

Newer Classification of COPD and Management Strategy

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is actually a cluster of diseases associated with nonreversible/partially reversible changes in lung. COPD is a burden for both developed and developing countries and management is also a great challenge. Comorbid or coexisted disease conditions have an impact on course, direction and outcome of treatment.

A new co-existed disease based classification is formulated which is directed more towards management of COPD. It's based on a self-made quotation "If Arterial Blood Gas (ABG) deteriorates, stable COPD Patient may turn out (PTO) to unstable COPD". Here actually 'A' means Asthma, 'B' means Bronchiectasis, G means Gastro-Esophageal Reflux Disease (GERD), 'P' means air Pollution, 'T' means Temperature changes and 'O' means Obstructive Sleep Apnea (OSA). These six risk factors act as trigger which are responsible for turning out stable COPD patient's to unstable COPD [1,4,5]. If we become able to control these factors, exacerbation of COPD can be prevented.

We have classified COPD as:

1. Stable COPD: (COPD - S) i.e. having no co-existed lung disease.
2. COPD with co-existed diseases: COPD- C
 - i. COPD with Asthma: COPD-A
 - ii. COPD and Bronchiectasis: COPD-B
 - iii. COPD and GERD: COPD-G
 - iv. COPD and OSA: COPD-O.
3. Unstable COPD: COPD U; means COPD patient having more than two exacerbations or one hospitalization per year.

Inflammation and infection - are responsible for development and progression of COPD. Br. Asthma, GERD, air pollution, temperature changes and OSA -all acts as irritants and perpetuate airways inflammation. About 40% to 56% COPD patients have asthma also. We advise to do FeNO in every COPD cases. If FeNO level is found ≥ 20 PPM, we sub-classify as 'COPD-A'. It's an strong indication to prescribe inhaled corticosteroids (ICS) whatever the stage of COPD, from stage 2 to 4.

In moderate to severe COPD, prevalence of bronchiectasis varies from 57 to 64%. Bronchiectasis in COPD initiates and maintain neutrophilic inflammation, ultimately airways destruction leads to much more peripheral bronchiectasis. COPD-B is more prone to infective exacerbations. HRCT scan of chest is important for both diagnostic confirmation and proper rehabilitation of COPD-B patients.

The prevalence of GERD is about 26.7% in COPD patients. The annual rate of exacerbation of COPD is about two times higher with GERD (COPD-G) compared to those without GERD symptoms. Aspiration into airway in GERD can trigger exacerbation of COPD and induces pulmonary fibrosis. Identification of COPD-G is very important for prevention of progression of disease.

29.5% COPD patient had associated OSA. The most significant sleep abnormality in COPD is nocturnal oxygen desaturation which is a marker of increased mortality in COPD.

Exposure to particle pollution enhances COPD exacerbation. As particulate materials can carry micro-organisms on the surface, may contribute to more frequent infective exacerbation also.

Study showed every 1°C increase above a threshold temperature of 29°C, risk of COPD hospitalization increased by 7.6%. Cold exposure cause bronchoconstriction, inflammation and mucous hypersecretion in COPD.

Keywords: COPD; Comorbidity; Inflammation; FeNO; Outcome

Abbreviation

COPD: Chronic Obstructive Pulmonary Disease; ABG: Arterial Blood Gas; GERD: Gastro-Esophageal Reflux Disease; OSA: Obstructive Sleep Apnea; PPM: Parts Per Million; HRCT: High Resolution Computed Tomography; FeNO: Fractional exhaled Nitric Oxide; NPV: Negative Predictive Value; Non-REM: Non-Rapid-Eye-Movement; REM: Rapid-Eye-Movement; CPAP: Continuous Positive Airway Pressure; BiPAP: Bilevel Positive Airway Pressure; PM: Particulate Materials; SO₂: Sulfur Dioxide; LABA: Long-Acting β -Agonist; LAMA: Long-Acting Muscarinic Antagonist; ICS: Inhaled Corticosteroids; LTOT: Long-Term Oxygen Therapy; PPI: Proton Pump Inhibitor

Introduction

Theme quotation

"If Arterial Blood Gas (ABG) deteriorates, stable COPD Patient may turn out (PTO) to unstable COPD"

(COPD Stable: COPD S and COPD Unstable: COPD U)

Chronic Obstructive Pulmonary Disease (COPD) is actually a cluster of diseases associated with progressive airflow limitation which is not fully reversible. Chronic inflammatory process throughout the airways, Parenchyma and pulmonary vasculature resulting in many structural and functional changes in the lung [1]. COPD is a burden for both developed and developing countries. COPD management is a great challenge even after following COPD GOLD guideline 2019 [2].

The term "co morbidity" has been used to indicate a medical condition existing simultaneously with but independently of another condition. Recently, however, use of the term co morbidity has broadened to suggest a reciprocal or causal relationship between two disease states. Certainly, in the case of chronic obstructive pulmonary disease (COPD), this perspective is intriguing from both an academic and a clinical perspective. It is likely that infection has a larger role than currently recognized in the pathogenesis of COPD, and the relationship between the two can be viewed as a complicated comorbid one, which may affect both the direction and course of each problem [3].

A new co-existed disease based classification is formulated which is directed more towards management of COPD. It's based on a self-made quotation "If Arterial Blood Gas (ABG) deteriorates, stable COPD Patient may turn out (PTO) to unstable COPD".

It is now clear that some internal and some external factors are responsible for turning out stable COPD patient's to unstable COPD [1,4,5]. If we become able to control six important factors which are recognized as triggers for exacerbation of COPD, it can be prevented. Out of six factors four are internal factors and two are external factors.

We can use mnemonic 'ABG' and 'PTO' for the risk factors for COPD. That's why we used the following quotation "If Arterial Blood Gas (ABG) deteriorates stable COPD patients may turns out (PTO) to unstable COPD.

Precisely two steps, initiation of inflammation and infection - both are responsible for development and progression of COPD. Br. Asthma, GERD, air pollution, temperature changes and OSA-all acts as irritants and perpetuate airways inflammation. Bronchiectasis in patients of COPD is the main cause that initiates and maintain neutrophilic inflammation, thick secretion, peripheral airways obstruction and ultimately airways smooth muscle necrotizing inflammation and destruction leads to much more peripheral bronchiectasis.

Risk factors			
Asthma	A	P	Pollution
Bronchiectasis	B	T	Temperature changes
Gastro-Esophageal Reflux Disease (GERD)	G	O	Obstructive Sleep Apnea (OSA)

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COPD S Vs COPD U Vs COPD C

Still there is no working definition for Stable or Unstable COPD. We define as per follows:

- COPD S means stable COPD i.e. COPD patient having no co-existed lung disease. That means COPD patient having no feature of Asthma, Bronchiectasis, OSA or GERD. Progression of disease in Stable COPD patient would be very slow as risk factors of exacerbation is mainly temperature change and air pollution.
- COPD C means COPD patient having more than one co-existed lung diseases. That means 'COPD patient' having features of 2 or more of co-existed illness i.e. Asthma, Bronchiectasis, OSA or GERD. It needs more observation for presence of 2 or more co-existed illness with COPD.
- COPD U patients are more prone to repeated exacerbation.

COPD with Asthma: COPD-A

It is well established that about 40% to 56% COPD patients have asthma along with COPD [6,7]. Typically, asthma is characterized by inflammation predominantly involving eosinophils, whereas COPD is characterized by neutrophilic inflammation [8,9]. FENO and blood eosinophil count have been considered as biomarkers of local and systemic eosinophilic inflammation, which got increased in patients with asthma [10,11]. Total serum IgE and antigen-specific IgE levels are also found elevated in those with allergic asthma [12].

A prospective clinical observational study showed nearly one third of COPD patients had sputum eosinophilia and the number of eosinophils was significantly correlated to the level of exhaled nitric oxide [13]. Fractional exhaled Nitric Oxide (FeNO) has been described as a marker of asthmatic airway inflammation [14].

In some COPD patients with asthma (i.e. COPD-A) FeNO level maybe normal due to effect of smoking or due to continuous use of inhaled corticosteroid [15,16]. But interestingly some patients have persistent elevation of FeNO levels despite treatment with high dose of corticosteroids [17]. In our protocol, after diagnosis of COPD, we advise to do FeNO in every cases. If FeNO level is found 20 PPM or more we sub-classify the case as 'COPD-A' and it's an strong indication to prescribe inhaled corticosteroids (ICS) whatever the stage of COPD, from stage 2 to 4. If FeNO level is less than 20 PPM, we advise not to prescribe inhaled corticosteroids (ICS). It indicates use of only long acting dual bronchodilators would be adequate for management of COPD.

Various combinations of these biomarkers showed a high specificity for COPD A diagnosis. Combination of FENO 23 ppb and IgE 434 IU/mL showed 94.1% specificity, 37.8% sensitivity, 51.9% positive predictive value (PPV) and 90.0% negative predictive value (NPV). Combination of FENO 23 ppb and eosinophil count 156.2/mm³ showed 85.5% specificity, 59.5% sensitivity, 40.7% PPV, and 92.6% NPV. Combination of IgE 434 IU/mL and eosinophil count 156.2/mm³ showed 92.3% specificity, 40.5% sensitivity, 46.9% PPV and 90.2% NPV. Triple combination (FENO 23 ppb, IgE 434 IU/mL, and eosinophil count 156.2/mm³) showed 96.8% specificity, 37.8% sensitivity, 66.7% PPV and 90.3% NPV [18].

High FENO level [19] and/or blood eosinophilia [20,21] have been identified as individual and/or surrogate markers of the response to steroids in patients with COPD A. These findings support the view that ICS treatment may be beneficial in patients with COPD A.

COPD and bronchiectasis: COPD-B

In moderate to severe COPD, prevalence of bronchiectasis varies from 57 to 64% [7-13,17-21]. Bronchiectasis independently increases risk of all cause of morbidity and mortality in patients with moderate to severe COPD. This sub-class of COPD is more prone to infective exacerbations. COPD patients with bronchiectasis (COPD-B) can be diagnosed by clinical history, sputum production more than 5 ml (1 TSF) per-day, persistent inspiratory crepitations along with chest x-ray findings with or without HRCT Scan chest findings are important to sub classify the disease. In chest x-ray persistent line shadow and/or inhomogeneous opacity not cleared by proper course of antibiotic, with or without ring shadows or cystic shadows in a patient with COPD may be a clue for diagnosis of COPD with bronchiectasis (COPD-B).

HRCT scan of chest is important not only for diagnostic confirmation of COPD-B, but it also essential helping tool to rehabilitate the patient properly. Normally the lower respiratory tract is free from any microorganism. In stable COPD patients, sputum neutrophils and IL8- levels are higher than those in healthy subjects, which suggests ongoing neutrophilic inflammation in the airways. This inflammation along with recurrent flare-up of infection, associated endobronchial obstruction by secretion and bronchoconstriction leads to development of bronchiectasis changes in COPD patients [22,23].

Recurrent COPD exacerbations are associated with a heightened airway inflammatory burden, and the presence of lower airway bacterial colonization [15,24,25], which in turn has been shown to be an independent stimulus to airway inflammation in COPD [25,26]. In addition, it is now clear that lower airway bacterial colonization in the stable state is associated with exaggerated symptoms and sputum purulence at exacerbation [15]. The possible role of unrecognized bronchiectasis in orchestrating such relationships in COPD has not been previously assessed.

HRCT is now accepted as the imaging modality of choice for the evaluation of bronchiectasis [27-33] and emphysema [34,35]. Thin-section CT has been shown to have discriminatory value in obstructive lung disease [36]. However, there is no consensus to date on the role of HRCT in quantifying the structural changes of bronchiectasis in patients with COPD, and its use may have had a number of limitations. Previous studies of HRCT scanning in patients with clinical bronchiectasis [37,38] and one study of patients with cystic fibrosis [39] found significantly higher mean bronchiectasis scores. The sensitivity and specificity of bronchiectasis detection by HRCT may therefore be lower, who had a relatively smaller burden of disease [40]. The extent of bronchiectasis has been shown to be negatively correlated with FEV₁% predicted [41], suggesting that in patients with COPD - bronchiectasis may develop in the presence of progressive airway obstruction.

A relationship is also found between the detection of radiologic bronchiectasis on HRCT and more severe COPD exacerbations, as assessed by time to symptom recovery. It was previously shown that exacerbation severity in COPD can be related to this parameter [42]. The extent of lower lobe bronchiectasis was also related to the presence of lower airway bacterial colonization. The presence of bacteria in the lower airway in COPD implies a breach of host defense mechanisms, which fuels a vicious cycle of structural damage, loss of epithelial cell integrity [43], impaired mucociliary clearance and mucus hypersecretion [44]. This results in further mucosal injury and inflammation, which could thereby provide the mechanism for longer and more severe COPD exacerbations. The correlation between total bronchiectasis score and PaO₂ also suggests that an imbalance between alveolar ventilation and pulmonary perfusion could be a complementary mechanism contributing to lower airway bacterial colonization in COPD. The findings therefore demonstrate that radiologic evidence of structural damage in the COPD airway, which may be driven in part by lower airway bacterial colonization, may have important clinical

implications. These findings could also explain why antibiotics have been shown to be of limited efficacy in modifying outcome measures in studies of COPD exacerbations [45]. The presence of these CT changes may provide a means of identifying those patients with COPD who are at risk of more severe COPD exacerbations.

There are a number of possible reasons why bronchiectasis is detected most frequently in the lower lobes. In a previous study of patients with chronic purulent sputum production [46,47] a predominantly lower lobe distribution of bronchiectasis was found in subjects with impaired mucociliary clearance, one of the impaired host defense mechanisms seen in COPD.

A lower lobe distribution is most often seen in patients with a history of childhood viral infections, a suggested risk factor for COPD. It is possible that multiple physiological and pathologic alterations, including damaged mucociliary transport, localized or diffuse peripheral obliteration of the bronchial tree or lung tissue scarring found in COPD. In the context of an already disrupted lung parenchyma, produced structural changes of bronchiectasis are seen on HRCT. Further longitudinal studies are now required to establish criteria for the detection of these structural changes and their significance in COPD and for clarifying how they may relate to the natural history of this condition.

Clinical history and examination findings correlate poorly with HRCT features, patients with bronchiectasis often being clinically indistinguishable from other study subjects [48,49]. A high prevalence of bronchiectasis has been demonstrated in an unselected group of patients with a primary care diagnosis of COPD [49] and studies of patients with α -1-antitrypsin deficiency disease have suggested that bronchiectasis may be present either concomitantly [50] or before the development of emphysema [51]. The α -1-antitrypsin status of all patients are not routinely ascertained. However, it is possible that some of these patients had bronchiectasis and then developed COPD with emphysema in addition to this at a later date.

About 50% of patients with COPD reports daily cough and sputum production, and no relationship was seen between these symptoms and bronchiectasis scores, suggesting that the HRCT findings were likely to represent subclinical changes. While HRCT continues to be an infrequently used tool in the assessment of COPD, subclinical bronchiectasis, which may nevertheless have important implications for some patients, is likely to remain undiagnosed. Patients with moderate lower lobe bronchiectasis experienced more severe exacerbations, were more likely to exhibit lower airway bacterial colonization, and had heightened levels of airway inflammation. This suggests that HRCT scanning may be useful in identifying particular subgroups of patients with moderate to severe COPD, who are prone to more severe exacerbations and to the increased morbidity associated with these. Moreover, this study provides further evidence linking the presence of lower airway bacterial colonization, and related structural airway changes, to important clinical parameters in COPD.

Management of COPD-B is mainly control of infection, prevention of infection flare up along with sustained bronchodilation. Azithromycin alternate day or thrice a week throughout the year may prevent. Tobramycin nebulization, influenza, pneumonia vaccine, sublingual lyophilized bacterial lysate may decrease recurrent infective exacerbations [52-59] in COPD-B patient [60].

COPD and GERD: COPD-G

The prevalence of gastro-esophageal reflux (GERD) is about 26.7% in COPD patients [61]. According to the report of Casanova, *et al.* [62] GERD is about 62% confirmed by esophageal 24 hour P^{hi} monitoring but 58% of them did not have any reflux symptoms. That means COPD patient with symptomatic GERD about 25 - 35%. Remaining 30 - 35% COPD have asymptomatic GERD with COPD.

The annual rate of exacerbation of COPD is about two times higher in patient with COPD with GERD (COPD-G) compared to those without GERD symptoms [63]. Aspiration into airway in GERD patients can trigger exacerbation of COPD and enhance inflammation and induces pulmonary fibrosis [64]. Identification of GERD subgroup of COPD (COPD-G) is very important for prevention of progression of disease.

An explanation for the association between GERD and exacerbations of COPD could be that the aspiration of gastric acid causes airway inflammation [65]. Proton pump inhibitors virtually abolish acid secretion in normal clinical doses [66]. There is a null- association between GERD and COPD in users of acid inhibitory treatment, which altogether suggest that the acidity of the reflux content could be the key to the link between reflux and COPD exacerbations. Among individuals with COPD exacerbations and coexisting night-time and day-

time GERD, around one third of their exacerbations could be attributed to lack of regular acid inhibitory treatment. This needs however, to be investigated in a randomized controlled trial [67,68]. Results from studies using proton-pump inhibitors aiming at lowering the risk of asthma exacerbations [69,70] or as treatment of poorly controlled asthma, have however been disappointing [71,72]. Furthermore, treatment with regular acid inhibitory treatment in COPD is symptomatic treatment and not without adverse effects. In fact, previous studies showed that the use of proton-pump inhibitors can be associated with an increased risk of pneumonia [73,74]. In addition, the effect of GERD on exacerbations could very well be influenced by other factors such as non-acidic reflux and pepsin [75].

Explanation linking GERD with exacerbations is that GERD could cause symptoms such as cough that could be perceived as an exacerbation by both patients and doctors, thereby resulting in the treatment with systemic corticosteroids. Treatment for GERD-related cough, using acid inhibitory treatment regularly, may reduce this symptom sufficiently to prevent treatment with systemic corticosteroids. Thus, an association between GERD and exacerbations could be a reflection of the association between GERD and respiratory symptoms as such. In fact, as in previous studies [76,77], it was observed that individuals with COPD and GERD report significantly more breathlessness, wheezing and chronic bronchitis and have more often a history of respiratory infections than individuals without GERD. Proton pump inhibitor therapy, anti-reflux therapy, change of food habit and sustained bronchodilation are very important to control COPD-G patient.

COPD and obstructive sleep apnea (OSA): COPD-O

Questionnaire based obstructive sleep apnea prevalence study in COPD patient demonstrated that 29.5% COPD patient had associated obstructive sleep apnea (OSA) [78,79]. COPD alone can cause subjective and objective changes during sleep. When those with either chronic bronchitis or emphysema were surveyed across a broad range of symptoms, “sleep difficulties” were endorsed as occurring “almost always” or “always” in 43% of subjects (third most common, after dyspnea and fatigue) [80]. Specifically, patients with COPD report more difficulty in both initiating and maintaining sleep than controls, and also complain of excessive daytime sleepiness [81,82]. Sleep architecture in some of these same patients was notable for many arousals. More than just the diagnosis of COPD, the presence of COPD symptoms such as cough or sputum production or wheezing strongly correlated with difficulty falling or staying asleep [83]. Other investigations have objectively confirmed poor sleep quality, with decreased total sleep time and decreased sleep efficiency [84].

Sleep and breathing

A brief review of the normal changes in respiration that occur with sleep onset and the various sleep stages is helpful to understand the changes that occur during sleep in those with COPD. In normal subjects, minute ventilation drops from wakefulness to non-rapid-eye-movement (non-REM) sleep, and drops further during REM sleep (about 15%, compared to the awake value). Most of the drop in minute ventilation is due to a decrease in tidal volume that is not fully compensated by a concomitant increase in respiratory rate. There is a blunted ventilatory response to hypoxia and hypercapnia, again with the greatest changes during REM sleep [85,86]. REM is characterized by skeletal-muscle atonia, except for the diaphragm, and shallow, irregular breathing. Finally, even in normal subjects without OSA, upper-airway resistance increases during sleep [87].

Nocturnal oxygen desaturation

The most significant sleep abnormality associated with COPD is nocturnal oxygen desaturation [88,89]. Even without any upper-airway contribution, various studies have reported that 27 - 70% of patients with COPD with awake oxygen saturation of 90 - 95% can experience substantial desaturation at night, particularly during REM sleep [90,91]. Nocturnal oxygen desaturation can be defined or measured in terms of oxygen nadir or time below some oxygen-saturation limit, such as 88% or 90%. The desaturation nadir is more profound than during exercise, with oxygen saturation falling an average of $6 \pm 4\%$ during peak exercise and $13 \pm 9\%$ during sleep [92]. Awake oxygen saturation has the greatest predictive value, although it imperfectly predicts nocturnal desaturation [93,94]. Daytime PCO_2 has also been found to be predictive. Perhaps most clinically relevant, nocturnal oxygen desaturation is a marker of increased mortality in COPD [95].

American Thoracic Society/European Respiratory Society guidelines also suggest that those with relatively mild COPD and evidence of pulmonary hypertension should be referred for overnight testing [96]. Daytime hypoxemia with or without hypercapnia and pulmonary hypertension in patients known to have only one disease (either OSA or COPD), whatever in severity, should prompt assessment for the

other disorder. CPAP therapy is an effective therapeutic option in the majority of patients with obstructive sleep apnoea, even if severe, and with normal awake respiratory function. For the subset of patients with OSA associated to COPD, especially when hypercapnia is present in whom CPAP may be ineffective or not tolerated; BIPAP may be an effective and well-tolerated treatment modality for them [97].

Major risk factors common to all COPD patients

Air pollution and temperature change

Air pollutants such as particulate materials (PM) from fossil fuel combustion can cause inflammation in the lung and further impairs the reduced pulmonary function in COPD patients. When exposed to particle pollution, patients with COPD usually have more emergency room visit, hospital admission, or even death in some cases. Infection is one of the inducing factors of exacerbations of COPD. As particulate materials can bring many micro-organisms on the surface, inhalation of such materials may contribute to more frequent infective exacerbation of COPD also. Other mechanisms including the detriment of mucociliary clearance, increased adherence of virus to respiratory mucus cells, and impairment of the resistance ability of immune system are all involved in the adverse effects of pollutants.

Several studies link outdoor air pollution to increased risk of COPD exacerbations. The Air Pollution and Health, a European Approach (APHEA) project analyzed data from 6 European cities and found increased risk of COPD hospital admissions with several air pollutants, including NO₂, O₃, sulfur dioxide (SO₂) and black smoke [98]. A study of PM₁₀ and hospital admissions for COPD found a 2.5% increase in admissions for every 10 µg/m³ increase in PM₁₀ [99]. In addition, a meta-analysis of 18 studies of PM₁₀ and exacerbations found a 10 µg/m³ increase in daily PM₁₀ was associated with a 2.7% increase in COPD hospitalizations [100]. The data linking air pollution with COPD exacerbations for O₃ is also convincing as higher O₃ concentrations have been shown to increase hospital and emergency department visits for lower respiratory disease, including COPD [101-103].

Temperature

There has been increased attention to the effects of heat exposure with the anticipated increases in temperature projected in the context of climate change [104-107]. Studies of heat exposure are often conducted in the context of heat waves, sustained periods of extreme heat that occur over consecutive days. Heat waves can have startling health consequences, as was seen during the summer of 2003 when over 70,000 deaths in Europe were attributable to extreme heat [108] and during the summer of 1995 when there were approximately 750 heat-related deaths in Chicago during only 5 days [109]. Studies have consistently found that elderly individuals and those with underlying cardiac and respiratory diseases, including COPD, are at increased risk for adverse health effects of heat exposure [110-114]. For example, a study across 12 U.S. cities estimated that the effect of hot temperatures during summertime can increase the risk of death attributable to COPD by as much as 25% [112]. A study in New York City found that the risk of COPD hospitalization increased by 7.6% for every 1°C increase above a threshold temperature of 29°C [115]. A large study in Taiwan using national health insurance registry data detected a 0.8% increase in COPD exacerbations for every 1°C decrease in mean daily temperature [116]. In East London, cold temperatures were linked to decreases in lung function in a study of 76 participants with COPD. Investigators found that FEV₁ was 45cc less during the coldest versus warmest weeks during a 12-month period [117]. In addition to bronchoconstriction and inflammation that may occur in the setting of cold exposure [118], recent evidence suggests a role for mucous hypersecretion as a potential mediator of the COPD response to cold temperature [119].

Some COPD patients are particularly susceptible to even low levels of air pollutant exposure. In addition, extremes of temperature, including both extremes of hot and cold, have also been linked to excessive morbidity and mortality among individuals with COPD. Studies suggest that there may even be subgroups of patients with COPD that have increased susceptibility to exposure, but these susceptible subgroups need to be further elucidated. Clearly delineating the harmful impact of air quality and temperature on susceptible groups of individuals with COPD is critical to help guide both policy recommendations and individual clinical recommendations.

Management

For all patients of COPD

1. Quit Smoking
2. Avoid exposure to Smoke or Temperature Fluctuations

3. Take Influenza vaccine yearly and Conjugated Pneumonia vaccine once in life

4. Participate to Pulmonary Rehab program regularly

	Stage 2 FEV₁ <80-50	Stage 3 FEV₁ <50-30	Stage 4 FEV₁ <30
COPD A	Triple therapy (LAMA+LABA+ICS) (Moderate Dose)	Triple therapy (LAMA+LABA+ICS) (Maximum Dose) +Montelukast +Theophylline	Triple therapy (LAMA+LABA+ICS) (Maximum Dose) +Montelukast +Theophylline +Nebulized Bronchodilator +Neb Budesonide ± LTOT
COPD B	Double therapy (LAMA+LABA) +Sublingual Lyophilized Bacterial Lysate (10 days /months and 3 months/year)	Double therapy (LAMA+LABA) +Theophylline +Sublingual Lyophilized Bacterial Lysate (10 days /month and 3 months/year) +Azithromycin (alternate day or thrice a week throughout the year)	Double therapy (LAMA+LABA) +Roflumilast +Sublingual Lyophilized Bacterial Lysate (10 days/month and 3 months/year) +Azithromycin (alternate day or thrice a week throughout the year) +Tobramycin nebulization 3 weeks 12 hourly then 3 weeks gap life long ± LTOT
COPD G	Double therapy (LAMA+LABA) +PPI+Domperidon Change food habit Sleep with double pillow Eating and drinking slow to avoid chocking.	Avoid theophylline/Doxophyllin + Double therapy (LAMA+LABA) +Nebulize Bronchodilator 1-2 times daily +PPI +DOMPERIDON Change food habit Sleep with double pillow Eating and drinking slow to avoid chocking.	Double therapy (LAMA+LABA) +Nebulize Bronchodilator 3-4 times daily + PPI +DOMPERIDON Change food habit Sleep with double pillow Eating and drinking slow to avoid chocking ± LTOT
COPD O	Double therapy (LAMA+LABA) -Always sleep in lateral Position -Do Sleep test/ polysomnography -Do Color doppler Echocardiography -Add CPAP or BIPAP	Double therapy (LAMA+LABA) +Theophylline -Always sleep in lateral Position -Do Sleep test/ polysomnography -Do ABG -Do Color-doppler Echocardiography -add CPAP or BIPAP	Double therapy (LAMA+LABA) +Theophylline +Nebulize Bronchodilator -Always sleep in lateral Position -Do Sleep test/ polysomnography -Do ABG -Do Color-doppler Echocardiography -add CPAP or BiPAP ± LTOT

COPD S	Double therapy (LAMA+LABA)	Double therapy (LAMA+LABA) + Theophylline	Double therapy (LAMA+LABA) + Theophylline + Nebulize Bronchodilator ± LTOT
COPD U	Triple therapy (LAMA+LABA+ICS) (Maximum Dose)	Triple therapy (LAMA+LABA+ICS) (Maximum Dose) +Montelukast +Theophylline +(Azithromycin alternate day or thrice a week throughout the year) +Sublingual Lyophilized Bacterial Lysate (10 days /month and 3 months/year)	Combine all (for maximum relief of Symptoms) + LTOT + BiPAP during sleep

Conclusion

1. This is important to find out four important contributing factors responsible for change from stable COPD to unstable COPD.
2. COPD is preventable and controllable disease needs proper co-disease control for prevention of progression and further deterioration of disease.

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