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Clinical Review

Chronic Bronchitis: Where Are We Now?

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; chronic bronchitis, **CB**; chronic mucus hypersecretion, **CMH**; St George's Respiratory Questionnaire, **SGRQ**; gastroesophageal reflux disease, **GERD**; quality of life, **QoL**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; body mass index, **BMI**; hazard ratio, **HR**; confidence interval, **CI**; forced expiratory volume in one second, **FEV_1**; relative risk, **RR**; phosphodiesterase, **PDE**; N-acetylcysteine, **NAC**; odds ratio, **OR**; cystic fibrosis, **CF**; cystic fibrosis transmembrane conductance regulator, **CFTR**; cyclic adenosine monophosphate, **cAMP**; airway surface liquid, **ASL**; inhaled corticosteroids, **ICS**; long-acting beta2 agonists, **LABA**; long-acting muscarinic antagonists, **LAMA**; short-acting beta agonists, **SABA**; short-acting muscarinic antagonists, **SAMA**; cyclic guanosine monophosphate, **cGMP**

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with different clinical and pathophysiologic phenotypes.[1,2] COPD is currently the third leading cause of death in the world.[3] Chronic bronchitis (CB) is common, affecting approximately 10 million people in the United States, the majority of which are between 44 and 65 years of age. CB is classically described as chronic cough and sputum for at least 3 months a year for 2 consecutive years[4] but many studies have used different definitions. No matter how it is described, it is clear that CB is associated with multiple clinical consequences, including hastening lung function decline, increasing risk of exacerbations, reducing health-related quality of life, and possibly raising all-cause mortality.[5–10] Recently there has been a growing body of literature that more carefully describes environmental risk factors, clinical sequelae and epidemiology associated with CB. There has been an increased interest in CB and COPD with the rise in the aging population and continued exposure to risk factors.[11] Herein, we describe the definitions, epidemiology, clinical presentation and management of CB, with an emphasis on current literature.

Methods

CB was originally defined by Dr. Charles Badham in 1814 as *"A cough…that remains for many weeks or months…such patients have always an uneasy respiration, often a sense of weight, or of fluttering…the sputa are usually copious, viscid, and tenacious."* Much later, CB was defined as chronic cough and sputum production for at least 3 months a year for 2 consecutive years.[12,13] This definition has been used for decades and remains the gold standard. However, several other definitions have been utilized in clinical studies. For example, chronic bronchitis defined as chronic mucus hypersecretion (CMH) in a large epidemiologic study was associated with both an excess rate of lung function decline and an increased risk of subsequent COPD-related hospitalization.[5] Other definitions include

bronchial hypersecretion, chronic cough and sputum production, chronic phlegm and chronic productive cough.[14]

The St George's Respiratory Questionnaire (SGRQ) has been used in several large COPD trials. The cough and sputum questions of the SGRQ have been used to create an alternative definition of CB in several studies. In the COPD Genetic Epidemiology study (COPDGene®), use of the SGRQ definition identified 50.9% more individuals compared to the classic definition (1801 versus 1179 individuals out of 4572, respectively).[15] Using the classic definition as the gold standard, the SGRQ definition had a sensitivity of 0.87 and specificity of 0.77.[15] Similar results were found in the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS).[16]

The clinical phenotype identified by the SGRQ definition is nearly identical to the one identified by the classic definition in the COPDGene® study. There were no differences in the history of COPD exacerbations, current smoking, gender distribution, presence of gastroesophageal reflux disease (GERD), upper airway symptoms, dyspnea, and health-related quality of life (QoL) between the patients identified by the SGRQ-CB and classic CB definitions.[15] A study by Kim et al showed that the presence of CB symptoms, defined by either classic or SGRQ definitions, was an independent predictor of exacerbation frequency in long-term follow-up. However, the SGRQ-CB definition was an independent predictor of severe exacerbations whereas the classic definition was not.[16] These features of the SGRQ definition suggest that it may be a more useful clinical definition than the classic one.

Additionally, the SGRQ definition is much simpler to use in clinical practice; patients are asked 2 questions, 1 on cough and 1 on sputum, and are asked to rate them from "not at all," "only with lung/respiratory infections," "a few days a month," "several days a week," or "almost every day." The SGRQ definition of CB is both cough and phlegm "almost every day" or "several days a week." In comparison, the classic definition requires answering multiple questions (6 to 12, see Table 1) on cough, sputum, months per year, and number of years. Despite the identification of more patients with the same clinical phenotype and what one could consider "active symptoms," the SGRQ-CB definition can be criticized by its short- term nature (4 weeks) and therefore lack of chronicity of symptoms. Therefore, we believe that repeated assessments of the SGRQ cough and sputum questions, over perhaps 6-12 months, would be a better way of defining CB. Further study is necessary in order to determine whether this operating definition is equal to or better than the classic definition in terms of classifying the phenotype and determining patient-reported outcomes.

Epidemiology

The prevalence of CB varies throughout the world, ranging from 3.4%–22.0% in the general population to up to 74.1% in patients with COPD.[14,17,18] Table 2 describes the prevalence of CB and/or respiratory symptoms in multiple studies from different areas of the world. CB affects approximately 10 million people in the United States.[19] According to recent statistics, the prevalence increases with age, is higher in females than in males (56.8 versus 29.6 cases/ 1000 persons, respectively) and is higher in non-Hispanic blacks and whites compared to Hispanics (48.6, 47.3 and 28.8/ 1000 persons, respectively) (Figure 1).[19] Of the 1955 participants in the COPDGene® study with CB by symptoms (18.9%), approximately 60% had COPD (i.e., had also airflow obstruction on spirometry), 10% had restriction, and 30% had normal spirometry (i.e., CB without COPD, unpublished data). In the largest study of current or former smokers without airflow obstruction (approximately 4900 participants), 12.2% had CB using the classic definition.[20]

In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), a multicenter international study, 749 out of 2161 (34.6%) patients with COPD Global initiative for Obstructive Lung Disease (GOLD)4 stages II-IV had CB, and its prevalence increased with greater COPD severity (30.8%, 37%, and 40% in COPD GOLD stage II, III, and IV, respectively).[2] The PLATINO (Proyecto Latino Americano de Investigacion en Obstruccion Pulmonar) study estimated the prevalence of CB as 7.8% to 19.7% in 5 major cities in South America. A total of 759 of 5314 participants more than 40 years old met spirometric criteria for COPD. Patients with COPD and CB had worse lung function and general health status, more respiratory symptoms, physical activity limitation and exacerbations compared to those with COPD but without CB (Figure 2).[18] A recent European study found a prevalence of CB of 18% in 972 patients with COPD. In this study, those with CB were older, more frequently current smokers,

Table 1. Comparison of Classic to St George's Respiratory Questionnaire Chronic Bronchitis Definitions

Classic Chronic Bronchitis Definition	Answers	SGRQ Chronic Bronchitis Definition	Answers
1. Do you usually have a cough? (Exclude clearing of throat.) If Yes, do you usually cough as much as 4 times a day, 4 or more days out of the week? 2. Do you usually cough at all on getting up or first thing in the morning? 3. Do you usually cough at all during the rest of the day or night? *If Yes to any of the above (1–3), answer the following:* *Do you cough like this on most days, for 3 consecutive months or more during the year?* *For how many years have you had this cough?* 4. Do you usually bring up phlegm from your chest? If Yes, do you usually bring up phlegm like this as much as twice a day, 4 or more days out of the week? 5. Do you usually bring up phlegm from your chest on getting up, or first thing in the morning? 6. Do you usually bring up phlegm from your chest during the rest of the day or at night? *If Yes to any of the above (4–6), answer the following:* *Do you bring up phlegm like this on most days for 3 consecutive months or more during the year?* *For how many years have you had trouble with phlegm?*	Yes/No for all questions	1. Over the last 4 weeks, I have coughed: 2. Over the last 4 weeks, I have brought up phlegm (sputum):	Almost every day Several days a week A few days a month Only with lung/ respiratory infections Not at all
	Chronic bronchitis= cough AND phlegm for at least 3 months a year for at least 2 consecutive years		Chronic bronchitis= cough AND phlegm almost every day or several times a week

SGRQ=St George's Respiratory Questionnaire

had a greater pack-year smoking history, worse airflow obstruction and lower QoL than those without CB.[34] A Chinese study which included 1668 patients with COPD showed that 30% of the participants met the diagnostic criteria for CB. In this study, age, body mass index (BMI) and comorbidities in COPD patients with or without CB were similar. Male gender, residence in a rural area, a lower level of education, exposure to tobacco smoke or biomass fuels, poor ventilation in the kitchen and a family history of respiratory disease were all associated with a higher risk of CB with COPD.[33]

Risk Factors

Many risk factors exist for developing CB and COPD but cigarette smoking is the most important risk factor (Table 3).[35] A Finnish study that followed 1711 men for up to 40 years showed that the cumulative incidence of CB was 42% in current smokers and 26% in ex-smokers.[6] A meta-analysis of 101 epidemiologic studies estimated that current smoking and ever smoking conferred relative risks of 3.41 and 2.69 for CB, respectively.[36] In SPIROMICS, over 50% of those with CB defined by either the classic or SGRQ definition were current smokers, regardless of the presence or

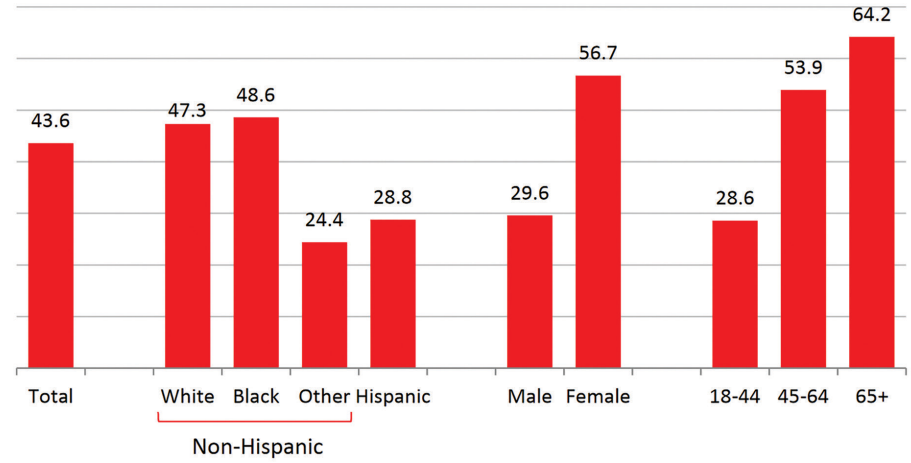
Table 2. Prevalence of Chronic Bronchitis and/or Respiratory Symptoms in Multiple Studies from Different Areas of the World

Study	Population	N	Findings	Comments
Lange et al, 1989[21]	General population (Denmark)	12,698	Bronchial hypersecretion 10.1%	
Sobardillo et al, 1999[22]	General population (Spain)	4035	Cough 13.5%; Expectoration 10.7%; CB 4.8%	
Pallasaho et al, 1999[23]	General population (Finland)	8000	Productive cough 27%	
Von Hertzen et al, 2000[24]	General population (Finland)	7217	CB and/or emphysema: 22% in men, 7% in women	
Cerveri et al, 2001[25]	General population, (Europe)	17,966	CB 2.6%	range 0.7–9.7% across countries
Janson et al, 2001[26]	General population, (Multinational)	18,277	Productive cough 10.2%	
Huchon et al, 2002[27]	General population, (France)	14,076	CB 4.1%, Chronic cough and/or expectoration 11.7%	
Lundback et al, 2003[28]	General population, (Sweden)	5892	Chronic productive cough 51%	in individuals with COPD as defined by GOLD
Miravitlles et al, 2006[29]	General population (Spain)	6758	Cough: 5% in never smokers,11% in smokers or ex-smokers Expectoration: 4% in never smokers, 11% in smokers and ex-smokers	
Pelkonen et al, 2006[6]	General population (Finland)	1711	Incidence of chronic productive cough: 42% current smokers, 26% past smokers, 22% never smokers	
De Marco et al, 2007[30]	General population with normal lung function (Multinational)	5002	Chronic cough/phlegm production: 9.2%	
Miravitlles et al, 2009[31]	General population (Spain)	4274	Chronic cough 3.4%, Chronic sputum production 11.7%	
Harmsen et al, 2010[32]	General population (Denmark)	21,130	chronic mucus secretion 10.7% in females and 8.7% in males	Twins cohort
Lu et al, 2010[33]	Patients with COPD (China)	1668	CB 30%	
De Oca et al, 2012[18]	General population (South America)	5314	CB 14.4% in patients with COPD and 6.2% in patients without CB	PLATINO study
Martinez et al, 2014[20]	General population without airflow obstruction (USA)	4880	CB in 12.2%	COPDGene® data
Vestbo et al, 2014[2]	Patients with COPD GOLD II-IV (Multinational)	2161	CB 34.6%	ECLIPSE study
Lahousse et al, 2017[34]	Patients with COPD (Europe)	972	CB 17.7%	

CB=chronic bronchitis; COPD=chronic obstructive lung disease; GOLD=Global initiative for chronic Obstructive Lung Disease

absence of airflow obstruction.[16] In support of the relationship between current smoking and CB are data that show reductions of CB with smoking reduction or cessation. Pelkonen et al analyzed trends of CB and current smoking and found that over 25 years, the prevalence of both current smoking and CB decreased.[37] Allinson et al analyzed the presence of CMH in over 4400 individuals across ages 20 to 64 and found that in each age range, current smoking was associated with an increase in CMH and smoking

Figure 1. Epidemiology of Chronic Bronchitis by Race, Gender and Age Groups



Source: CDC. NHIS 2011.

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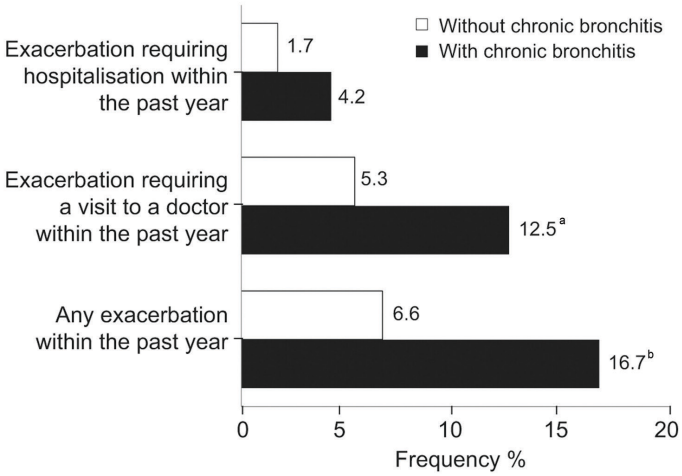
Figure 2. Exacerbations in Patients With COPD With or Without Chronic Bronchitis, Defined by the Classic Definition



[a]$p<0.05$
[b]$p<0.01$

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cessation was associated with a decrease.[38] Similarly, an analysis of the COPDGene® study found that current smoking over the course of 5 years was linked to increased rates of CB, quitting smoking increased the likelihood that CB would resolve, and resuming smoking during the 5-year interval increased the likelihood of developing CB.[39]

A substantial proportion of CB, however, is not related to cigarette smoking, especially in young adults, females, and residents of developing countries. In the aforementioned Finnish study, the cumulative incidence of CB was 22% in nonsmokers.[6] An analysis of 2 separate cross sectional surveys in 1998/2000 and 2007/2010 showed similar prevalence of CB but an increase in never smokers (7.6% to 9.1%), an overall decrease in current smoking (33.6% to 26.9%) and an increase in allergic rhinitis (19.5% to 24.5%).[40]

Specific occupational exposure studies (coal and hard-rock miners, tunnel workers, concrete-manufacturers, and non-mining industrial workers) and world-wide community-based studies have demonstrated a link between these exposures, respiratory symptoms and the development of COPD.[35] Livestock farming has also been recognized as a risk factor for developing CB. A study of 4735 Norwegian farmers showed that livestock farmers had an increased risk of CB and COPD and had lower lung function compared to crop farmers. The adverse respiratory health outcomes in livestock farmers are believed to be secondary to increased levels of allergens, organic dusts, endotoxins, peptidoglycans and animal confinement gases.[41,42] Data from a French study (AGRICAN) assessing associations between specific farming activities showed prevalence of CB in 8.4% out of 1207 farmers, specifically in those exposed to pesticides in potato farming.[43] A meta-analysis by Mamane et al showed that exposure to agricultural pesticides was associated with respiratory symptoms, impaired respiratory function and increased prevalence of CB.[44] Air pollution may also be a risk factor; a comprehensive study by the Committee on the Medical Effects of Air Pollutants (COMEAP) in the United Kingdom showed a possible association between the incidence and prevalence of CB and long-term exposure to air pollution.[45] A systematic review showed associations between the use of solid fuels and COPD and CB, especially with wood smoke compared to other biomass fuels.[46] Additionally, smoking marijuana is associated

Table 3. Chronic Bronchitis Risk Factors

Risk Factor	Association
Cigarette Smoking	Strong
Occupational Exposures:	Moderate
1. Coal miners	
2. Hard-rock miners	
3. Tunnel workers	
4. Concrete manufacturers	
5. Livestock farming	
Exposure to Agricultural Pesticides	Moderate
Use of Domestic Solid Fuels	Moderate
Electronic Cigarettes	Weak
Marijuana Smoking	Weak
Air Pollution	Weak

with CB[47] and there is emerging data that electronic cigarettes may be associated with CB.[48] A recent study by Reidel et al showed that induced sputum from smokers of electronic cigarettes had similar levels of the airway mucin MUC5AC as the induced sputum of cigarette smokers.[49]

Clinical Manifestations

CB was once under the umbrella term of COPD and was thought to be one end of its spectrum of disorders. However, it is now known that CB is a separate entity that can exist with or without airflow limitation (Table 4). In the COPDGene® study, non-obstructed individuals (current or former smokers with at least a 10 pack-year history) with CB (n=597) and without CB (n=4283) were compared. Individuals with CB were younger, had a greater pack-year history of smoking and were more frequently current smokers. They had a lower QoL and exercise capacity and had more respiratory exacerbations.[20] In another study, smokers with CB without airflow obstruction (n=864) were compared to smokers with mild to moderate COPD but without CB (n=2510). The non-obstructed CB patients were younger, had a lower pack-year history of smoking, and had a worse QoL compared to those with COPD and no CB.[50]

CB is also a known risk factor for development of airflow obstruction. A study by Guerra et al followed 1400 adults in the Tucson Epidemiologic Study of Airway Obstructive Disease (TESAOD) who had no airflow obstruction or asthma at enrollment. Baseline CB was associated with increased risk of developing airflow obstruction (22 years follow-up) and all-cause mortality (31 years follow-up) among participants <50 years old (hazard ratio [HR] 2.2, 95% confidence interval [CI] 1.3–3.8 and HR 2.2, 95% CI 1.3–3.8, respectively).[7] The same trend was not seen in those over the age of 50, however. Longitudinal data on a random cohort of nearly 4000 patients followed for 12 years showed that the presence of cough and phlegm at the initial visit was associated with a more rapid decline of lung function after adjustment for height, age, and cigarette smoking.[51] The Copenhagen City Heart Study (n=9435) followed patients with spirometry every 5 years and showed that CMH was significantly associated with forced expiratory volume in 1 second (FEV_1) decline after adjusting for age, height, weight change and smoking.[5] An international cohort of 5002 patients with normal lung function at baseline followed for 12 years showed that patients with chronic cough or phlegm had nearly a 2-fold increased risk of developing airflow obstruction.[30]

CB is not only associated with an accelerated lung function decline, but also with an increased risk of COPD exacerbations. A study by Lindberg et al showed that patients with COPD and productive cough had the highest rate of exacerbations after adjusting for age, gender, BMI, heart disease and smoking status.[52] A Finnish study which followed over 47,800 individuals for up to 30 years showed that individuals with CB had almost double the number of hospitalization days compared to patients without CB.[53] Kim et al compared patients with severe emphysema and severe CB (using the SGRQ definition and presence of "chest trouble," n=74) to patients without severe CB (n=576). Patients with severe CB had a shorter time to hospitalization and worse health-related QoL.[54] Another study by Kim et al compared patients with COPD GOLD stage II-IV with (n=290) and without CB (n=771) and showed that those with CB were younger, had a greater pack-year smoking history, were more likely to be current smokers and had higher rates of exacerbations.[8] In a multicenter French study, patients with COPD and CB (n=321) had greater numbers of exacerbations than patients without CB (n=112).[17]

Many but not all studies of CB on all-cause mortality demonstrate an increased risk of death (Table 5). The relationship of CMH and death from all causes and

Table 4. Chronic Bronchitis is a Separate Entity That Can Exist With or Without Airflow Obstruction[a]

	Airflow Obstruction[b]	No Airflow Obstruction
Chronic Bronchitis Symptoms[c]	COPD and chronic bronchitis	chronic bronchitis
No Chronic Bronchitis Aymptoms	COPD	None

[a]A given patient can have either, both, or none.
[b]$FEV_1/FVC<0.7$ in spirometry
[c]Chronic cough and sputum production for at least 3 months a year for 2 consecutive years;

CB=chronic bronchitis; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity

Table 5. Chronic Bronchitis Associated Mortality in Different Studies

Study	Patient Group	Follow up (years)	Risk
Annesi and Kaufman 1986[57]	1061 men	22	RR 1.35
Tockman and Comstock 1989[58]	884 men	10	OR 1.65 for chronic phlegm (0.95-2.89)
Copenhagen City Heart Study 1996[5]	16,756 men and women	10	RR 1.1 (0.9-1.3) women, 1.3 (1.1-1.4) men
Buist 1997 (Lung Health Study)[59]	5887 men and women	12.5	HR 1.27 (1.02-1.59)
Pelkonen et al, 2006[6]	1711 men	40	HR 1.49 (1.19-1.88)
Guerra et al, 2009[7] (7)	1412 men and women	30	Adjusted HR 2.2 (1.30-3.79) for age<50
Kim et al, 2012 (NHANES I)[60]	5542 men and women	22	HR 1.2 (0.97-1.40)
Lindberg et al, 2015[52]	1983 men and women	10	HR 1.48 for both, HR 1.63 for men
Pelkonen et al, 2017[53]	47,896 men and women	25	HR 1.25 (2.89 in current smokers, 1.69 in ex-smokers)

RR=relative risk; OR=odds ratio; HR=hazard ratio

death from obstructive lung disease (CB, emphysema and asthma) was studied in approximately 14,000 men and women in the Copenhagen City Heart Study.[55] CMH was associated with a slightly higher risk of death from all causes (relative risk [RR] = 1.1 for women, 1.3 for men). The association between CMH and death from obstructive lung disease increased as lung function worsened.[55] A Finnish study followed approximately 1700 patients for up to 40 years. In patients with CB, all-cause mortality was increased compared to patients without CB (HR 1.30, 95% CI 1.02-1.65). Of note, smokers with CB who decreased their daily cigarette consumption increased their median life span by 2.4 years.[6] The TESAOD followed 1412 patients, of which 97 patients (6.9%) had CB at enrollment. Patients with CB at enrollment had significantly increased risk for all-cause mortality among patients<50 years old but not among patients ≥50 years old (HR 2.2, 95% CI 1.3-3.8 and HR 1.0, 95% CI 0.7-1.3, respectively).[7] In the Lung Health Study, cough alone (17% of patients) or phlegm alone (12% of patients) were not associated with death, but the combination of cough and phlegm (31% of patients) was associated with increased risk of death after adjustment for covariates (HR 1.27, 95% CI 1.02-1.59).[56] Another large Finnish study (FINRISK) followed approximately 48,000 individuals for 3 decades. CB was associated with increased all-cause mortality (HR 1.23) and mortality from respiratory causes, cardiovascular diseases and cancer. Smokers and ex-smokers with CB had an increased risk of death (HR 2.89 and 1.69, respectively) compared with never-smokers without CB.[53] Table 5 summarizes the data for the association between CB and mortality.

Management

Pharmacologic therapy for CB is directed towards 3 major goals: relieving symptoms during stable disease (mucoactive agents, beta-agonists, muscarinic antagonists), reducing loss of lung function (smoking

cessation), preventing exacerbations (mucoactive agents, macrolides, phosphodiesterase-4 [PDE-4 inhibitors]) and treating exacerbations (antibiotics, glucocorticoids) when they occur (Table 6).

Mucoactive Agents

Mucoactive agents can be characterized into 4 major groups according to their mechanism of action: expectorants, mucoregulators, mucolytics and mucokinetics.[61] However, overlap in their mechanisms is common. The goals of mucoactive agents are to reduce overproduction and hypersecretion of mucus, and to increase the elimination of mucus by increasing ciliary transport, reducing mucus tenacity, and increasing shear stress to augment mucus detachment.[62] A large meta-analysis identified 23 double-blind, randomized, placebo-controlled trials on 7335 patients treated with mucoactive agents compared to placebo.[63] The most common medication studied was N-acetylcysteine (NAC) (12 studies), followed by carbocysteine (3 studies). Twenty-one of the 23 studies included CB patients and 2 included COPD patients. Compared with placebo, the number of exacerbations was reduced by 29% in patients who took mucolytics. The number of patients with no exacerbations in the study period was greater in the mucolytic group (odds ratio [OR] 2.22, 95% CI 1.93-2.54, $p < 0.0001$). There was no difference in lung function or adverse events reported between treatment groups.[63]

NAC is an antioxidant and an anti-inflammatory drug that works by increasing synthesis of glutathione and reducing mucus viscosity via cleavage of mucin disulfide bonds.[64] NAC is often prescribed in divided doses of 300 mg–1200 mg daily. Studies regarding the efficacy of NAC have yielded mixed results. The BRONCUS study was a randomized, multicenter study which compared COPD patients treated with NAC (600 mg daily) versus placebo (n=523). There were no significant differences in rate of decline in FEV_1 or exacerbations over the 3-year follow-up period. However, a secondary analysis of functional residual capacity data showed that NAC reduced hyperinflation, but the mechanism of this finding was not clear.[65] The PANTHEON study was a prospective, randomized, placebo-controlled, parallel-group study on patients with moderate-to-severe COPD (n=1006).[66] The exacerbation rate was lower (1.16 versus 1.49 exacerbations/patient/year) in patients who were treated with NAC (600 mg twice daily) compared to placebo. However, this study did not include patients with CB or those without airflow obstruction (GOLD 0).[66] Another randomized, controlled, double-blinded trial of patients with COPD and CB prescribed high-dose oral NAC (1800 mg) or placebo twice daily for 8 weeks. The trial was terminated prematurely due to safety concerns, based on data that showed that vitamin E and NAC stimulated tumor growth and proliferation in mouse models and cell lines. The data collected on 51 patients showed no significant difference in SGRQ or secondary outcomes.[67] Finally, a meta-analysis on 13 studies including 4155 COPD patients showed that those treated with NAC had significantly fewer exacerbations of CB or COPD (RR 0.75, 95% CI 0.66-0.84; $p<0.01$). Interestingly, this effect was more apparent in patients without airflow obstruction.[68] Based on these data, the GOLD 2018 guidelines state that *"currently available data do not*

Table 6. Summary of Pharmacologic Treatments and Suggested Mechanisms for Chronic Bronchitis

Therapy	Mechanism
Smoking Cessation	Improves mucociliary function, increases ASL hydration
Mucoactive Agents	Reduces overproduction and hypersecretion, increases elimination
Hypertonic Saline	Stimulation of productive cough and decreases sputum viscoelasticity
Antibiotics	Antibacterial effects; Immune-modulatory and anti-inflammatory effects (macrolides)
PDE-4 Inhibitors	Augments ASL volume, stimulates ciliary beat frequency
Beta Agonists	Promotes mucus clearance by increasing airway luminal diameter and ciliary beat frequency, reduces hyperinflation, improves peak expiratory flow
Muscarinic Antagonists	Decreases contractility of smooth muscle in the lung, inhibits bronchoconstriction and mucus secretion
Glucocorticoids	Reduces inflammation and mucus production, decreases goblet cell and mucin gene expression and stimulates mucociliary clearance

ASL=airway surface liquid; PDE-4=phosphodiesterase-4

allow one to identify precisely the potential target population for antioxidant agents in COPD."[69]

Erdosteine is a recently developed mucoactive medication with antioxidant and anti-inflammatory properties that modify bacterial adhesiveness.[70] The RESTORE study, a prospective randomized, double-blind, placebo-controlled study of patients with GOLD stage II and III COPD, showed that patients who received erdosteine 300 mg twice daily added to usual treatment reduced exacerbation rates by 19.4% (0.91 versus 1.13 exacerbations/patient/year, p=0.01), mostly due to a reduction of mild exacerbations. No statistically significant difference was observed in the rate of moderate-to-severe exacerbations between the treatment and placebo arms (0.68 versus 0.59 exacerbations/patient/year, p=0.054). Erdosteine did decrease the duration of all exacerbations by 24.6% (9.55 versus 12.63 days, p=0.023).

Hypertonic Saline

Nebulized hypertonic saline stimulates productive cough, decreases sputum viscoelasticity, increases mucociliary clearance and improves lung function in patients with cystic fibrosis (CF).[71,72] It has been shown to be effective in a double-blind, parallel-group trial on 164 patients with stable CF. Patients were randomly assigned to inhale either 7% hypertonic saline or 0.9% saline twice daily for 48 weeks. The rate of change in lung function did not differ between groups, but the absolute difference in lung function between groups favored the hypertonic saline group. The hypertonic saline group also had significantly fewer pulmonary exacerbations (relative reduction 56%, p=0.02) and a significantly higher percentage of patients without exacerbations (76% versus 62% in the control group, p=0.03).[73] Despite the clinical benefits seen in CF, little evidence exists in patients with COPD or CB.[74] Only one study, Valderramas et al, has shown the benefit of hypertonic saline in COPD patients.[75] In this study, hypertonic saline improved dyspnea and exercise capacity when given before rehabilitation sessions. However, whether the improved functional exercise capacity was due to the hypertonic saline or the exercise training remains unclear.[75] Interestingly, even though hypertonic saline is commonly associated with acute respiratory adverse effects, only the latter study reported acute bronchospasm in 4 patients (12%).

Antibiotics

Macrolide antibiotics have immune-modulatory, anti-inflammatory and antibacterial effects. The MACRO study in 2011 was a randomized trial of azithromycin 250 mg once daily versus placebo for one year in 1142 patients with COPD at high risk of exacerbations. In the azithromycin arm, the median time to first exacerbation was longer (266 versus 174 days, p<0.0001) and the exacerbation frequency was lower (1.48 versus 1.83 exacerbations/patient/year, p=0.01). However, hearing decrements were more common (25% versus 20%, p=0.04), and the incidence of macrolide resistance was significantly higher (81% versus 41%, p<0.001) in those treated with azithromycin.[76] A post hoc analysis of the MACRO trial was done to identify the types of exacerbations and subgroups most likely to benefit from azithromycin therapy. Azithromycin was found to be most effective in preventing exacerbations requiring both antibiotics and steroids. There was no difference in efficacy of azithromycin when the groups were stratified by gender, presence of CB, use of oxygen, severity of airflow obstruction, or concomitant COPD therapy. There was, however, no significant effect of azithromycin in those that were currently smoking, probably secondary to the upregulation of mucin secretion (MUC5AC) and down regulation of the respiratory immune function of active smoking which counteracts the down regulation of mucin and reduction of the bacterial load by azithromycin.[77]

Phosphodiesterase-4 Inhibitors

Two major determinants of effective mucociliary clearance are directly regulated by cyclic adenosine monophosphate (cAMP): ciliary beat frequency and cystic fibrosis transmembrane receptor (CFTR) activity.[78,79] PDEs break down cAMP, thereby reducing intracellular cAMP concentrations. PDE4 inhibitors, such as roflumilast, affect mucociliary function in bronchial epithelial cells by increasing CFTR activity, augmenting airway surface liquid [ASL] volume, and stimulating ciliary beating.[80]

Roflumilast has been shown to improve outcomes in CB associated with COPD. Two double-blind, multicenter trials, one using salmeterol (n=466) and the other using tiotropium (n=371) in both arms, randomly assigned patients with moderate-to-severe COPD to roflumilast 500 µg or placebo once daily for 24 weeks. The majority of patients in both studies had CB at study entry. Compared with placebo,

roflumilast significantly improved both pre- and post-bronchodilator FEV_1, increased median time to first exacerbation and improved dyspnea in both studies.[81]

The Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy (REACT) trial randomized 1945 patients with COPD, severe airflow obstruction, and CB with at least 2 exacerbations in the year prior to enrollment to roflumilast 500 µg daily or placebo for 52 weeks. All patients took inhaled corticosteroids (ICSs) and a long-acting beta2 agonist (LABA) during the study, and a background long-acting muscarinic antagonist (LAMA), tiotropium, was allowed. The rate of moderate-to-severe exacerbations was lower in the roflumilast group than in the placebo group.[82] Similarly, the Roflumilast Effect on Exacerbations in Patients on Dual (LABA/ICS) Therapy (RE^2SPOND) study recruited 2254 patients with a nearly identical clinical profile as the REACT trial and randomized them to the U.S. formulation of roflumilast (500 µg daily) or placebo for 52 weeks. Overall, moderate or severe exacerbation frequency was not significantly lower with roflumilast versus placebo. However, in a post-hoc analysis, roflumilast significantly reduced the rate of moderate and severe exacerbations in participants with greater than 3 exacerbations per year and/or one or more hospitalizations in the prior year.[83]

In all studies, withdrawal from the study due to adverse events was more common in those receiving roflumilast. The most frequent adverse effects were gastrointestinal (diarrhea, nausea, reduced appetite, weight loss, abdominal pain), sleep disturbance, and headache.[84] They seemed to occur early during treatment but diminished over time. Based on these studies, the GOLD 2018 report recommended considering the addition of roflumilast in patients with exacerbations and severe airflow obstruction and CB who are not controlled on an ICS/LABA with or without a LAMA.[85]

Bronchodilators

Short-acting beta2 agonists (SABAs) promote mucus clearance by increasing airway luminal diameter and ciliary beat frequency.[62] The regular use of SABA in stable COPD is associated with improvements in lung function and breathlessness.[86] Short-acting muscarinic antagonists (SAMAs) such as ipratropium bromide decrease intracellular concentration of cyclic guanosine monophosphate (cGMP), resulting in decreased contractility of smooth muscle in the lung, inhibiting bronchoconstriction and mucus secretion.[87] Both LABAs and LAMAs improve lung function, dyspnea, and health status and reduce exacerbation rates in patients with COPD.[85] Studies have shown an increased ciliary beat frequency and improved mucociliary clearance with LABAs, and decreased cough with LAMAs. However, there are no data on the use of bronchodilators in CB specifically.[62]

Glucocorticoids

Glucocorticoids have been shown to reduce inflammation and mucus production, decrease goblet cell and mucin gene expression and stimulate mucociliary clearance in vitro.[62] ICSs are a potential treatment option in combination with LABAs and/or LAMAs in COPD GOLD groups C or D, respectively.[85] Systemic glucocorticoids are recommended for the treatment of exacerbations and reduce treatment failure and relapse rates by 1 month, shorten hospital length of stay and improve lung function and symptoms in patients with COPD.[88] The long-term use of systemic glucocorticoids has numerous adverse effects and is not recommended because of the unfavorable risk benefit profile.[85] The effects of either inhaled or systemic glucocorticoids in CB are not known.

Summary

CB is a common disorder that is associated with an accelerated lung function decline, increased risk of exacerbations, and a higher mortality. How it is defined is under evolution. There is a growing need for more studies using a uniformly accepted contemporary definition that reflects not only its clinical phenotype but also embodies its prognostic and therapeutic implications. Cigarette smoking is the most well-established risk factor, but more exposures are being elucidated. As marijuana and electronic cigarette smoking may become increasingly common, more information regarding their harmful effects in regards to CB will come to light. A great need for more information regarding therapy is also apparent. Although a number of options exist, they are either not supported by robust data or are fraught with side effects. Hope exists on the horizon for further research to reveal new therapeutic strategies for this dangerous condition.

Declaration of Interest

Over the last three years, Dr. Kim reports personal fees from Medscape, CSA Medical, Concert Pharmaceuticals, Gala Therapeuatics, AstraZeneca, Boehringer Ingelheim, the American Board of Internal Medicine Critical Care Test-writing Committee and a grant from the National Heart Lung and Blood Institute (K23HL094696), outside the submitted work. All other authors have nothing to declare.

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