Chronic Obstructive Pulmonary Disease Treatment Guidelines

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Abstract

Chronic obstructive pulmonary disease (COPD) affects one-tenth of the world's population and has been identified as a major global unmet health need by the World Health Organization. Increased healthcare resource use is common among patients with frequent exacerbations, and exacerbations are a major cause of the high 30-day hospital re-admission rates associated with COPD. Timely and appropriate maintenance pharmacotherapy, particularly dual bronchodilators for maximizing bronchodilation, can significantly reduce exacerbations in patients with COPD. Additionally, multidisciplinary disease-management programs include pulmonary rehabilitation, follow-up appointments, aftercare, inhaler training, and patient education that can reduce hospitalizations and readmissions for patients with COPD. With the availability of newer pharmacotherapy options, treatment recommendations are made on the basis of a review of the latest literature and directed by symptom burden and health care utilization.

Key words: *COPD; GOLD; bronchodilators; exacerbations; inhaler corticosteroids; LAMA/LABA*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major social, economic and health burden since it is the third most common cause of death worldwide [1]. COPD prevalence in Europe ranges between 4% and 10% [2]. COPD is underdiagnosed and often misdiagnosed, which contributes to the continuing increases in the prevalence, morbidity, and mortality. It is a common, preventable, and treatable disease which is characterized by persistent respiratory symptoms and airflow obstruction that is due to airway and/or alveolar abnormalities. These are usually caused by significant exposure to noxious particles and/or gases. It has been repeatedly suggested that management of the very large number of patients with COPD can be improved by the development and implementation of evidence-based diagnostic/screening and treatment guidelines. The objective of this review is to overhaul the evidence recently published in order to define COPD characteristics able to suggest a therapeutic algorithm.

BASIC MECHANISMS OF COPD

COPD is characterized by a partially reversible airflow obstruction and an abnormal inflammatory response in the lungs. The latter represents the innate and adaptive immune responses to long-term exposure to noxious particles and gases, particularly cigarette smoke. All cigarette smokers have some inflammatory burden in their lungs, but those who develop COPD have an abnormal response to inhaling toxic agents. This amplified response may result in mucous hypersecretion (chronic bronchitis), tissue destruction (emphysema), and disruption of normal repair and defense mechanisms, causing

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small airway inflammation and fibrosis (bronchiolitis). These pathological changes result in increased resistance to airflow in the small airways, increased compliance of the lungs, air trapping, and progressive airflow obstruction-all of which are characteristic features of COPD. Inflammation is present in the lungs, particularly the small airways, of all people who smoke. This normal protective response to the inhaled toxins is amplified in COPD, leading to tissue destruction, impairment of the defense mechanisms that limit such destruction, and disruption of the repair mechanisms. In general, the inflammatory and structural changes in the airways increase with disease severity and persist even after smoking cessation. Besides inflammation, two other processes are involved in the pathogenesis of COPD-an imbalance between proteases and antiproteases and an imbalance between oxidants and antioxidants in the lungs [3]. Neutrophils, macrophages and T lymphocytes are inflammatory cells which release a plethora of cytokines and mediators that participate in the disease process, such as Leukotriene B4, TNFa, TGFβ, IL-1B and IL-6. Increased production of proteases (cathepsins G, E, A, L, metalloproteases, protease 3 and serine proteases elastase) and inactivation of antiproteases including a1-antitrypsin and secretory leucoprotease inhibitor results in imbalance. Oxidative stress can lead to inactivation of antiproteases or stimulation of mucous production. It can also amplify inflammation by enhancing transcription factor activation (such as nuclear factor κB) and hence gene expression of pro-inflammatory mediators [3].

AETIOLOGY OF COPD

Worldwide, the most common cause of COPD is tobacco smoking. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater decline in FEV1 and a greater mortality rate than non-smokers. There is a significant correlation between indoor and outdoor air pollution including burning of the wood and other biomass fuels and the incidence of COPD. Genetic factors such as severe hereditary deficiency of alpha-1 antitrypsin, the gene encoding matrix metalloproteinase 12 (MMP-12) and glutathione S-transferase, as well as aging and female sex have been related to a decline in lung function or risk of COPD. Chronic bronchitis, any type of infections, asthma and airway hyperreactivity may increase the frequency and severity of exacerbations [4].

DIAGNOSTIC CRITERIA AND CLASSIFICATION OF SEVERITY OF COPD

Early screening for COPD is based on early detection in primary care medicine. Recent studies have highlighted the need for the application of scores to increase diagnosis of COPD by using spirometers in general primary practice [5]. The objective of screening is to accurately detect airflow obstruction, even in patients with few symptoms. COPD should be considerate in any patient who has dyspnea, chronic cough and sputum production and/or a history of exposure in risk factors. Spirometry is the most objective method to make the diagnosis. The presence of post-bronchodilator FEV1/FVC <0.70 confirms the airflow limitation and thus of COPD in patients with appropriate symptoms and significant exposures to noxious stimuli. Despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its weak specificity [6].

There is a wide use of the FEV1/FVC ratio as the primary factor in determining the presence or absence of airway obstruction but there are differences of opinion about what value of FEV1/FVC should be used for this purpose. Currently, there are two main schools of thought; those that advocate the use of the GOLD fixed 70% ratio and those that instead advocate the use of the lower limit of normal (LLN) for the FEV1/FVC ratio. There is some evidence that individuals with an FEV1/FVC ratio below 70% tend to have more significant lung disease and a higher mortality. Numerous studies, however, have shown that the GOLD threshold overestimates airway obstruction in the elderly and the tall and underestimates it in the young and the short. The main predictors beyond the FEV1/FVC ratio for an expert diagnosis of COPD were the FEV1 % predicted, and the residual volume/total lung capacity ratio (RV/TLC). Adding FEV1 and RV/TLC to GOLD or LLN improved the diagnostic accuracy, resulting in a significant reduction of up to 50% of the number of misdiagnoses. GOLD criteria over-diagnose COPD, while LLN definitions under-diagnose COPD in elderly patients as compared to an expert panel diagnosis. Incorporating FEV1 and RV/TLC into the GOLD-COPD or LLN-based definition brings both definitions closer to expert panel diagnosis of COPD, and to daily clinical practice [7,8].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposes that patients are stratified according to disease severity, with the incorporation of symptoms determined with the modified Medical Re-

search Council (mMRC) scale or the state of health using the COPD Assessment Test (CAT), as well as the patient's history of exacerbations and post-bronchodilator (pb) FEV1%. Patients are classified according to risk: low risk (pbFEV1%≥50% or <2 exacerbations in the previous year) and high risk (pbFEV1%<50% or ≥2 exacerbations in the previous year). The risk index must be determined according to airflow limitation and history of exacerbations. Depending on the symptomatic impact, patients are classified as having less symptoms (CAT<10 or mMRC 0–1) or more symptoms (CAT≥10 or mMRC≥2). Thus, four categories are identified: A (low risk, less symptoms), B (low risk, more symptoms), C (high risk, less symptoms), D (high risk, more symptoms). The proposed therapeutic approach is different for each group [9,10] (Figure 1).

COPD MANAGEMENT

Reduction in the risk of exacerbation, along with symptom management, is the cornerstone of the current strategy for management of COPD. The main components of COPD management are appropriate pharmacotherapy (that addresses both symptom management and exacerbation prevention), promotion of smoking cessation, pulmonary rehabilitation, and regular follow-up monitoring for disease progression.

Smoking cessation and risk factor avoidance

Smoking cessation remains the only intervention definitively known to halt the progression of COPD, and several studies have demonstrated that early smoking cessation has the potential to slow down or even reverse accelerated decline in lung function, highlighting the importance of intervention in early disease [11]. As previously shown by Anthonisen et al., special programs in supporting smoking cessation can achieve a reduction in terms of all-cause mortality, even if those interventions are successful only in a minority of patients [12]. One explanation of a better survival in former smokers is partly attributable to the prevention of smoking damage over time -lower functional decay of the lung [13] and increased risk of cancer and cardiovascular diseases in smokers [12] and partly to the greater pharmacological efficacy of compounds containing ICS [14]. Interestingly, in a recent Delphi consensus project run in Italy, the most effective step to reduce lung functional decline were considered by the 207 specialists interviewed to be smoking cessation [15].

Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates [16]. Legislative smoking bans and counseling, delivered by health-care professionals, improve quit rates. Nonethe-

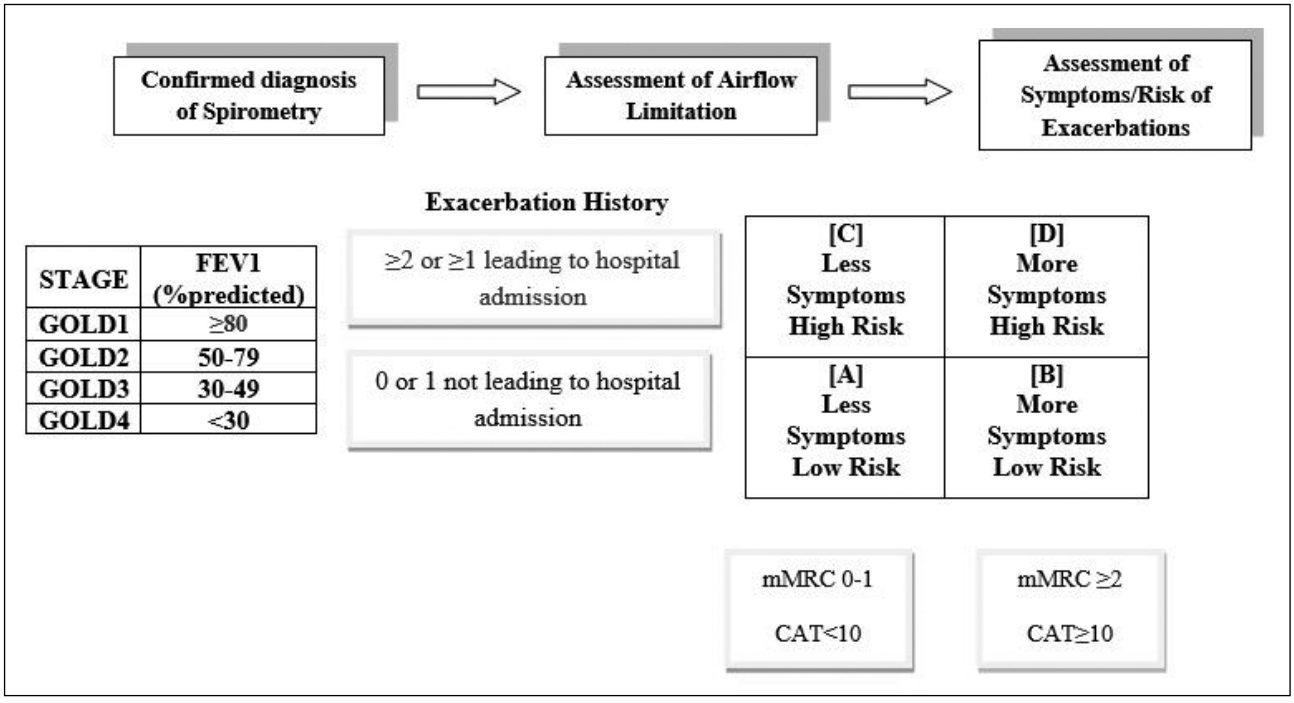

Figure 1. ABCD assessment tool.

less, the effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present [17].

Vaccination for stable COPD

Patients with COPD and other chronic respiratory diseases are especially vulnerable to viral and bacterial pulmonary infections, which are major causes of exacerbations, hospitalization, disease progression, and mortality in COPD patients [18]. The WHO and CDC recommend SARS-CoV-2 and influenza vaccination as they reduce serious illness in COPD patients [19]. While COPD itself is not a risk factor for acquiring a SARS-CoV-2 infection, existing lung damage due to COPD means people are more likely to experience severe complications of COVID-19. Recent studies highlight that having COPD can increase a person's risk of hospitalization, ICU admission, and death from COVID-19. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has shown lower incidence of community-acquired pneumonia aged <65 years with an FEV1<40% predicted, while the 13-valent conjugate pneumococcal vaccine (PCV13) in the group of patients >65 years reduced bacteremia and serious invasive pneumococcal disease [20]. Furthermore, the CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis for adults with COPD who were not vaccinated in adolescence and Zoster vaccine to protect against shingles for adults with COPD aged >50 years [21].

Oxygen Therapy and Ventilatory Support

The long- term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has shown to increase survival in patients with severe resting hypoxemia [22]. In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance [23,24].

The role of NIV in COPD is to decrease work of breathing and improve respiratory mechanics through effects on several pathophysiologic abnormalities present in severe COPD. Hyperinflation together with other pathobiological mechanisms related to muscle dysfunction in severe COPD lead to diaphragm muscle atrophy. The combination of diaphragm muscle atrophy and the airflow obstruction central to COPD pathophysiology leads to increased respiratory muscle load. The goal of NIV in COPD is to offset this diaphragmatic dysfunction and achieve control of spontaneous breathing with near-abolition of diaphragm activity, reducing chronic hypercapnia. Although the direct impact that impaired gas exchange has on work of breathing is unclear, there is evidence that hypoxemia can impact skeletal muscle strength and endurance and that chronic hypercapnia can induce skeletal muscle dysfunction. In addition, emerging data indicate that chronic hypercapnia suppresses innate immunity and that a reduction in CO_2 levels may have a mechanistic effect in reduction of COPD exacerbations leading to hospital admissions [25]. So, noninvasive ventilation (NIV) in the form of noninvasive positive pressure ventilation (NPPV) is the standard of care for decreasing morbidity and mortality in patients hospitalized with an exacerbation of COPD and acute respiratory failure, particularly in those with pronounced daytime persistent hypercapnia PCO2 >52mmHg [26, 27]. In patients with both COPD and obstructive sleep apnea there are clear benefits associated with the use of continuous positive airway pressure (CPAP) to improve both survival and the risk of hospital admissions [28].

Pulmonary Rehabilitation

Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and emotional condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors [29].

Physical inactivity is an important determinant of health-related quality of life in patients with COPD and is a predictor of hospitalization and mortality [30]. Physical deconditioning that follows leads to even more exertional dyspnea and further deconditioning. Studies have demonstrated reduced skeletal muscle strength even in patients with mild airflow obstruction as well as in smokers without airflow obstruction, suggesting that physical deconditioning is present in early disease [31,32].

Traditionally, pulmonary rehabilitation was prescribed for patients with severe disease. However, recent data, including a systematic review of the available data for pulmonary rehabilitation in patients with mild COPD, showed evidence of improved exercise capacity and health-related quality of life, and improvement in 6-min walk test, suggesting their potential benefit even in early disease [31].

There is currently not enough capacity to deliver conventional pulmonary rehabilitation for large numbers of patients with early disease, and new modes of increasing exercise and fitness levels such as digital interventions will need to be tested in the context of these patient groups [33].

Totally, pulmonary rehabilitation not only improves dyspnea, health status and exercise tolerance in patients with stable COPD, but also, leads to a reduction in symptoms of anxiety and depression and reduces hospitalization among those with a recent exacerbation (<4 weeks from prior hospitalization).

Surgical Interventions

Lung Volume Reduction Surgery (LVRS) is a surgical technique that may be beneficial for some patients with advanced emphysema who have poor control of their disease despite maximal medical therapy. LVRS entails reducing the lung volume by wedge excision of emphysematous tissue. Subsequent modifications to LVRS include non resectional lung volume reduction [34,35]. LVRS reduces the elastic recoil pressure of the lung and thus improves expiratory flow rates and reduces exacerbations [36,37].

Bullectomy is the surgical removal of a bulla, which is a dilated air space in the lung parenchyma measuring more than 1 cm. It is carried out in selected patients and it is associated with decreased dyspnea, improved lung function and exercise tolerance [38].

Due to the morbidity and mortality associated with LVRS, less invasive bronchoscopic approaches to lung reduction have been examined. These include a variety of bronchoscopic procedures such as endobronchial valves, lung coils and vapor ablation. Although these techniques differ markedly from one another, they are similar in their objective to decrease thoracic volume to improve lung, chest wall and respiratory muscle mechanics [39].

Last but not least, lung transplantation in appropriately selected patients with severe COPD has been shown to improve quality of life and functional capacity, but not prolong survival [40].

PHARMACOLOGICAL THERAPY FOR COPD

Bronchodilators

Bronchodilators are central to the treatment of COPD, notwithstanding that there is often limited reversibility of airflow obstruction. The existing drug classes ($beta_2$-agonists and muscarinic receptor antagonists) work by relaxing airway smooth muscle tone, leading to reduced respiratory muscle activity and improvements in ventilatory mechanics, making it easier for patients to breathe. Bronchodilation aims at alleviating bronchial obstruction and airflow limitation, reducing hyperinflation, and improving emptying of the lung and exercise performance [41,42].

The principal action of $beta_2$-agonists is to relax airway smooth muscle by stimulating $beta_2$-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. There are short-acting (SABA) and long-acting (LABA) $beta_2$-agonists. Regular and as-needed use of SABAs improves FEV_1 and symptoms. LABAs show duration of action of 12 or more hours and do not preclude additional benefit from as-needed SABA therapy [43]. Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV_1 and lung volumes, dyspnea, exacerbation rate and number of hospitalizations, but have no effect on mortality rate or decline of lung function.

Additionally, antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle [44]. Short-acting (SAMAs) antimuscarinics, namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction. Long acting antimuscarinic antagonists (LAMAs) such as tiotropium, aclidinium, glycopyrronium bromide and umeclidinium have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect. Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment versus LABA treatment [45].

Regular treatment with inhaled corticosteroids (ICS) alone does not modify the long-term decline of FEV_1 nor the mortality in patients with COPD. Glucocorticoids act at multiple points within the inflammatory cascade, although their effects in COPD are more modest as compared with bronchial asthma. Data from large patient studies suggest that inhaled corticosteroids can produce a small increase in post-bronchodilator FEV_1 and a small reduction in bronchial reactivity in stable COPD [46,47]. In patients with more advanced disease (usually classified as an FEV_1 <50% pred), there is evidence that the number of exacerbations per year and the rate of deterioration in health status can be reduced by inhaled corticosteroids in COPD. Evidence

from four large prospective 3-year studies has shown no effect of inhaled corticosteroids on rate of change of FEV_1 in any severity of COPD [48].

Theophylline exerts a small bronchodilator effect in stable COPD and it is associated with moderate symptomatic benefits [49].

Combination Bronchodilator Therapy

The GOLD ABCD tool combines symptom severity, using either the COPD Assessment Test score or the modified Medical Research Council scale, together with exacerbation risk, determined by either spirometry-defined airflow limitation or exacerbation history, to categorize patients into disease "risk stratification" groups ABCD to guide pharmacotherapy [50] (Figure 2).

The preference for long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) combinations over inhaled corticosteroid (ICS)-containing regimens is supported by evidence from several studies. In the LANTERN and ILLUMINATE studies, a combination of glycopyrronium/indacaterol (LAMA/LABA) significantly improved lung function compared with salmeterol/fluticasone (LABA/ICS) and decreased the incidence of pneumonia in patients with moderate-to-severe COPD [51,52). Similarly, a LAMA/LABA combination of tiotropium/olodaterol provided a greater improvement in lung function than salmeterol/fluticasone in patients with moderate-to-severe COPD in the ENERGITO study [53]. In the FLAME study, glycopyrronium/indacaterol was more effective than salmeterol/fluticasone in reducing the rate of COPD exacerbations and increasing the time to first exacerbation in patients with a history of exacerbations in the previous year [54]. Notably, compared with LABA/ICS, LAMA/LABA combination therapy significantly reduced the rate of COPD exacerbations in patients with moderate-to-severe COPD who experienced either up to 1 or at least 1 exacerbation in the previous year.

If patients have persistent exacerbations despite being on the LAMA/LABA or LABA/ICS treatment regimens, LAMA/LABA/ICS triple therapy should be considered. A switch from LAMA/LABA to a triple therapy should be guided by the biomarker assessment (i.e., patients with eosinophil counts of ≥100 cells/μL are more likely to benefit from the triple therapy). The IMPACT Study (**I**nfor**M**ing the **Pa**thway of **C**OPD **T**reatment) has shown new evidence about the role of single inhaler triple therapy (ICS/LABA/LAMA) compared to ICS/LABA and LAMA/LABA. The main results of this study were obtained on reduction of exacerbation rate, lung function improvement (in terms of trough FEV_1 improvement), mortality data and incidence of pneumonia [55].

Other Anti-inflammatory Therapy for Stable COPD

Roflumilast is a selective inhibitor of the enzyme phosphodiesterase-4 (PDE-4), and targets systemic inflammation associated with COPD. Several clinical trials have reported benefit of roflumilast over placebo in patients with COPD in terms of FEV1 and exacerbations. Currently, there is no evidence for its use in patients with early disease, but only in severe and very severe COPD [56].

Macrolides have demonstrated a measurable ef-

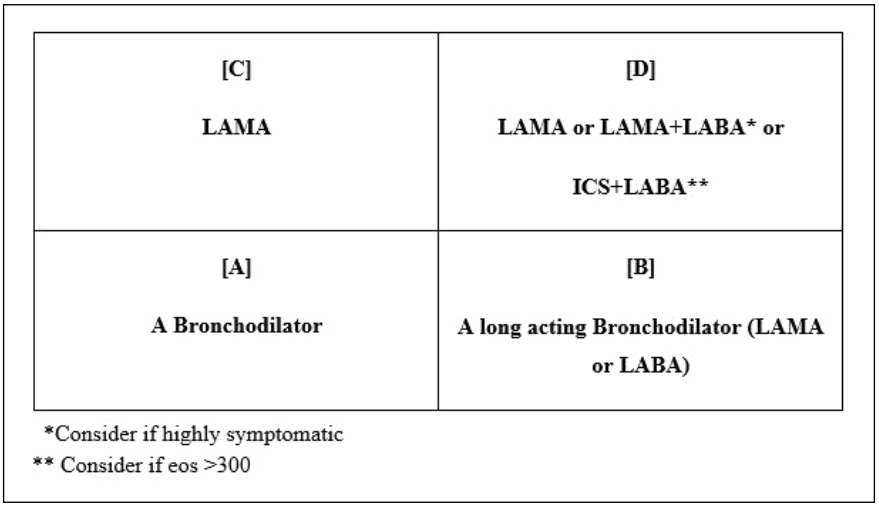

Figure 2. Pharmacological treatment recommendations based on 2022 GOLD Classification

ficacy in preventing exacerbations. However, their use in a chronic/preventive manner needs to be decided carefully balancing the potential efficacy in the right patients with the potential risk connected to an antibiotic overuse and potential antibiotic resistance in a single patient and/or a community [57].

Long-term use of oral corticosteroids has numerous side effects with no evidence of benefits. Regular treatment of mucolytics such as erdostein, carbocystein and NAC reduces the risk of exacerbations in selected populations. Furthermore, observational studies have shown that statins may have a positive effect on patients with COPD who receive them for cardiovascular and metabolic disease. Leukotriene modifiers have not been adequately tested in COPD patients. Finally, intravenous augmentation a1-antitrypsin therapy may slow down the progression of emphysema.

Mortality Data

Several studies have recently reported on the long-term mortality rate in COPD patients. The 5-year mortality of COPD patients was about 25.4%. Higher mortality was observed in males and the elderly. The 5-year mortality rate in males was about 1.5 times higher than in females. The common causes of death in COPD were chronic lower respiratory disease, lung cancer, cardiovascular disease, and cerebrovascular disease.

CONCLUSIONS

Early COPD remains poorly explored. The diagnosis of COPD as defined by currently established criteria indicates an established disease process which is irreversible. As no current pharmacological treatment is known to halt or reverse the progression of established COPD, it is essential for disease to be diagnosed early and prior to establishment of irreversible pathology, in order to allow timely interventions. Identification of pathological factors involved in the development of early disease will facilitate development of therapies targeting these early changes, and therefore potentially arrest or even reverse the disease process.

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