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Clinical Predictors of Frequent Exacerbations in Subjects with Severe Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Background—Acute exacerbations are a significant source of morbidity and mortality associated with chronic obstructive pulmonary disease. Among patients with COPD, some patients suffer an inordinate number of exacerbations while others remain relatively protected. We undertook a study to determine the clinical factors associated with "frequent exacerbator" status within a population of subjects with severe COPD.

Methods—Case-control cohort recruited from two Boston-area practices. All subjects had GOLD stage 3 or 4 (FEV_1 ≤50% predicted) COPD. "Frequent exacerbators" (n=192) had an average of ≥2 moderate-to-severe exacerbations per year while "non-exacerbators" (n=153) had no exacerbations in the preceding 12 months. Multivariate logistic regression was performed to determine the significant clinical predictors of "frequent exacerbator" status.

Results—Physician-diagnosed asthma was a significant predictor of frequent exacerbations. Within a subset of our cohort, the modified Medical Research Council dyspnea score and $FEF_{25–75}$ % predicted were also significant clinical predictors of frequent exacerbator status ($p<0.05$). Differences in exacerbation frequency were *not* found to be due to increased current tobacco use or decreased rates of maintenance medication use.

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Conclusions—Within our severe COPD cohort, a history of physician-diagnosed asthma was found to be a significant clinical predictor of frequent exacerbations. Although traditional risk factors such as decreased FEV1% predicted were not significantly associated with frequent exacerbator status, lower mid-expiratory flow rates, as assessed by FEF 25–75 % predicted, were significantly associated with frequent exacerbations in a subset of our cohort.

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disorder which is projected to become the fourth leading cause of death globally by 2030(1). Acute exacerbations are a major source of the morbidity(2,3) and mortality(4) associated with the disease and are estimated to represent 35–60% of the total direct costs associated with COPD(5–12). Clinical features which have demonstrated association with the development of acute exacerbations include lower forced expiratory volume in the first second (FEV_1) % predicted (2,13–17), increasing GOLD stage or BODE category(2,18,19), chronic cough(20) and sputum production(13), advanced age(13,16,19), and clinical depression(17,21).

The clinical observation that some patients with COPD consistently experience a higher rate of exacerbations than their peers despite having comparable reductions in FEV_1 has led researchers to postulate the existence of a distinct subgroup of "frequent exacerbators"(22–24). Several studies have demonstrated that the number of exacerbations from year to year in a single subject is highly reproducible and that a history of exacerbations predicts future exacerbations(15,23,25). Although exacerbation frequency generally increases with declining lung function, recent work suggests the "frequent exacerbator" phenotype remains a distinct subgroup in all GOLD stages(23).

Recent work has also brought attention to a subset of patients who experience remarkably few exacerbations *despite* significantly impaired lung function. This group of "non-exacerbators" is likely systematically underrepresented and understudied given their less frequent indications for medical contact and frequent exclusion from therapeutic trials(15,26). Careful characterization of both of these extreme phenotypes within a cohort of severe COPD subjects may offer additional insights into why certain patients are prone to frequent exacerbations while others remain relatively protected. We hypothesized that frequent exacerbators would have more severe airflow obstruction and a higher prevalence of respiratory symptoms including cough, phlegm, and dyspnea, than non-exacerbators.

Methods and Materials

Study Design and Patient Population

The study was designed as a cross sectional, case-control cohort. Subjects were ambulatory patients between the ages of 30–80 years old who were evaluated at two Boston-area practices, Fallon Clinic and Harvard Vanguard Medical Associates. Subjects were enrolled from December 2006 – October 2009. All subjects had ≥10 pack-year smoking history and a diagnosis of severe COPD which was defined as GOLD Stage 3 or 4: a post-bronchodilator FEV_1/FVC ratio of ≤0.7 *and* a post-bronchodilator FEV_1 of ≤50% predicted(27). Exclusion criteria included pregnancy, a history of lung cancer, tuberculosis, pulmonary fibrosis, asbestosis, organ transplantation, lung volume reduction surgery or previous lung resection. The protocol was approved by the Partners Institutional Review Board (Partners Human Research Committee, 617-424-4100) and written informed consent was obtained from all participants.

Subjects were assessed at their baseline status, defined as ≥4 weeks since their most recent lower respiratory tract infection (if any). Subjects were administered a modified version of

the standardized American Thoracic Society-Division of Lung Diseases Respiratory Epidemiology Questionnaire(28) by trained study personnel. Spirometry was performed on an Easy One™ spirometer (ndd, Inc., Andover, MA, USA) according to published guidelines(29) both before and approximately 20 minutes following the administration of inhaled short-acting bronchodilator (180 mcg albuterol by metered dose inhaler through an Aerochamber® spacer).

Variables and definitions

Acute exacerbations were defined as worsening symptoms requiring treatment with systemic steroids (oral or parenteral) or antibiotics, a visit to the emergency room, and/or admission to a hospital. Acute exacerbations in the previous 12 months were assessed by patient history. Patient reports were verified by review of their medical records within the last 24 months. All subjects were further classified as either cases or controls based upon the following criteria: "frequent exacerbators" reported an average of ≥2 exacerbations per year (either ≥2 exacerbations in the last 12 months or ≥4 exacerbations over the preceding 24 months with at least one exacerbation in the last 12 months) while "non-exacerbators" had no exacerbations over the last 12 months. All exacerbations were separated by ≥14 days (reports occurring within 14 days of each other were considered a single event).

Additional variables assessed during the study were recorded as follows. Pack-years of smoking were calculated as the average number of cigarettes per day divided by 20 and then multiplied by the number of years smoked. Chronic cough was considered present if the subject answered in the affirmative to the question: "Do you usually cough like this on most days for 3 consecutive months or more during the year?" and answered ≥2 years to the question "For how many years have you had this cough?". Chronic phlegm was considered present if the subject answered in the affirmative to the question: "Do you usually bring up phlegm like this on most days for 3 consecutive months or more during the year?" and answered ≥2 years to the question "For how many years have you had trouble with phlegm?". Chronic bronchitis was defined as the presence of both chronic cough and chronic sputum production. Exposure to a dusty job was considered present if the subject answered affirmatively to the question: "Have you ever worked for a year or more in any dusty job?". Dyspnea was assessed using the modified Medical Research Council (MMRC) questionnaire(30). Physician-diagnosed asthma (ever) was considered present if the subject responded affirmatively to the questions “Have you ever had asthma?” and “Was it confirmed by a doctor?”

A list of each subject's current medications was obtained during the study visit – these lists were reviewed and medication use in the following categories was recorded as being present or absent: short or long acting beta-agonists, short or long acting muscarinic antagonists, inhaled corticosteroids, systemic steroids, theophylline, leukotriene inhibitors, chronic home oxygen use, hydroxymethylglutaryl CoA (HMG-CoA) reductase inhibotors ("statins"), aspirin, diuretics, and additional cardiac medications (defined as anti-hypertensive or anti-arrhythmic medications).

Statistical Analysis

All analyses were performed using SAS version 9.1.3 (Carey, NC, USA) on a SUN Unix system (SunOS 5.10, Santa Clara, CA, USA). Univariate comparisons were performed using an unpaired two-tailed Student's t-test or Wilcoxon rank sum test for normal and non-normally distributed variables, respectively. Comparisons between binary and ordinal variables were performed using Fisher's exact test and the Chi-squared test for trend respectively.

Stepwise multivariable logistic regression was performed to identify the significant clinical predictors of "frequent exacerbator" status. All variables with a univariate p-value <0.3 were considered candidates in the multivariate regression; medication use variables were not included as candidates due to concern for confounding by indication. All analyses included adjustment for FEV_1% predicted. Candidate variables with a p-value ≤0.05 were considered significant and were retained in the final model. Candidate variables not retained using stepwise model-building were re-introduced singly to assess for confounding (defined a priori as ≥20% change in the effect estimate). Because a significant proportion of subjects were missing the MMRC dyspnea score(30), a separate multivariate analysis was performed on the subset of subjects with the MMRC score available utilizing the same procedure as outlined above.

Results

Descriptive statistics and univariate comparisons between frequent exacerbators and non-exacerbators are summarized in Table 1. There were no significant differences in age, sex, or pack-years smoked between frequent exacerbators and non-exacerbators. Interestingly, despite comparable mean FEV_1% predicted, frequent exacerbators had significantly lower maximal mid-expiratory flow rates as assessed by $FEF_{25–75}$ % predicted. A trend towards *increased* current smoking was observed in non-exacerbators (p=0.07). Frequent exacerbators reported more physician-diagnosed asthma and had higher MMRC scores than non-exacerbators. Although the MMRC score was not available in 22.6% of the subjects because many subjects indicated that they were disabled from walking by conditions other than heart or lung disease, the missing rate was similar between frequent exacerbators (22.9%) and non-exacerbators (22.2%).

Previous reports have noted that prior exacerbations are strongly associated with the risk of future exacerbations(20,23). Even within our frequent exacerbator group, there was evidence for an association between previous exacerbation frequency and future exacerbation risk. The correlation between the number of exacerbations in this group 0–12 months before enrollment and 12–24 months before enrollment was statistically significant (Rho = 0.24, p-value 0.0004).

The rates of medication use and exposure to environmental variables are summarized in Table 2 and Supplementary Table A respectively. Frequent exacerbators demonstrated significantly *higher* rates of long-acting bronchodilators and inhaled and systemic steroid use – this likely represents confounding by indication. There were no significant differences in the rates of non-pulmonary medication use (aspirin, diuretics, HMG-CoA reductase inhibitors, antihypertensive or anti-arrhythmic medications). Similarly, there were no significant differences in the measured environmental exposures between frequent and non-exacerbators.

In the multivariate model including all subjects, a history of physician-diagnosed asthma was a significant predictor of frequent exacerbator status (Table 3). In the subgroup with MMRC score available, MMRC score, post-bronchodilator $FEF_{25–75}$ % predicted, and physician-diagnosed asthma were significant predictors of frequent exacerbator status in the multivariate model (Table 4). There were no significant confounders in either of the final models.

Discussion

COPD exacerbations are a major cause of morbidity and mortality. Recent reports in the medical literature support the long-held clinical notion that COPD subjects vary widely in

their susceptibility towards acute exacerbations. The existence and characterization of "frequent exacerbators" and relatively resistant "non-exacerbators" in a recent large observational study has challenged the association of traditional risk factors with acute exacerbations(23). The findings from our study support the existence of these distinct COPD phenotypes and introduce new plausible risk factors.

The major finding in the recently published ECLIPSE cohort study was the description of stable sub-phenotypes relating to exacerbation susceptibility which appear to be *independent* of lung function impairment(23). Thus, although low FEV_1 has been well established as a risk factor for acute exacerbations(13,14), its utility may be limited to comparisons between COPD subjects with extremely disparate levels of FEV_1 impairment or of different GOLD stages. The disassociation of airflow obstruction with exacerbation frequency is echoed in our cohort in that no significant difference in mean FEV_1 % predicted was noted between our frequent and non-exacerbator groups. Likewise, despite inclusion in our multivariate models, FEV_1 % predicted was not found to be a significant predictor of frequent exacerbator status. Additional findings which support the concept of these sub-phenotypes as independent phenomena include the *lack* of differences in age, gender, or rates of chronic cough or sputum between frequent exacerbators and non-exacerbators. The lack of association with these traditional risk factors may be attributable to the fact our cohort has been enriched with these extreme phenotypes.

Two additional apparent paradoxes regarding the rates of current smoking and medication use in our cohort deserve discussion. First, the trend towards *increased* rates of current smoking noted in our nonexacerbator group is not an isolated event – similar observations have been described in other studies(2,13,16,23,31). We believe this reflects a "healthy smoker effect" (whereby subjects who are frequently ill are more likely to quit smoking) rather than a biologically protective effect of smoking. A similar statement can be made regarding the significantly higher rates of maintenance medication use among frequent exacerbators. The efficacy of bronchodilators and inhaled and systemic steroids in the treatment and prevention of acute exacerbations has been studied previously(32–36). Our results suggest that certain patients with COPD will continue to suffer frequent exacerbations *despite* aggressive medical maintenance therapy.

In our cohort, self-reported physician-diagnosed asthma was a significant clinical predictor of frequent exacerbator. The interpretation of this finding can be challenging. First, subjects with asthma and COPD often report a formal diagnosis of both diseases – studies have suggested an overlap rate between 15–34%(37–43). Whether this degree of overlap represents a true biological or pathophysiological entity, as outlined by the Dutch hypothesis(44), or some degree of misclassification remains unresolved. Even in studies that employ rigorous measures such as bronchodilator reversibility testing or methacholine challenge, differentiating between or establishing the co-existence of COPD and asthma remains challenging; subjects with asthma may not demonstrate complete, immediate reversibility(39,45) and a significant proportion of COPD subjects will demonstrate some degree of BDR(41,46) and a positive response to methacholine challenge(47). In our cohort, despite the high self-reported rates of physician-diagnosed asthma, the rates of bronchodilator responsiveness and asthma diagnosed before age 18 were low and did not vary by frequent / non-exacerbator status. Furthermore, although significantly more subjects in the frequent exacerbator group reported a diagnosis of asthma, a greater change from baseline FEV1 was observed in the non-exacerbator group (Supplementary Table B).

Regardless of whether true biological overlap exists, the significance of physician-diagnosed asthma as a risk factor for exacerbations is plausible. COPD subjects with a history of physician-diagnosed asthma report more respiratory symptoms(48), worse health status(42),

and are at increased risk of requiring emergency room services or hospitalization(37,38,42). In the United States, COPD subjects with a concurrent diagnosis of asthma have significantly increased respiratory related costs(37,38). Thus, the term “physician-diagnosed asthma” may capture an aspect of more symptomatic or severe disease not well quantified by lung function or other traditional risk factors.

Within the subgroup with MMRC dyspnea scores available, several additional clinical predictors of exacerbations were identified, including post-bronchodilator $FEF_{25–75}$ % predicted and the MMRC score. The modest but significant difference in $FEF_{25–75}$ % predicted between cases and controls despite a lack of difference in FEV_1 % predicted values may reflect worse obstruction at the level of the smallest airways(49), perhaps beyond some critical threshold, in frequent exacerbators. The significance of the modified MRC dyspnea scale in predicting exacerbations may be due in part to the continued reliance on the subjective report of increased shortness of breath in defining acute exacerbations – whether some subjects perceive or are more likely to report dyspnea and hence be at greater likelihood to meet criteria for an acute exacerbation is debatable. Regardless, the utility of the modified MRC score in predicting frequent exacerbator status beyond FEV_1 alone is suggested by this subgroup analysis. The generalizability of the association with the MMRC score is limited by the high rate of missingness for the variable which resulted from strict adherence to a skip pattern in the questionnaire after subjects reported a disability from walking other than heart or lung disease. Post hoc review revealed that the majority of subjects who did not have an MMRC score skipped these questionnaire items due to orthopedic complaints, with a minority of subjects opting out due to vascular or neurological problems. Although there was no difference in the rates of missingness between cases and controls, differential missingness with regards to other variables (such as current smoking) limits this analysis.

We acknowledge several limitations to this study in addition to the ones outlined above. The retrospective and cross sectional nature of the cohort, as well as the reliance upon patient reported exacerbations, predisposes our study to recall bias and resultant misclassification bias with regards to case/control status. The review of medical records for the majority of the subjects to verify reported exacerbations is an advantage of our study design – correlation rates between subject reported exacerbations and the medical record review were high (Rho=0.7, p-value <0.0001). Though the requirement for severe airflow obstruction adds to the uniqueness of our cohort, it also limits the generalizability of our findings. In addition, while we did not directly assess for potentially confounding co-morbid conditions such as heart failure, the non-differential rates of use of cardiac medications such as diuretics, antihypertensive and antiarrhythmic medications argues against differential rates between frequent and non-exacerbators. Lastly, the modest size of our cohort may limit detection of clinical variables with less profound effect sizes (i.e. subject us to false negatives).

Despite these limitations, our study suggests that physician-diagnosed asthma is a significant clinical predictor of frequent exacerbator status in our cohort. Significant differences in FEV1 % predicted, suboptimal medical management, and increased rates of current tobacco use were *not* the primary causes of frequent exacerbations in our severe COPD subjects. Additional anatomical, environmental, or genetic factors may account for differences in exacerbation frequency phenotypes. Future studies should investigate the role of inflammatory markers and genetic polymorphisms on the risk of frequent exacerbations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of study subjects

	Frequent exacerbators	Non-exacerbators	p-value
Total Number of Subjects	192	153	--
Age	68 (8.4)	69.3 (8.1)	0.14
Male (%)	43.2	49.7	0.28
Non-white race (%)	5.7	3.3	0.31
Did not complete high school (%)	21.9	17.7	0.35
BMI	28.3 (6.4)	28.8 (7.1)	0.48
Pack-years	60.8 (32.6)	64.0 (36)	0.55
Current smoker	18.9	27.5	0.07
Chronic cough	50.0	43.1	0.23
Chronic sputum	47.9	50.3	0.67
FEV_1 % predicted*	34.7 (8.8)	35.9 (8.6)	0.20
FVC % predicted*	63.9 (15.8)	64.4 (14.7)	0.78
FEV/FVC ratio*	0.42 (0.11)	0.43 (0.11)	0.47
$FEF_{25–75}$ % predicted*	15.1 (6.5)	16.1 (6.1)	0.05
MMRC†§	2.6 (0.8)	2.3 (1.1)	0.02
Physician diagnosed asthma (ever)	36.5	25.5	0.04

Data are presented as percent or mean (SD).

*Lung function variables reported are post-bronchodilator values.

§Modified Medical Research Council Dyspnea scale (0–4, 4 representing severe shortness of breath).

†22.6% subjects did not have MRC score available.

Table 2

Medication use

	Frequent	Non-exacerbators	p-value
Inhaled corticosteroids (ICS)	83.4	54.7	<0.0001
Short acting beta agonists (SABA)	89.3	79.3	0.0100
Short acting muscarinic antagonists (SAMA)	47.1	36.7	0.06
Long acting beta agonists (LABA)	58.8	38.7	0.0003
Long acting muscarinic antagonists (LAMA)	43.9	29.3	0.0067
Leukotriene inhibitor	8.6	1.3	0.0029
Theophylline	3.7	1.3	0.31
Home oxygen use (current)	5.9	2.0	0.10
Chronic oral steroids	18.8	3.92	<0.0001
HMG-COA Reductase Inhibitor ("statin")	41.7	41.3	1.0
Diuretic	41.2	37.3	0.50
Aspirin	34.2	39.3	0.36
Anti-hypertensive or anti-arrhythmic medications	57.2	58.7	0.82

Data are presented as percent.

Table 3

Multivariate model for frequent exacerbator status

Variable	Unadjusted OR [95%CI]	p-value	Adjusted OR [95% CI]	p-value
Physician diagnosed asthma	1.68 [1.05–2.68]	0.03	1.76 [1.09–2.83]	0.02
FEV_1 % predicted*†	0.85 [0.67–1.09]	0.20	0.82 [0.64–1.06]	0.13

*Post bronchodilator value.

†Data are reported as per 10% change in predicted value. Non-significant variables tested but not retained in final model include post-bronchodilator FEF 25–75 % predicted, age, wheezing, history of hypertension, maternal history of COPD, and sex. FEV_1 % predicted was force included into the model.

Table 4

Multivariate model for frequent exacerbations in subgroup with MMRC score

Variable	Unadjusted OR [95%CI]	p-value	Adjusted OR [95% CI]	p-value
FEF_{25-75} % predicted*†	0.6 [0.39–0.91]	0.02	0.53 [0.28–0.98]	0.04
MMRC score	1.46 [1.13–1.89]	0.004	1.50 [1.15–1.97]	0.003
Physician diagnosed asthma	1.61 [0.94–2,74]	0.08	2.05 [1.16–3.64]	0.01
FEV1 % predicted*†	0.77 [0.58–1.03]	0.08	1.08 [0.71–1.64]	0.71

MMRC = modified Medical Research Council. n = 267 (148 frequent/119 non-exacerbators).

*Post bronchodilator values,

†data are reported as per 10% change in predicted value. Non-significant variables tested but not retained in the final model include current smoking, age, wheezing, chronic cough, history of hypertension, maternal history of COPD, and sex. FEV1 % predicted was force included into the model.