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BANGLADESH GUIDELINES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Mohammad Rashidul Hassan

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MOHAMMAD RASHIDUL HASSAN

PREFACE

By the grace of Almighty Allah, we are able to publish our own Bangladeshi COPD guidelines, which is evidence based and not a true copy of any other guidelines. We tried to focus that pin point diagnosis is important for a COPD patient as COPD is not a single disease, rather it's a cluster of diseases.

Spirometry assessment is important for diagnosis of severity and staging on the basis of FEV_1. But post-bronchodilator FEV_1/FVC ratio <0.7 is not a reliable tool for diagnosis of COPD as a number of patient including under 50 years with COPD and some may have associated mixed Lung parenchymal fibrosis and/or multiple Bullae which may cause post-bronchodilator FEV_1/FVC ratio >0.7.

We intentionally avoided "ABCD" assessment tool of GOLD guidelines as many co-existed pulmonary diseases may have same symptoms and affects CAT Score and/or breathlessness of COPD by the Modified British Medical Research Council (mMRC) Questionnaire. We tried to explain that simple COPD diagnosis and spirometry assessment is not sufficient for a management plan of COPD. The combination of airflow limitation along with clinical parameters and investigation tools makes it clear to find out clusters of diseases present in an individual with COPD. All diagnostic point should be evaluated for diagnosis, staging and classification of disease. Our assessment tool acknowledges Disease diagnosis, rate of exacerbations per year and FEV_1 which will determine treatment plan for an individualized COPD patient. It will highlight the importance of patients' cluster of disease and exacerbation risks in patient with COPD. Spirometry remains an important key in the diagnosis of FEV_1 staging, prognostication and treatment with non-pharmacological therapies.

GOLD 2020 revised guidelines stated that the blood eosinophil count as a biomarker and as a guide to prescribe and use inhaled corticosteroids for the prevention of exacerbations. But it is only one parameter for diagnosis of asthma in COPD patient and they used in group D patient only.

We emphasize that asthma and COPD are different disorders although they share some traits and features (e.g., eosinophilia, some degree of reversibility). It is now clear that like asthma in a COPD patient, a physician should try to find out other diseases like bronchiectasis, GERD and OSA. They are also not less common than asthma and they are developing during the progress of COPD.

Meticulous observation and follow up is required to establish this concept of COPD management and patient will get more dependable management from care giver throughout the world.

We are grateful to our committee for their support to make this effort successful.

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LIST OF ABBREVIATIONS:

ABG	Arterial Blood Gas
AF	Atrial Fibrillation
BNP	B-type natriuretic peptide
CAT	COPD Assessment Test
CBC	Complete Blood Count
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease.
CPFE	Combined Pulmonary Fibrosis and Emphysema
CRF	Chronic Renal Failure;
CRD	Chronic Respiratory Disease
DEF	Disease Based Classification
ECMO	Extra-Corporeal Membrane Oxygenation
FeNO	Fractional Exhaled Nitric Oxide
GERD	Gastro-Esophageal Reflux Disease
GPAQ	Global Physical Activity Questionnaire
HIC	High Income Countries
HR	Heart Rate
HRCT	High resolution computed tomography
HRD	Heart burn, Regurgitation, Dysphagia
HTN	Hypertension
ICS	Inhaled Corticosteroid
LABA	Long Acting Beta-2 Agonist
LAMA	Long-Acting Muscarinic Antagonists
LLN	Lower Limit of Normal
LMIC	Low- and Middle-Income Countries
LTOT	Long Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
M-CPET	Modified Cardio-Pulmonary Exercise Test
MET	Metabolic Equivalent Task
mMRC	Modified Medical Research Council

MS	Metabolic Syndrome
NCD	Non-Communicable Diseases
NIV	Non-Invasive Ventilation
OSA	Obstructive Sleep Apnea
OSAS	Obstructive Sleep Apnea Syndrome
PA	Physical Activity
PiA	Physical inactivity
PHRHF	Pulmonary Hypertension and Right Heart Failure
PR	Pulmonary Rehabilitation
PTO	Patient may Turn Out
REM	Rapid-Eye-Movement
VTE	Venous Thrombo-Embolism

Disclaimer:

Recommendation of this guideline might not be successful in every situation. Clinical judgement, patient's preference, and overall practice protocol should be considered in every point of implementation of the guideline. The guideline echoes the best evidence-based data, recommendation, and guidance for the best care of COPD patients. Furthermore, updated information should be added once available because of rapidly budding evidence in medical science. As a part of continuously upgrading medical care, this guideline will be re-published once major alterations are available to imitate new data.

Bangladesh COPD Guidelines

A. BACKGROUND

The aim of this guideline is to provide an evidence-based deliverable, user-friendly guideline for Bangladeshi and physicians who are working in low- and middle-income countries (LMICS), as well as those who are interested to give more precise support to COPD patients throughout the world. We want to develop and spread a new strategy of COPD management.

Aim of this guideline firstly is to establish proper diagnosis of COPD, secondly, to diagnose coexisting diseases and all possible comorbidities. Thirdly, is to classify COPD severity on the basis of spirometry, i.e. Lung Function. This is based on FEV_1 and is called COPD staging to understand patient's disease progression, by which severity of airflow limitation can be tracked. Fourthly, is to establish diagnosis whether patient has COPD Stable state, COPD with/ or without coexisting illnesses and with/ or without unstable COPD on the basis of frequency of exacerbations or hospitalization per year[1]. Much is now known about the characteristics of patients in the different COPD stages. Risk of exacerbations, hospitalization, and death of COPD patients depends more on coexisting illnesses and comorbidities than COPD staging[2]. For this reason, at an individual patient level, FEV_1 may be an unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment. Level of management depends on 3 basic assessments: Diagnosis of Diseases, Frequency of Exacerbations and Staging of COPD (DEF i.e. Disease Exacerbation and FEV_1).

B. Executive Summary:

- COPD is one of the progressively deteriorating burden in the health care system of Bangladesh.
- Evidence-based, appropriate, deliverable management guideline is the greatest standing in this field.
- Protocol of COPD management in High-Income Countries (HICs) might not be deliverable and applicable in Bangladesh as well as in LMICS.
- Aim of this guideline:
  - Provide fundamentals of accurate diagnosis of COPD
  - Identifying the coexisting diseases and co-morbidities
  - Spirometric classification of the severity disease (on FEV_1)
  - Disease based classification (DEF) for ensuring optimal therapy.
  - Identifying COPD as:
    - Stable COPD
    - ± coexisting disease
    - ± unstable COPD (based on exacerbation or hospitalization rate)
- Risk of exacerbations, hospitalization, and death of COPD patients depends more on coexisting illnesses and comorbidities than conventional COPD staging.
- Despite sputum production being a common symptom, usually it is under-reported by most of the patients[3].
- The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute.
- Biological dust exposures include substances of microbial, plant or animal origin such as bacteria, fungi, allergens, endotoxins, peptidoglycans, glucans, pollens, and plant fibers.
- Lung function usually deteriorate after exacerbations and usually never return to previous state after each exacerbation in COPD,
- How fast the lung function will deteriorate, depends on the commencing risk factors of the disease.
- Coexisting and comorbid conditions of COPD upsurges the morbidity and mortality.
- Compared to smokers with COPD, nonsmokers with chronic airflow limitation have fewer symptoms, milder disease and lower burden of systemic inflammation, however, non-smokers have higher risk of pneumonia.
- The development of COPD is most likely a series of complex interactions between noxious airborne agents together with a genetic predisposition.
- FEV_1 may be an unreliable marker of the severity and symptom score marker

- The goals of effective COPD management are to:
  - o Prevent disease progression by controlling Risk factors
  - o Relieve symptoms by modern Pharmacological medicine
  - o Improve exercise tolerance by Pulmonary Rehabilitation Program
  - o Improve health status by controlling coexisting diseases and comorbidities
  - o Prevent and treat complications by precise diagnosis of all components of COPD
  - o Prevent and treat exacerbations by vaccination and avoiding air pollution, temperature changes and early detection and treating infection
  - o Reduce mortality by reducing exacerbations, hospitalizations frail syndrome and by controlling coexisting diseases and comorbidities.
- Management plan depends on 3 basic parameters of COPD:
  - o Diagnosis of Diseases, - (D)
  - o Frequency of Exacerbations and (E)
  - o Severity of COPD (FEV_1).(F)
- Theme sentence of this guideline is: *"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).
- Stable COPD: (COPD- S) i.e. Indolent COPD, having no coexisting lung disease with having one or less exacerbation per year and virtually no hospitalization for COPD
  - • COPD with coexisting diseases: COPD-C
  - • COPD with Asthma: COPD-A
  - • COPD and Bronchiectasis: COPD-B
  - • COPD and GERD: COPD-G
  - • COPD and Obstructive Sleep Apnea (OSA): COPD-O
  - • Unstable COPD: (COPD – U); COPD U means COPD patient having more than two exacerbations per year without hospitalization or one exacerbation with hospitalization per year.
- Any one of 15 subtypes of COPD C group may turn to COPD U if they develop frequent exacerbations or hospitalization in a year
- For precise diagnosis and sub-categorization (single or combinations) of COPD C, we need some investigations i.e. a good quality Chest X-ray, HRCT scan of chest (if possible), CBC, and total circulating eosinophil count, sputum cytology with differential count, Blood total IgE level and FeNO.

- Diagnosis part has Three Components:
  - o Diagnosis of COPD
  - o Diagnosis of Coexisting Diseases
  - o Diagnosis of Comorbidities
- For the diagnosis of COPD, comorbidity and coexisting diseases certain investigations have paramount importance e.g. CBC, radiological examination of chest, sputum examination, exercise testing (modified CPET), FeNO, ABG, biochemistry values, ECG, and Sleep studies.
- Common comorbid conditions of COPD are, heart failure, osteoporosis, frailty syndrome, falls in COPD, aspiration, lung cancer, and combined fibrosis with emphysema.
- Management of COPD: for the proper management of COPD precious diagnosis and classification is mandatory. This guideline suggests DEF classification for specifying the management option. Thereafter, Non-pharmacological and pharmacological therapy should be determined (Table16).
- Non-pharmacological therapy includes, reducing exposure to risk factors including quitting smoking, avoidance of temperature fluctuation, Pulmonary Rehabilitation, increasing physical activities, developing skill for self-care, chronic NIV, long-term, ambulatory, and short burst oxygen therapy, ECMO, and surgical intervention.
- Management of comorbidity deserves paramount importance in the care of COPD, as such proper identification and appropriate intervention is statutory.
- Anxiety and depression are common in COPD and that should be addressed sensibly.
- COPD is punctuated by exacerbation, that's why an 'exacerbation management plan' should be pre-defined. In this guideline we used the acronym the plan as 'ABCO' (A-Antibiotic, B-Bronchodilator, C-Corticosteroid, and O-Oxygen)-Chapter
- Before the surgical intervention a precise assessment of lung function is mandatory which is described in chapter 15
- New epoch of the management of COPD is stem cell therapy which is discussed briefly in chapter 16.

1   CHAPTER 1: INTRODUCTION

According to WHO estimates, 65 million people have moderate to severe chronic obstructive pulmonary disease (COPD)[4]. COPD is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2030.

More than 3.2 million people died of COPD in 2015[5], which corresponds to 5% of all deaths globally. It is known that almost 90% of COPD deaths occur in LMICs[6]. At one time, COPD was more common in men, but because of increased tobacco use among women in HICs and the higher risk of exposure to indoor air pollution (such as biomass fuel used for cooking and heating) in LMICs, the disease now affects men and women almost equally[7].

1.1   Bangladesh perspective:

According to Burden of Obstructive Lung Diseases Bangladesh (BOLD BD study 2007), in Bangladesh prevalence of COPD in total population of Bangladesh was 4.24% and estimated 6.0 million people were suffering from COPD[8]. The Prevalence in population of 40 years and above was found to be 21.58% with a total of 60,42,400 people. Majority (45.13%) of the COPD patients were suffering from GOLD spirometry classification of moderate stage of COPD. In general, males suffer more than females (62.47% vs. 37.26%). Prevalence in urban areas (61.52%) is higher than that of rural areas (38.48%). Interestingly, among the female COPD patients, these figures are almost equal (urban ~ 50.21% vs. rural 49.79%), indicating higher prevalence of the disease in village women[8].

From these findings, it is obvious that COPD is a disease for the poorer people (~80% of total population) of Bangladesh. People of the productive age group (40-50 years) was the main victim (42%). The prevalence decreases with the increase of age (lowest in more than 80 years group – 2.5%). About 50% patients with COPD were illiterate.

Majority (63%) COPD patients were current smokers. Smoker group was extremely high in male COPD patients – about 88% were smokers, whereas only 20% of female COPD patients were smokers. We found a positive relation between gradual raise in COPD prevalence with increased pack-years of cigarette or equivalent smoking tobacco consumption. It showed that majority of smokers (80%) need only around 10 pack-years of smoking to develop the disease. Exposure to biomass gas (open stove/wood burn) appears to be a significant risk factor in COPD. More than 42% COPD patients are exposed to it. The figure was even higher among female COPD patients (more than 86%).
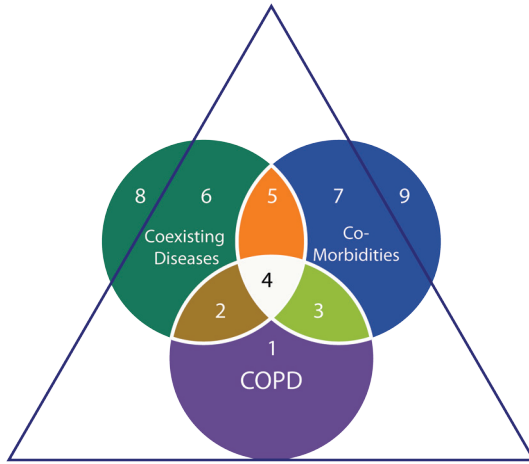
Figure 1:Different phenotypes of COPD

1. COPD
2. COPD with coexisting diseases
3. COPD with comorbidities
4. COPD with coexisting diseases and comorbidities
5. 6. 7. Some diseases without COPD but having other obstructive lung diseases like asthma
8. 9. Some diseases without obstructive lung disease

- The large Triangle represents total diagnosed and undiagnosed Obstructive Pulmonary Diseases.
- The circles represent the Nonproportional overlapping of patients with COPD with coexisting Lung Diseases and co-morbidities.

COPD represents an important non-communicable health problem that should be diagnosed properly before treatment and to determine a management plan. COPD is a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in the upcoming decades because of continued exposure to risk factors and association of other

> Disease, Exacerbation and FEV_1 (DEF) based classification is more appropriate than Symptom, Exacerbation and FEV_1 (SEF) based classification for COPD management[1]

coexisting illnesses responsible for deterioration of disease[9-13]. Recent study shows that DEF is better than SEF in the management of COPD in LMICs.

1.2   Management strategy of COPD[1]:

According to WHO management Strategy of COPD, an effective COPD management plan includes four fundamental components:

(1) assess and monitor disease;
(2) reduce risk factors;
(3) manage stable COPD;
(4) manage exacerbations of COPD.

The goals of effective COPD management are to:
- o Prevent disease progression by controlling Risk factors
- o Relieve symptoms by modern Pharmacological medicine
- o Improve exercise tolerance by Pulmonary Rehabilitation Program
- o Improve health status by controlling coexisting diseases and comorbidities
- o Prevent and treat complications by precise diagnosis of all components of COPD
- o Prevent and treat exacerbations by vaccination and avoiding air pollution, temperature changes and early detection and treating infection
- o Reduce mortality by reducing exacerbations, hospitalizations frail syndrome and by controlling coexisting diseases and comorbidities.

2   CHAPTER 2: METHODOLOGY

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline has been employed from 2001 to till 2008 in Bangladesh. We made our national prevalence survey BOLD BD study 2007[14].

In 2008 we developed and published a COPD guideline based on Symptom, Exacerbations and Function (SEF) classification for COPD[10]. However, disease-based classification (DBC) appears to be a better than the SEF. That's

> There exists under-reporting of productive cough as most patient swallow their sputum. As such, symptom-based classification might be misleading in the management of COPD

why we worked on DBC and developed a new thought which includes the diagnosis of every component of the 'disease cluster' of COPD and formulate an individualized-tailored management protocol.

2.1   Guideline development:

We conducted an extensive search on PubMed using the search term 'COPD', AND/OR 'Chronic Obstructive Pulmonary Disease' with a limit to 'abstracts', 'Clinical Trial' or 'Meta-analysis study type' and COPD related review papers. We have also conducted manual search for NICE guideline, Australian Guideline, GOLD 2020 and SEF Bangladeshi guidelines. The pre-defined selected articles were evaluated by Bangladesh COPD guideline committee. We have used The Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument for evaluation of various guidelines and review papers. From review of different guidelines and papers our committee made an evidence-based consensus statement which is, supported by various papers and/ or guidelines. Moreover, the guideline is anchored on the background of our relevant published review paper[15].

3   CHAPTER 3: DEFINITION

3.1   Definitions in short

COPD: Chronic Obstructive Pulmonary Disease (COPD) is a cluster of at least two or more pulmonary diseases that is characterized by persistent **exertional dyspnea and/ or chronic cough with or without expectorations** and airflow limitation, and that is due to airway and/or alveolar abnormalities with or without Pulmonary hypertension usually induced by significant exposure to noxious particles or gases.

Cluster of disease: Aggregation of different disease entities is various phenotypes of COPD is defined as 'cluster of COPD' in this guideline e.g. 'Chronic Bronchitis + Emphysema', 'Emphysema + Asthma', 'Chronic Bronchitis + Emphysema + GERD' etc.

Co-morbidity: The term "comorbidity" has been used to indicate a medical condition existing simultaneously with but independently of another condition.

Co-existing disease: Although comorbidity and coexisting diseases terminology is synonymous but, in this guideline, coexisting diseases are defined as the conditions which develop as a consequence during progression and raising degree of severity of COPD.

Persistent respiratory symptoms: Exertional dyspnea and/ or chronic cough ± expectorations are defined as persistent respiratory symptoms in this guideline.

Note: by definition pure chronic bronchitis, Pure Pulmonary Emphysema and pure asthma even severe persistent asthma is not included in the definition of COPD, as by definition COPD is a cluster of at least 2 or more diseases. For example.
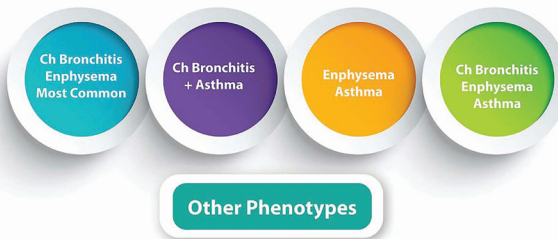
COPD, in most of the cases is a cluster of, "chronic bronchitis and emphysema", which is not included in the definition[16].

Figure 2:Clusters of COPD phenotype

Emphysema, by definition is destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD[17].

COPD-S means stable COPD i.e. Usually this group of COPD patient having no coexisting lung disease.

Unstable COPD: (COPD – U); COPD U means COPD patient having more than two exacerbations per year without hospitalization or one exacerbation with hospitalization per year

COPD-C means COPD patient having at least one coexisting lung disease. Two or more coexisting lung disease may be present in an individual COPD patient

3.2   Clinical definition of COPD:

COPD is defined as above, and it's various clusters are described in the figure below:
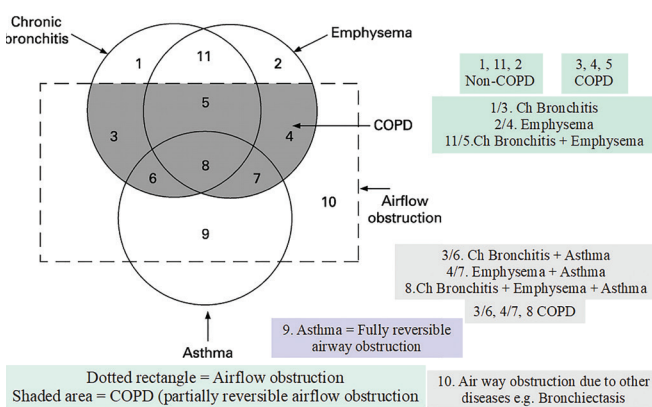
Figure 3: Non-proportional Phenotypes of COPD
(Reproduced by the permission of ATS)

Although non-proportional Venn diagram represents only the component of the cluster of disease however, by proportional diagram we can understand the relative burden of components of the cluster of COPD as shown in figure below.

The following labels point to the diagram:
- Chronic bronchitis
- Emphysema
- No defined phenotype
- Asthma

- ❑ The large black rectangle represents the full study group.
- ❑ The clear circles within each coloured area represent the proportion of subjects with COPD
- ❑ The isolated clear circle represents subjects with COPD who did not have an additional defined phenotype of asthma, chronic bronchitis or emphysema.

Figure 4: Proportional Venn Diagram of COPD

(Reproduced by seeking permission) Proportional Venn diagram presenting the different phenotypes within the Wellington Respiratory Survey study population[18].

Few facts and findings of COPD are:
• Despite sputum production being a common symptom, usually it is under-reported by most of the patients[3].
• The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute.
• Furthermore, exposure to smoke and/or smoking, host factor influences are also important to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging[3].
• Lung function usually deteriorate after exacerbations and usually never return to previous state after each exacerbation in COPD as shown in the figure below:
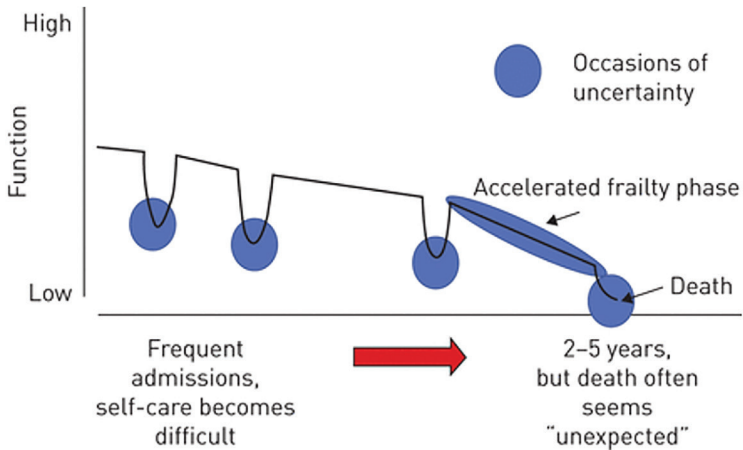
Figure 5: Disease trajectory of COPD

A stylized model depicting the end-of-life trajectory for a proportion of patients with COPD[19]

COPD may be associated with coexisting pulmonary diseases and significant other comorbid chronic diseases, which increase its morbidity and mortality[2,15].

After commencement of COPD, the lung function progressively worsens with increasing severity and this is determined by the inducing factors i.e. smoke, host factors, abnormal lung development, recurrent infection, allergic inflammation and hypoxic spell during sleep and during exacerbations.
Significant coexisting pulmonary diseases and comorbidities may have an impact on morbidity and mortality[2]. There may be significant lung pathology (e.g. emphysema) in the absence of airflow limitation that needs further evaluation as simple emphysema is not defined as COPD.
The chronic and non-reversible or partially reversible airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease and parenchymal destruction (emphysema), the relative contributions of which vary from person to person[20].
These changes do not always occur together at a time but evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to airflow limitation

and mucociliary dysfunction is a characteristic feature of the disease[21]. Airflow limitation is usually measured by spirometry as this is the most widely available and reproducible test of lung function[22].

Exertional shortness of breath, barrel shaped chest, obliteration of 'area of cardiac dullness', low down diaphragm and silent chest are the diagnostic features of emphysema component of COPD.
Chronic bronchitis[23], by definition is presence of cough and sputum production for at least 3 months in each of two consecutive years, still remains a clinically and epidemiologically useful term with spirometrically normal lung function. This definition is usually not used during diagnosis of COPD.

After widespread small airway obstruction, changes in spirometry measurement will show FEV_1 /FVC % <0.7 or lower limit normal (LLN) and FEV_1 80% or less[24]. These changes are defined as Chronic Obstructive Bronchitis, an important component of early COPD.

In COPD, presence of chronic cough and sputum production for more than 2 years is a useful diagnostic point of chronic bronchitis component of COPD. Persistent respiratory symptoms also exist in individuals showing normal spirometry[25] and a significant number of smokers without airflow limitation have structural evidence of lung disease manifested by the varying presence of emphysema, airway wall thickening and gas trapping. They are by definition not COPD.

3.2.1   Pre-COPD or Early COPD[26]:

These are group of patients who have history of significant exposure to smoke and/or smoking along with some of the early symptoms of COPD include coughing with or without expectorations, excess mucus, shortness of breath, and tiredness or structural changes clearly like emphysema like hyperinflated lung but spirometry showing FEV_1 /FVC % >0.7 or LLN and FEV_1 80% or more. Identifying these patients is imperative to prevent progression of disease.

4   CHAPTER 4:
DEVELOPMENT AND PROGRESSION of COPD

Cigarette smoking is the most well studied COPD risk factor for commencement of disease. But it is not the only risk factor and there is consistent evidence from epidemiologic studies that non-smokers may also develop chronic airflow limitation[27]. Much of the evidence concerning risk factors for COPD comes from cross-sectional epidemiological studies that identify associations rather than causal relationships. Nevertheless, compared to smokers with COPD, nonsmokers with chronic airflow limitation have fewer symptoms, milder disease and lower burden of systemic inflammation[28]. Interestingly, non-smokers with chronic airflow limitation do not appear to have an increased risk of lung cancer, or cardiovascular comorbidities, compared to those with chronic airflow limitation from smoking. That's why tobacco cessation is warranted in smokers with COPD[28].

However, there is evidence that some non-smoker COPD have an increased risk of pneumonia and mortality from respiratory failure[29]. Biomass fuels (coal, wood, dung, crop waste etc.) exposure is important risk factors in rural and suburban areas of Bangladesh[30]. Occupational dust exposure might be responsible for 20 to 30% of COPD[31]. A summary of the risks of COPD associated with biological or mineral dusts, gases, fumes / vapors, diesel exhaust, chemical gas / fumes and various other occupational exposures appears in Figure 4[32]
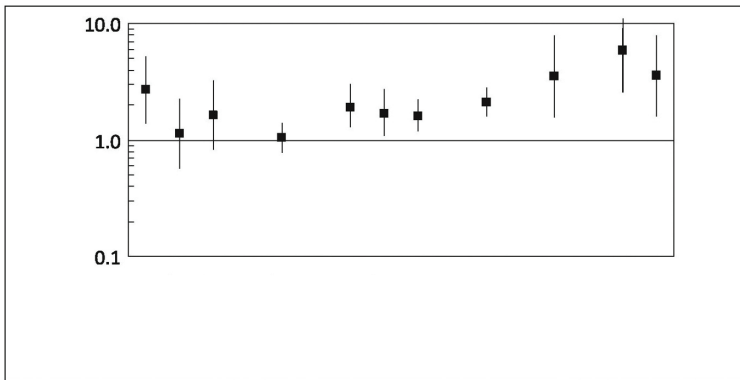
Figure 6: Risk of occupational exposure for COPD

Risk of occupational exposure for COPD adapted from Australian and New Zealand Guidelines 2019

Biological dust exposures include substances of microbial, plant or animal origin such as bacteria, fungi, allergens, endotoxins, peptidoglycans, glucans, pollens, and plant fibers[33].

This occupational risk factors study clearly demonstrated that biological dust, Diesel exhaust, mineral dust, irritant gases and vapors, Dusts (PM 10 and PM 2.5) and chemical gas and fumes have significant association for development of COPD[33-37].

The development of COPD is most likely a series of complex interactions between noxious airborne agents together with a genetic predisposition[38]. Exposure to cigarette smoke and air pollution as well exposure to infectious agents are commonly associated with the development of COPD[39]. Because COPD does not develop in all smokers and it is interesting that even for heavy smokers, fewer than 50% develop COPD during their lifetime. Genetic predisposition such as protease-antiprotease imbalance is a plausible explanation for the development of airways inflammation and airflow obstruction[40].

5   CHAPTER 5: OVERVIEW

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 & pulmonary vasculature resulting in many structural and functional changes in the lung. COPD is a burden for both developed and developing countries. COPD management is a great challenge even after implementing COPD guidelines properly[41].

The term "comorbidity" has been used to indicate a medical condition existing simultaneously with but independently of another condition[42]. Recently, however, use of the term comorbidity has broadened to suggest a causal relationship between two disease states. Certainly, in case of chronic obstructive pulmonary disease (COPD), assessment of all other components of disease is very important from both an academic and a clinical point of view. 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[43].
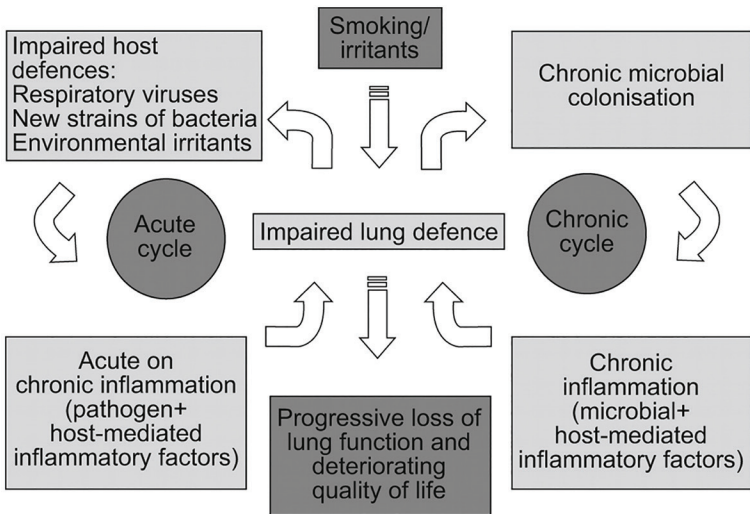
Figure 7[43]: Two distinct infection cycles in COPD

A new coexisting disease[44]-based classification is formulated which is directed more towards management of COPD. It's based on a self-made theme quotation "If Arterial Blood Gas (ABG) deteriorates, stable COPD Patient may Turn Out (PTO) to unstable COPD".

Although comorbidity and coexisting diseases terminology is synonymous but, in this guideline, coexisting diseases to describe: few definite conditions which develop during progression and stage changes of COPD[45]. These coexisting diseases may be developed as a sequel or consequence of progression of COPD which leads to more frequent exacerbations and changes from stable status of COPD to COPD with coexisting diseases and then gradually towards unstable COPD.

It is now clear that stable COPD patient due to continuous exposure to smoke or smoking with recurrent infection, bronchospasm, exposure to air pollutant and temperature changes with genetic and hormonal susceptibilities changes gradually progresses to unstable COPD over the years. That's why our theme quotation is very simple to recapitalized with the acronym 'ABG' and 'PTO'. It is now clear that some internal and external factors are responsible for turning out stable COPD patient's to unstable COPD[9]. If we can control six important factors which are recognized as triggers for exacerbation of COPD, exacerbation may be curtailed and may 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 theme quotation. (Table 1)

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

Table 1: Mnemonic meaning of 'ABG' & 'PTO'

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).

Precisely two steps for commencement and progression of COPD: initiation of inflammation from interaction with smoke/ smoking plus genetic factors along with recurrent infection – both are responsible for development and progression of COPD[38,41,43,46]. Asthma, GERD, air pollution, temperature changes and OSA -all developed during the progress of COPD are responsible to perpetuate airways and lung parenchymal inflammation. Recurrent infection in patients of COPD is the main cause that initiates and maintain neutrophilic inflammation, thick secretion, peripheral airways obstruction. This persistent

neutrophilic inflammation ultimately causes necrotizing inflammation and destruction of the airways smooth muscle that perpetuate to much more peripheral bronchiectasis.

6 CHAPTER 6: DEF CLASSIFICATION AND STAGING

DEF Classification of COPD is as follows[15]:

1. Stable COPD: (COPD- S) i.e. Indolent COPD, having no coexisting lung disease with having one or less exacerbation per year and virtually no hospitalization for COPD

2. COPD with coexisting diseases: COPD-C
- COPD with Asthma: COPD-A
- COPD and Bronchiectasis: COPD-B
- COPD and GERD: COPD-G
- COPD and Obstructive Sleep Apnea (OSA): COPD-O

3. Unstable COPD: (COPD – U); COPD U means COPD patient having more than two exacerbations per year without hospitalization or one exacerbation with hospitalization per year

COPD-S, COPD-C and COPD-U:

Still there is no internationally accepted definition of Stable or Unstable COPD. We developed a working definition for Stable or Unstable COPD for patient management. It is defined as per follows:

• COPD-S means stable COPD i.e. Usually this group of COPD patient having no coexisting lung disease. That means COPD patient having no feature of Asthma, Bronchiectasis, OSA or GERD. Progression of disease in Stable COPD patient depends mainly on temperature change, air pollution and/ or Smoking effect. That's why nature of progression would be slow with infrequent exacerbation, i.e. less than two exacerbations per year and virtually no hospitalization in a year for COPD.

• COPD C means COPD patient having at least one coexisting lung disease. Two or more coexisting lung disease may be present in an individual COPD patient. For example, asthma and bronchiectasis may coexist simultaneously, which may be designated as COPD C: AB subtypes or subcategories. Thereby COPD C: subtypes may be presented as single (A/B/ G/O) or as different subtype combinations. That's why in COPD-C group, in addition to 4 single sub-categories, COPD AB, or AG or AO or BG or BO or GO or ABG or ABO or AGO or BGO or ABGO – total 11 possible combinations of multiple coexisting illness may be present in an individual. All the COPD C patients are prone to repeated exacerbations and vulnerable to become COPD U.

• COPD U patients are group of patients who experience repeated exacerbations. Any one of 15 subtypes of COPD C group may turn to COPD U if they develop frequent exacerbations or hospitalization in a year.

6.1　Distinct pathophysiological features:

Four distinct pathophysiological features are crucial for development and perpetuation of unstable COPD: i.e. recurrent exacerbations and hospitalization

1. Recurrent or persistent Eosinophilic Inflammation[47,48]: Features like Asthma.

2. Recurrent infection and neutrophilic inflammation[11]: Features like Bronchiectasis, para-septal Bullae are likely to develop.

3. Acid/Bile aspiration and micro-aspiration of food particles, throat content with or without micro-organism with neutrophilic inflammation[49]: Features like recurrent right and left basal pulmonary inflammation, distortion of small airways and to some extent pulmonary fibrosis is likely to develop.

4. Hypoxic spell during sleep and during exacerbations may lead to development of pulmonary hypertension[50]
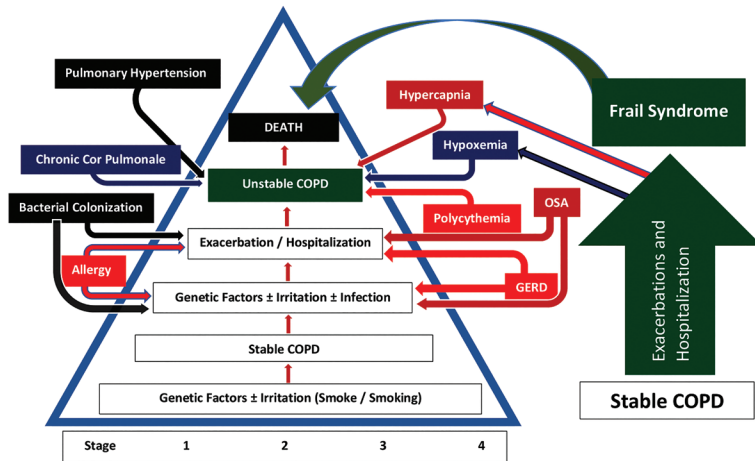
Figure 8: A Journey of Stable to Unstable COPD

For precise diagnosis and sub-categorization (single or combinations) of COPD C, we need some investigations i.e. a good quality Chest X-ray, HRCT scan of chest (if possible), CBC, and total circulating eosinophil count, sputum cytology with differential count, Blood total IgE level and FeNO[51] [preferably at least 2 weeks not getting oral Corticosteroids (OCS) or inhaled Corticosteroids (ICS). If patient is getting OCS and/or ICS then at least 2-3 times FeNO should be done in 1 to 3 months interval to find out rising trends of FeNO in COPD.
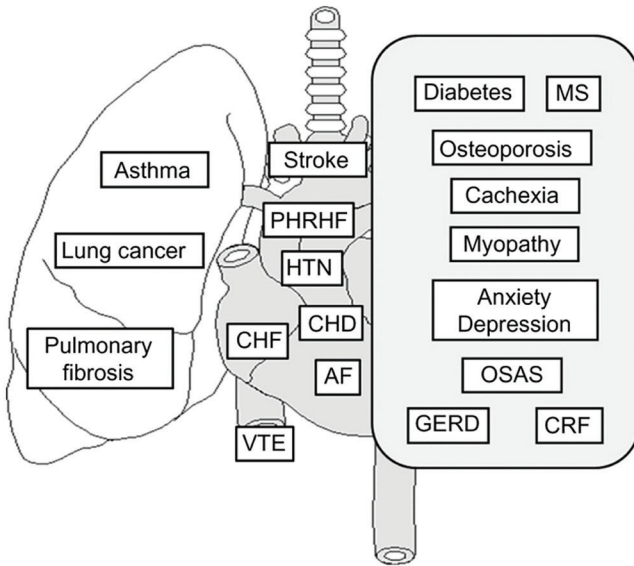
Figure 9[52] Coexisting diseases and comorbidities in COPD.

6.2   Cardio-Pulmonary Exercise Test (CPET)

It is important for the management plan of COPD particularly for rehabilitation program of COPD[53]. As it needs a costly Ergometry machine, we developed Modified CPET (M-CPET) test, that means a combination of Spirometry with reversibility test, Incremental Shuttle walk test[54], pre-exercise ECG and 6-minute cycling with Tele-cardiac monitoring[55].

Modified CPET (M-CPET) can't check anaerobic threshold (AT) and VO_2 Max. But this can measure lung function with reversibility status effectively, exercise capacity before and after rehabilitation program and find out evidence of cardiac ischemia and different types of arrhythmias during exercise. This test will measure Level of increment instead of VO_2 Max.

Spirometry is important for staging of COPD[56] and Modified CPET starts with spirometry with reversibility testing, this test is also important to diagnose and classify stage of COPD as well as simultaneously diagnosis of COPD– A sub-group. In COPD-A reversibility test may be partially positive, i.e. either improvement of FEV_1 at least 200ml alone or at least 12% improvement of FEV_1.

6.3   SEVERITY OF COPD:

Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV_1, in patients with FEV_1/FVC Ratio <0.7)		
STAGE 1	MILD	$FEV_1 \geq$ 80% PREDICTED
STAGE 2	MODERATE	50%$\leq FEV_1 <$ 80% PREDICTED
STAGE 3	SEVERE	30% $\leq FEV_1 <$ 50% PREDICTED
STAGE 4	VERY SEVERE	$FEV_1 <$ 30% PREDICTED

Table 2: Severity of COPD on the basis of FEV1 GOLD 20203.

In some COPD cases Spirometry may not meet criteria FEV_1/FVC ratio <0.7, due to presence of other coexisted diseases or comorbidities, obesity, presence of multiple bullae, chest wall muscle or diaphragmatic muscle weakness, electrolyte imbalance etc[57].

By definition in COPD patient, airflow limitation is not fully reversible, after administration of bronchodilator medication, the ratio of FEV_1 to forced vital capacity (FVC) is <70% even the FEV_1 is $\geq$80% of the predicted value. The ratio of FEV_1 to vital capacity (VC) is a sensitive indicator for mild COPD. FEV_1/FEV_6 has a high level of agreement with FEV_1/ FVC on both the fixed ratio and Lower Limit of Normal (LLN) criteria for the diagnosis of COPD. There is controversy regarding the optimal cut-off to define airflow limitation (FEV_1/ FVC less than 0.7 versus lower limit of normal). There is evidence that the fixed ratio can lead to over diagnosis of COPD in older populations, under diagnosis in younger people[58-60] and may lead to gender imbalances as women have higher FEV_1/ FVC ratio than their male counterparts[61]. A systematic review of 11 studies which examined the relationship of each criterion with clinical outcomes found both were related to clinical outcomes and concluded that on current evidence one could not be preferred over the other. The LLN appeared to be a better criterion in older patients with less severe airflow limitation[57]; however, a study shows that the fixed cut-off of 0.7 identified more people with CT diagnosed emphysema[62,63].

7   CHAPTER 7: DIAGNOSIS

Diagnosis part has Three Components:
- Diagnosis of COPD
- Diagnosis of Coexisting Diseases
- Diagnosis of Comorbidities

7.1   Summary notes:

COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, a history of recurrent lower respiratory tract infections and/ or a history of exposure to risk factors for the disease.

Spirometry is required to make the diagnosis; the presence of a postbronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation although various contributing factors may limit the presence of a post-bronchodilator $FEV_1/FVC\% < 0.70$. Under 50 years age we should practice lower limit normal (LLN) $FEV_1/FVC\%$. Always FEV_1 is important to understand stage of COPD and consider limitation of FEV_1/FVC ratio <0.70 under 50 years of age.

After diagnosis of COPD, diagnosis of coexisting illnesses would be established for sub-classification of COPD.

The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.

Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer.

Coexisting diseases and comorbidities should be actively sought and treated appropriately when present as they can influence morbidity, hospitalization, and mortality independently.

Algorithm for Diagnosis of COPD

Clinical
- Expectational Dyspnea
- Expectorations
- Chronic cough
- Chest cage changes
- Changes breath sound: Prolong Expiration /Ronchi
- Soft Breath sound

Initiating Factor
- Smoke: Tobacco/Wood
- Occupation
- Pollution: Indoor/Outdoor
- Host Factors

Investigations
- Spirometry
- Chest X-Ray

Algorithm for Diagnosis of Coexisting Diseases

Clinical
- ASTHMA: Phenotypes
- Bronchiectasis: Chronic Sputum production
- GERD: HRD
- SLEEP APNEA: Hypoxic Spell, Pulmonary HTN,

Initiating Factor
- Virus infection /Allergen /Occupation and dust
- Recurrent Infection
- Incompetent LES
- Hypoxic spell during sleep

Investigations
- FeNO
- Sputum C/S during color change
- Sputum: Eosinophil/Neutrophil
- HRCT CHEST
- Color Doppler ECHO
- Polysomnography

Figure 10: Algorithm of diagnosis of COPD and Coexisting disease

Algorithm for Diagnosis of Comorbidities

Clinical
- Diabetes Mellitus
- IHD
- Dyspepsia
- Osteoporosis
- Anxiety / Depression
- Insomnia
- Malignancy

Initiating Factor
- Sedentary work
- Food Habit
- Hormone defect
- Stress
- Lack of sun exposure
- Use of different Medicine

Investigations
- Blood Sugar
- TSH
- Stress ECG
- BMD
- S. Vitamin D3
- Endoscopy of Upper GI

Algorithm for Management of COPD

Compile diagnosis
1. COPD +
2. Coexisting diseases+
3. Co-morbidities
   = 1 ± 2 ± 3 = Final Dx

Assess Problems
1. Stage of COPD
2. Level of Symptoms (CAT or/mMRC Score)
3. Frequency of Exacerbations
4. Physical Fitness
5. Mental condition
6. Financial condition

MANAGEMENT
- COPD = DUAL Bronchodilator
- + Asthma = + ICS (Triple Therapy)
- + Bronchiectasis = Azithrocin Pulse Therapy ± *Sublingual Lyophilized Bacterial Lysate*
- + GERD = PPI + Domperidone
- + OSA= CPAP/ BiPAP
- Comorbidities Management

Figure 11: Algorithm for Management of COPD

CAT score or / mMRC Score: any one score can be used during follow up of patient and to understand level of symptom control and pre and post Pulmonary Rehab assessment.

Figure 12: CAT SCORE[64]

CAT™ ASSESSMENT

For each item below, place a mark ✓ in the box that best describes you currently.
Be sure to only select one response for each question.

			SCORE
EXAMPLE: I am very happy	⓪ ① ② ③ ④ ⑤	I am very sad	
I never cough	⓪ ① ② ③ ④ ⑤	I cough all the time	
I have no phlegm (mucus) in my chest at all	⓪ ① ② ③ ④ ⑤	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	⓪ ① ② ③ ④ ⑤	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	⓪ ① ② ③ ④ ⑤	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	⓪ ① ② ③ ④ ⑤	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	⓪ ① ② ③ ④ ⑤	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	⓪ ① ② ③ ④ ⑤	I don't sleep soundly because of my lung condition	
I have lots of energy	⓪ ① ② ③ ④ ⑤	I have no energy at all	

TOTAL SCORE: ◯

Figure 13: CAT SCORE (Bangla Version)

CAT SCORE (BANGLA VERSION)

আপনার নাম ঃ		আজকের তারিখ ঃ	

নিম্নোক্ত প্রশ্নাবলী আপনাকে ও আপনার স্বাস্থ্য সেবা প্রদানকারীকে আপনার ভাল থাকা ও প্রাত্যহিক জীবনে সিওপিডি (ক্রনিক অবস্ট্রাকটিভ পালমোনারী ডিজিজ) অসুখটির প্রভাব পরিমাপে সহায়তা করবে। আপনার উত্তর ও আপনার প্রাপ্ত স্কোর আপনাকে ও আপনার স্বাস্থ্যসেবা প্রদানকারীকে আপনার চিকিৎসার উন্নয়নে ও তা থেকে সর্বোচ্চ উপকার কিভাবে পাওয়া যাবে তা নির্ণয়ে সহায়তা করবে।

আপনার সিওপিডি অসুখটি কোন পর্যায়ে আছে? সিওপিডি অসুখটির অবস্থা যাচাই করুন।

নীচের প্রতিটি আইটেম এর জন্য, যে কষ্টটি আপনার বর্তমান অবস্থা বর্ণনা করবে তাতে টিক (√) চিহ্ন দিন। প্রতিটি প্রশ্নের জন্য একটি মাত্র উত্তর দান নিশ্চিত করুন।

উদাহরণঃ আমি খুবই সুখী	✓①②③④⑤	আমি খুবই বিষন্ন।	স্কোর
আমার কাশি হয়না	⓪①②③④⑤	আমার সর্বদাই কাশি হয়	
আমার বুকে শ্লেষ্মা জমে নেই	⓪①②③④⑤	আমার বুকে শ্লেষ্মায় পরিপূর্ণ	
আমি বুকে মোটেও চাপ অনুভব করিনা	⓪①②③④⑤	আমি বুকে প্রবল চাপ অনুভব করি	
যখন ঢাল বা সিঁড়ি বেয়ে ওপরে উঠি তখন মোটেও শ্বাসকষ্ট হয়না	⓪①②③④⑤	ঢাল বা সিঁড়ি বেয়ে উপরে ওঠার সময় প্রবল শ্বাসকষ্ট হয়	
আমি সব গৃহকর্মই করতে পারি	⓪①②③④⑤	আমি কোন গৃহকর্ম করতে পারিনা	
আমার শ্বাসতন্ত্রের সমস্যা সত্ত্বেও আত্মবিশ্বাস নিয়ে বাড়ীর বাইরে যাই	⓪①②③④⑤	শ্বাসতন্ত্রের সমস্যার জন্য আমি বাড়ীর বাইরে যেতে পারিনা	
আমার সুনিদ্রা হয়	⓪①②③④⑤	আমার মোটেও সুনিদ্রা হয় না	
আমার প্রচুর প্রাণশক্তি	⓪①②③④⑤	আমার মোটেও শক্তি নেই	

সর্বমোট স্কোরঃ ☐☐

Table 3: Modified Medical Research Council (mMRC) Scale
Grading the severity of breathlessness during daily activities[65]

Grade Description of Breathlessness
Grade 0: I only get breathless with strenuous exercise
Grade 1: I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2: On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for 2 breath when walking at my own pace on the level
Grade 3: I stop for breath after walking about 100 metres or after a few minutes on level ground
Grade 4: I am too breathless to leave the house or I am breathless when dressing or undressing

Table 4: Modified Medical Research council scale in Bangla

Mdified MRC Scale: (MRC Score)	
Score	Scale
0	প্রচন্ড পরিশ্রম ছাড়া শ্বাসকষ্ট হয়না।
1	সমতলে দ্রুত হাঁটলে অথবা সামান্য উঁচুর দিকে হাঁটলে শ্বাসকষ্ট হয়।
2	সমবয়সী লোকদের তুলনায় আস্তে হাঁটতে হয়।
3	শ্বাস নেয়ার জন্য সমতলে ১০০ গজ হাঁটার পরে অথবা কয়েক মিনিট পরেই বিশ্রাম নিতে হয়।
4	এত শ্বাসকষ্ট যে বাড়ি থেকে একা বের হতে সাহস হয়না অথবা জামা কাপড় পরতে গেলে হাঁপিয়ে উঠি।

8   CHAPTER 8: INVESTIGATIONS[63]

8.1   CBC:
Complete blood count is important to understand
- Polycythemia (More in Ch bronchitis predominant COPD)
- Anemia (More in Emphysema predominant COPD)
- Higher count with High polymorph may indicate RTI
- Eosinophil $\geq$ 300 per µL indicating, may need ICS therapy
- Low MCV, MCH with anemia indicating Iron deficiency anaemia.

8.2   Chest X-Ray
A plain Posterio-Anterior and Lateral Chest x-ray helps to exclude other conditions such as lung cancer. Limitation of CXR are non-specificity of lung hyperinflation and identifying nodules < 1 cm. But Chest X-Ray is important to identify other coexisting diseases e.g.
- Bronchiectasis, Lung Cancer, Lung Fibrosis etc.
- Pneumonia or Respiratory tract infection old PTB with fibrosis etc.
- Pneumothorax, Bulla
- Cardiomegaly or Tubular heart
- Emphysematous changes

8.3   Sputum examination
Sputum culture is recommended when an infection is not responding to antibiotic therapy or when a resistant organism is suspected. Sputum examination is recommended to understand
- Sputum Eosinophil: $\geq$3 or more per HPF; indication ICS therapy in COPD
- Sputum Neutrophil: plenty in Bronchiectasis, Lung infection with COPD and need of Pulse Azithromycin therapy
- Sputum Gene X-pert and AFB for Typical and/or atypical Mycobacterial Infection
- Sputum culture during exacerbation to identify drug-resistant organism.

8.4   Spirometry
Spirometry is the most reproducible and objective measurement of airflow limitation. It is a noninvasive and readily available test.
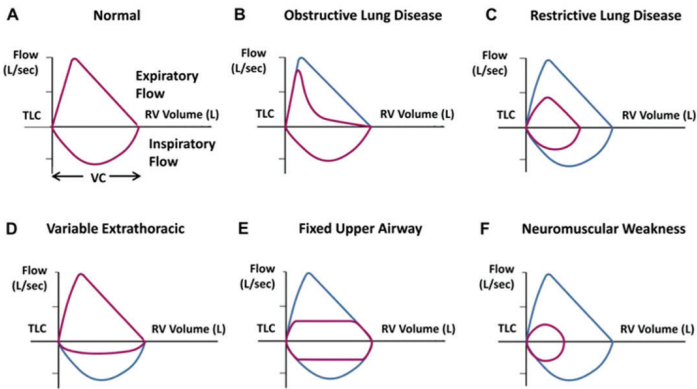
Figure 14: Comparison of different flow-volume curves

The spirometry is very much dependent on patient effort and cooperation, and there are important quality criteria that should be met in conducting spirometry[60].

Indications for Spirometry:
- Breathlessness that seems to be inappropriate;
- Chronic (daily more than 3 weeks) cough or intermittent,
- Unusual cough;
- Frequent or unusual sputum production
- Relapsing acute infective bronchitis; and
- History of risk factors such as exposure for COPD.
- Strong family history of COPD or Asthma

8.5   Exercise testing
Exercise testing is carried out to find out three questions:
1.   Is exercise capacity normal?
2.   What is the cause of abnormal exercise capacity?
3.   Is exercise training safe to perform?
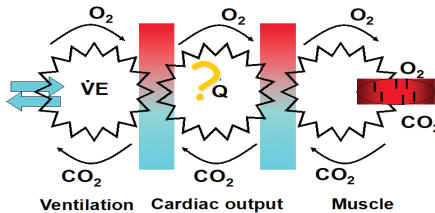
Figure 15:Causes of breathlessness

Three principal causes of exercise intolerance are mainly identified, ventilatory limitation, Cardiac limitation, and Muscular limitation.

Cardio-Pulmonary Exercise Tasting (CPET) is the gold-standard, however, many facilities have no such expensive cycle ergometer for the test. We developed a 'Modified Cardio-Pulmonary Exercise Tasting (CPET)' for our Bangladeshi Patients:

8.5.1   Components of Modified CPET:

• Spirometry with Reversibility test
• Resting ECG
• Incremental shuttle walk test or 6-minute walk Test
• Tele- Cardiac Monitoring (TCM) before, during and after Exercise
We do Modified CPET test to find out-
• Baseline (Before Rehab) and after Rehab Lung Function (Pre and post bronchodilator FEV_1, FVC and FEV_1/FVC ratio)
• Patient Endurance before and after Rehab by Incremental shuttle walk test or 6-minute walk Test
• Cardiac arrhythmias and ischemia before, during and after exercise
Why for Bangladeshi patient, develop this test protocol instead of Standard Ergometry?
• Ergometry is a costly machine (usually not possible to purchase by most of physician and it is available only in few referral center of Bangladesh)
• To Understand clearly patients pre-Rehab and post-Rehab Endurance (Stamina)
• To understand Lung Function changes before and after Rehabilitation
• To prevent patients' Cardiac Catastrophe by early diagnosis of Ventricular Extra Systole with the help of Tele-Cardiac Monitoring
• Incremental shuttle walk test (ISWT) or 6 Minute Walk Test (6MWT) can be used by primary care physician
Therefore, Followings are the indications of M-CPET
• Pre-Rehab assessment of patient
• To understand and to explain the real endurance (stamina) and CardioPulmonary Function of patient
• Post -Rehab assessment of patient
• To assess patient before Cardio-Pulmonary Surgery

Note: Physician may use 6 Minute walk test[66] or Incremental Shuttle walk test[67-70] and other components of M-CPET separately for patient assessment

8.6   Fractional exhaled Nitric Oxide (FeNO)[51,71]

FeNO should be tested to all COPD patients to prescribe Inhaled Corticosteroids (ICS) appropriately

• Differentiation of types of airway inflammation is very important in the management of chronic respiratory illnesses like COPD having with or without asthma.

• Presence of eosinophilic inflammation means Inhaled Corticosteroids (ICS) should be used in the management of asthma and COPD.

• Presence of Non-eosinophilic Inflammation means only bronchodilator is enough to control symptom; i.e. ICS has little role to control inflammation of COPD.

What is FeNO breathing test?

This is a simple, quantitative, noninvasive way to measure eosinophilic airways inflammation i.e. FeNO is a surrogate biomarker of eosinophilic inflammation.

Advantages of FeNO:

1. Detects eosinophilic airway inflammation- justifies use of Inhaled Corticosteroids (ICS)
2. It can determine likelihood of corticosteroid responsiveness
3. Can be used as a monitoring tool in ICS treated patients

Interpretation of FeNO (ATS Recommendation)[72] Levels under 20 parts per billion (PPB) in children and under 25 parts per billion (PPB) in adults are considered normal.

Japanese Recommendation[73,74]:

1. FeNO NO less than 22 ppb– Minimum eosinophilic inflammation and responsiveness to inhaled corticosteroids is less likely
2. FeNO 22 ppb or more- indicate eosinophilic inflammation and likely to responsiveness to Inhaled corticosteroids

FeNO- in monitoring: ATS Recommendation[72]:

1. Significant increase in FeNO: > 20% for values over 50 ppb or more than 10 ppb for values < 50 ppb from one visit to the next
2. Significant response to anti-inflammatory therapy: Fall at least 20% of FeNO for Values more than 50 ppb or fall at least 10 ppb for values lower than 50 ppb from one visit to the next

For this reason, one can advise to do FeNO at random, if result is inconclusive or very low, should stop ICS. If patient is symptomatic or after 2 months recheck FeNO to find out relapse of eosinophilic inflammation. If FeNO level increases, indicating need to use Inhaled Corticosteroids (ICS).

8.7 Saturation of pulsatile O_2 (SpO_2)[75-77]

Oximeters typically have an accuracy of $\pm 2\%$, which is satisfactory for routine clinical practice. They are more useful for monitoring trends than in single

measurement. Oximetry does not provide any information about carbon dioxide status and is inaccurate in the presence of poor peripheral circulation (e.g., cold extremities, cardiac failure) and when SpO_2 readings are consistently below 90%.

Table 5[78]: Calculation for PaO_2 assessment as

SpO_2	Calculation for PaO_2	Resultant PaO_2 range
100%-90%	Decrease PaO_2 by 4 mmHg for every single percent reduction in SpO_2	100-60 mmHg
90%-80%	Decrease PaO_2 by 1.5 mmHg for every single percent reduction in SpO_2	60-45 mmHg
<80%	Decide SpO_2 by 2 to reach to a PaO_2 level	≤ 40 mmHg

This formula, which is not an exact mathematically proven entity, can be of extreme help to ICU doctors and Respiratory practitioners. For example, if the monitor is showing a SpO_2 of 70%, we can almost consider a value of PaO_2 to be around 35 mmHg and take appropriate measures for the patient.

This hypothesis can have some pitfalls, for example, this calculation will not effective in cyanide poisoning and certain hemoglobinopathies, but still, a fair and working assessment may be drawn from this calculation.
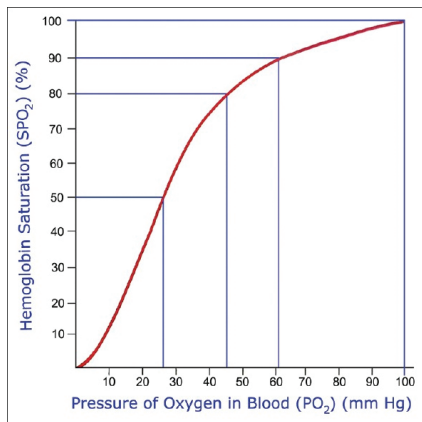
Figure 16[78]: Oxyhemoglobin dissociation curve

8.8   Arterial blood gas measurement[76-80]

Arterial blood gas analysis should be considered in all patients
• with severe COPD
• when considered for domiciliary oxygen therapy (e.g., whose FEV_1 is <40%

predicted or <1 L, whose oxygen saturation as measured by pulse oximetry [SpO_2] is <92%)

• those with pulmonary hypertension

• those with breathlessness out of proportion to their clinical status

• Respiratory failure is defined as a PaO_2<60mmHg (8kPa) with or without $PaCO_2$ >50mmHg (6.7kPa). The latter is termed 'ventilatory failure or hypercapnic respiratory failure" and is accompanied by either compensated (chronic) or uncompensated (acute) acidosis. Acute respiratory acidosis indicates a need for assisted ventilation.

8.9   Biochemistry

• High IgE level may be used in COPD A for Omalizumab therapy[81]

• Hyperthyroidism and acidosis are associated with breathlessness[82,83].

• Hyperventilation states are associated with respiratory alkalosis[84].

• Hypothyroidism aggravates obstructive sleep apnea[85].

• COPD with an association between thrombocytosis (400/μL on admission) and mortality[86]. Thrombocytosis (after controlling for confounders) was associated with an increased 1-year all-cause mortality and an increased in hospital mortality (OR 1.53 (95% CI 1.03 to 2.29, p=0.030) and OR 2.37 (95% CI 1.29 to 4.34, p=0.005)) respectively[87].

• Severe homozygous (ZZ) alpha[1] antitrypsin deficiency (alpha-AT) has been estimated at between 1/4,348 and 1/5,139 in European populations[88]. No such data available in Bangladeshi population, but 75 to 85% of such individuals will develop emphysema[89]. Genetically pure emphysema without Chronic Bronchitis or asthma should be regarded as genetic disease. It is not COPD.

• Tobacco smoking is still the most important risk factor for COPD[90] even in this group of alpha[1] antitrypsin deficiency. Targeted screening suggests between 1.0 to 4.5% of patients with COPD have underlying severe alpha[1] AT deficiency[91]. The index of suspicion should be high in younger patients with predominantly basal emphysema and a family history of COPD.

• The diagnosis can be made by measuring serum levels of alpha[1] antitrypsin (if available) and if reduced, genotyping should be performed.

8.10   E.C.G and Echo[63] ?

Cardiovascular disease is common in patients with chronic obstructive pulmonary disease but is often under-recognized.

• Electrocardiography (ECG) may be useful to alert the clinician to its presence in COPD. In a retrospective Dutch study of patients entering pulmonary rehabilitation, ischemic changes were present on ECG in 21% of all patients and in 14% of those without reported cardiovascular comorbidity.

• Electrocardiography is also indicated to confirm arrhythmias suspected on clinical grounds. Multifocal atrial tachycardia is a rare arrhythmia (prevalence < 0.32% of hospitalised patients) but over half the cases reported in the literature had underlying COPD.

• Atrial fibrillation commonly develops when pulmonary artery pressure rises, leading to increased right atrial pressure.

Usefulness of Echocardiography in COPD:
• Pulmonary Hypertension   • Chronic Cor-Pulmonale
• Cause of breathlessness is out of proportion to the degree of respiratory impairment • Ischemic heart disease   • Embolus in atrium
• Left heart failure. Patients with COPD may have poor quality images on transthoracic examination and transesophageal echocardiography may be more helpful.

Patients with COPD are prone to other conditions associated with cigarette smoking, including accelerated cardiovascular, cerebrovascular and peripheral vascular disease, and oropharyngeal, laryngeal and lung carcinoma. Conversely, there is a high prevalence of COPD among patients with ischemic heart disease, peripheral vascular disease and cerebrovascular disease and smoking-related. These patients should be screened for symptoms of COPD, and spirometry should be performed after diagnosis of smoking related any disorder.

8.11   High resolution computed tomography[92-94]
High resolution computed tomography (HRCT) scanning gives precise images of the lung parenchyma and mediastinal structures.
• The presence of emphysema and the size and number of bullae can be determined. This is necessary if bullectomy or lung reduction surgery is being considered.
• HRCT is also appropriate for detecting bronchiectasis. Vertical reconstructions can provide a virtual bronchogram.
• Helical computed tomography (CT) scans with intravenous contrast should be used in other circumstances, such as for investigating and staging Lung Cancer or diagnosis of Pulmonary Embolism etc.

8.12   Sleep studies[95,96]
It is recommended for COPD patients with the following conditions:
• Suspected of having a coexisting sleep disorder e.g. Obstructive Sleep Apnea (OSA)
• With hypercapnia • Pulmonary hypertension in the absence of daytime hypoxemia
• To diagnose Hypoxic spells during sleep • Right heart failure
• Polycythemia
• Continuous overnight oximetry may be used to assess a need for overnight domiciliary oxygen therapy
• Patients receiving long-term domiciliary oxygen therapy during follow up to assess whether hypoxemia has been adequately corrected.

9 CHAPTER 9: SUB-CLASSIFICATION OF COPD

9.1 COPD with Asthma: COPD-A

It is well established that about 40% to 56% COPD patients have asthma along with COPD[9,61]. Typically, asthma is characterized by inflammation predominantly involving eosinophils, whereas COPD is characterized by neutrophilic inflammation[97]. Diagnosis of Asthma with COPD is possible with the help of clinical findings and with the help of some investigations (Table 6) Fractional exhaled Nitric Oxide FeNO and blood eosinophil count have been considered as biomarkers of local and systemic eosinophilic inflammation, which got increased in patients with asthma[98]. Total serum IgE and antigen specific IgE levels are also found elevated in those with allergic asthma[99].

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[100]. Fractional exhaled Nitric Oxide (FeNO) has been described as a marker of asthmatic airway inflammation[101].

In some COPD patients with asthma (i.e, COPD-A) FeNO level may be normal due to effect of smoking or due to continuous use of inhaled corticosteroid[102] But interestingly some patients have persistent elevation of FeNO levels despite treatment with high dose of corticosteroids[71,103] In this protocol, after diagnosis of COPD, we advise to do FeNO in every cases. If FeNO level is found 20 PPB or more we sub-classify the case as 'COPD-A' and it's a strong indication to prescribe inhaled corticosteroids (ICS) whatever the stage of COPD, from stage 2 to 4. If FeNO level is less than 20 PPB, it is advised not to prescribe inhaled corticosteroids (ICS). It indicates use of only long acting dual bronchodilators and it may be adequate for management of COPD.

High FeNO level[103] and/or blood eosinophilia[104,105] 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.

Table 6: Diagnosis of COPD-A:

History and Symptoms	Physical Findings	Investigations
Phenotypes: Childhood Onset asthma / Adulthood onset asthma may have seasonal variation / Allergy to multiple Allergens	Prolonged Expiration Polyphonic Ronchi	Sputum Eosinophil ≥3/HPF[106]
Recurrent variable Cough/SOB and/or wheeze	Scattered Ronchi	Blood Total Eosinophil ≥ 300/ µL[107]
Variable amount of sputum	Hyper inflated Lung (±)	Blood IgE ≥ 100iu/ µL[108]
History of atopy e.g.; Allergic Rhinitis	Crepitation infrequent	FeNO ≥ 20 PPB[100,101,109]
Family history of Bronchial Asthma		Spirometry partially Reversible (not fit with asthma)[110] Experience of Ingenious *Pulmo-fit suggest that absolute ratio improvement of FEV_1(in ml) / FVC (in ml) > 1 indicating asthma component more significant and absolute Improvement of FEV_1(in ml) / FVC (in ml) < 1 indicating COPD component more important.
Smokers/exposure to smoke - Long time		HRCT scan shows air trapping[111] but it did not show any strong association with the physiologic parameters of airway obstruction, either FEV_1 or FEF^{25-75}.
		Skin prick test positive to multiple triggers including House Dust Mites and pollens[112]

*If sputum Eosinophil plenty or IgE ≥ 400 IU or blood Eosinophil ≥ 600/ml or FeNO ≥ 40 ppm, any single criteria of investigation may suggestive of COPD-A. Summation of more and more criteria confirm diagnosis.

*Pulmo-fit suggest that absolute ratio improvement of FEV$_1$(in ml) / FVC (in ml) > 1 indicating asthma component more significant and < 1 indicating COPD component more important.

How to calculate absolute ratio of improvement:
Interpretation: COPD-A >1< COPD

50 yrs man with pre-bronchodilator:
FEV$_1$ 2000 ml
FVC 3000 ml
FEV$_1$/FVC%=2000/3000 (66.7%)

15 minutes after bronchodilator:
☐   FEV$_1$ 2200 ml
☐   FVC 3100 ml
FEV$_1$/ FVC%=2200/3100 (70.9%)
Absolute improvement:
(2200-2000)/ (3100-300) = 2

>1 = COPD-A

15 minutes after bronchodilator:
FEV$_1$ 2100 ml
FVC 3200 ml
FEV$_1$/ FVC%=2200/3100 (65.6%)
Absolute improvement:
(2100-2000)/ (3200-3000) = 0.5

<1 = COPD

Figure 17: Calculation of absolute ratio of improvement

9.2   COPD and Bronchiectasis: COPD-B

In moderate to severe COPD, prevalence of bronchiectasis varies from 57% to 64%[9,113]. Bronchiectasis independently increases risk of all cause of morbidity and mortality in patients with moderate to severe COPD[114,115]. This sub-class of COPD is more prone to infective exacerbations[46]. COPD patients with bronchiectasis (COPD-B) can be diagnosed by clinical history, sputum production more than 5ml (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[116]. 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)[117].

Table 7: Diagnosis of COPD-B

History and Symptoms	Physical Findings	Investigations
Symptoms after 40 years of age	Usually near normal size Lung	Sputum Neutrophilia[118]
No history of atopy/ Allergy	Prolonged Expiration	Blood Total Eosinophil < 300/μL[106]
Long time Smokers / exposure to smoke	Scattered crepitations more in basal	Blood IgE <100iu/μL[108]
Less variable Symptoms, usually progressive and more persistent Symptoms	Scattered Ronchi	FeNO low, <20 PPB[100,101,109]
Frequent mucoid, muco-purulent or purulent sputum		Spirometry: usually not Reversible
		CXR and or HRCT scan shows multiple cystic or tram line shadows[119]
Severity of Bronchiectasis Should be measured by FACED Score: Mild: 1-2; Moderate: 3-4; Severe: 5-7	Severity of score should be measured by Modified FACED SCORE[120]. The FACED score consists of five dichotomized variables: F – FEV_1 (≥ 50% = 0, < 50% = 2) A – Age (< 65 years = 0, ≥ 65 years = 2) C – Chronic colonization (no Pseudomonas = 0, presence of Pseudomonas =1) E – Extension (1 – 2 lobes affected = 0, > 2 lobes affected= 1) D – Dyspnea – mMRC 0 – 2 = 0, mMRC 3 – 4 = 1	

NOTE: For Bangladeshi Patient: we used 65 years cut off point for age instead of 70 years, which is in original FACED score. FACED score is important for diagnosis of severity of bronchiectasis in COPD.

Symptoms, physical findings, X-Ray Chest and or-HRCT scan chest and any 2 investigation findings of Table 7 along with post-Bronchodilator FEV_1/FEV <0.7 is important for diagnosis of suggestive of COPD-B.

If sputum Neutrophil plenty or IgE less than 50 IU or blood Eosinophil less than 100/μL with FeNO less than 10 PPB: Presence of more and more criteria suggestive of COPD B.

HRCT scan of chest is important not only for diagnostic confirmation of COPD-B, but it is also an 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[121]. This inflammation along with recurrent flare-up of infection, associated endobronchial obstruction by secretion and bronchoconstriction leads to development of bronchiectatic changes in COPD patients[15].

Recurrent COPD exacerbations are associated with a heightened airway inflammatory burden, and the presence of lower airway bacterial colonization, which in turn has been shown to be an independent stimulus to airway inflammation in COPD[122] 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[123]. The possible role of unrecognized bronchiectasis in orchestrating such relationships in COPD has not been previously assessed[124].

HRCT is now accepted as the imaging modality of choice for the evaluation of bronchiectasis and emphysema[125]. Thin-section CT has been shown to have discriminatory value in obstructive lung disease[128] 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[126] and one study of patients with cystic fibrosis, found significantly higher mean bronchiectasis scores[127]. The extent of bronchiectasis has been shown to be negatively correlated with FEV_1% predicted[128] suggesting that in patients with COPD and bronchiectasis may develop more features of progressive airway obstruction. Severity of Bronchiectasis Should be measured by FACED Score (Table 7), which is better than Chest X-Ray, HRCT or FEV_1 alone to measure extent of bronchiectasis.

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 predominantly lower lobe distribution of bronchiectasis was found in subjects with impaired muco-ciliary clearance, one of the impaired host defense mechanisms seen in COPD[129].

A lower lobe distribution is most often seen in patients with a history of childhood viral infections, a suggested risk factor for COPD[4,9,15]. 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 are found in COPD[130]. In the context of an already disrupted lung parenchyma, produced structural changes of bronchiectasis are seen on HRCT[124] It is important 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[131].

A high prevalence of bronchiectasis has been demonstrated in an unselected group of patients with a primary care diagnosis of COPD[132] and studies of patients with Alpha[1] antitrypsin deficiency disease have suggested that bronchiectasis may be present either concomitantly before 50 years of age, and bronchiectasis may be developed before the development of emphysema[133] The Alpha[1] antitrypsin status of all patients are not estimated. However, it is possible that some of these patients had bronchiectasis and then developed COPD with emphysema in addition to this at a later age[113].

Management of COPD-B is mainly control of infection, prevention of infection flare up along with sustained bronchodilation[139]. Azithromycin alternate day or thrice a week throughout the year may prevents exacerbations[134]. Tobramycin nebulization[135], influenza[136,] pneumonia vaccine[137], sublingual lyophilized bacterial lysate may decrease recurrent infective exacerbations[138] in COPD-B patient.

9.3   COPD and GERD: COPD-G

The prevalence of gastro-esophageal reflux (GERD) was about 26.7% in COPD patients[9] According to the report of Casanova et al[139] GERD was about 62% confirmed by esophageal 24-hour PH 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[9,15] Aspiration into airway in GERD patients can trigger exacerbation of COPD and enhance inflammation and induces pulmonary fibrosis[9]. Identification of GERD subgroup of COPD (COPD-G) is very important for prevention of progression of disease (Table 8).

An explanation for the association between GERD and exacerbations of COPD could be that the aspiration of gastric acid causes airway inflammation[140]. Proton pump inhibitors virtually abolish acid secretion in normal clinical doses[141].

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[142]. There are two ways for exacerbations of COPD. (A) Reflux theory: a direct mechanism by which micro-aspiration of gastro-duodenal contents can cause damage to the pulmonary tree. (B) Reflex theory: an indirect mechanism in which distal esophageal reflux stimulates the vagal nerve which on its turn leads to bronchoconstriction[143]. 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[144,145]. In addition, the effect of GERD on exacerbations could very well be influenced by other factors such as nonacidic reflux and pepsin[146].

Explanation linking GERD with exacerbations is that GERD could cause symptoms such as cough that could be perceived[147]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[148,149]. In fact, as in previous studies 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[140]. Proton pump inhibitor therapy, anti-reflux therapy, change of food habit and sustained bronchodilation are very important to control COPD-G patient[150].

HRCT scan may show basal fibrosis may mimic Idiopathic Pulmonary Fibrosis pneumonia (IPF) with or without esophageal dilatation[151,152.] Basal lung fibrosis with or without esophageal dilatation may a very good marker of GERD in COPD patient.

Table 8: Diagnosis of COPD-G

1	Symptoms	Physical Findings	Investigations
2	Symptoms after 40 years	Usually near normal size Lung	Sputum Neutrophilia
3	Heartburn, Regurgitation, Dysphagia (HRD) score (Table 9) suggestive of GERD	Recurrent wheeze after taking food	Blood Total Eosinophil less than 300/ML

4	Long time Smokers/exposure to smoke	Basal Crepitations like Lung fibrosis or ILD	Blood IgE less than 100/ML
5	Coughing and shortness of breath after taking food or drinks	Ronchi after taking food	FeNO very low, at least less than 20 PPB
6	Coughing and Shortness of breath few hours after sleep		Esophageal pH monitoring is important[140]
7	Basal fibrosis in HRCT scan may mimic Idiopathic Pulmonary Fibrosis (IPF) with or without esophageal dilatation. Esophageal dilatation (ED)[153] is defined as the presence of air bubbles greater than 10 mm in the supra ventricle (SV) and ventricle (CV), and air bubbles >15 mm at the ventricle to the lower esophageal sphincter (V-LES).		

Table 9: HRD score Uploaded by Rachel Mary Thomson

Symptom	Description	Score
Heartburn **(H)**	None	0
	Occasional, brief episodes; readily controlled by simple antacids (e.g, Liquid Antacid	1
	Frequent (>2/week) episodes causing moderate discomfort & requiring medication prescribed by your doctor for relief	2
	Daily attacks causing interference with work/activities; night time attacks interfering with sleep; only controlled by prescription medication	3
Regurgitation **(R)**	None	0
	Occasional episodes; mostly after meals & not predictable	1
	More frequent attacks; predictable by posture	2
	Daily episodes interfering with life: severe night time episodes causing choking coughing or the sensation of acid/food/fluid is going into the lungs	3

	None	0
Dysphagia **(D)**	Occasional transient sensation of food "sticking" in the gullet	1
	Episodes of food getting stuck requiring liquids to clear	2
	Progressive difficulty swallowing solids requiring medical attention/admission to hospital. Need for gastroscopy/telescopic examination of the stomach/gullet.	3
	Total	0-9

The DeMeester symptom score for GERD[154]. 4 or less was considered mild GERD, scores between 5-6 were regarded as moderate GERD, and a score 7-9 was regarded as severe GERD. Due to pulmonary fibrosis patient may have FEV_1/ FVC % >0.7 due to concomitant restriction.
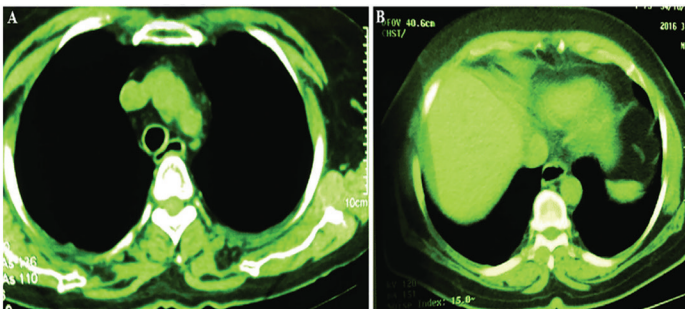
Figure 18: CT Scan at upper and lower level of chest

NOTE: Dilated esophagus showing in CT SCAN of chest at the level of upper chest and lower chest[153].

Symptoms, physical findings HRD score 4 or more and Esophageal pH monitoring (if available findings) -along with post-Bronchodilator FEV_1/FVC Ratio 0.7 or less is important for diagnosis of suggestive of COPD-G.

9.4   COPD and Obstructive Sleep Apnea (OSA): COPD-O

When obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) coexist in the so-called "overlap" syndrome, a high risk for mortality and morbidity has been reported. There is high prevalence (29% to 65.9%) of Obstructive Sleep Apnea in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease[155,156]. COPD alone can cause subjective and ob-

jective 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)[157,158]. Specifically, patients with COPD report more difficulty in both initiating and maintaining sleep than controls, and also complain of excessive daytime sleepines[159]. 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[160,161]. Other investigations have objectively confirmed poor sleep quality, with decreased total sleep time and decreased sleep efficiency[96,162]. (Table 10).

9.4.1   Sleep and Breathing[162]

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. 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[163].

9.4.2   Nocturnal Oxygen Desaturation[155]

The most significant sleep abnormality associated with COPD is nocturnal oxygen desaturation. 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[164]. 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[165]. Awake oxygen saturation has the greatest predictive value, although it imperfectly predicts nocturnal desaturation[166.] 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[167].

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[168]. 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[162]. CPAP therapy is an effective therapeutic option in the majority of patients with obstructive sleep apnea, even if severe, and with normal awake respiratory function[169]. For the subset of patients with OSA associated to COPD, especially when hypercapnia is present in whom CPAP may be ineffective and/or not tolerated.; BiPAP may be an effective and well-tolerated treatment modality for them[170,171].

Table 10: Diagnosis of COPD-O

Symptoms	P/E	Investigations
Symptom after 40 years	Usually near normal size Lung	ABG showing Hypoxemia i.e. PO_2 less than 80mm of Hg or 10.6 mmol [172,173]
Excess snoring during sleep and day time sleepiness		PASP >30mm[174]
Long time Smokers/ exposure to smoke		Fall of SpO_2 >4% during sleep[175].
Day time Feelings of Shortness of breath, malaise and easy fatigability		Sleep test is most important tool to diagnose COPD-O[155]
Chest radiography Pulmonary Arterial: Hypertension (PAH) can be diagnosed with 98% sensitivity, if the diameter of the right descending pulmonary artery (PA) is increased (>16 mm, posteroanterior projection) together with an increased diameter of the left descending PA (>18 mm, left lateral projection)[176]		
HRCT scan CHEST may show prominent vascular markings. The typical radiographic appearance described is that of a diffuse bilateral reticulonodular pattern associated with enlarged central pulmonary arteries[50,177]		
Echocardiography: As non-invasive tool for the diagnosis of PAH in COPD. Color Doppler transthoracic echocardiography is the most important diagnostic test used for PAH in COPD[178-180].		

NOTE: Symptoms, physical findings and any 2 investigation findings suggestive of COPD-O.

Sleep test is the gold standards test for OSA along with post-Bronchodilator FEV_1/FVC <0.7 or less is important for diagnosis of COPD-O. Due to Obesity patient may have FEV_1/FVC % >0.7 due to concomitant restriction.

9.4.3 Screen for Obstructive Sleep Apnea (OSA):

9.4.3.1 Epworth Sleepiness Scale

The Epworth Sleepiness Scale is used to diagnose obstructive sleep apnea (OSA)[181].

If you suspect you might have OSA, answer the following questions and take your answers to GP.

Description of Epworth Sleepiness Scale:

How likely are you to fall asleep in the following situations, in comparison to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

> 0 = would never doze
> 1 = slight chance of dozing
> 2 = moderate chance of dozing
> 3 = high chance of dozing

It's important that you answer each question as best you can.

Table 11: Epworth Sleepiness Scale

Situation	Chance of dozing (0 = low, 3 = high)
Sitting and reading	0 to 3
Watching TV	0 to 3
Sitting still in a public place (e.g. a theatre, a cinema or a meeting)	0 to 3
As a passenger in a car for an hour without a break	0 to 3
Lying down to rest in the afternoon when the circumstances allow	0 to 3
Sitting and talking to someone	0 to 3
Sitting quietly after lunch without having drunk alcohol	0 to 3
In a car or bus while stopped for a few minutes in traffic	0 to 3
TOTAL	0 to 24

9.4.3.2 What does the score mean?

Scores can be interpreted as follows:

- 0-5 lower normal daytime sleepiness
- 6-10 normal daytime sleepiness
- 11-12 mild excessive daytime symptoms
- 13-15 moderate excessive daytime symptoms
- 16-24 severe excessive daytime symptoms

Table 12: STOP-BANG Questionnaire

It is another Practical Approach to Screen for Obstructive Sleep Apnea182,183. STOP-Ban questionnaire is a useful tool for screening OSA (Fig. 19)

STOP-Bang questionnaire

Please answer the following questions by checking "yes" or "no" for each one.

	Yes	No
Snoring (Do you snore loudly?)	❑	❑
Tiredness (Do you often feel tired, fatigued, or sleepy during the daytime?)	❑	❑
Observed Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)	❑	❑
High Blood **P**ressure (Do you have or are you being treated for high blood pressure?)	❑	❑
BMI (Is your body mass index more than 35 kg per m²?)	❑	❑
Age (Are you older than 50 years?)	❑	❑
Neck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)	❑	❑
Gender (Are you male?)	❑	❑

Score 1 point for each positive response.

Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk, ≥5 = high risk.

Source: University Health Network, Toronto, Ontario, Canada (www.stopbang.ca/ osa/screening/php). Used with permission from Sauk Prairie Healthcare.

Figure 19: STOP-Bang questionnaire

9.5 Mixed Disorder:

When multiple coexisting illnesses develop and perpetuated during the progress and stage change of COPD, amalgamated symptoms, signs and investigation findings, are sometimes difficult to differentiate various coexisting illnesses. In those cases, clinical judgement of each component is important for pin point diagnosis and for management plan of COPD.

10 CHAPTER 10: COMMON PROBLEM FOR COPD ■

10.1 Major triggers, common to all COPD patients:

10.1.1 Air Pollution[9]:

Air pollutants such as particulate materials (PM) from fossil, diesel or octane combustion can cause inflammation in the lung and further impairs the reduced pulmonary function in COPD patients[184-186]. When exposed to particle pollution, patients with COPD usually have more emergency room visit, hospital admission and/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 impairment 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[187].

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 NO_2, O_3, sulfur dioxide (SO_2) and black smoke[188]. A study of PM10 and hospital admissions for COPD found a 2.5% increase in admissions for every 10μg/m3 increase in PM. In addition, a meta-analysis of 18 studies of PM10 and exacerbations found a 10μg/m3 increase in daily PM10 was associated with a 2.7% increase in COPD hospitalizations[189.] The data linking air pollution with COPD exacerbations for O_3 is also convincing as higher O_3 concentrations have been shown to increase hospital and emergency department visits for lower respiratory disease, including COPD[190]

10.1.2 Temperature

Extremes of temperature—both heat and cold—have been associated with increased respiratory morbidity in COPD[190].

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[191]. For example, a study across 12 European cities estimated that the effect of hot temperatures during summertime can increase the risk of death attributable to COPD by as much as 25%[192]. 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[9,193]. 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[194]. Bronchoconstriction and inflammation that may occur in the setting of cold exposure[195]. Recent evidence suggests a role for mucous hypersecretion as a potential mediator of the COPD response to cold temperature[196].

11   CHAPTER 11: COMORBIDITIES IN COPD

11.1   Comorbidities[52]:

Comorbidities such as cardiac disease, diabetes mellitus, hypertension, osteoporosis, and psychological disorders are commonly reported in patients with chronic obstructive pulmonary disease (COPD) but with great variability in reported prevalence197,198. The most common comorbidities differ between men and women. Men have more IHD and stroke than women. Women are more likely to demonstrate anxiety, depression and Osteoporosis than men199.

11.2   Cardiac Disease

COPD patients possess an increased burden of Ischemic heart disease, cardiac arrhythmias and heart failure when compared to the normal population[200,201].

Ischemic Heart Disease (IHD) is an important cause of hospitalization and mortality in COPD, even affecting those with mild COPD. In addition to the high separate prevalence of COPD and IHD, these conditions share same risk factors, e.g. advanced age, smoking, low socioeconomic condition and sedentary lifestyle. Systemic inflammation, oxidative stress, hypoxia particularly hypoxic spell during sleep, acidosis, bacterial colonization and haemo-dynamic derangements are likely to be added contributing factors[122]. Independent of smoking and other risk factors, impaired lung function with or without hypoxemia is a major risk factor for IHD and arrhythmia (with or without hyperlipidemia), with the relationship being strongest for fatal cardiac events[202]. In COPD, arterial stiffness increases during exacerbation and is associated with COPD severity (measured as airflow limitation or degree of emphysema), inflammation, oxidative stress and sympathetic nervous system (SNS) tone, which increases risk of acute ischemic cardiac events[130].

It is now well documented that a statistically significant improvement in ischemic heart disease after standard pulmonary rehabilitation and after treatment with combination ICS/LABA or LAMA as well as possible improvement with supplemental oxygen[203].

Ingenious Pulmo-Fit, Dhaka Registry demonstrated that in total 2551 cases tele-cardiac ECG monitoring done in 2019. Out of 2551, 1652 (64.8%) patients were COPD stage 1 to 4 and 899 (35.2%) patient were Non-COPD. COPD patients with tele-cardiac monitoring during Modified Cardio-Pulmonary Exercise (M-CPET) demonstrated more arrhythmias than those without COPD; atrial fibrillation/flutter or atrial ectopic were identified in 426(16.7%) versus 107 (4.2 %) (OR 2.572 95% CI 2.043 - 3.237), and non-sustained Ventricular extra systole to non-sustain ventricular tachycardia in 136 (8.2%) versus 24(2.7%) (OR 3.271 95% CI 2.103 - 5.088).

This study population of Ingenious Pulmo-Fit, Dhaka might be highly selected group, which potentially limits the broad application of the results. However, one may understand potential arrhythmias may develop during exercise of COPD patients. These Cardiac arrhythmias sometimes may be an important obstacle during pulmonary rehab program. If palpitations continue and are so bothersome that they prevent patients from exercising, then the appropriate next step is to look into fixing the problem. Many arrhythmias can be treated or cured with medications[204].

Medications used in the treatment of COPD also have potential to impact on cardiac morbidity and mortality, due to intrinsic effects on chronotropy and muscle action potentials or due to side effects such as hypokalemia[205]. Medications concerned include beta-agonist and antimuscarinic bronchodilators and methylxanthines. More recently, macrolide antibiotics, which in chronic dosing have been shown to reduce respiratory exacerbations, have been added to the list, due to an association with QT prolongation and bradycardia[206]. Randomized controlled trials (RCT) of chronically dosed azithromycin have not demonstrated adverse cardiac effects in the clinical setting[207], particularly when known drug interactions are avoided. Likewise, for most inhaled bronchodilators, when used at therapeutic dose in stable COPD, there are no proven adverse effects on safety[3].

11.3   Heart Failure

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are both common diseases with major impact and seem to coexist more frequently than expected from their distinct population prevalence[208,209].
The natriuretic peptides, including BNP and NT-pro BNP, can assist in identifying heart failure in the setting of acute breathlessness, but do not exclude comorbid COPD, but currently it has an unclear diagnostic role in stable disease[210]. The prevalence of heart failure in COPD patients is estimated at 20 to 32%. For the converse situation in heart failure, COPD prevalence has been previously quoted as 10 to 33%[63].

11.3.1   Role of BNP and NT-proBNP in clinical practice[211]

B-type natriuretic peptide, which is also called brain-type natriuretic peptide (BNP), was first described in 1988 after isolation from swine brain. However, it was soon found to originate mainly from the heart, representing a cardiac hormone. BNP belongs to the natriuretic peptide family together with other structurally similar peptides, namely atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and urodilatin. The natriuretic peptides have in common a characteristic biochemical structure which consists of a 17 amino acid ring and a disulfide bridge between two cysteine molecules. The major source

of BNP synthesis and secretion is the ventricular myocardium. Whereas ANP is stored in granules and can be released immediately after stimulation, only small amounts of BNP are stored in granules and rapid gene expression with de novo synthesis of the peptide is the underlying mechanism for the regulation of BNP secretion. BNP is synthesized as a prohormone (pro-BNP) comprising 108 amino acids. Upon release into the circulation it is cleaved in equal proportions into the biologically active 32 amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP). Both molecules are constantly released and can be detected in the blood. The main stimulus for increased BNP and NTproBNP synthesis and secretion is myocardial wall stress. Furthermore, factors such as myocardial ischemia and endocrine (paracrine) modulation by other neurohormones and cytokines are also of importance. In the systemic circulation BNP mediates a variety of biological effects by interaction with the natriuretic peptide receptor type A (NPR-A) causing intracellular cGMP production. The physiological effects of BNP are manifold and comprise natriuresis/diuresis, peripheral vasodilatation, and inhibition of the renin– angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS). BNP is cleared from plasma by binding to the natriuretic peptide receptor type C (NPR-C) and through proteolysis by neutral endopeptidases. In contrast, NT-proBNP is mainly cleared by renal excretion. However, recent studies suggest that there might also be other important clearing mechanisms for NTproBNP. The halflife of BNP is 20 mins whereas NT-proBNP has a half-life of 120 mins, which explains why NT-proBNP serum values are approximately six times higher than BNP values, even though both molecules are released in equimolar proportions.

Cut-off values of BNP[212] and NTproBNP[213] for the diagnosis of heart failure of patients presenting with dyspnea.

Table 13: Cut-off values of BNP and NTproBN

	HF likely	HF likely
BNP (pg/ml)	100	500
NT-proBNP (pg/ml), age <50 years	300	450
NT-proBNP (pg/ml), age more than 50 years	300	900

The diagnostic performance of BNP and NT-proBNP is comparable and there is no meaningful difference between them. They reflect hemodynamic myocardial stress independent of the underlying pathology, thus they are not specific for a distinct pathology of heart failure. Their particular strength is to rule out heart failure in patients presenting to the emergency department with shortness of breath.

Table 14: Diagnosis of COPD and Heart Failure

History and Symptoms	Physical Findings	Investigations
Age usually 60 or more and post bronchodilator FEV_1/FVC and/or FEV_1 evidence of COPD	Prolonged Expiration	BNP[212] or NT-proBNP[213] = Rule in HF (Table 13)
History of old MI/ Angina like chest pain during exertion/ PND/ Orthopnea	Ronchi and bilateral crepts	
Persistent and/or disproportionate shortness of breath and marked limitation of activities despite taking adequate Dual bronchodilator LABA/LAMA	Hyper inflated Lung and Apex beat may be shifted due to cardiomegaly	Color doppler[214] • Hyperdynamic= LVEF greater than 70% • Normal = LVEF 50% to 70% (midpoint 60%) • Mild dysfunction = LVEF 40% to 49% (midpoint 45%) • Moderate dysfunction = LVEF 30% to 39% (midpoint 35%) • Severe dysfunction = LVEF less than 30%
History of Smoking and or smoke exposure -Long time		Color doppler ECHO[50] PAH PASP$\geq$ 35 mm of Hg Evidence of TR
Presence of risk factor of IHD e.g. Hyperlipidemia, Diabetes and/or Hypertension[215]		

NOTE: Symptoms / History, physical findings and any one positive investigation findings suggestive of COPD-and Heart Failure. Post-Bronchodilator FEV_1/ FVC% <70% may not be diagnostic of COPD due to associated HF associated pulmonary edema may cause restriction (FEV_1/FVC% > 70%).

Since COPD and heart failure present with similar symptoms and frequently do coexist, the clinical implication is that the opportunity for intervention will be missed unless both diagnoses are specifically sought using careful clinical assessment in conjunction with appropriately directed investigations[63].

11.3.2   Use of Cardio-selective Beta Blocker in COPD[63]:

A number of observational studies also lead confidence to cardio selective betablocker prescribing in COPD patients[216]. There is no evidence to suggest that baseline Beta-blocker therapy reduces the respiratory benefits or increases the cardiovascular risk of inhaled long-acting Beta-agonists in patients with chronic obstructive pulmonary disease and heightened cardiovascular risk[217].

11.4   Osteoporosis

Patients with COPD are at increased risk for fracture due to the disease itself, the use of high dose corticosteroids and coexisting risk factors such as hypogonadism (induced by corticosteroid therapy itself in high doses in men and women), immobilization reduced muscle mass and other factors[218]. These patients may have reduced bone mineral density (BMD) due to a reduction in bone formation and perhaps increased bone resorption, the latter being primarily due to the underlying disease itself. A systematic review described an overall mean prevalence of osteoporosis of 35.1% (range 9-69%) with increasing odds ratios for osteoporosis associated with lower FEV_1, lower BMI and lower fat-free mass index[219]. Patients with vertebral compression fractures, visualized on a lateral chest x-ray, had more frequent admissions, longer length of hospital stay, and increased mortality in the two years after admission[220]. Evidence for fracture risk reduction is available for alendronate, risedronate, etidronate and parathyroid hormone[221]. Although calcium supplementation has not been demonstrated to reduce the risk of fracture in osteoporosis, a reduction in remodeling rate with some possible benefit in slowing bone loss is possible so calcium supplements are appropriate. In Bangladesh Vitamin D insufficiency is epidemic 85.5%[222]. Therefore, vitamin D level should be corrected with supplements in all cases of COPD.

11.5   Frailty and COPD[63]

Frailty is common in seniors and is characterized by diminished physiological reserves and increased vulnerability to stressors[223]. In other words, Frailty is a state of vulnerability to poor resolution of homeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime. Frailty is a state of older patient where physically or mentally patient is vulnerable and less able to recover quickly after illness or a stressful event.

Criteria for Diagnosis of the Frailty Syndrome: Three or More of Following Symptoms[224]

Table 15: Criteria for Diagnosis of the Frailty Syndrome

1.	Weakness
2.	Slow walking speed
3.	Self-reported exhaustion
4.	Low level of physical activity i.e. Low energy expenditure
5.	Unintentional weight loss

Table 16: FRAIL SYNDROME: QUESTIONNAIRE BASED DIAGNOSIS[225]

THE FRAIL NON-DISABLED (FIND) QUESTIONNAIRE

Domain	Question	Answer	Score
DISABILITY	A Have you any difficulties at walking 400 meters?	a. No or some difficulties	0
		b. A lot of difficulties or unable	1
	B Have you any difficulties at climbing up a flight or stairs?	a. No or some difficulties	0
		b. A lot of difficulties or unable	1
FRAILTY	C During the last year, have you involuntarily lost more than 4.5 kg?	a. No	0
		b. Yes	1
	D How often in the last week did you feel than everything you did was an effort or that you could not get going	a. Rarely or sometimes (2 times or less/week)	0
		b. Often or almost always (3 or more times per week)	1
	E Which is your level of physical activity?	a. Regular physical activity (at least 2-4 hours per week)	0
		b. None or mainly sedentary	1

if A+B≥1, the individual is considered as "disabled"
if A+B=0 and C+D+E ≥1 the individual is considered as "frail"
if A+B+D+E=0 the individual is considered as "robust"

Figure 20: Self-reported questionnaire tool for frailty[226]

Frailty affects older people and particularly those with chronic conditions such as COPD. The mechanism underlying increased frailty in COPD is likely to be multifactorial. COPD affects older adults in whom other health conditions are more prevalent. In addition, COPD is associated with inflammation that affects multiple body systems, increased exacerbations, as well as lifestyle factors such as smoking and reduced physical activity, all of which may increase risk of frailty[227].

11.5.1   Management of Frailty:

Frailty affects one in four patients with COPD referred for pulmonary rehabilitation and is an independent predictor of program non-completion.

In summary, frailty is common in COPD and associated with poorer health outcomes, hospital admissions and failure to complete pulmonary rehabilitation[228]. Measuring frailty is useful in COPD and may identify vulnerable patients and allow earlier interventions such as pulmonary rehabilitation to minimize the development and impact of frailty on patients and careers as well as health and social care services[229].

Table 17: Treatments of Frailty Syndrome

Treatment	Potential effect	Evidence
Vitamin D	Improve Balance and Strength	Systematic review and meta-analysis[230].
Vitamin and Carotenoid	Improved Walk-Speed, IStrength	Cross-sectional study [231]
Fruit and vegetables[232], Vit E[233] and Omega-3 fatty Acids[234], Nutritional Supplementation Combined with Low-Intensity Rehab Exercise[235]	Improve systemic inflammation and improve lung function	A Randomised Case control study (CCS)[232] Animal model CCS[233] Prospective CCS[234] A prospective RT[235]
Creatine	Increase Strength	RCT[236]

Testosterone+ Exercise[237] Nandrolone+ Exercise[238] (No effect without exercise program) A dietary pattern with more phyto- nutrient-rich plant foods, tea, omega-3-rich deep sea fish, and other protein-rich foods such as shellfish and milk had a reduced preva- lence of frailty[239]	Increase Strength	RCT[237] RCT[238] Cross-sectional[239]
Beta-hydroxy-beta-methyl butyrate	Increase Strength	A Systematic Re- view[240]
Rehabilitation for Older People in Longterm Care[241] Pulmonary Rehabilitation and COPD[242] Physical frailty and pul- monary rehabilitation in COPD[228]	Improve Strength, Balance and In- crease endurance	Cochrane Review[241] A Systematic Re- view[242] A prospective cohort study[228]

11.6   Falls in COPD[63]

Chronic Obstructive Pulmonary Disease (COPD) and other chronic respiratory issues can cause shortness of breath, which may cause feelings of dizziness, weakness, and fatiguability[243,244]. Chronic cough in COPD may lead to cough syncope and that leads to fall[245].

Patients with COPD were 55% more likely to have an incident record of fall than non-COPD subjects (adjusted HR, 1.55; 95% CI 1.50 to 1.59). The greater falls risk in patients with COPD needs special consideration during management of COPD[246].

In fact, COPD patients in moderate-severe stages and especially those in exac- erbation have a high risk of falls[247].

For this reason, it's especially important for seniors with breathing issues to be incorporated in pulmonary Rehab program for prevention of accidental falls[248].

11.7   Aspiration and COPD

Aspiration of food and liquid is very common with COPD.

Subjective swallowing symptoms seems to be a common problem in patients with stable COPD. This problem is seen in all stages of the disease, but is more common in symptomatic patients and in patients with lower physical capaci-

ty[249]. Up to 70% COPD patients difficulty in swallowing or dysphagia leads to aspiration[250].

Patients with COPD exhibit disrupted coordination of the respiratory cycle with deglutition. Disrupted breathing–swallowing coordination could increase the risk of aspiration in patients with advanced COPD and may contribute to exacerbations[251].

The risk factors of aspiration in COPD reported include dyspnoea, dysphagia, emphysema, weakness or incoordination of throat muscles, decreased throat sensitivity, and an impaired cough reflex[252]. Impairment of the swallowing function, also referred to as oropharyngeal dysphagia (OD), can lead to pneumonia, aspiration, COPD exacerbations and malnutrition[253].

Silent aspiration has also been reported in those with COPD, which can complicate dysphagia detection and management[254].

Dysphagia in COPD is thought to be due to the disrupted coordination of the exhale-swallow-exhale respiratory cycle during swallowing[251]. Dysphagia and aspiration risk can be determined from adequate history of patients and from their spouse or care givers and clinical swallow examination[255,256].

Management for swallowing problem will be provided on an individual basis and may involve the following:

11.7.1   Eating strategies which may prevent dyspnea

- Sit up straight
- Clear the airways of mucus before eating
- If supplemental oxygen is used, make sure this is worn while eating
- Avoid eating large meals, instead eat small nutritious meals and snacks more frequently
- Avoid drinking with meals, can take sips of water to facilitate swallowing.
- Take time, Eat slowly and take small bites and sips
- Reduce talking and distraction during meals
- Make sure mouth is empty before talking the next mouthful.
- Choose softer foods that are easier to chew and swallow, e.g. mashed boiled rice, potato, soups, bananas
- Limit foods that can cause bloating, e.g. beans, onions, cauliflower, soft drinks
- Rest for at least 20-30 minutes after eating in an upright position
- In patients who are underweight, protein and calorie intake can be boosted using high energy, nutrient-rich foods that are easily accessible, such as milk powder, cheese, cream, custard, peanut butter and milkshakes or a nutritionally complete oral supplement

Management for dysphagia and aspiration will be provided on an individual basis and may involve the following:[257]
• Rehabilitation exercises
• Swallowing – breathing retraining (compensatory swallowing techniques)
• Texture modification of diet and fluids
• Postural strategies
• Safe swallowing strategies

11.8 Lung cancer and chronic obstructive pulmonary disease:

Lung cancer is a serious health problem for Bangladesh. The first leading causes are in males are lung cancer and in females are breast cancer[258]. The risk of lung cancer in people who have pre-existing lung disease has been studied using case- control studies, which found an increased risk of lung cancer in people with bronchitis and emphysema, even after correcting for the smoking history[259]. Chronic obstructive pulmonary disease (COPD) and lung cancer are devastating pulmonary diseases that commonly coexist and present a number of clinical challenges[260]. COPD is a negative prognostic factor for lung cancer patients. The presence of COPD may alter the treatment plan (radiotherapy, surgical approach) for lung cancer. Clinical management of patients with coexistence of COPD and lung cancer requires a multidisciplinary oncology board that includes a pulmonologist. Detailed evaluation (lung function tests, cardiopulmonary exercise test) and management (inhaled drugs, smoking cessation, pulmonary rehabilitation) of COPD should be taken into account for lung cancer treatment (Microablation, surgical approach, palliative therapy, radiotherapy)[261].

11.9 Combined Pulmonary Fibrosis and Emphysema

Combined Pulmonary Fibrosis and Emphysema (CPFE) is suspected based on the presence of upper zone emphysema and lower zone fibrosis[63]
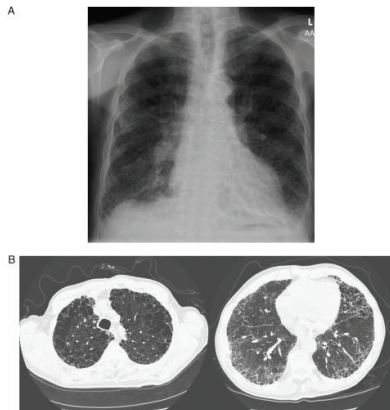
Figure 21: Images of combined pulmonary fibrosis and emphysema

Images from a male smoker aged 77 years with combined pulmonary fibrosis and emphysema demonstrating upper-lobe emphysema and lower-lobe pulmonary fibrosis. A, Chest radiograph. B, CT image. Pulmonary function tests showed an FEV$_1$ of 108% predicted, FVC of 107% predicted, total lung capacity of 121%, and diffusing capacity of lung for carbon monoxide of 36% predicted. Echocardiography demonstrated grade I diastolic dysfunction and estimated pulmonary artery pressure of 30 to 40 mm Hg[262].

Spirometry is frequently normal due to opposing effects of hyperinflation and obstruction from emphysema and restriction from fibrosis. Gas transfer however, is usually severely impaired due to the additive effect of dual pathology[263]. Cigarette smoking is a major risk factor for CPFE[264]. It occurs predominantly in males (up to 9:1 male:female ratio). In non-smokers, CPFE has been described in people with occupational dust exposure and genetic mutations[262].

CPFE is frequently complicated by pulmonary hypertension, lung cancer, acute lung injury and coronary artery disease. Mortality is significant, especially in the presence of pulmonary hypertension[265].

Even in patients who do not fulfil criteria for IPF, the presence of interstitial features in addition to emphysema carries a significantly higher mortality[63].

In most cases, high resolution computed tomography (HRCT), spirometry and diffusing capacity of lung for carbon monoxide (DLCO) test are adequate to diagnose CPFE[63]. The prevalence of lung cancer is higher in CPFE than COPD[266]. Therefore, more vigilant follow up of pulmonary nodules is recommended, though no specific screening guideline has been developed for CPFE[262,265] Squamous Cell Carcinoma was the most common type (42.3%), followed by adenocarcinoma (34.4%).

The median survival for CPFE patients with lung cancer (19.5 months) was significantly shorterthan in non-CPFE (53.1 months)[266].

Currently, no specific treatment exists for CPFE. Post-hoc data from nintedanib trials,which included patients with concurrent emphysema, showed attenuation of rate of decline in forced vital capacity (FVC) in IPF with emphysema, similar to IPF without emphysema[267,268]. An observational cohort study of real-world patients who were commenced on pirfenidone also showed similar rate of progression between CPFE and IPF without emphysema[269]. Hence, antifibrotic therapy can be considered in CPFE, where presence of IPF is confirmed, Stem Cell therapy may be a good option for rapidly declining lung function[270].

Holistic Management of COPD
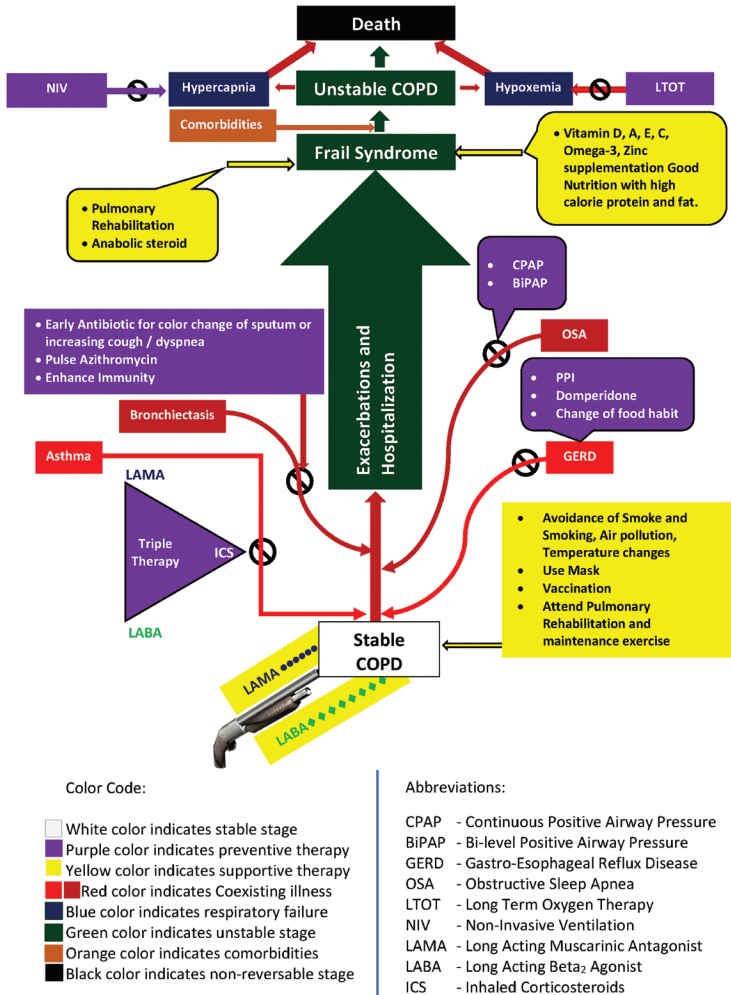
Figure 22: Algorithm of COPD MANAGEMENT

Color Code:

White color indicates stable stage
Purple color indicates preventive therapy
Yellow color indicates supportive therapy
Red color indicates Coexisting illness
Blue color indicates respiratory failure
Green color indicates unstable stage
Orange color indicates comorbidities
Black color indicates non-reversable stage

Abbreviations:

CPAP - Continuous Positive Airway Pressure
BiPAP - Bi-level Positive Airway Pressure
GERD - Gastro-Esophageal Reflux Disease
OSA - Obstructive Sleep Apnea
LTOT - Long Term Oxygen Therapy
NIV - Non-Invasive Ventilation
LAMA - Long Acting Muscarinic Antagonist
LABA - Long Acting Beta$_2$ Agonist
ICS - Inhaled Corticosteroids

12 CHAPTER 12: NON-PHARMACOLOGICAL MANAGEMENT

12.1 For All Patients of COPD:

Table 18: Non-pharmacological therapy for all COPD

1.	Asses every patient by MRC dyspnea scale or CAT score and CPET for pulmonary rehabilitation	2.	Classify COPD with all possible comorbidities and staging
3.	Avoid smoking and smoke	4.	Avoid air pollution and temperature: cold and hot
5.	Immunization	6.	Pulmonary Rehabilitation

For Selected Patients of COPD:

Table 19: Non-pharmacological therapy for specific COPD

1.	• Long Term Oxygen Therapy (LTOT) • Ambulatory Oxygen Therapy	2.	Short-Burst Oxygen Therapy
3.	Non-Invasive Ventilation (NIV): Acute NIV Chronic NIV	4.	Surgery: Bullectomy, Lung Volume Reduction Surgery (LVRS) and Endobronchial Procedures
5.	Extracorporeal Membrane Oxygenation	6.	Exosome Therapy and Stem cell Therapy
7.	Lung Transplantation	8.	End of Life (EOL) Care:

1. Quit Smoking: Smoking cessation has the greatest capacity to influence the natural history of COPD

• Nicotine Replacement Therapy (NRT): NRT has a 2-fold increase in smoking cessation rates when compared to placebo. The goal of NRT is to provide the patient with the addictive nicotine without using the harmful tobacco, facilitating avoidance from cigarettes. There are many formulations, including gum, lozenge, transdermal patch, inhaler and a nasal spray. The transdermal patch is the preferred method, as it has the most reliable and steady delivery of nicotine[271].

- **A**sk and identify smokers. Document smoking status in the medical record.
- **A**ssess the degree of nicotine dependence and motivation or readiness **TO QUIT**
- **A**dvise smokers about the risks of smoking and benefits of quitting and discuss options
- **A**ssist cessation — this may include specific advice about pharmacological interventions or referral to a formal cessation program.
- **A**rrange follow-up to reinforce messages.

2. Avoid exposure to Smoke or Temperature Fluctuations

3. Immunization: Vaccinations are a good way to reduce exacerbations. It has been demonstrated that inactivated influenza vaccines in COPD patients resulted in a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo[272]. Wongsurakiat P et al. described an absolute 21.3% reduction in the incidence of acute respiratory illness following influenza vaccination[273]. Pneumococcal vaccination is recommended to be given in addition to annual influenza vaccination in people with COPD[274].

12.2   Pulmonary Rehabilitation (PR):
12.2.1   Patho-physiology of exercise limitation:

Breathlessness on exertion and its phobia is very common in COPD and other Chronic Respiratory Disease (CRD). Inactivity leads to deconditioning, mainly caused by breathlessness which leads to avoidance of physical and social activities, thrusting the patient into a vicious circle leading to further isolation and depression, accompanied by a reduced HRQoL(Fig. 17)[242]. Pathophysiological features of exercise limitation are described in the figure below:
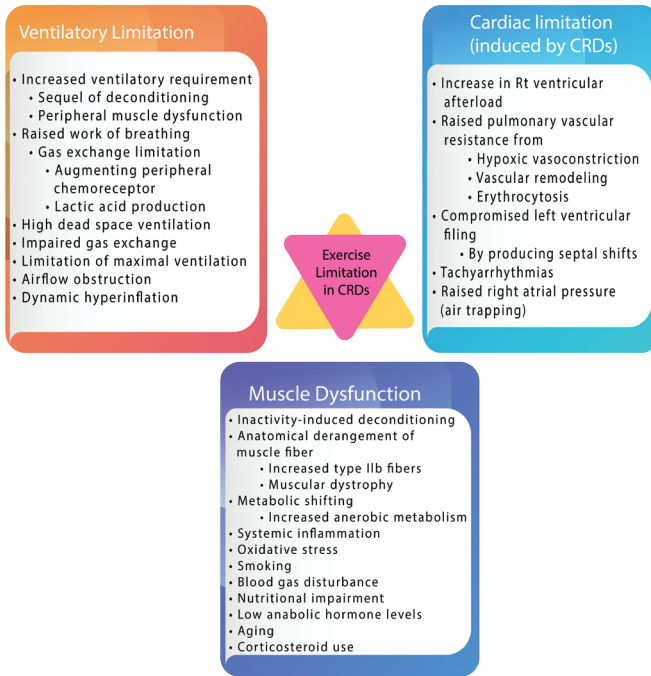
Figure 23: Patho-physiology of exercise limitation
(Reproduced from Habib GM with permission)

12.2.2 Integrative Care in COPD Pulmonary Rehabilitation

Maintaining physical activity and muscle strength is important for every patient suffering from COPD. Physical activity can be achieved through enrollment in an organized program, such as pulmonary rehabilitation (PR) It is a proven effective modality in the treatment of COPD and is part of COPD management guidelines[275]. Ideal candidates for PR are both males and females with moderate, severe or very severe COPD[276]. It should be offered to those patients with COPD who remain symptomatic despite bronchodilator therapy and should be implemented within one month following an acute exacerbation.

• Pulmonary rehabilitation programs involve patient assessment, supervised exercise training, education, behavior change, nutritional intervention and psychosocial support[277].

• Exercise training is considered to be the cornerstone of pulmonary rehabilitation[277].

• The benefits of pulmonary rehabilitation include a reduction in symptoms (dyspnea and fatigue), anxiety and depression, and improvements in health-related quality of life (HRQoL), peripheral muscle function and exercise capacity.

• Some patients who experience marked oxygen desaturation on exertion may benefit from ambulatory oxygen during exercise training and activities of daily living

• Duration of pulmonary rehabilitation program in Bangladesh (for example in Pulmo-FIT) ranges from 2 to 8 weeks.

• It is clearly demonstrated that

• Doing any physical activity is better than doing none[63];

• Be active on most, preferably all, days every week;

• Accumulate 150 to 300 minutes of moderate intensity physical activity or 75 to 150 minutes of vigorous intensity physical activity, or an equivalent combination of both moderate and vigorous activities, each week;

• Do muscle strengthen activities on at least 2 days each week.
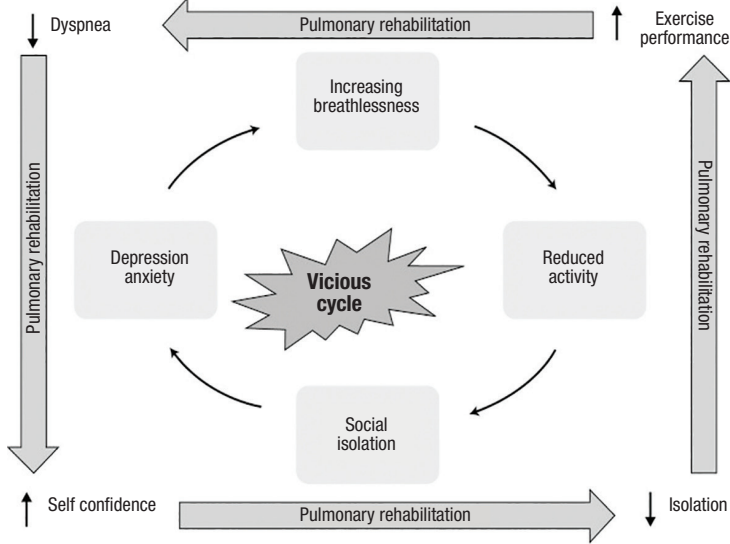
Figure 24: COPD's vicious circle (reproduced from[242]).

12.2.3   Physical Activity
What is physical activity?
Optimal physical activity is the key component to maintaining sustainable benefit of successful PR.

Any bodily movement produced by skeletal muscle that leads to energy expenditure. This includes[278]:

1. At least 30 minutes moderate intensity physical activity for 5 or more days a week.
2. Vigorous physical activities for 20 minutes 3 days every week

3. Shorter bouts three-times moderate 10 minutes or two-times vigorous 10 minutes[278,279]

Physical activity is measured during, work, commuting, and recreation by MET (Metabolic Equivalent Task); sitting 1; moderate 4; vigorous 8. The total PA score is calculated by the sum of all MET/min/week from moderate to severe PA performed in work, commuting, and recreation[280].

The patterns of PA and energy expenditure differs between the developed and developing countries because of their of their diverse way of life dynamics[281].

<div align="center">WHO define[282]</div>

Physical Activity	Exercise
"Physical activity" is bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits.	"Exercise" is a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness.

Classifying the physical activity level:

Degree of PA is divided in three groups according to the GPAQ analysis framework: low, moderate, and high[280].

<div align="center">Table 20: Degree of Physical Activity</div>

Level of PA	
High level	A person reaching any of the following criteria: (a) Vigorous-intensity activity on at least three days and accumulating at least 1500 MET-minutes/week OR (b) Seven or more days of any combination of walking, moderate- or vigorous-intensity activities accumulating at least 3000 MET-minutes/week

Moderate	A person not meeting the criteria for the 'High' category, but meeting any of the following criteria is classified in this category: 1. (a) Three or more days of vigorous-intensity activity of at least 20 min per day OR 2. (b) Five or more days of moderate-intensity activity and/or walking of at least 30 min per day OR 3. (c) Five or more days of any combination of walking, moderate- or vigorous-intensity activities accumulating at least 600 MET minutes/week.
Low	A person not meeting any of the above-mentioned criteria falls in this category. No activity is reported or some activity is reported but not enough to meet high and moderate categories

Prevalence of PA and Physical inactivity (PiA):

• Globally, 1 in 4 adults is not active enough. 23% of adults aged 18 and over have PiA in 2010 (M-20%, F-27%); in HICs M-26% & F-35%; LMICs M-12%, F-24%.

• More than 80% of world's adolescent population (11-17 years) is insufficiently physically active (M-78%, F-84%)

• Policy for addressing the PiA is taken by 56% of the member countries of WHO

• WHO member countries agreed to reduce PiA by 10% by 2025 PA data from Bangladeshi population[283]:
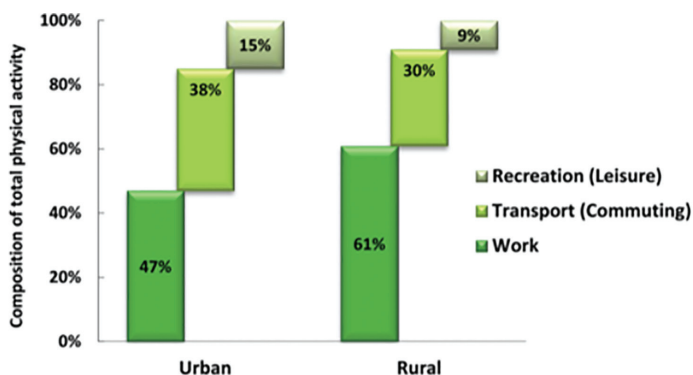
Figure 25: physical activity in urban and rural of Bangladesh.
Composition of total physical activity (%) in urban and rural areas of Bangladesh.

The country wide prevalence of PA levels in a study in Bangladesh (Moniruz-zaman et al 2016) was low 34.5% moderate 46.0% and high 19.5%. Composition of total PA in urban and rural areas[283]:

Table 21:Components of Physical Activity

Domain	Rural	Urban
Workplace activity	61%	47%
Commuting activity	31%	38%
Leisure-time activity	9%	15%

Why physical activity is important?[282]
• Regular PA of moderate intensity e.g. walking, cycling, doing sports has significant benefits both in prevention and care of many NCDs.
• It improves skeleto-muscular and cardio-pulmonary fitness
• Improves functional and mental health
• Reduces the risk of hypertension, coronary heart disease, stroke, diabetes, various types of cancer including breast and colon cancer and depression.
• Plays a role both in primary and secondary prevention
• Improves balance impairment and reduce fall incidence
• Optimise balance between energy intake and burning resulting weight control • Reduces mortality from NCDs

How to increase PA?
National, local, social, and individual initiative and rationale strategy might increase the PA for people. These might be:
• Awareness and promotion of PA through activity of daily life in association with the relevant sectors of PA
• Planned urbanisation to providing walking, cycling, and other forms of transport accessible and safe for all
• Work place and labour policy should be organised in a way that encourage physical activity
• Sports and PA programme should be organised during free time in school and colleges
• Physical educator should be appointed in every institute
• Sports and recreation facilities involving PA should be arranged to reach as much as people can avail.
• Follow WHO recommendation:
      o Develop and implement national guideline for PA
      o Integration of PA with other related policy sectors
      o Use of mass media to raise awareness of the benefits of PA
      o Surveillance and monitoring the PA implementation programme
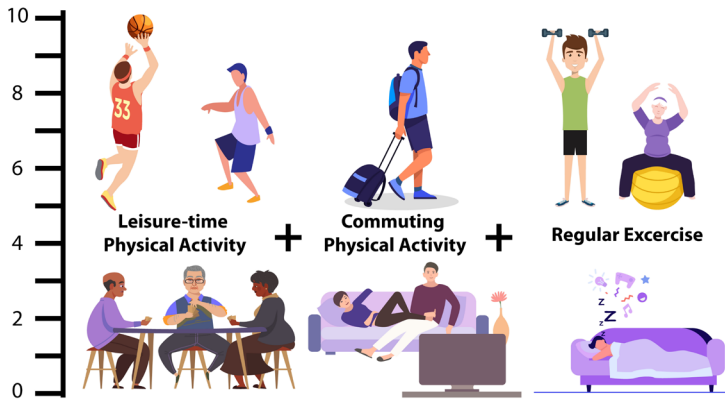
Assesment of Physical Activity in our setting

Figure 26: Assessment of Physical Activity in Pulmo-Fit

12.2.4   Education and self-management

• Education alone has not been shown to be effective without physical training and self-management plan[284]

• Self-management means intervention with communication with a health care professional to improve health status and decreases hospitalizations and emergency department visits of COPD patients.

12.3   Non-Invasive Ventilation (NIV):
12.3.1   a. Acute NIV:

Non-Invasive positive pressure ventilation (NIPPV) is a proven modality to decrease morbidity, improve survival and decrease the need for mechanical ventilation in COPD patients who develop acute respiratory failure. Its benefit has been proven in various settings, including the ICU, ward and emergency department in patients with moderate to severe respiratory acidosis[285]. NIV is also effective in facilitating extubation in patients mechanically ventilated for an acute exacerbation. Patients extubated to NIV had fewer re-intubations, fewer tracheostomies, shorter ICU stays, improved ICU survival and fewer complications including nosocomial pneumonia[286]. Because of these positive results, NIV should be considered in patients that require mechanical ventilation for respiratory failure particularly in those who have failed traditional weaning.

12.3.2   b. Chronic NIV:

The use of chronic NIV in patients with COPD is more controversial. Struik et al[287] have demonstrated that the use of NIV in COPD improvements in daytime

$PaCO_2$ and nocturnal transcutaneous PCO_2 measurements in the NIV group. But Number of exacerbations, lung function, mood state, daily activity levels or dyspnoea was not significantly different from standard treatment without COPD. Despite this lack of convincing evidence for its use, there are some clear situations where chronic NIV proves beneficial. One of these situations is in the patient with combination of COPD and obstructive sleep apnea (OSA)[288]. Patients with combined COPD and OSA who are not treated with appropriate NIV, like continuous positive airway pressure (CPAP/BiPAP) for example, experience higher rates of hospitalizations and mortality when admitted with a COPD exacerbation. The use of CPAP/BiPAP for combined OSA and COPD also reduces pulmonary hypertension rates and nocturnal hypoxemia[288].

12.4   Long Term Oxygen Therapy (LTOT):
According to the British Thoracic Society (BTS)[289], long term oxygen therapy is recommended for patients with a PaO_2 ≤55 mm of Hg or ≤7.3kPa or a PaO_2 between 55 mm of Hg or 7.3kPa or 60 mm of Hg ≤8kPa with signs of peripheral edema, polycythemia (hematocrit>55%) or pulmonary hypertension. In this population, long term oxygen therapy is one of the few interventions that prolong life expectancy[290]. It also reduces pulmonary hypertension and hematocrit. Continuous oxygen therapy for 24h/d is superior to nocturnal oxygen in those with severe hypoxemia (PaO_2 ≤7.3kPa or a PaO_2 of ≤8kPa cor-pulmonale)[291]. Situational oxygen is also recommended for those who desaturate with exertion or have hypoxemia at night[292].

12.5   Ambulatory Oxygen Therapy
In patients with COPD with moderate hypoxia, current evidence on ambulatory oxygen therapy reveals improvements in dyspnoea post exercise and in the dyspnoea and fatigue domain of quality of life[293]. For patients on LTOT who are motivated to use oxygen outside the home, ambulatory oxygen should be prescribed. Ambulatory oxygen is also indicated for those patients not on LTOT but who have exercise arterial desaturation[292]. In this population, arterial oxygen desaturation is defined as a fall in SaO_2 of 4% to a value <90%. In addition to desaturation, these patients must also demonstrate improvement in exercise capacity and/or dyspnea with oxygen. The goal is to maintain oxygen saturation >90% during exercise.

12.6   Short-Burst Oxygen Therapy
Short burst oxygen therapy (SBOT) refers to the intermittent use of oxygen, usually from a static cylinder. It is widely prescribed for the alleviation of breathlessness in patients with chronic obstructive pulmonary disease (COPD), despite little convincing evidence of benefit[294]. It should only be considered for episodes of severe breathlessness in patients with COPD not relieved by

inhaler or other reliever treatments. This mode of oxygen delivery should only continue to be prescribed if patient feels improvement in breathlessness with its use[295].

12.7   Extracorporeal Membrane Oxygenation (ECMO):

Extracorporeal membrane oxygenation, or ECMO, is a therapy that adds oxygen to blood and pumps it through their body like the heart. The process takes place outside the body.

ECMO is used when usual treatments are not working. ECMO does not cure heart or lung disease, it only provides time for the patient's heart or lungs to heal[296].

The ECMO pump pulls blood that has no oxygen attached from a vein and pushes it into the machine's artificial lung, or oxygenator. That's where carbon dioxide is removed from the blood and oxygen is added. There's a color change as the darker blood with no oxygen turns bright red when oxygen is attached to it. As the red blood leaves the oxygenator it is warmed before returning to the patient. Because ECMO is also helping do the work of the patient's lungs, the ECMO team can lower the settings of the ventilator, allowing the lungs to rest and heal.
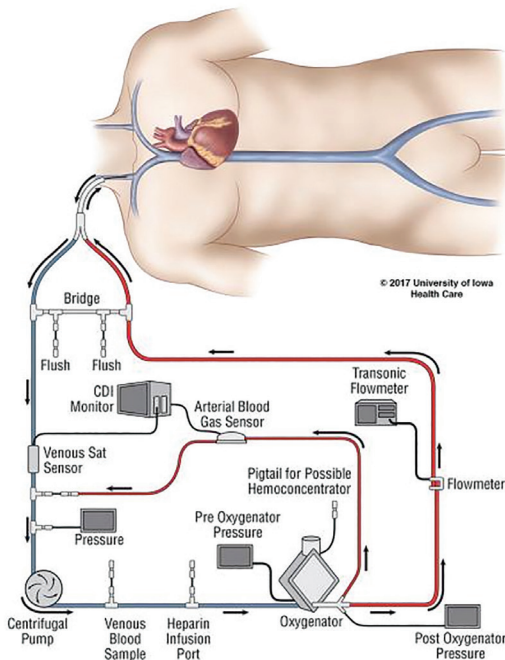
Figure 27: Mechanism of ECMO

(Copied from the webpage of the University of Lowa applying for permission) ECMO handles the body's blood in two stages. First it draws blood out of the body and brings it into the ECMO machine for oxygenation and removal of CO_2. Second it delivers blood from the machine back into the body[296].

This is a new modality being used to treat COPD exacerbations to prevent the need for mechanical ventilation and the associated morbidity associated with intubation. As demonstrated above, non-invasive ventilation is superior to mechanical ventilation in terms of mortality, complications and hospital length of stay. However, 15-26% of patients with an acute exacerbation of COPD fails non-invasive ventilation and requires transition to mechanical ventilation. These patients have a higher mortality than those initially treated with mechanical ventilation[276]. There are no current guidelines on the use of ECMO for COPD exacerbations as its use in this indication is new. Studies have shown that the Novalung could prevent intubation in 90% of patients with a trend to decreasing hospital length of stay[289]. It is likely that in the future we will see this modality being used more in centers that have access to it.

12.8   Surgery
None of the current surgical approaches in patients with COPD provides a survival advantage. In view of the potential for serious morbidity and mortality, all surgical treatments require careful assessment by an experienced thoracic medical and surgical team.

12.8.1   Bullectomy
This operation involves resection of large bullae (larger than 5cm). The procedure is most successful where there are very large bulla compressing adjacent apparently normal lung. Giant bullae can be defined as occupying more than 50% of the hemithorax with definite displacement of adjacent lung tissue[297].

12.8.2   Lung Volume Reduction and Endobronchial Procedures:
LVRS is an effective treatment option in patients with heterogeneous upper zone emphysema and reduced exercise tolerance[298]. According to the National Emphysema Treatment Trial (NETT) trial, LVRS has shown to be superior to medical treatment. LVRS has improved maximal ventilation rate and tidal volume and has lower BORG dyspnea scores[299]. However, surgery carries a high risk of morbidity, particularly in patients with severe COPD, who often have additional co-morbidities. Thus, newer, non-surgical, less invasive strategies have been developed to potentially offer benefit to those patients who would not be candidates for LVRS. These non-surgical procedures are referred to as bronchoscopic lung volume reduction[300].

12.8.3   Lung Transplantation:

Lung transplant is offered to people with untreatable, end-stage lung disease with a limited life expectancy. COPD is one such lung disease and is currently the most common indication for a double lung transplant[301]. According to the International Society for Heart and Lung Transplantation, the disease specific criteria for referral of patients with COPD include an $FEV_1 \leq 30\%$ while having maximized both pharmacological and non-pharmacological therapy, including bronchodilators, home oxygen, smoking cessation and pulmonary rehabilitation. In addition, they should have a BODE index exceeding 5[302]. Other criteria for transplantation include patients with a BODE index of 7-10 plus a history of hospitalization for exacerbation associated with acute hypercapnia, pulmonary hypertension or cor pulmonale or an FEV_1 of less than 20% with either a DLCO of less than 20% or a homogeneous distribution of emphysema[301].

The survival benefit for patients with COPD receiving a transplant is not as robust as for transplant in other respiratory conditions, such as pulmonary fibrosis (DPLD), cystic fibrosis and primary pulmonary hypertension[302]. If a patient seems like an appropriate candidate and is willing, a referral to a transplant centre should be made.

12.9   End of Life (EOL)Care:

Patients with COPD typically experience the last few months to years of their life marked by progressive dyspnea, functional decline and social isolation[302]. Their quality of life has been compared to those with lung cancer[303]. As with any non-curable chronic illness, goals of care and end of life discussions must occur[304]. The discussion should focus on education of the disease course and management of end of life issues, such as symptom control and advanced health care directives. The prognosis of COPD is often difficult to predict as the disease is marked by progressive decline in lung function with increasing symptoms. There are episodes of acute illness and associated co-morbid conditions. Because prognosis is difficult to predict, it is often unclear as to when to begin end of life care discussions and palliative symptom management[305]. These discussions should definitely occur when the FEV_1 is <30%, abnormal blood gases are present or when cor-pulmonale with pulmonary hypertension develops as these patients are found to have the poorest prognosis. The major symptoms experienced by end-stage COPD patients include dyspnea, pain, fatigue and insomnia[305]. Insomnia is often improved simply through dysnpea control[305]. Low dose Benzodiazepines can be used as adjuncts to opioids to control severe dyspnea along with BiPAP and oxygen.

13 CHAPTER 13: PHARMACOLOGICAL TREATMENT OF COPD

13.1 Pharmacotherapy in COPD

The current pharmacological treatment of COPD is symptomatic and is mainly based on bronchodilators, such as selective Beta$_2$-adrenergic agonists (short- and long-acting), anticholinergics, theophylline, phosphodiesterase-4 antagonists, such as roflumilast or a combination of these drugs[306]. Inhaled corticosteroids (ICS) are not generally recommended for patients with COPD without features of Asthma due to their lack of efficacy, side effects, and high costs. However, oral or parenteral glucocorticoids may be given during exacerbations of COPD. A number of novel long-acting anticholinergics e.g. Glycopyrronium and Beta$_2$-agonists e.g. Indacaterol/with once daily are now clinically using[307]. Montelukast has been not yet been established in chronic obstructive pulmonary disease (COPD)[308]

Patients with characteristics of both COPD and asthma, sometimes referred to as asthma COPD overlap (ACO), in our classification COPD -A may be more likely to benefit from montelukast therapy[309]

Table 22: Pharmacotherapy in COPD

Stage	Therapy
Stage 1: FEV$_1$ ≥ 80%	SMART THERAPY As per need Budesonide and Formoterol inhaler therapy[310]
Stage 2 FEV$_1$ <80–50	TRIPPLE: THERAPY[311] (LAMA+LA-BA+ICS) (Moderate Dose (FEV$_1$ <80% to≥ 60% to Maximum dose if FEV$_1$≤60%) and + add on ± Montelukast to control COPD A plus, Ipratropium & salbutamol as per need[312]
Stage 3 FEV$_1$ <50-30	TRIPPLE THERAPY:[311] (LAMA+LABA+ICS)(Maximum Dose) +Doxophylline[313] ± Mon-telukast[309] plus Ipratropium & salbutamol as per need[312]
Stage 4 FEV$_1$ <30	TRIPPLE THERAPY:[311] (LAMA+LA-BA+ICS)(Maximum Dose)+Mon-telukast + Doxophylline[313] +Nebulized Bronchodilator +Neb Budesonide[314]± LTOT[294]

Table 23: Pharmacotherapy for COPD-B

Stage:1 As per need Salbutamol and ipratropium inhalation[311]
Stage:2 DOUBLE THERAPY:[307] (LAMA+LABA) +Sub-lingual Lyophilized Bacterial Lysate[138] (10 days / months & 3 months/ year)
Stage:3 DOUBLE THERAPY: (LAMA+LABA)+Doxophylline[313] +Sublingual Lyophilized Bacterial Lysate (10 days /month & 3 months/ year) +Azithromycin[140] (alternate day or thrice a week throughout the year)
Stage:4 DOUBLE THERAPY: (LAMA+LABA) +Roflumilast[306]+Sublingual Lyophilized Bacterial Lysate (10 days /month & 3 months/ year) +Azithromycin (alternate day or thrice a week throughout the year) +Tobramycin[135] nebulization 3 weeks 12 hourly then 3 weeks gap life-long ± LTOT[289]

Table 24:Pharmacotherapy of COPD-G

Stage:1 PPI[149,150] + Domperidone C h a n g e food habit Sleep with double pillow Eating & drinking slowly to avoid cough, wheeze or choking plus As per need Salbutamol and ipratropium inhalation[311]
Stage:2 DOUBLE THERAPY: (LAMA+LA-BA)+PPI +DOMPERIDON Change food habit Sleep with double pillow Eating & drinking slowly to avoid cough, wheeze or choking. Plus, as per need Salbutamol and ipratropium inhalation[311]
Stage:3 Avoid theophylline / Doxophylline as it may cause GERD[315] DOUBLE THERAPY: (LAMA+LABA) +Nebulize Bronchodilator 1-2 times daily +PPI +DOMPERIDON Change food habit Sleep with double pillow Eating & drinking slowly to avoid cough, wheeze or choking. + as per need Salbutamol and ipratropium inhalation[311]
Stage:4 DOUBLE THERAPY: (LAMA+LABA)+Nebulize Bronchodilator 3-4 times daily + PPI +DOMPERIDON Change food habit Sleep with double pillow Eating & drinking slowly to avoid cough, wheeze or choking . ± LTOT

Table 25: Pharmacotherapy of COPD - O & S

Stages	COPD – O	COPD - S
Stage 1: FEV$_1$ >80%	Weight Reduction and CPAP [170,171] plus As per need Salbutamol and ipratropium inhalation[311]	As per need Salbutamol and ipratropium inhalation[311]
Stage 2: FEV$_1$ 50-79%	**Double therapy:** (LAMA+LABA) Always sleep in lateral Position -Add CPAP or BIPAP plus As per need Salbutamol and	**Double therapy:** (LAMA+LABA)
Stage 3: FEV$_1$ 30-49%	Double therapy: (LAMA+LABA) +Doxophylline Always sleep in lateral Position ± add CPAP or BiPAP	**Double therapy:** (LAMA+LABA) +Doxophylline Always sleep in lateral Position ± add CPAP or
Stage 4: FEV$_1$<30%	Double therapy: (LAMA+LABA)+Doxophylline +Nebulize Bronchodilator Always sleep in lateral Position ± add BiPAP ± LTOT	Double therapy: (LAMA+LABA) + Doxophylline+Nebulize Bronchodilator ± LTOT

Table 26: Pharmacotherapy of COPD - U

Stages	COPD – U
Stage 1: FEV$_1$ >80%	Practically nil case stage 1 with Unstable COPD
Stage 2: FEV$_1$ 50-79%	TRIPPLE THERAPY (LAMA+LA-BA+ICS) (Maximum Dose)
Stage 3: FEV$_1$ 30-49%	TRIPPLE THERAPY (LAMA+LA-BA+ICS) (Maximum Dose) +Montelukast+Doxophylline +Azithromycin (alternate day or thrice a week throughout the year) +Sublingual Lyophilized Bacterial Lysate (10 days /month & 3 months/ year)
Stage 4: FEV$_1$ <30%	COMBINE ALL (for maximum relief of Symptoms) + LTOT + BiPAP during sleep

13.2 Treatment of anxiety and depression in COPD

Anxiety and depression are the most **common** psychiatric **comorbidities** associated with **COPD**. Varying prevalence rates have been reported from various parts of world ranging from 5% to more than 40% both because of variation in the study participants to various psychological tools having been used for screening[316,317].

Anxiety symptoms in COPD are associated with worse quality of life[318] selfmanagement and exercise performance and with increased medical symptom reporting[63] exacerbations hospitalizations, length of hospitalizations, medical costs and mortality[318]. The prevalence of one anxiety disorder in particular, is panic disorder, it is approximately 10 times greater in COPD than the population prevalence of 1.5 to 3.5%, and panic attacks are commonly

experienced[319].

Selective serotonin reuptake inhibitors (SSRIs) such as sertraline, have been recommended as first line pharmacological therapies for anxiety in COPD[320]. **Benzodiazepine** users **were** at "significantly **higher risk**" for outpatient respiratory **exacerbations**, emergency room visits for either **COPD** or pneumonia, and that hospitalizations among this group compared to nonusers[321].

Table 27: Classification of Benzodiazepine[322]

	Physical Findings	Investigation
Half-life designation	Half-life (h)	Name of Drugs
Long-acting	25–100	Bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flurazepam, nitrazepam
Intermediate-acting	5–24	Alprazolam, lorazepam, oxazepam, temazepam
Short-acting	< 5	Triazolam, Midazolam

Among individuals with more severe COPD, 35.4 % of incident (Aspiration, Pneumonia, Respiratory Failure) use occurred during a COPD exacerbation[322]. In severe COPD hospitalizations due to exacerbations and pneumonia risks were "significantly elevated" in COPD patients that used benzodiazepines.

The potential adverse respiratory effects of benzodiazepines in COPD may also be heightened in older adults given their altered pharmacokinetics that increase benzodiazepine half-life[322].

Adverse effects associated with benzodiazepine use in COPD patients, may include hypoxemia, decreased respiratory drive, hypercapnea, and decreased respiratory muscle strength[323].

NOTE: Low dose benzodiazepines and opioids with Oxygen may be safe for severe COPD and terminally ill patient. But at higher doses it might increase mortality[324].

14. CHAPTER 14: MANAGEMENT OF EXACERBATIONS OF COPD (Plan ABCO)

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are treated with oxygen (in hypoxemic patients), inhaled beta$_2$ agonists, inhaled anticholinergics, antibiotics and systemic corticosteroids. Methylxanthine therapy may be considered in patients who do not respond to other bronchodilators[325]. Antibiotic therapy is directed at the most common pathogens, including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. Mild to moderate exacerbations of COPD are usually treated with older broad-spectrum antibiotics such as amoxicillin-clavulanate potassium, doxycycline, and Levofloxacin. Treatment with augmented penicillins, fluoroquinolones, third-generation cephalosporins and/ or aminoglycosides may be considered in patients with more severe exacerbations and/or Psudomonas infection[326,327].

14.1   Exacerbations of COPD[3]

An exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy. COPD exacerbations are complex events usually associated with **increased airway inflammation** presented as increased cough and wheeze, **increased mucus production** presented as excess sputum production and sputum color changes and **marked gas trapping in lung** presented as markedly increased dyspnea. As other comorbidities that may worsen respiratory symptoms are common in COPD patients, clinical assessment to rule out differential diagnoses should be considered before diagnosis of a COPD exacerbation.

Always exclude following conditions before establishing diagnosis of acute exacerbations of COPD

These are 5 P and 1 C: 5 P: 1. Pneumonia, 2. Pneumothorax, 3. Pleural effusion, 4. Pulmonary embolism, 5. Pulmonary edema and 1.C: Cardiac arrhythmias. Differential diagnosis of acute exacerbations of COPD:

P1: Pneumonia

History and Symptoms

Table 28: Diagnostic features of Pneumonia

History of running nose or sore throat	Temp more than 99^0F	Chest Xray CBC
Fever, shortness of breath and increasing cough	Tachypnea Tachycardia	Sputum for C/S
Dull Chest pain	May be Low pressure	C Reactive protein
Scanty Hemoptysis	Features of consolidation	Procalcitonin high in bacterial pneumonia. (optional) If suspect, viral or atypical pneumonia

P2: Pneumothorax

Table 29: Diagnostic features of Pneumothorax

History and Symptoms	Physical Findings	Investigations
Sudden onset sharp, one-sided chest pain	Tachypnea Tachycardia Cyanosis	Chest X-ray Chest ultrasound
Sudden shortness of breath	May be Low pressure	CT scan Chest
Percussion: hyperresonance on one side of the chest. It is like Tympanic sound: hollow, high, drum like sounds		
Auscultation: Breath sound diminished or absent		

Pneumothorax in COPD: Spontaneous pneumothorax is defined by the presence of air in the pleural cavity without history of trauma. This is a significant clinical problem. COPD is a common cause of pneumothorax. The risk of recurrence of spontaneous pneumothorax secondary to COPD is high and various studies quote rates 20-60%.

P3: Pleural Effusion;

Table 30: Diagnostic features of Pleural effusion

COPD with SOB usually admitted in hospital or in ICU for SOB	Unilateral Or Bilateral	Chest X-ray Chest ultrasound CT scan Chest Echocardiography
Most are due to CHF and/or parapneumonic effusions		Transudate – CHF Exudate – paraneumonic
With or without fever		BNP or Pro-BNP

P4: Pulmonary Embolism

Table 31: Features of Pulmonary embolism

History and Symptoms	Physical Findings	Investigations
Usually patient of COPD with sudden SOB	No change in physical findings except occasional P2 Loud	D-Dimer CT scan with contrast Duplex study of lower extremeties CT Pulmonary Angiogram (Optional)

P5: Pulmonary edema

Table 32: Features of Pulmonary edema

History and Symptoms	Physical Findings	Investigations
Disproportionate shortness of breath and marked limitation of activities despite taking adequate Dual bronchodilator LABA/ LAMA	High or Low pressure Tachycardia Arrhythmias like Atrial Fibrillation	• X-ray Chest • USG of both chest • BNP or NT-pro BNP • Colour doppler Echo-cardiogram
History of old MI/ Angina like chest pain during exertion/ PND/ Orthopnea	Basal Crepts and ronchi with prolong expiration associated features of Pleural Effusion	

C1: Cardiac Arrhythmias

Table 33: Identifying Cardiac arrythmias

Feelings of palpitation Sudden feelings of extra beats with SOB	Irregular pulse e.g. Atrial Fibrillation	• ECG • Telecardiac monitoring during 6 minute exercise test/ Incremental Schuttle test or Cardio-Pulmonary Exercise Tests

14.2   COPD Exacerbations PLAN (ABCO):

Antibiotics (A), Bronchodilator (B), Systemic corticosteroids (C) and Oxygen (O): ABCO

14.3   A. Antibiotics for treatment of Exacerbations:

Exacerbations with clinical features of infection (increased volume and change in color of sputum and/or fever) usually will benefit from antibiotic therapy. Bacterial infection may have either a primary or secondary role in about 50% of exacerbations of COPD[328,329]. Haemophilus influenzae, Streptococcous pneumoniae and Moraxella catarrhalis are most commonly involved[330]. Mycoplasma pneumoniae and Chlamydia pneumoniae have also been reported[328,331]. As lung function deteriorates ($FEV_1 < 35\%$), Pseudomonas aeruginosa and Staphylococcus aureus are often encountered[326,332]. Multi drug resistant Ps. aeruginosa is associated with 6 fold increased risk of death[333].

It is clearly demonstrated that COPD exacerbations treated in primary care, use of point-of-care C-Reactive Protein (CRP) testing to guide prescribing of antibiotics lowered patient- reported antibiotic use (OR 0.31, 95% CI 0.20 to 0.47)[334]. The judicious use of CRP testing in primary or tertiary care may assist in determining the need for antibiotics for exacerbation management.

Table 34[335]: Cut off Values of CRP for COPD needs antibiotics

Typical clinical cut off concentrations: Conventional C Reactive Protein (CRP)	Cutoff: approximately 10 mg/L. Apparently healthy individuals: less than or equal to 5 mg/L Acute range: 20-500 mg/L

Procalcitonin (PCT) is an acute phase reactant. Procalcitonin levels increase in bacterial infections but do not increase in viral infections or auto-immune inflammation[336]. Procalcitonin has been proposed as a measure to determine if

patients with an exacerbation of COPD require oral antibiotics. In most clinical trials, use of antibiotics was discouraged if procalcitonin was 0.1ng/ml or lower and encouraged if procalcitonin was above 0.25ng/ml (Figure 19)[337].
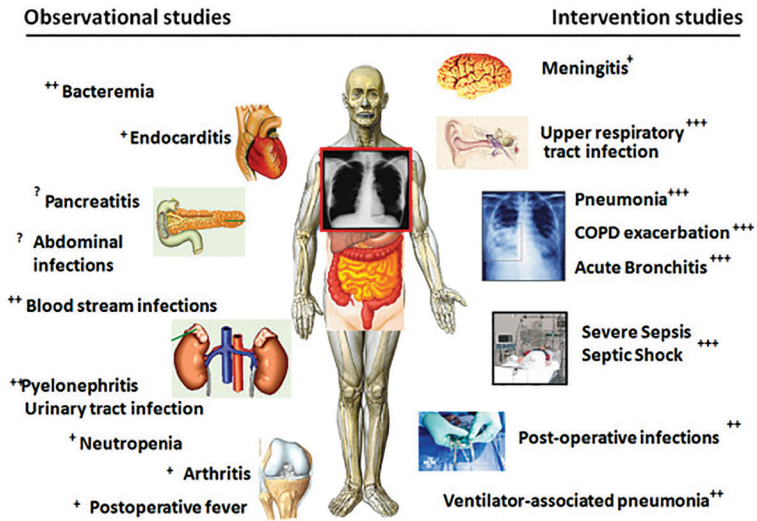
Figure 28: PCT in different infections

Available evidence concerning PCT in different infections derived from observational and randomized-controlled intervention studies. While for some infections, intervention studies have investigated benefit and harm of using PCT for antibiotic decisions (right side), for other infections only results from diagnostic (observation) studies are available with mixed results (left side). Abbreviations: PCT, procalcitonin. + moderate evidence in favor of PCT; ++ good evidence in favor of PCT; +++ strong evidence in favor of PCT; ? evidence in favor or against the use of PCT still undefined[337].
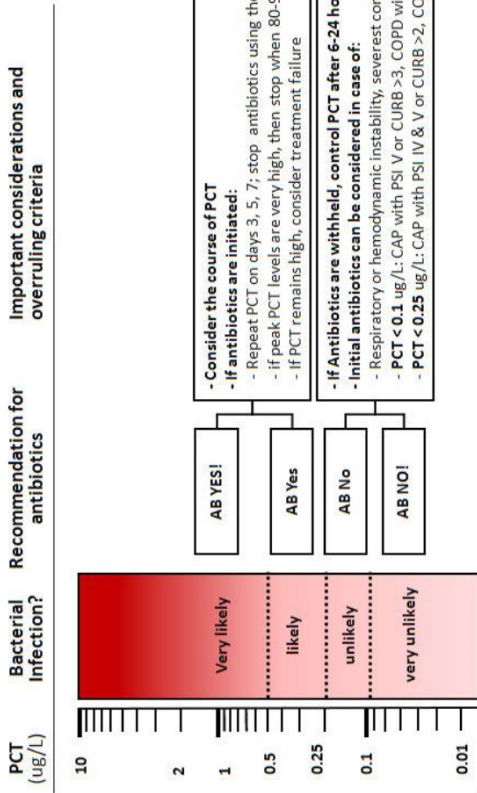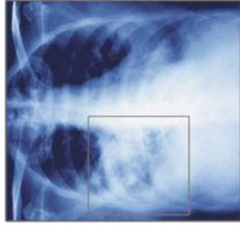
Figure 29: PCT algorithm with respiratory tract infections in A & E

PCT algorithm in patients with respiratory tract infections in the Emergency Department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the Emergency Department encourages (>0.5 μg/l or >0.25 μg/l) or discourages (<0.1 μg/l or <0.25 μg/l) initiation or continuation of antibiotic therapy more or less based on PCT specific cutoff ranges. Abbreviations: AB, antibiotic; LRTI, lower respiratory tract infection; PCT, procalcitonin; PSI, Pneumonia Severity Score[337].

Figure 30: PCT algorithm with sepsis in the ICU

PCT algorithm in patients with sepsis in the ICU. In critically ill patients in the ICU, cut-offs are higher and initial empiric antibiotic therapy should be encouraged in all patients with suspicion of sepsis. PCT cut-offs are helpful in the subsequent days after admission to shorten the courses of antibiotic therapy in patients with clinical improvement. Abbreviations: AB, antibiotic; PCT, procalcitonin[337] .

14.4   systemic corticosteroids + antibiotics for exacerbation

A randomized placebo-controlled trial has provided evidence to support the traditional practice of treating exacerbations with a combination of systemic corticosteroids and antibiotics[338]. In this study, hospitalised patients were commenced on a tapering dose of prednisolone and randomized to receive doxycycline 200mg daily or placebo for 7 days. Clinical cure, defined as complete resolution of signs and symptoms, at day 10 was significantly higher in the antibiotic treated group compared to placebo (OR 1.9, 95%CI 1.2 to 3.2, NNT = 7, 95% CI 4 to 523)[338].

Therapeutic guidelines: antibiotic recommend the use of oral agents such as Co-amoxyclav or Levofloxacin or Doxycycline for volume and/or color change of sputum in COPD with CRP 20 or more[335]. If patients do not respond to the above antibiotics or If pneumonia, Acinetobacter, Pseudomonas or staphylococci are suspected, appropriate antibiotics should be used[339,340].

14.5   B. Inhaled bronchodilators in exacerbations
14.5.1   Effectiveness of Inhaled BD COPD exacerbations

In exacerbations of COPD, the immediate bronchodilator effect is small, but may result in significant improvement in clinical symptoms in patients with severe obstruction.

Studies of acute airflow limitation in asthma indicate that beta-agonists are as effectively delivered by metered dose inhaler and spacer as by nebulizer[341] but in COPD this effect is unknown.

People with COPD often have cardiac co-morbidities, although these may be undiagnosed at the time of presentation with a COPD exacerbation. Such patients may be susceptible to adverse events from high dose, frequent short acting beta agonists. A systematic review demonstrated that higher (5mg versus 2.5mg) doses of salbutamol were associated with increased risk of tremors, elevated heart rate, palpitations and lower blood pressure, but without evidence of any additional benefit of brochodilatations[342].

It is advised to use 2.5mg sabutamol nebulization at a time to avoid cardiac toxicity.

In Bangladesh Combination (Ipratropium 500µg and Salbutamol 2.5 mg/3ml) nebulizer solution is used to control symptoms of exacerbations[343].

14.5.2   C. Short course Systemic corticosteroids

Walters et al reported that there is high-quality evidence that systemic corticosteroids reduce (around 5 days) the severity of exacerbations and shorten duration of recovery from exacerbations[344].

1. Treatment failure (defined as additional treatment, hospital admission/ re-admission for index episode, return to emergency department, unscheduled physician visit for the index episode),
2. Improve lung function,
3. Shorten duration of recovery
4. And reduce the severity of exacerbations of COPD. In summary, a 5-day course of oral prednisolone of 30mg to 40mg is adequate to control COPD exacerbations. In patients who have been on oral corticosteroids for longer than 14 days, tapering may be necessary. Patients on long-term oral corticosteroid therapy (>7.5 mg prednisolone daily for more than 6 months) are at risk of developing osteoporosis. Prevention and treatment of corticosteroid-induced osteoporosis should always be considered.

14.6   O. Oxygen during exacerbations:
14.6.1   Controlled oxygen therapy:
This is indicated in patients with hypoxia, with the aim of improving oxygen saturation (SpO_2) to 88 to 92%. Use nasal prongs at 1–2.0 L/minute or a face mask at 2 to 4 L/minute. Minimize excessive oxygen administration, which can worsen hypercapnia.

14.7   Non-Invasive Ventilatory assistance:
BiPAP is indicated for treating hypercapnia and acidosis. This Non-invasive ventilation by means of a mask is the preferred method.

15 CHAPTER 15: COPD AND ASSESSMENT FOR SURGERY

15.1 Pre-operative Assessment for COPD patient:

Patients with COPD are at increased risk of post-operative pulmonary complications after any thoracic or non-thoracic surgery. COPD was independently associated with higher postoperative length of hospital stay, morbidity and mortality[345], including abdominal operations[346]. Careful pre-operative work-up of patients with COPD minimises post-operative complications.

15.1.1 Lung function assessment for lung surgery

In all patients on the basis of measured preoperative lung functional parameters, we predicted postoperative lung function[347,348].

In all patients the residual pulmonary function was predicted as follows: it is assumed that each segment of the lung, and there are total 19 of them (upper right lobe - 3, right middle lobe - 2, right lower lobe - 5; upper left lobe - 3, lingula - 2, lower left lobe - 4 segments) in the healthy lung contributes equally to ventilation that is 1/19 (nineteenth part) or 5.26% of total lung ventilation (100%).

Predicted postoperative FEV_1 (Ppo FEV_1) in absolute values (1-L) is calculated as follows:

• Ppo FEV_1 = preoperative $FEV_1 \times$ (19 segments–the number of segments to be removed) ÷ 19 or by the formula.

• Ppo FEV_1 =preoperative $FEV_1 \times$ (1–(S x 5.26) ÷ 100. (S = number of segments to be removed).

Both formulas provide the same result.

Ppo FEV_1 should be 1L or more for Preoperative fitness

Other tests:

If performance on the low technology exercise test is satisfactory (stair climbing altitude > 22 m or shuttle walk distance > 400 m), patients are regarded as at low risk of anatomic resection.

16   CHAPTER 16. REGENERATIVE THERAPY

16.1   A. Stem cell therapy for (COPD)

Stem cells have the unique ability to change into any cell in the body, called differentiation. Studies have shown that expanded cord tissue-derived mesenchymal cells have incredibly high anti-inflammatory properties and tissue regeneration capabilities. When delivered, intravenously MScs (mesenchymal stem cells) will travel to the lungs (or any area of inflammation) and combat the issue. They can be administered intravenously and find damaged tissues around organs. When used in regards to COPD patients, stem cells can repair damaged lung tissue to combat emphysema or chronic bronchitis. Stem cells have natural anti-inflammatory properties, which can clear airways for those with chronic bronchitis. Completed studies have shown the ability to quantify the effects of stem cell therapy. According to a report done by the Lung Institute called Autologous Stem Cell Therapy and its Effects on COPD, over 82% of patients that attempted stem cell treatment had noticeable improvements in their quality of life after their therapies. Many of these patients reported increased lung capacity and the ability to walk following transfusion. These reports have positioned stem cells as one of the best viable options for current patients with COPD. While stem cell treatment has not shown the ability to cure COPD, its ability to repair damaged tissue and relatively invasive nature makes it an attractive alternative to patients. This path becomes even more desirable when considering the current treatment protocols requiring the use of ventilators or even total lung transplants, which are rare and extremely expensive. But no published data yet recommended for its general use for COPD[349].

16.2   B. Eoxosome in COPD :

Stem cells-based therapy may be a prospective way for diseases that are irreversible and incurable at present[350]. Specifically, regenerative medicine contains two goals: one is efficiently and safely transferring stem cells into injured organs and tissues, which may replace the transplantation of the entire organ in the near future; the other is to develop strategies in order to improve the regenerative potential and function of adult stem cells residing in various organs[351].

A key component of paracrine secretion is extracellular vesicles (EVs), particularly the exosome fraction that mainly contributes to the action of stem cells in which genetic information can be horizontally transferred between stem cells and tissue-injured cells. On the basis of the ability of microvesicles (MVs) to mimic stem cell properties, it is speculated that stem cell-derived MVs especially exosomes represent a relevant therapeutic option in regenerative medicine[352]. But still need further effort to explore exact therapeutic use of exosome for COPD[350].

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BANGLADESH GUIDELINES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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