CHEST

Airway Clearance Techniques in Bronchiectasis

Analysis From the United States Bronchiectasis and Non-TB Mycobacteria Research Registry

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BACKGROUND: In patients with bronchiectasis, airway clearance techniques (ACTs) are important management strategies.

RESEARCH QUESTION: What are the differences in patients with bronchiectasis and a productive cough who used ACTs and those who did not? What was the assessment of bronchiectasis exacerbation frequency and change in pulmonary function at 1-year follow up?

STUDY DESIGN AND METHODS: Adult patients with bronchiectasis and a productive cough in the United States Bronchiectasis and NTM Research Registry were included in the analyses. ACTs included the use of instrumental devices and manual techniques. Stratified analyses of demographic and clinical characteristics were performed by use of ACTs at baseline and follow up. The association between ACT use and clinical outcomes was assessed with the use of unadjusted and adjusted multinomial logistic regression models.

RESULTS: Of the overall study population (n = 905), 59% used ACTs at baseline. A greater proportion of patients who used ACTs at baseline and follow up continuously had *Pseudomonas aeruginosa* (47% vs 36%; $P = .021$) and experienced an exacerbation (81% vs 59%; $P < .0001$) or hospitalization for pulmonary illness (32% vs 22%; $P = .001$) in the prior two years, compared with those patients who did not use ACTs. Fifty-eight percent of patients who used ACTs at baseline did not use ACTs at 1-year follow up. There was no significant change in pulmonary function for those who used ACTs at follow up, compared with baseline. Patients who used ACTs at baseline and follow up had greater odds for experiencing exacerbations at follow up compared with those patients who did not use ACTs.

INTERPRETATION: In patients with bronchiectasis and a productive cough, ACTs are used more often if the patients have experienced a prior exacerbation, hospitalization for pulmonary illness, or had *P aeruginosa*. There is a significant reduction in the use of ACTs at 1-year follow up. The odds of the development of a bronchiectasis exacerbation are higher in those patients who use ACTs continuously, which suggests more frequent use in an ill bronchiectasis population.

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KEY WORDS: airway clearance technique; bronchiectasis; sputum

FOR EDITORIAL COMMENT, SEE PAGE 1298

ABBREVIATIONS: ACTs = airway clearance techniques; BRR = Bronchiectasis and NTM Research Registry; EMBARC = European Multicentre Bronchiectasis Audit and Research Collaboration; NTM = nontuberculous mycobacteria

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Take-home Points

Study Question: Are there differences in patients with bronchiectasis and a productive cough who use airway clearance techniques (ACTs) compared with those who do not?

Results: In this study from the United States Bronchiectasis and NTM Research Registry, ACTs were used more often by patients if they had a prior exacerbation, had had hospitalization for pulmonary illness, or had *Pseudomonas aeruginosa*. Patients who used ACTs at baseline and follow up had greater odds for experiencing exacerbations at follow up compared with those who did not use ACTs.

Interpretation: The study findings suggest more frequent use of ACTs in an ill bronchiectasis population.

Non-cystic fibrosis bronchiectasis (referred to here as bronchiectasis)[1] is a disorder that is defined by inflammation, dilatation, and irreversible damage to the bronchial tubes.[2] In bronchiectasis, the mucus itself is often abnormal[3] and more complex.[4] Retained sputum can cause mucus plugs, airway obstruction, and damage that results in chronic infection. The inflammatory response, which involves neutrophils, lymphocytes, and macrophages, results in further bronchiectasis.[5] Impaired mucociliary clearance may maintain the vicious cycle of inflammation that develops in bronchiectasis and perpetuates further lung damage.[6] As a result, bronchiectasis may lead to progressive symptoms and worsening quality of life.[7]

The goal of airway clearance techniques (ACTs) is to improve symptoms, reduce exacerbation frequency, and improve quality of life.[8] ACTs include the use of instrumental techniques, such as positive expiratory pressure devices and high frequency chest wall oscillation, and various manual techniques, such as manual chest physical therapy, chest percussion, postural drainage, and active cycle breathing techniques. ACTs may be useful in the setting of patients with bronchiectasis and chronic productive cough. It may also benefit patients who have difficulty expectorating mucus.[9] Studies suggest that ACTs may reduce exacerbations[10] and improve symptoms, exercise capacity,[11] and quality of life.[12] A number of clinical guidelines recommend ACT use in patients with bronchiectasis, albeit with a majority of recommendations based on low-to-moderate quality of evidence.[13] A *CHEST* expert panel report also stressed the importance of airway clearance in those with productive cough and bronchiectasis.[14] However, ACTs remain significantly underused. Data from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) reported that only 50.5% of data registrants performed ACTs regularly.[15] The Indian Bronchiectasis registry reported that less than one-half of their cohort were prescribed ACTs.[16] Furthermore, rates of adherence to ACTs are low.[17] Large-scale studies on the utility of ACTs in bronchiectasis are lacking, and the efficacy of ACTs is largely unknown, although strongly clinically recommended by consensus opinion. Current data are limited to retrospective studies, small single-center prospective clinical trials, national registries, and Cochrane database reviews.[18-21] Studies that will evaluate the clinical benefit of ACTs in bronchiectasis are needed and have been identified as a high research priority.[22,23] Specifically, randomized clinical trials that compare efficacy of different ACT modalities are needed, because no one ACT has been shown to be superior to another.[8,19] In this study, with the use of

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a large national database registry, we sought to analyze clinical outcomes in patients with bronchiectasis and productive cough who were performing ACTs. The primary outcome of the study was to describe differences in patients with productive cough and bronchiectasis who used ACTs and those who did not. Of specific interest were the numbers of exacerbations and hospitalizations prior to baseline, as well as differences with various microorganisms, given the propensity for increased exacerbations with certain microorganisms in bronchiectasis.[24] Secondary outcomes included 1-year follow up assessment of ACT use on pulmonary function[25] and the effect of ACT use as an independent factor on the frequency of bronchiectasis exacerbations.

Methods

Study Design

The United States Bronchiectasis Research Registry (BRR) is a centralized database of patients with bronchiectasis who were identified at 16 clinical sites throughout the United States and is sponsored by the COPD Foundation. The goal of the BRR is to support collaborative research and assist in the planning of multicenter clinical trials for the treatment of bronchiectasis and non-tuberculous mycobacteria (NTM) lung disease. Study coordinators received training from the data collecting center and the COPD Foundation. Quality control occurred in real time, because the data management system incorporated expected range checks. The institutional review board of each participating site approved the study, as did the administrative institutional review board for the data collecting center. After informed consent was provided, medical records were queried by a study coordinator or principal investigator who used standardized recording forms. Data were entered through a centralized internet-based entry system at DatStat, Inc. Data from the database were queried for this study. Patients from the registry who were included in this study were seen clinically from 2008 to 2019.

Adult patients who were >18 years old with a CT scan-established diagnosis of bronchiectasis and productive cough met inclusion criteria. Patients with cystic fibrosis (based on history, positive sweat chloride, genetic studies, or a combination of these) were excluded from the analyses. There are other techniques, which included mucoactive agents and pulmonary rehabilitation, that may also aide with mucus clearance.[8] However, these modalities were not categorized as an ACT for this study and were also excluded from the analyses. Analyses were performed with the use of data that were collected at enrollment (baseline data) and at 1-year follow-up visit.

For the purpose of the present study, use of ACTs was stratified into three groups: group 1: continuous use (at baseline and follow up); group 2: intermittent use (either at baseline or follow up); and group 3: no use (neither at baseline nor at follow up).

ACTs included the use of instrumental techniques, such as Aerobika (Monaghan Medical Corporation), Acapella (DHD Healthcare), Flutter (Scandipharm), Lung flute (Medical Acoustics LLC), and high frequency chest wall oscillation devices. ACTs also included manual techniques, such as chest percussion, postural drainage, and cough/active cycle breathing techniques. Although the authors recognize that there are other commonly performed ACTs elsewhere in the world, such as autogenic drainage and the slow expiration with the glottis opened in a lateral posture,[26] data on these techniques are not available in the BRR. In addition, data on the frequency of ACT use are also not available in the BRR.

The BRR data collection forms define bronchiectasis exacerbation as a deterioration in three or more of the following key symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, hemoptysis, and a determination from a clinician that a change in bronchiectasis treatment was required.[27]

For the purposes of these analyses, a diagnosis of NTM was defined as a history of NTM lung disease prior to enrollment, two or more acid-fast bacilli positive sputum cultures, or at least one acid-fast bacilli positive culture from BAL or a transbronchial biopsy.[28] The presence of *Pseudomonas aeruginosa* and other microorganisms was defined as one or more positive cultures at baseline.

Statistical Analysis

Descriptive statistics were calculated for the main demographic and clinical characteristics of the overall study sample and stratified by use of ACTs at baseline and follow up. All results were reported as frequencies and proportions for categoric variables and as means (±SD) for continuous variables. Values between the strata were compared with the use of chi-square tests for categoric variables and analysis of variance for continuous variables. Mean changes in lung function measured in liters by FEV_1 and FVC between baseline and follow-up visit were computed for each group and compared with the use of repeated measures analysis of variance. Considering the categoric nature of the variable that reflected the number of exacerbations, ordinal regression models initially were considered for the analyses, but the proportional odds assumption that was assessed with the use of the score test was found not to be supported by the data. Thus, multinomial regression models were used to assess the association between the number of exacerbations at follow up and ACT use at baseline and follow up. Both unadjusted and adjusted results were obtained. In the adjusted regression models, we controlled for variables that had clinical importance and statistically significant difference between the ACT use groups in the stratified analyses. The final model included the number of exacerbations at baseline and the presence of *P aeruginosa* at baseline and had the best fit for the data with the use of the Akaike information criterion. Missing data analyses compared the included study population with those patients who were excluded from the multivariable analyses due to missing or incomplete data. The significance level was set at .05. Statistical analyses were performed with SAS software (version 9.4; SAS Institute Inc).

Results

Baseline Characteristics of the Cohort

Table 1 gives the main demographic and clinical characteristics at baseline for the overall cohort (n = 905) and for those patients who were using ACTs continuously or intermittently or not using ACTs. About one-quarter of the patients were using ACTs continuously; 39% were using ACTs intermittently, and 36% were not using ACTs at baseline or follow up. The overall cohort had a mean age of 63 (SD = 15) and were predominantly white (91%) and female (78%). The cause of bronchiectasis from patients in the BRR were described in a prior publication.[29] Patients who used ACTs at baseline and follow up continuously were more likely to have experienced an exacerbation (81% vs 59%; $P < .0001$) or hospitalization for pulmonary illness (32% vs 22%; $P = .001$) in the prior 2 years, compared with those patients who were not using ACTs at baseline and follow up. Similar associations with prior exacerbations and hospitalizations were also seen in those patients who were using ACTs at baseline and follow up intermittently, compared with those not using ACTs (Table 1). A significantly greater proportion of patients in the continuous and intermittent ACT groups had presence of *P aeruginosa* at baseline (47% and 40%, respectively vs 36%; $P = .021$). There was no significant difference with dyspnea in the groups (data not shown); data on other symptoms were not available.

Use of ACTs at Follow Up

Table 2 gives the different ACT modalities used at baseline and 1-year follow up. Fifty-nine percent of patients (535/905) used ACTs at baseline. The majority of ACTs that were used were positive expiratory pressure devices, such as Aerobika, Acapella, Flutter, and Lung flute, or a combination of methods. Of the patients using ACTs at baseline, more than one-half of the patients (288/535; 58%) did not report the use of ACTs at follow up.

Pulmonary Function at Follow Up

Table 3 gives the mean change in pulmonary function at 1-year follow up, compared with baseline. There was no significant difference in the mean change of FEV_1 or FVC at 1-year follow up, compared with baseline, in all three groups. The mean change in FEV_1 for those who used ACTs continuously or intermittently and no ACT use was -0.03 L, -0.02 L, and -0.01 L, respectively. The mean change in FVC for patients using ACTs continuously, intermittently, and no ACT use was 0.03 L, 0.01 L, and -0.03 L, respectively.

Exacerbation Frequency at Follow Up

Table 4 gives the results of the multinomial regression analysis of exacerbation frequency at follow up by ACT use, unadjusted and adjusted for the number of baseline exacerbations and presence of *P aeruginosa* at baseline. At 1-year follow up, 47% of the patients reported having no exacerbations; 28% had one exacerbation, and 25% had two or more exacerbations within the past year. In unadjusted analyses, patients who used ACTs continuously or intermittently had increased odds for the development of bronchiectasis exacerbations compared with patients who did not use ACTs at baseline or follow up. After we adjusted for the number of exacerbations and the presence of *P aeruginosa* at baseline, patients who used ACTs continuously had increased odds for one bronchiectasis exacerbation vs none, compared with those who did not use ACTs.

Missing data analyses did not reveal any significant differences in age, sex, race, or pulmonary function between the patients who were included and those who were excluded from the multivariable analyses due to incomplete data. However, we identified a greater proportion of patients with NTM among those who were not included in the analyses (36% vs 28%; $P = .027$) (e-Table 1).

Discussion

It is of expert consensus opinion that airway clearance is an important component in the treatment and preventative regimen of a patient with bronchiectasis. Multiple clinical guidelines in bronchiectasis do recommend the use of ACTs in patients with bronchiectasis.[13] However, ACT use is far from widespread. In a study from the BRR, only 56% of patients with bronchiectasis were using non-pharmacologic strategies in the United States.[30] Data elsewhere in the world have found similar results, with 50.5% of patients reporting regular use of chest physiotherapy in the EMBARC registry.[15] In our current study from the registry, 59% of patients with productive cough and bronchiectasis used ACTs at baseline. However, more than one-half of these patients did not use ACTs at 1-year follow up. Although recommended, our study again highlights the underuse of ACTs and a significant decrease in their use over time. There may be many reasons for the lack of ACT use. There is an

TABLE 1] Main Demographic and Clinical Characteristics of the Study Sample at Baseline

Variable	Data Available, No.	Overall Sample (N = 905)	Continuous Use of Airway Clearance at Baseline and Follow Up (n = 226; 25%)	Intermittent Use of Airway Clearance at Baseline and Follow Up (n = 351; 39%)	No Use of Airway Clearance at Baseline and Follow Up (n = 328; 36%)	*P* Value
Age, mean (SD), y	871	63 (15)	62 (15)	63 (15)	64 (14)	.285
Female, No. (%)	903	706 (78)	172 (76)	278 (79)	256 (78)	.658
Race, No. (%)	901	…	…	…	…	.001
White	…	823 (91)	209 (93)	329 (94)	285 (87)	…
African American	…	19 (2)	3 (1)	3 (1)	13 (4)	…
Asian	…	27 (3)	1 (1)	10 (3)	16 (5)	…
Other[a]	…	32 (4)	12 (5)	8 (2)	12 (4)	…
Experienced an exacerbation within the past 2 y, No. (%)	900	620 (69)	182 (81)	245 (70)	193 (59)	< .0001
Exacerbations in the past 2 y, No. (%):	772	…	…	…	…	< .0001
0		254 (33)	38 (20)	89 (31)	127 (43)	
1		151 (20)	44 (23)	58 (20)	49 (17)	
2		135 (18)	31 (17)	57 (20)	47 (16)	
≥3		232 (30)	75 (40)	83 (29)	74 (25)	
Hospitalized for pulmonary illness or exacerbation in the past 2 y, No. (%)	864	228 (26)	70 (32)	90 (27)	68 (22)	.001
Hospitalizations for pulmonary illness or exacerbation in the past 2 y, No. (%)	861	…	…	…	…	.036
0	…	636 (74)	147 (67)	240 (73)	249 (79)	…
1	…	140 (16)	47 (22)	51 (16)	42 (13)	…
2	…	50 (6)	14 (6)	22 (7)	14 (4)	…
≥3	…	35 (4)	10 (5)	14 (4)	11 (3)	…
Non-tuberculous mycobacteria at baseline,[b] No. (%)	805	255 (32)	64 (30)	104 (33)	87 (32)	.674
Pseudomonas aeruginosa,[c] No. (%)	717	293 (41)	95 (47)	117 (40)	81 (36)	.021
Haemophilus influenzae,[c] No. (%)	715	71 (10)	18 (9)	27 (9)	26 (12)	.337
Staphylococcus aureus,[c] No. (%)	684	106 (16)	34 (17)	39 (14)	33 (16)	.755
Aspergillus fumigatus,[c], No. (%)	279	83 (30)	20 (27)	41 (35)	22 (25)	.286

[a]Included Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Unknown.
[b]Defined as history of non-tuberculous mycobacteria lung disease prior to enrollment or ≥2 acid-fast bacilli positive sputum cultures or ≥1 acid-fast bacilli BAL or transbronchial biopsy cultures.
[c]Defined as one or more positive cultures at baseline.

TABLE 2] Airway Clearance Technique Modalities at Baseline and Follow up Among Those Who Used Them

Variable	Baseline (n = 535), No. (%)	Follow Up (n = 247), No. (%)
Positive expiratory pressure device (only)	233 (44)	113 (46)
High-frequency chest wall oscillation (only)	51 (10)	34 (14)
Chest percussion/postural drainage (only)	16 (3)	9 (4)
Directed cough/active cycle of breathing (only)	3 (1)	1 (0.4)
Multiple modalities	232 (43)	90 (36)

increased need for physician awareness in prescribing ACTs. This may be, in part, due to the lack of high-quality randomized clinical trials that are studying the efficacy of ACTs. Further research in the true clinical benefit of ACTs is needed. A patient also may be burdened already from many other time-consuming treatments, which can cause a decrease in ACT use.[31] Patients may benefit from continued reinforcement and education in use of ACTs.

In patients who used ACTs at baseline, there was no significant change in pulmonary function at 1-year follow up in this study. Although one may anticipate an improvement in pulmonary function with mucus clearance, there may be other factors that can influence pulmonary function in bronchiectasis, including older age, medical comorbidities, and the persistent inflammatory process present in bronchiectasis.[32] Thus, it is possible that these factors continue to effect pulmonary function in bronchiectasis, independent of ACT use.

In our study, patients who experienced a higher number of hospitalizations or exacerbations for pulmonary illnesses reported use of ACTs. Moreover, as shown in Table 4, the odds of the development of an exacerbation was higher in those patients who used ACTs continuously, compared with those who did not use ACTs. This may suggest that ACTs are used and/or prescribed more often in a bronchiectasis population that is ill. Patients may also be more inclined to use ACTs when they are feeling symptomatic or when they have experienced events such as exacerbations or hospitalizations. Similar results have been reported in EMBARC, with frequent exacerbations being one of the independent predictors for the use of chest physiotherapy.[15] There may also be other factors that explain the increased exacerbation frequency despite ACT use, which include the microbiome in the patient with bronchiectasis.[33] There was a significant higher percentage of *P aeruginosa* in those patients who used ACTs in our study, which may also explain the higher

TABLE 3] Mean Change of Pulmonary Function From Baseline to Follow-Up Visit

Variable	Data Available, No.	Continuous Use of Airway Clearance (n = 226; 25%)	Intermittent Use of Airway Clearance (n = 351; 39%)	No Use of Airway Clearance (n = 328; 36%)	*P* Value
FEV_1					
Before bronchodilator, mean (SD), L					
At baseline	783	1.82 (0.76)	1.77 (0.68)	1.88 (0.72)	.205
At 1-year follow-up visit	434	1.81 (0.76)	1.82 (0.69)	1.87 (0.72)	.821
Mean change from baseline to 1-year follow-up visit	394	−0.03 (0.40)	−0.02 (0.33)	−0.01 (0.35)	.899
FVC					
Before bronchodilator, mean (SD), L					
At baseline	770	2.70 (0.90)	2.67 (0.86)	2.72 (0.93)	.763
At 1-year follow-up visit	432	2.71 (0.94)	2.75 (0.85)	2.77 (0.85)	.805
Mean change from baseline to 1-year follow-up visit	390	0.03 (0.42)	0.01 (0.37)	−0.03 (0.31)	.431

TABLE 4] Results of Multinomial Regression Analyses for Number of Exacerbations at Follow Up According to Airway Clearance Technique Use at Baseline and Follow-Up Visit

Airway Clearance Technique Use at Baseline and Follow-Up Visit	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Continuous use vs none		
≥2 Exacerbations vs none	2.30 (1.46-3.62)	1.63 (0.91-2.93)
1 Exacerbation vs none	3.10 (1.98-4.87)	2.48 (1.41-4.37)
Intermittent use vs none		
≥2 Exacerbations vs none	1.36 (0.87-2.14)	1.33 (0.75-2.38)
1 Exacerbation vs none	1.67 (1.06-2.62)	1.72 (0.97-3.02)

[a]Adjusted for number of exacerbations at baseline and presence of *Pseudomonas aeruginosa* at baseline.

rates of exacerbations and hospitalizations that were seen in this group. Prior literature has described a frequent exacerbator phenotype in bronchiectasis, where *P aeruginosa* was shown to be an independent predictor for future exacerbations. This frequent exacerbator phenotype had worse quality of life, higher rates of hospitalizations, and higher mortality rates.[24] Further investigation of the microbiome in patients with bronchiectasis and potential differences in the microbiome during exacerbations, hospitalizations, and ACT use is warranted.

Our study does have several limitations. It is difficult to ascertain standardization of ACT use across different centers. It is also difficult to assess patient compliance and technique with ACTs throughout the study period and during different time points, because this was an observational study from a large database registry. The data presented are subject to the accuracy of patient reporting and medical record keeping. The frequency of ACT use between time points was also not collected. Moreover, there are several other ACTs that may be performed commonly elsewhere in the world; data on these techniques were not collected in the BRR. Quality-of-life data were also not included in the BRR but would be of interest to study prospectively in terms of potential change with ACT use. Due to a lack of follow-up data on symptoms, a change in productive cough with ACT could not be analyzed in this current study. Finally, the study describes a cohort of patients who were enrolled from tertiary referral centers with an interest in bronchiectasis, in which demographic information and practice habits may not be reflective of other centers in the country or worldwide.

Interpretation

ACTs are used more often in patients with bronchiectasis and a productive cough if they have experienced a prior exacerbation, hospitalization for pulmonary illness, or have had *P aeruginosa.* There is a significant reduction in use of ACTs at 1-year follow up. Compared with baseline, there is no significant change in pulmonary function for those patients who use ACTs at 1-year follow up. The odds of the development of an exacerbation are higher in those patients who use ACTs continuously, which suggests more frequent use in a population with bronchiectasis that is ill. Further studies that will assess the best candidates for ACT use and factors to improve accessibility and adherence to ACTs are needed.

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

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