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Mortality in non-cystic fibrosis bronchiectasis: A prospective cohort analysis☆

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Summary
Introduction: There is limited data on mortality and associated morbidity in non-cystic fibrosis bronchiectasis (NCFB). Our aim was to analyze the overall mortality for all newly diagnosed patients from June 2006 onwards and to evaluate risk factors for mortality in this cohort.
Methods: 245 patients who had a new diagnosis of NCFB between June 2006 and October 2012 at the University Hospital of Leuven, Belgium, were included in the analysis. Death was analyzed until end of November 2013. All patients had chest HRCT scan confirming the presence of bronchiectatic lesions and had symptoms of chronic productive cough. Univariate and multivariate Cox proportional hazard survival regression analysis was used to estimate hazard ratios (HR) and their 95% confidence intervals (CI) of variables possibly predicting mortality.
Results: Overall mortality in NCFB patients who had a median follow-up of 5.18 years was 20.4%. Patients with NCFB and associated chronic obstructive pulmonary disease (COPD) had a mortality of 55% in that period. Univariate analysis showed higher mortality according to age, gender, smoking history, *Pseudomonas aeruginosa* status, spirometry, radiological extent, total number of sputum bacteria and underlying etiology. Multivariate analysis showed significant higher mortality with increasing age (HR = 1.045; $p = 0.004$), with increasing number of lobes affected (HR = 1.53; $p = 0.009$) and when patients had COPD associated NCFB (HR = 2.12; $p = 0.038$). The majority of the 50 deaths were respiratory related ($n = 29$; 58%).

☆Prior abstract presentation: Data were presented in an oral presentation at the American Thoracic Society congress 2013 Philadelphia.

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Conclusion: NCFB patients with associated COPD disease had the highest mortality rates compared to the other NCFB patients. Additional risk factors for lower survival were increasing age and number of lobes affected.

Background

Bronchiectasis is defined as permanently dilated airways due to chronic bronchial inflammation caused by inappropriate clearance of various microorganisms and recurrent or chronic infection [1]. With the exception of cystic fibrosis (CF), there is a lack of research into bronchiectasis. Recently, De Soyza et al. proposed several research priorities in non-cystic fibrosis bronchiectasis (NCFB). They state that from an epidemiological point of view, more prospective data are needed on mortality and associated morbidity [2].

Several retrospective analyses have already been performed. In England and Wales, just under 1000 people die from bronchiectasis with the number increasing 3% per year [3]. In a hospital setting, mainly older age (>65 years), male gender, smoking history, mechanical ventilation, socioeconomic status (SES) and lower lung function show higher mortality [4—7]. In a cross-sectional retrospective analysis of patients known with a radiological diagnosis of bronchiectasis (including asymptomatic interstitial lung disease and thoracic tumor patients), we previously showed a 41-month death rate of 10.6% [8]. These data are in line with the long term prospective analysis by Loebinger et al. They found that over a 13-year period, 29.7% of the 91 patients died, and male gender, older age, lung function and *Pseudomonas aeruginosa* (PA) were correlated with higher mortality [9]. Another prospective analysis from Turkey showed an even poorer outcome with 4-year survival of only 58%. They suggest that the presence of hypoxemia, hypercapnia, dyspnea levels and radiographic extent lead to higher mortality [10].

Our primary aim was to analyze the overall mortality for all newly diagnosed patients from June 2006 onwards. We assessed the known risk factors such as age, gender, smoking history, number of lobes affected, type of bronchiectasis and PA and evaluated the impact on mortality of etiology, number of different bacteriological species in retrospective and prospective sputa, azithromycin and other long-term antibiotic use and presence/development of pulmonary hypertension (PH).

Materials and methods

Patient selection

Patients who had a new diagnosis of bronchiectasis between June 2006 and October 2012 at the University Hospital of Leuven, Belgium, were included in the analysis. Death was analyzed until end of November 2013. Patients with clinically significant and radiologically proven bronchiectasis were included in the analysis.

Bronchiectasis diagnosis

All patients had a chest high resolution computed tomography (HRCT) scan confirming the presence of bronchiectatic lesions and had symptoms of chronic productive cough. HRCT scans were evaluated by two experienced independent radiologists. Images obtained using 1 mm collimation at full inspiration were reviewed and bronchiectasis was deemed to be present if there was one or more of the following criteria: a bronchoarterial ratio greater than 1, lack of tapering of the bronchi and visualization of bronchi within 1 cm of costal or paravertebral pleura or abutting the mediastinal pleura [11]. Exclusion criteria were patients with a diagnosis of CF (CF transmembrane regulator sequences present on genotyping), an underlying tumoral problem causing the bronchiectatic lesions (post-radiation, secondary immunodeficiency due to chemotherapy or postinfectious due to tumoral obstruction) and patients with traction bronchiectasis caused by interstitial lung disease or sarcoidosis. Each patient with a diagnosis of NCFB was further evaluated for an underlying cause with serum protein electrophoresis, immunoglobulines (IgA, IgE, IgM, IgG, $IgG_{1\text{-}3}$), specific IgE to *Aspergillus fumigatus*, specific IgG to *A. fumigatus*, nasal NO measurement, sputum microbiology and ororhinolaryngological evaluation. Spirometry and plethysmography were performed to evaluate impact on lung function. Additional investigations were guided by clinical indication. Postinfectious NCFB was defined as NCFB where there is a clear medical history of a respiratory infection with a distinct isolated pathogen that meant the start of the chronic respiratory complaints or (when no such pathogen could be isolated), a history of recurrent childhood respiratory infections that meant the start of the chronic respiratory complaints. If patients with a primary diagnosis of idiopathic NCFB also had concomitant COPD, they were categorized in the COPD associated NCFB group. COPD was defined using the definition suggested by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). More precisely, patients needed to have symptoms of shortness of breath, chronic cough or sputum production, and a history of exposure to smoke. Patients also needed persistent airflow limitation defined as the presence of a post-bronchodilator FEV_1/FVC ratio lower than 0.7 (www.goldcopd.org). The initial diagnosis of COPD was made by the general practitioner, the referring respiratory physician or by the outpatient clinic of COPD at the University Hospital of Leuven.

Data collection

The following patient data were collected at inclusion: age, gender, smoking habits (four categories: active, former, passive or never smoker), PA infection status according to the criteria defined by Lee et al. [12], total number of