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Efficacy of *N*-acetylcysteine on idiopathic or postinfective non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis protocol

Ai Luo,[1] Xuemei Liu,[1,2] Qiongqiong Hu,[3] Mei Yang,[1] Hongli Jiang,[1] Wei Liu [1]

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AL and XL contributed equally.

AL and XL are joint first authors.

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[1]Division of Respiratory Medicine, Department of Integrated Traditional and Western Medicine, Sichuan University of West China Hospital, Chengdu, Sichuan, China
[2]Department of Pulmonary Disease, State Key Laboratory of Biotherapy of China, Sichuan University of West China Hospital, Chengdu, Sichuan, China
[3]West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

Correspondence to
Dr Wei Liu;
liuwei0929@wchscu.cn

ABSTRACT

Introduction Non-cystic fibrosis (non-CF) bronchiectasis is a chronic pulmonary disorder that causes destruction and permanent dilatation of the airways, resulting in excessive sputum production, repeated infection and inflammation. A need for high-quality and specialised care has been highlighted in recent years. *N*-acetylcysteine (NAC) is a widely used mucolytic agent in respiratory diseases that not only possesses a property to enhance secretion clearance, but also exhibits antioxidant and anti-inflammatory effects. However, the efficacy and safety of NAC are not well described in idiopathic or postinfective non-CF bronchiectasis.

Objective This study aims to evaluate the efficacy and safety of NAC in patients with idiopathic or postinfective non-CF bronchiectasis.

Methods and analysis PubMed/Medline, Embase, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials will be searched from inception to 1 March 2022 for eligible randomised controlled trials that investigating the effects of NAC on exacerbations, health-related quality of life, lung functions, sputum volume and colour, inflammation markers, exercise capacity and adverse events in patients with idiopathic or postinfective non-CF bronchiectasis, with ongoing trials being identified by searches on the websites of Chinese Clinical Trial Registry and ClinicalTrials.gov. Two independent reviewers will identify eligible studies, two will fulfil the data extraction and three will perform the quality appraisal. To generate more accurate analyses, the Grading of Recommendations Assessment, Development and Evaluation will be used to grade the evidence. χ^2 test and I^2 statistic will be used to assess heterogeneity. Subgroup analyses and meta-regression will be used to explore potential sources of heterogeneity. The potential publication bias will be examined using funnel plots.

Ethics and dissemination No research ethics approval is required in this study because it is a systematic review. The results of this study are expected to be disseminated through peer-reviewed journals and conferences.

Trial registration number CRD42021239438.

Strengths and limitations of this study

- ► This systematic review and meta-analysis will comprehensively summarise the available evidence on the efficacy and safety of *N*-acetylcysteine (NAC) in patients with idiopathic or postinfective non-cystic fibrosis (non-CF) bronchiectasis, which may be able to determine the appropriate place of NAC in routine care in this group of patients.
- ► We will assess risk of bias for each outcome and use the Grading of Recommendations Assessment, Development and Evaluation to assess the overall quality of evidence.
- ► Subgroup analyses will be conducted to comprehensively identify the influence of patient characteristics and interventions on the efficacy of NAC, which will be helpful to determine the optimal administration of NAC against non-CF bronchiectasis.
- ► Comprehensive outcome measurements will be evaluated to address not only the short-term effect of NAC on symptoms, infections and inflammations, but also the long-term effect on the risk of exacerbations.
- ► Since idiopathic or postinfective non-CF bronchiectasis patients with a severe lung dysfunction (forced expiratory volume in one second≤30% of the predicted value) will be excluded, the conclusion of this study may not be applied in patients with severe lung dysfunction or with other non-CF bronchiectasis causes.

INTRODUCTION

Non-cystic fibrosis (non-CF) bronchiectasis (henceforth referred to as bronchiectasis) is a chronic suppurative lung disease characterised by permanent dilation of bronchi and bronchioles.[1] Although bronchiectasis has a substantial impact on healthcare systems with a high frequency of annual exacerbations and increased attributable mortality,[2 3] it is underappreciated for a long time because of a similarity in symptoms to other chronic lung diseases. Renewed interests have been increasing in recent years and contributing to more recognitions and intervention development in this condition.[4] In patients with bronchiectasis, there is hypertrophy of the mucus-secreting glands and impaired mucociliary system, causing

ineffective clearance of secretions and secondarily repeated airway bacterial infections and inflammations.[5] Although approximately 27% of bronchiectasis patients have a form of the disease called dry bronchiectasis, most patients do experience an overproduction of sputum accompanied by chronic bacterial infections.[6] As a result, mucoactive agents that aim to improve mucus properties and facilitate mucociliary clearance have long been used in this condition.[7–10]

N-acetylcysteine (NAC) is a common mucolytic drug that hydrolyses the disulfide bonds of mucus proteins to decrease mucus viscosity, thereby facilitating its clearance.[11] Besides, it is deacetylated to cysteine, containing a thiol group, which accounts for its antioxidant properties.[12] Recently, in vitro studies have strongly supported good antibacterial properties and the ability to disrupt biofilms in NAC.[13] Therefore, the beneficial effects of NAC may be caused by not only its mucolytic effect, but also the antioxidant and antibacterial potentialities.[13]

NAC is widely used in respiratory diseases with a good safety profile considering the possible beneficial effects.[14] However, the use of NAC in these conditions remains controversial. Meta-analysis studies identified the effect of NAC in improving symptoms, spirometry, health-related quality of life (HRQoL) and decreasing the frequency of exacerbations in asthma,[8] chronic bronchitis,[15] chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), with good tolerance.[16] However, some randomised trials showed no efficacy with the use of NAC, especially on the decrease of exacerbation risks and decline of lung functions.[8 17] Besides, mild-to-moderate side effects were reported.[18] The variable dosage use, administration forms and treatment courses among studies may partially explain the inconsistent outcomes. Most of the studies have used the oral form (usually 600 mg, two times or three times a day), while inhalation (usually 300 or 352 mg, two times per day) has been suggested as a more effective administration form as it can help the medication directly and rapidly act on the airways with a higher bioavailability to respiratory secretions.[12 19 20] Studies have shown a similar effect of inhaled NAC with a smaller daily dose on disease manifestations in patients with IPF,[18] and even a better effect with the same doses in patients with COPD, compared with oral NAC.[21] However, most studies have suggested that low-dose and short-term NAC therapy may not enhance the antioxidant potential of glutathione.[20] Moreover, even long-term administration at low doses does not always have anti-inflammatory potential. Therefore, substantially higher doses may ensure a better response in respiratory diseases as in vitro studies have already demonstrated.[13] As to the safety, a recent review has demonstrated that the safety profile of NAC in chronic respiratory diseases is similar at both high doses and standard doses of 600 mg/day with the oral formulation, with gastrointestinal symptoms as the most common adverse events being reported.[14] However, existing studies mainly focus on patients with COPD, IPF, chronic bronchitis and CF. Evidence on non-CF bronchiectasis is still lacking.

Given that bronchiectasis shares similar clinical features with other chronic respiratory diseases in terms of expectorations and airway inflammations, NAC has been widely used in patients with bronchiectasis; however, its clinical efficacy and safety have not been well reviewed, and there is no sufficient evidence.

Aim

This study aims to undertake a systematic review and meta-analysis to summarise the evidence on the efficacy and safety of NAC in patients with idiopathic or postinfective non-CF bronchiectasis from randomised controlled trials (RCTs), which may help to determine the appropriate place of NAC in routine care of non-CF bronchiectasis.

METHODS AND ANALYSIS

Protocol and registration

This systematic review has been registered in the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero), and will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.[22]

Eligibility criteria

Study design

Only RCTs with a treatment duration of at least 3 months will be considered. Reviews, editorials, letters, commentaries, unpublished papers and conference reports with insufficient information regarding participant ascertainment, study design and outcome data will be excluded.

Participants

Patients aged 18–80 years old with a diagnosis of idiopathic or postinfective non-CF bronchiectasis will be included, regardless of gender, ethnicity, disease duration and severity. Diagnosis of bronchiectasis is made according to clinical manifestations and imaging features, including the internal lumen diameter of the bronchi being greater than that of the adjacent artery, the bronchi failing to taper in the periphery, or the bronchi terminating in a cyst.[4] The disease condition should be stable for at least 4 weeks prior to randomisation.

Patients will be excluded if they fulfil any of the following criteria: CF or other aetiologies (such as immunodeficiency, allergic bronchopulmonary aspergillosis, traction bronchiectasis caused by emphysema, tuberculosis, advanced pulmonary fibrosis, etc); primary diagnosis of COPD or asthma; pulmonary function test results showing a forced expiratory volume in one second (FEV_1)≤30% of the predicted value; comorbidity with severe cardiovascular disease, liver disease, kidney disease, malignant tumour, gastric ulcer or intestinal malabsorption; pregnancy or lactation (for women). Studies included both children and adults will be excluded.

Comparison

Studies comparing oral or inhaled NAC in a daily dose of at least 600 mg with placebo, routine treatment or

non-NAC mucolytics will be included. The treatment duration is at least 3 months. Studies that use long-term anti-inflammatory agents such as inhaled corticosteroids, statins, antibiotics in any groups will be excluded.

Outcomes

The primary outcome is the incidence of bronchiectasis associated exacerbations during active treatment therapy. Bronchiectasis associated exacerbation is defined as (1) 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; haemoptysis and (2) a clinician determines that a change in bronchiectasis treatment is required, according to a consensus definition for clinical research.[23]

The secondary outcomes include the percentage of patients remaining exacerbation-free throughout the follow-up, time to the first exacerbation, hospitalisations, pulmonary function, HRQoL, systemic inflammation markers, sputum volume and purulence, exercise capacity, and adverse events during active treatment or at follow-up. Pulmonary function measurements will include forced vital capacity (FVC), FEV_1, percentage of predicted FEV_1 and FEV_1/FVC ratio. HRQoL will be assessed using COPD Assessment Test (CAT) scores, Leicester Cough Questionnaire (LCQ), disease-specific Quality of Life-Bronchiectasis (QoL-B) questionnaire, Chronic Respiratory Disease Questionnaire (CRDQ) or non-disease-specific St George's Respiratory Questionnaire (SGRQ) scores. The CAT is a valid and reproducible instrument in patients with bronchiectasis, presenting a good correlation with clinical, functional and QoL measurements.[24 25] The LCQ is a symptom-specific questionnaire designed to assess the impact of cough, a significant symptom of bronchiectasis. It can discriminate disease severity, and is responsive to change and is reliable for use in non-CF bronchiectasis.[26 27] The QoL-B questionnaire is a self-administered patient-reported outcome measurement, which assesses symptoms, functioning and HRQoL for patients with non-CF bronchiectasis with 37 items on 8 scales.[11] The CRDQ is designed to assess HRQoL in chronic respiratory conditions, and is reliable and validated in mild-to-moderate non-CF bronchiectasis.[28] The SGRQ has been validated in bronchiectasis and has been the most widely used questionnaire in this condition.[29 30] Inflammatory markers include serum C reactive protein, erythrocyte sedimentation rate, procalcitonin, interleukin (IL)-6 and IL-8. Patients' exercise capacity will be assessed using incremental shuttle walk distance or a 6-minute walk test.[31 32]

Search strategy

PubMed/Medline, Embase, Web of Science, Cochrane Library and Cochrane Central Register of Controlled Trials will be searched for eligible RCTs from inception to 1 March 2022. Ongoing studies will be searched on the Chinese Clinical Trial Registry (http://www/chictr.org.cn) and ClinicalTrials.gov (http://www.clinicaltrials.gov/). Additional eligible studies will be identified from bibliographies of included studies, and previous systematic reviews. The search strategy will be performed using a combination of Medical Subject Headings and free terms including 'non-cystic fibrosis bronchiectasis', 'non-CF bronchiectasis', 'bronchiectasis', '*N*-acetylcysteine', 'acetylcysteine', 'NAC', 'randomized controlled trial', 'randomized clinical trial', 'controlled clinical trial', 'randomly', 'randomized' and 'trial' in the aforementioned databases (online supplemental file 1). The search terms will be appropriately modified to suit the instructions of individual databases. No language restriction will be imposed.

Study selection

Two independent reviewers (AL and XL) will independently identify the studies via the search strategy. First, we will carry out the initial search and remove duplicated studies using the citation manager EndNote X9. Second, we will check the included titles and abstracts to identify potential articles. Lastly, we will make full-text screening to determine the final inclusions according to prespecified inclusion criteria. Disagreement will be resolved by consensus or be settled by the third reviewer (WL).

Data extraction

The following information will be extracted from studies that meet the inclusion criteria by two independent reviewers (QH and MY): name of the first author, year of publication, study design, study sample, age, gender, diagnosis, treatment, length of treatment, length of follow-up, outcomes and side effects.

Management of missing data

When information regarding any of the above is insufficient, unclear or missing, we will contact the corresponding authors for further details. We will ask if any outcomes not reported in their publications have been collected. If the authors provide the information, it will be included in our analyses and acknowledged appropriately.

Quality assessment

Three reviewers (AL, XL and MY) will independently assess the methodological quality of each RCT using the Cochrane risk-of-bias tool. This tool consists of seven domains. Each domain is presented as high, unclear and low risk of bias. Any disagreements will be solved by a fourth review researcher (WL) joining in through discussion. The level of agreement for each domain and the overall domains will be assessed using the Kappa statistics.

Evaluating the quality of evidence

We will assess the evidence quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach at the outcome level for each comparison between interventions, according to five criteria: limitation of study design, publication bias, imprecision, inconsistency and indirectness.[33] GRADE

ratings are defined as very low, low, moderate or high, reflecting the extent to which we are confident in the effect estimation. The quality of evidence will be downgraded by one level for study design limitation when more than a quarter of the studies included in analysis are considered at high risk of bias. Serious or very serious issues of inconsistency, indirectness, imprecision and publication bias reduce the evidence quality.

Data synthesis and analysis

Data analysis will be conducted by two reviewers (AL and XL) using RevMan V.5.3 and Stata V.15.1. The pooled estimates of mean differences between treatment groups in the yearly incidence of bronchiectasis associated exacerbations, time to the first exacerbation, hospitalisations, pulmonary function indicators, HRQoL scores, inflammation markers, sputum volume, and exercise capacity, and ORs in sputum purulence, and adverse events will be calculated, with corresponding 95% CIs. A χ^2-based test of homogeneity will be performed using Cochran's Q statistic and I^2. A fair and reasonable heterogeneity is defined as a value of $I^2 \leq 50\%$. Otherwise, it will be regarded as having substantial heterogeneity. If $I^2 \leq 50\%$, the outcome data will be pooled using fixed-effect models, and a meta-analysis will be carried out. Otherwise, random-effect models will be used. Meta-regression will be applied to exploring the causes of heterogeneity by fitting a covariable (eg, mean age, percentage of female, treatment duration (≤6 months or longer), follow-up duration, dosage form (oral or inhalation) and dose of daily NAC (1800 mg or less)) in multiple models. Then, subgroup analysis will be conducted according to the results of meta-regression. If the heterogeneity is still significant postsubgroup analysis, a narrative summary will be presented instead of the meta-analysis. Sensitivity analysis will be performed based on the leave-one-out approach. A value of $p<0.05$ indicates statistical significance.

Publication bias assessment

Where possible, publication bias will be assessed by visual inspection of funnel plots if more than 10 eligible studies are included.[34] In addition, Egger's and Begg's tests will be conducted to identify whether the funnel plot is asymmetry.[35]

DISCUSSION

The importance of underlying local and systemic oxidative stress and inflammation in idiopathic or postinfective non-CF bronchiectasis has long been established. In view of the lack of therapy that might inhibit the progress of the disease, there is an urgent need for a successful therapeutic approach that works on the symptoms and the underlying mechanisms. NAC is a mucolytic and antioxidant drug that may also influence infections and inflammations. Therefore, it has been reported to be beneficial in chronic respiratory diseases characterised by productive cough and airway inflammations, by means of decreasing sputum viscosity, cleaning airways and inhibiting inflammatory responses.[20] Nevertheless, its actions in these conditions are still debatable according to current evidence, especially on the outcomes of exacerbations and lung function parameters.[7 15 16]

Besides, the optimal use of NAC is also uncertain. Although most studies have shown a better effect in inflammation and oxidative stress in high dosages, the inflammatory and oxidative stress markers seem to be also influenced at low dosages, even with a better safety profile.[36–38] Furthermore, although NAC is orally used in a traditional way, the inhaled form as a novel method of drug delivery has been evaluated in patients with CF and patients with COPD, with variable outcomes and tolerance being reported.[21 39]

Although NAC is widely used and considered as a promising medication in patients with idiopathic or postinfective non-CF bronchiectasis, there is still a lack of solid evidence.[8] This comprehensive review and meta-analysis will provide evidence regarding the efficacy and safety of NAC in these patients.

ETHICS AND DISSEMINATION

No ethical statement will be required for the performance of this review and meta-analysis. Results of this research will be published. These results will contribute towards identifying and optimising the therapeutic use of NAC in patients with non-CF bronchiectasis.

Contributors WL and HJ conceived and designed the protocol, they contributed to the development of the study protocol and review of the manuscript. AL and XL participated in trial registration and manuscript draft. AL, XL, QH and MY piloted the searching strategy and data extraction format. All authors critically revised the manuscript and approved the final version of this manuscript.

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Competing interests None declared.

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ORCID iD

Wei Liu http://orcid.org/0000-0001-6929-5984

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