ORIGINAL ARTICLE

Patients hospitalized with an infective exacerbation of bronchiectasis unrelated to cystic fibrosis: Clinical, physiological and sputum characteristics

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ABSTRACT

Background and objective: Bronchiectasis is a growing health burden both globally and in Australasia. Associated with repeated respiratory infections, the disease often results in hospital admission, impaired quality of life, reduced lung function and shortened life expectancy. We describe the local clinical, physiological and sputum characteristics in patients hospitalized with an infective exacerbation of bronchiectasis.

Methods: This study examined the medical records of all 61 adults admitted to a metropolitan Australian hospital with an infective exacerbation of bronchiectasis in a calendar year.

Results: Baseline characteristics include: mean (SD) age of participants was 66 (14) years; 56% were women and 42% were current or ex-smokers. The majority had other coexisting medical conditions, with asthma in 44%, COPD in 59% and both asthma and COPD in 31%. Seventy-two percent were on regular inhaled medication, 23% on cyclical antibiotics and 26% undertook regular respiratory physiotherapy. Bronchodilator reversibility was present in 17% and small airway reversibility in 41%. Sputum demonstrated normal flora in 17%, Pseudomonas aeruginosa in 32%, Haemophilus influenzae in 15% and both organisms in 17%. Mean numbers of exacerbations per year requiring hospitalization was 2.3. Sixty-two percent of subjects had an Index of Relative Socio-Economic Disadvantage in deciles 1–5. Risk factors for exacerbations included a history of asthma or COPD, documented small airway reversibility and presence of P. aeruginosa.

Conclusion: Patients hospitalized with an infective exacerbation of bronchiectasis are predominantly older with co-morbidities and of lower socio-economic status. Presence of P. aeruginosa was a risk factor for repeated exacerbations, as was a history of asthma, COPD or small airway reversibility.

SUMMARY AT A GLANCE

In addition to pathogenic microorganisms, especially Pseudomonas aeruginosa, frequent exacerbations requiring hospitalization in bronchiectasis are associated with co-morbidities of asthma and COPD, and bronchodilator reversibility. Patients are often from lower socio-economic backgrounds.

Key words: asthma, bronchiectasis, exacerbation, Pseudomonas, socio-economic.

INTRODUCTION

Bronchiectasis is a significant and growing health burden, both globally and in Australasia. The clinical course of cystic fibrosis (CF) bronchiectasis has been widely studied. However, less is known regarding non-CF bronchiectasis. Clinically characterized by symptoms of productive cough and recurrent chest infections, and pathologically and radiologically by inflamed and dilated airways,1 bronchiectasis often results in prolonged hospital admissions, frequent antibiotic treatment, impaired quality of life and reduced lung function.2 Repeated exacerbations, specifically three or more in 1 year, are associated with higher mortality the following year.3 Populations identified as being at greatest risk of developing bronchiectasis include: indigenous groups, socio-economically deprived persons, individuals...
suffering with co-morbidities and individuals with moderate (50% < forced expiratory volume in 1 s \( FEV_1 \) < 70%) or severe \( FEV_1 < 50% \) COPD. These patients often have increased rates of bronchial infections and increased mortality. Reduced lung function alone, independent of smoking history, has also been associated with increased mortality in bronchiectasis.

It is well documented in the literature that COPD-related bronchiectasis is associated with more severe disease as is rheumatoid arthritis-related disease. More recently, the existence of asthma has been associated with an independent increase in risk of bronchiectasis exacerbations.

Characteristics of sputum colonization and chronic infection in bronchiectasis exacerbations are a growing area of interest. The two most common pathogens isolated are \( \text{Pseudomonas aeruginosa} \) and \( \text{Haemophilus influenzae} \). Chronic infection with \( P. \text{aeruginosa} \) is associated with a threefold increased risk of death, a higher rate of hospital admission, greater exacerbations and lower \( FEV_1 \), compared with \( H. \text{influenzae} \).

Since the widespread use of computed tomography (CT) in the identification and diagnosis of bronchiectasis, there has been increasing global interest in phenotyping patients with bronchiectasis. The aim of this study was to describe the clinical, physiological and sputum characteristics in an Australian group of patients hospitalized to a metropolitan healthcare provider with an infective exacerbation of bronchiectasis. Western Health (WH) serves over 800 000 people in the Western suburbs of Melbourne. The community served by WH draws from diverse cultural and linguistic backgrounds and socio-economic disadvantage exists in a great part of the region.

**METHODS**

**Subjects**

The medical records of all adult patients \( n = 65 \) with an acute exacerbation of bronchiectasis admitted in a calendar year were examined. All the electronic hospital notes with a clinical coding for bronchiectasis and a positive CT diagnosis of bronchiectasis were included \( n = 61 \).

**Data collection**

Patient information was retrospectively gathered from both electronic and written inpatient and outpatient notes, laboratory results, discharge summaries, radiological images and reports. Bronchiectasis was diagnosed according to standard guidelines, namely the presence of symptoms and a positive CT chest scan. An exacerbation was defined as admission to hospital, and an increase in one or more of the following: cough, sputum, dyspnoea and/or wheeze. Exacerbations managed in the community were not included. Respiratory symptoms including haemoptysis and associated co-morbidities were documented directly from the patient records. Asthma was documented from patient history, and COPD was documented from patient history with spirometry evidence of persistent airflow limitation.

Examination findings and laboratory tests were recorded. In particular, this included routine sputum microscopy, culture and sensitivity (MCS) and lung function tests, namely \( FEV_1 \), forced expiratory flow at 25–75% \( \text{FEF}_{25-75} \) of forced vital capacity reflecting small and medium airway function and response to bronchodilator undertaken during a period of patient stability prior to exacerbation. The presence of bronchodilator reversibility was defined by the American Thoracic Society (ATS) criteria as a ≥12% and 200 mL improvement in post-bronchodilator \( FEV_1 \) from baseline spirometry. Small and medium airway \( \text{FEF}_{25-75} \) reversibility was documented using the above-described criteria. Bronchiectasis severity using a validated composite multidimensional score, the FACED \( (FEV_1, \text{Age, Chronic colonization, Extension, Dyspnoea}) \) score, a predictor of mortality, was calculated. Inpatient treatment and outpatient treatment were recorded. The number of exacerbations in one calendar year was calculated.

The study received approval from the regional Ethics Committee and was conducted in accordance with The Australian Code for Responsible Conduct of Research 2007 and The National Statement on Ethical Conduct in Human Research 2007.

**Statistical analysis**

Descriptive statistics were used to summarize the clinical characteristics of participants. Normality of the outcome data was tested. Data were recorded as count (percentage). Correlations were calculated with a Pearson or a Spearman correlation coefficient depending on normality of data. Generalized linear model analyses were used to determine the variables independently associated with an exacerbation, namely history of asthma, history of COPD, presence of \( P. \text{aeruginosa} \), \( FEV_1 \) and \( \text{FEF}_{25-75} \) reversibility: A Poisson regression model analysis was undertaken for exacerbation frequency, and binary logistic regression analysis was undertaken for two or more exacerbations as the dependent variable. Significance was noted at \( P \leq 0.05 \). Data analysis was performed using SPSS version 22 statistical software (IBM, USA).

**RESULTS**

Clinical coding identified 65 patients with a diagnosis of bronchiectasis, of which four were excluded with negative (normal) CT results. Sixty-one sets of patient notes were examined and totalled 87 admissions. Baseline patient characteristics are described in Table 1. Mean (SD) age of participants was 66 (14) years and included...
of 16 (18) %. Bronchiectasis severity classification using the FACED score was available in 33 of 61 patients; 88% were categorized with moderate or severe disease.

Sputum microbiological characteristics
Study findings are described in Table 3. Normal flora was present in 17% of cases, *P. aeruginosa* in 32%, *H. influenzae* in 15% and both organisms in 17%.

Exacerbations
Mean (SD) exacerbation rate was 2.3 (1.9) per year with 15% having no previous exacerbation and 12% with five or more exacerbations in the previous year. Sixty-six percent (n = 40) of patients had one or more exacerbations in one year. Of all *P. aeruginosa* exacerbations, 5% were antibiotic resistant, defined by routine culture and sensitivity as part of MCS. [Corrections added on 1 March 2017, after first online publication: ‘two or more exacerbations in one calendar year’ has been amended to ‘one or more exacerbations in one year’.]

Socio-economic decile
The majority of patients (62%) had an IRSD recorded in the lowest 5 deciles with 22% of individuals amongst the most disadvantaged (decile 1). Of those that grew *P. aeruginosa*, 69% of subjects had an IRSD recorded in the lowest 5 deciles. Individuals from lower socio-economic areas experienced increased rates of exacerbation: 76% of those who experienced three or more exacerbations in 1 year were recorded in the lowest 5 IRSD deciles, with 17% from decile 1.

Correlations with exacerbation frequency
Significant correlations were noted with: age (correlation coefficient (r) = 0.29, P = 0.03); symptoms of sputum production (r = 0.34, P = 0.02); history of asthma (r = 0.31, P = 0.02) and history of COPD (r = 0.39, P = 0.003); FEV$_1$ = –0.42, P = 0.05; P = 0.04); FEF$_{25-75}$ reversibility (r = 0.48, P = 0.01); the presence of organisms in sputum (r = 0.3, P = 0.04) and the presence of *P. aeruginosa* in sputum (r = 0.56, P = 0.001).

Predictors of exacerbation frequency and two or more exacerbations
Significant predictors of exacerbation frequency included: asthma (regression coefficient β = 1.6, P = 0.04); COPD (β = 2.0, P = 0.03); *P. aeruginosa* (β = 2.86, P = 0.02); FEV$_1$ = 0.57, P = 0.03 and FEF$_{25-75}$ reversibility (β = 0.97, P = 0.01). A significant risk association was noted with two or more exacerbations and FEF$_{25-75}$ bronchodilator reversibility (β = 0.46, P = 0.013) but not with FEV$_1$ reversibility.

DISCUSSION
Adult patients hospitalized with an infective exacerbation of bronchiectasis in our series were predominantly older, with co-morbidities and of lower socio-economic status with antibiotic-responsive *P. aeruginosa*. These
frequent exacerbations compared with bronchiectasis alone.20 Mao et al. found that patients with both bronchiectasis and asthma had 2.6 times increased risk of experiencing an exacerbation than those without associated asthma.10 Thirty-one percent of patients with bronchiectasis had a history of both asthma and COPD. Recent literature has reported increased prevalence of bronchiectasis in patients with asthma and COPD overlap syndrome (ACOS), compared with asthma or COPD alone.22 The effect of coexisting ACOS and bronchiectasis in terms of disease progression and exacerbation frequency is unknown and requires further investigation. Small airway inflammation and reactivity is of increasing importance in bronchiectasis.28 Studies are demonstrating that measures of small airway function such as forced mid-expiratory flow (FEF25–75) may reflect mucus plugging and sputum clearance,29 and improvements in FEF25–75 have been noted with mucolytic treatment in COPD.30 A significant association was noted between FEF25–75 reversibility and exacerbation frequency with each 0.46 change in FEF25–75 reversibility associated with an increased risk of two or more exacerbations. The definition of significant reversibility for this measurement remains broad, under-researched and debatable, often ranging from 20% to 40%.31 In this study we chose a priori to standardize the definition used to determine significant reversibility for both large and small airway functions.20 While the results need to be interpreted with caution given the known variability of FEF25–75, this associative signal warrants further research with larger patient numbers and prospective trials given the rapidly growing body of evidence within the literature.29

Older age, sputum production, the presence of poorer lung function (measured by FEV1) and the presence of *P. aeruginosa* in sputum are factors known to be associated with exacerbations and this was confirmed.23 This study reports greater rates of readmission than others recently published. Roberts et al. reported a 46% readmission rate within a 12-month period.4 The authors found significant associations between ethnic origin and deprivation score.4 Similarly, the current study found that over 60% of patients admitted for an infective exacerbation were deemed the lowest five deciles in terms of disadvantage. Given a large percentage of our subjects were from low socio-economic deciles, we were unable to determine further significance between *P. aeruginosa* culture and socio-economic status. Only 26% of patients were undergoing regular physiotherapy, a surprising finding given current guidelines for the treatment of non-CF bronchiectasis recommend routine respiratory physiotherapy.1 A recent meta-analysis found patients undergoing regular exercise training had fewer exacerbations over 12 months.31 Patients undergoing a supervised outpatient exercise or pulmonary rehabilitation programme experienced short-term improvements in exercise capacity and health-related quality of life.31 Research examining the clinical benefit of airway clearance techniques in bronchiectasis is sparse.32 Adherence to respiratory physiotherapy with airway clearance techniques is low in bronchiectasis. McCullough et al. demonstrated in a randomized controlled trial prospective 1-year study that only 41% of

### Table 3 Baseline microbiological sputum characteristics

| Sputum culture          | Percentage, % | n, % | Exacerbations |
|-------------------------|---------------|-----|---------------|
| No culture              | 17            | 17  |               |
| *P. aeruginosa*         | 32            | 57  | 52.7%         |
| *H. influenzae* total   | 15            | 24  | 22.2%         |
| *H. influenzae* in isolation | 4       |     |               |
| *P. aeruginosa* and *H. influenzae* | 17 | 14 |               |
| Aspergillus             | 6             |     |               |
| Viral Influenza Type A  | 3             |     |               |
| S. aureus               | 3             |     |               |
| Others (MRSA, Legionella, Mycobacterium, Candida, Nocardia, Klebsiella, Achromobacter and *M. catarrhalis)* | <3 |     |               |

*H. influenzae, *Haemophilus influenzae*; *M. catarrhalis, Moraxella catarrhalis; MRSA, methicillin-resistant *S. aureus; n, number; *P. aeruginosa, *Pseudomonas aeruginosa; *S. aureus, Staphylococcus aureus.*

characteristics are similar to those observed in clinically stable patients with bronchiectasis.25

In the current study, cultured *P. aeruginosa* of 32% of the population was responsive to antibiotics, whereas in 5% cultured *P. aeruginosa* was antibiotic resistant. Similar to other studies,24 *P. aeruginosa* culture was associated with increased exacerbation frequency while *H. influenzae* was associated with lower exacerbation frequency.15 Exacerbation frequency was 3.5 times greater with the presence of both *H. influenzae* and *P. aeruginosa* isolated together (Table 3), compared with *H. influenzae* alone, which is a novel finding according to our knowledge. Less frequent isolates included *Aspergillus*, *Mycobacterium*, *Legionella*, *Achromobacter* and viral *Influenza A*. Gao et al. found that the prevalence of viral infections, namely *Rhinovirus, Coronavirus* and *Influenza*, detected by PCR was higher in individuals with bronchiectasis during exacerbations than with clinical stability.25 The presence of any substantial bacterial or viral population in the bronchial tree is of clinical concern; however, given the small number of isolates other than *P. aeruginosa* or *H. influenzae*, further analysis regarding the influence of the microbiota and targeted antibiotic use is beyond the scope of this study.

Coexisting COPD and bronchiectasis are associated with poorer outcomes and this is well established.6,7 Approximately half of exacerbations occurred in patients with both COPD and bronchiectasis, 44% occurred in patients with a history of asthma; of which 19% had evidence of airway reactivity on lung function tests. Patients with a history of asthma had 1.6 times increased risk of experiencing an exacerbation compared with those individuals without a history of asthma. Recent literature suggests that asthma coexisting with bronchiectasis is associated with more

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participants with bronchiectasis maintained regular airway clearance techniques at the end of 1 year. Regulation of airway clearance was however associated with improvement within the treatment burden and respiratory symptom domains of the Quality of Life Bronchiectasis Questionnaire. Thus, lower rates of adherence are not unexpected in a ‘real life’ study such as this. Furthermore, the association between socio-economic status, education, access and adherence to regular physiotherapy and subsequent exacerbations were not determined.

Limitations of this study include the retrospective design and the small sample size as well as the accuracy of the diagnoses of asthma and COPD obtained during the admission. Asthma is normally defined by the presence of episodic symptoms such as breathlessness, wheeze, cough and chest tightness, with supportive evidence of reversibility either by spirometry or test of airway hyper-responsiveness. While asthma was defined historically for this study, the same spirometric criteria were applied. Similarly, COPD was defined on patient history with evidence of persistent airflow limitation on spirometry. Nine patients with COPD were classified as non-smokers. These patients were included in the analysis, as while smoking remains the predominant cause of COPD, exposure to other environmental pollutants including passive smoke and genetic causes such as alpha 1 antitrypsin deficiency could not be excluded. Furthermore, variable smoking histories where non-smoker indicated current status rather than never-smoker status combined with the lack of pack-year data in a significant proportion of patients reflects the limitations of patient admission records; yet, they provide a snapshot of our hospitalised patients.

This study characterizes patients admitted to hospital with an infective exacerbation of bronchiectasis. It confirms that lower socio-economic status, the co-morbidities of asthma and COPD and the growth of potential pathogenic microorganisms (PPMs) in sputum are associated with increased rates of exacerbation. It confirms that the burden of care with bronchiectasis is high in the Australian setting with 66% of subjects in the current study readmitted with at least one further exacerbation within a 12-month period. Management should target socio-economic factors, optimization of coexisting morbidities, as well as eradication of PPM with sputum clearance techniques, respiratory physiotherapy and appropriate antibiotic therapy.

Disclosure Statement

This research study was previously presented at the European Respiratory Society Congress in 2016.

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