ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Four-week daily airway clearance using oscillating positive-end expiratory pressure *versus* autogenic drainage in bronchiectasis patients: a randomised controlled trial

Galit Livnat, Naama Yaari, Nili Stein, Lea Bentur, Moneera Hanna, Maya Harel, Yochai Adir, Michal Shteinberg

Please cite this article as: Livnat G, Yaari N, Stein N, *et al*. Four-week daily airway clearance using oscillating positive-end expiratory pressure *versus* autogenic drainage in bronchiectasis patients: a randomised controlled trial. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00426-2021).

Four-week Daily Airway Clearance Using Oscillating Positive-end Expiratory Pressure Versus Autogenic Drainage in Bronchiectasis Patients: A Randomized Controlled Trial

Galit Livnat MD[1,2,7], Naama Yaari BPT [3], Nili Stein MPH[4], Lea Bentur MD [5,7], Moneera Hanna RT[5], Maya Harel RN[6], Yochai Adir MD, MPH[6,7], Michal Shteinberg MD, PhD[2,6,7]

1. Pediatric Pulmonology, Carmel Medical Center, Haifa, Israel
2. Cystic Fibrosis Center, Carmel Medical Center, Haifa, Israel
3. Department of Physical therapy, Carmel Medical Center, Haifa, Israel
4. Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel
5. Pediatric pulmonology and CF center, The Ruth Rappaport Children's Hospital, Rambam Medical Center, Haifa, Israel
6. Pulmonology Institute, Carmel Medical Center, Haifa, Israel
7. Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Corresponding author: (Review and publication)

Michal Shteinberg

Pulmonology Institute, Carmel Medical Center, 7 Michal St. Haifa 3436212, Israel

michalsh@technion.ac.il , phone: +972506265846

Abbreviated title: oPEP vs AD in bronchiectasis

Key words: Airway clearance; Bronchiectasis; Lung clearance index.

Ethics approval: The study protocol was approved by Carmel Medical Center Helsinki committee (approval no. CMC-87-16). All participants gave written informed consent before data collection began.

Competing interests: MS Received research grants from GSK, Novartis, Trudell Medical International; travel grants- Novartis, Actelion, Boeringer Ingelheim, GSK, Rafa. Speaker's fees- Boeringer Ingelheim, GSK, Astra Zeneca, Teva, Novartis, Kamada. Advisory fees- GSK, Boeringer Ingelheim, Horizon pharma, Vertex pharmaceuticals. NY, NS, MH[5], MH[6], and YA report no conflicts of interests relating to this work.

Source(s) of support: Trudell medical international (London, Canada) provided Aerobika devices and financial support.

Acknowledgements: We thankfully acknowledge the assistance of Amir Shama and Amer Ubeid for performing spirometry, and of Sharon Avital and Esther Schneider for assistance conducting the clinical research

Data sharing: Data sharing can be provided to researchers who provide a methodologically sound proposal.

Provenance: N/A

Correspondence: Michal Shteinberg

Pulmonology Institute, Carmel Medical Center, 7 Michal St. Haifa 3436212, Israel

michalsh@technion.ac.il , phone: +972506265846

Prior abstract acceptance: This work was presented at the 2020 ERS conference (virtual).

Abstract

Background: Airway clearance (AC) is a fundamental component of bronchiectasis care. Lung clearance index (LCI) is a measurement of ventilation inhomogeneity. Its responsiveness to long-term AC is unknown. We aimed to compare two methods of daily AC over four weeks: autogenic drainage (AD) and oscillating positive airway pressure (oPEP), and to to determine effects of AC on LCI and clinical outcomes.

Methods: Adults with bronchiectasis naive to airway clearance were randomized to daily AC with either AD or oPEP. Difference in LCI as primary outcome, spirometry, sputum volume and purulence, and quality of life were evaluated at randomization and after four weeks of AC.

Results: Fifty-one patients (32 women, 19 men, mean age 66.2±12.8 years) were randomized and 49 completed the study (25 AD, 24 oPEP). The LCI and forced expiratory volume in the first second (FEV_1) did not change between visits between groups (difference between groups 0.02), nor between visits in either group. Sputum quantity decreased in 12/24 (50%) of the oPEP group, and in 6/25 (24%) of the AD group (p=0.044). The 'treatment burden' worsened or was unchanged in 70% of participants randomized to AD and 55% randomized to oPEP (p=0.038).

Conclusion: Sputum quantity decreased in more participants randomized to oPEP group after one month of daily AC, with a better treatment burden. The effects of four weeks of AC on LCI were not significant in either treatment group.

Summary at a glance

The effects of airway clearance on lung clearance index (LCI) are undetermined. We randomized people with bronchiectasis to four weeks of two methods of daily airway clearance. Sputum volume decreased in more people randomized to oPEP than AD. LCI did not change in either group.

Introduction

Bronchiectasis is a chronic airway disease characterized by productive cough and bronchial inflammation with abnormal dilatation of the bronchi. Bronchiectasis is associated with poor quality of life and frequent exacerbations[1,2]. A major component of bronchiectasis is the self-perpetuating process of bronchial infection, inflammation, impaired muco-ciliary clearance, and structural lung damage[1]. Therefore, a basic part of bronchiectasis treatment is airway clearance (AC), aimed to prevent mucus stasis[3]. While airway clearance is accepted as a first line treatment, current knowledge on the preferred method is limited. A major obstacle to determining the efficacy of an AC technique is the limitations of currently used endpoints[4]. Traditional endpoints that have been used include spirometry, exacerbation frequency, and quality of life. However, these endpoints are relatively insensitive to AC in bronchiectasis patients[5,6]. There is therefore a need to define more sensitive endpoints in evaluating interventions to improve AC in bronchiectasis[7].

The lung clearance index (LCI) measured by multiple breath washout (MBW) is a measure of ventilation inhomogeneity and was shown to be sensitive to early ventilation impairment[8]. Its usefulness has been demonstrated in cystic fibrosis

(CF), particularly in children and adults with mild disease, with LCI reduction of -0.6 to -1 following therapeutic interventions[9–12]. The LCI has been assessed in bronchiectasis patients and found to be higher (worse) than in healthy subjects, inversely correlating with FEV_1[13,14]. LCI was found to be non-significantly higher among exacerbating vs. stable bronchiectasis patients, and a single session of AC had no effect on LCI[14]. In a study of 60 patients with bronchiectasis, LCI was found to correlate with both radiological severity and FEV_1, although LCI was abnormal in more patients than FEV_1[15]. Similar findings were seen in CF patients[16–18].

To the best of our knowledge, no study has been performed to test the long-term effect of any lung clearance technique or device on LCI.

Aerobika (Trudell medical international, London, Ontario, Canada)[19] is an oscillating positive expiratory pressure (oPEP) device, developed for mobilization and clearance of secretions in people with suppurative lung diseases. It has been tested and found safe and effective in chronic bronchitis[20,21]. Autogenic drainage (AD) is a method of AC that aims to propel secretions by controlling the depth of a patient's breathing effort, from low, medium, and high breathing volumes, gradually, followed by huffing and expectoration of mucus that finally reaches the larynx[22,23]. The two methods- AD and oPEP- are commonly used methods in bronchiectasis; superiority of either one has not been established[24,25].

The aims of our study were: 1. To explore the effects of four weeks of AC on LCI, and 2. To compare the effects between two methods of AC, AD and oPEP, on LCI, spirometry, sputum quantity, and quality of life in bronchiectasis patients.

Methods

Study Population

The study population consisted of patients diagnosed with bronchiectasis, followed at our institution in Carmel Medical Center, Haifa, Israel. Subjects were included if they were ≥ 18 y old, able to give informed consent, had bronchiectasis in at least two lung lobes confirmed by high-resolution computed tomography, were clinically stable, with a predicted FEV_1 ≥50%, and had not regularly performed AC. Patients taking mucolytics, including inhaled isotonic or hypertonic saline, 3 weeks or more and maintaining the same treatment during the trial were included. Exclusion criteria included a diagnosis of CF or primary ciliary dyskinesia (PCD), and an exacerbation or any change in respiratory medications during the four weeks before randomization. The rationale for excluding people with PCD was that in Israel, a diagnosis of CF or PCD entitles patients to daily physiotherapy treatments by therapists who may not comply with the study protocol. Written informed consent was obtained at inclusion. The study protocol was approved by Carmel Medical Center Helsinki committee (approval no. CMC-87-16) and was registered in ClinicalTrials.gov (trial registration no. NCT03013452).

Study Design

At baseline, patient history was recorded and validated against the participants' electronic medical record (EMR) of medications, past pulmonary exacerbations (PEx), and quality of life using the quality of life-questionnaire for bronchiectasis (QOL-B)[26]. Past pulmonary exacerbations were defined as an increase in at least three respiratory symptoms for two days that led to a change in medications[27]. Exacerbations were recorded as separate events if at least 21 days apart. The daily amount of sputum expectorated (e.g. amount in teaspoons, tablespoons, or cups), was recorded in equivalent milliliters, and the sputum purulence was quantified according to a validated score on a visual scale[28]. Spirometry and MBW were performed. Participants were randomized by simple randomization (a random number was generated by an online application for every participant, with even numbers allocated to AD and odd numbers to oPEP) and instructed how to perform the selected method by a study physiotherapist trained in both AD and oPEP. Typical instruction sessions lasted 30 minutes but were not limited in time. An oPEP device (Aerobika, Trudell Medical International) was provided to patients randomized to this intervention. All participants were instructed to perform the assigned AC technique daily for 15-20 minutes or until no further sputum was produced, for the duration of the study (four weeks), and not to perform any other form of AC (this was also specified in a letter to the primary physician given at the first visit).Exacerbations, adverse events, and patient-reported adherence to airway clearance were recorded daily by the participants and reported weekly by telephone calls. Sputum purulence was assessed

grading on a four-scale visual chart[29]. After four weeks all participants performed an end-of-study visit, which included history and physical examination, review of medications, review of exacerbations since last visit, recording of adverse events and PEx, a repeat QOL-B questionnaire, and performance of MBW and spirometry. The technicians and investigators performing and interpreting spirometry and MBW were blinded to the treatment allocation.

Lung Function Assessments

Multiple breath washout measurements were performed using the Easy-One Pro, MBW Module (NDD Medical Technologies, Zurich, Switzerland) as described[30]. The system consists of a side stream ultrasonic transducer for temperature- and humidity-independent sampling of the molar mass, a mainstream ultrasonic transducer for flow sampling, and a side stream infrared carbon dioxide (CO_2) analyzer to correct the molar mass signal for exhaled CO_2. The WBreath software (NDD, Zurich, Switzerland) was used for data acquisition, storage, and analysis.

The LCI was calculated as the cumulative expired volume during the washout phase divided by the functional residual capacity (FRC), which is the number of FRC turnovers required to washout nitrogen[31]. An increased LCI indicated more FRC turnovers required for the washout, reflecting ventilation inhomogeneity[8]. As recommended, the minimum re-equilibration time between trials was the time needed for washout in the previous trial[30]. All MBW tests underwent visual quality control before analysis, ensuring regular tidal breathing before washout and absence of a leak.

Spirometry was performed in accordance with the ATS/ ERS (American Thoracic Society/European Respiratory Society) Task Force, using a Jaeger MasterScope spirometer (Erich Jaeger AG, Würzburg, Germany)[32].

Statistical Analysis

The primary endpoint was defined as the LCI change. Assuming an LCI of 10-12 and a standard error of 0.31-3.4 [13–15], a sample size of 22 subjects in each group was calculated to detect a difference of 1 in LCI with a power of 90%.

Continuous variables are presented as means and standard deviations (SD) or medians and interquartile range (IQR). Categorical variables are presented as numbers and proportions. Differences in demographical and clinical characteristics between the two treatment groups (oPEP vs. AD) were analyzed using the Chi square test for categorical variables; and independent t-test or Mann-Whitney, as appropriate, for the continuous variables.

Pre/post absolute change and percent change was calculated. Correlation between two continuous variables (such as FEV1 and LCI) was analyzed using the Pearson or Spearman correlation, as appropriate. Paired t-test or Wilcoxon sign rank test was used to check pre/post difference in each group separately for the continuous variables.

Statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM, New York, New York, USA). For all analyses, $P<0.05$ (for the two-tailed tests) was considered statistically significant.

Results

A total of 51 patients were recruited between March 2017 and October 2019 (AD group, *n*=26; oPEP group, *n*=25 ;Figure 1) Baseline characteristics were similar, except that FEV_1 was higher, with more past exacerbations in patients randomized to AD (Table 1).

At baseline, LCI was inversely correlated with FEV_1 (correlation coefficient, 0.552; p<0.0001). Baseline LCI was not correlated with age (r=0.17, *p*=0.26), gender (*p*=0.63), PEx in previous 12 months (*p*=0.18), sputum volume (r=-0.005, *p*=0.97), sputum purulence (*p*=0.412), Reiff index (r=0.07, *p*=0.65), or any domain of the QOL-B questionnaire (correlation coefficients for the various domains were in the range of -0.09 to 0.65).

Self- reported adherence to airway clearance routine was 88±2% and 87±3% for the AD and oPEP groups, respectively (*p*=0.63). Adverse events were recorded in 13(59%) AD participants and 11 (48%) of the oPEP participants (*p*=0.45); all were mild and deemed unrelated to treatment. One participant in each group stopped the study due to adverse events (chest pain in one participant performing AD, a pulmonary exacerbation in a participant performing oPEP, both deemed unrelated to the interventions); they were both unavailable for end-of-study assessment, leaving 49 patients eligible for analysis at week 4 (AD, 25; oPEP, 24) (Figure 1). In both groups, several participants reported increases in symptoms which necessitated a change in treatment and qualified as a PEx during the study period (6 in the AD group; 5 in the oPEP group).

After four weeks of regular airway clearance, there was no significant change in LCI between groups (Figure 2): in the oPEP group, LCI changed from mean 9.38 ±1.6 to 9.97±2.5. In the AD group, LCI changed from 10.04±2.1 to 9.88±2.0. The difference between groups after 4 weeks was 0.02. Spirometry parameters did not change in either treatment group (Table 2). At four weeks, median (IQR) LCI increased by a mean of 0.6 in the oPEP group and decreased by 0.16 in the AD group: mean of difference between groups -0.56 (95%CI (-1.27; 0.21), p=0.142).

Self-reported daily sputum quantity was reduced in 12 (52%) oPEP participants, compared to 6 (24%) AD participants after 4 weeks (*p*=0.04, Table 2). Sputum quantity was reduced from a median (IQR) of 17.5 ml (5–42.5) to 15 ml (5–45) in the AD group (p=0.969) and from 15 ml (5–25) to 5 ml (5–20) (p=0.493) in the oPEP group. In the QOL-B domains, Vitality improved from a median (IQR) of 44 (27.5–66.8) to 67 (44–67) *p*=0.027, and Social Functioning from 50 (21–67) to 58 (37.5–76.5), *p*=0.042 in the AD group. In the oPEP group, the score for Health Perceptions improved from 33 (25–58) to 42 (33–64.5) *p*=0.048. (Table 3). Treatment burden score in the QOL-B did not change for the entire cohort but was worsened or unchanged in 17 of 20 participants (85%) who reported at least 70% adherence in the AD group, and in only 11 of 20 (55%) in the oPEP group (*p*=0.038).

Spirometry did not change in either group (Table 2). There was no association between 33% or more sputum volume reduction and LCI change of 0.5 or more (p=0.532); sputum change and increase of 8 or more units in QOL-respiratory domain (*p*=0.770); and an increase of 8 or more units in QOL-respiratory domain

and LCI change of 0.5 or more (p=0.371). 8 units is the established minimally clinically important difference (MCID) in the QOL-B[33]. To the best of our knowledge, the MCID for sputum volume was not established; 33% was arbitrarily chosen to reflect a significant reduction in sputum volume.

Discussion

This study was designed to test the effects of two AC methods in bronchiectasis on LCI and other outcome measures. We compared two established AC methods: AD and oPEP, practiced daily for four weeks. After four weeks, there was no difference in LCI between treatment groups, and LCI did not change significantly between visits in either group. The minimally important difference in LCI is not well established; we chose a low cutoff of 0.5, which was the difference between groups reported in an intervention with inhaled hypertonic saline in children with CF[10]. Self- reported daily sputum quantity was reduced compared to baseline in significantly more patients randomized to oPEP than to AD (52% vs. 24%, respectively; p=0.04). Improvements in various domains of the QOL-B were seen in both groups. In contrast to studies investigating the benefits of a single AC session, in which an *increase* in expectorated sputum was desired, we considered a *reduction* in 24-hour sputum quantity to reflect less inflammation and a beneficial outcome in bronchiectasis. A reduction in sputum volume was seen in several studies of long-term treatments in bronchiectasis[34–40], including mannitol, a mucoactive agent[34,35]. The recruited bronchiectasis patients were either newly diagnosed or referred. However, according to local practice in our center, the majority of participants in both groups (73% and 80%) started

treatment with inhaled hypertonic saline prior to study inclusion. Hypertonic saline inhalation itself may decrease sputum purulence[41] and promote sputum clearance by coughing. Therefore, some effect of treatment may have occurred prior to randomization to the study, and this may have lessened the treatment effect observed in the study.

The difference between these two AC methodologies may reflect the efficacy in clearing sputum from the airways. However, training to perform AD may require more time than for oPEP. Since the study protocol limited training to a single session with the study therapist, the oPEP results may reflect the ease of training participants in self-managing their sputum production. Treatment burden was worsened or unchanged in 55% oPEP vs. 85% of AD (p=0.038) participants who reported adherence to daily AC of 70% or above. The better results obtained by the oPEP group may reflect the ease of performing and persisting in using a self-managing device, in comparison to AD.

The LCI was not reduced by either method after four weeks of daily AC. Similar to our findings, a previous study also did not find a good correlation between LCI and QOL in people with bronchiectasis[15]. In bronchiectasis, LCI is elevated compared to healthy controls [15]. This is believed to reflect lung inhomogeneity, with poorly ventilated areas contributing to delayed clearance of inert gas. Elevated LCI in bronchiectasis may be explained by mucous plugs obstructing and delaying gas mixture from portions of the bronchial tree, and clearance of mucous is hypothesized to improve LCI [31]. However, LCI was not found to significantly improve after a single AC session [14,23]. In CF, LCI was found to be

responsive to long-term treatment with inhaled hypertonic saline, with a reduction of -0.63 units in preschool children [11], and is increasingly used as an endpoint in clinical trials. To the best of our knowledge, LCI has never been reported to respond to a long-term intervention in adults with bronchiectasis, although evaluated as an exploratory endpoint in a randomized trial of inhaled Tobramycin[42,43]. In contrast to studies of long-term interventions in CF, we did not find that LCI improves significantly after four weeks of AC. This may reflect a difference between bronchiectasis patients, in whom changes to lung structure may be irreversible, from younger patients with CF, or may result from insufficient effect of physiotherapy. It will be interesting to see the effect on LCI by other bronchiectasis interventions.

Our study has some limitations. First, this study may have been under-powered to detect a change in LCI, as power analysis was bases on cross- sectional studies of LCI in bronchiectasis, rather than response to treatment[13–15]. Second, we included patients with a relatively preserved lung function. This was intentional as LCI performed better in people with preserved lung function but may limit the extension of our results to more severely affected patients. The study design of four weeks, and once daily AC, may have not been extensive enough to see changes in lung ventilation. While researchers were blinded to treatment allocations, participants were not, and this may have potentially affected results (mainly QOL-B but also sputum quantity). Finally, estimation of adherence and sputum volume were done by questioning rather than weighing, and thus may be subject to bias.

Despite the above limitations, to the best of our knowledge, this is the first study to compare the long-term effects of AC on LCI. Future studies testing the responsiveness of LCI to therapeutic interventions in bronchiectasis are needed.

Author contributions:

MS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. GL participated equally in study design, interpretation of LCI, analysis of results, and drafting the manuscript. NY, NS, MH, MH, and YA contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Role of the sponsor: Trudell Medical International (London, Canada) provided Aerobika devices and financial support, but did not influence the study design or interpretation of results.

Bibliography

1. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. *Lancet*. 2018;392(10150):880-890. doi:10.1016/S0140-6736(18)31767-7

2. Shteinberg M, Flume PA, Chalmers JD. Is bronchiectasis really a disease? *Eur Respir Rev*. 2020;29(155). doi:10.1183/16000617.0051-2019

3. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50(3). doi:10.1183/13993003.00629-2017

4. Spinou A, Chalmers JD. Respiratory physiotherapy in the bronchiectasis guidelines: is there a loud voice we are yet to hear? *Eur Respir J*. 2019;54(3). doi:10.1183/13993003.01610-2019

5. Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. *Eur Respir J*. 2009;34(5):1086-1092. doi:10.1183/09031936.00055509

6. Figueiredo PHS, Zin WA, Guimarães FS. Flutter valve improves respiratory mechanics and sputum production in patients with bronchiectasis. *Physiother Res Int*. 2012;17(1):12-20. doi:10.1002/pri.507

7. Smith MP, Hill AT. Evaluating success of therapy for bronchiectasis: what end points to use? *Clin Chest Med*. 2012;33(2):329-349. doi:10.1016/j.ccm.2012.03.001

8. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J*. 2013;41(3):507-522. doi:10.1183/09031936.00069712

9. Rodriguez Hortal MC, Nygren-Bonnier M, Hjelte L. Non-invasive Ventilation as Airway Clearance Technique in Cystic Fibrosis. *Physiother Res Int*. 2017;22(3). doi:10.1002/pri.1667

10. Stahl M, Wielpütz MO, Ricklefs I, et al. Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS). A Randomized, Double-Blind, Controlled Study. *Am J Respir Crit Care Med*. 2019;199(10):1238-1248. doi:10.1164/rccm.201807-1203OC

11. Ratjen F, Davis SD, Stanojevic S, et al. Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2019;7(9):802-809. doi:10.1016/S2213-2600(19)30187-0

12. Grosse-Onnebrink J, Mellies U, Olivier M, Werner C, Stehling F. Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients. *Pediatr Pulmonol*. 2017;52(5):625-631. doi:10.1002/ppul.23670

13. Gonem S, Scadding A, Soares M, et al. Lung clearance index in adults with non-cystic fibrosis bronchiectasis. *Respir Res*. 2014;15:59. doi:10.1186/1465-9921-15-59

14. Grillo L, Irving S, Hansell DM, et al. The reproducibility and responsiveness of the lung clearance index in bronchiectasis. *Eur Respir J*. 2015;46(6):1645-1653. doi:10.1183/13993003.00152-2015

15. Rowan SA, Bradley JM, Bradbury I, et al. Lung clearance index is a repeatable and sensitive indicator of radiological changes in bronchiectasis. *Am J Respir Crit Care Med*. 2014;189(5):586-592. doi:10.1164/rccm.201310-1747OC

16. Horsley A. Lung clearance index in the assessment of airways disease. *Respir Med*. 2009;103(6):793-799. doi:10.1016/j.rmed.2009.01.025

17. Fuchs SI, Gappa M, Eder J, Unsinn KM, Steinkamp G, Ellemunter H. Tracking Lung Clearance Index and chest CT in mild cystic fibrosis lung disease over a period of three years. *Respir Med*. March 2014. doi:10.1016/j.rmed.2014.03.011

18. Owens CM, Aurora P, Stanojevic S, et al. Lung Clearance Index and HRCT are complementary markers of lung abnormalities in young children with CF. *Thorax*. 2011;66(6):481-488. doi:10.1136/thx.2010.150375

19. AEROBIKA* OPEP Device | Trudell Medical International. https://www.trudellmed.com/products/aerobika-opep-device. Accessed April 24, 2020.

20. Svenningsen S, Paulin GA, Sheikh K, et al. Oscillatory positive expiratory pressure in chronic obstructive pulmonary disease. *COPD*. 2016;13(1):66-74. doi:10.3109/15412555.2015.1043523

21. Burudpakdee C, Near AM, Huang H, Coppolo D, Kushnarev V, Suggett J. A Real-World Evidence Study Assessing the Impact of Adding the Aerobika Oscillating Positive Expiratory Pressure Device to Standard of Care Upon Healthcare Resource Utilization and Costs in Post-Operative Patients. *Pulm Ther*. 2018;4(1):87-101. doi:10.1007/s41030-018-0055-9

22. Pryor JA. Physiotherapy for airway clearance in adults. *Eur Respir J*. 1999;14(6):1418-1424. doi:10.1183/09031936.99.14614189

23. Poncin W, Reychler G, Leeuwerck N, et al. Short-Term Effect of Autogenic Drainage on Ventilation Inhomogeneity in Adult Subjects With Stable Non-Cystic Fibrosis Bronchiectasis. *Respir Care*. 2017;62(5):524-531. doi:10.4187/respcare.05194

24. O'Neill K, O'Donnell AE, Bradley JM. Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis. *Respirology*. 2019;24(3):227-237. doi:10.1111/resp.13459

25. Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. *Cochrane Database Syst Rev*. 2015;(11):CD008351. doi:10.1002/14651858.CD008351.pub3

26. Quittner AL, Marciel KK, Salathe MA, et al. A preliminary quality of life questionnaire-bronchiectasis: a patient-reported outcome measure for bronchiectasis. *Chest*. 2014;146(2):437-448. doi:10.1378/chest.13-1891

27. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J*. 2017;49(6). doi:10.1183/13993003.00051-2017

28. Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. *Eur Respir J*. 2009;34(2):361-364. doi:10.1183/09031936.00163208

29. McKane M, Crichton M, Dicker A, Chalmers J. Validation of a four point sputum colour chart in chronic obstructive pulmonary disease. In: *5.2 Monitoring Airway Disease*. Vol 46. European Respiratory Society; 2015:PA3349. doi:10.1183/13993003.congress-2015.PA3349

30. Fuchs SI, Sturz J, Junge S, Ballmann M, Gappa M. A novel sidestream ultrasonic flow sensor for multiple breath washout in children. *Pediatr Pulmonol*. 2008;43(8):731-738. doi:10.1002/ppul.20825

31. Kent L, Reix P, Innes JA, et al. Lung clearance index: evidence for use in clinical trials in cystic fibrosis. *J Cyst Fibros*. 2014;13(2):123-138. doi:10.1016/j.jcf.2013.09.005

32. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805

33. Quittner AL, O'Donnell AE, Salathe MA, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax*. 2015;70(1):12-20. doi:10.1136/thoraxjnl-2014-205918

34. Bilton D, Tino G, Barker AF, et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. *Thorax*. 2014;69(12):1073-1079. doi:10.1136/thoraxjnl-2014-205587

35. Bilton D, Daviskas E, Anderson SD, et al. Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. *Chest*. 2013;144(1):215-225. doi:10.1378/chest.12-1763

36. Wilson R, Welte T, Polverino E, et al. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. *Eur Respir* J. 2013;41(5):1107-1115. doi:10.1183/09031936.00071312

37. Stockley R, De Soyza A, Gunawardena K, et al. Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. *Respir Med*. 2013;107(4):524-533. doi:10.1016/j.rmed.2012.12.009

38. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med*. 2014;189(8):975-982. doi:10.1164/rccm.201312-2208OC

39. Lourdesamy Anthony AI, Muthukumaru U. Efficacy of azithromycin in the treatment of bronchiectasis. *Respirology*. 2014;19(8):1178-1182. doi:10.1111/resp.12375

40. Watz H, Nagelschmitz J, Kirsten A, et al. Safety and efficacy of the human neutrophil elastase inhibitor BAY 85-8501 for the treatment of non-cystic fibrosis bronchiectasis: a randomized controlled trial. *Pulm Pharmacol Ther*. 2019;56:86-93. doi:10.1016/j.pupt.2019.03.009

41. Ramsey KA, Chen ACH, Radicioni G, et al. Airway Mucus Hyperconcentration in Non-Cystic Fibrosis Bronchiectasis. *Am J Respir Crit Care Med*. 2020;201(6):661-670. doi:10.1164/rccm.201906-1219OC

42. Loebinger MR, Polverino E, Blasi F, et al. Efficacy and safety of tobramycin inhalation powder in bronchiectasis patients with P. aeruginosa infection: Design of a dose-finding study (iBEST-1). *Pulm Pharmacol Ther*. 2019;58:101834. doi:10.1016/j.pupt.2019.101834

43. O'Neill K, Ferguson K, Cosgrove D, et al. Multiple breath washout in bronchiectasis clinical trials: is it feasible? *ERJ Open Research*. 2020;6(4). doi:10.1183/23120541.00363-2019

Table 1: Baseline Characteristics of Patients

Parameter	**AD (*n*=26)**	**oPEP (*n*=25)**
Age (years, mean±SD)	66.7±12.3	65.7±13.4
Sex (female *n*(%)/male *n*(%))	19 (73.1)/7(26.9)	14(56.0)/11 (44.0)
Lung function: FEV_1% (mean±SD)	96.1±18.3**	81.3±18.1**
Lung function: FVC% (mean±SD)	101.7±16.5*	89.6±20.0*
LCI (mean±SD)	10.0±2.1	9.0±2.5
Daily sputum production: ml (median; IQR)	17.5 (5.0; 41.3)	15.0 (5.0;20.0)
Sputum bacterial infection*: *n* (%)	9 (34.6)	13 (54.2)
Sputum purulence# (0-1/2-3)	13 (59.1)/9 (40.9)	15 (62.5)/9 (37.5)
Previous PEx/year (median, IQR)	*n*=26 2 (1;4)*	*n*=24 1 (0;2)*
Treatment at Baseline:		
ICS: *n* (%)	5 (19.2)	8 (32.0)
LABA: *n* (%)	5 (20.0)	9 (36.0)
LAMA: *n* (%)	0 (0)	3 (12.0)
Hypertonic saline: *n* (%)	19 (73.1)	20 (80.0)
Performing exercise: *n* (%)	14 (53.8)	12 (48.0)

CT Findings:		
No. of infected lobes on CT (median, IQR)	*n*=21 2.0(2.0,3.5)	*n*=20 2.0(2.0,3.75)
Reiff index (median, IQR)	*n*=24 3.0(2.0,4.0)	*n*=25 3(2,4.5)
Findings on auscultation:		
Wheeze: No. (%)	1 (3.8)	3 (12.0)
Rales: No. (%)	9 (34.6)	9 (36.0)

Sputum bacterial infection relates to any positive culture from a respiratory sample in the past 12 months. Sputum purulence was noted on a scale from 0 to 3, with 0 indicating transparent-yellow and 3 being green with traces of blood. AD, autogenic drainage; CT, computed tomography; FEV_1%, forced expiratory volume in 1 second, percent predicted; FVC, forced vital capacity, percent predicted; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting beta agonists; LAMA, long-acting muscarinic agonists; LCI, lung clearance index; oPEP, oscillating positive expiratory pressure; PEx, pulmonary exacerbations in the previous 12 months; SD, standard deviation. *p<0.05; **p<0.001

Table 2: Effects of Treatment on Symptoms and Lung Function

	AD (*n*=25)	oPEP (*n*=24)	P value
Change in sputum purulence[§]: *n* (%)			>0.99
Improved	4 (20)	5 (23)	
Unchanged	13 (65)	13 (59)	
Worsened	3 (15)	4 (18)	
Change in sputum quantity: *n* (%)			**0.044**
Less sputum	6 (24)	12 (52)	
More sputum	19 (76)	11 (48)	
Change in sputum quantity (ml); median (range) randomization to end of study	17.5 ml (5–42.5) to 15 ml (5–45)	15 ml (5–25) to 5 ml (5–20)	0.386
LCI change after 4 weeks*: No. (%)			0.847
Improved	8 (32)	6 (25)	
Unchanged	7 (28)	8 (33)	
Worsened	10 (40)	10 (42)	
FEV_1% change after four weeks: median (range)	0.05 (-23–7.6)	0 (-11.8–10.5)	0.71

*improvement, a decrease of 0.5 or more; worsening, an increase of 0.5 or more; unchanged, difference less than 0.5 in any direction; § sputum purulence was recorded on a four-point scale.

AD, autogenic drainage; FEV1, forced expiratory volume in 1 second; LCI, lung clearance index; oPEP, oscillating positive expiratory pressure

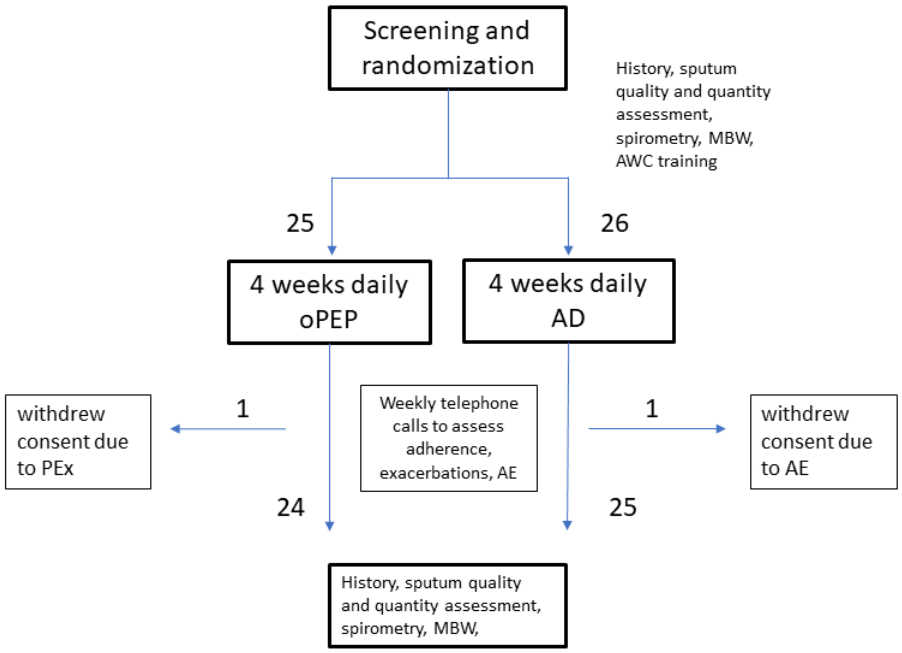
Table 3. Effects on Quality of Life

QOL	AD (*n*=25)		p-value	oPEP (*n*=24)		p-value
Domain	Baseline (median, IQR)	4 weeks (median, IQR)		Baseline (median, IQR)	4 weeks (median, IQR)	
Respiratory Symptoms	67 (44-79.5)	70 (50-79.5)	0.732	65 (46-77)	72 (48.8-80.3)	0.139
Physical Functioning	60 (20-83.5)	67 (37-86.5)	0.393	53.5 (21.8-93)	60 (36.5-87)	0.412
Vitality	44 (27.5-66.8)	67 (44-67)	**0.027**	44 (1-100)	50 (33-67)	0.231
Role Functioning	73 (53-87)	87 (56.5-93)	0.073	70 (41.8-87)	73 (48.5-80)	0.970
Emotional Functioning	83 (54-100)	83 (62.5-100)	0.611	79 (60.3-92)	79 (67-98)	0.690
Social Functioning	50 (21-67)	58 (37.5-76.5)	**0.042**	*n*=23 58 (42-83)	*n*=23 58 (44-75)	0.919
Treatment Burden	n=20 56 (33-78)	*n*=20 44 (33-64.3)	0.085	*n*=20 56 (35.8-75.3)	*n*=20 56 (33.3-67)	0.458

Health Perceptions	42 (33-67)	58 (42-75)	0.177	33 (25-58)	42 (33-64.8)	**0.048**

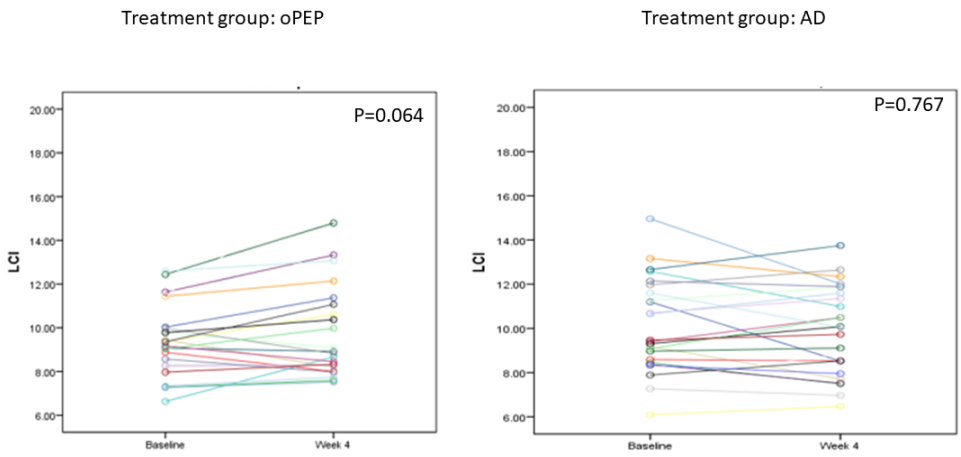
Domains of the quality of life-questioner for bronchiectasis (QOL-B) questionnaire (21) were scored on a scale of 0 (worst) to 100 (best) and compared between baseline and end-of-study visits. Scores presented as median interquartile range (IQR).

AD, autogenic drainage; IQR, interquartile range; oPEP, oscillating positive expiratory pressure, QOL, quality of life.



Legend to Figure 1:

Flow of participants through the study. AD, autogenic drainage; AE, adverse event; AWC, airway clearance; MBW, multiple breath washout; oPEP, oscillating positive expiratory pressure; PEx, pulmonary exacerbation.



Legend to Figure 2:

Results of lung clearance index (LCI) before and after 4 weeks of daily airway clearance according to method of airway clearance. AD, autogenic drainage; oPEP, oscillating positive expiratory pressure.