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REVIEW

Clinical issues of mucus accumulation in COPD

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Abstract: Airway mucus is part of the lung's native immune function that traps particulates and microorganisms, enabling their clearance from the lung by ciliary transport and cough. Mucus hypersecretion and chronic productive cough are the features of the chronic bronchitis and chronic obstructive pulmonary disease (COPD). Overproduction and hypersecretion by goblet cells and the decreased elimination of mucus are the primary mechanisms responsible for excessive mucus in chronic bronchitis. Mucus accumulation in COPD patients affects several important outcomes such as lung function, health-related quality of life, COPD exacerbations, hospitalizations, and mortality. Nonpharmacologic options for the treatment of mucus accumulation in COPD are smoking cessation and physical measures used to promote mucus clearance. Pharmacologic therapies include expectorants, mucolytics, methylxanthines, beta-adrenergic receptor agonists, anticholinergics, glucocorticoids, phosphodiesterase-4 inhibitors, antioxidants, and antibiotics.
Keywords: chronic obstructive pulmonary disease, chronic bronchitis, mucus, sputum

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a persistent airflow limitation that is associated with an enhanced chronic inflammatory response to noxious particles or gases.[1] The World Health Organization estimates that over 200 million people have COPD worldwide, and it also predicts that COPD will be the third leading cause of death in the world by 2030, which is higher than its place in 2004 as the fourth leading cause of death.[2] The increased output from goblet cells and mucous glands in COPD patients is variably described as "chronic mucus hypersecretion", "chronic sputum production", or "chronic bronchitis" (CB). Sputum and mucus are commonly used interchangeably, but these are distinct substances. While mucus is generally cleared by cilia, the ciliated epithelium becomes damaged with chronic inflammation and the increased volume of secretions often requires clearance by cough. Sputum refers to the expectorated secretions.[3] CB is commonly defined as the presence of a chronic, productive cough and sputum production for at least 3 consecutive months in 2 consecutive years. This review presents the normal anatomy and physiology related to airway mucus and the pathophysiology of increased mucus production in COPD. Clinical consequences of mucus overproduction, as well as its therapeutic options, are also discussed.

Normal anatomy and physiology related to airway mucus

Airway mucus is secreted by goblet cells found in the superficial mucosa and the mucous glands in the submucosa. Goblet cells decrease in number further into the

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airways, and they eventually disappear at the level of the terminal bronchioles. The quantity of mucous glands, which produce the majority of the airway mucus, decrease distally as they approach the respiratory bronchioles. The mucosa is a surface layer of pseudostratified columnar epithelial cells that have cilia on their luminal surfaces. The rhythmic beating of the cilia enables the "mucociliary elevator" that transports mucus and liquid, as well as inhaled particles, pathogens, and dissolved chemicals, from distal to proximal airways. After the mucus ascends the trachea, it is driven through the vocal cords by the larynx ciliary epithelium. The mucus is then swallowed after the pharynx is entered. The vocal cords are covered by squamous epithelium, so they do not have cilia, but they promote cough clearance by closing, while expiratory pressure builds; they then open suddenly so airflow is forceful.[4,5] The secreted mucins – in particular, the polymeric mucins MUC5AC and MUC5B – serve as the organizing framework of the mucus gel in the airways. The mucins also prevent barrier dehydration, present carbohydrate ligands to sequester the pathogens, and via binding to other components of the secretion, they have the potential to act as sinks for host-protective proteins and peptides.[6]

Airway mucus is part of the lung's innate immune function that traps particulates and microorganisms, facilitating their clearance from the lung by means of ciliary transport or cough.[3,6] In normal conditions, mucin production efficiently defends the airways. However, in mucin secretory cell hyperplasia and metaplasia, there is overproduction, with pathological consequences.[6,7]

Mechanism of mucus accumulation in COPD

Mucus hypersecretion and chronic productive cough is a feature of CB.[1] The primary mechanisms responsible for excessive mucus production in CB in COPD are the overproduction and hypersecretion by goblet cells, and the decreased elimination of mucus.[7] There is also hypertrophy of the submucosal glands that Reid[8] described with a ratio of the thickness of the submucosal glands and the thickness between the epithelium and cartilage that covers the bronchi. The size of the submucosal glands correlates with the degree of airway inflammation (Figure 1).[9]

Mucus hypersecretion in COPD is a consequence of cigarette smoke exposure,[10,11] acute and chronic viral infection,[12] bacterial infection,[13] or inflammatory cell activation of mucin gene transcription.[13] This leads to the overproduction of mucus and to hypersecretion from increased degranulation, primarily by neutrophil elastase. This is compounded by a difficulty in clearing secretions because of poor ciliary function, distal airway occlusion, and an ineffective cough that is secondary to respiratory muscle weakness and reduced peak expiratory flow.[13–15]

Under increased airway inflammation, the airway epithelium remodels and undergoes metaplasia, implying that there is a phenotypic change that occurs within an adult cell type, and that hyperplasia also occurs, denoting an increase in the total cell number within a given tissue type.[16] Saetta et al's[17] study of surgical specimens shows that smokers with both CB and airflow limitation have an increased number

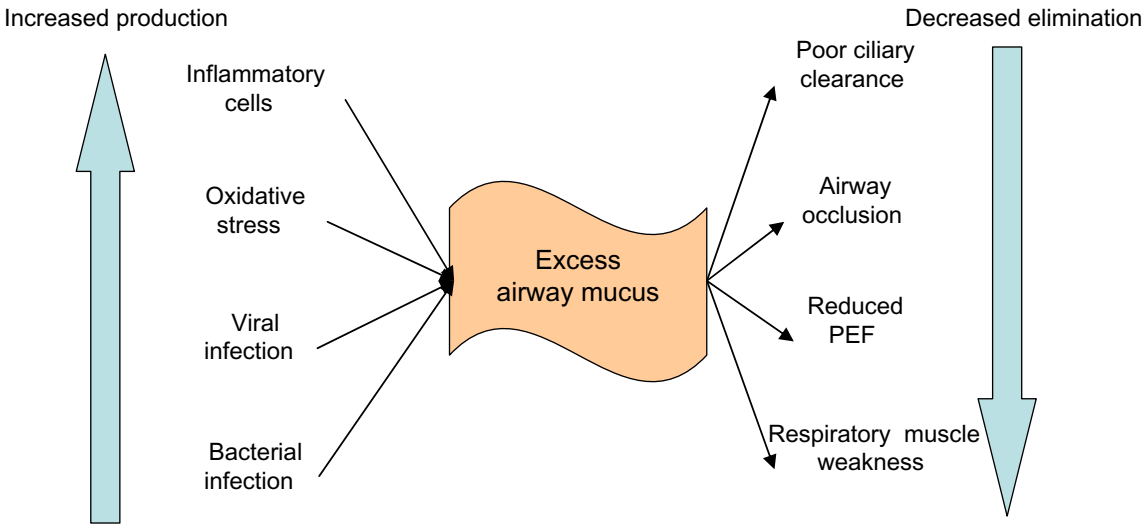

Figure 1 Causes of excessive mucus in COPD.
Notes: Reprinted with permission of the *American Thoracic Society*. Copyright © 2013 American Thoracic Society. Kim V, Criner GJ, 2013, Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 187(3):228–237.[7] Official journal of the American Thoracic Society.
Abbreviations: PEF, peak expiratory flow; COPD, chronic obstructive pulmonary disease.

of goblet cells and inflammatory cells in peripheral airway epithelium. Innes et al[18] revealed that goblet cell hypertrophy and hyperplasia occur in the large airways of habitual cigarette smokers, and this hypertrophy results in epithelial mucin stores that are significantly higher than normal; Figures 2 and 3 show examples of airway epithelium remodeling.

Cellular and molecular mechanisms in the pathogenesis of mucus hypersecretion in CB include acquired cystic fibrosis transmembrane conductance regulator dysfunction[19] and activation of the epidermal growth factor receptor.[20] Smokers with and without COPD have reduced chloride conductance in the lower airway, and this ion transport abnormality is associated with the presence of CB and dyspnea.[19] Cigarette smoke also increases mucin MUC5AC synthesis via epidermal growth factor receptor activation in the airway epithelial cells.[20] Upregulation of the basic fibroblast growth factor[21] and transforming growth factor-β,[22] as well as a higher frequency of the tumor necrosis factor-α polymorphism[23] have also been implicated in the pathogenesis of CB.

Epidemiology

From a review of population-based studies, Kim and Criner[7] estimated the prevalence of CB to be between 3.4%–22% among adults. The wide range of prevalence estimates may be due to varying definitions of CB (ie, chronic phlegm versus chronic cough and phlegm), as well as the possible inclusion of subjects with bronchiectasis.

The prevalence of CB is higher in COPD patients.[13,24,25] In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort,[25] 34.6% of the 2,161 subjects reported the presence of CB, as defined by the American Thoracic Society–Diffuse Lung Disease (ATS-DLD) questionnaire ("phlegm on most days for 3 or more consecutive months during the year and trouble with phlegm for 2 or more years"). Of the 1,061 Global initiative for chronic Obstructive Lung Disease (GOLD) 2–4 subjects in the COPDGene study,[24] CB, by the same definition, was found in 27.3% of patients. The sex predilection of CB is unclear, with some studies finding males more affected,[24,26,27] while others report a female predominance.[28–30]

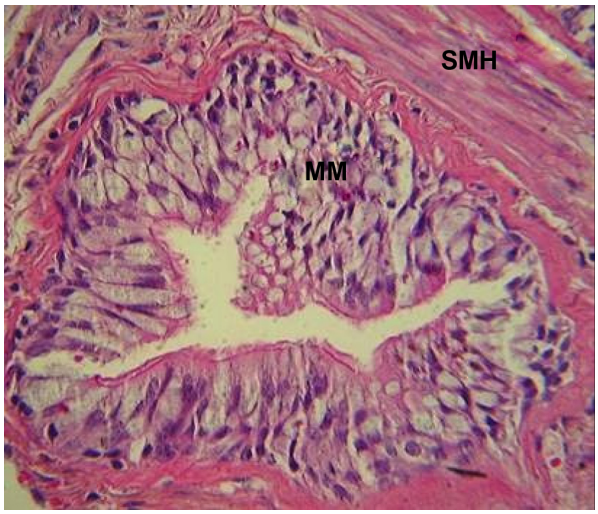

Figure 2 MM and smooth muscle hypertrophy in a small airway from a COPD patient.
Note: Hematoxylin and eosin stain.
Abbreviations: MM, mucous metaplasia; SMH, smooth muscle hypertrophy; COPD, chronic pulmonary disease.

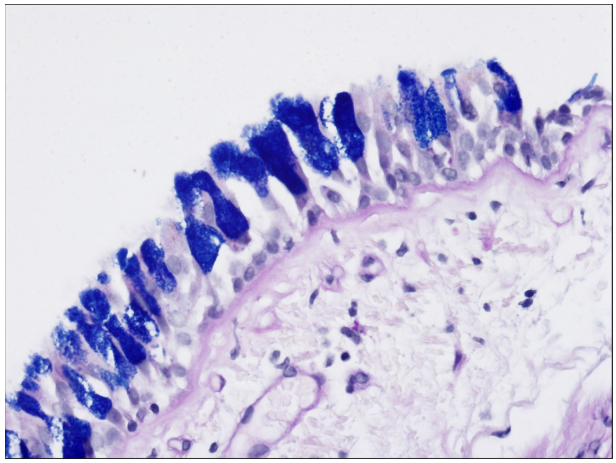

Figure 3 Goblet cell hyperplasia.
Notes: Periodic acid Schiff–Alcian Blue stain. Higher magnification of a small airway quadrant is shown here. Goblet cells appear in an intense blue–purple color with periodic acid Schiff–Alcian Blue stain.

Smoking is the primary risk factor for CB. In one study,[31] the 30-year cumulative incidence of CB was 42% in continuous smokers, 26% in ex-smokers, and 22% in never-smokers. Occupational exposure to biological dust[32] or to combustion byproducts, inorganic dusts, or fumes and organic dusts[33] may also be risk factors. Gastroesophageal reflux disease is another possible risk factor for CB.[34]

Mucus accumulation and outcomes

CB affects important outcomes in COPD, including declines in lung function, health-related quality of life, as well as COPD exacerbations and hospitalizations, and mortality. Table 1 summarizes the findings of select studies.

Lung function

Several studies demonstrated that chronic mucus production is related to a progressive decline in lung function.[35,36] In a longitudinal study that followed 1,757 men and 2,191 women for 12 years, the presence of chronic sputum production was associated with an accelerated loss in forced expiratory

Table 1 Selected studies on chronic bronchitis and outcomes

Outcome	Study	Subjects	Important findings
Lung function	Sherman et al[35]	3,948	Adjusted FEV_1 decline: 4.5±2 mL per year (SE) in males;* 1.7±1.5 mL per year (SE) in females
	Vestbo et al[36]	9,435	Adjusted FEV_1 decline: 22.8 mL/year (95% CI: 8.2–37.4) in males;* 12.6 mL/year (95% CI: 0.7–24.6) in females
	Lindberg et al[39]	963	FEV_1/FVC <0.7 and FEV_1 <80% predicted, OR: 2.56 (95% CI: 1.32–4.95)*
	de Marco et al[37]	5,002	FEV_1/FVC <0.7, IRR: 1.85 (95% CI: 1.17–2.93)*
	Guerra et al[38]	1,412	FEV_1/FVC <0.7, HR: 2.2 (95% CI: 1.3–3.8) in <50 years;* 0.9 (95% CI: 0.6–1.4) in ≥50 years
Health-related quality of life	Agusti et al[25]	2,164	CB+ versus CB–: GOLD II: SGRQ total 50.3±18 versus 38.9±20.5;* mMRC 1.5±1 versus 1.3±1* GOLD III: SGRQ total 58.8±17.6 versus 51.2±18.2;* mMRC 1.8±1 versus 1.8±1.1 GOLD IV: SGRQ total 65±16.5 versus 59.4±15.2;* mMRC 2.4±1 versus 2.3±1
	Kim et al[24]	1,061	CB+ versus CB–: SGRQ total 49.9±19.7 versus 36.6±20* SGRQ respiratory 62.5±19 versus 38±22.4* mMRC, median (interquartile range) 3(2–4) versus 2(1–3)*
	de Oca et al[26]	759	CB+ versus CB–: Short Form-12 physical score 44.6±1.01 versus 49.5±0.36* Limitation due to physical health 39 (40.6) versus 148 (22.4)*
COPD exacerbation and hospitalization	Vestbo et al[36]	9,435	COPD-related hospitalization, RR: 2.4 (95% CI: 1.3–4.5) in males;* 2.6 (95% CI: 1.2–5.3) in females*
	Burgel et al[40]	433	All exacerbations: OR: 4.15 (95% CI: 2.43–7.08)* Moderate exacerbations: OR: 4.65 (95% CI: 2.54–8.48)* Severe exacerbations: OR: 4.08 (95% CI: 1.18–14.09)*
	Agusti et al[25]	2,164	CB+ versus CB–, exacerbations in past year: GOLD II: 0.7±1.1 versus 0.6±1 GOLD III: 1±1.2 versus 1±1.4 GOLD IV: 1.2±1.6 versus 1.2±1.3
	Kim et al[24]	1,061	CB+ versus CB–, exacerbations in past year: Total, number/patient: 1.21±1.62 versus 0.63±1.12* Severe, %: 26.6 versus 20*
	de Oca et al[26]	759	CB+ versus CB–, exacerbations in past year: 5.3±3.83 versus 2.1±0.95
Mortality	Annesi and Kauffmann[43]	1,061	All-cause, RR: 1.35±0.111*
	Speizer et al[27]	8,427	COPD-related, OR: 3.75 (95% CI: 1.28–11) in males;* 11.04 (95% CI: 2.52–48.5) in females* All-cause, OR: 1.37 (95% CI: 1.09–1.72) in males;* 0.98 (95% CI: 0.68–1.41) in females
	Tockman and Comstock[44]	884	All cause, RR: 1.65 (95% CI: 0.95–2.89)
	Lange et al[42]	13,756	All-causes, RR: 1.3 (95% CI: 1.1–1.4) in males* and 1.1 (95% CI: 0.9–1.3) in females
	Prescott et al[41]	14,223	COPD-related with pulmonary infection, RR: 3.5 (95% CI: 1.8–7.1)* COPD-related without pulmonary infection, RR: 0.9 (95% CI: 0.5–1.8)
	Mannino et al[45]	5,542	All-cause, RR: 1.2 (95% CI: 0.97–1.4)
	Pelkonen et al[31]	1,711	Respiratory-related, HR: 2.54 (95% CI: 1–6.46)* All-cause, HR: 1.64 (95% CI: 1.23–2.19)*
	Guerra et al[38]	1,412	All-cause mortality, HR: 2.2 (95% CI: 1.3–3.8) in <50 years;* 1 (95% CI: 0.7–1.3) in ≥50 years

Notes: *Statistically significant. Data are presented as mean ± SD or number (percentage), except as indicated. IRR, OR, RR, and HR are all from multivariate analyses with adjustments for covariates.

Abbreviations: FEV_1, forced expiratory volume in 1 second; SE, standard error; CI, confidence interval; FVC, forced vital capacity; OR, odds ratio; IRR, incidence rate ratio; HR, hazard ratio; CB+, group with chronic bronchitis; CB–, group without chronic bronchitis; GOLD, Global initiative for chronic Obstructive Lung Disease; SGRQ, St George's Respiratory Questionnaire; mMRC, modified Medical Research Council; RR, relative risk; SD, standard deviation; COPD, chronic obstructive pulmonary disease.

volume in one second (FEV_1) in men of 4.5±2 mL/year after adjusting for height, age, and cigarette smoking, but a statistically insignificant decline in FEV_1 in women of 1.7±1.5 mL/year.[35] Using data from the Copenhagen City Heart Study,[36] which was conducted with 5,354 females and 4,081 males, comparing two spirometry results 5 years apart, Vestbo et al found an excessive FEV_1 decline of 22.8 mL/year (95% confidence interval [CI]: 8.2–37.4), after adjusting for age, height, weight change, and smoking, in males with chronic mucus hypersecretion compared with males without mucus hypersecretion; in women, the adjusted excess decline was not statistically significant at 12.6 mL/year (95% CI: 0.7–24.6).

The presence of CB may also predict the development of airflow obstruction.[37–39] In an international population-based cohort study of young adults with normal lung function, chronic cough and phlegm predicts the development of COPD (defined as a ratio of FEV_1 to forced vital capacity [FVC] <0.7)

with an incidence rate ratio of 1.85 (95% CI: 1.17–2.93) after adjusting for smoking.[37] Subjects who reported chronic cough and phlegm have a nearly threefold increased risk of developing COPD ($FEV_1/FVC < 0.7$) with respect to asymptomatic subjects (incidence rate ratio: 2.88; 95% CI: 1.44–5.79). Among the 1,412 participants in the Tucson Epidemiological Study of Airway Obstructive Disease,[38] the presence of CB is an independent risk factor for incident airflow limitation among subjects <50 years old (adjusted hazard ratio [HR]: 2.2; 95% CI: 1.3–3.8), but not among subjects ≥50 years old (adjusted HR: 0.9; 95% CI: 0.6–1.4).

Health-related quality of life

Several analyses show that chronic sputum production correlates with a worse quality of life and more limitations due to physical health.[24–26] Our analysis of the COPDGene study reports higher modified Medical Research Council (mMRC) dyspnea scores and St George's Respiratory Questionnaire (SGRQ) scores in COPD subjects with CB symptoms.[24] In the ECLIPSE cohort, the presence of CB is related to worse total scores on the mMRC and SGRQ across all COPD disease severities (GOLD II to IV).[25] Among subjects with COPD in the Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) study, those with CB have a worse general health status and more physical activity limitations.[26]

COPD exacerbations and hospitalization

Vestbo et al[36] showed that hospitalization due to COPD is associated with chronic mucus hypersecretion with a relative risk of 2.4 (95% CI: 1.3–4.5) for males and 2.6 (95% CI: 1.2–5.3) for females. A cross-sectional multicenter analysis of 433 COPD subjects found that chronic cough and sputum were associated with frequent COPD exacerbations during the previous year (adjusted odds ratio [OR]: 4.15 [95% CI: 2.43–7.08]; $P<0.0001$), including severe exacerbations requiring hospitalizations (adjusted OR: 4.08 [95% CI: 1.18–14.09]; $P=0.03$).[40] Examination of the COPDGene cohort concludes the fact that a history of exacerbations in the previous year is higher in the CB group (1.21±1.62 versus 0.63±1.12 per patient; $P=0.027$), and more subjects in that group reported a history of severe exacerbations (26.6% versus 20%; $P=0.024$).[24]

However, not all studies link CB with exacerbations and hospitalizations. In ECLIPSE,[25] exacerbation frequency in the year before recruitment in those with and without CB was the same. In addition, an analysis of the PLATINO study[26] showed a nonsignificant difference in exacerbation frequency between COPD subjects with and without CB.

The differing results could be explained by the numerous differences in the study population and in the design of the comparison of the selected studies that report COPD exacerbations or hospitalizations. Two studies are population-based and involve patients from Denmark[36] or Latin America.[26] The other three are cross-sectional studies involving patients from France,[40] the United States,[24] or from multiple nations.[25] Vestbo et al[36] used a definition of chronic mucus hypersecretion, while the other studies use the more classic definition of CB.[24–26,40] The prevalence of CB in COPD patients using the classic definition is 14%,[26] 27%,[24] 35%,[25] and 74%.[40] Across the studies, there were also small differences in the percentage of current smokers and the severity of disease, as measured by airflow obstruction. In two studies with similar demographics and the number of current smokers, the study that showed a positive association between CB and exacerbations had more patients with frequent exacerbations,[24] while the other did not show an association and it had fewer patients with frequent exacerbations.[25] Therefore, prospective studies are needed to clarify the association between CB and COPD exacerbations and hospitalizations.

Mortality

CB is a risk factor for respiratory-related[27,31,41] and all-cause[31,38,42,43] mortality. In a Finnish study of 1,711 middle-aged males with 40-year mortality data, persistent CB predicts risk of respiratory-related deaths (adjusted HR: 2.54; 95% CI: 1–6.46; $P=0.049$) and all-cause mortality (adjusted HR: 1.64; 95% CI: 1.23–2.19; $P=0.001$), after adjusting for pulmonary function.[31] Prescott et al,[41] who followed 14,223 participants for 10–12 years, reported that chronic mucus hypersecretion is a significant predictor of death from pulmonary infection, with a multivariate relative risk (RR) of 3.5 (95% CI: 1.8–7.1), but not of death without pulmonary infection. In a 9- to 12-year mortality follow-up of 8,427 Caucasian adults, Speizer et al[27] reported the association of cough or phlegm and an increase in COPD mortality with an adjusted OR of 3.75 (95% CI: 1.28–11) in men and 11.04 (95% CI: 2.52–48.5) in women. In the Tuscon Epidemiologic Survey of Airway Obstructive Disease,[38] the risk of all-cause mortality was higher in patients younger than 50 years of age with CB (HR: 2.2; 95% CI: 1.3–3.8), but not among subjects 50 years of age or older (HR: 1; 95% CI: 0.7–1.3). In an analysis of the 13,756 subjects in the Copenhagen City Heart Study,[42] the presence of chronic mucus hypersecretion increased mortality from all causes with an adjusted RR of 1.3 (95% CI: 1.1–1.4) in males and 1.1 (95% CI: 0.9–1.3) in females. An investigation of 1,061 French males showed

a multivariate RR of 1.35 ($P<0.01$) for the relationship between chronic mucus hypersecretion and mortality during a 22-year follow-up.[43] The mechanism behind this association in unclear, but a possible cause could be the increased inflammatory state seen in those with CB, leading to increased cardiovascular events.[38]

Other studies, however, have not shown a statistically significant relationship between chronic mucus production and mortality. There is a statistically insignificant trend towards death in Tockman and Comstock's study[44] of 10-year mortality in 884 males with chronic phlegm production (RR: 1.65; 95% CI: 0.95–2.89). Mannino et al[45] reported similar findings for risk of death in the presence of respiratory symptoms (cough, sputum, or wheeze) without obstructive lung disease.

Numerous differences are apparent after comparing the different studies that report mortality. These differences could account for the inconsistent relationship between CB and mortality. First, as mentioned previously, the definition used of mucus accumulation with or without spirometry-defined airflow obstruction varies. The negative studies use chronic phlegm production[44] or a combination of respiratory symptoms (cough, sputum, or wheeze).[45] The positive studies use the classic CB definition,[31,38] or symptoms of chronic mucus hypersecretion,[41,42] or chronic phlegm[27,43]. All of the symptoms are self-reported, and so responses may be varied depending on how the question is phrased. Second, standard of care likely varies in the populations being studied, as the research on this subject matter includes patients from all areas of the globe at different points in time. Third, the association of mortality and chronic sputum, phlegm production, or CB may be influenced by factors such as the presence of COPD or smoking history. Most of the studies report results that have adjusted for these covariates, but unmeasured differences associated with the presence of these factors may influence the findings. Fourth, some authors suggest that the relationship between mucus accumulation and mortality is further affected by severity of airflow obstruction,[27] infection,[41] and age.[38]

Treatment options

The main goals of therapy should target the different pathophysiologic mechanisms of CB by reducing mucus overproduction, decreasing mucus hypersecretion by controlling inflammation, facilitating mucus elimination by increasing ciliary transport, reducing mucus tenacity, increasing shear stress to augment mucus detachment, and modifying cough (Table 2).

Table 2 Summary of therapeutic interventions for chronic bronchitis

Intervention	Mechanism of action
Smoking cessation	Improves mucociliary function, decreases goblet cell hyperplasia
Physical measures (chest PT, HFCWO, flutter valve)	Augments shear stresses to improve mucociliary clearance
Expectorants	Vagally mediated increase in airway secretions
Mucolytics (hypertonic saline, dornase alpha)	Rehydration of airway mucus, hydrolysis of mucus DNA
Methylxanthines	Improves lung function, increases ciliary beat frequency
SABA	Improves lung function, increases ciliary beat frequency
LABA	Improves lung function, increases ciliary beat frequency, reduces hyperinflation, improves PEF
Anticholinergics	Improves lung function, decreases mucus secretion
Glucocorticoids	Reduces inflammation and mucus production
PDE-4 inhibitors	Reduces inflammation, improves lung function
Antioxidants	Breaks down mucin polymers, reduces mucus production
Macrolides	Reduces inflammation, reduces goblet cell secretion

Abbreviations: PT, physiotherapy; HFCWO, high frequency chest wall oscillation; DNA, deoxyribonucleic acid; SABA, short-acting beta agonist; LABA, long-acting beta agonist; PEF, peak expiratory flow; PDE-4, phosphodiesterase-4.

Nonpharmacological therapy

Smoking cessation

Smoking cessation can improve cough in many patients with CB by improving mucociliary function and by decreasing goblet cell hyperplasia.[46] Smoking cessation has also been shown to decrease airway injury and lower levels of mucus in exfoliated sputum tracheobronchial cells when compared to those that continued to smoke.[47] A large longitudinal follow-up study found that the incidence rates of CB were much higher in current smokers compared to ex-smokers (42% versus 26%, respectively).[31] Unfortunately, there is a paucity of data regarding the effects of smoking cessation on sputum symptomatology.

Physical measures

Mucus clearance is aided by maneuvers that promote coughing and increase minute ventilation. This augments shear stresses on mucosal surfaces generated by increased airflow. It also increases humidification of the airway and regulates mucus hydration. Thus, methods such as the application of positive expiratory pressure and use of flutter valves

or high-frequency chest compression vests may be of value, but they have not been studied for use in COPD in large clinical trials. Although cystic fibrosis studies have demonstrated that chest percussion and postural drainage improve mucociliary clearance,[48] these methods have not been well studied in the COPD patient population. There are a few trials that have studied chest physiotherapy or directed coughing techniques in COPD.[49] These trials have shown some improvements in mucus clearance, but no changes in lung function.

Pharmacological therapy

Expectorants and mucolytics

Guaifenesin works by promoting vagally-mediated increases in airway secretions.[50] Long-term use of guaifenesin has not been shown to be of benefit in COPD or CB.[51] Inhaled hypertonic saline works by rehydrating mucus by drawing water from the epithelial cells and by promoting cough.[52,53] While this method has shown improvement in lung function in cystic fibrosis, it has only been shown in one study in COPD to improve dyspnea and exercise capacity.[54] Inhaled dornase alfa hydrolyzes deoxyribonucleic acid (DNA), thereby improving lung function and decreasing exacerbation frequency in cystic fibrosis patients, in whom airway mucus concentrations of DNA are high. However, the concentration of DNA in the sputum of COPD patients is much lower,[55] and studies have shown that dornase alfa is not beneficial and, in fact, it may be harmful.[56]

Methylxanthines and beta-adrenergic receptor agonists

Both methylxanthines and short-acting beta-adrenergic receptor agonists promote mucus clearance by increasing airway luminal diameter, increasing ciliary beat frequency via an increase in intracellular cyclic adenosine monophosphate levels, and increasing mucus hydration by stimulating airway Cl^- secretion via activation of the cystic fibrosis transmembrane regulator. This decreases mucus viscosity, allowing for easier transport by airway cilia.[57–59]

In animal models, short-term administration of beta-agonists is associated with upregulation of mucociliary clearance.[60,61] Similarly, methylxanthines improve mucociliary clearance not only via their bronchodilatory properties, but also by stimulating ciliary beat frequency, augmenting airway epithelial ion transport to increase mucus hydration, and promoting mucus secretion in the lower airways.[62] Clinical studies of theophylline in CB have shown improved lung function, but no consistent change in cough and sputum production.[63,64]

The effects of long-acting beta-adrenergic receptor agonists on mucociliary function have been attributed to their beneficial effects on lung function.[64–67] Long-acting beta-adrenergic receptor agonists also reduce hyperinflation and increase peak expiratory flow, which are essential components of effective cough.[68] In vitro evidence has shown that salmeterol can stimulate ciliary beat frequency.[58] Similarly, formoterol significantly improves mucociliary clearance when compared with placebo in patients with bronchitis.[69]

Anticholinergics

Anticholinergics, by their action on the muscarinic receptor, are believed to help mucus clearance by increasing luminal diameter and by decreasing surface and submucosal gland mucin secretion.[70–72] They are also thought to facilitate cough-induced mucus clearance. However, anticholinergics may desiccate airway secretions by depleting airway surface liquid, thereby making secretions more difficult to expectorate. In vivo, the literature does not support the use of anticholinergics for the treatment of CB. Ipratropium bromide has been shown to reduce the quantity and severity of coughs in CB,[72] but it is not effective in improving the mucociliary clearance in COPD.[73] Tiotropium has been shown to improve lung function[74] and reduce cough, but mucociliary clearance was not improved.[75]

Glucocorticoids

There is in vitro evidence that glucocorticoids reduce inflammation and mucus production.[76,77] In a murine model of asthma, inhaled corticosteroids decrease goblet cell hyperplasia.[78] Dexamethasone has also been shown to decrease epithelial mucin gene, *MUC5AC*, expression in human bronchial epithelial cells;[79] glucocorticoids may also hasten mucociliary clearance.[80] Inhaled corticosteroids reduce exacerbation frequency and improve quality of life scores in COPD.[81–83] Whether inhaled corticosteroids are more beneficial in COPD patients with CB or in airway-predominant phenotypes remains to be determined.

Phosphodiesterase-4 inhibitors

Phosphodiesterase-4 (PDE-4) inhibition decreases inflammation and promotes smooth-muscle relaxation in the airways by preventing the hydrolysis of cyclic adenosine monophosphate to its inactive metabolite. Cilomilast and roflumilast are highly specific second-generation oral PDE-4 inhibitors. A meta-analysis of 23 randomized trials of roflumilast or cilomilast compared with placebo found that treatment with a PDE-4 inhibitor only modestly increased FEV_1 (45.59 mL; 95%

CI: 39.1–52.03), but it reduced the likelihood of an exacerbation (OR: 0.78; 95% CI: 0.72–0.85).[84] Roflumilast has been shown to significantly improve prebronchodilator FEV_1, decrease the rate of moderate to severe exacerbations, and decrease the total number of exacerbations by 17% (95% CI: 8–25).[85] Two trials have evaluated the use of roflumilast in moderate to severe COPD patients.[86] The majority of patients (78%–100%) enrolled had chronic cough and sputum production at baseline. One study randomized patients to roflumilast plus salmeterol or salmeterol alone, and the second study randomized patients to roflumilast plus tiotropium or tiotropium alone.[87] In both trials, roflumilast significantly improved the primary endpoint, prebronchodilator FEV_1, as well as the exacerbation rate. Thus, as CB increases the risk for exacerbation, PDE-4 inhibitors may play a preferential role in preventing the development of exacerbation in patients with CB and COPD.

Antioxidants

Given that oxidative stress is crucial to the pathogenesis of COPD,[87] antioxidant therapy may be of benefit in COPD treatment. Thiol compounds are powerful antioxidants and include N-acetylcysteine (NAC), N-acestyln, carbocysteine, erdosteine, and fudosteine. The two most extensively studied antioxidant medications for COPD are NAC and carbocysteine. NAC is a precursor of L-cysteine and reduced glutathione, which reduces the cellular levels of oxidative stress and the production of reactive oxygen species. NAC also reduces disulfide bonds and sulfhydryl bonds that link together mucin polymers, thereby reducing sputum viscosity. Carbocysteine is a blocked thiol derivative of L-cysteine with in vitro free radical scavenging and anti-inflammatory properties, and it may work on the fucose and sialic acid content in mucus.[88]

The Bronchitis Randomized On NAC Cost-Utility Study[89] (BRONCHUS) is the largest trial of N-acetylcysteine use in COPD to date. In this multicenter study, 523 patients with a mean predicted FEV_1 of 57% were randomized to NAC 600 mg daily or placebo, and they were followed for 3 years. The mean exacerbation rates of the subjects were 2.4–2.5 exacerbations/year. There were no differences in FEV_1 decline in terms of time or health-related quality of life between the two groups. There was also no overall difference in the number of exacerbations. However, in a post hoc analysis, those without inhaled corticosteroids (about 30% of the entire group) had a significant reduction in exacerbations with NAC when compared to placebo.

A more recent study, the High-Dose N-Acetylcysteine in Stable COPD (HIACE) study,[90] enrolled 120 subjects with stable COPD who were randomized to receive NAC 600 mg twice daily or placebo daily for 1 year. The primary outcomes were change in small airway function, as assessed by forced expiratory flow at 25% to 75% (FEF 25%–75%) and forced oscillation technique parameters, which were measured by applying external oscillatory pressure during tidal breathing. The secondary outcomes measurements were change in symptoms, as assessed by the mMRC dyspnea scale and SGRQ scores, exacerbation frequency, and hospitalizations. The patients were predominantly male (93.2%) with a mean age of 70.8±0.74 years and a predicted FEV_1% of 53.9%±2.0%. There were no differences in baseline $FEF_{25–75}$, mMRC dyspnea score, and exacerbation frequency within the previous year prior to enrollment between the two groups. Patients in the NAC group had exhibited decreased small airway resistance over the duration of the study when compared to the placebo group. The NAC group had a statistically significant increase (P=0.037) in $FEF_{25–75}$ (0.72±0.07 L/second versus 0.80±0.07 L/second) compared to placebo (0.679±0.07 L/second to 0.677±0.07 L/second), and the reactance at 6 Hz improved in the NAC group by 23%, which was compared to a decrease in the placebo group by 10.7% (P=0.04). Additionally, the mean exacerbation frequency in the NAC group was lower (0.96/year) compared to the placebo group (1.71/year) (P=0.19).

The Effect of Carbocysteine on Acute Exacerbation of Chronic Obstructive Pulmonary Disease (PEACE) study randomized 709 patients with at least two exacerbations within the 2 years prior to enrollment to carbocysteine 500 mg three times daily or placebo, with the primary endpoint of exacerbation rate over 1 year.[91] Numbers of exacerbations per patient per year declined significantly in the carbocysteine group when compared with the placebo group (1.01 [standard error: 0.06] versus 1.35 [standard error: 0.06]); RR: 0.75 (95% CI: 0.62–0.92; P=0.004). There were no significant interactions between COPD severity, smoking, and use of inhaled corticosteroids, and the primary endpoint. These three studies provided conflicting results on the efficacy of antioxidants on exacerbation frequency. A 600 mg daily dose of NAC may be too low to see a clinical effect when compared to a 600 mg twice daily dose, which was used in the HIACE study,[90] and a 600 mg three times daily dose used in patients with idiopathic pulmonary fibrosis. Additionally, patients in the PEACE trial and HIACE trial had a lower mean predicted FEV_1 (44% and 53.9%, respectively) compared to 57% in the BRONCHUS trial.[89,90,91] Therefore, it is possible that antioxidant therapy is more efficacious in those with lower lung function.

Poole et al[92] performed a meta-analysis of mucolytic agents for CB or COPD. They included randomized, placebo-controlled studies of at least 2 months' duration. They found 30 trials involving 7,436 participants to be methodologically acceptable for further analysis. The majority of the studies involved the use of NAC (n=15) or carbocysteine (n=4). Compared to placebo, there was a 17% reduction in the number of exacerbations per patient with oral mucolytics (a reduction of 0.04 exacerbations per participant per month; 95% CI: –0.04 to –0.03). This may not be clinically relevant since there was very high heterogeneity (I^2=87%) in assessing the exacerbation frequency outcome. There was no overall effect on lung function or increase in adverse effects from the medications.

Antibiotics

Chronic antibiotic therapy is generally not indicated for patients with emphysema or CB. Macrolide therapy, however, has been shown to have anti-inflammatory properties and may play a role in the treatment of those with CB. These therapies have been shown to inhibit proinflammatory cytokines, decrease neutrophil burst, inhibit migration and increase apoptosis, decrease eosinophilic inflammation, increase mucociliary transport, reduce goblet cell secretion, and decrease bronchoconstriction.[93] The effect of chronic macrolide therapy on COPD exacerbations was assessed in 109 patients with COPD who were randomly assigned to receive erythromycin 250 mg or placebo twice daily for 1 year.[94] The erythromycin group had significantly fewer exacerbations than the placebo group. A recent, large, prospective, placebo-controlled, randomized trial on the use of azithromycin (250 mg daily for 1 year) to prevent acute exacerbations of COPD showed that azithromycin was associated with a significant decrease in exacerbation frequency and an improvement in health-related quality of life.[95] There was, however, no significant additional benefit of azithromycin in those with CB at baseline.

Future therapy

There is a novel inhaled therapy, BIO-11006, that is currently undergoing Phase II testing (BREATH 1 trial[96]) in patients with CB. This drug inhibits the function of the myristoylated alanine-rich C kinase substrate protein (MARCKS), which has been shown to be a vital component for the secretion of mucus and inflammatory mediators. Preliminary results indicated that patients have improvements in lung function and reductions in both cough and sputum production.[96]

Microbiology

There is no available evidence of the benefit of performing routine microbiologic cultures of mucus from COPD patients. Sputum production is one of the characteristic symptoms of COPD, and a change in amount or quality of sputum beyond a day-to-day variation may indicate an exacerbation.[1] The presence of purulent sputum is 94.4% sensitive and 77% specific for the yield of a high bacterial load, and it indicates a clear subset of patient episodes identified at presentation that is likely to benefit most from antibiotic therapy.[97] Thus, the 2013 GOLD guidelines[1] recommend that the presence of purulent sputum during an exacerbation can be a sufficient indication for starting empirical antibiotics, and that a sputum culture with antibiotic sensitivity testing should be performed when there is lack of response to the initial antibiotic treatment.

Future directions

We believe more studies are needed on why some smokers develop CB and others do not, and on how smoking cessation affects the natural history of CB. In addition, more research on the pathophysiology of this disease process will help in the development of better therapies that directly target CB in order to improve symptoms, while decreasing exacerbations and mortality. The effects of the presence of radiology-confirmed bronchiectasis, a clinically similar phenotype, on the symptoms and outcomes of CB deserve further study.

We believe that the additional study of higher doses of antioxidants such as NAC, and more in-depth studies of selective PDE-4 inhibitors like roflumilast are needed. The identification of more therapeutic targets is necessary for drug development in order to improve outcomes specifically related to CB.

Disclosure

The authors report no conflicts of interest in this work.

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