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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.

Abbreviations: ACOS, asthma and COPD overlap syndrome; ATS, American Thoracic Society; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FACED, FEV_1, Age, Chronic colonization, Extension, Dyspnoea; $FEF_{25–75}$, forced expiratory flow at 25–75%; FEV_1, forced expiratory volume in 1 s; IRSD, Index of Relative Socio-Economic Disadvantage; MCS, microscopy, culture and sensitivity; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; PPM, potentially pathogenic microorganism; SEIFA, Socio-Economic Indexes for Area; WH, Western Health.

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

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suffering with co-morbidities[4] and individuals with moderate (50% < forced expiratory volume in 1 s (FEV_1) < 70%) or severe (FEV_1 < 50%) COPD.[5] These patients often have increased rates of bronchial infections[5,6] and increased mortality.[5,7] Reduced lung function alone, independent of smoking history, has also been associated with increased mortality in bronchiectasis.[3]

It is well documented in the literature that COPD-related bronchiectasis is associated with more severe disease[7,8] as is rheumatoid arthritis-related disease.[8,9] More recently, the existence of asthma has been associated with an independent increase in risk of bronchiectasis exacerbations.[9,10]

Characteristics of sputum colonization and chronic infection in bronchiectasis exacerbations are a growing area of interest. The two most common pathogens isolated are *Pseudomonas aeruginosa* and *Haemophilus influenzae*.[11,12] Chronic infection with *P. 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. influenzae*.[12,13]

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.[14–18] 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.[1]

Patient demographics were collected, including postcode to assess socioeconomic status with the Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD). The IRSD categorizes socio-economic status based on postcode (using deciles 1–10), where the lowest decile represents the most disadvantaged and the higher decile represents the least disadvantaged.

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.[19]

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% ($FEF_{25–75}$) 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.[20,21] Small and medium airway ($FEF_{25–75}$) reversibility was documented using the above-described criteria. Bronchiectasis severity using a validated composite multidimensional score, the FACED (FEV_1, Age, Chronic colonization, Extension, Dyspnoea) score, a predictor of mortality, was calculated.[22] 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. aeruginosa*, FEV_1 and $FEF_{25–75}$ 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

Table 1 Baseline characteristics of study subjects

Characteristics	Value
Age (years), mean (SD)	66 (14)
Female (%)	56
FEV_1 mean (SD)	
Litres	1.36 (0.68)
% Predicted	54 (24)
Bronchodilator reversibility (%)	17
Non-smoker (%)	58
Current/ex-smoker (%)	42
Combination inhalers (%)	72
Long-term oxygen (%)	14
Cyclical antibiotics (%)	23
Regular physiotherapy (%)	26
Mucolytics (%)	6
IRSD <1–5 decile (%)	62
FACED *n* = 33	Mild 12.1% Moderate 21.2% Severe 66.7%

n=61

Values are means (SD) or percentages (absolute numbers) based on imputed data (FACED score).[22]

FACED, FEV_1, Age, Chronic colonization, Extension, Dyspnoea; FEV_1, forced expiratory volume in 1 s; IRSD, Index of Relative Socio-Economic Disadvantage; SD, standard deviation. [Corrections added on 1 March 2017, after first online publication: three types of exacerbation outcomes in Table 1 were removed as requested by the authors.]

56% female subjects, 58% non-smokers and 42% current and ex-smokers. Pack-years were available for 53% of previous and current smokers; the mean (SD) pack-year history was 9 (14). Coexisting medical conditions are described in Table 2; history of asthma was noted in 44% and COPD in 59%. Seventy-two percent of patients were on regular inhalers, 23% on cyclical antibiotics and 26% undertook regular respiratory physiotherapy.

Moderate airflow obstruction was noted on lung function tests with a mean of FEV_1 of 1.38 L (1.22), 55% predicted. Bronchodilator reversibility of large airways (FEV_1) was present in 17% of subjects with recorded spirometry (n = 43). A positive mannitol test of airway hyper-responsiveness was present in one patient without bronchodilator reversibility. Thus, 19% of patients (8 out of 43) had supportive spirometry evidence of asthma. Medium to small airway reversibility was documented in 41% with a mean (SD) reversibility 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.

Table 2 Coexisting medical co-morbidities of the study subjects

Coexisting diagnoses	Co-morbidity of bronchiectasis (%)
Asthma	44 (*n* = 27)
COPD	59 (*n* = 36)
Asthma + COPD	31 (*n* = 19)
Reflux	36 (*n* = 22)
Rhinosinusitis	8 (*n* = 5)
Hypertension	45 (*n* = 28)
Heart failure	31 (*n* = 19)

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

Table 3 Baseline microbiological sputum characteristics

Sputum culture	Percentage, %	*n*, % exacerbations
No culture	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.[23]

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.[12] 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 stablility.[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.[5,7] 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 frequent exacerbations compared with bronchiectasis alone.[26] 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.[27] 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 ($FEF_{25–75}$) may reflect mucus plugging and sputum clearance,[29] and improvements in $FEF_{25–75}$ have been noted with mucolytic treatment in COPD.[30] A significant association was noted between $FEF_{25–75}$ reversibility and exacerbation frequency with each 0.46 change in $FEF_{25–75}$ 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%.[21] In this study we chose a priori to standardize the definition used to determine significant reversibility for both large and small airway functions.[20,21] While the results need to be interpreted with caution given the known variability of $FEF_{25–75}$, 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 FEV_1) 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

participants with bronchiectasis maintained regular airway clearance techniques at the end of 1 year.[33] Regular airway clearance was however associated with improvement within the treatment burden and respiratory symptom domains of the Quality of Life Bronchiectasis Questionnaire.[33] 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.[34] 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.[19] 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-smoked' status combined with the lack of pack-year data in a significant proportion of patients reflect the limitations of patient admission records; yet, they provide a snapshot of our hospitalized 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.

REFERENCES

1 Chang AB, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, Holland AE, O'Mara P, Grimwood K. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Med. J. Aust.* 2015; **202**: 21–3.

2 Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; (65 Suppl. 1): i1–58.

3 Lim A, Puah S, Abisheganaden J. Factors associated with mortality in hospitalised patients with bronchiectasis [abstract]. *Am. J. Respir. Crit. Care Med.* 2014; **189**: A6251.

4 Roberts ME, Lowndes L, Milne DG, Wong CA. Socioeconomic deprivation, readmissions, mortality and acute exacerbations of bronchiectasis. *Intern. Med. J.* 2012; **42**: e129–36.

5 Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, Reznek RH, Wedzicha JA. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2004; **170**: 400–7.

6 Martinez-Garcia MA, Soler-Cataluna JJ, Donat Sanz Y, Catalan Serra P, Agramunt Lerma M, Ballestin Vicente J, Perpina-Tordera M. Factors associated with bronchiectasis in patients with COPD. *Chest* 2011; **140**: 1130–7.

7 Martinez-Garcia MA, de la Rosa Carrillo D, Soler-Cataluna JJ, Donat-Sanz Y, Serra PC, Lerma MA, Ballestin J, Sanchez IV, Selma Ferrer MJ, Dalfo AR *et al.* Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2013; **187**: 823–31.

8 Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, Polverino E, Van de Kerkhove C, Rutherford R, Davison J *et al.* Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Ann. Am. Thorac. Soc.* 2015; **12**: 1764–70.

9 Gao Y, Guan W, Liu S, Wang L, Cui J, Chen R-C, Zhang G. Aetiology of bronchiectasis in adults: a systematic literature review. *Respirology* 2016; **21**: 1376–83.

10 Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. *Eur. Respir. J.* 2016; **47**: 1680–6.

11 King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Microbiologic follow-up study in adult bronchiectasis. *Respir. Med.* 2007; **101**: 1633–8.

12 Rogers GB, Zain NM, Bruce KD, Burr LD, Chen AC, Rivett DW, McGuckin MA, Serisier DJ. A novel microbiota stratification system predicts future exacerbations in bronchiectasis. *Ann. Am. Thorac. Soc.* 2014; **11**: 496–503.

13 Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. *Ann. Am. Thorac. Soc.* 2015; **12**: 1602–11.

14 Aliberti S, Lonni S, Dore S, McDonnell MJ, Goeminne PC, Dimakou K, Fardon TC, Rutherford R, Pesci A, Restrepo MI *et al.* Clinical phenotypes in adult patients with bronchiectasis. *Eur. Respir. J.* 2016; **47**: 1113–22.

15 Martinez-Garcia MA, Vendrell M, Giron R, Maiz-Carro L, de la Rosa Carrillo D, de Gracia J, Olveira C. The multiple faces of non-cystic fibrosis bronchiectasis: a cluster analysis approach. *Ann. Am. Thorac. Soc.* 2016; **13**: 1468–75.

16 Anwar GA, McDonnell MJ, Worthy SA, Bourke SC, Afolabi G, Lordan J, Corris PA, DeSoyza A, Middleton P, Ward C *et al.* Phenotyping adults with non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Respir. Med.* 2013; **107**: 1001–7.

17 Guan WJ, Jiang M, Gao YH, Chen RC, Zhong NS. In Reply: Towards precision medicine: phenotyping bronchiectasis with unsupervised learning technique. *Int. J. Tuberc. Lung Dis.* 2016; **20**: 710.

18 Smith DJ. Phenotyping bronchiectasis: is it all about sputum and infection? *Eur. Respir. J.* 2016; **47**: 1037–9.

19 Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2016. [Accessed 10 Jun 2016.] Available from URL: http://goldcopd.org/

20 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P *et al.* Standardisation of spirometry. *Eur. Respir. J.* 2005; **26**: 319–38.

21 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Griten CP, Gustafsson P, Hankinson J *et al.*

Interpretative strategies for lung function tests. *Eur. Respir. J.* 2005; **26**: 948–68.
22 Martinez-Garcia MA, de Gracia J, Vendrell Relat M, Giron RM, Maiz Carro L, de la Rosa Carrillo D, Olveira C. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur. Respir. J.* 2014; **43**: 1357–67.
23 King PT, Holdsworth SR, Freezer NJ, Villanueva E, Gallagher M, Holmes PW. Outcome in adult bronchiectasis. *COPD* 2005; **2**: 27–34.
24 Rogers GB, van der Gast CJ, Cuthbertson L, Thomson SK, Bruce KD, Martin ML, Serisier DJ. Clinical measures of disease in adult non-CF bronchiectasis correlate with airway microbiota composition. *Thorax* 2013; **68**: 731–7.
25 Gao YH, Guan WJ, Xu G, Lin ZY, Tang Y, Lin ZM, Gao Y, Li HM, Zhong NS, Zhang GJ *et al.* The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: a prospective study. *Chest* 2015; **147**: 1635–43.
26 Guan WJ, Gao YH, Xu G, Li HM, Yuan JJ, Zheng JP, Chen RC, Zhong NS. Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. *J. Thorac. Dis.* 2016; **8**: 14–23.
27 Chung WJ, Kong K, Lee JH, Lee SJ, Ryu YJ, Chang JH. Characteristics and self-rated health of overlap syndrome. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2014; **9**: 795–804.
28 Guan WJ, Yuan JJ, Gao YH, Li HM, Zheng JP, Chen RC, Zhong NS. Impulse oscillometry and spirometry small-airway parameters in mild to moderate bronchiectasis. *Respir. Care* 2016; **61**: 1513–22.
29 Guan WJ, Yuan JJ, Gao YH, Li HM, Zheng JP, Chen RC, Zhong N. Maximal mid-expiratory flow is a surrogate marker of lung clearance index for assessment of adults with bronchiectasis. *Sci. Rep.* 2016; **6**: 28467.
30 Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, Loo CK, Chan MH. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest* 2013; **144**: 106–18.
31 Lee AL, Hill CJ, McDonald CF, Holland AE. Pulmonary rehabilitation in individuals with non-cystic fibrosis bronchiectasis: a systematic review. *Arch. Phys. Med. Rehabil.* 2016. DOI: 10.1016/j.apmr.2016.05.017
32 Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. *Cochrane Database Syst. Rev.* 2015; **11**: CD008351.
33 McCullough AR, Tunney MM, Quittner AL, Elborn JS, Bradley JM, Hughes CM. Treatment adherence and health outcomes in patients with bronchiectasis. *BMC Pulm. Med.* 2014; **14**: 107.
34 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2016. [Accessed 5 Jun 2016.] Available from URL: http://www.ginasthma.org

