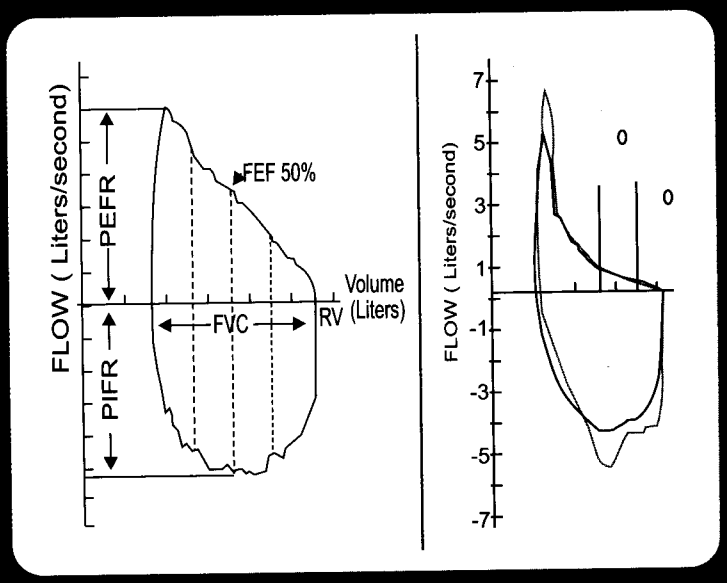
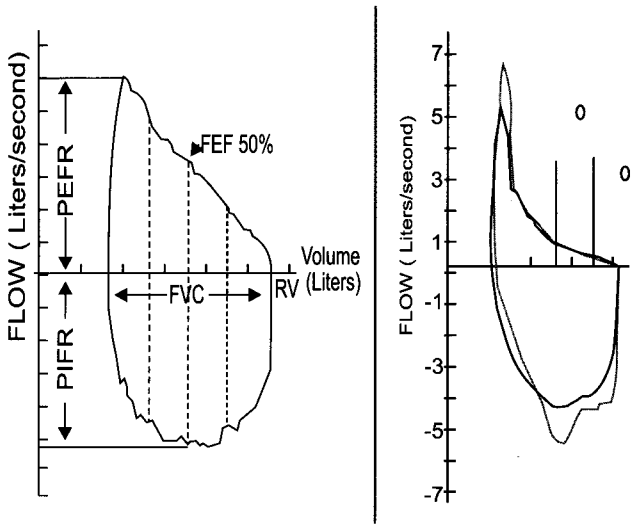


National Institute for Research in Environmental Health
Indian Council of Medical Research
Kamla Nehru Hospital building Bhopal- 462 001

GUIDELINES FOR MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN MIC EXPOSED SUBJECTS AT BHOPAL



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सत्यमेव जयते

डॉ विश्व मोहन कटोच
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स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक, आई सी एम आर

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Foreword

The consequences of the World's worst chemical disaster that occurred on the night of 2-3 December 1984 from a pesticide plant in Bhopal continue to haunt the survivors even today. There was an immediate death of nearly 2000 people and surviving people continued to suffer. The respiratory and ophthalmic morbidities were predominant in the acute phase and continued to be the main morbidities among survivors. The 44th round of epidemiological study conducted by the National Institute for Research in Environmental Health (ICMR) has revealed that even after 25 years of exposure 13.2% of gas exposed population has respiratory morbidity compared to 2.56% in the control population (NIREH Annual Report, 2011-12). There are evidences from published literature that chronic airway obstruction persists in a large number of exposed population and many of them now present with complications of chronic airway obstruction. The treatment of chronic obstructive pulmonary disease (COPD) based on the currently available scientific evidences is not standardised in this population. As a result, patients are treated with unwanted and unnecessary medications. Realising the importance of having a scientifically valid guideline for management of COPD in this population, the Indian Council of Medical Research (ICMR) constituted an expert committee of eminent Pulmonologists of the country to develop guidelines suitable for use in this population. The committee after detailed deliberations has developed guidelines with both pharmacologic and non-pharmacologic forms of treatment. It is noteworthy that the Expert Committee has laid a greater emphasis on non-pharmacologic treatment especially pulmonary rehabilitation programmes that include smoking cessation and pulmonary physiotherapy to improve the quality of life. As the problem of chronic respiratory diseases in the gas exposed population is huge, there is a need to develop pulmonary rehabilitation programmes at community level so that the benefit of the programme can be provided to the victims near their residences. The document also provides guidelines for management of complications such as chronic respiratory failure that these patients may develop as time passes. It has been planned to disseminate these guidelines to the physicians in Bhopal by organising continuing medical education programmes. It is hoped that these guidelines will be useful to the physicians and the patients will benefit by implementation of a standardised treatment programme. We would like to convey our appreciation to all experts for their work and look forward to their continued support to regularly update these guidelines with growing experience in future.

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Guidelines for Management of Chronic Obstructive Pulmonary Disease (COPD) in MIC Exposed subjects in Bhopal

Introduction

Chronic obstructive pulmonary disease (COPD) is a term that is coined for the diseases that were previously known as chronic bronchitis and emphysema. COPD is a progressive disease characterized by airflow limitation that is either not reversible at all or only partially reversible. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently defined COPD as "a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patient" (1). COPD does not include asthma in which the airflow obstruction is largely reversible. The airflow obstruction in COPD is associated with abnormal inflammatory response of the lungs to chronic inhalational exposure from smokes, dusts and other air pollutants. Chronic bronchitis results from overproduction and hypersecretion of mucus by goblet cells and this lead to chronic cough and sputum production for at least 3 months per year for two consecutive years. Emphysema is a condition characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis. In the entity of COPD, chronic bronchitis occupies one end of the spectrum, emphysema on the other and most patients are in between.

Individuals exposed to methyl isocyanate (MIC) have chronic persistent inflammatory changes in the lower respiratory tract (2). In addition, a proportion of subjects exposed to methyl isocyanate have persisting airflow limitation that is indistinguishable from COPD (3). Many MIC exposed subjects

have respiratory symptoms such as chronic cough and breathlessness which are also the cardinal symptoms of COPD (4). 13 years after accidental exposure to sulphur dioxide, obstructive impairment in ventilatory function had been reported and some patients in this study had symptoms of chronic bronchitis (5) and this is similar to the single massive exposure of MIC. The common pulmonary function abnormality observed in gas exposed individuals admitted to the Pulmonary Medicine ward of Bhopal Memorial Hospital and Research Centre and seen in the Respiratory Clinic at National Institute for Research in Environmental Health, Bhopal and presenting with cough and breathlessness is obstructive airway disease, a finding consistent with a diagnosis of COPD (Vijayan VK, Personal observation). These observations suggest the need for a guideline for management of people exposed to MIC.

COPD progresses with time ultimately leading to respiratory disability and death. Acute exacerbations of COPD occur due to repeated episodes of respiratory tract infections (both upper and lower respiratory tract) or to complications such as pulmonary embolism, heart failure, pneumothorax etc. There is worsening of symptoms, deterioration of clinical condition and increased impairment or further impairment of lung function during the period of exacerbation (6).

Epidemiology

COPD is primarily a disease of the adults. There are wide variations in the prevalence of COPD across countries. This variation in the estimated prevalence is due to the method of diagnosis (questionnaire or pulmonary function based) and classification of COPD. It has been observed that the prevalence estimates were higher when COPD has been diagnosed by spirometry compared with methods using symptoms (7). COPD is common in older population and is highly prevalent in those aged more than 75 years. The global prevalence of physiologically defined chronic obstructive pulmonary disease (GOLD stage 2 or more) in adults aged > or =40 years is approximately 9-10% (8). It has been observed that there is

significant heterogeneity of clinical presentation and disease progression within COPD. These heterogeneities can be related to clinical manifestations, physiological changes, imaging characteristics, COPD exacerbations, systemic inflammation, comorbidities, response to treatment, decline in lung function and survival. It has been proposed that COPD phenotypes could be associated with clinically meaningful outcomes which may lead to focused therapy in COPD. Future research in COPD phenotypes may lead to better understand this complex disease for fine tuning of management (9).

One of the earliest studies to know the prevalence of COPD in India was carried out by Wig et al in 1964 in rural Delhi. The prevalence was 3.36% in males and 2.54% in females in this study (10). Viswanathan in 1966 reported that the prevalence is 2.12% in males and 1.33% in females in Patna (11). Jindal in 1993 reported that the prevalence was 6.2% in men and 3.9% in women in rural area, and 4.2% and 1.6% in urban area (12). All these studies were from North India and studies from South India were few. Thiruvengadam et al in 1977 from Madras (South India) reported the prevalence of COPD of 1.9% in males and 1.2% in females (13). However, Ray et al in 1995 from South India found that the prevalence is 4.08% in males and 2.55% in females (14). All these studies were questionnaire or interview based studies except the study by Jindal et al in 1993 which used peak expiratory flow in addition to a questionnaire. Recently, the Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARECH) involving a total of 85105 men 84470 women from 12 urban and 11 rural sites were reported (15). Though the INSEARCH study was also a questionnaire based one, a validated questionnaire was used in this study. This study had shown that the overall prevalence of chronic bronchitis in adults > 35 years was 3.49% (ranging 1.1% in Mumbai to 10% in Trivandrum). Further studies are required to understand the reasons for the low and high prevalence of COPD in different parts of India. Thus there are wide variations in the prevalence of COPD in Indian subcontinent. Based on this study,

the national burden of chronic bronchitis was estimated at 14.84 million. In a prevalence study from rural India using both questionnaire and post-bronchodilator spirometry, it was observed that there was 2-fold higher prevalence of COPD (16). A structured comprehensive literature review to quantify the burden of COPD in eleven developed countries has revealed that mortality increased in the last 30–40 years. Recently it has been observed that mortality decreased in men in several countries, but it is increasing or stabilizing in women (17). The prevalence of COPD in India based on the various published studies is given in Table 1 (18).

Table 1

Prevalence of COPD in India from published studies

Authors	Population	Method of Study	COPD prevalence %	
			Male	Female
Wig et al (1964)	Rural, Delhi	Interview	3.4	2.5
Viswanathan (1996)	Patna	Questionnaire	2.1	1.3
Sikand et al (1966)	Delhi	Miniature X-ray, Symptom enquiry	7.0	4.3
Bhattacharya et al (1975)	Rural, UP	Questionnaire	6.7	4.5
Viswanathan & Singh (1977)	Delhi	Questionnaire	8.0	4.3
Thiruvengadam (1977)	Madras	Interview	1.9	1.2
Charan (1977)	Rural, Punjab	Questionnaire	2.3	1.6
Radha et al (1977)	New Delhi	Questionnaire and PEF	8.1	4.6
Malik (1986)	Chandigarh	Questionnaire and PEF	5.5	2.9
Jindal (1993)	Punjab	Questionnaire and PEF	5.0	2.7
Ray et al (1995)	Tamil Nadu	Questionnaire	4.1	2.5
Jindal et al (2006)	Multicentric	Validated structured questionnaire	5.0	3.2
Jindal et al (2012)	Multicentric (INSEARCH study)	Validated structured questionnaire	4.3	2.7

[(Adapted with modifications from Indian J Med Res 2006; 124: 619-630 with permission) (Reference 18)]

Risk Factors

Tobacco smoke

Tobacco smoke, which is a mixture of over 4000 chemical constituents, is the most important cause. Amongst males, tobacco smoking is responsible for more than 80% of patients (19). Both cigarette and 'bidi' smoking are equally responsible (20). Pipe and 'hookah' smoking are also important in causing COPD. There is no reliable information on smoking associated COPD in women in whom the overall prevalence of smoking is very low. Besides active tobacco smoking, exposure to smoking from others i.e. passive smoking, better termed as Environmental Tobacco Smoke (ETS) exposure, may also play a contributory role especially in nonsmoker individuals including women (21, 22).

Solid fuel combustion

The smoke from combustion of solid fuels such as dried dung cakes, wood and crop residue used for cooking and heating, especially in rural areas , semi urban and slum areas, is an important cause of indoor air pollution in India. It is responsible for a large number of COPD in the rural inhabitants in general and women in particular (22, 23).

Air pollution

Exhausts from vehicles and occupational exposure to dusts and fumes constitute important sources of air pollution. Chronic exposure to polluted air is an important cause of chronic respiratory diseases such as the COPD (24-26).

Other risk factors

Other risk factors associated with COPD and reduced FEV1 are previous tuberculosis, maternal smoking, child-hood asthma and childhood respiratory infections (27).

Pathogenesis and Pathophysiology

Although cigarette smoking is the most important cause of COPD, only 10-15% of long-term smokers develop clinically significant COPD, and approximately half will never develop any

symptomatic physiological deficit. Presumably the inflammation caused by tobacco smoke interacts with other host or environmental factors to produce rapid decline in lung function that results in COPD. It is believed that inhaled noxious particles and gases result in lung inflammation, induce tissue destruction, and impair defense mechanisms that serve to limit or repair this damage. This damage leads to the mucous hypersecretion, airway narrowing and fibrosis, destruction of lung parenchyma and vascular changes. In turn, these pathological changes lead to airflow limitation and other physiological abnormalities characteristic of COPD. It is characterized by an increase in neutrophils, macrophages and CD8+ T-lymphocytes in various parts of the lung. These activated inflammatory cells release a variety of chemical mediators, many of which (e.g. leukotreine B4, interleukin-8, and tumour necrosis factor-alpha) are capable of damaging lung structures and/or sustaining neutrophilic inflammation. In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD are an imbalance of proteinases and antiproteinases in the lung, and oxidative stress (28). Although both these processes may themselves result from ongoing inflammation, they can also arise from genetic (e.g. alpha-1 antitrypsin deficiency) or environmental (e.g. oxidant compounds in cigarette smoke) factors.

The peripheral airways are the major site of airways obstruction in patients with COPD and this is the earliest abnormality that is detectable on pulmonary function testing. The structural changes in the airway wall, as well as airway edema and mucus hypersecretion contribute to airway narrowing. The irreversible component of airflow limitation is primarily due to remodeling of the smaller airways; lung parenchymal destruction may also play a role. In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnea (29). Ventilation-perfusion mismatch is the dominant mechanism of

hypoxemia and hypercapnea in COPD and hypercapnea may also result from central hypoventilation.

Diagnosis of COPD

Suspecting COPD

COPD can be suspected in most patients on the basis of symptoms and signs (30). Alternate diagnosis such as bronchial asthma, pulmonary tuberculosis, bronchiectasis, malignancies and other chronic lung diseases may require exclusion. Investigations would be required to confirm the diagnosis.

Clinical history

Diagnosis is considered in any individual who presents with characteristic symptoms and presence of one or more risk factors. The important clinical indicators are as follows:

1. Chronic cough: Present on most days for at least 3 months in a year for 2 or more consecutive years (31). Cough may be either present throughout the day or only intermittently. Cough is sometimes nocturnal in nature.
2. Chronic sputum production: Cough may or may not be associated with production of mucoid or mucopurulent sputum. Both cough and sputum productions are characteristically more in the early morning, on waking up.
3. Breathlessness (dyspnoea): Dyspnoea may not be present initially, but develops later in the course. It is progressive over the time. Dyspnoea is worse on exercise and during acute exacerbations.
4. Acute exacerbations: There are repeated episodes of acute bronchitis causing worsening of symptoms. Most patients would seek medical help only during these episodes of worsening.
5. Risk factors: History of tobacco smoking is present in most male patients. Nonsmoker patients (especially women) are significantly exposed to other risk factors such as the combustion of solid fuels or occupational exposures to dusts and fumes.

Physical examination

Though physical examination including recording of blood pressure is an important component of clinical assessment, it is rarely diagnostic in COPD. It is essential to record the height and weight of COPD patients to calculate the body mass index and also for pulmonary function measurements. Physical signs of airflow limitation are rarely present until significant impairment of lung function has occurred. However, certain findings on clinical examination point towards the diagnosis of COPD (32-34).

The chest examination may reveal signs of emphysema such as the barrel shaped chest (increased antero-posterior diameter, more horizontally set ribs, prominent sternal angle and wide subcostal angle). Due to the elevation of sternum, the distance between the suprasternal notch and the cricoid cartilage is reduced from the normal 3-4 finger breadths. The patient may use accessory muscles of respiration. Chest percussion will reveal findings of hyperinflation with obliteration of cardiac dullness and downward displaced upper border of liver dullness. Elsewhere, the note will be hyperresonant. Breath sounds will have a prolonged expiratory phase with a uniformly diminished intensity. Fine inspiratory crepitations and rhonchi are commonly heard. Forced expiratory time (FET) will be prolonged to more than 6 seconds and patient may have pursed lip breathing (35). The physical findings may change in the presence of complications. Blood gas estimation may show hypoxemia and hyper capnea. The important symptoms and signs of hypoxemia are restlessness, confusion, palpitation, agitation, tremor, cyanosis, tachycardia, cardiac arrhythmias, lethargy and coma. The symptoms and signs of hypercapnea include headache, drowsiness/sleepiness, flushed skin, dizziness, tachypnea, flapping tremor, hypertension, tachycardia, extra systoles, muscle twitches, convulsions, disorientation and unconsciousness. Pulmonary hypertension (PH) is an important complication of COPD. Dyspnea on exertion, fatigue and rapid exhaustion are the typical complaints of PH especially in the early stages. Dyspnea in COPD is the consequence of airflow

limitation and pulmonary hyperinflation rather than pulmonary hypertension. Symptoms of overt right heart failure are seen in advanced stages of the disease manifesting as dyspnea at rest and fluid retention. Physical findings in right heart failure include left parasternal heave, a prominent pulmonary component of S2, though heart sounds may be muffled in COPD due to hyperinflation of the lungs. A systolic murmur can be heard if tricuspid regurgitation is present. Other findings in right heart failure are extended neck veins, leg edema, ascites and hepatomegaly. Electrocardiography may show evidence of right ventricular hypertrophy; however normal ECG does not exclude the presence of pulmonary hypertension. Doppler echocardiography is the best method for non-invasive diagnosis of PH. The maximal velocity of the tricuspid regurgitation jet allows the calculation of the right ventricular- to- right atrial gradient.

Differential diagnosis

Important differential diagnosis of COPD is listed in Table 2. Asthma is generally excluded on the basis of history. It is usually present from childhood and is characterized by episodes of breathlessness and wheezing with asymptomatic periods in between. Rhonchi are more prominent and extensive on physical examination. More importantly, there is greater variability and reversibility of symptoms, physical signs and tests of airway obstruction in asthma than COPD.

Table 2

COPD: Differential Diagnosis

1. Bronchial asthma
2. Congestive heart failure
3. Bronchieactasis
4. Pulmonary tuberculosis
5. Lung cancer
6. Interstitial lung disease
7. Obliterative bronchiolitis
8. Diffuse panbronchiolitis

Diseases such as tuberculosis and bronchiectasis are common causes of chronic cough in this country. Bronchiectasis and tuberculosis can co-exist with COPD. Tobacco smoking predisposes to COPD, tuberculosis and lung cancer. They are usually not confused with COPD. Physical findings of fibrocavitary disease support a diagnosis of tuberculosis. Sputum is purulent and greater in amount in patients with bronchiectasis. Coarse crepitations and finger clubbing are generally present in bronchiectasis. Any chronic lung disease can occasionally pose a problem in differential diagnosis. Whenever, there is confusion, investigations will help.

Complications

i. Respiratory failure: Chronic respiratory failure results from disease progression. It is suspected from the presence of tachypnea, cyanosis, flapping tremors, and altered sensorium.

ii. Acute on chronic respiratory failure

iii. Acute exacerbations

iv. Recurrent lower respiratory tract infections (viral and bacterial).

v. Pneumothorax.

vi. Chronic cor pulmonale: Almost all cases of COPD will progress to chronic cor pulmonale in due course of time. It is detected from the presence of signs suggestive of pulmonary hypertension and right ventricular enlargement and/or failure, such as a loud second heart sound, parasternal heave and raised jugular venous pressure (JVP). Prognosis is not good once congestive cardiac failure develops in these patients

Investigations

Investigations are required for exclusion of an alternate diagnosis, confirmation of diagnosis of COPD, assessment of severity of disease and diagnosis of complications. Chest radiograph is helpful to rule out pneumonia, tuberculosis, lung

cancer, pneumothorax, pulmonary hypertension, and cardiomegaly. Other investigations that are required for management are hemogram, blood sugar estimation, 12-lead electrocardiogram, pulse oximetry for O2 saturation, arterial blood gas analysis, hs-C-reactive protein (CRP) to monitor disease activity and 6-minute walk test. Metabolic syndrome has been found to be associated with COPD (36). The metabolic syndrome can be defined as per the criteria laid down by the National Cholesterol Education Program's Adult Treatment Panel III criteria which are as follows: triglycerides >150 mg/dl, HDL Cholesterol <40 mg/dl in men (<50 mg/dl in women), blood pressure >130/85 mm Hg, fasting glucose >110 mg/dl and abdominal obesity defined as waist circumference >102 cm in men (>88 cm in women) (37). However, the World Health Organization guidelines for South Asians define abdominal obesity when waist circumference >90 cm for men and >80 cm for women (38). Since osteopenia and osteoporosis are frequently seen in COPD, bone densitometry scans (as DEXA scans) can be used to diagnose osteoporosis and to assess the risk of osteoporosis developing. A DEXA bone scan can also help detect osteopenia. Evaluation of pulmonary artery pressure by Doppler echocardiography (dependent on tricuspid valve regurgitation jet velocity) may also be required in some patients.

Excluding alternate diagnosis

It is especially important to exclude tuberculosis in all patients having chronic cough of more than two weeks. Examine sputum smears for acid-fast bacilli (AFB), at least twice. Chest radiograph will help to identify alternate diseases such as fibrocavitary tuberculosis, bronchiectasis, and lung tumors and to detect complications such as chronic cor pulmonale, pneumothorax or bronchopneumonia. High Resolution Computed Tomography (HRCT) may help ruling out bullae, infection especially tuberculosis (tree-in-bud appearance) and lung cancer. Additional tests such as the spirometry may be carried out where physician feels the diagnosis of asthma is under consideration. Bronchodilator reversibility testing is useful to help rule out a

diagnosis of asthma and to establish patient's best attainable lung function.

Confirmation of the diagnosis

Spirometry is the most reproducible and objective measurement of airflow limitation. Spirometry is used to measure the forced vital capacity (FVC), i.e. maximal volume of air forcibly exhaled from the point of maximal inhalation; the volume of air exhaled during the first second of this maneuver (FEV1), and the ratio of these two measurements (FEV1/FVC). The presence of a postbronchodilator FEV1<80% of the predicted value in combination with a FEV1/FVC <70% confirms the presence of airflow limitation that is not fully reversible. Predicted values of different spirometric parameters are available as nomograms for Indian subjects.

Assessment of COPD

The assessment of COPD is performed to determine the severity of the disease, its impact on patient's health status and the risk of future events (exacerbations, hospital admissions or death) in order to guide therapy. The COPD assessment is done with the following aspects (1):

a. Current level of patient's symptoms
b. Severity of the spirometric abnormality
c. Exacerbation risk
d. Presence of comorbidities

Assessment of symptoms

GOLD guidelines recommend Modified British Medical Research Council (mMRC) questionnaire (Table 3) or the COPD Assessment Test (CAT) for the assessment of symptoms (Table 4). The CAT is an 8-item unidimensional measure of health status impairment in COPD. The score ranges from 0-40 (> 10 is abnormal) and the format of the test are available at http://www.catestonline.org.

Table 3

The modified Medical Research Council (mMRC) Dyspnoea Scale:

Grade Degree of breathlessness related to activities

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

Table 4

COPD Assessment Test (CAT)

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.

Example: I am very happy | 0 | X | 2 | 3 | 4 | 5 | I am very sad

			SCORE
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 hill Or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up 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	

Less symptoms: CAT score <10; More Symptoms: CAT score ≥10

Assessment of airflow limitation

The spirometric assessment of severity of airflow limitation is given in Table 5. Spirometric evaluation is to be done after administration of inhaled short-acting bronchodilator. Based on the results of spirometry, COPD is categorized into four stages: mild, moderate, severe and very severe.

Table 5

Classification of severity of airflow limitation (Based on Post-bronchodilator FEV1)

In patients with FEV1/FVC < 70:		
GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	FEV1predicted <80% and ≥ 50%
GOLD 3	Severe	FEV1predicted <50% and ≥30%
GOLD 4	Very Severe	FEV1 predicted <30%

Assessment of exacerbation risk

An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication. The best predictor of having frequent exacerbations (2 or more per year) is a history of previous treated events and the risk of exacerbation also increases as airflow limitation worsens. Up to 20% of GOLD 2 patients may experience frequent exacerbations requiring treatment with antibiotics and/or with corticosteroids. However, the risk of exacerbations significantly increases in GOLD 3 and GOLD 4 patients.

Assessment of comorbidities

Co morbidities associated with COPD are cardiovascular disorders (coronary artery disease and chronic heart failure), hypertension, metabolic diseases (diabetes mellitus, metabolic syndrome and obesity), bone disease (osteoporosis and osteopenia), stroke, lung cancer, cachexia, skeletal muscle weakness, anaemia, depression and cognitive decline.

Comorbidities can occur in all patients with mild, moderate and severe airflow limitation. Patients with COPD should be assessed for comorbidities. The diagnosis, assessment of severity and treatment of these comorbidities are same as for the similar conditions in other situations.

Combined COPD assessment

A combined assessment to understand the impact of COPD on individual patient is done by the combination of symptomatic assessment with the spirometric classification and/or the risk of exacerbations (Table 6). The assessment of symptoms based on mMRC questionnaire or CAT scale indicate the level of symptoms. A high level of symptom is indicated when the mMRC grade is >2 or the CAT score is >10. Only one scale either mMRC grade or CAT scale is sufficient to assess the symptoms, preferring the CAT scale. Exacerbation risk can be assessed based either on the GOLD spirometric classification or on the individual patient's history of exacerbations. High risk individuals are those in the GOLD 3 or 4 categories or those with two or more exacerbations in the preceding year. While assessing the risk if there is any discrepancy between the risk assessed by spiromretric classification and by exacerbation history, the highest risk according to GOLD grade or exacerbation history should be used.

Table 6
Combined Assessment of COPD

Patient Group	Characteristic	Spirometric Classification	Exacerbation per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	**≤ 1**	**≥ 2**	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

mMRC=Modified Medical Research Council dyspnoea scale;
CAT=COPD Assessment Test
[Adapted from GOLD Guidelines (Reference 1)]

The patient groups based on combined assessment are as follows (1):

- **Patient Group A** (Low risk, less symptoms): GOLD 1 or 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year and mMRC grade 0-1 or CAT score <10
- **Patient Group B** (Low risk, more symptoms): GOLD 1 or 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year and mMRC grade >2 or CAT score >10
- **Patient Group C** (High risk, less symptoms): GOLD 3 or 4 (severe or very severe airflow limitation) and/or > 2 exacerbation per year and mMRC grade 0-1 or CAT score <10
- **Patient Group D** (High risk, more symptoms): GOLD 3 or 4 (severe or very severe airflow limitation) and/or > 2 exacerbation per year and mMRC grade > 2 or CAT score >10

Pharmacologic agents

The pharmacologic agents that are currently available for treatment of COPD are listed in Tables 7 & 8.

Bronchodilators

Inhaled bronchodilators are the main pharmacological agents that improve symptoms, decrease exacerbations and improve quality of life in COPD (39). Bronchodilators can cause only a small (<10 percent) increase in FEV1 in patients with COPD. Though there is only a small improvement in spirometric measurements, bronchodilators may improve symptoms especially dyspnea by reducing hyperinflation (40, 41).

Inhaled bronchodilators can be either β2-adrenergic–receptor agonists or cholinergic receptor antagonists. B2-adrenergic–receptor agonists can be short-acting (e.g., salbutamol) or long-acting (e.g., formoterol fumarate and salmeterol xinafoate). Similarly, cholinergic receptor antagonists can be short-acting (e.g., ipratropium bromide) or long-acting (e.g., tiotropium bromide). The duration of action of inhaled short-acting β2-

agonists is 4 to 6 hours and that of short-acting inhaled anticholinergics lasts up to 8 hours. The duration of action of inhaled long-acting β2-agonists is 12 hours or more and the action of inhaled long-acting anticholinergics lasts more than 24 hours. The adverse effects of inhaled short-acting β2-agonists include sinus tachycardia, somatic tremor and hypokalemia. The important adverse effects of inhaled anticholinergics are dry mouth and occasional prostatic symptoms.

Table 7
COPD Medications: Beta$_2$-agonists and Anticholinergics

Drug	Inhaler (MDI/DPI) (µg)	Solution for nebulizer (mg/ml)	Oral	Duration of action (Hours)
Beta$_2$-agonists				
Short-acting				
Salbutamol	100, 200	5	2-4 mg (Tablet)	4-6
Levo-salbutamol	100, 200	-	1, 2 mg (Tablet)	4-6
Terbutaline	250, 500	-	2.5, 5 mg (Tablet)	4-6
Long-acting				
Formoterol	4.5-12	0.01	-	12
Salmeterol	25-50	-	-	12
Indacaterol	75-300	-	-	24
Anticholinergics				
Short-acting				
Ipratropium bromide	20, 40	0.25-0.5	-	6-8
Long-acting				
Tiotropium	18	-	-	24
Glycopyrronium bromide	50 once daily	-	-	24
Aclidinium bromide	200-400 twice daily	-	-	24

MDI=Metered dose inhaler; DPI=Dry powder inhaler
[Adapted from GOLD Guidelines with modification (Reference no 1)]

Patients with mild airflow limitation can be treated with a single short-acting inhaled bronchodilator, either with salbutamol or with ipratropium. Both drugs are equally effective to relieve symptoms and to improve airflow. Patients with moderate airflow limitation require treatment with either a long-acting β2-adrenergic–receptor agonist (formoterol or salmeterol) or long-acting cholinergic receptor antagonist (tiotropium). A short-acting bronchodilator, not a long-acting inhaled bronchodilator, is the appropriate treatment for relief of acute symptoms. Combination of short-acting bronchodilators, a β2-adrenergic–receptor agonist and a cholinergic receptor antagonist (e.g., salbutamol and ipratropium) has been shown to have a greater bronchodilation than either drug used alone (42). Combining a long-acting β2-adrenergic–receptor agonist (e.g., salmeterol) with a short-acting cholinergic receptor antagonist (e.g., ipratropium) has shown to improve airways obstruction (43). In a randomized, double-blind trial in patients with COPD, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study has demonstrated that treatment with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV1 (44).

Indacaterol is an "ultra" long-acting β2-adrenergic agonist that is distinguished by once-daily dosing. The duration of action of inhaled indacaterol is > 24 hours compared to twice-daily dosing of other long-acting β2-adrenergic agonists such as salmeterol and formoterol that have a bronchodilator action of ~12 hours. Indacaterol has a faster onset and produces sustained bronchodilation. It relaxes bronchial smooth muscles to reduce the symptoms of COPD and is well tolerated. Indacaterol with a dosage of 75-300 μg per day is intended for the long-term maintenance treatment of COPD (45).

Glycopyrronium is a novel long-acting anticholinergic and is a synthetic quaternary ammonium compound acting as a competitive antagonist by binding to muscarinic receptors in bronchial smooth muscle. It is currently in development for the

treatment of COPD. The effect of glycopyrronium 50 µg is similar to that of tiotropium in reducing dyspnoea and the risk of exacerbations, as well as improving lung function, exercise tolerance, and health status in patients with COPD (46, 47).

Aclidinium bromide is a new long-acting muscarinic antagonist found to be useful in the treatment of COPD (48). Aclidinium bromide given in a dosage of 200 µg and 400 µg had shown significant improvements in trough FEV1 (49). The most common adverse events were coughing and dysphagia and were mild (50).The FDA has approved aclidinium dry powder inhalation 200 to 400 µg twice daily in the treatment of moderate to severe COPD (51).

Corticosteroids

The fact that COPD is associated with chronic inflammation is the rational for the use of inhaled corticosteroids in COPD. There is no evidence that inhaled or oral steroids suppress inflammation in COPD (52). This is in contrast to the beneficial effects of inhaled steroids in the treatment of chronic asthma. However, there are evidences that inhaled and systemic steroids have beneficial effects in acute exacerbations of COPD (53, 54). Inhaled steroids have been shown to improve symptoms, lung function, quality of life and to reduce the frequency of exacerbations in COPD patients with FEV1 <50% predicted (55-57). Adverse effects of inhaled corticosteroids are oral candidiasis, hoarseness of voice and skin bruising. Long-term treatment with inhaled corticosteroids has been shown to be associated with an increased risk of pneumonia (55, 58, 59). Oral corticosteroids are not recommended as long-term monotherapy in COPD patients and have numerous side effects.

Table 8
COPD Medications: Corticosteroids, Methylxanthines and Phosphodiesterase-4 inhibitors

Drug	Inhaler (MDI/DPI) (µg/dose)	Solution for Nebulizer (mg/ml)	Oral	Duration of action (Hours)
Inhaled corticosteroids				
Beclomethasone	50-400	0.2-0.4	-	-
Budesonide	100, 200, 400	0.2,0.25, 0.5	-	-
Fluticasone	50, 250,500	-	-	-
Systemic corticosteroids				
Prednisolone	-	-	5-60 mg (Tablet)	-
Methyl-prednisolone	-	-	4, 8, 16 (Tablet)	-
Phosphodiesterase inhibitors				
Aminophylline	-	-	200-600 mg (Tablet)	Variable, up to 24 hours
Theophylline (SR)	-	-	100-600 mg (Tablet)	Variable, up to 24 hours
Roflumilast			500 µg (Tablet)	24

MDI=Metered dose inhaler; DPI=Dry powder inhaler
[Adapted from GOLD Guidelines with modification (Reference 1)]

Phosphodiesterase inhibitors

Theophylline, a weak oral bronchodilator is a non-selective phosphodiesterase inhibitor and has some anti-inflammatory properties. However, its narrow therapeutic index is a concern requiring frequent monitoring of blood levels, adverse drug reactions and drug interactions. COPD patients, if continued to be symptomatic despite combined inhaled bronchodilator treatment, can be prescribed theophylline and it provides additional improvement in lung function with few exacerbations (60). Important adverse effects of theophylline are atrial and ventricular arrhythmias, convulsions, headache, insomnia and nausea. Theophylline has also interactions with many commonly used medications.

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor and it reduces inflammation by inhibiting the breaking down of intracellular cyclic AMP. It is administered orally with a once a day schedule (500 μg) and it reduces acute exacerbations in patients with severe COPD (61). Roflumilast used concomitantly with long-acting β2 agonists has been shown to reduce exacerbations in COPD (62, 63). Adverse reactions with roflumilast include nausea, diarrhoea, sleep disturbances, headache, and weight loss.

Treatment

i. Pharmacologic treatment

The management of COPD in MIC exposed individuals and others affected in the region is recommended on same principles as for COPD elsewhere. The drug treatment of stable patients with COPD is given in Table 9.

Table 9

Pharmacologic Therapy for Stable COPD

Patient Group	First Choice	Second Choice	Alternative Choices*
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA	Theophylline
B	LAMA *or* LABA	LAMA and LABA	SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA	PDE-4 Inhib. SABA *and/or* SAMA Theophylline
D	ICS + LABA *or* LAMA	ICS and LAMA *or* ICS + LABA and LAMA *or* ICS+LABA and PDE-4 Inh. *or* LAMA and LABA *or* LAMA and PDE-4 Inh.	Carbocysteine SABA *and/or* SAMA Theophylline

SABA=short-acting $beta_2$-agonist;

SAMA=short-acting muscarinic antagonist;

LABA=Long-acting $beta_2$-agonist;

LAMA= long-acting muscarinic antagonist;

ICS=inhaled corticosteroid;

PDE-4 inh.=Phosphodiesterase-4 inhibitor; prn=as needed

* Medications in this column can be used alone or in combination with other options in other first and second choice columns

[Adapted from GOLD Guideline (Reference No. 1)]

Group A patients (low risk, less symptoms) are treated with a short-acting bronchodilator (either short-acting anticholinergic prn or short-acting β2-agonist prn) as the first choice. The second choice is a combination of short-acting bronchodilators (short-acting anticholinergic and short-acting β2-agonist) or a long-acting bronchodilator (either long-acting anticholinergic or long-acting β2-agonist). Theophylline is an alternative choice.

Group B patients (low risk, more symptoms) can be treated with a long-acting bronchodilator (either long-acting anticholinergic or long-acting β2-agonist). Patients with severe breathlessness in Group B can be treated with a combination of long-acting anticholinergic and long-acting β2-agonist. Alternate choice is short-acting bronchodilators (short-acting anticholinergic and/or short-acting β2-agonist) and theophylline.

Group C patients (high risk, less symptoms) require treatment with a fixed combination of inhaled corticosteroids and long-acting β2-agonist or long-acting anticholinergic. The second choice of treatment is with a combination of long-acting anticholinergic and long-acting β2-agonist. Alternate treatment is with short-acting bronchodilators (short-acting anticholinergic and/or short-acting β2-agonist) and theophylline. A phosphodiesterase-4 inhibitor can also be added.

Group D patients (high risk, more symptoms) can be treated with a fixed combination of inhaled corticosteroids and long-acting β2-agonist or long-acting anticholinergic. Different drug combinations are recommended as second choice for treatment of Group D patients. The combinations are inhaled corticosteroid and long-acting anticholinergic or inhaled corticosteroid + long-acting β2-agonist and long-acting anticholinergic or inhaled corticosteroid + long-acting β2-agonist and phosphodiesterase-4 inhibitor or long-acting β2-agonist and long-acting anticholinergic or long-acting anticholinergic and phosphodiesterase-4 inhibitor. Alternate treatment is with short-acting bronchodilators (short-acting anticholinergic and/or short-acting β2-agonist) and theophylline and carbocysteine.

ii. Oxygen Therapy

Patients with COPD with respiratory failure and with severe resting hypoxemia on long-term oxygen therapy (LTOT) (>15 hours per day) have been found to have increased survival. LTOT is prescribed to COPD patients with PaO2 < 7.3 kPa (55 mm Hg) or SaO2 < 88% with or without hypercapnia confirmed twice over a three-week period or PaO2 between 7.3 kPa (55 mm Hg) and 8 kPa (60 mm Hg) with evidence of pulmonary

Group B patients (low risk, more symptoms) can be treated with a long-acting bronchodilator (either long-acting anticholinergic or long-acting β2-agonist). Patients with severe breathlessness in Group B can be treated with a combination of long-acting anticholinergic and long-acting β2-agonist. Alternate choice is short-acting bronchodilators (short-acting anticholinergic and/or short-acting β2-agonist) and theophylline.

Group C patients (high risk, less symptoms) require treatment with a fixed combination of inhaled corticosteroids and long-acting β2-agonist or long-acting anticholinergic. The second choice of treatment is with a combination of long-acting anticholinergic and long-acting β2-agonist. Alternate treatment is with short-acting bronchodilators (short-acting anticholinergic and/or short-acting β2-agonist) and theophylline. A phosphodiesterase-4 inhibitor can also be added.

Group D patients (high risk, more symptoms) can be treated with a fixed combination of inhaled corticosteroids and long-acting β2-agonist or long-acting anticholinergic. Different drug combinations are recommended as second choice for treatment of Group D patients. The combinations are inhaled corticosteroid and long-acting anticholinergic or inhaled corticosteroid + long-acting β2-agonist and long-acting anticholinergic or inhaled corticosteroid + long-acting β2-agonist and phosphodiesterase-4 inhibitor or long-acting β2-agonist and long-acting anticholinergic or long-acting anticholinergic and phosphodiesterase-4 inhibitor. Alternate treatment is with short-acting bronchodilators (short-acting anticholinergic and/or short-acting β2-agonist) and theophylline and carbocysteine.

ii. Oxygen Therapy

Patients with COPD with respiratory failure and with severe resting hypoxemia on long-term oxygen therapy (LTOT) (>15 hours per day) have been found to have increased survival. LTOT is prescribed to COPD patients with PaO2 < 7.3 kPa (55 mm Hg) or SaO2 < 88% with or without hypercapnia confirmed twice over a three-week period or PaO2 between 7.3 kPa (55 mm Hg) and 8 kPa (60 mm Hg) with evidence of pulmonary

hypertension, peripheral edema indicating congestive cardiac failure or polycythemia (hematocrit >55) (64, 65). Oxygen is supplied in three forms: as compressed gas, as liquid, or as a concentrated form taken from the air. Oxygen concentrators filter out other gases in the air and store only oxygen. Portable oxygen concentrators are available which is useful for home oxygen therapy. Oxygen concentrators cost less than the other oxygen therapy systems. However, oxygen concentrators require electricity. Portable oxygen concentrators may be made available to gas victims who require home oxygen therapy free of cost. Some patients with COPD and carbon dioxide retention may require non-invasive ventilation using Bi-level Positive Airway Pressure (BiPAP). This device can also be used in the home for COPD patients with chronic respiratory failure with adequate training of the patient or family members and may be made available to gas victims free of cost.

iii. Exacerbations

The treatment of exacerbations in COPD is with bronchodilators, corticosteroids and antibiotics. Short-acting inhaled β2-agonists or short-acting anticholinergics are the preferred bronchodilator for the treatment of exacerbations (66). Short-acting bronchodilators can be given either by metered-dose inhalers or by nebulizers and there are no differences in FEV1 whether given by metered-dose inhalers or by nebulizers (67). When there is insufficient response to inhaled short-acting bronchodilators, intravenous methylxanthines (theophylline or aminophylline), keeping in mind the adverse effects and drug interactions of methylxanthines (68). Systemic corticosteroids have been found to shorten recovery time and arterial hypoxemia (54). The systemic corticosteroids also reduce the risk of early relapse; treatment failure and length of hospital stay (69). Oral prednisolone 30-40 mg daily is given for 10-14 days. Alternative treatment is with nebulized budesonide. Increase in dyspnea, sputum volume and sputum purulence are the cardinal features of exacerbations in COPD. Antibiotics for 5 to 10 days are prescribed if two of the three cardinal symptoms (increased

purulence of symptoms is one of the symptoms) are observed. The COPD Clinical Research Network undertook a study to determine whether azithromycin decreased the frequency of exacerbations in patients with COPD, as macrolide antibiotics have immunomodulatory, antiinflammatory, and antibacterial effects (70). 1142 COPD patients with a history of prior exacerbation were randomised to receive azithromycin 250 mg daily or a placebo and continued their usual care. The study showed that azithromycin 250 mg daily taken daily for one year, when added to usual treatment in COPD patients, decreased the frequency of exacerbations and improved quality of life. However, azithromycin caused hearing decrements in a small percentage of subjects (71). Supplemental oxygen is required to maintain arterial oxygen saturation 88 to 92%. Ventilatory support either non-invasive mechanical ventilation or mechanical ventilation based on proper indications is required in patients in COPD patients with severe exacerbations admitted to hospitals. Course of disease in stable patients during follow-up can be monitored with 6-minute walk test. Patient education on the use of non-invasive ventilator especially in the home should be an integral component of treatment.

Non-Pharmacologic treatment

i. Smoking cessation

Smoking cessation is the most important step in the treatment of COPD. Smoking cessation has been found to reduce the decline of FEV1 (72). Nicotine replacement treatment with nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet or lozenges has been found to increase long term smoking-abstinence rates. Varenicline and bupropion are pharmacologic agents for the treatment of tobacco addiction. Smoking cessation counselling is also effective to treat tobacco addiction. It has been reported that even a 3 minute counselling to a smoker enable smoking cessation rates of 5 to 10% (73). Patients with COPD who smoke and receive intensive counselling or a combination of intensive counselling and pharmacotherapy had significantly higher abstinence rates (74).

ii. Pulmonary Rehabilitation

Pulmonary rehabilitation is an important component of therapy of COPD. The components of a comprehensive pulmonary rehabilitation programme include exercise training, smoking cessation, nutrition counselling and education. The benefits of pulmonary rehabilitation include improvement in exercise capacity, reduction in the perceived intensity of breathlessness, improvement in health-related quality of life, reduction in the number of hospitalizations and days in the hospital and reduction in anxiety and depression associated with COPD. In an evidence-based review of the literature surrounding treatment strategies for patients with COPD, pulmonary rehabilitation including at least 4 weeks of exercise training lead to clinically and statistically significant improvements in Health Related Quality of Life (HRQOL) in patients with COPD and pulmonary rehabilitation also lead to a clinically and statistically significant improvement in functional exercise capacity (75). In a randomized, double-blind, placebo-controlled trial (tiotropium, n = 47; placebo, n = 44), tiotropium (18 µg) administered to COPD patients participating in 8 weeks of pulmonary rehabilitation (treadmill training three times a week; > 30 min per session), it has been demonstrated that tiotropium in combination with pulmonary rehabilitation produced clinically meaningful improvements in dyspnoea and health status compared to pulmonary rehabilitation alone. Improvements with tiotropium were sustained for 3 months following pulmonary rehabilitation completion (76).

Pulmonary rehabilitation is an important component in the management of MIC exposed individuals presenting with chronic respiratory diseases and with evidence of airflow limitation. As pulmonary rehabilitation is a life-long process, emphasis should be to develop community based pulmonary rehabilitation programmes near the residences of such patients so that continuous rehabilitation and educational programmes can be provided to them. This community based rehabilitation programme should be managed with the help of dedicated

respiratory physiotherapists and councillors. These units should have space for imparting training in rehabilitation and should be equipped with nebulisers, pulse oximeters and blood pressure instruments. This unit can be integrated with a yoga training programme. Facilities to monitor and educate patients with chronic respiratory failure due to COPD for continuous oxygen therapy and home-based non-invasive ventilation should also be developed at these rehabilitation centres. Yoga therapy may also be made an integral part of the pulmonary rehabilitation programme. ICMR can establish a model Pulmonary Rehabilitation facility in one of the severely gas affected areas and other governmental and non-governmental agencies can replicate this in other gas affected areas.

iii. Nutritional support

Patients from the Copenhagen City Heart Study involving 1,218 men and 914 women, aged 21 to 89 year, with airway obstruction defined as an FEV1/FVC ratio < 0.7 were prospectively examined to know whether body mass index (BMI) is an independent predictor of mortality in subjects with COPD. This study has shown that low BMI is an independent risk factor for mortality in subjects with COPD, and that the association is strongest in subjects with severe COPD (77). In a prospective cohort study from Korea, it has been observed that the risk of death from respiratory causes was higher among subjects with a lower BMI (78). Survival analysis studies have shown that body weight has an independent effect on survival in COPD and the negative effect of low body weight can be reversed by appropriate therapy in some of the patients with COPD (79). Chailleux et al had showed that nutritional depletion is an independent risk factor for mortality and hospitalization in patients with COPD receiving LTOT and the best prognosis was observed in overweight and obese patients (80). European Society for Parenteral and Enteral Nutrition (ESPN)) guidelines state that enteral nutrition (EN) in combination with exercise and anabolic pharmacotherapy has the potential to improve nutritional status and function in COPD patients and frequent

small amounts of oral nutritional supplements are preferred in order to avoid postprandial dyspnoea and satiety as well as to improve compliance (81). It has been reported that nutritional supplementation may have a role in the management of COPD when provided as part of an integrated rehabilitation program incorporating a structured exercise component as an anabolic stimulus (82).

Surgical treatment

i. Lung Volume Reduction Surgery

The National Emphysema Treatment Trial is a randomized, multicenter clinical trial that compared lung-volume-reduction surgery (LVRS) with medical treatment. Patients with emphysema who have a low FEV1 and either homogeneous emphysema or a very low carbon monoxide diffusing capacity are at high risk for death after surgery and also are unlikely to benefit from the surgery(83). LVRS has been shown to improve mortality, exercise capacity, and QOL in selected patients with upper lobe emphysema and poor exercise capacity. Patients with non-upper-lobe emphysema and high base-line exercise capacity are poor candidates for lung-volume-reduction surgery, because of increased mortality and negligible functional gain (84). Bilateral LVRS procedures result in greater short-term improvement than unilateral LVRS. Improvement has also been reported in dyspnoea and health status after LVRS and this is better preserved over longer-term follow-up than physiological improvement. It has also been observed that physiological benefits are similar with video-assisted thoracoscopy (VATS) or median sternotomy (MS) techniques (85). It has been reported that LVRS produces superior patient outcomes compared to medical treatment in terms of exercise capacity, lung function, quality of life and long-term (>1 year postoperative) survival especially for patients with upper-lobe-predominant disease and low exercise capacity, but with a much greater cost per person over five years (86).

ii. Lung Transplantation

Lung transplantation is an option in COPD patients who have FEV1 below 25% predicted and/or the paCO2 is > or = 55 mm Hg. Both single- and double-lung transplant have been reported in COPD. The reported survival rates after lung transplantation are approximately 80% 1-year, 50% 5-year, and 35% 10-year. The most important long-term complication after lung transplantation is bronchiolitis obliterans resulting in decreased pulmonary function (84). Despite significant progress over the past 25 years, both short- and long-term outcomes remain significantly inferior for lung recipients relative to other "solid" organs (87).

Immunisation

Vaccinations can prevent some of the infections that cause COPD exacerbations and can be administered to patients with COPD (88). Influenza vaccination reduces lower respiratory tract infections and death in patients with COPD (89). In a study of 177,120 patients with COPD (mean age 65 years) with a mean follow-up of 6.8 years between 1988 and 2006, it had been observed that influenza but not pneumococcal vaccination was associated with a reduced risk of all-cause mortality in COPD (90). Two types of pneumococcal vaccines, polysaccharide and polysaccharide conjugated vaccines, are available. Studies have shown conflicting results with regard to the effectiveness and efficacy of the 23-valent polysaccharide vaccine. Pneumococcal polysaccharide vaccine is useful in COPD patients 65 years and older and in younger patients with significant comorbid conditions such as cardiac disease (91, 92) and these observations are based on expert opinion and not evidence-based. However, conjugate vaccine is found to have superior immunogenicity (93). The pneumococcal polysaccharide conjugate vaccine (PCV) comprises capsular Streptococcus pneumoniae polysaccharide serotypes that are individually conjugated to nontoxic diphtheria protein. Immunization with conjugated vaccines results in the development of T-cell-dependent immune responses, whereas unconjugated vaccines do not lead to booster responses on

revaccination (94). PCV13 has been approved by FDA for immunisation against pneumococcal disease. GOLD guidelines recommend influenza and pneumococcal vaccinations to COPD patient and state that they are more effective in older patients and those with severe disease or cardiac morbidity (1).

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