

**REVIEW ARTICLE**

# **Chronic Obstructive Pulmonary Disease: Part I Overview of epidemiology, pathophysiology, diagnosis and staging with 2020 Updates**

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Email address: [Joyce.akwe@emory.edu](mailto:Joyce.akwe@emory.edu)**Abstract**

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease.<sup>1</sup> It is among the fastest growing chronic diseases diagnosed in the world today. COPD is the third most common cause of death in the United States<sup>2</sup> and is predicted to get worse. It is characterized by the development of an exaggerated inflammatory response of the lungs to noxious substances such as tobacco or air pollution. If the exposure becomes recurrent or persistent, the lungs develop chronic inflammatory response leading to lung parenchymal damage, air trapping and progressive airflow limitation. The Diagnosis of COPD is usually made in the contest of symptoms, exposure to risk factors and spirometry evidence of airway obstruction with post bronchodilator spirometry FEV1/FVC < 0.70. Most patients with COPD first seek medical attention when they develop dyspnea.<sup>1</sup>

Once the diagnosis of COPD has been confirmed, the treatment is geared mainly towards preventing exacerbations and eliminating risk factors and exposures. Several treatments combinations can be used in patients with stable COPD to prevent exacerbations and to improve their quality of life. Patients with COPD exacerbations have to be appropriately diagnosed and promptly treated to prevent complications. Patient's symptoms, the degree of airflow limitation, risk of exacerbations and the presence of comorbidities have to be assessed. Both pharmacological and non-pharmacological interventions have been used in the management of COPD.

## **Introduction and Epidemiology**

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities. COPD is usually caused by significant exposure to noxious particles and gases. Host factors such as abnormal lung development also play a significant role in the development of COPD.<sup>1</sup> COPD is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. Significant comorbidities have a major impact on morbidity and mortality.<sup>1</sup>

COPD is the third most common cause of death in the United States.<sup>2</sup> It is the fourth leading cause of death in the world and projected to get worse because of the continuous exposure to noxious particle, the aging world population, increasing smoking rates and decrease in other common causes of death like ischemic heart disease and infections. Vaping was advertised as a nicotine replacement therapy, but it has turned out to be a recruiting tool for people

who were nonsmokers. This is because tobacco is a major product in some of the vaping /e-cigarette products. Tetrahydrocannabinol (THC), cannabinoid (CBD) oils, Vitamin E and other flavoring substances and additives have been added to nicotine and promoted to non-smoking adolescents and young adults.<sup>3-6</sup> It is unclear if e-cigarettes actually decrease the incidence of tobacco use.

COPD is a very common and treatable condition that affects 5-22% of the adult population aged 40 and above. COPD is one of the leading causes of hospitalizations and has very high health care cost.<sup>7-9</sup> Gershon et al. found an overall incidence of 5.9 cases per 1000 person per year of COPD. The lifetime risk of COPD was 26.6% in this study. This risk was higher in men, smokers, people older than forty, and in people living in rural areas. This means far more people will be diagnosed with COPD than with heart failure, acute myocardial infarction and some common cancers.<sup>10</sup> The estimates of morbidity, mortality and general burden of COPD are underestimated due to the lack of adequate evidence. Most of the estimates on COPD have not been obtained by consistent methods and there is some evidence that these estimates may be

underestimates.<sup>7,11,12</sup> According to the Center for Disease Control (CDC) 9.0 million adults were diagnosed with chronic bronchitis in 2018. Three point six percent of adults were diagnosed with chronic bronchitis in the same years. The number of adults who had ever been diagnosed with emphysema is 3.8 million or 1.5% of adults. The cost of COPD in the USA was projected to be approximately \$50 billion in 2010. Costs increase with increasing severity of disease, and hospital stays account for the majority of these costs. The costs of care for COPD can be expected to continue to rise since COPD is a progressive disease.<sup>13</sup> FEV1/FVC ratio drops with age in healthy people; this may result in over-diagnosis of early COPD in adults of age 50 years and

above. This early stage of COPD does not greatly contribute to the social economic burden of COPD.<sup>7</sup> In 1998, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Health and Global Initiative for Chronic Obstructive Lung Disease (GOLD) created a cooperation to increase awareness of the burden of COPD, and to improve prevention and management of COPD worldwide.<sup>1</sup>

**Pathogenesis**

Patients with COPD have an amplified inflammation in response to chronic irritants such as tobacco smoke. This type of lung inflammation persist lung after the cessation of tobacco smoking. The mechanism of this type of inflammation is unknown.<sup>1</sup>

**Table 1:** Other mechanisms that maybe important in amplifying the persistent inflammatory process in COPD.

<b>Oxidative stress</b>	Inflammatory biomarkers such as hydrogen peroxide have to been shown to increase in airways of people with COPD and oxidative stress increase during exacerbations.
<b>Protease anti- protease imbalance</b>	Patients with COPD have an imbalance in protease that breakdown connective tissue and anti-protease that oppose this action. <sup>14</sup>
<b>Increase number of inflammatory cells and Inflammatory Mediators</b>	Patients with COPD have increased macrophages, activated neutrophils and lymphocytes in their airways. All these cells release multiple inflammatory mediators. <sup>15</sup>
<b>Interstitial and Peri-bronchiolar fibrosis</b>	Peri- bronchial fibrosis and interstitial fibrosis have been reported in patients with COPD and in asymptomatic smokers. <sup>16,17</sup>

## **Pathophysiology**

When the lungs are exposed to noxious substances such as tobacco, they develop persistent inflammatory response. If the exposure becomes a recurrent process, the lungs develop chronic inflammatory response which causes lung parenchymal damage (emphysematous changes) and fibrosis leading to air trapping and progressive airflow limitation.<sup>1</sup>

These inflammatory changes with tissue damage and fibrosis are mainly seen in the airways, lung parenchyma, and pulmonary vasculature<sup>18</sup> and usually get worse with increased exposures. The inflammatory changes noted in patients with COPD are amplified and persist even in the absence of exposures. Specific patterns of inflammation characterized by an increase in CD8+ and Tc1 lymphocytes have been noted in smokers that develop COPD.<sup>19</sup> These cells, together with neutrophils and macrophages, release inflammatory mediators and enzymes that interact with structural cells in the airways, lung parenchyma and pulmonary Vasculature.<sup>18</sup> Severe acute lung injury, eosinophilic pneumonia, alveolar hemorrhage, respiratory bronchiolitis and other forms of lung abnormalities have been reportedly linked to E-cigarette use.<sup>1</sup>

Oxidative stress and an excess of proteinases in the lung further modify the inflammatory response in the lung. Autoantigens and persistent microorganisms have also been noted to play an important role in the inflammatory process.<sup>20</sup> Patients with COPD have more oxidative stress in their lungs which further worsen COPD exacerbations. Secondly, there is an imbalance between proteases that break down connective tissue components and anti-proteases that protect against connective tissue breakage in patients with COPD. Protease-mediated destruction of elastin which is a major connective tissue component in lung parenchyma is a common finding in patients with emphysema. Inflammation and narrowing of peripheral airways lead to decreased FEV1. Parenchymal destruction due to emphysema also contributes to airflow limitation. FEV1 and FEV1/FVC ratio directly correlate to the extent of inflammation, fibrosis, and luminal exudates in small airways.<sup>18</sup> This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Hyperinflation reduces inspiratory capacity particularly during exercise leading to increased dyspnea and limitation of exercise capacity.<sup>21</sup> Hypoxic vasoconstriction of small pulmonary arteries lead to intimal

hyperplasia and smooth muscle hypertrophy leading to pulmonary hypertension. Progressive pulmonary hypertension promotes right ventricular hypertrophy and eventually, right-side heart failure.

### **Risk Factors**

The most commonly reported risk factors for COPD include:

- Tobacco smoke
- Air pollution
- Occupational exposure
- Genetic factors
- Age and sex
- Lung development
- Socioeconomic status
- Asthma
- Intrinsic lung disease
- Family history of COPD
- Hyper-reactive airway
- Chronic bronchitis
- Infections

Tobacco use is considered to be the most common risk factor for developing COPD even though nonsmokers may also develop COPD.<sup>1</sup> Long term exposure to noxious gases and particles in patients with a variety of host factors such as poor lung growth, hyper responsive airways, and poor lung growth all contribute to the development of COPD.<sup>22-24</sup> Tobacco smoke leads to

significant annual decline in lung function and a very high prevalence of respiratory symptoms. Compared with current and former smokers, never smokers with COPD have fewer symptoms, less burden of systemic inflammation and milder disease limited to the lungs. However, morbidity due to lung-related hospital admissions is still substantial in never smokers with COPD. Pneumonia and mortality from respiratory failure is common in never smokers with COPD.<sup>25</sup> Alpha 1 antitrypsin is the most commonly associated genetic risk factor associated with COPD.<sup>26</sup>

### **Diagnosis**

COPD is a chronic disease which is usually diagnosed clinically, but in the appropriate clinical context, spirometry is needed for definitive diagnosis. A clinical diagnosis of COPD should be considered in all patients who present with symptoms including dyspnea, chronic cough or sputum production, and risk factors for the disease such as family history, environmental history and smoking history.<sup>1</sup> Smoking history should include the age at which smoking was initiated, average amount smoked per day since initiation and current

smoking status or stop date. Smoke from any forms of tobacco, smoke from home cooking and heating fuels, occupational dusts and chemicals are all important risk factors for the development of COPD.

The clinical signs and symptoms that lead to the clinical diagnosis of COPD include: chronic cough with variability in the production of sputum from day to day and progressively worsening dyspnea.<sup>27,28</sup>

These are also the main symptoms that have to be looked into in order to determine the need for antibiotics. Sputum production may start several years prior to airway limitations confirming the presence of COPD.<sup>28</sup> Some patients have been found to have airway obstructions without the classic symptoms of cough or sputum production.

The first symptom which develops in patients who have been exposed to COPD is cough. Usually the cough is intermittent, and then progresses to a daily and even to an all-day symptom. The chronic cough in COPD may be unproductive.<sup>29</sup>

Sputum production is harder to evaluate. Large amounts of sputum may warrant evaluation for bronchiectasis. Worsening sputum production and purulence may be a sign of bacterial infection leading to COPD exacerbation.<sup>30</sup>

The main symptom which causes patients to seek medical attention is dyspnea. Progressively worsening dyspnea is one of the main symptoms of COPD and is usually described as a sense of increased effort to breathe, heaviness, air hunger, or gasping.<sup>31</sup>

Other non-specific symptoms commonly found in patients with COPD include wheezing and chest tightness. Fatigue, weight loss and anorexia are common in patients with severe and very severe COPD.<sup>32</sup>

A thorough medical history has to be obtained for each patient presenting with a possible diagnosis of COPD. The history should include exposure to noxious substances like tobacco, occupational and environmental factors. The past medical history should include any history of asthma, allergies, nasal polyps, sinusitis, and respiratory infections. A family history of COPD and other chronic medical disease patterns need to be clearly documented. The characteristics of patient's respiratory symptoms including what times of the year patient usually has symptoms, how long they last and how long ago the patient first experience the symptoms. A history of exacerbations and how many times in a year the patient has been hospitalized is important. All comorbidities should be

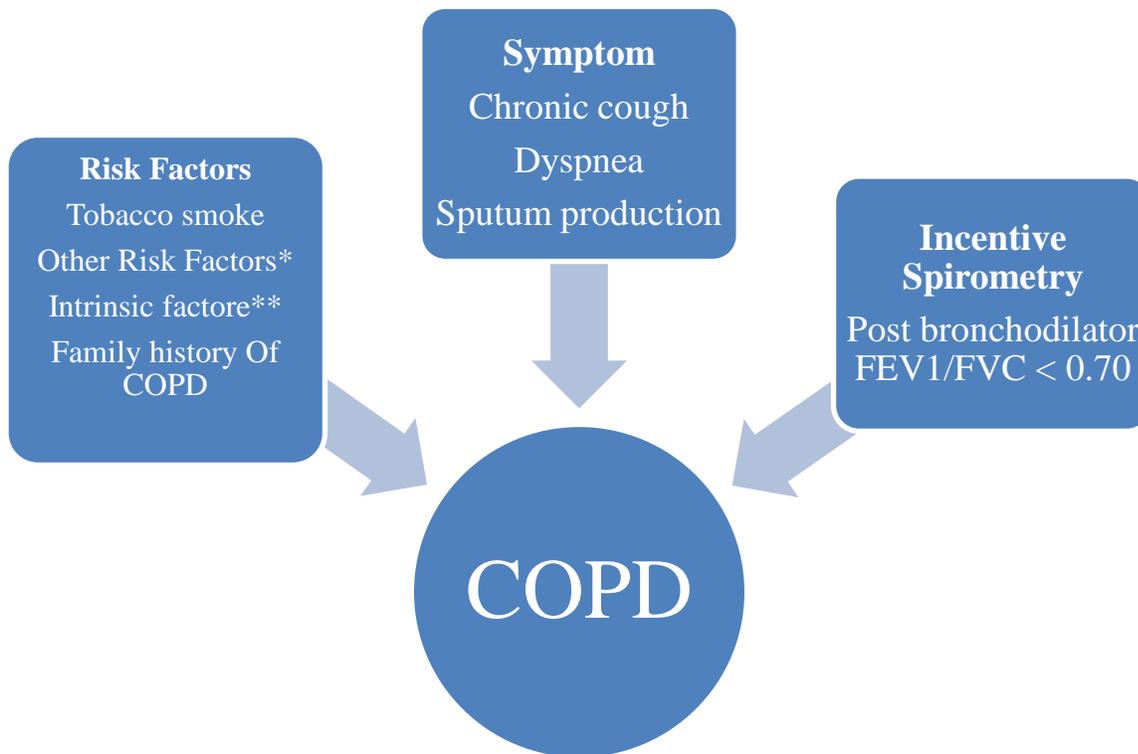
evaluated and the impact of COPD on patient's social life, economic activities, feeling of depression or anxiety and any effects on sexual activities need to be appropriately addressed.

The diagnosis of COPD is confirmed by a post bronchodilator spirometry FEV1/FVC < 0.70.<sup>27,33</sup> Spirometry is the most reproducible and objective measurement of airflow limitation available. Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race. The presence of a post bronchodilator FEV1/FVC < 0.70 confirms the presence of airflow limitation.<sup>34</sup> Note that FEV1 is used mainly used for classifying the severity of COPD. Certain major pathologies of the lung such as emphysema may not cause any airflow limitations, but they still need to be

further evaluated and managed appropriately.<sup>1</sup>

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**Figure 1:** Diagnosing COPD



\*Other risk factors are as noted above under risk factors

\*\*Intrinsic factors include low birth weight and recurrent childhood respiratory infections

**Table 2:** Differential diagnosis of chronic cough <sup>1</sup>

Intra-Thoracic Causes	Extra-Thoracic Causes
<ul style="list-style-type: none"><li>• Asthma</li><li>• Lung cancer</li><li>• Tuberculosis</li><li>• Left Heart Failure</li><li>• Interstitial Lung Disease</li><li>• Cystic fibrosis</li><li>• And idiopathic cough</li></ul>	<ul style="list-style-type: none"><li>• Chronic Allergic Rhinitis</li><li>• Post Nasal Drip Syndromes</li><li>• Upper airways cough Syndromes</li><li>• Gastroesophageal Reflux</li><li>• Medications</li></ul>

### Prognostic Factors

Several prognostic factors have been noted to accelerate the decline of lung function. These factors cause a decline in the FEV1, functional status, exercise tolerance morbidity or mortality of a patient with COPD. <sup>2,35-43</sup> The risk of death in people with COPD is usually calculated using the BODE index. The BODE index is calculated based on four factors: weight (BMI), airway obstruction (FEV1), dyspnea (Medical Research Council dyspnea score), and exercise capacity (six-minute walk distance).<sup>2,41</sup> Eklof et al. recently published a large observational study in which they

found that *Pseudomonas aeruginosa* colonization independently predicted an increased risk of hospitalization for exacerbation and all-cause mortality.<sup>44</sup> Solid fuel use for cooking was associated with higher risks of major respiratory disease admissions and death in a cohort study of 280,000 Chinese never-smokers. Additionally, Chan *et al.* 2019 Switching to cleaner fuels or reducing exposure can reduce the risk of non-smokers developing COPD.<sup>45</sup> Results from a population-based UK Biobank study on air pollution, lung function and COPD showed an association between ambient levels of particulate matter

(PM2.5/10) and COPD prevalence.<sup>46</sup> C-reactive protein (CRP) and procalcitonin can be used in restricting antibiotic usage during exacerbations, although the observed sputum color remains highly sensitive and specific for a high bacterial load during such episodes.

Other common prognostic factors include

- Male gender
- HIV infection
- Elevated C-reactive protein
- Airways responsiveness
- Cigarette smoking
- Low body-mass index (BMI  $\leq 21$ )
- Increased airway bacterial load
- Decreased exercise capacity
- Peak oxygen consumption (VO<sub>2</sub>), measured by cardiopulmonary exercise testing
- Chest computed tomography showing presence of emphysema

### Staging

**Table 3:** The Gold classification of COPD severity is based on the post bronchodilator spirometry.<sup>1</sup>

Severity of airflow limitation in COPD (based on post bronchodilator FEV <sub>1</sub> ) with <b>FEV<sub>1</sub>/FVC &lt;0.7</b>	
GOLD 1: Mild	FEV <sub>1</sub> $\geq 80$ percent predicted
GOLD 2: Moderate	50 percent $\leq$ FEV <sub>1</sub> <80 percent predicted
GOLD 3: Severe	30 percent $\leq$ FEV <sub>1</sub> <50 percent predicted
GOLD 4: Very severe	FEV <sub>1</sub> <30 percent predicted
FEV <sub>1</sub> : Forced Expiratory Volume in one second; FVC: forced vital capacity	

This classification does not take into consideration the experience of the patient with COPD.

The Revised Gold classifications use different tools to evaluate the severity of symptoms, risk of exacerbations, and the presence of comorbidities. These are all major factors that contribute to the disease

course, prognosis and most importantly to the experience of the patient with COPD.<sup>7,47</sup>

**Tools to evaluate the severity of symptoms**

Gold Guidelines have proposed several tools to evaluate the severity of symptoms. These tools include:

- A: Modified Medical Research Council (mMRC) dyspnea scale which gives a grade from 0 to 4 depending of the description of breathlessness of the patient.
- B: COPD Assessment Tool (CAT)). This tool has questions on the level of dyspnea and the feeling caused by shortness of breath, the presence of cough and the characteristics of the cough and exercise tolerance. <sup>1,47-51</sup>

C: St. George's Respiratory Questionnaire (SGRQ). This is the most widely used tool. This questionnaire has 76 items which focus on three: symptoms, activity, and impact on daily life. It scores each of the components and a total score is given.

In order to assess exacerbations and guide therapy, the GOLD system has combined the symptoms, history of exacerbations and FEV1 to place patients in 4 groups.<sup>1</sup>

**Table 4:** Classification of COPD based on symptoms, history of exacerbations and FEV1.<sup>1</sup>

Groups	RISK OF EXACERBATION/SYMPTOMS	SEVERITY OF FLOW BASED ON FEV1	NUMBER OF EXACERBATIONS PER YEAR	mMRC grade	CAT SCORE
A	Low risk/less symptoms	GOLD 1 or 2	0-1	0-1	<10
B	Low risk/ more symptoms	GOLD 1 or 2	0-1	<2	10 or more
C	High risk/ less symptoms	GOLD 3 or 4	2 or more	0-1	<10
D	High risk/more symptoms	GOLD 3 or 4	2 or more	<2	10 or more

**Conclusion**

COPD is still clearly a chronic medical condition that warrants more international

attention. COPD is both preventable and treatable, but transplant apparently is the only treatable option available at this time.

Morbidity and mortality secondary to COPD are still very high and are predicted to get worse. The Economic burden is enormous. In Europe, COPD accounts for 56% of the costs for respiratory disease care according to the European Respiratory Society. The most common symptoms of COPD (Cough, dyspnea and sputum production) are under reported by the patients and therefore COPD is still under diagnosed. Tobacco smokes as well as other environmental exposures including air pollution and biomass full are major risk factors for the development and progression of COPD. Other major risk factors which need to be considered for the development and progression of COPD include host factors such as abnormal lung development, genetic factors, and a family

history of COPD. COPD symptoms can be worse during periods of exacerbations. COPD is frequently associated with other comorbidities which contribute to its prognosis.

The goals of management as described in Part II of this article is based on COPD patients should have an assessment of the severity of their airflow obstruction, symptoms, history of exacerbations, exposure to risk factors and comorbidities

Current pharmacological managements are unable to cure COPD. The main focus of COPD management teams is to increase awareness of COPD among health professionals, health authorities, and the general public.

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