with anaerobic exercise (WMD 5.58%, 95% CI 1.34 to 9.82), but no difference for FVC.[45] The other study (3 mo, $n = 20$) showed no difference between the groups, though no data were provided.[46] Our search also identified 2 studies (6 and 8 wk, $n = 44$) examining the effects of respiratory resistance training or inspiratory muscle training (IMT) on lung function in CF.[28,29] No statistically significant differences in FVC or FEV_1 were reported.

Arterial Oxygen Saturation

The studies that assessed ACT-induced changes in arterial oxygen saturation (S_{aO_2}) included trials of PEP and exercise (see Table 3).

PEP: Our search found one study (2 d, $n = 17$), which showed no difference in S_{aO_2} following PEP compared with no therapy.[23]

Exercise: There was one in-patient (mean duration 18.7 d, $n = 44$) study assessing ACT-induced changes in S_{aO_2}.[45] The study demonstrated that less arterial oxygen desaturation occurred during aerobic exercise following a period of training compared with control (WMD 0.62%, 95% CI 0.32 to 0.92), although the difference did not reach statistical significance. The same study showed less desaturation occurred during anaerobic exercise following training compared with control (WMD 0.33%, 95% CI 0.04 to 0.62), but again the difference was not statistically significant.

Exercise Tolerance

Exercise: The only studies that assessed changes in exercise tolerance included 2 studies of aerobic exercise ($n = 109$) and 2 studies of anaerobic exercise ($n = 64$) (see Table 3). One short-term (mean 18.7 d) in-patient study of aerobic exercise ($n = 44$) demonstrated increased exercise capacity as measured by peak oxygen uptake ($\dot{V}_{O_2}$peak) during a treadmill exercise test (WMD 8.53 mL/kg/min, 95% CI 4.85 to 12.21),[45] while a long-term (3 years) study of aerobic exercise ($n = 65$) saw no differences in the annual rate of decline of exercise capacity measured by cycle ergometry.[44] One short-term (mean 18.7 d) trial ($n = 44$) reported no improvements in exercise tolerance with anaerobic training during a hospital admission,[45] while a long-term (3 mo) trial ($n = 20$) reported significantly greater exercise capacity as measured by cycle ergometry in the anaerobic training versus control group (WMD 2.10 mL/kg/min, 95% CI 0.12 to 4.08).[46]

Exacerbations

Exercise: Only 1 study was identified that assessed the ACT-induced effects on exacerbations (see Table 3). A 3-year study of aerobic exercise ($n = 65$) compared with no exercise program reported no significant difference between groups for mean number of hospitalizations or mean number of days in hospital.[44]

Adverse Events

There were no studies identified that addressed the effects of ACTs compared with no therapy on adverse events (see Table 3).

Mortality

There were no studies that addressed the effects of ACTs on mortality (see Table 3).

Quality of life

Exercise: There were 5 studies that assessed the effects of an ACT on quality of life and all involved exercise. There were 2 studies of aerobic exercise ($n = 131$)[44,45] and 2 studies of anaerobic exercise ($n = 86$).[45,46] Positive effects were experienced by 43 out of 49 individuals following exercise in one long-term (3 years) study of aerobic exercise.[44] The other aerobic study (in-patient, mean 18.7 d) reported a significantly higher improvement in the quality of life in the exercise group utilizing the Quality of Well-Being Scale,[47] (WMD 0.10, 95% CI 0.03 to 0.17).[45] Both studies of anaerobic exercise (short-term mean 18.7 d, long-term 3 mo) reported no significant difference between the exercise and control groups. A study of inspiratory training (8 wk, $n = 29$)[29] reported significantly lower anxiety and depression scores in the exercise groups compared with the control group, utilizing the Hospital Anxiety and Depression Questionnaire[48] and the Chronic Respiratory Disease Questionnaire.[49]

Patient Preferences

Exercise: The studies that assessed patient preferences for an ACT compared with no therapy involved exercise only (see Table 3). One study ($n = 65$) reported on attitudes toward physical activity with stable, high rates of adherence to aerobic exercise at the end of each of 3 years.[44]

Table 4. Comparison of Airway Clearance Therapies and Their Effect on Sputum Production

	P&PD	PEP	ACBT	AD	OPEP	HFCC	Exercise
P&PD	ND	ND	ND	ND	ND	ND	ND
PEP	9 trials[40,41,51-57], $n = 155$ No difference	ND	ND	ND	ND	ND	ND
ACBT	4 trials, $n = 123$ No difference[38,53,58,59]	ND	ND	ND	ND	ND	ND
AD	2 trials, $n = 38$ 1 favored AD[52] 1 no difference[60]	1 trial[32], $n = 15$ Favored hPEP	1 trial, $n = 18$ No difference[66]	ND	ND	ND	ND
OPEP	4 trials, $n = 74$ 1 favored OPEP[62] 3 no difference[21,22,61]	ND	2 trials, $n = 31$ 1 favored ACBT[65] 1 no difference[26]	1 trial, $n = 14$ No difference[64]	ND	ND	ND
HFCC	4 trials, $n = 87$ 2 favored HFCC[20,63] 2 no difference[19,22]	ND	1 trial[27], $n = 10$ Favored ACBT	ND	1 trial[22], $n = 24$ Favored OPEP	ND	ND
Exercise	ND	1 trial, $n = 13$ No difference[67]	ND	ND	ND	ND	ND

P&PD = percussion and postural drainage
PEP = positive expiratory pressure
ACBT = active cycle of breathing technique
AD = autogenic drainage
OPEP = oscillatory PEP
HFCC = high-frequency chest compression
ND = no data reported

A short-term (7 d) study ($n = 24$) comparing dance and movement therapy with no training found no difference in adherence to general exercise regimens between the group exposed to dance therapy and the control group (no data were presented).[30] Finally, patient preference was studied in a 12-week trial of anaerobic exercise ($n = 20$).[46] Mean ± SD attendance rate at the training sessions was 98.1 ± 4.3%; the high attendance implies patient preference.

Recommendation

A Cochrane review (updated in 2006) concluded that ACTs have short-term effects in terms of increasing mucus transport, but there are insufficient data to draw any conclusions concerning the long-term effects.[13] A 2001 review by Hess also concluded that the effect of ACTs on long-term outcomes and quality of life in patients with CF is unknown, lamenting that "despite the clinical observation that retained secretions are detrimental to respiratory function…there is a dearth of high-level evidence to support any secretion clearance technique."[15] However, the author also noted that a lack of evidence does not mean lack of benefit. It has been suggested that efficacy studies of ACTs in infants and children are largely "underpowered and otherwise methodologically suboptimal."[50]

The Pulmonary Therapies Committee agreed with these opinions. Although it would be desirable to have properly designed and performed trials comparing ACTs with no therapy, the committee felt that a lack of equipoise in the clinical community on this issue made success in performing such studies highly unlikely. The committee felt that ACT should not be studied further in a placebo-controlled manner. The committee concludes that the evidence quality overall for the use of ACT in CF is fair. The committee determined that the overall benefit of ACT is moderate based upon the cumulative findings of the outcome measures, including short-term effects (eg, increased sputum production and lung function) and long-term effects (eg, rate of decline of lung function and increased exercise tolerance) (see Table 3). The committee recommends airway clearance be performed on a regular basis in all patients.

1. ACT is recommended for all patients with cystic fibrosis for clearance of sputum, maintenance of lung function, and improved quality of life. Level of evidence, fair; net benefit, moderate; grade of recommendation, B.

Question: What Is the Efficacy of One Method of ACT Compared With Other Methods of ACT?

The comparative effects of ACTs on sputum production and lung function are summarized in Tables 4 and 5, respectively.

Table 5. Comparison of Airway Clearance Therapies and their Effect on Lung Function

	P&PD	PEP	ACBT	AD	OPEP	HFCC	Exercise
P&PD	ND	ND	ND	ND	ND	ND	ND
PEP	13 trials[34,40,41,51,53,55-57,68-71,81], $n = 264$ No difference	ND	ND	ND	ND	ND	ND
ACBT	5 trials[38,39,53,58,59], $n = 186$ No difference	ND	ND	ND	ND	ND	ND
AD	4 trials[52,60,69,72], $n = 92$ No difference	1 trial[32], $n = 14$ Favored AD	ND	ND	ND	ND	ND
OPEP	4 trials[21,61,73,74], $n = 71$ No difference	4 trials[79-82], $n = 100$ No difference	2 trials[26,65], $n = 31$ No difference	1 trial[64], $n = 14$ No difference	ND	ND	ND
HFCC	2 trials, $n = 65$ 1 favored HFCC[78] 1 no difference [76]	1 trial[24], $n = 15$ No difference	1 trial[27], $n = 10$ Favored ACBT	ND	1 trial[25], $n = 29$ No difference	ND	ND
Exercise	1 trial[42], $n = 17$ Favored P&PD	ND	ND	ND	ND	ND	ND

P&PD = percussion and postural drainage
PEP = positive expiratory pressure
ACBT = active cycle of breathing technique
ND = no data reported
OPEP = oscillatory PEP
HFCC = high-frequency chest compression
ND = no data reported

Sputum Production

P&PD and PEP: There were 9 trials ($n = 155$) comparing P&PD with PEP that reported sputum production.[40,41,51-57] Three studies had but a single treatment, while the others ranged between 1–9 months. There was no significant difference in sputum production between P&PD and PEP groups.

P&PD and ACBT: Four trials ($n = 123$) compared sputum production by P&PD and ACBT (FET).[38,53,58,59] Two studies had but a single treatment, while the others lasted 2 and 4 weeks. A meta-analysis of these data calculated a pooled effect size of 0.27 SD (95% CI −0.65 to 0.10), suggesting a small (3.3 g sputum) but statistically insignificant trend favoring ACBT compared with P&PD.[14]

P&PD and AD: There was 1 study, presented as an abstract only (2 mo, $n = 28$), that reported that AD resulted in more sputum expectoration compared with P&PD, although no statistical analysis was presented.[52] Another small study ($n = 10$) comparing single treatments of P&PD with AD reported no significant difference in sputum; again no statistical analysis was presented.[60]

P&PD and OPEP: There were 4 trials ($n = 74$) comparing sputum production by P&PD and OPEP.[21,22,61,62] One in-patient study ($n = 22$) showed there was no difference in clinical score, which included sputum expectorated, between the 2 treatments.[61] A second study ($n = 18$), comparing a single treatment of OPEP with a control that would be considered P&PD by some authors, reported statistically significantly higher sputum production with OPEP (Flutter).[62] A short-term study (2 d, $n = 24$) found no statistically significant difference in wet sputum weight between P&PD and OPEP (intrapulmonary percussive ventilation [IPV]) groups,[22] and a comparison of P&PD and OPEP (Percussive Tech HF) (1 d, $n = 10$) found no statistically significant difference in either wet or dry sputum weights between the groups.[21]

P&PD and HFCC: We identified 4 studies ($n = 87$) comparing P&PD with HFCC (see Table 4). One in-patient study (2 d each treatment, $n = 29$) found a greater sputum weight produced in the HFCC group compared with the P&PD group.[63] A 1-day study ($n = 22$) reported no difference in wet sputum weights between groups using P&PD and the Frequencer electro-acoustical transducer for HFCC,[19] and a short-term comparison of P&PD and HFCC (2 d, $n = 24$) found no statistically significant difference in dry sputum weight between groups.[22] Finally, a somewhat longer study (7 d, $n = 12$) reported statistically significant differences favoring HFCC over P&PD in wet sputum weights (13.6 g ± 8.6 vs 10.3 g ± 7.7, $P < .05$), with no significant difference in dry sputum weights (0.60 g ± 0.37 in the HFCC group vs 0.47 g ± 0.40 in the P&PD group, $P = .07$).[20]

Other Comparisons: There are an additional 8 studies that have looked at sputum production. One study (1 treatment, $n = 15$) demonstrated hPEP produced statistically significantly more sputum (50 g wet weight) than either AD (35 g) or AD followed by hPEP (39 g).[32] A comparison of OPEP with AD (7 d, $n = 14$) reported no

significant differences in sputum weight.[64] ACBT produced significantly greater sputum than did OPEP (Flutter) together with ACBT (1 treatment, $n = 24$).[65] A comparison of AD with ACBT found no difference in secretion clearance between the 2 techniques (2 d, $n = 18$).[66] A 1-day trial ($n = 7$) showed no significant differences in 24-hour wet sputum values between groups using OPEP (Flutter) or ACBT.[26] Sputum production by groups using OPEP and HFCC was compared in a trial (2 d, $n = 24$) that found that there was statistically significant ($P < .05$) greater wet sputum weight in the OPEP (IPV) group (mean = 6.84 g) compared with the HFCC group (mean = 4.77 g).[22] A 1-day trial ($n = 10$) of ACBT and HFCC reported a statistically significant ($P < .005$) higher wet sputum weight in the ACBT group (mean = 5.2 g) compared with the HFCC group (mean = 1.1 g).[27] Finally, a study comparing aerobic training with PEP found no significant difference in weight of sputum expectorations between the 2 treatment groups (1 treatment, $n = 13$)[67]; however, no statistical analysis was presented.

Lung Function

P&PD and PEP: There were 13 trials ($n = 264$) assessing lung function outcomes in trials comparing P&PD with PEP.[34,40,41,51,53,55-57,68-72] The duration of the studies ranged between a single treatment and 1 year of therapy. There were no statistically significant differences in FEV_1, FVC, or $FEF_{25\%-75\%}$ for any of the durations of therapy. A meta-analysis[14] of 6 of these studies[40,41,51,53,55,57] ($n = 146$) calculated an effect size of 0.02 SD units (95% CI −0.32 to 0.43) for FEV_1; this translates to a non-statistically-significant increase of 4 mL in FEV_1 in the PEP group.

P&PD and ACBT: We identified 5 studies comparing ACBT plus P&PD with ACBT alone ($n = 186$).[38,39,53,58,59] Two studies lasted only 1 treatment, while the others lasted 2 weeks, 4 weeks, and 3 years. The 3-year study ($n = 63$) compared lung function outcomes in P&PD and ACBT treatment groups and reported an annual decline in $FEF_{25\%-75\%}$ that was worse in the ACBT group compared with the P&PD group.[39] A pooled effect size (of all 5 studies) for FEV_1 was 0.13 SD (95% CI −0.17 to 0.43), suggesting no difference between the groups (0.07% difference in FEV_1 % predicted).[14]

P&PD and AD: There were 4 studies comparing P&PD and AD ($n = 92$) that included lung function outcomes. The studies ranged from 1 treatment to 1 year of therapy, but there was no overall difference between treatment groups at any duration.[52,60,69,73]

P&PD and OPEP: Four studies ($n = 71$) compared lung function outcomes in P&PD and OPEP treatment groups. The study durations ranged between 1 day and 6 months, but showed no overall difference in lung function between groups at any duration.[21,61,74,75]

P&PD and HFCC: Three studies reported lung function outcomes ($n = 145$) comparing P&PD with HFCC or other mechanical devices,[76-78] although only one of the studies truly evaluated HFCC[77] ($n = 50$). These studies lasted 2 weeks to 2 months, but there was no overall difference between the groups at any duration. There was one 22-month before-after study ($n = 15$) that reported improved lung function in HFCC compared with manual CPT.[79]

P&PD and exercise: One in-patient study lasting 2 weeks ($n = 17$) compared lung function outcomes in aerobic exercise and P&PD treatment groups, and reported significantly greater improvement in lung function in the P&PD group.[42] The difference in FEV_1 % predicted was 7.05 (95% CI 3.15–10.95, $P < .001$). It has been noted that these results should be interpreted with caution, as the P&PD group had significantly lower lung function than the exercise group at baseline.[12]

Other Comparisons: There were 4 studies ($n = 100$) comparing PEP with OPEP.[72,80-82] The study durations ranged between 2 weeks and 13 months, but there was no significant difference in FEV_1 between the groups at any duration. In a small ($n = 16$) short-term (2 d) study no significant difference in FEV_1 was induced between PEP, PD, and HFCC.[34] A study comparing PEP with HFCC ($n = 15$) reported statistically significant increases in FEV_1 and FVC in the acute phase (within 48 h of admission) in both treatment groups, but there was no effect on FEV_1/FVC and $FEF_{25\%-75\%}$.[24] No statistical analysis comparing the 2 groups was presented. In a study (1 treatment, $n = 14$) comparing hPEP with AD, FVC and FEV_1 were significantly lower after AD followed by hPEP, compared with AD alone.[32]

Lung function outcomes were also examined in a 7-day crossover study of OPEP (Flutter) and AD[64] ($n = 14$), and a 1-day crossover study of OPEP (Flutter) and ACBT[65] ($n = 24$). No significant difference was found between treatments in either study. A crossover study of OPEP (Flutter®) and ACBT (1 d, $n = 7$) also showed no significant difference between treatments in FEV_1 or FVC outcomes.[26]

Lung functions outcomes were compared in a 4-week study ($n = 29$) of OPEP (Flutter) and HFCC techniques.[25] No statistically significant difference in lung function values (FEV_1, FVC, $FEF_{25\%-75\%}$) was found. A comparison of HFCC and ACBT (1 d, $n = 10$) found significant improvement from baseline values following ACBT but not HFCC in the morning (mean increase $FEV_1 = 0.1$ L, $P = .02$, mean increase FVC = 0.12 L, $P = .02$) and in the afternoon (mean increase FVC = 0.06 L, $P = .01$).[27]

Arterial Oxygen Saturation

P&PD and PEP: We identified 4 studies ($n = 51$) comparing P&PD with PEP that assessed S_{aO_2}.[56,72,83,84] The treatment durations ranged between 1 treatment and 1 year.

The studies reported no differences in S_{aO_2}, although no statistical analysis was presented for some.

Other Comparisons: One study reported an increase in peripheral oxygen saturation (S_{pO_2}) during PEP therapy and a decrease during HFCC ($P < .001$, $n = 15$) that returned to baseline immediately after treatment.[24] The effect of aerobic training compared with PEP (1 treatment, $n = 13$) found no significant difference in oxygen saturation, but no statistical analysis was presented.[67] A comparison of PET to other therapies reported no significant change in S_{aO_2} after 2 days of treatment, but no data were provided.[23] There were no reported comparisons involving hPEP, OPEP, or AD.

Exercise Tolerance

P&PD and ACBT: We identified 1 long-term (3 years) study ($n = 63$) comparing the effect of P&PD with ACBT on exercise tolerance.[39] No difference was found between the groups, though no statistical analysis was presented. There were no reported comparisons involving PEP, hPEP, OPEP, HFCC, AD, or exercise.

Exacerbations

P&PD and PEP: We identified 2 studies comparing P&PD with PEP that addressed this outcome. One ($n = 36$) study lasting 1 year reported a statistically insignificant difference between the 2 groups in the number of admissions per year.[68] A second 1-year study ($n = 27$) reported that the number of days on antibiotic therapy was higher in the PEP group (29.6 d) than in the P&PD group (18.2 d), although no statistical analysis was presented.[83]

P&PD and OPEP: One study (6 mo, $n = 16$) comparing P&PD with OPEP (IPV) used 2 indicators to measure exacerbations—number of days in hospital per year and number of admissions per year—and found no difference between the P&PD and OPEP groups.[75] There was also one randomized controlled in-patient trial ($n = 22$) that compared P&PD with OPEP (Flutter) with no significant difference in length of hospital stay and number of respiratory treatments.[61]

P&PD and ACBT: There was one long-term (3 years) study comparing P&PD with ACBT ($n = 63$) that used 2 indicators to measure exacerbations—number of days in hospital per year and number of admissions per year—with no difference between the 2 groups.[39]

Other Comparisons: We identified 2 studies ($n = 72$) that reported the number of respiratory exacerbations severe enough to require hospitalization. A long-term study (1 year, $n = 31$) reported significantly more exacerbations in the OPEP (Flutter) group compared to the PEP group, though no data were provided.[80] A second long-term study compared PEP with OPEP (Flutter) (13 mo, $n = 41$) and also suggested a reduction in exacerbations in favor of PEP.[81] There were no reported comparisons involving hPEP, HFCC, AD, or exercise.

Adverse Events

P&PD and PEP: There were 2 studies ($n = 63$) comparing P&PD with PEP, both lasting 1 year, that reported on occurrence of adverse events. In one study, 3 individuals from the P&PD group suffered from severe gastroesophageal reflux and were withdrawn from the study (RR 0.12, 95% CI 0.01 to 2.18).[83] In the other study there were no adverse events reported by either group.[68]

P&PD and OPEP: Our search identified a 1-day study ($n = 10$) comparing P&PD with an OPEP (Percussive Tech HF).[21] One patient in the P&PD group reported hemoptysis and dropped out of the study.

P&PD and HFCC: One study (2 wk, $n = 70$) reported mild hemoptysis in one individual in the HFCC group and 2 in the P&PD group.[77] Some participants in the HFCC group experienced mild chest pain and nausea during the first 3 days, which subsequently resolved.

Other Comparisons: There were no reported comparisons involving hPEP, AD, or exercise.

Mortality

There were no reported comparisons involving any therapies with respect to mortality.

Quality of Life

P&PD and PEP: One study ($n = 61$) assessed quality of life, comparing P&PD with PEP over 2 years.[70] No difference or change in quality of life, as measured by the Quality of Well-Being Scale, was found. There were no reported comparisons involving OPEP, HFCC, AD, or exercise.

Patient Preferences

P&PD and PEP: There were 6 studies ($n = 131$) comparing P&PD with PEP, ranging from a single treatment to a full year of follow-up[53,56,68,69,71,83]; patients preferred PEP in 4 of the studies. Reasons for preference included comfort, convenience, independence, ease of use, more control and flexibility over treatment times, and less interruption to daily living.

P&PD and AD: Two studies ($n = 36$), both lasting 2 months, noted a greater preference for AD compared to P&PD, which was quite marked in some patients.[69,73]

P&PD and OPEP: There was one 6-month study ($n = 16$) of P&PD and IPV; all of the patients using IPV expressed satisfaction and a desire to continue with this form of therapy.[75] In a 1-day study comparing P&PD with the Percussive Tech HF device, 6 out of 9 participants (66.7%) preferred the device.[21] In both studies, the reason cited for preference for the devices was that they were self-administered and facilitated independence. We also identified a 2-day study ($n = 24$) comparing OPEP (IPV) with P&PD and HFCC using a Likert-type study-specific scale to evaluate patient preference, comfort, efficacy, and ease of use.[22] There was no statistically significant difference in any of these categories among the 3 therapy groups: 7 partici-

pants preferred P&PD, 7 participants preferred IPV, and 10 participants preferred HFCC.

P&PD and HFCC: Two studies comparing P&PD with HFCC ($n = 121$) addressed patient preference. A 2-week study ($n = 51$) utilized a telephone survey and reported that among respondents, 48% preferred HFCC and 26% preferred P&PD (26% reported no preference).[76] No statistical analysis was presented. The other study ($n = 70$), also 2 weeks, reported that 88% of participants expressed satisfaction with HFCC; however, satisfaction was not assessed in the P&PD group.[77]

Other Comparisons: A 2-day study comparing PEP with PEP and PD together reported a preference for PEP in 11 of 14 patients.[56] Patient preference was assessed in a 4-week study ($n = 21$) comparing OPEP (Flutter) with HFCC.[25] On the study-specific scale, 12 participants (50%) preferred HFCC, largely due to a belief in its efficacy, and 9 participants (37%) preferred the Flutter, based on convenience of use. A 1-day study ($n = 10$) comparing HFCC with ACBT reported that a larger number of participants found it easier to clear secretions using ACBT compared with HFCC.[27] There were no reported comparisons involving hPEP or exercise.

Recommendations

Prior systematic reviews have concluded that there is no advantage for any particular ACT over another, although some reported a trend for participants to prefer self-administered forms of therapy.[12,14,16] Main et al described the limitations of their review based upon the "paucity of well-designed, adequately-powered, long-term trials."[12] The Pulmonary Therapies Committee felt that the studies reviewed were inadequately powered to demonstrate superiority or equivalence. Rather than stating that these methods are equivalent, we choose to state that none has been demonstrated to be superior to the others. There may be advantages and disadvantages of particular therapies for individual patients (Table 6). Patient preference should be considered with the anticipation that this will be associated with greater adherence to therapy.

2. In general, there is no ACT that has been demonstrated to be superior to others. Level of evidence, fair; grade of recommendation, B.

3. For the individual, one form of ACT may be superior to the others. The prescription of ACT should be individualized based on factors such as age, patient preference, and adverse events, among others. Level of evidence, fair; grade of recommendation, consensus recommendation, B.

In addition, the committee recognized the benefits of aerobic exercise. Although there was insufficient evidence to support exercise as a sole method of airway clearance, there is evidence that aerobic exercise may have an adjunctive benefit to airway clearance. Given the other recognized benefits of aerobic exercise (including a reduced risk of cardiovascular disease, stroke, hypertension, osteoporosis, depression, and anxiety[85]), the committee determined that promoting aerobic exercise should be a priority for the patient with CF.

4. Aerobic exercise is recommended for patients with cystic fibrosis as an adjunctive therapy for airway clearance and its additional benefits to overall health. Level of evidence, fair; net benefit, moderate; grade of recommendation, B.

Key Points of Discussion

There are a great many questions regarding ACTs for CF that remain unanswered:

1. **When should airway clearance be initiated?** There is a paucity of evidence of the benefit of ACTs in infants with CF. The presence of lung disease early in life is well-established, and the committee feels that airway clearance should be instituted in the first few months of life. The committee believes there is potential benefit and little harm in teaching ACT to parents early and encouraging airway clearance to be part of the child's daily routine. In most cases, the form of ACT for infants will be P&PD.

2. **How should the clinician choose an ACT for a patient?** The individual circumstances for each patient will help dictate the choice of airway clearance regimen. There are advantages and disadvantages of each of the therapeutic options (see Table 6), and decisions regarding prescription of airway clearance may include age of the patient, patient preference, severity of disease, availability of a partner, and observed efficacy based on patient reporting (subjective measures) and objective measures (eg, lung function). It should be noted that the prescribed therapies may change as the patient's situation changes (eg, becomes older and more independent) and the efficacy and appropriateness of the ACT therapy should be periodically reassessed.

3. **What is the optimal method of performing each of the ACTs?** There are published descriptions for the applications of these therapies, but no studies have demonstrated optimal methods, such as duration or number of treatments per day. The airway clearance regimen may need to be changed during acute illness or when there is an increase in sputum volume and consistency. This could mean an increase in the time spent with therapy, an increased frequency of therapies, or even a change in the type of therapy.

4. **Who should educate the patients on ACTs?** Airway clearance is best taught by an experienced health care

Table 6. Considerations When Selecting an Airway Clearance Therapy

Technique	Age of Patient	Assistant Needed	Equipment Needed	During Exacerbation	Concurrent Nebulizer	Notes	Cost
P&PD	Any age	Yes	Positioning aids Percussor/vibrator Devices for infants	Yes	Only in upright position	May need to modify positions because of gastroesophageal reflux[93,94] or elevated intracranial pressure[95,96] Repetitive motion injuries Can be combined with other techniques Can focus on specific problem areas Inappropriate for patients with chest pain, instability of chest wall or spine	Expensive if performed by caregiver long-term
PEP	Begin to teach at 3–4 years of age	Until 8–10 years of age	Mouthpiece or mask PEP device Manometer	Yes	Yes	Sinusitis, epistaxis, or ear infection may contraindicate Risk of pneumothorax[97-99] May impair venous return in patients who have hemodynamic instability Portable	Minimal, but devices need replacement
ACBT	Begin to teach at 3–4 years of age	Until 8–10 years of age	Positioning aids Percussor/Vibrator	Yes	Only in upright position	Precautions are for head-down positions May be augmented by other techniques, such as percussion, vibration, and chest compressions	Cost is low if done independently
AD	≥ 12 years of age	No	None	Best to use an alternative	No	Takes time to learn Requires concentration Not useful when anxious	No cost
OPEP	Adolescents and adults	While in hospital	Home unit Unit for hospital setting	May not be well tolerated	Yes except Flutter	Titrate for comfort and visible chest movement Easy to perform Portable Can be used as adjunct to other physiotherapies	Moderate expense
HFCC	≥ 2–3 years of age	For young children	Air pulse generator Appropriate size vest	Yes	Yes	Precautions needed with chest tubes, indwelling catheters, or other devices in/on chest Provides therapy to a large area of the chest Pressure and frequency settings can be individualized to optimize sputum production May be used in toddlers and small children who are not cooperative with other airway-clearance modalities Substantially less portable than other therapies Contraindicated in presence of unstabilized head and/or neck injury or active hemorrhage with hemodynamic instability	Very expensive
Exercise	Children, adolescents, and adults	For young children	Variable	No	Premedicate prior to exercise	Exercise-induced bronchospasm Oxygen desaturation Adjunct to ACT May provide multiple health benefits	Depends on type of exercise

P&PD = percussion and postural drainage
PEP = positive expiratory pressure
ACBT = active cycle of breathing technique
AD = autogenic drainage
OPEP = oscillatory PEP
HFCC = high-frequency chest compression
ACT = airway clearance techniques

practitioner. Airway clearance is performed in the hospital setting, typically with the assistance of a respiratory or physical therapist. Airway clearance is a part of their educational curriculum, and they are the most experienced in its practice. There may be others in a CF center who are well-trained in the application of ACTs, such as a nurse, physician, nurse practitioner, physician's assistant, or exercise physiologist. The committee recommends that the education of patients and families be performed by those who have been trained to do so. This should be someone who can devote the time to the patient and who will periodically reassess the educational needs of the patient and family.

5. **How should we evaluate new methods of airway clearance?** As stated earlier, the literature on airway clearance in CF lacks controlled, long-term studies that have been powered to adequately compare therapies. New devices or techniques should be consistent with the known pathophysiology, and studies should be powered for either equivalence or superiority to existing therapies using meaningful outcome measures such as lung function (either an increase of lung function or slowing the rate of decline), effect on exacerbations, patient preference, and quality of life.

Conclusions

We have reviewed and evaluated the evidence supporting the use of ACTs for the maintenance of lung function in individuals with CF. We have developed recommendations based on the quality of the published evidence and the estimate of the net benefit demonstrated within those publications. These recommendations will be amended as new data are reported.

This document should be viewed as a guideline regarding CF care. The introduction and use of specific ACTs will depend upon the individual, his or her social situation, and parental or patient preferences. We are hopeful that clinicians will find these recommendations helpful in their care of patients with CF.

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Appendix

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