Bronchoscopic airway clearance therapy for acute exacerbations of bronchiectasis

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Supplemental materials 1

Study protocol

Background: Bronchiectasis is a progressive respiratory disease characterized by permanent and irreversible bronchial wall dilatation and thickening. Compared with mild patients, moderate to severe patients showed increased risk of mortality, hospitalization rate and number of exacerbations. Therefore, additional consideration about the influence of disease severity on therapeutic efficacy should be taken into account by doctors when formulating treatment schemes. Persistent cough and sputum production are dominant symptoms of bronchiectasis. Bronchiectasis guidelines recommend that the clearance of excessive purulent sputum from the lung of bronchiectasis is important strategies to fight against recurrent acute exacerbation. Airway clearance therapy (ACT) is a kind of airway physiotherapy and is indicated for patients with altered mucociliary escalator or compromised ability to expectorate airways secretions. Guidelines recommend ACT as stable state treatment for bronchiectasis, but there was limited evidence on which to base guideline recommendations. Moreover, ACT recommendations for bronchiectasis largely rely on

studies during a clinically stable stage, the effect of ACT on bronchiectasis with acute exacerbation is not clear.

Objective: The aims of this study were to explore the benefits and risks of B-ACT therapy in managing hospitalized bronchiectasis with acute exacerbation and identify special group patients that benefit most from the newly promising treatment.

Hypothesis: B-ACT therapy could significantly prolong the time to first acute exacerbation after discharge and improved healthy related scores for bronchiectasis patients with acute exacerbation.

Study design: A randomised controlled trial had been conducted at Shanghai Pulmonary Hospital from February 1, 2018 to February 28, 2019. Patients were screened and recommended through five hospitals in Bronchiectasis Treatment and Research Alliance of China (BEChina, http://www.chinabronchiectasis.com/) and then were uniformly introduced and admitted into Shanghai Pulmonary Hospital.

Study participants:

Inclusion criteria:

(1) Patients were ≥18 years of age;

(2) Patients were diagnosed with bronchiectasis according to guideline for bronchiectasis in adults (British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010; 65 Suppl 1: i1-58);

(3) Patients had a history of acute exacerbation;

(4) Patients were eligible for bronchoscopy and were willing to receive B-ACT therapy.

Exclusion criteria:

(1) Patients did not receive a high-resolution CT (HRCT) chest scan in the past three months;

(2) Physicians determined that patient had other medical conditions that could affect the results of this study;

Exit criteria:

(1) Patients that lost to follow-up or with major protocol violations.

Sample size estimation，randomisation and blinding: Based on ten patients observed in preliminary clinical trial, we found that the time to first acute exacerbation in the B-ACT treatment group was 17 days longer than that of the control group, with standard deviations of 87 and 75 days, respectively. Considering the small number of observed cases in the pre-experiment, we set the margin of non-inferiority (NIM) as 30 when calculating the sample size. Setting the significance level alpha (α) to 0.025, test power 1-β to 0.9, set the sample size ratio between the experiment group and the control group to 3:1, applying the software PASS 11, and calculate the sample size of control group was 40 cases and the experiment group was 120 cases. That is to say, when the final number of cases in the two groups is greater than or equal to the above value, the statistical difference test level can be reached. In this study, the random coding table with serial number 001-200 in proportion (3:1) was generated by the use of computer Excel software. Patients whose random number was less than or equal to 150 were assigned to the B-ACT group, and those whose random number was greater than 150 were assigned to the control group. The assessors were blinded in this study. That is, researchers who are responsible for assessing the improvement of patient's symptom

score (CAT, LCQ, 6 MWD) and for recording information of acute exacerbation were blinded, which means that clinicians who determined that an exacerbation had occurred were blinded to allocation. Specifically, in this study Dr. Y Liu, WW Wang and Y Zhang were responsible for the assessment and recording of the patients' information, they did not participant the clinical treatments of the patients. In order to avoid the subjective bias of the evaluator, the non-blind person should not disclose the blind information to the evaluator.

Study treatments: For patients in control group, they were given medical treatment according to the European Respiratory Society guideline, which including antibiotic and dispelling sputum therapies. During the hospitalization, all patients were given antibiotics as the physicians wish, the course of anti-infective treatment was 14 days. And for patients in B-ACT group, on the basis of the same treatment as the control group, they were also treated with B-ACT by attending physicians in respiratory department of our hospital. The operation steps of B-ACT are as follows:

Firstly, a comprehensive assessment of patients' condition was conducted to determine whether the patient was able to tolerate bronchoscopy. Mainly through the following examinations: electrocardiogram, chest imaging data, blood test, infectious diseases related indicators detections and lung function examination if necessary. Preoperative analysis and discussion were conducted according to the requirements of bronchoscopy. Patients and their families were fully informed before bronchoscope, and the informed consents were signed.

Before the bronchoscopy, 2% lidocaine solution were used for laryngeal spray or

atomized inhalation, and lidocaine gel were used for nasal cavity. Operators checked whether the patient had active denture and removed it in time to prevent aspiration. Oxygen was given to one side of the nasal tract and oxygen saturation and pulse were monitored. The sputum aspirator with negative pressure suction device was prepared before the operation and was connected to the bronchoscope. Continuous suction was performed from the trachea to the subsegmental during the entering of bronchoscope to remove the visible secretions from entire respiratory tract. After that, the bronchoscope entered the lavage segments, a total amount of 120 to 200ml normal saline was used for lavage (the volume various depending on the operator's judgement, generally 30-40ml each time, 3-5 times in total). Suction immediately after each lavage and a certain amount of lavage fluid was collected. Check for bleeding carefully before the withdrawal of the bronchoscope.

Follow-up flow chart:

Trial phase	Visit 1 Screening Period Day 0	Visit 2 Treatment Day Day 1	Visit 3 Day 3	Visit 4 Day 7	Followed up for AE by telephone (every three months)
Medical information collection					
Sign informed consent	√				
History of disease and medication	√				
Demographic characteristics	√				
Check the inclusion and exclusion criteria	√				
Clinical assement					
Physical examination and symptom evaluation	√	√	√	√	
Vital signs	√	√	√	√	
Sputum culture (drug sensitivity test + identification)	√			√	
Lung function tests	√				
BSI score	√				
CAT+LCQ+mMRC score	√	√	√	√	
6MWD	√	√			
Acute exacerbation assessment and recording	√	√	√	√	√
Safety observation					
Blood routine	√				
Urine routine	√				
ECG	√				
Hepatorenal function	√				
Electrolyte	√				
The application of combined drugs	√				
Study treatment		√			
Adverse events recording		√	√	√	

Pulmonary exacerbation in patients with bronchiectasis was required to meet three or

more of the following key symptoms for at least 48h: Cough; Sputum volume and/or consistency; Sputum purulence; Breathlessness and/or exercise tolerance; Fatigue and/or malaise; Haemoptysis, and a clinician determines that a change in bronchiectasis treatment is required (Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. The European respiratory journal 2017; 49(6)). In order to improve the accuracy of acute exacerbation information, patients were informed of the definition of acute exacerbation in advance, and were followed up by telephone every three months. Meanwhile, patients were given the phone number of the follow-up doctor and were told to contact in time when acute exacerbation occurred, so as to timely record acute exacerbation information

Data management: A standardized data collection spreadsheet was designed to obtain patients' data from electronic medical records. Data on general conditions, clinical symptoms, radiographic manifestations, lung function indexes and healthy related scores such as St George's Respiratory Questionnaire (SGRQ), CAT, modified Medical Research Council (mMRC), LCQ and the 6 Minute Walking Distance (6-MWD) of all patients were recorded at different time points for in-depth analysis. Lung function parameters included forced expiratory volume in 1s (FEV1), percentage of predicted FEV1 value (FEV1%), forced vital capacity (FVC) and FEV1/FVC ratio. The primary outcome was the time to first acute exacerbation after discharge. Secondary outcomes included the change of health-related scores, lengths of hospital stay, hospitalization expenses and incidences of adverse events. Two attending physicians independently reviewed the data collection forms to double check the data validity.

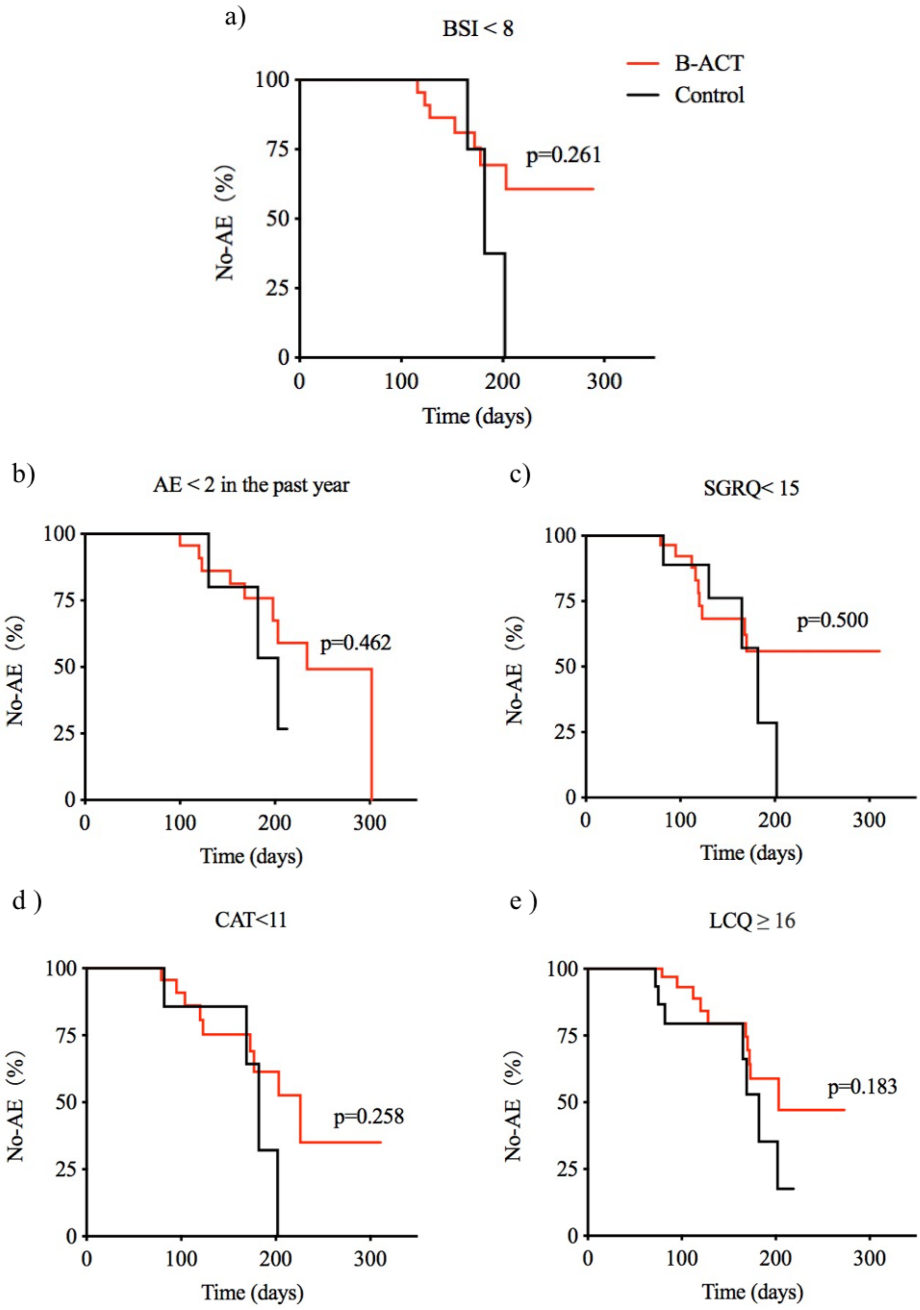
Outcome assessment: The multivariable analysis of relevant factors associated with the time to first acute exacerbation after discharge were analyzed. The efficiency of the B-ACT therapy for bronchiectasis with acute exacerbation was reported. The difference in the time to first acute exacerbation after discharge was compared between control and B-ACT groups, and the difference of the change of healthy related scores such as CAT and LCQ scores were compared in both groups. Moreover, a detailed consultation in the experimental group to evaluate the occurrence of adverse events related to B-ACT therapy was conducted.

Statistical analysis plan: Categorical variables were presented as frequencies and percentages, while continuous variables were tabulated as mean (standard deviation) for normally distribute variables or median (IQR) for non-normally distribute variables. The Kolmogorov-Smirnov test and Levene test were applied for analysing the normality and homogeneity of variables. Independent group t-test was used for normally distributed variables, and Mann-Whitney U test was applied for non-normally distributed variables. Categorical variables were compared by the Chi-square test or Fisher's exact test. The multivariable analysis (Cox proportional hazards model) was applied to assess independent risk factors for the time to first acute exacerbation after discharge. The difference of primary outcome between two groups were compared by the method of Kaplan-Meier and the log-rank test. The repeated measures ANOVA was adopted to compare the score changes at different time points. Statistical significance was considered when the two-tailed $p < 0•05$. All statistical analyses and diagramming were performed by SPSS (version 23•0), GraphPad Prism (version 8•0), Origin Pro

(version 26•0) and Ziostation2 (version 2•4•0•2) softwares.

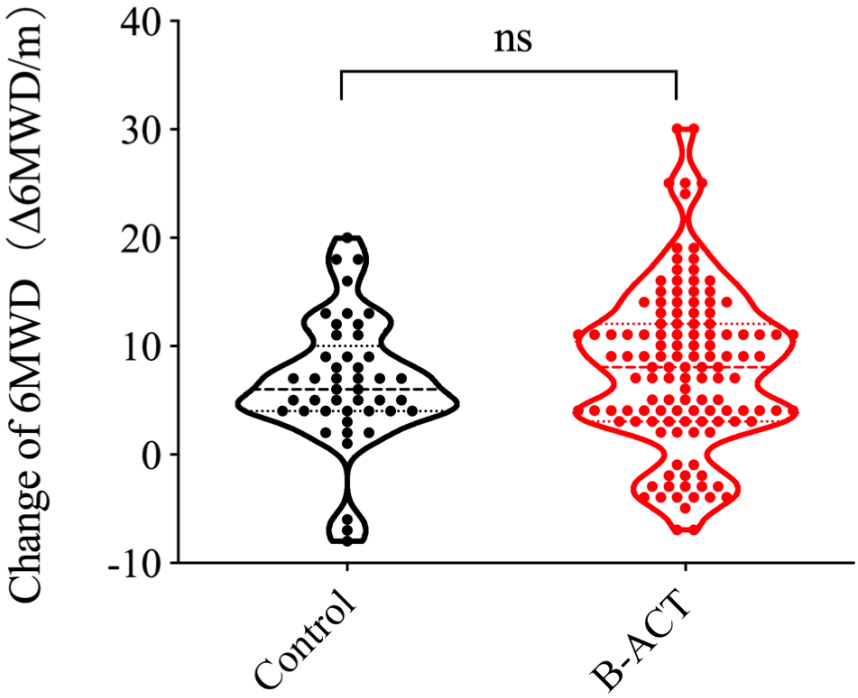
Ethics approval: The study was approved by the Research Ethics Committee of Shanghai Pulmonary Hospital (approval number K17-112).

Supplemental materials 2



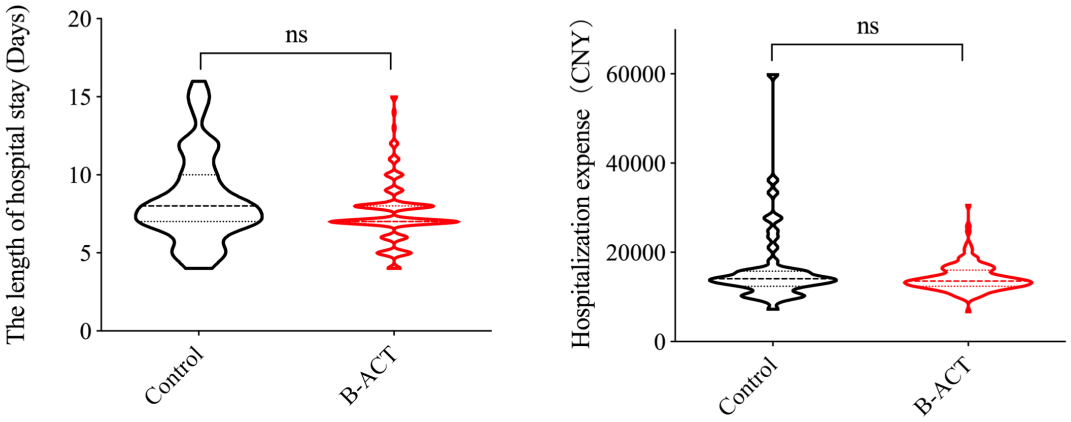
Supplemental Figure S1. Subgroups analysis of the special populations who did not benefit from the B-ACT therapy according to comparison of the time to first acute exacerbation after discharge, related to figure2

Differences of the time to first acute exacerbation after discharge for patients with BSI scores <8, the number of acute exacerbations in the past year <2, SGRQ scores <15, CAT scores <11, or LCQ scores ≥16 between the two different treatment groups are shown in panel a), b), c), d) and e) respectively.



Supplemental Figure S2. The improvement of 6WMD between admission day and the first day of treatment in both groups

Shown was the comparison of the improvement of 6WMD between admission day and the first day of treatment in both groups. ns: no significant.



Supplemental Figure S3. Comparison of the length of hospital stay and hospitalization expense in both group

Shown was the comparison of the length of hospital stay and hospitalization expense in both groups. ns: no significant.

Supplemental materials 3

Video A short video file was provided to show the operation steps of B-ACT therapy.