

# Effects of a Long-Term Use of Carbocysteine on Frequency and Duration of Exacerbations in Patients with Bronchiectasis

Jordan Minov<sup>1\*</sup>, Sasho Stoleski<sup>1</sup>, Tatjana Petrova<sup>2</sup>, Kristin Vasilevska<sup>3</sup>, Dragan Mijakoski<sup>1</sup>, Jovanka Karadzinska-Bislimovska<sup>1</sup>

<sup>1</sup>*Institute for Occupational Health of Republic of Macedonia, Skopje, Republic of Macedonia;* <sup>2</sup>*Department of Pharmacy Practice, Chicago State University, Chicago, USA;* <sup>3</sup>*Institute for Epidemiology and Biostatistics, Skopje, Republic of Macedonia*

## Abstract

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**\*Correspondence:** Jordan Minov. Institute for Occupational Health of Republic of Macedonia, Skopje, Republic of Macedonia. E-mail: [minovj@hotmail.com](mailto:minovj@hotmail.com)

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**BACKGROUND:** The failure of mucus clearance in bronchiectasis can be improved by chest physiotherapy or/and mucoactive agents.

**AIM:** To assess the effects of long-term use of carbocysteine on frequency and duration of exacerbations in patients with bronchiectasis.

**METHODS:** We performed an observational, non-randomized, open study (a real-life study) including 64 patients with bronchiectasis divided into two groups, examined group (EG) and control group (CG). All participants were treated with appropriate treatment for the stable disease, but in the study, subjects of EG two capsules 375 mg carbocysteine three times a day was added over three months. Daily diary cards realised collection of data regarding the occurrence and duration of exacerbation in all study subjects.

**RESULTS:** Over the study period 43 exacerbations were documented, 17 in the EG and 26 in the CG, 10 (23.4%) of which required hospital treatment (four in the EG [23.5%] and six in the CG [23.1%]). A mean number of exacerbations over the study period was significantly lower in the EG ( $0.5 \pm 0.1$ ) as compared to their mean number in the CG ( $0.8 \pm 0.2$ ) ( $P = 0.0000$ ). Mean duration of exacerbations expressed in days needed for complete resolution of symptoms or return of the symptoms to their baseline severity in the EG was significantly shorter than the mean duration of exacerbations in the CG ( $10.1 \pm 2.6$  vs  $12.8 \pm 2.1$ ;  $P = 0.0000$ ). The frequency of adverse effects, i.e. mild gastrointestinal manifestations and headache which did not require discontinuation of the treatment, in the EG during the study period was 15.6%.

**CONCLUSION:** Our findings indicated positive effects of carbocysteine regarding the frequency and duration of exacerbations, as well as its good tolerability in the patients with bronchiectasis.

## Introduction

Bronchiectasis is a heterogeneous disease with highly variable impact to patients (varying from patients without daily symptoms and infrequent exacerbations to patients requiring lung transplantation), so the treatment should be appropriate to stage and severity of disease in a certain patient. On the other side, so far, the treatment of bronchiectasis is not strongly supported by clinical trial evidence, and clinical practice guidelines have largely been formulated through consensus in expert opinion.

As main goals of the treatment of bronchiectasis, i.e. the treatment of stable disease and the treatment of exacerbation, are considered: to improve airway mucus clearance through

physiotherapy with or without adjunctive therapies; to suppress, eradicate and prevent airway bacterial colonisation; to reduce airway inflammation; to prevent exacerbations; and to improve physical functioning and quality of life [1], [2].

Improving airway clearance is considered as one of the cornerstones of the bronchiectasis treatment. The failure of mucus clearance can be improved by chest physiotherapy (breathing techniques, postural drainage, instrumental techniques, etc.) and mucoactive agents (hypertonic saline, dry mannitol powder, cysteine derivatives, etc.). Treatment choice should be influenced by clinical experience, as by research, reflecting the limited evidence in this domain, as well as by patient's status and preference [3], [4], [5].

Mucoactive agents can be used for both management of stable disease and exacerbations.

Available as oral, inhaled, or nebulised agents, they reduce sputum viscosity and aid expectoration, thereby theoretically shorten exacerbation frequency and length and improve symptoms and quality of life [6].

According to the European Bronchiectasis Guidelines and the European Respiratory Society guidelines for the management of adult bronchiectasis, a long-term mucoactive treatment, i.e. use of cysteine derivatives, hypertonic saline, mannitol or isotonic saline three months or more, is suggested in patients who have difficulties in expectorating sputum and poor quality of life and where standard airway clearance techniques have failed to control symptoms [7], [8]. Similarly, according to the Spanish Guidelines on Treatment of Bronchiectasis in Adults, a long-term mucoactive treatment, i.e. use of mucolytics or hypertonic substances may improve sputum purulence a lung function and reduce exacerbation frequency [9]. Also, the British Guidelines for the Management of Bronchiectasis in Primary Care recommended a long term mucoactive treatment, i.e. nebulised hypertonic saline or carbocysteine for 6 months in patients with excessive viscous mucus. The dosage of carbocysteine should be two 375 mg capsules three times a day, and the treatment should be stopped if no benefit [10]. According to the recent Australian recommendations for treatment of bronchiectasis in adults, mucoactive agents should be used by patients with substantial sputum burden, difficulty expectorating sputum, poor quality of life and/or frequent exacerbations despite standard airway clearance techniques [11]. Carbocysteine, i.e. S-Carboxymethyl-L-cysteine, is a mucolytic that reduces the viscosity of sputum, allowing its easily bringing up. As a mucolytic, it is used for some time in respiratory diseases characterised by hypersecretion of viscous mucus, such as acute bronchitis, chronic bronchitis, COPD and bronchiectasis [12]. Due to the antioxidant properties of carbocysteine and other mucolytics (i.e. free radicals scavenging and anti-inflammatory effects), several studies indicated their immunomodulatory and anti-inflammatory effects [13].

The present study aimed to assess the effects of long-term use of carbocysteine on incidence and duration of exacerbations in patients with bronchiectasis. This study is a continuum of our investigating the effects of carbocysteine in the treatment of lung diseases characterised by excessive production of viscous mucus [14], [15].

## Methods

### *Study design and setting*

An observational, non-randomized, open-label study (a real life-study) was realised as a comparison

of frequency and duration of exacerbations between a group of patients with bronchiectasis who received carbocysteine over three months and a group of patients with bronchiectasis who did not receive carbocysteine in the same period. The study was performed in the period February-December 2019 at the Institute for Occupational Health of R. North Macedonia, Skopje.

### *Study subjects*

The study population included 64 subjects with bronchiectasis who had to have difficulties in expectorating sputum and poor quality of life and who was not able to perform standard airway clearance techniques, or these techniques failed to control symptoms of the disease. The study subjects were divided into two groups similar by their characteristics: examined group (EG) and control group (CG).

EG included 32 patients with bronchiectasis, 18 males and 14 females, aged 46 to 76 years. The study subjects from EG besides the appropriate treatment of stable disease were treated with two 375 mg capsules carbocysteine three times a day over three months in which number and duration of exacerbations were registered.

Also, an equal number of patients with bronchiectasis (19 males and 13 females, aged 47 to 74 years) with similar characteristics as those from EG were treated only with the appropriate treatment of stable disease and followed over three months.

All participants were informed about the study, and their written consent was obtained.

### *Demographic and other characteristics of the study subjects*

Demographics of the study subjects, including sex, age, smoking status, body mass index (BMI), previous or current occupational exposure to noxious particles and gases, and comorbidities were collected by questionnaire at the initial visit.

Classification of the smoking status of the study subjects was done by the World Health Organization (WHO) recommendations [16]. Passive smoking or exposure to environmental tobacco smoke was defined as exposure to tobacco combustion products from smoking by others (at home, workplace, etc.), i.e. as a presence of at least one smoker in the household and/or in the workplace [17].

The Body Mass Index (BMI) as a measure of body fat based on height and weight that applies to adult population was determined in all study subjects by computed calculation using BMI calculator [18].

Daily stable respiratory symptoms, medication use and history of exacerbations in the last 12 months were noted in all subjects before entering the study.

All study subjects underwent baseline and post-bronchodilator spirometry according to the actual recommendations [19]. Also, microbiological evaluation of sputum was performed in all study subjects in the stable phase of the disease, as well as when the exacerbation was diagnosed [20].

### Diagnosis and assessment of bronchiectasis

Diagnosis of bronchiectasis was based on the findings of high resolution computed tomography (HRCT) as it is currently considered as the best tool for its diagnostics [21], [22]. Patients with diagnosed bronchiectasis underwent a range of investigations to determine the underlying cause, as well as to determine the severity of the disease [23]. Diagnosis and assessment of COPD were made following the actual recommendations of the Global Initiative for COPD (GOLD) [24]. Following the recommendation of the Bronchiectasis Severity Index (BSI), bronchiectasis was classified as mild, moderate and severe [25].

### Diagnosis and treatment of BE exacerbation

BE exacerbations were diagnosed according to the criteria from the actual guidelines mentioned above [26]. The antibiotic therapy lasted 14 days being etiological or empirical depending on the results of sputum culture [27], [28]. The course of exacerbation was evaluated as a function of the resolution of symptoms, and the treatment was considered to be successful if cure or clinical improvement, i.e. return of the symptoms to their baseline severity, was achieved.

### Data collection (Daily diary card)

Collection of data regarding the occurrence and duration of exacerbation in all study subjects was realised by daily diary cards following the model used by Patel et al., (2004) in the study on bronchiectasis and exacerbation indices [29]. The mentioned model was used and explained in our previous studies on exacerbations in COPD patients with bronchiectasis [30].

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages. Analyses of the data included testing the differences in prevalence and comparison of the means by chi-square test (or Fisher's exact test where

appropriate) and independent-samples *T*-test. A *P*-value of less than 0.05 was considered as statistically significant.

## Results

Demographic and other characteristics of the study subjects are shown in Table 1. In both groups, there was not any patient receiving long-term treatment with systemic or inhaled antibiotics. Patients with accompanied COPD (about one third in both groups) were treated according to the actual GOLD recommendations [24].

Table 1: Characteristics of the study subjects

Variable	EG (n = 32)	CG (n = 32)
M/F ratio	1.3	1.4
Mean age (years)	54.3 ± 7.8	53.9 ± 8.4
Mean BMI (kg/m <sup>2</sup> )	25.6 ± 2.8	25.3 ± 3.7
Smoking status	9 (28.0%)	10 (31.2%)
Never smokers	14 (43.7%)	13 (40.6%)
Active smokers	9 (28.0%)	9 (28.0%)
Ex-smokers Exposed to ETS	15 (46.8%)	13 (40.6%)
Mean duration of disease after diagnosis (years)	8.6 ± 3.4	9.0 ± 3.9
Classification of disease severity by the BSI score		
Mild	12 (37.5%)	13 (41.9%)
Moderate	14 (43.3%)	13 (41.9%)
Severe	6 (18.7%)	6 (18.7%)
Mean values of spirometric parameters (% pred.)		
FVC	74.6 ± 6.1	76.1 ± 7.2
FEV <sub>1</sub>	52.3 ± 4.8	56.1 ± 4.3
FEV <sub>1</sub> /FVC ratio	0.70 ± 0.04	0.70 ± 0.07
Positive sputum culture when clinically stable over the last 12 months		
<i>Haemophilus influenzae</i>	10 (31.2%)	11 (34.4%)
<i>Moraxella catarrhal</i>	4 (12.5%)	5 (15.6%)
<i>Streptococcus pneumoniae</i>	3 (9.4%)	3 (9.4%)
<i>Pseudomonas aeruginosa</i>	3 (9.4%)	2 (6.2%)
<i>Serratia marcescens</i>	2 (6.2%)	3 (9.4%)
<i>Staphylococcus aureus</i>	1 (3.1%)	1 (3.1%)
Other	2 (6.2%)	2 (6.2%)
No bacteria isolated	7 (21.8%)	5 (15.6%)
Accompanied COPD	10 (31.2%)	9 (28.0%)
Mean number of exacerbations in the last 12 months	2.7 ± 0.4	2.6 ± 0.5

Numerical data are expressed as mean value with standard deviation; frequencies as number and percentage of study subjects with certain variable; EG: examined group; CG: control group; M: male; F: female; BMI: body mass index; kg: kilogram; m: meter; ETS: environmental tobacco smoke; BSI: Bronchiectasis Severity Index; % pred.: % of the predicted value; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in one second; COPD: chronic obstructive pulmonary disease.

Over the study period 43 exacerbations were documented (17 in the EG and 26 in the CG), 10 (23.4%) of which required hospital treatment (four in the EG [23.5%] and six in the CG [23.1%]).

A mean number of exacerbations over the study period was significantly lower in the EG (0.5 ± 0.1) as compared to their mean number in the CG (0.8 ± 0.2) (*P* = 0.0000) (Figure 2).

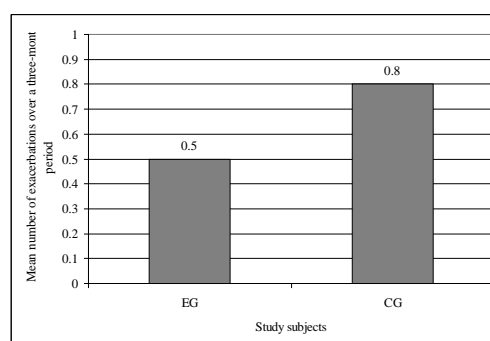


Figure 1: Mean number of exacerbations in the study subjects over a three-month period

Positive sputum culture was obtained in 34 exacerbations (14 in the EG and 20 in the CG) (Table 2).

Table 2: Findings of sputum culture in exacerbations

Sputum culture	EG (n = 17)	CG (n = 26)
<i>Haemophilus influenzae</i>	7 (41.1%)	9 (34.6%)
<i>Moraxella catarrhalis</i>	2 (11.8%)	3 (11.5%)
<i>Streptococcus pneumoniae</i>	2 (11.8%)	3 (11.5%)
<i>Pseudomonas aeruginosa</i>	1 (5.9%)	2 (7.7%)
Other	2 (11.8%)	3 (11.5%)
No bacteria isolated	3 (17.6%)	6 (23.1%)

Majority of exacerbations (33 of 43 exacerbations [76.7%]) were treated with systemic antibiotics (12/17 [70.6%] in the EG and 21/26 [73.1%] in the CG). Also, 10 exacerbations (23.3%) were treated with systemic antibiotics and systemic corticosteroids.

Mean duration of exacerbations expressed in days needed for complete resolution of symptoms or return of the symptoms to their baseline severity in the EG was significantly shorter than the mean duration of exacerbations in the CG (10.1 ± 2.6 vs 12.8 ± 2.1; P = 0.0000) (Figure 2).

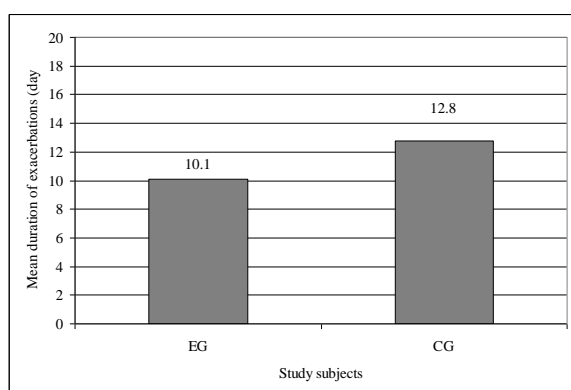


Figure 2: Mean duration of exacerbations in the study subjects

The frequency of adverse effects in EG during the study period was 15.6%. Mild and self-limited gastrointestinal manifestations (epigastric pain, nausea, vomiting, and diarrhoea) and headache, which did not require discontinuation of the treatment were registered in five patients (Figure 3).

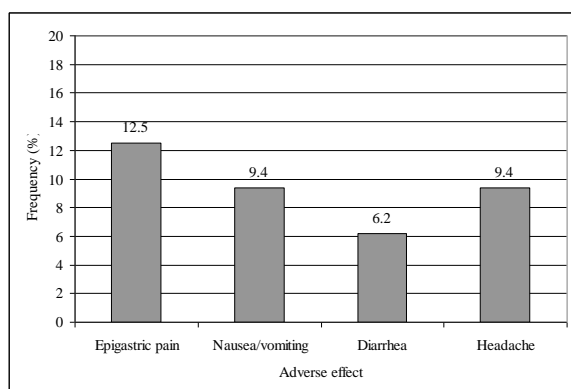


Figure 3: Adverse effects registered in the EG

## Discussion

Impaired mucociliary clearance and mucus retention contribute to the chronic cycle of airway inflammation, infection and damage in bronchiectasis [31], [32]. There is a strong rationale for the use of pharmacological strategies to aid airway clearance, often in combination with chest physiotherapy. On the other side, despite the availability of many candidate mucoactive agents for many years, the evidence base for recommending these agents is still limited [33].

Carbocysteine (S-Carboxymethylcysteine – S-CMC), although commonly regarded as a mucolytic, has a mechanism of action that differs from that of classical mucolytics (e.g. N-Acetylcysteine). Mucus produced under the action of carbocysteine shows an increase in sialomucin content. Sialomucins, which are structural components of mucus, influence the viscoelastic properties of mucus. Carbocysteine, also exerts anti-inflammatory action decreasing levels of the cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) and reducing neutrophil influx into the airway lumen [34], [35].

Aim of the present study was to assess the effect of long-term use of carbocysteine on frequency and duration of exacerbations in patients with bronchiectasis. According to the actual recommendations, the study population included patients with bronchiectasis who had to have difficulties in expectorating sputum and poor quality of life and who was not able to perform standard airway clearance techniques, or these techniques failed to control symptoms of the disease. The study subjects were divided into two groups with similar characteristics regarding the treatment with carbocysteine besides the appropriate treatment of stable disease. In both groups there was a large proportion of active and passive smokers, as well as a low proportion of ex-smokers, that was similar to their prevalence in general population documented in our previous studies [36], [37]. These findings suggest insufficient anti-smoking activities, i.e. they indicate a need for improvement of the control of tobacco use in R. Macedonia. According to the results of studies on smoking status conducted in developed countries, e.g. New Jersey Adult Tobacco Survey and Australian National Health Survey, in the countries with more effective anti-smoking strategies, there is a significantly lower prevalence of active and passive smokers and significantly higher prevalence of ex-smokers as compared to their prevalence registered in our studies [38], [39]. Results of the present study indicated lower frequency and lower duration of exacerbations in the group who received carbocysteine over three months as compared to exacerbations frequency and duration in the group who did not receive carbocysteine. The majority of clinical studies of cysteine derivatives have been performed in COPD, with conflicting results [15], [40],

[41]. The evidence supporting the use of cysteine derivatives in bronchiectasis is even more limited.

Results from the study conducted by Yi-Fong Su et al., in Taiwan which included 831 patients with bronchiectasis-chronic obstructive pulmonary disease overlap (BCO) indicated that a long term use (more than 90 days) of carbocysteine is associated with significantly lower risk of exacerbations. Similar results were obtained for a long-term use of N-acetylcysteine, ambroxol, and bromhexine, but not for iodinated glycerol [42]. Over the treatment mild gastrointestinal effects and headache occurred in about 15% of the study subjects who received carbocysteine. Nausea, stomach upset, diarrhea, and headache are considered as common side effects of carbocysteine which do not require discontinuation of the treatment. In addition, during the use of carbocysteine may occur severe side effects including severe allergic reactions, symptoms of low blood sugar (dizziness, drowsiness, weakness, fainting, tremor, etc), and bleeding from gastrointestinal tract (blood in vomit or black stools). These side effects occur rarely, affecting less than 1 in 1,000 people [43], [44]. The findings of this study should be interpreted within the context of its limitations. First, the study design, i.e. neither blinded nor randomized, could have certain implications on data obtained and its interpretation. Second, relatively small number of the study subjects also could have certain implications on data obtained and its interpretation. On the other hand, the study design may be its strength, as it is documented by other real life-studies. In addition, the study results could improve the limited knowledge about the role of carbocysteine in the treatment of stable bronchiectasis.

In conclusion, in an observational, non-randomized, open-label study aimed at assessment of effects of a long-term use of carbocysteine on frequency and duration of exacerbations in patients with bronchiectasis we found significantly lower frequency and duration of exacerbations in patients treated with carbocysteine over three months as compared to their frequency and duration in patients not treated with carbocysteine. Our findings also indicate a need for further studies in this domain to obtain more effective management of bronchiectasis.

### **Ethical Approval**

The Ethical Committee of the Institute of Occupational Health of R. North Macedonia, Skopje approved for performing the study and publishing the results obtained (03-0302-572/1-12.09.2019).

### **Authors Participations**

JM participated in the study design, data collection, managing the analyses of the study, and

writing all versions of the manuscript. JKB and TP participated in the study design, managing the analyses of the study, as well as writing all versions of the manuscript. KV performed the statistical analysis and participated in the managing of the analyses of the study. SS and DM participated in the data collection and the managing of the analyses of the study. All authors read and approved the final manuscript.

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