Review Article

Mucus Hypersecretion in Chronic Obstructive Pulmonary Disease and Its Treatment

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Most patients diagnosed with chronic obstructive pulmonary disease (COPD) present with hallmark features of airway mucus hypersecretion, including cough and expectoration. Airway mucus function as a native immune system of the lung that serves to trap particulate matter and pathogens and allows them to clear from the lung via cough and ciliary transport. Chronic mucus hypersecretion (CMH) is the main factor contributing to the increased risk of morbidity and mortality in specific subsets of COPD patients. It is, therefore, primarily important to develop medications that suppress mucus hypersecretions in these patients. Although there have been some advances in COPD treatment, more work remains to be done to better understand the mechanism underlying airway mucus hypersecretion and seek more effective treatments. This review article discusses the structure and significance of mucus in the lungs focusing on gel-forming mucins and the impacts of CMH in the lungs. Furthermore, we summarize the article with pharmacological and nonpharmacological treatments as well as novel and interventional procedures to control CMH in COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a pathological entity with heterogeneous and multisystem involvement characterized by a persistent airflow limitation due to enhanced chronic inflammatory response to noxious particles or gases, resulting in progressive loss of lung function and increased morbidity and mortality [1]. COPD greatly reduces patients’ quality of life (QOL) and is the third leading cause of death worldwide [2]. Underdiagnoses remain a common problem due to less awareness of lung function testing in some clinicians, and therefore its prevalence is projected to increase in the coming decades [3]. The death rate of COPD increased by 11.6% in the past 30 years, from 2.8 million in 1990 to more than 3.23 million in 2019 [2, 4]. About 90% of COPD deaths under 70 years of age occurred in low- and middle-income countries [2]. Based on a population survey in China, China has a higher prevalence (8.2%–13.7%) vs. a global age-standardized prevalence of 3.2% (male)/2.0% (female) with a higher mortality rate [5].

COPD includes emphysema and chronic bronchitis (CB) with features of chronic mucus hypersecretion (CMH). CMH is defined by a medical history of chronic cough and sputum production with an increase in goblet cells, enlarged submucosal glands, and mucus production, leading to airway obstruction [6]. Patients with CMH are more likely to have increased severe airway bacterial colonization, frequent and severe exacerbation, reduced lung function, and deterioration of their health status as compared with patients without CMH. It is unknown whether clinical features due to CMH affect the response to COPD treatment, so understanding the impact of CMH may help to predict treatment response and potentially promote the development of new therapies [7].
2. Airway Mucus Expression

2.1. Anatomy and Physiology of Mucus Hypersecretion. The intrapulmonary airway consists of two types of cells: ciliated and secretory cells. Based on their microscopic appearance, secretory cells are further divided into Clara cells, goblet cells, and serous cells [8]. Secretory cells release mucus, antimicrobial, immunomodulatory, and protective molecules [9]. The mucus consists of a mixture of transudative fluid and secretions from the surface epithelium and submucosal glands. It is predominantly composed of water (95%) and macromolecular glycoproteins known as mucins (2%–3%) with smaller components of proteoglycans (0.1%–0.5%), lipids (0.3%–0.5%), proteins, and DNA [10]. Mucus in the airways is made up of a polymeric matrix of large, oligomeric, gel-forming glycoproteins, called mucin, with a protein backbone composed of a variable number of tandem repeats rich in proline, threonine, and serine as well as cysteine-rich regions at the amino and carboxy terminals resembling bottle-brush appearance [11]. Mucins have a molecular weight between $2 \times 10^6$ and $40 \times 10^6$ Da and are composed of 50%–85% carbohydrates [12, 13]. In addition to its physiological role in humidifying the airway, mucus also acts as a physical barrier against infections and toxins, facilitates mucociliary transport, and contributes to the innate defense system of mucosal immunity.

Mucus has largely been implicated in health and disease. It possesses unique biophysical features, including viscoelasticity and a self-healing capability [14]. Constant cilia beating propels the viscoelastic gel layer from the lower airway to the larynx. Owing to this mechanism, pathogens and inhaled particles arriving at the upper airway can be expelled by coughing or swallowing [15]. This host defense mechanism of the lung is known as mucociliary clearance (MCC). In determining the ability of an agent to promote clearance of secretions, both MCC and cough clearance need to be addressed [16].

2.2. Mucin Types. The airway luminal surface is coated with a multiphase mucus film composed of an upper gel layer and a lower liquid sol layer [17]. The upper gel layer, also known as the mucus layer, consists of water, mucins, lactoferrin, and various peptides, and the lower sol or periciliary liquid layer mainly consists of water (Figure 1). The two layers act like a defense barrier known as the “cilia-mucus blanket” [18].
There is a surfactant layer between the mucus gel and peri-
ciliary sol layer, which acts as a lubricant and also facilitates
the transfer of energy from beating cilia to mucus [19].

Twenty-one different human mucins genes are categorized
based on the backbone of their proteins, which are represented
by a MUC gene (MUC1, MUC2, MUC3A, MUC3B, MUC4,
MUC5AC, MUC5B, MUC6, MUC7, MUC8, OVGP1, MUC12,
MUC13, EMCN, MUC15, MUC16, MUC17, MUC19, MUC20,
MUC21, and MUC22), of which 14 are expressed in the respi-
ratory system (Table 1). Different types of mucins with their
chromosome locations are presented in Table 1 [20, 21]. The
mucin family is divided into two subfamilies: secreted mucin
and tethered cell surface-associated mucin. Secreted mucin con-
sists of two nonpolymeric glycoproteins (MUC7 and MUC8)
and five oligomeric gel-forming mucins (MUC2, MUC5AC,
MUC5B, MUC6, and MUC19). The remaining three mucins
are oviductal glycoprotein 1 (formerly known as MUC9), endo-
mucin (also known as MUC14), and MUC22, in contrast to the
11 tethered cell surface-associated mucins (MUC1, MUC3A,
MUC3B, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17,
MUC19, MUC20, and MUC21) [22, 23].

MUC5AC and MUC5B are gel-forming mucins, which
form the most abundantly secreted mucins in the respiratory
tract, accounting for about 75% of all mucins, mainly responsi-
able for the rheological properties of mucus, making up the
glycoprotein component [24]. MUC5AC is mostly produced
in the proximal airway of healthy individuals by surface
goblet cells, while MUC5B is produced by submucosal glands
and surface secretory cells throughout the airway [25]. These
mucins are released in both normal and under stress condi-
tions. Individuals with chronic respiratory disorders have
higher MUC5AC and MUC5B levels in their airways and
sputum. MUC5AC is primarily metabolized by the goblet
airway epithelium, and an abnormal amount or quality of
MUC5AC may impair airway function, leading to serious
airway diseases, including COPD [26].

2.3. COPD Pathogenesis Associated with Mucus Hypersecretion.
In normal situations, the pseudostrati-
fied ciliated bronchial
epithelium contains a mixture of goblet, ciliated, and basal
cells. Exposure to cigarette smoke or pathogens may induce
goblet cell hyperplasia, decrease number of ciliated cells, and
ultimately increase mucus production. Reduced airflow caused
by the mucus-clogged airway contributes to the pathogenesis
of COPD, seriously affecting the workability and QOL of the
patients. Nearly 50% of COPD patients have CMH, with 3.5
fold higher risk of death than those without CMH [27].

2.4. Smoking and COPD. Smoking is a complex mixture of
free radicals and other oxidants, which may cause an imbal-
ance in oxidants/antioxidants in COPD [28]. Cigarette smoke
can cause direct damage to the lung matrix components such
as collagen and elastin. Certain chemicals, including uric acid,
 glutathione, vitamin E, and ascorbate, are decreased in smo-
kers, which is found to be associated with the severity of
COPD exacerbation [29]. Smoking results in mucus dysfunc-
tion, which has severe negative effects on the structure and
function of the cilia by activating ErbB receptors and impair-
ing the cystic fibrosis (CF) transmembrane conductance reg-
ulator function. In addition, the pro-inflammatory activity of
cigarette smoking increases mucin synthesis and decreases
mucus hydration and clearance [30]. Cigarette smoking com-
prises a variety of carcinogens, including particulate matter,
reactive chemicals, and other organic compounds, among which acrolein can strongly stimulate mucus production [31].

2.5. Infection and COPD. Studies have shown that increased mucin formation and decreased luminal fluids in COPD reduce airway mucus clearance, thus increasing the risk of airway infection, inflammation, and fibrosis. The sputum from 25% to 50% of COPD patients carries *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and other bacteria or bacilli, which can trigger the body to produce more mucus [32]. In addition to Gram-negative bacteria, Gram-positive bacteria such as staphylococcus aureus and streptococcus pyogenes can trigger MUC2 gene transcription in epithelial cells [33]. Increased mucus production during COPD exacerbation is often linked to *H. influenzae*. A nontypeable *H. influenzae* upregulates the MUC5AC gene via TLR2-MyD88-dependent p38 MAPK (mitogen-activated protein kinase) pathway [34]. The infection rate increases with the disease severity, and COPD exacerbation is associated with the acquisition of new bacterial strains.

2.6. Alveolar Cells and COPD. The pulmonary alveoli are coated with two distinct types of cells, namely type I and type II pneumocytes. The former type accounts for 95% of the surface area of lung alveoli, while the latter type covers only 5% of the area and is comparatively resistant to damage [35]. In situations where typeII cells undergo damage, typeI cells undergo proliferation, migration, and dispersion along the depleted basement membrane surface. This process leads to the reformation of the epithelium, followed by differentiation into typeI cells. Thus it may help to restore the alveolar epithelial barrier. TypeII cells are responsible for the synthesis, storage, and secretion of pulmonary surfactant, which serves to decrease surface tension within the alveoli and promotes the stabilization of alveolar units, thereby facilitating optimal gas exchange. In addition, they produce diverse cytokines and proteins that have the ability to alter the inflammatory and oxidative stress response, as well as hinder the proliferation of fibroblasts and the synthesis of collagen, both of which are involved in the development of COPD [36].

2.7. Body Weight and COPD. Individuals diagnosed with COPD are more susceptible to the development of obesity due to reduced levels of physical activity and prolonged use of glucocorticoids. Prior studies have indicated approximately 65% of individuals with COPD exhibit excess weight or obesity [37]. While the correlation between obesity and a rise in mortality and morbidity in chronic disease has been well documented, studies have identified a potential protective association between obesity and COPD patients. The term “obesity paradox” describe the inverse correlation between body mass index (BMI) and chronic illness. It has been observed that a higher BMI can have significant protection on the outcome of COPD, while a lower BMI level may accelerate the decline of lung function. Also, overweight (BMI 25–29.99)/obese (BMI > 30) patients exhibit a notable increase in systemic inflammation, particularly in tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-8, and leptin plasma levels, as well as 3.3 times higher C-reactive protein as compared to normal-weight patients. They exhibit a higher average length of hospital stay and utilization of invasive and noninvasive ventilation, indicating a greater strain on the healthcare system [38].

2.8. Immunometabolism of Cells Involved in COPD. The complex interaction between the metabolism and immune response is a crucial factor in the pathogenesis of COPD. Patients in different stages of COPD exhibit a gradual elevation of systemic leptin, a hormone with cytokine-like properties that is primarily secreted by adipocytes. This hormone has been demonstrated to play a significant role in the development of COPD by enhancing Th1/Th17 proinflammatory responses and at high concentrations hindering T cells’ ability to engage in glycolysis and to generate regulatory T cells. The deprivation of these immunoregulatory pathways in COPD instigated the hyperstimulation of effector T cells, which in turn escalated inflammation, ultimately resulting in a gradual deterioration of lung function. Leptin plays a significant role in the enhancement of both innate and adaptive immunity. It directly stimulates the phagocytic activity of macrophages and potentiates the production of different cytokines that are typically involved in the pathogenesis of COPD [39].

2.9. Neutrophil Elastase (NE) and Epidermal Growth Factor Receptor (EGFR) Singling Pathway. The correlation between the number of neutrophils in sputum and decreased pulmonary function suggests a close relationship between neutrophil inflammation and airway mucus obstruction [40]. Patients with chronic airway illnesses have a large amount of NE, a serine protease produced by neutrophils, which can ultimately result in mucus obstruction [41], damage the cilia, and impair their function, leading to mucin production, secretion, and release, secretory cell metaplasia and hyperplasia within the airway. MUC5AC mRNA levels are raised by NE, which improves mRNA stability. Recent investigations have also discovered that MUC5AC gene expression is induced by NE via reactive oxygen species (ROS) [42]. Additionally, NE has been linked to mucin synthesis via EGFR activation and TNF-α secretion, which induces EGFR expression in airway epithelial cells [43]. Mucus hyperssecretion in COPD is affected by inflammatory neutrophils, NE, ROS, EGFR, and neutrophil necrosis [44].

2.10. Cytokines Induce Mucin Production. Cytokines, particularly T helper 2 cytokines such as IL-4, IL-9, IL-13, IL-17A, etc., have been demonstrated as potential stimulators of mucus production [45, 46]. A study postulated that the sterile alpha motif-pointed domain-containing Ets transcription factor (SPDEF) may participate in controlling prostate growth and cancer [47]. However, another study has revealed that SPDEF is also expressed in the airway, where it controls the differentiation of airway epithelial cells. IL3, STAT6, SPDEF, and MUC5AC are the primary singling pathways causing the differentiation of epithelial cells to goblet cells [48]. IL-13 activates Janus kinase 1, which phosphorylates STAT6 after binding to a receptor that
contains the IL-4Rα subunit. Although MUC5AC lacks a consensus STAT6-binding site, STAT6 activation increases the expression of SPDEF, which in turn upregulates numbers of genes involved in mucous metaplasia, and decreases the synthesis of forkhead box A2 (Foxa2), which negatively regulates MUC5AC.

TNF-α binds to cell surface receptors and induces the expression of the EGFR gene in airway epithelial cells, which has been linked to the synthesis of mucin in COPD. IκB kinase (IKK) activation is induced by receptor stimulation. The IκB subunit of intracellular NF-κB is then phosphorylated (P) by IKK at its regulatory site, allowing for transactivation and degradation. This, in turn, releases NF-κB dimers and causes free NF-κB to move into the nucleus, where it activates the expression of target genes MUC5AC. IL-13 activates Janus kinase 1 (Jak1) to phosphorylate (P) STAT6 after binding to IL-4Rα receptors. STAT6 activation increases the expression of SPDEF, which upregulates mucous metaplasia genes and reduces forkhead box A2 (Foxa2), which negatively regulates MUC5AC.

2.11. Immune Cells and COPD. The functionality of the immune system is the outcome of the interplay between diverse immune cells and cytokines. T lymphocytes, B lymphocytes, and NK cells are crucial constituents of immune cells. Mature T cells have the ability to differentiate into distinct cell subsets, including CD3+CD4+CD8-T and CD3+CD4-CD8+ T-cell subsets. Numerous cytokines are released by activated CD4+ T cells, and these cells control the action of other inflammatory cells by producing perforin,
granzyne B, and TNF-α to reduce infected cells and help in the degradation and apoptosis of alveolar epithelial cells. Studies show a high correlation between the proportion of CD8+ T cells and the development of COPD. Depending upon the type of cytokines produced, CD4+ T cells produce type 1 T helper (Th1) or Th2 cells. TNF-α, IFN-γ, and IL-2 are the primary product of Th1 cells, while Th2 cells produce IL-4, IL-10, and IL-16, which stimulates B lymphocyte growth to produce IgG and IgE, which is a key factor in humoral immunity. Studies have shown acute exacerbation of COPD (AECOPD) patients had elevated IL-17 levels, which may encourage neutrophil recruitment and infiltrates into COPD inflammatory areas. Compared to patients with stable COPD, AECOPD exhibits greater levels of IL-2, IFN-γ, IL-4, IL-10, IL-17, and IgE, and they have lower Th1/Th2 and IL-17/IgE ratios probably due to increased production of Th2 cells [53, 54].

2.12. Innate Lymphoid Cells and COPD. Innate lymphoid cells (ILCs)—ILC1, ILC2, and ILC3, are specialized cells of lymphoid origin that are present in the lung at a steady state and are active contributors to the progression of chronic lung diseases. ILCs are detected in the parenchyma in healthy individuals and also in lymphoid aggregated COPD and smokers. Studies suggest an elevated level of ILC1 in COPD patients correlating the risk of exacerbations, suggesting they could be used as a marker for the disease progression. ILC2s can turn into ILC1s in the context of COPD, indicating a skew into type 1 inflammation. In the setting of smoking-induced COPD, ILC2s play a role in neutrophil recruitment. Their absence protected against emphysema while promoting fibrosis by increasing IL-13 and IL-33 levels. ILC2s have also been linked to the promotion of Th2 adaptive responses during AECOPD [55].

2.13. Treatment. The prevalence of cough and expectoration, along with the anticipated role of mucus in the pathogenesis of COPD, leads to develop medications to treat CMH. The main objective of mucus control should be aimed at reducing the mucus secretion rate and a reasonable viscosity of the mucus to ensure effective clearance. Smoking cessation is a simple but most effective way to reduce excesses mucus production. Bronchodilators, inhaled corticosteroids (ICS), and expectorant therapy have been used to treat mucus hypersecretion to prevent or attenuate airway stenosis and slow down the deterioration of lung function (Table 2).

3. Pharmacological Treatment

3.1. Hypertonic Saline (HS) Aerosol. Sputum expectoration has traditionally been induced by HS aerosol for diagnostic evaluation as well as for respiratory care [56]. Hypertonic solution inhalation facilitates water movement down the concentration gradient across the water-permeable airway epithelium into the luminal compartment. This additional volume of water is expected to reduce the mucus solid concentration, thus improving the airway secretion transportability. HS can also disrupt ionic bonds and improves MCC [57]. The MCC rate is reduced in CF. Studies have demonstrated that either single or repeated HS inhalation in CF patients can produce long-term effects on MCC and reduce exacerbation [58]. Despite the beneficial effects of HS on CF, no convincing evidence or long-term study of the therapeutic value of HS in COPD has been reported.

3.2. Oral Guaifenesin (GGE). The effects of oral GGE as an expectorant and a cough suppressant have been investigated. It stimulates receptors in the gastrointestinal (GI) mucosa via the gastro-pulmonary reflex. Increased stomach vagal stimulation and consequent vagal activity in the airways may promote MCC [59]. Studies on CB patients have shown that GGE reduces secretion, viscosity, elasticity, mucin synthesis, mucociliary transport, and cough reflex sensitivity [60]. The US Food and Drug Administration has approved GGE as an over-the-counter expectorant [59], but few clinical trial data are available to provide sufficient evidence to support the hypothesis that this oral expectorant can improve the subjective well-being or lung function of COPD patients.

3.3. Bronchodilators. The use of bronchodilators has a central role in COPD treatment. Bronchodilator relaxes the airway smooth muscle tone, reduces respiratory muscle activity, and improves ventilation. It lowers airway resistance and inspiratory muscle elastic load during constant work rate exercise. In the peripheral airway, it reduces air trapping and, thus, lung volumes [61]. Currently, three classes of bronchodilators are available: beta2-agonist, anticholinergic, and methylxanthines. These can be used alone, or in combination with one another, or with or without ICS.

3.4. Beta2-Agonists. They act by activating beta2 adrenergic receptors, which increase cyclic AMP and provide functional antagonism to bronchoconstriction and are able to relax airway smooth muscles and reduce bronchoconstriction. They also help to improve MCC in COPD and thus reduce the rate of COPD exacerbations [7]. It includes short-acting beta2 agonists (SABA) and long-acting beta2 agonists (LABA). SABA includes salbutamol and terbutaline and has been used as a rescue medication for COPD with a duration of action of 4–6 hr. So its efficacy is limited for a maintenance dose. Regular and as-needed SABA administration improves both symptoms and FEV1 [62, 63]. On the other hand, LABA is used in stable COPD. It shows the duration of action more than 12 hr. Salmeterol and formoterol are used as two times daily doses, whereas indacaterol and olodaterol, and vilanterol are used as once-daily doses [64]. However, beta2-agonists can increase heart rate and produce sinus tachycardia, dose-dependent tremor, and hypokalemia by stimulating Na+, K+–ATPase-driven pump connected to beta2 adrenoceptors in skeletal muscles. In addition, they induce glycoegenolysis and raise blood sugar, and also temporarily lower the partial pressure of arterial oxygen, but the therapeutic importance of these changes is unknown [63, 65].

3.5. Anticholinergic. By acting on the muscarinic receptor, anticholinergic is believed to facilitate mucus clearance by increasing luminal sizes and reducing surface and submucosal gland mucin secretion. Muscarinic receptors are mostly present on autonomic effector cells supplied by postganglionic
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of action</th>
<th>Drug name</th>
<th>Adverse effects</th>
<th>Note</th>
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</thead>
<tbody>
<tr>
<td>Inhaled short-acting β2-agonist (SABA)</td>
<td>Stimulates β2 adrenergic receptors, increasing cyclic AMP with functional antagonism to bronchoconstriction</td>
<td>Albuterol (salbutamol), levalbuterol</td>
<td>Sinus tachycardia, dose-dependent tremors, and hypokalemia, temporarily lower partial pressure of arterial oxygen</td>
<td>In most cases, used for mild diseases with low symptoms or more advanced diseases to relieve acute symptoms in addition to maintenance inhalers</td>
</tr>
<tr>
<td>Inhaled long-acting β2-agonist (LABA)</td>
<td></td>
<td>Salmeterol, formoterol, indacaterol, olodaterol, vilanterol</td>
<td>Headache, sinus tachycardia, dose-dependent tremor, and hypokalemia, temporarily lower partial pressure of arterial oxygen</td>
<td>Selected as maintenance therapy when short-acting bronchodilators do not give adequate relief of symptoms</td>
</tr>
<tr>
<td>Inhaled short-acting muscarinic antagonist (SAMA)</td>
<td>Blocks bronchoconstriction effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscles</td>
<td>Ipratropium bromide, oxitropium bromide</td>
<td>Foul smell, dry mouth, urinary retention, impaired vision, progressive narrow-angle glaucoma, and cataracts</td>
<td>In most cases, used for mild diseases with low symptoms or more advanced diseases to relieve acute symptoms in addition to maintenance inhalers</td>
</tr>
<tr>
<td>Inhaled long-acting muscarinic antagonist (LAMA)</td>
<td>Inhibition of cyclic nucleotide phosphodiesterases with competitive antagonism of adenosine receptors with bronchodilator and anti-inflammatory effects</td>
<td>Tiotropium bromide, aclidinium bromide, glycopyrronium bromide, umeclidinium, glycopyrroate, revefenacin</td>
<td>Headache, restless, insomnia, nausea, vomiting, cardiac flutter, tachycardia, seizure, and status epilepticus with higher doses</td>
<td>Not suggested unless other long-acting bronchodilators are either intolerable or costly</td>
</tr>
<tr>
<td>Methylxanthine</td>
<td>Anti-inflammatory and suppression of IL-13-induced goblet cell metaplasia and reduce MUCSAC and ATP-stimulated mucus secretion</td>
<td>Theophylline, doxofylline</td>
<td>Oral candidiasis, pneumonia, skin bruises, hoarse voice</td>
<td>Typically combined with a long-acting bronchodilator rather than administered alone in patients at risk for exacerbation</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>Selective inhibitors of PDE-4 inhibiting the breakdown of intracellular cyclic AMP with anti-inflammatory effects</td>
<td>Fluticasone, budesonide, beclomethasone</td>
<td>Diarrhea, weight loss, insomnia, and depressive moods</td>
<td>In patients with moderate to severe COPD, it is recommended as a maintenance therapy for the prevention of exacerbations</td>
</tr>
<tr>
<td>Phosphodiesterase-4 inhibitors</td>
<td>Reduce airway mucus secretion with anti-inflammatory effects</td>
<td>Roflumilast</td>
<td>Nausea, diarrhea, abdominal pain</td>
<td>Recommended as a maintenance therapy for the prevention of exacerbations</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Expectorant with mucokinetic, antioxidant, and anti-inflammatory properties and can induce surfactant formation with inhibition of neuronal sodium channels</td>
<td>Azithromycin</td>
<td>Occasional GI side effects but are mild in nature</td>
<td>As an expectorant with antioxidative and anti-inflammatory properties, it enhances antibiotic levels in the lung tissue and mucus and minimizes exacerbation when given with antibiotics</td>
</tr>
<tr>
<td>Ambroxol</td>
<td>Mucolytic agents act by lowering S-S bonds with antioxidant, anti-inflammatory properties</td>
<td>Ambroxol</td>
<td>Nausea, vomiting, foul smell, dry mouth</td>
<td>As mucolytic agents with antioxidants, anti-inflammatory, and antibacterial properties, it reduces mucus viscosity by lowering S-S bonds in mucus proteins and acts as a source of replacement for intracellular glutathione level</td>
</tr>
</tbody>
</table>
parasympathetic neurons [65, 66]. As many as five distinct muscarinic receptors (M₁–M₅) have been identified, of which three (M₁–M₃) are present in the lung. Antimuscarinic drugs block acetylcholine’s bronchoconstriction actions on the M₃ receptor in the airway [66]. Ipratropium, which is a short-acting antimuscarinic antagonist, inhibits M₂ inhibitory neuronal receptors that contribute to vagally produced bronchoconstriction. Tiotropium, which is a long-acting antimuscarinic antagonist (LAMA), has a longer duration of binding to M₃ receptors with a faster duration of dissociation from M₂ receptors, extending the duration of the bronchodilator effect [67, 68]. Antimuscarinic drug administration frequently causes a foul smell and dry mouth [69]. Older males who use these substances may develop urinary retention. Therefore, these drugs should be taken with caution in individuals who have prostatic hypertrophy or bladder outlet obstruction [62]. Inhaled antimuscarinic medications have been associated with a number of ophthalmic side effects, such as impaired vision, increased intraocular pressure, progressive narrow-angle glaucoma, and cataracts [65]. Possible links between antimuscarinic medications and cardiovascular morbidity and death have given rise to concerns [70, 71].

3.6. *Methyloxanthines*. Methyloxanthines is a bronchodilator and anti-inflammatory agent that acts by increasing water flux toward the lumen and stimulating the ciliary beat frequency to improve mucus clearance. By increasing cyclic adenosine monophosphate in cells, they can increase the airway lumen diameter, promote cilia motion, and activate transmembrane regulators to induce chloride ion secretion and mucus hydration, resulting in airway cilia transport. Because of its narrow therapeutic window and drug–drug interaction, it is considered a third-line therapy in COPD [72]. Theophylline, a xanthine derivative, has been used to treat COPD for a long time not only because they are afford-able and widely available but also because it improves both FEV₁ and forced vital capacity in COPD patients as well as increases exercise tolerance [73]. Withdrawal of theophylline produces significant clinical deterioration in patients with severe COPD, despite therapy with alternative bronchodila-tors, showing its added utility [74]. Nevertheless, recommendations for theophylline in the treatment of COPD differ among national guidelines, most likely due to the fact that it is less effective and tolerated than inhaled long-acting bronchodi-lators and ICS that show superior anti-inflammatory action [75]. Because of its narrow therapeutic window and the tend-ency of pharmacological interactions, theophylline is downgraded to the second or third line of therapy, making its usage difficult, particularly in older individuals with comorbidities receiving many classes of medicine [72, 76]. Another xanthine derivative, doxofylline, differs structurally from theophylline in that position 7 of the xanthine ring contains a dioxyanol group [77]. There is evidence that at least doxofylline is a useful bronchodilator for alleviating airway obstruction and has a safer profile than theophylline, with a favorable risk-to-benefit ratio. These data imply that it may be a feasible option for theophylline in the management of COPD patients [78].

3.7. *Inhaled Corticosteroids (ICS)*. Corticosteroids are a group of potent anti-inflammatory drugs commonly used in the treatment of AECOPD. The use of ICS can suppress IL-13-induced goblet cell metaplasia and reduce MUC5AC and ATP-stimulated mucus secretion, and also restore MUC5B protein levels [79]. ICS therapy is used in half of COPD patients, but its effectiveness in clinical settings is limited. The use of ICS is based on the association between COPD–Asthma overlap syndrome. ICS therapy reduces exacerbation and lowers the course of respiratory symptoms with little or no effect on lung function or mortality. However, ICS is not suggested as monotherapy. A long-term decline in FEV₁ and mortality related to COPD have not been reported to be affected by regular use of ICS alone [80, 81]. A randomized clinical trial (RCT) provides more evidence that the use of ICS alters airway microbes and is linked to an increased risk of oral candidiasis, pneumonia, skin bruises, hoarse voice, etc. [81, 82]. Numerous studies have shown a relation between COPD patient’s blood eosinophil counts and the effects of ICS. The thresholds of <100 and 300 cells/µl should be viewed as estimated rather than specific cutoff values that can anticipate various probabilities of treatment benefits [83]. In moderate-to-severe COPD patients, compared to LAMA alone or LABA + LAMA or LABA + ICS, the step-up inhalation therapy with LABA + LAMA + ICS (triple therapy) has been documented to improve lung function with reduced exacerbation rate and patients outcomes [84, 85].

3.8. *Phosphodiesterase-4 (PDE4) Inhibitors*. PDE4 inhibitors are a group of nonsteroidal anti-inflammatory medications that control cough reflexes and prevent mucus secretion from the airway. Roflumilast, a selective PDE4 inhibitor, has been extensively studied for its efficacy and safety in COPD. In addition to use as a baseline therapy, PDE4 reduces neutrophilic and eosinophilic inflammatory mediators in the sputum of COPD patients [86]. A 24 weeks clinical study in Roflumilast-treated patients showed both pre- and postbronchodilator FEV₁ and QOL were significantly improved as measured by St. George Respiratory Questionnaire [87]. Another multicenter RCT in severe COPD patients who experienced frequent exacerbation showed that the addition of Roflumilast to ICS/LABA or ICS/LABA/LAMA could reduce the severity of COPD exacerbation and the frequency of hospitalization. However, the occurrence of GI adverse events such as diarrhea, weight loss, insomnia, and depressive moods was higher in the Roflumilast treatment group [88, 89].

3.9. *Macrolide Antibiotics*. The cause of airway infection in COPD is multifactorial and bacterial infections are involved in almost half of the cases of COPD, so empirical antibiotics are indicated [90]. Most clinical guidelines suggest a risk stratification approach in selecting antibiotics. Beyond antimicrobial effects, some antibiotics also have mucoactive effects. Macrolide antibiotics are characterized by a macro-cyclic lactone ring, with better bioavailability and extensive tissue penetration with broad-spectrum antibiotic effects, which makes them effective for treating various respiratory infections. Studies have also shown that macrolide possesses
a variety of immune modulatory anti-inflammatory and antiviral effects by reducing mucus secretion and inhibiting bacterial virulence [91]. Macrolides or other antibiotics are not used prophylactically for long-term care of patients with COPD. But for most patients, the benefits of long-term use of antibiotics do not outweigh the risks. However, in selected patients with severe COPD with frequent exacerbation (≥2/year), macrolide prophylactics may be advantageous despite optimal medical treatment. When prescribing a macrolide for long-term prophylaxis, azithromycin 250 mg is usually used daily, or 250–500 mg three times per week. Although the long-term duration is not defined, a 12 month course is commonly used [92, 93]. A systemic review shows the number of patients who experienced ≥1 exacerbation was reduced after the use of prophylactic antibiotics. As a result, their QOL and FEV1 were improved, serious adverse events such as long QT interval and tinnitus were reduced, and the frequency of hospital admission was shortened [90]. The risk associated with the development of antibiotic resistance should be taken into account in deciding long-term prophylaxis with macrolide antibiotics [94].

3.10. Ambroxol. Ambroxol is an expectorant with mucociliary activity in addition to its mucokinetin, antioxidant, and anti-inflammatory properties. It can induce the formation of surfactants in alveolar type II cells and provide a local anesthetic effect as well [95]. Some studies have demonstrated its potential to enhance the antibiotic level in the lung tissue and mucus as well as ability to minimize exacerbation in patients in a more severe state when given in conjunction with antibiotics [96, 97]. The use of ambroxol in COPD patients can stimulate sputum clearance, relieve clinical symptoms, and improve lung and immunological functions in AECOPD, thus improving the QOL of the patients and shortening the length of hospital stay [95, 98].

3.11. Thiol Derivatives. Thiol derivatives such as N-acetylcysteine (NAC), erdosteine, and carbocysteine have typically been viewed as mucolytic medications as they can reduce the viscosity and flexibility of transbronchial secretion by lowering S–S bonds in mucus proteins and acting as a source of replacement for intracellular glutathione level [99]. In addition, they possess antioxidant, anti-inflammatory, and antibacterial properties to improve antibiotic therapy [100]. A meta-analysis study that compared the effectiveness of thiol-based drugs showed mucolytic/antioxidant agents significantly reduced the risk of AECOPD, and the effectiveness was erdosteine > carbocysteine > NAC [101]. Carbocysteine, when available, may be an option for treating frequent COPD exacerbations in patients who are unable to use ICS in combination with LABA or LAMA. However, there is no conclusive evidence that these agents can effectively reduce exacerbations when added to more established inhaled regimens [102].

3.12. Novel Therapy. Targeted treatment of pathological airways improves symptoms of cough and dyspnea, decreases the frequency of disease-related exacerbations, and slows down disease progression. But most current treatments mainly aim at relieving symptoms; they face difficulties in clinical efficacy with poor adherence. There is a lack of fully developed therapeutic approaches that can alter metabolism to combat COPD. Novel therapeutic strategies for COPD patients are the subjects of interest and ongoing studies in the future.

3.13. Peptides Related to Myristoylated Alanine-Rich C Kinase Substrate (MARCKS). MARCKS protein has been found to play an important role in airway mucin secretion control. It is a crucial intracellular molecule involved in mucin granule intracellular migration and exocytosis. Studies showed that MARCKS synthesis was inhibited using an antisense oligonucleotide, which reduced both mRNA and protein levels of MARCKS and mucin secretion as well. In addition, MARCKS inhibition was suppressed by a synthetic peptide to its N-terminus (MANS peptide) in vitro and in vivo by normal human bronchial epithelial cells and mouse airway epithelial cells [103, 104].

3.14. Human Alveolus Retinoic Acid (RA). Alveolar regeneration is aided by angiogenesis, which is stimulated by either endogenous RA or an exogenous retinoid activating RA signaling in the microvascular endothelium. Several RA receptors (RAR), including RAR-gamma, are studied as inhibitors of alveolar damage. The receptor RAR-alpha, on the other hand, appears to be implicated in mucin expression as well as the establishment and maintenance of hyperecretory phenotype. Some of these functions could be inhibited by RAR-alpha antagonists such as RO-41-5253 [105], and therefore it would be of interest to develop selective RAR-alpha antagonists for the treatment of mucus hypersecretion in respiratory disorders, including COPD [106, 107].

3.15. Inhibitors of Phosphodiesterase 5 (PDE5). PDE5 has been reported to have anti-inflammatory effects. Sildenafil, a powerful PDE5 inhibitor, has been shown to have anti-inflammatory effects on the respiratory tract, goblet cell metaplasia, and the production of MUC5A by cGMP signaling pathway [108].

3.16. Calcium-Activated Chloride Ion Channel 1 (CLCA1). Patients with chronic lung diseases like COPD have goblet cell hyperplasia, which is expressed by the human CLCA1 [109]. Human CLCA 1 inhibition reduces mucin expression. Nilumic acid, a relatively specific CLCA inhibitor, has been shown to inhibit human CLCA 1 and reduce the expression of mucin in both animal and human airway mucosa [110].

3.17. Immune Cell Therapy (ICT). The potential of ICT as a novel treatment for COPD is under investigation. The field of ICT refers to regulating the immune system and reducing lung inflammation through the utilization of immune cells, including macrophages, regulatory T cells, and NK cells. The safety and efficacy of these medications have been demonstrated in animal testing. A study shows ACT can greatly enhance the level of immune cells in the body while maintaining it for a long time. However, more studies are necessary to determine their therapeutic potential in more human clinical trials in COPD [54].
3.18. **EGFR Tyrosine Kinase Inhibitor.** Through the EGFR pathway, NE and ROS can cause mucus hypersecretion leading to exacerbation of COPD associated with a decline in FEV1 [43]. The role of selective EGFR tyrosine kinase inhibitors has been studied in the treatment of mucus hypersecretion in vivo (BIBX 1522) [111, 112]. Human trials are necessary to define the role of EGFR inhibitors in the treatment of mucus hypersecretion.

3.19. **Surfactants.** The lubricating properties of surfactant between the mucus gel and periciliary sol layer facilitate the transfer of energy from cilia beating to mucus. Although the use of surfactants is still experimental, aerosolized surfactants in stable CB patients show an increase in sputum transport by cilia and an improvement in pulmonary function [113, 114].

3.20. **Interventional Bronchoscopy Therapy.** Despite extensive treatment, symptoms of CB progress over time, and it is challenging to treat them. Numerous experimental bronchoscopy therapies are recently studied, but larger studies are required to validate the benefits of this interventional therapy which are still in the early stages of clinical testing. A more significant idea of this therapy evaluation has revealed encouraging results on the frequency of exacerbation [115, 116]. Some of the bronchoscopy therapies are noted in Table 3.

### Table 3: Interventional bronchoscopy procedure.

<table>
<thead>
<tr>
<th>Interventional bronchoscopy procedure</th>
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<tr>
<td>Bronchial rheoplasty</td>
<td>Reduces symptoms and goblet cell hyperplasia by delivering nonthermal pulsed electric fields to mucus-producing airway cells</td>
</tr>
<tr>
<td>Resector balloon desobstruction</td>
<td>Through bronchial lumen, a resector latex balloon is inflated and deflated causing disruption of hyperplastic goblet cells</td>
</tr>
<tr>
<td>Targeted lung denervation (TLD)</td>
<td>Bronchoscopy radiofrequency ablation is used to disrupt pulmonary parasympathetic nervous system, which is responsible for airway inflammation and mucus hypersecretion</td>
</tr>
<tr>
<td>Spray cryotherapy</td>
<td>Uses nitrogen spray, which can induce airway tissue repair without scarring by destroying hyperplastic goblet cells and excess submucosal glands</td>
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4. **Nonpharmacological Treatment**

4.1. **Exercise in COPD.** Patients with COPD often have a disproportionate metabolic cost of performance compared to healthy people of the same age, including early onset lactic acidosis and decreased optimum effort and oxygen consumption. Patients’ QOL is often adversely affected since they are confined to their homes and are unable to engage in their usual activities of everyday life. However, early research from the 1990s showed that patients with COPD who engaged in high-intensity training showed improvements in their skeletal muscle oxidative capacity and exercise-induced lactic acidosis. Low-intensity training is safe for those with COPD and is recommended for individuals with more advanced diseases [117]. According to the American Lung Association, COPD patients should engage in (1) pulmonary rehabilitation (programs that teach about lungs and disease and how to exercise and be more active while experiencing less shortness of breath), (2) stretching, (3) aerobic exercises like walking, riding, and swimming, and (4) resistance training [118].

4.2. **Smoking Cessation.** Cutting down the number of cigarette smoking is one of the prime interventions that should be initiated by patients themselves as well as policymakers should implement new strategies for it [119]. It is the most cost-effective method to prevent lung function deterioration in COPD patients [120].

4.3. **Chest Physiotherapy.** Chest physiotherapy is an essential component of COPD management. For individuals with severe COPD, chest physiotherapy may provide further clinical benefits [121]. Over the years, numerous methods have been proposed for treating COPD, including postural drainage, forced expiratory technique, assisted coughing, oscillatory positive-expiratory pressure devices, autogenic drainage, high-frequency chest wall oscillation, intrapulmonary percussive ventilation, intermittent positive pressure breathing, and temporary positive expiratory pressure. All these methods aim to clear secretions of the bronchial tree [122]. The question of whether or not these methods are effective during an acute exacerbation or stable disease remains unclear.

5. **Conclusion**

COPD is one of the major causes of morbidity and mortality in the world, imposing an expanded financial and social burden. The prevalence of COPD is directly related to the rate of smoking in the country and among different groups, though environmental air pollution is additionally likewise a sizeable hazard issue. Due to solid continuing exposure to risk factors and the aging of the population, the burden and prevalence of COPD will increase in the coming decades. Overproduction and hypersecretion of goblet cells and a decreased elimination of mucus are reasons behind hypersecretion leading to exacerbation and decreased QOL. Given the consensus that mucus hypersecretion contributes significantly to the pathophysiology of chronic airway diseases, inhibition of CMH should be a therapeutic focus in future research. The conventional guidelines, including both pharmacological and nonpharmacological treatment, are not fully effective. Therefore, it is ideal to optimize the strongest possible results aiming at developing effective molecules as well as interventional procedures that can hinder pathophysiological pathways and explore strategies to prevent and treat disease exacerbation.
Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

CW and SX contributed to the conception, design, and drafting of the manuscript. All authors contributed to the acquisition, review, and approval of the final version of the manuscript.

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