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Exacerbations of chronic obstructive pulmonary disease and chronic mucus hypersecretion

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Abstract

Chronic obstructive pulmonary disease (COPD) exacerbations are an important cause of the considerable morbidity and mortality found in COPD. COPD exacerbations increase with increasing severity of COPD, and some patients are prone to frequent exacerbations leading to hospital admission and readmission. These frequent exacerbations may have considerable impact on quality of life and activities of daily living. Factors that increase the risk for COPD exacerbations are associated with increased airway inflammation caused by common pollutants and bacterial and/or viral infections. These inflammatory responses cause mucus hypersecretion and, thereby, airway obstruction and associated exacerbations. While chronic mucus hypersecretion is a significant risk factor for frequent and severe exacerbations, patients with chronic mucus hypersecretion have a lower rate of relapse after initial treatment for acute exacerbation. The benefit of antibiotics for treatment of COPD exacerbations is small but significant. While the mechanisms of actions are not clear, mucolytic agents reduce the number of days of disability in subjects with exacerbations. Reducing mucous cell numbers in small airways could be a useful way to reduce chronic mucus hypersecretion. Our studies suggest that programmed cell death is crucial in the resolution of metaplastic mucous cells, and understanding these mechanisms may provide novel therapies to reduce the risk of COPD exacerbations.

Keywords: Airway epithelium; Apoptosis; Mucous cell metaplasia; Small airways; Inflammation; Hospitalization

Abbreviations: CMH, chronic mucus hypersecretion; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GCM, goblet cell metaplasia; IL, interleukin; LPS, lipopolysaccharide; NAC, *N*-acetylcysteine; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; URI, upper respiratory infection.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic condition whereby airflow is limited. This limitation can be caused by a combination of underlying conditions, most notably chronic bronchitis and emphysema. Chronic mucus hypersecretion (CMH) is a hallmark of chronic bronchitis. CMH is a common cause of morbidity and mortality, with an annual prevalence of diagnosed chronic bronchitis of 8.8 million in the United States [1]. In emphysema, alveolar destruction is associated with a loss of elastic recoil of the lung. Cigarette smoking is the major etiologic factor. The predominance of each condition varies among individuals. COPD causes significant morbidity, mortality, and economic consequences to individuals. COPD is the fourth leading cause of death and, of the five major diagnoses, only COPD is projected to have an increase in annual deaths by 2020 [2]. Once COPD has developed, there is no known cure for it. Despite the fact that COPD is often underdiagnosed, over 16 million people in the United States are estimated to have COPD, resulting in over 500 000 hospitalizations and 16 million office visits annually. COPD costs $24 billion annually [3], with 70% of medical expenditures occurring for hospitalization due to acute exacerbations [4].

Hospitalization is required when there is poor response to management such as unrelenting dyspnea and inability to perform activities of daily living. Of all COPD patients hospitalized, over 25% are admitted for acute exacerbations [4], and 25% of these are readmitted [5], often due to incomplete recovery [6]. About 30% of patients will have a recurrence within 6 months, and about 50% of these are readmitted within a year. The percentage of predicted forced expiratory volume in 1 second (FEV_1) is used to measure the severity of COPD and is associated with increasing occurrence of exacerbations as well as mortality. For example, Mannino et al. [3] found that patients with an FEV_1 of $<40\%$ have 2.3 exacerbations annually. Miravitlles et al. reported that those with less severe disease (FEV_1 $>60\%$) have an average of 1.6 exacerbations annually [7]. Frequent exacerbations in the past is the best predictor of exacerbations in the future.

Spencer and Jones demonstrated that recovery from exacerbations can take up to 26 weeks, with a pattern of rapid improvement over 4 weeks followed by prolonged recovery lasting up to 6 months [8]. In one of the most systematic studies of symptoms in exacerbations by Seemungal et al., 101 subjects were prospectively evaluated for 2.5 years [9]. Of this number, 91 had >1 exacerbation and 78 had ≥ 2, with 85% of exacerbations identified by symptom diary cards. Of a total 504 exacerbations, only 250 (49.6%) were actually reported to the investigators [9]. Mortality increases with exacerbations, with death rates during hospital admission reported to be as low as 8% but increasing to 23% within a year. In those with high-risk factors, the 6-month mortality is 43%. For those requiring mechanical ventilation, mortality is 24%, with half of those >65 years dying within 1 year [10].

2. Definition

There is no universal definition of exacerbations [11], likely because no single cause has been identified and often two patients can present on different occasions with different pathologic findings as well as a different constellation of symptoms. A frequently accepted