Airway Bacterial Colonization in COPD under the Therapy of Inhaled Corticosteroid/long-acting β2 Agonist- the Relationship with COPD Assessment Test

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Abstract

Airway bacterial colonization is often seen as a surrogate of acute exacerbation of chronic obstructive pulmonary disease (COPD). The COPD assessment test (CAT) can assess the disease status and exacerbation. The relationship between airway bacterial colonization and disease status evaluated by the CAT in moderate to severe COPD under the treatment of inhaled corticosteroid (ICS) and long-acting β2 agonist (LABA) is unclear. The study was conducted from February 2011 to April 2012. Moderate to severe COPD patients with ICS and LABA combination therapy were included in this study. All participants produced sputum for bacterial cultures after sputum induction and underwent CAT and spirometry at the start of the study and every three months until the end of the study period. Seventeen participants made a total of 37 visits. Thirty-five percent of the sputum cultures yielded potentially pathogenic microorganisms (PPM), implying positive cultures. The most common pathogens were *Haemophilus* species. Forty-four percent of the visits with a CAT score of more than 20 had positive cultures, whereas 25% of the visits with a CAT score of 20 or less had positive cultures. Sixty percent of the follow-ups with an increment of more than two from the baseline CAT score had positive cultures, whereas only 30% of the follow-ups with an increment of two units or less had positive cultures. Subjects with baseline CAT scores of more than 20 or a two unit increment from baseline score might have a higher risk of PPM colonization. (J Intern Med Taiwan 2013; 24: 487-494)

Key Word: Pulmonary disease, Chronic obstructive; Bacteria; Disease exacerbation pneumonia

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and significant extrapulmonary comorbidities, resulting from inflammatory reaction of the lung to noxious stimuli. Traditionally, the severity of COPD is classified by spirometry; however discrepancies between spirometry data and the clinical severity of COPD can arise. In clinical practice, it is vital to obtain reliable and valid information on the severity of COPD. Investigations have demonstrated that the COPD assessment test (CAT) is a simple and easy-to-use questionnaire that can distinguish between different degrees of COPD severity[1]. The CAT was introduced into the evaluation of COPD in the 2011 revision of

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the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[2]. Furthermore, some studies have shown that CAT scores increase during exacerbations and possibly provide an evaluation tool for exacerbation severity[3].

Patients with COPD suffer from episodes of acute exacerbations leading to additional morbidity and mortality, and also a further decline in lung function[4]. It has been well-established that bacterial colonization is prevalent in COPD, especially in moderate to severe COPD, and airway bacterial colonization is known to play an important role in the development of pneumonia and exacerbations[5]. On the other way, inhaled corticosteroid (ICS) and long acting β2 agonist (LABA) were recommended in the treatment of moderate to severe COPD[6]. Though there were some evidences that ICS had some protective effects on airway mucosa against bacteria invasion [7,8], the locally immunosuppressive effects of ICS is still a concern. Indeed, the incidence of pneumonia was higher than the control group, not only in the Towards a Revolution in COPD Health (TORCH) study but also in various studies and meta-analyses.[9-15] We hypothesized that airway bacteria colonization is associated with disease severity, and that disease status can be identified by CAT scores and changes of CAT scores. We therefore conducted this prospective, observational study in which CAT scores and sputum cultures were assessed in moderate to severe COPD patients with the combination therapy of ICS and LABA every three months during the study period. The primary end-point is the condition of potential pathogenic microorganisms (PPM) colonization in view of CAT scores. The second end-point was the changes of PPM colonization in association with CAT changes during follow-up. By the mean of CAT follow-up, it could possibly provide a surrogate about the risk of exacerbation and pneumonia under the combination therapy of ICS and LABA.

Methods

The study was conducted from February 2011 to April 2012. Patients with clinical diagnosis of COPD was screened. The spirometry within 3 months before the entry of the study was required. The inclusion criteria were as below: spirometry showed obstructive ventilatory defect (a ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of less than 0.7) and FEV_1 less than 80% of predicted value and patients receiving the combination therapy of ICS and LABA. The exclusion criteria were: (1) use of antibiotics or corticosteroids within eight weeks before study entry; (2) pneumoconiosis; (3) apparent inactive tuberculosis fibrosis or bronchiectasis (fibrosis involved in more than one third of one lung field as determined by chest radiography); and (4) asthma and atopic history.

This is a prospective, observational study. Chest plain films were interpreted by two independent physicians. If there was any question about plain films, another physician determined whether or not there was significant bronchiectasis, inactive tuberculous fibrosis or pneumoconiosis. All participants produced sputum for bacterial cultures after induction every three months. Sputum was induced by inhalation of normal saline for 15-20 minutes using an air-jet nebulizer[16]. Potential pathogenic microorganisms (PPM) are those recognized as causative pathogens of respiratory tract infections, e.g. *Haemophilus influenzae(H. influenzae)*, *Streptococcus pneumoniae* (*S. pneumoniae*), *Moraxella catarrhalis* (*M.catarrhalis*), and others. The CAT was also assessed at the same time. Sputum cultures were collected again during an admission if the admission was due to an exacerbation. Exacerbation was defined as a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids in outpatient clinics, emergency room visit or hospitalization. The ethics of the study

was approved by Institutional Review Board of Far Eastern Memorial Hospital (099850-C). All subjects signed written informed consents. The study was registered at the website of ClinicalTrials.gov (NCT: 01819298)

All data were expressed as mean ± SD (standard deviation of the mean) unless otherwise stated. Statistical analysis was performed using SPSS version 19 software (SPSS Inc., Chicago, IL, USA). The correlation of pathogenic bacteria in sputum cultures and CAT scores was calculated by Fisher extract test. A p value of less than 0.05 was considered statistically significant.

Results

Seventeen subjects were included into the study, with a total of 37 visits. Two subjects had 4 visits, two had 3 visits, ten had 2 visits and three had one visit . The characteristics of the subjects are shown in Table 1. Two subjects did not have a history of smoking, and the remaining 15 had a cigarette consumption of at least 20 pack-years. All patients had CAT scores of more than 10. Fourteen subjects received fluticasone 1000 μg / salmeterol 100 μg per day (Seretide 250 Evohaler, GlaxoSmithKline, 2 puffs twice per day). The other three patients received budesonide 640 μg / formoterol 18 μg (Symbicort Turbuhaler, AstraZeneca, 2 doses twice per day).

The results of the sputum cultures are shown in Table 2. All sputum cultures were collected in outpatient clinic setting. Two subjects had acute exacerbations during half a year after completing the follow-up. The CAT scores were between 10 to 20 in 16 visits, and more than 20 in 21 visits. PPM colonization in the sputum were found in 4 (25%) visits with CAT scores of 20 or less, and 9 (44%) visits with CAT scores of more than 20. *Haemophilus* species were the most common pathogens. The average CAT score was 24.4±7.9 in subjects with PPM colonization and 21.7±7.9 in those without

Table 1. Clinical characteristics of the subjects

Age (year)	67.2±8.6
Sex (M/F)	16/1
Current smoking (n)	5 (29.4%)
Ex-smoking (n)	10 (58.8%)
Post-BD FEV1 %	43.4 ± 18.1%
COPDAE in one year	
Yes	8
No	9
CAT	22.7±7.6
≦10	0
11-20	7
21-30	7
31-40	3
Combination therapy	
SFC (n)	14 (82.4%)
BUD + F (n)	3 (17.6%)

BD: post-bronchodilator.
FEV1%: predicted percent of forced expiratory volume in one second.
COPDAE: acute exacerbation of chronic obstructive pulmonary disease.
CAT: chronic obstructive pulmonary disease assessment test.
SFC (Seretide Evohaler 250): fluticasone 250μg / salmeterol 25μg per puff.
BUD+F (Symbicort) : budesonide 160μg / formoterol 4.5μg per dose.

Table 2. Results of sputum cultures grouped by CAT score

CAT	
≦ 20 (n=16)	
Total	4 (25%)
Haemophilus species	3 (18.8%)
Klebsiella pneumoniae	1 (6.3%)
> 20 (n=21)	
Total	9 (44.4%)
Haemophilus species n(%)	6 (28.6%)
Moraxella catarrhalis n(%)	1 (4.8%)
Pseudomonas aeruginosa n(%)	1 (4.8%)
Stenotrophonomas maltophila n(%)	1 (4.8%)

CAT: chronic obstructive pulmonary disease assessment test.

PPM colonization. Bacterial colonization was more common in patients with CAT scores of more than 20, although the difference did not reach statistical significance (p= 0.315). *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*, usually seen in nosocomial infections, were found exclusively in the patients with CAT scores of more than 20.

The nature of PPM colonization was dynamic with changes in CAT scores (Table 3). There were twenty sequential CAT score comparisons in this study period. Six (60%) of the CAT score changes (ΔCAT) with an increment of more than 2 had airway bacterial colonization. The halves of airway PPM colonization had positive sputum cultures in previous visits, and the others were negative initially converted to positive. Two patients with a ΔCAT > 2 subsequently had acute exacerbations. Three (30%) patients with a ΔCAT ≤ 2 had positive sputum cultures. There was a trend that the rate of positive sputum cultures in the patients with a ΔCAT > 2 was higher than those with ΔCAT≦ 2 (p = 0.367).

Table 3. The dynamic changes of sputum culture according to the changes of CAT score

ΔCAT (n=20)	
> 2 (n=10)	
Sputum culture negative n(%)	4 (40%)
Sputum culture positive n(%)	6 (60%)
Negative -> positive n(%)	3 (30%)
Positive -> positive n(%)	3 (30%)
≦ 2 (n=10)	
Sputum culture positive* n(%)	3 (30%)
Sputum culture negative n(%)	7 (70%)
Sputum culture positive -> negative n(%)	2 (20%)

CAT: chronic obstructive pulmonary disease assessment test.
ΔCAT: the changes of CAT.
*: all 3 were negative culture converted to positive culture.

Discussion

The results of this study suggest that PPM colonization is more prevalent in COPD patients with CAT scores of more than 20, and that PPM colonization is also more frequent in patients with ΔCAT > 2.

It is important to recognize the potential risk of exacerbations and pneumonia in COPD, especially when combination therapy is used. However, the difficulty is that the signs and symptoms of pneumonia may mimic those of exacerbation of COPD. Mackay and colleagues suggested that CAT scores provide a reliable indicator for the severity of exacerbations[3]. The mean change in CAT score from baseline to exacerbation in need of healthcare use was 5.2 units, and the mean change in CAT score from baseline to exacerbation for patients who received increased inhaled therapy alone was 2.0 units[3]. We also found that PPM colonization, especially *Haemophilus* species, was more frequent in patients with ΔCAT > 2. Two subjects with ΔCAT > 2 who had positive PPM colonization subsequently developed exacerbations. Many studies have reported a relationship between bacterial colonization and disease status[17,18]. Sethi and colleagues suggested that isolation of a new strain of *H. influenzae* was associated with a significantly increased risk of an exacerbation[19]. Bacterial load is known to correlate with airway inflammation[20], and treatment with antibiotics has been shown to reduce bacterial load in patients with COPD which may then further decrease airway inflammation[21]. Therefore, we suggest that ΔCAT > 2 be a sign of a high risk of subsequent exacerbation and PPM colonization. It may also be a warning sign of the possibility of developing pneumonia, and may suggest the initiation of antibiotic treatment.

Before the TORCH study, there were some evidences that inhaled corticosteroid (ICS) reduced lung inflammation by the observation of decreased sputum neutrophil count and the levels of cytokines[22,23]. Furthermore, the combination therapy of ICS and LABA has been shown to increase the distal ICS delivery to the alveolar bed when

compared with monotherapy, which could further propagate the anti-inflammatory effects of ICS[24]. Although there is some evidence that ICS has some protective effects on airway mucosa against bacterial invasion[7,8], the locally immunosuppressive effects of ICS are still a concern. The incidence of pneumonia was higher than the control group not only in TORCH study, but also in various studies and meta-analyses [9-15].

Pneumonia in patients with COPD is usually more severe and complicated than those without COPD[25]. However, whether or not combination therapy would have an adverse prognostic effect on the mortality rate of pneumonia is controversial. Airway bacterial colonization plays a critical role in pneumonia and exacerbations[5]. In the literature, non-typable *H. influenzae* is the most commonly isolated bacteria from airway samples in COPD[19], consistent with the results of the current study. Crim et al analyzed the data from the TORCH studies and suggested that the risk factors for pneumonia in COPD are old age, $FEV_1 < 50\%$ predicted, COPD exacerbations in the previous year, worse Medical Research Council dyspnea scores and body mass index < 25 kg.m^{-2} [12]. We substituted CAT score for Medical Research Council dyspnea score to observe the high risk of pneumonia in COPD population. Though not to achieve the statistical significance, there was a relatively higher prevalence of PPM colonization in those with a CAT score > 20 than in those with a CAT score ≤ 20. Patients with advanced COPD may be uniquely susceptible to the local immunosuppressive effects of combination therapy[15].

Exacerbations of COPD are related with bacteria, virus infection or air pollutant. The study of Bafadhel et al. showed that bacteria and virus related exacerbactions were 55% and 29% respectively[26]. The result of the current study might only represent the part of bacteria induced exacerbation. Many biomarkers are developed to differentiate from bacteria and non-bacteria related exacerbation. Among these markers, procalcitonin (PCT) is markedly elevated in patients with bacterial infections compared to those with viral infections or other inflammatory conditions[27,28]. PCT guidance for antibiotics therapy in exacerbation of COPD proposed by the study of Stolz et al, recommended antibiotics administration for PCT levels > 0.25 m g/L, They found that the principle could offer a sustained advantage over standard therapy in reducing antibiotic use for up to 6 months[29]. But PCT level was not significantly associated with sputum bacteria isolation[29]. The reason may be that the bacterial infections are occasionally too locally restricted to show a notable increase in PCT[30]. Thereafter, there was no clear-cut point of PCT to distinguish bacterial from viral and noninfectious causes of exacerbation[31].

Several studies proposed a unique phenotype of COPD combined with bronchiectasis[18,32,33]. The incidence of COPD with coexisting bronchiectasis was about a half of moderate to severe COPD[18,32,33]. These COPD patients with bronchiectasis have the characteristics of higher airway inflammatory cytokines, more frequent exacerbation, longer recovery from exacerbation and more risk of mortality[18,33]. The rate of this phenotype was higher especially in patients with more severe airflow obstruction and PPM colonization[32,34]. On the other way, PPM colonization was more frequent in COPD with bronchiectasis than COPD without bronchiectasis[18,34] The subjects in the current study belonged to moderate to severe COPD. Though apparent bronchiectasis and structural lung disease were excluded to the current study by chest plain films, plain film was not very sensitive to diagnose bronchiectasis. It is possible that subjects with identification of PPM colonization were partly the overlapping syndrome of COPD and bronchiectasis.

Some methological issues should be mentioned in this study. First, the case number was small, which

might influence the statistical power of PPM colonization between CAT scores ≤ 20 and >20. Second, we tried to analyze the relationship between CAT and PPM colonization by the visits of participants, but not by the participants. The characteristics of specific subjects possibly overweighed in the statistics while pooling the CATs and PPM colonization of visits. A large scale prospective study with uniform visits are needed in the further to clarify more clearly the relation between CAT and PPM colonization.

In conclusion, the results of this study suggested that there was a higher risk of bacterial colonization in those with moderate to severe COPD in view of the CAT scores. PPM colonization was also more frequent in those with a change in CAT of more than 2. This may indicate an increased risk of exacerbations and pneumonia, and antibiotic treatment may be necessary.

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慢性阻塞性肺病接受吸入性類固醇及長效性乙二型支氣管擴張劑治療者其慢性阻塞性肺病評估測試分數與呼吸道細菌叢生的關係

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摘 要

呼吸道細菌叢生常常與慢性阻塞性肺病急性惡化有關，而慢性阻塞性肺病評估測試(CAT)可以用來評估疾病的嚴重度及惡化的情形。但針對中重度慢性阻塞性肺病接受吸入性類固醇及長效性乙二型支氣管擴張劑的病人，慢性阻塞性肺病評估測試是否與呼吸道細菌叢生的關係仍不清楚。2011年二月至2012年四月中重度慢性阻塞性肺病接受吸入性類固醇及長效性乙二型支氣管擴張劑的病人納入這項研究。所有受試者在一開始及每三個月都會接受痰液細菌培養，慢性阻塞性肺病評估測試(CAT)及肺功能檢查直到研究結束。十七位受試者完成37次追蹤。35%的痰液培養發現可能致病菌。最常見的病原菌是嗜血桿菌。追蹤時慢性阻塞性肺病評估測試(CAT)大於20分者，44%痰液有可能致病菌；小於等於20分者，只有25%。在一系列追蹤中若慢性阻塞性肺病評估測試(CAT)增加大於兩分者，60%痰液有可能致病菌；若慢性阻塞性肺病評估測試(CAT)變化小於等於兩分者，30%痰液有可能致病菌。慢性阻塞性肺病評估測試(CAT)大於20分或者慢性阻塞性肺病評估測試(CAT)增加大於兩分，呼吸道細菌叢生機會就高。