

# Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint ICS/NCCP (I) recommendations

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## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major public health problem in India. Although several International guidelines for diagnosis and management of COPD are available, yet there are lot of gaps in recognition and management of COPD in India due to vast differences in availability and affordability of healthcare facilities across the country. The Indian Chest Society (ICS) and the National College of Chest Physicians (NCCP) of India have joined hands to come out with these evidence-based guidelines to help the physicians at all levels of healthcare to diagnose and manage COPD in a scientific manner. Besides the International literature, the Indian studies were specifically analyzed to arrive at simple and practical recommendations. The evidence is presented under these five headings: (a) definitions, epidemiology, and disease burden; (b) disease assessment and diagnosis; (c) pharmacologic management of stable COPD; (d) management of acute exacerbations; and (e) nonpharmacologic and preventive measures. The modified grade system was used for classifying the quality of evidence as 1, 2, 3, or usual practice point (UPP). The strength of recommendation was graded as A or B depending upon the level of evidence.

**KEY WORDS:** Asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, guidelines

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### Access this article online

#### Quick Response Code:



#### Website:

www.lungindia.com

#### DOI:

10.4103/0970-2113.116248

## METHODOLOGY

The process of development of guidelines for diagnosis and management of patients of chronic obstructive pulmonary disease (COPD) in India was undertaken as a joint exercise of the two National Pulmonary Associations (Indian Chest Society (ICS) and National College of Chest Physicians (NCCP)), by the Department of Pulmonary

Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh. The committee constituted for this purpose included representation of the two associations, and experts from other institutes and medical colleges including those from disciplines of internal medicine, microbiology, pharmacology, radiodiagnosis, and community medicine.

For development of guidelines, an extensive desk-review was followed by a joint workshop. The review of literature was performed by searching electronic sources (PubMed, EmBase). The major international guidelines available from the Global Initiative for Chronic Obstructive Lung Diseases (GOLD), American Thoracic Society (ATS), and National Institute of Clinical Excellence (NICE) were also reviewed.

The search was conducted under five subgroups: (a) definitions, epidemiology, and disease burden; (b) disease assessment and diagnosis; (c) pharmacologic management of stable COPD; (d) management of acute exacerbations; and (e) nonpharmacologic and preventive measures. Important questions were framed on the basis of discussions on issues with reference to the Indian context. Literature review and discussions in each area were coordinated by group chairs and recorded by rapporteurs. The available evidence as well as the questions were circulated to all the group members before the joint workshop. Discussions for grading of evidence and recommendations were held independently in five parallel group sessions, and thereafter together in the joint meeting of all the groups. Final decisions in the joint group were based on a consensus approach on the majority voting.

The modified grade system was used for classifying the quality of evidence as 1, 2, 3, or usual practice point (UPP) [Table 1].<sup>[1]</sup> The strength of recommendation was graded as A or B depending upon the level of evidence

**Table 1: Classification of level of evidence and grading of recommendation based on the quality of evidence supporting the recommendation**

Classification of level of evidence	
Level 1	High-quality evidence backed by consistent results from well-performed randomized controlled trials, or overwhelming evidence from well-executed observational studies with strong effects
Level 2	Moderate-quality evidence from randomized trials (that suffer from flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or other limitations)
Level 3	Low-quality evidence from observational evidence or from controlled trials with several serious limitations
Useful practice point	Not backed by sufficient evidence; however, a consensus reached by working group, based on clinical experience and expertise
Grading of recommendation based on the quality of evidence	
Grade A	Strong recommendation to do (or not to do) where the benefits clearly outweigh the risk (or vice versa) for most, if not all patients
Grade B	Weaker recommendation where benefits and risk are more closely balanced or are more certain

[Table 1]. Grade A recommendations in the guidelines should be interpreted as “recommended” and the grade B recommendations as “suggested”. While making a recommendation, the issues of practicality, costs, and feasibility in the country at different levels of healthcare was also taken into consideration.<sup>[2]</sup>

The final document was reviewed by all the committee members, as well as by other external experts.

### Synopsis of recommendations

COPD is a common, preventable lung disorder characterized by progressive, poorly reversible airflow limitation often with systemic manifestations, in response to tobacco smoke and/or other harmful inhalational exposures. As of now valid spirometry-based nationwide prevalence data for COPD in India are not available. In most of the critical analyses, validated questionnaire based data has been accepted as reasonable for assessment of prevalence of COPD despite its limitations. COPD poses enormous burden in terms of morbidity and mortality globally and in India. COPD poses a huge economic burden in terms of direct and indirect costs.

### What are the risk factors for COPD?

1. Tobacco smoking is the most well established risk factor for COPD. (1A)
2. Both smokeless and smoking forms of tobacco are associated with serious health hazards, although only smoking tobacco is primarily responsible for COPD. (1A)
3. Bidi and other indigenous forms of tobacco smoking are at least as (or even more) harmful than cigarette smoking. (1A)
4. Low tar or filtered cigarettes are not “less harmful”. (2B)
5. There is no minimum number of cigarettes/bidi per day below which the risk for COPD decreases. (1A)
6. Exposure to environmental tobacco smoke (ETS) is a definitive risk factor for COPD. (1A)
7. Exposure to biomass fuel smoke is a strong risk factor for COPD. (1A)
8. There is limited data on the association of ambient air pollution and COPD, and its causative role in COPD needs further evaluation.
9. There is insufficient evidence to attribute an etiological role of pulmonary tuberculosis in causing COPD.
10. A subgroup of chronic asthma may clinically behave like COPD; whether it is true COPD remains to be established. (UPP)

### When to suspect COPD?

1. A diagnosis of COPD should be considered in persons having chronic symptoms of cough, sputum production, shortness of breath, and/or wheezing, especially among those with prolonged exposure to risk factors for the disease. (1A)
2. A diagnosis of COPD should not be excluded in the absence of physical signs. (2A)
3. Forced expiratory time (FET) of more than six seconds is suggestive of airflow obstruction. (2B)

**What is the role of spirometry in the diagnosis of COPD? Whether fixed ratio or lower limit of normal (LLN) should be used for diagnosis?**

1. Spirometry should be performed in all patients suspected of having COPD. (1A)
2. In the absence of availability of spirometry, patients suspected of having COPD should be referred for spirometric evaluation to a center with the facility. (UPP)
3. A post-bronchodilator forced expiratory volume in first second (FEV<sub>1</sub>)/forced vital capacity (FVC) below the LLN (lower fifth percentile of values from a reference population) should be preferably used as the criterion for diagnosis of airflow obstruction. (1A)
4. However, in the absence of reference equations for LLN, FEV<sub>1</sub>/FVC < 0.7 may be used as the cutoff for defining airflow obstruction. (1A)

**What is the role of reversibility testing in COPD?**

Absence of bronchodilator reversibility does not differentiate COPD from asthma, and its presence does not predict the response to treatment (1A). However, all FEV<sub>1</sub> values should be reported post-bronchodilator.

**What is the role of screening spirometry?**

Spirometry should not be used as a screening tool in asymptomatic individuals to detect airflow obstruction. (2A)

**What is the role of peak expiratory flow in diagnosis and monitoring of COPD?**

PEF should not be routinely used for screening, diagnosis, or monitoring of COPD. (1A)

**How should the severity of COPD be classified?**

1. Classification of severity of the disease should be done for all COPD patients based on the FEV<sub>1</sub> and exacerbation frequency [Table 2]. (1A)
2. Level of patient's disability due to symptoms should be assessed using modified Medical Research Council (mMRC) dyspnea questionnaire or the COPD assessment test (CAT) and recorded at each clinical visit. (1A)

**What is the role of additional investigations in COPD?**

1. All new COPD suspects with cough of more than 2 weeks' duration should undergo sputum smear examination for acid fast bacilli to rule

2. out pulmonary tuberculosis as per the standard practice of Revised National Tuberculosis Control Program (RNTCP). (UPP)
2. Pulse oximetry should be used to screen for hypoxemia in stable disease with FEV<sub>1</sub> < 50% and in the presence of clinical suspicion of hypoxemia. (3A)
3. An arterial blood gas analysis should be done if arterial saturation by pulse oximetry is less than 90%. (2A)
4. Diagnosis of COPD should not be made on the basis of a chest radiograph. (2A)
5. Chest radiograph may be done during the initial evaluation of COPD to look for comorbidities, complications, and alternative diagnoses. (2B)
6. Special investigations like high-resolution computed tomography (HRCT) scan, lung volumes, diffusing capacity for carbon monoxide (DLCO), and exercise testing should be done in situations of diagnostic difficulty or whenever clinically indicated. (2A)
7. 6MWT may be used for monitoring of exercise capacity in COPD. (1A)
8. Testing for alpha-1 antitrypsin deficiency may be done in young patients with lower lobe emphysema. (UPP)

**What is the role of multidimensional assessment tools in COPD?**

Composite scores including BODE (body mass index (BMI), obstruction, dyspnea, exercise capacity) and DOSE (dyspnea, obstruction, smoking, exacerbation) should not be used to assess severity or prognosis in COPD unless they are validated in Indian patients. (2A)

**What are the comorbidities associated with COPD?**

COPD patients should be routinely evaluated and appropriately treated for comorbid conditions. (2A)

**What is the role of inhaled antimuscarinic agents, inhaled beta-agonists, and inhaled corticosteroids in COPD?**

1. Short-acting antimuscarinic agent (SAMA) can be used as rescue medication to relieve patient symptoms. (1A)
2. Long term SAMA monotherapy on regular basis is not recommended. (1A)
3. Long-acting antimuscarinic agents (LAMA) are useful in stable COPD (FEV<sub>1</sub> < 80%) to control symptoms and decrease the risk of exacerbations. (1A)
4. LAMA should be preferred over SAMA. (1A)
5. We suggest close monitoring of patients with coronary artery disease who are treated with LAMA. (UPP)
6. Short-acting beta-agonist (SABA) can be used to relieve symptoms of dyspnea as and when needed. (1A)
7. Long term SABA monotherapy on regular basis is not recommended. (2A)
8. Long-acting beta-agonist (LABA) monotherapy can relieve symptoms and decrease the exacerbation rate in patients with stable COPD (FEV<sub>1</sub> < 80%). (1A)
9. Patients with symptomatic coronary artery disease receiving inhaled beta-agonists should be closely monitored. (UPP)
10. ICS have a beneficial effect in subgroup of COPD patients with FEV<sub>1</sub> < 50%. (1A)

**Table 2: Classification of severity of COPD**

Severity*	Postbronchodilator FEV <sub>1</sub> , % predicted	mMRC grade	Exacerbation frequency <sup>†</sup>	Complications <sup>‡</sup>
Mild	≥80	<2	<2	No
Moderate	50-79	≥2	<2	No
Severe	<50	≥2	≥2	Yes

\*The category with the worst value should be used for severity classification, <sup>†</sup>number of exacerbations in the last year, <sup>‡</sup>complications include respiratory failure (defined by pO<sub>2</sub> < 60 mmHg and/or SpO<sub>2</sub> < 88% and/or pCO<sub>2</sub> > 50 mmHg), cor pulmonale, and secondary polycythemia (hematocrit > 55%); FEV<sub>1</sub>: Forced expiratory volume in first second, mMRC: Modified medical research council questionnaire, COPD: Chronic obstructive pulmonary disease

11. ICS have a beneficial effect in subgroup of COPD patients with frequent exacerbations ( $\geq 2$  exacerbations/year). (1A)
12. The risk-benefit profile favors use of ICS in patients with severe COPD. (1A)
13. LAMA is superior to LABA monotherapy. (1A)
14. ICS monotherapy should not be used. (1A)
15. SABA and SAMA are equally effective when used for COPD. (2A)
16. LAMA plus LABA may be used in patients who continue to have symptoms on monotherapy, except for those with frequent exacerbations. (1A)
17. LABA plus ICS should be preferred over LABA alone in patients with  $FEV_1 < 50\%$  or those having frequent exacerbations. (1A)
18. In patients of severe COPD ( $FEV_1 < 50\%$ ), triple therapy may be used in those who are symptomatic despite single or dual bronchodilator therapy. (1B)
19. There is lack of sufficient data to recommend ICS-LABA or ICS-LAMA combination over LAMA monotherapy.

**What is the role of oral bronchodilators in management of stable COPD?**

1. Oral methylxanthines are not recommended as first line therapy in patients with COPD. (1A)
2. Oral methylxanthines can be used
  - a. As alternative in patients noncompliant with inhalers for any reason. (1B)
  - b. As add-on therapy in patients continuing to have symptoms despite optimum inhaled therapy. (3A)
3. Patients on oral methylxanthines need to be monitored for side effects and drug interactions. (UPP)
4. Roflumilast may be used in frequent exacerbators as an add-on or substitute to ICS. (2B)

**What is the role of mucolytic agents?**

Routine use of mucolytic agents is not recommended in patients with COPD. (2A)

**What should be the Indian strategy for management of COPD?**

The strategy for management of stable COPD is shown in Table 3 below.

**Table 3: Suggested guidelines for treatment of patients of stable COPD**

Category	Initial therapy		Add-on therapy (if patient continues to have symptoms)
	First choice	Alternative choice	
Mild	SABA or SAMA prn	Methyl xanthines	-
Moderate	LAMA	LABA	Methylxanthines to LAMA/ LABA
Severe	ICS plus LABA	LAMA	Methylxanthines to LAMA or ICS plus LABA

SABA (salbutamol or levosalbutamol) or SAMA (ipratropium) are to be used in all patients as a reliever therapy as and when needed; SABA: Short-acting beta-agonist, SAMA: Short-acting antimuscarinic agent, LABA: Long-acting beta-agonist, LAMA: Long-acting antimuscarinic agent, ICS: Inhaled corticosteroids, COPD: Chronic obstructive pulmonary disease

**What is the definition of acute exacerbation of COPD (AECOPD)?**

An exacerbation of COPD is an acute event characterized by sustained worsening of any of the patient's respiratory symptoms (cough, sputum quantity and/or character, dyspnea) that is beyond normal day-to-day variation and leads to a change in medication, and where other causes of acute breathlessness have been clinically excluded.

**How to investigate an exacerbation of COPD?**

1. No investigations apart from pulse oximetry are routinely required in patients with acute exacerbations managed in an outpatient setting. (IIA)
2. In those hospitalized with AECOPD, serum electrolytes, liver and renal function tests, complete blood count, chest radiograph, electrocardiogram, and arterial blood gas analysis (if available) should be performed. (IA)
3. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiotic sensitivity test should be performed. (IIA)

**How to decide the site of management of a patient with COPD exacerbation?**

The decision to admit the patient can be made on the level of severity as shown in Table 4 below while BAP-65 (elevated blood urean nitrogen (BUN), altered mental status, pulse  $> 109$  beats/min, age  $> 65$  years) score may help in deciding patients who need management in an intensive care unit (ICU) [Figure 1].

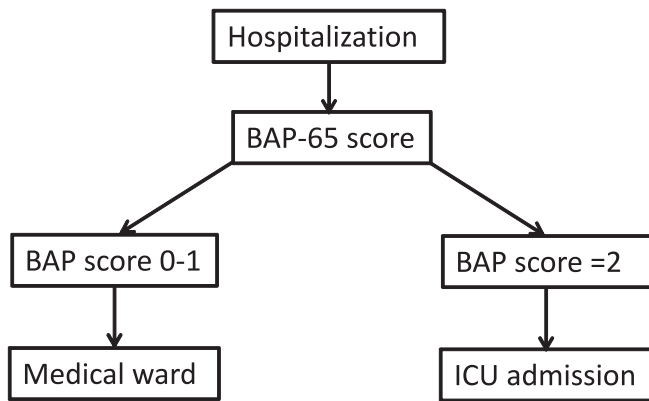
**What is the role of short-acting bronchodilators in AECOPD?**

1. Inhaled route is the preferred route of administering bronchodilators. (IA)
2. Inhaled SABAs should be used as the first-line agent because of quicker onset of action (IIIA). SAMAs are however, in no way inferior to SABAs.

**Table 4: Severity assessment (indications for hospitalization) of exacerbation of COPD\***

Symptoms
Marked reduction in activity of daily living due to dyspnea
Altered sensorium
New onset cyanosis
Signs
Use of accessory respiratory muscles
Paradoxical chest wall movements
Central cyanosis
Systolic blood pressure $< 90$ mmHg
RR $> 30$ /min
Heart rate $> 110$ /min
Asterixis
Altered mental status
Others
Presence of severe comorbid conditions
Lack of social support
Pulse oximetry
$SpO_2 < 90\%$

\*Presence of any of these qualifies a patient with need for admission; The ultimate decision to admit depends on the overall clinical assessment of the physician; COPD: Chronic obstructive pulmonary disease, RR: Respiratory rate



**Figure 1:** Algorithm for deciding place of management after hospitalization. B: Blood urea nitrogen > 24 mg/dL, A: altered mental status, P: pulse rate > 110/min, 65 = age > 65 years, BAP-65 scores: 0 = age < 65 years, 1 = age > 65 years, 2 = one risk factor, 3 = two risk factors, 4 = three risk factors

3. Nebulized salbutamol at a dose of 2.5 mg every 20 min (or salbutamol pressurized metered dose inhaler (pMDI) 100 µg 2-4 puffs every 20 min) for 1 h can be given initially. (IIIA) Further dosing would depend on the clinical response, generally every 4-6 h. (IIIA)
4. If additional bronchodilatation is desired, a combination of ipratropium (500 µg nebulized or 20 µg 2-4 puffs with pMDI) and salbutamol (2.5 mg nebulized or salbutamol pMDI 100 µg 2-4 puffs) every 4-6 h can be used. (IIIA)
5. Nebulizer or pMDIs with spacer are equally effective. (IIA)
6. Nebulization should not be driven by oxygen; patients should receive oxygen separately through nasal cannula, with monitoring of oxygen saturation. (IIA)
7. Intravenous methyl xanthines should not be routinely used. (IA)
8. The use of intravenous or subcutaneous route of administering bronchodilators should be reserved in the most seriously ill mechanically ventilated patient demonstrating inadequate response to inhaled therapy. (IIIB)

#### What is the role of glucocorticoids in AECOPD?

1. Systemic steroids shorten recovery time, improve lung function, oxygenation, reduce length of hospital stay, and are associated with fewer treatment failures. (IA)
2. A short course of oral prednisolone (or equivalent) at a dose of 30-40 mg/day is recommended for managing acute exacerbations. (IIA)
3. The duration of systemic steroid therapy should be 5-10 days. (IIA)
4. Intravenous steroids should be given in patients who are being mechanically ventilated or cannot tolerate oral medication. (UPP)
5. ICS are not routinely recommended in management of AECOPD. (IA)

#### Should antibiotics be used in patients with acute exacerbations of COPD?

1. Antibiotics should be prescribed for all exacerbations of COPD. (IIA)

2. The choice of antibiotics should be guided by local flora and sensitivity pattern. (IIA)
3. Fluoroquinolones should not be used routinely in treating AECOPD. (IA)
4. Patients with AECOPD being managed in the outpatient setting may be treated with first line antibiotics. (IIA)
5. Hospitalized patients or those requiring mechanical ventilation (noninvasive/invasive) should be treated with second line drugs. (IIA)
6. The duration of therapy should be 5-7 days. (IIA)

#### What is the role of procalcitonin in deciding for antibiotic therapy?

1. Biomarkers do not have any role in management of acute exacerbation of COPD. (IIA)
2. Procalcitonin should not be used routinely in guiding antibiotic usage in COPD. (IIA)

#### When should oxygen be prescribed, and at what dose?

1. Oxygen should be prescribed to hypoxemic patients with a target SpO<sub>2</sub> between 88-92%. (IA)
2. Oxygen should be delivered preferably by a Venturi mask, and by nasal cannula upon recovery. (IIA)
3. Arterial blood gas monitoring is recommended in patients receiving oxygen therapy, wherever available. (IIA)

#### What is the indication of noninvasive ventilation during exacerbation of COPD?

1. NIV should be used early in the management of respiratory failure due to AECOPD. (IA)
2. NIV can be used even in settings where arterial blood gas monitoring is not routinely available. (UPP)

#### Should smoking cessation be advised? What are the methods of smoking cessation?

1. A smoking history, including pack years or smoking index (number of bidis/cigarettes smoked per day multiplied by number of years smoked; mild, moderate, and heavy smokers are defined as having a smoking index of < 100, 100-300, and > 300, respectively) should be documented for all patients with COPD. (UPP)
2. All COPD patients, regardless of age, should be encouraged to stop smoking, and offered help to do so, at every opportunity. (1A)
3. Nicotine replacement therapies, varenicline or bupropion, combined with an appropriate support program should be offered to people who are planning to stop smoking. (1A)

#### What is the role of health education in COPD?

1. Health education is an integral component of a COPD management program. Special importance should be given to inhaler technique, which should be demonstrated to the patient and accompanying attendants and reinforced at every visit. This is particularly true for elderly patients. (UPP)
2. For COPD patients who are not active smokers, potential etiological exposures (environmental tobacco smoke, biomass fuel smoke, and others) should be asked for and avoided. (UPP)

**What is the role of pulmonary rehabilitation?**

1. Structured pulmonary rehabilitation programs should be set up where feasible. (1A)
2. In the absence of structured programs, patients should be advised regarding unsupervised daily physical activity. (3A)
3. All patients should be assessed for nutritional status (at least by BMI) at the initial visit and followed up by serial BMI estimation at every visit. Any patient found to be malnourished should be referred for nutritional advice to a specialist. (UPP)

**What are the indications for oxygen therapy in stable COPD?**

1. Long term supplemental oxygen therapy is indicated for those with severe daytime resting hypoxemia (1A) defined as:
  - a. PaO<sub>2</sub> of < 55 mmHg (or pulse oxygen saturation of < 88%), or
  - b. PaO<sub>2</sub> of 56-60 mmHg (or pulse oxygen saturation of 88-92%) with evidence of end-organ dysfunction such as pulmonary hypertension, congestive cardiac failure, and erythrocytosis with hematocrit > 55%
  - c. Determined on two occasions at least 3 weeks apart in the stable patient
2. The role of oxygen supplementation in other situations is currently not clear and should be decided on a case to case basis. (2B)
3. Supplemental oxygen should be titrated to achieve a pulse oximetric saturation of 90-92% or a PaO<sub>2</sub> of 60-65 mmHg. (3A)
4. Patients should breathe supplemental oxygen for at least 16 h a day. (1A)
5. Patients on long-term oxygen therapy should be reviewed at regular intervals with either pulse oximetry or arterial blood gas analysis as indicated. (UPP)
6. Patients should be warned about the risk of fire if smoking is continued during the period of oxygen supplementation. (UPP)

**What is the role of NIV in stable COPD?**

1. NIV may be used in patients with recurrent exacerbations who require frequent use of mechanical and noninvasive ventilation during the acute episodes; the patient should be referred to a specialist center for management. (3A)
2. The choice of the machine for NIV depends on the presence of coexistent sleep apnea syndromes. (UPP)

**What are the bronchoscopic techniques useful in stable COPD?**

Bronchoscopic techniques are upcoming modalities of treatment; the data is too sparse to make an evidence-based recommendation.

**What are the surgical treatments that can be offered for the treatment of COPD at appropriate centers?**

1. Bullectomy in properly selected patients. (3A)
2. Lung volume reduction surgery (LVRS) may be offered to properly selected patients. (1A)

3. Lung transplantation may be offered to properly selected patients. (1A)

**Are influenza and pneumococcal vaccinations useful in patients of COPD?**

1. Influenza vaccination is likely to be beneficial in patients with severe COPD and/or frequent exacerbations. (UPP)
2. Pneumococcal vaccination is likely to be beneficial in patients with severe COPD and/or frequent exacerbations. (UPP)

**What is the role of prophylactic antibiotics in COPD?**

Antibiotics should not be prescribed as a routine for the prevention of exacerbations of COPD. (2A)

**What should be the advice for patients of COPD regarding air travel?**

Patients with severe COPD and those on long-term oxygen therapy should be assessed before air travel by a specialist. (UPP)

**INTRODUCTION**

COPD is a common, preventable lung disorder characterized by progressive, poorly reversible airflow limitation often with systemic manifestations, in response to tobacco smoke and/or other harmful inhalational exposures. As of now valid spirometry-based nationwide prevalence data for COPD in India are not available. In most of the critical analyses, validated questionnaire based data has been accepted as reasonable for assessment of prevalence of COPD despite its limitations. COPD poses enormous burden in terms of morbidity and mortality globally and in India. COPD poses a huge economic burden in terms of direct and indirect costs.

**Definition, epidemiology and risk factors of COPD****What is the definition of COPD?**

Obstructive airway diseases, emphysema, and chronic bronchitis as separate disease entities were first defined in Ciba Guest symposium in 1958.<sup>[3]</sup> Later, various organizations came with their own definitions in their respective guidelines. Modifications have been made over the years with subsequent updates of guidelines. Till date there is no single satisfactory definition of this common disease. Different definitions given by various organizations have focused on common features of COPD.<sup>[4-7]</sup> The definition endorsed by Global Initiative for Obstructive lung disease (GOLD), in its latest edition is comprehensive and elaborate, but complex.<sup>[8]</sup> Retaining the key components of various definitions and using simple terms, we recommend the following definition of COPD:

“Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable lung disorder characterized by progressive, poorly reversible airflow limitation often with systemic manifestations, in response to tobacco smoke and/or other harmful inhalational exposures.”

***What is the prevalence of COPD?***

COPD affects more than 400 million people worldwide. The reported prevalence of COPD is highly variable ranging from 0.2% in Japan to 37% in the United States. According to the 12-site Burden of Obstructive Lung Disease (BOLD) study, the average prevalence of COPD is 10.1%, with wide variations.<sup>[9]</sup> Prevalence estimates based on spirometry are reported to be higher than those based on questionnaire-based studies.<sup>[10,11]</sup> Before the turn of 20<sup>th</sup> century, there were few studies from India, which reported the prevalence of COPD. Most of them were limited by small sample size and were based on unvalidated questionnaire interviews making them unreliable for any national assessment.<sup>[12-14]</sup> Nevertheless, the prevalence of COPD reported in these studies varied from 2-22% in men and from 1.2-19% in women. There were three attempts to systematically review and analyze available data until the results of the 'Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults' (INSEARCH) phase II was published.<sup>[13-15]</sup> All the reviews concluded that data was insufficient to derive national representative figures of prevalence of COPD. After publication of the results of INSEARCH II, some nationwide prevalence data are available. Together, the INSEARCH I and II involved 16 centers across the country, included 121,776 individuals of more than 35 years of age, and was based on a well-validated questionnaire.<sup>[16]</sup> The study population had rural and urban representation of both genders.<sup>[17,18]</sup> The prevalence of COPD in India according to these studies was 3.67% (4.46 and 2.86% among males and females, respectively). The estimated burden of COPD in India is about 15 million cases (males and females contributing to 9.02 and 5.75 million, respectively). These figures may however underestimate the true burden since questionnaire based prevalence rates tend to underestimate the true spirometry-based prevalence of COPD.

As of now, valid spirometry based nationwide prevalence data for COPD in India are not available. In most of the critical analyses, validated questionnaire based data has been accepted as reasonable for assessment of prevalence of COPD despite its limitations.

***What are the implications of COPD on morbidity and mortality?***

Globally, COPD is the ninth leading cause of loss of disability adjusted life years (DALYs) according to the baseline projections made in the Global Burden of Disease Study (GBDS).<sup>[19]</sup> In India, chronic respiratory diseases (CRDs) account for 3% of DALYs, and COPD is the major cause among CRDs.<sup>[20]</sup> COPD also accounts for more than 3 million deaths per year globally making it the third leading cause of death worldwide.<sup>[21]</sup> It accounts for 2.3-8.4% of all deaths. This proportion is more among men than women, and more among the elderly as compared to the young.<sup>[11,22]</sup> In India, COPD causes about 500,000 deaths per year.<sup>[23]</sup> A review of data from multiple sources suggested that COPD causes more death than tuberculosis

and pneumonia.<sup>[24]</sup> Recently, the State Health Systems Resource Center reported that COPD is the leading cause of death in Maharashtra state; surpassing coronary artery disease, cerebrovascular accident, and diabetes combined together.<sup>[25]</sup> According to the preliminary report of the "Million Death Study", CRDs were the second common cause of death among Indian adults. They are second and the third common causes of death in rural and urban population, respectively.<sup>[26]</sup>

COPD poses enormous burden in terms of morbidity and mortality globally and in India.

***What is the economic impact of COPD?***

The estimated economic loss in India due to COPD is about Rs. 35,000 crores for year 2011 and is predicted to exceed Rs. 48,000 crores for year 2016.<sup>[20]</sup> These economic losses are more than the annual budget of the Ministry of Health and Family Welfare (MOHFW) for year 2010-2011, which was Rs. 25,124 crores.<sup>[23]</sup> In a study that assessed the costs of treatment amongst 423 COPD patients in India, it was found that patients spent 15% of their annual income on smoking products and 30% on disease management.<sup>[27]</sup> It has been calculated that proper program-based or guideline-based management of COPD can reduce these costs by approximately 70%.<sup>[20]</sup>

*COPD poses a huge economic burden in terms of direct and indirect costs.*

***What are the risk factors for COPD?***

There are numerous factors that are thought to affect lung function at various stages of development and ageing of lung [Table 5]. Some of them have strong evidence to qualify as being causative for COPD; however there are others for which such causative associations are yet to be established. Exposure to multiple risk factors tends to have an additive effect.

***Tobacco smoking***

Noncommunicable diseases (NCDs) account for approximately 36 million deaths per year across the globe; among them tobacco alone causes approximately 6 million deaths and is the leading modifiable risk factor for NCDs.<sup>[28,29]</sup>

Tobacco is abused in two main forms, mainly smoking and smokeless tobacco. Globally, the rate of current smokers is estimated to be about 1 billion.<sup>[29]</sup> In the INSEARCH study, prevalence of tobacco use was 28.5 and 2.1% among adult men and women, respectively.<sup>[18]</sup> According to the Global Adult Tobacco Survey (2009-2010) conducted in India, the prevalence of tobacco use in any form was 34.6% (47.9 and 20.3% among men and women, respectively). Of them, 14% (24.3% men and 2.9% women) smoked tobacco. The rise in COPD incidence has paralleled the rise in tobacco smoking throughout the world.<sup>[30,31]</sup> There is a strong dose-response relationship (for amount and duration) between tobacco smoking and COPD.<sup>[16,32]</sup> In INSEARCH II,

the adjusted odds ratio (OR) for developing COPD among smoker as compared to nonsmoker was 4.08. In addition, smoking tobacco has additive effect with most of the other risk factors for COPD.<sup>[29]</sup>

Tobacco is consumed in both smoked and smokeless forms. It is well-known that tobacco smoke contains more than 4,000 harmful chemicals, of which over 50 are known carcinogens. Smokeless tobacco (chewing, sniffing, and others) is associated with cancer, hypertension, and heart disease. No association has been reported with COPD. In developing countries including India, indigenous forms of smoking tobacco are more prevalent than cigarette smoking.<sup>[32,33]</sup> It was thought that, having low tobacco content, bidi smoking would be less harmful than cigarette smoking. However, contrary to this belief, COPD is more common among bidi and hookah smokers as compared to cigarette smokers.<sup>[17,18,32-34]</sup> Chutta, chillum, and hookah are other traditional methods of smoking prevalent in India, and they are associated with even greater risk for developing COPD than cigarette smoking.<sup>[32,33,35]</sup> Low tar cigarettes are filtered to prevent tar from being inhaled. However, the adverse effects of tobacco smoking are not limited to the amount of tar. Shifting to low tar cigarettes in an attempt to decrease the risk of lung cancer was not effective.<sup>[36]</sup> Another review suggested that the effect of low tar cigarettes on COPD are inconsistent.<sup>[37]</sup>

The risk of COPD increases with increase in the number of cigarettes/bidis as well as with the duration of smoking. Any amount of smoking is harmful, although the risks are lower at low dose.<sup>[38]</sup> In one study the prevalence of CRDs among smokers with 2.5 and > 13.5 pack years was found to be approximately 13 and 60%, respectively.<sup>[32]</sup> Similarly, another study reported that prevalence of COPD in smokers with less than 20 pack years was 9.6%, which increased to 18% in subjects who smoked more than 20 pack years.<sup>[16]</sup>

### ETS

About 25-45% of patients with COPD are never smokers. Recent evidence suggests that factors other than smoking are strongly associated with COPD.<sup>[39,40]</sup> In INSEARCH phase II study, approximately 60% of chronic bronchitis

patients were nonsmokers.<sup>[18]</sup> ETS exposure among nonsmokers, especially women and children is common in many Asian countries. The INSEARCH study established the association of ETS exposure with COPD. The adjusted OR for COPD among those with ETS exposure was reported to be 1.99 (95% confidence intervals (CI), 1.69-2.34).<sup>[18]</sup> The odds for combined childhood and adult exposure was higher than that with ETS exposure during either childhood or adulthood alone, suggesting a cumulative effect.

### Burning of biomass fuel

The combustion of biomass fuel such as dried dung, wood, and crop residue is associated with generation of several toxic gases and particles which are responsible for various health hazards, including respiratory problems.<sup>[41,42]</sup> Globally, about 3 billion people are exposed to biomass fuel smoke, compared with 1.01 billion people who smoke tobacco.<sup>[39,43]</sup> According to the third National Family Health Survey, about 75% of households in India still continue to use biomass fuel for cooking. Respiratory symptoms were reported in 13% of 3,608 nonsmoking women involved in domestic cooking.<sup>[44]</sup> One study found the prevalence of airflow limitation to be almost double in residents of households using biomass fuel compared to households using liquefied petroleum gas (LPG) (8.1 vs 3.6%).<sup>[45]</sup> Contrary to previous studies, this study displayed similar patterns for males as well as females. Two recent meta-analyses suggest that exposure to biomass fuel combustion is an important risk factor for COPD.<sup>[46,47]</sup> In fact, it has been argued that in India, where more than 70% people use biomass fuel for cooking purposes compared to 25% who smoke, exposure to biomass fuel may be a bigger risk factor for COPD in India.<sup>[40]</sup>

### Occupational exposures

A systematic review of epidemiological data by the ATS suggests that about 15% of COPD cases might be related to exposure at workplace.<sup>[48]</sup> In subsequent studies, the proportion of patients with COPD attributable to occupation was about 19% overall and 31% in never smokers.<sup>[49]</sup> The list of occupations associated with increased risk of COPD include; rubber, plastics, and leather manufacturing; textile mill product manufacturing; and food product manufacturing.<sup>[50]</sup>

### Alpha-1 antitrypsin deficiency and other genetic factors

AAT deficiency is the only well-known genetic risk factor for emphysema.<sup>[51]</sup> While the prevalence of AAT deficiency is significant in Europe and North America, it is not very commonly reported from the Asian continent including India. Two studies from India suggest that few interleukin genotypes, and mutations in glutathione s-transferase 1, have some association with COPD.<sup>[52,53]</sup>

### Outdoor air pollution

Ambient air pollution in metropolitan cities has been frequently implicated as a causative agent for various respiratory diseases including COPD, especially in Asian

**Table 5: Risk factors for COPD**

Established	Probable
Tobacco smoking	Outdoor air pollution
Environmental tobacco smoke	Pulmonary tuberculosis
Exposure to biomass fuel smoke	Poorly treated asthma
Occupational exposure	Intrauterine growth retardation
Alpha-1 antitrypsin deficiency	Poor nourishment
	Repeated lower respiratory infections during childhood
	Others
	Age
	Male gender
	Low socioeconomic status

COPD: Chronic obstructive pulmonary disease



countries where urban air pollution is high.<sup>[54]</sup> In one study, respiratory symptoms were found to be more common in the higher pollution zones among 4,171 randomly selected residents. Also, the emergency room visits for COPD increased by 24.9% when the levels of pollutants in ambient air exceeded the acceptable limits.<sup>[55]</sup>

#### *Pulmonary tuberculosis*

The association of pulmonary tuberculosis with COPD has occasionally been described. The prevalence of airflow obstruction varies from 28 to 68% of patients with treated pulmonary tuberculosis.<sup>[56]</sup> In a nationwide survey of 13,826 adults in South Africa, a history of pulmonary tuberculosis was associated with COPD with odds of 4.9 for men and 6.6 for women.<sup>[57]</sup> Whether this finding of obstructive functional defect in post tubercular sequel behaves as COPD, or is different, remains to be established in long term-prospective cohort studies.

#### *Asthma*

Patients with active asthma were found to have 10-fold increased risk of chronic bronchitis and 17-fold increased risk of emphysema as compared to those without asthma even after adjustment for confounding factors.<sup>[58]</sup> A subsequent review also suggests that a subset of patients with asthma may have COPD phenotype.<sup>[59]</sup>

#### *Miscellaneous factors*

An increased association of COPD is reported with demographic and socioeconomic factors such as advancing age, low socioeconomic status, and urban residence with lower socioeconomic status. This association may perhaps be attributed to the greater prevalence of smoking and cumulative effects of smoking and other exposures with age. Low socioeconomic status and infections have been listed as additional risks.

#### *Recommendations*

1. Tobacco smoking is the most well-established risk factor for COPD. (1A)
2. Both smokeless and smoking forms of tobacco are associated with serious health hazards, although only smoking tobacco is primarily responsible for COPD. (1A)
3. Bidi and other indigenous forms of tobacco smoking are at least as (or even more) harmful than cigarette smoking. (1A)
4. Low tar or filtered cigarettes are not "less harmful". (2B)
5. There is no minimum number of cigarettes/bidi per day below which the risk for COPD decreases. (1A)
6. Exposure to ETS is a definite risk factor for COPD. (1A)
7. Exposure to biomass fuel smoke is a strong risk factor for COPD. (1A)
8. There are limited data on the association of ambient air pollution and COPD, and its causative role in COPD needs further evaluation.
9. There is insufficient evidence to attribute an etiological role of pulmonary tuberculosis in causing COPD.
10. A subgroup of chronic asthma may clinically behave

like COPD; however whether it is true, COPD remains to be established. (UPP)

### **Diagnosis and Assessment of COPD**

#### *When to suspect COPD?*

COPD is one of the important differential diagnosis in patients presenting with symptoms of chronic cough, sputum production, breathlessness, and/or wheezing.<sup>[60-62]</sup> This is especially true when patients have a history of prolonged exposure to risk factors. There is no definite duration of exposure to the risk factors that can result in COPD. However, in general, a prolonged exposure to risk factors is required for the development of disease.

Some patients presenting differently from the aforementioned symptoms (as detailed under the next subheading) might also be detected to have COPD on further evaluation.

#### *Recommendation*

1. A diagnosis of COPD should be considered in persons having chronic symptoms of cough, sputum production, shortness of breath, and/or wheezing; especially among those with prolonged exposure to risk factors for the disease. (1A)

#### *What are the symptoms of COPD?*

COPD patients may present to a healthcare facility in four typical ways:

- a. With one or more of the characteristic respiratory symptoms of chronic progressive breathlessness, cough, sputum production, wheezing, and/or chest tightness. Recent studies reveal that presence of one or more of these symptoms increases the odds for the diagnosis of COPD.<sup>[60-62]</sup>
- b. Without respiratory symptoms like breathlessness, because patients might have reduced their physical activity unknowingly to very low levels. They might just complain of fatigue.
- c. With symptoms attributed to complications of the disease like weight loss (COPD related cachexia) or leg swelling (due to cor pulmonale).
- d. With an exacerbation (as discussed in the section on exacerbation).

#### *Breathlessness*

Patients may variously describe their breathlessness as: "My breathing requires effort", "I cannot get enough air in", "I feel out of breath", or "I feel hunger for more air".<sup>[63]</sup> There may be individual and cultural variations in the description of breathlessness.<sup>[64]</sup> Breathlessness is usually present on exertion until late in the course of the disease. Orthopnea occurs early and more commonly in heart failure, which is an important differential diagnosis, while it is reported infrequently and late (if ever) in patients with COPD. The severity of breathlessness may be graded on various scales. A simple and widely used scale is the modified Medical Research Council (mMRC) questionnaire,<sup>[65]</sup> illustrated in Table 6.

**Cough and sputum production**

Cough may be the only presenting symptom. On the other hand, a smoker might consider his cough to be a natural consequence of smoking, and might neglect it as a symptom. An increasing intensity, or change in the nature, of cough may be reported. It may be more prominent in the morning. Cough may be accompanied by mucoid or purulent sputum production that may vary greatly in amount.<sup>[66]</sup> Again, patients may find it a normal phenomenon associated with smoking and might even feel that smoking helps in easing out the passage of sputum. Immediately following smoking cessation, cough and sputum may become more bothersome, but generally improve with continued abstinence.<sup>[67]</sup> The epidemiological definition of chronic bronchitis (regular production of sputum for 3 or more months for 2 consecutive years) is arbitrary and might not apply to a given patient. However, it might identify an “at risk” individual.

**Wheezing**

Patients may complain of wheezing, variously described as noisy breathing or a whistling sound. Wheezing may have diagnostic value when seen in the light of other clinical features.<sup>[60-62]</sup>

**Chest tightness**

Patients may complain of chest tightness, chest congestion, or an obstructed chest.

**Chest pain and hemoptysis**

These are not the usual symptoms of COPD. Their presence is often a pointer to an alternative diagnosis (e.g., lung malignancy, pulmonary tuberculosis, etc.)

**What are the signs of COPD?**

COPD patients may demonstrate various physical signs that may either be due to the primary disease or an associated complication [Table 7].<sup>[68]</sup> Diminished breath sounds and wheezing on auscultation have been shown to increase the odds for a diagnosis of COPD.<sup>[60]</sup> An important clinical sign is the forced expiratory time (FET).<sup>[69]</sup> An FET of more than 6 seconds suggests airway obstruction.

Importantly, COPD patients, especially those presenting early, might lack any of the above mentioned signs. A diagnosis of COPD cannot be rejected due to the mere presence of a normal physical examination.

**Table 6: Modified medical research council grading of breathlessness**

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

**Recommendations**

1. A diagnosis of COPD should not be excluded in the absence of physical signs. (2A)
2. Forced expiratory time (FET) of more than 6 seconds is suggestive of airflow obstruction. (2B)

**What medical history should be obtained from patients suspected of having COPD?**

A patient suspected to have COPD should be asked about the exposure to risk factors, especially tobacco smoking and exposure to smoke from biomass fuel combustion. A history of allergic disorders, asthma and other respiratory diseases, presence of comorbidities, family history of allergic and respiratory disorders, history of previous exacerbations and hospitalizations, and impact of disease on patient's life (including limitations of activities of daily living and the associated psychosocial morbidity) should also be documented.

**What is the role of spirometry in the diagnosis of COPD? Whether fixed ratio or LLN should be used for diagnosis?**

Demonstration of airflow obstruction is essential to make a definitive clinical diagnosis of COPD. Spirometry is a simple and accurate tool to assess airflow obstruction. Spirometry should be performed as per standard guidelines.<sup>[70,71]</sup> Table 8 summarizes some of the important points elaborated in these guidelines regarding the equipment and performance of spirometry.<sup>[70,71]</sup> Both FEV<sub>1</sub> and FVC should be assessed, and the FEV<sub>1</sub>/FVC ratio calculated.

The criterion for defining airflow obstruction has been

**Table 7: Useful physical signs in the diagnosis of COPD**

Inspection	Pursed-lip breathing
	Use of accessory muscles of respiration
	Jugular venous distension during expiration
	Retraction of suprasternal, supraclavicular and intercostal spaces during inspiration
	Short trachea
	Pulsus paradoxus
	Increased anteroposterior diameter of the chest (barrel-shaped chest)
	Reduced chest movements
	Peripheral edema
	Dyspnea-relieving posture
	Muscle wasting
Palpation	Restricted chest expansion
	Subxiphoid shift of maximum impulse of the heart
Percussion	Chest hyperresonance
	Obliteration of cardiac dullness
	Lower level of liver dullness
	Lower diaphragmatic levels
Auscultation	Diminished breath sounds
	Early inspiratory crackles
	Loud pulmonic component of second heart sound
Special maneuver	Forced expiratory time
	Snider's match test

COPD: Chronic obstructive pulmonary disease

a subject of much debate in recent years.<sup>[72,73]</sup> The GOLD committee suggests use of a post-bronchodilator FEV<sub>1</sub>/FVC less than an arbitrarily fixed value of 0.7 (FR<sub>0.7</sub>) as the criterion for diagnosis of COPD.<sup>[8]</sup> However, guidelines on spirometry recommend the use of statistically derived LLN of FEV<sub>1</sub>/FVC as the cutoff to define airflow obstruction.<sup>[70]</sup> The LLN is defined as the lower fifth percentile of values in the reference population. The age and gender adjusted reference equations for this purpose are generated from spirometric data from a cohort of normal healthy nonsmoking individuals sampled from the particular population in a geographical area. LLN is then computed as the difference between predicted value and 1.645 times the standard error of estimate of the reference equation.

A systematic review analyzed the findings of 18 studies that compared these two spirometric definitions.<sup>[74]</sup> Most of these studies reported that use of FR<sub>0.7</sub> leads to a much higher proportion of subjects being diagnosed as having airflow obstruction than use of LLN.<sup>[75-86]</sup> FR<sub>0.7</sub> misclassifies more than 20% of subjects as having airflow obstruction when compared to LLN.<sup>[67]</sup> Further, discordance between the two methods in classifying obstruction increases in the elderly as LLN values decrease with advancing age.<sup>[68]</sup> Thus, elderly individuals having a FEV<sub>1</sub>/FVC value which might be within a statistically normal range for their age and gender, face the risk of being diagnosed as having COPD by using FR<sub>0.7</sub>.

Two studies analyzing longitudinal data have concluded that subjects having FEV<sub>1</sub>/FVC above the LLN, but below FR<sub>0.7</sub> (the so called “discordant” group) had an increased risk of mortality than those having FEV<sub>1</sub>/FVC > 0.7.<sup>[80,89]</sup> However, the comparison of mortality was between the “discordant” group and a group of healthy individuals without respiratory symptoms, thus it does not hold valid for those who consult the physician for respiratory symptoms.<sup>[90]</sup> Also, as the relationship between lung function and risk of death is a continuum, it follows that any arbitrary cutoff would potentially have a difference in mortality among subjects falling on either side without representing true disease.<sup>[91]</sup> A recent study has shown that rate of decline of lung function in the discordant group is half the value observed in those with FEV<sub>1</sub>/FVC below LLN, while it is similar to those with FEV<sub>1</sub>/FVC above both LLN and FR<sub>0.7</sub> cutoff.<sup>[90]</sup> Thus, the LLN has better discriminatory value for identifying subjects with a higher rate of lung function decline. An analysis of the aforementioned studies suggests that using FR<sub>0.7</sub> criterion leads to over diagnosis of the disease as compared to a more statistically sound LLN criterion. Moreover, studies have also shown that FR<sub>0.7</sub> also potentially ‘underdiagnoses’ younger patients with airflow obstruction.<sup>[92]</sup> Young subjects, especially below the age of 40 years might have a FEV<sub>1</sub>/FVC below the LLN for their age, but might get misclassified as normal as the ratio may be greater than the fixed cutoff of 0.7.<sup>[88]</sup>

### Table 8: Equipment and performance of spirometry

#### Equipment

It is the responsibility of the manufacturers to manufacture pulmonary function systems that satisfy the latest accepted published guidelines. It is also the duty of the user that the system being used complies with the latest recommendations and gives accurate measurements during the course of its running

The equipment should meet the recommended requirements for volume, flow, resistance, and time of flow

Calibration checks for volume, leak, and volume and flow linearity should be performed regularly

#### Performance

Each test performed should meet certain within-maneuver and between-maneuver criteria

Individual spirometry tests are acceptable if they are free from artifacts (cough during first second of exhalation, glottis closure, early termination, submaximal effort, or obstructed mouthpiece), have good starts with extrapolated volume < 5% of FVC or 0.15 L, whichever is greater and show satisfactory exhalation (duration of ≥ 6 seconds or a plateau in the volume-time curve)

Acceptable spirometry tests should meet the between-maneuver criteria. Out of three acceptable spirometry tests, the two largest values of FVC should be within 0.15 L of each other, the two largest values of FEV<sub>1</sub> should also be within 0.15 L of each other. If these criteria are not met, testing should be continued until the above criteria are met with additional acceptable spirometry tests or a total of eight maneuvers have been performed

Bronchodilator administration and post-bronchodilator testing

Four separate doses of salbutamol 100 µg and/or ipratropium bromide 40 µg are delivered through a valved spacer device at 30 seconds intervals.

Spirometry should be performed after 10-15 min later for salbutamol and 30 min later for ipratropium bromide

#### Evaluation

A post-bronchodilator FEV<sub>1</sub>/FVC less than the lower limit of normal, signifies obstruction. Further severity classification is done according to the FEV<sub>1</sub> value

Appropriate reference equations should be used for determining the lower limit of normal

FEV<sub>1</sub>/FVC: Forced expiratory volume in first second/forced vital capacity

Going by the current evidence, LLN is a more robust criterion for diagnosis of airflow obstruction than the FR<sub>0.7</sub>. Several reference equations derived from healthy subjects from various regions of India are available for this purpose.<sup>[93-98]</sup> However, there are still concerns among the experts regarding validity of these equations for populations from all parts of the country. It is imperative that spirometry reference equations should be generated for various population subsets in India. Meanwhile, the criterion of FR<sub>0.7</sub> might be used only in the absence of a valid reference equation for FEV<sub>1</sub>/FVC in a particular region of the country.

### Recommendations

1. Spirometry should be conducted in all patients suspected of having COPD. (1A)
2. In the absence of availability of spirometry, patients suspected of having COPD should be referred for a spirometric evaluation to a center with the facility. (UPP)
3. A post-bronchodilator FEV<sub>1</sub>/FVC below the LLN (lower fifth percentile of values from a reference population) should be used as the criterion for diagnosis of airflow obstruction. (1A)
4. In the absence of reference equations for LLN, FEV<sub>1</sub>/FVC

< 0.7 may be used as the cutoff for defining airflow obstruction. (2A)

### **What is the role of reversibility testing in COPD?**

It has been traditionally believed that COPD patients do not show reversibility in airflow obstruction after administration of bronchodilators, and this concept was considered useful to differentiate COPD from asthma.<sup>[99]</sup> Numerous studies have shown that patients with COPD may also show significant spirometric reversibility to bronchodilators.<sup>[100-103]</sup> Besides, bronchodilator reversibility is not a variable that essentially signifies the presence of disease; it has also been demonstrated in healthy subjects.<sup>[104]</sup> Thus, reversibility testing does not help diagnosis of COPD.<sup>[105]</sup> Also, lack of reversibility in COPD does not preclude a subsequent benefit from long-term maintenance bronchodilator therapy.<sup>[103,106]</sup> Moreover, the response to ICS is not predicted by bronchodilator reversibility in COPD patients.<sup>[107]</sup> Finally, bronchodilator reversibility varies temporally and does not correlate with clinically relevant outcomes such as mortality, hospitalization or exacerbation experience, making it an unreliable phenotype.<sup>[108]</sup>

### **Recommendation**

1. Absence of bronchodilator reversibility does not differentiate COPD from asthma, and its presence does not predict the response to treatment (1A). However, all FEV<sub>1</sub> values should be reported post-bronchodilator.

### **What is the role of screening spirometry?**

Screening spirometry may help in detecting subjects with airflow obstruction before they develop clinical symptoms. This can be potentially beneficial in two ways: (a) diagnosis of COPD might improve smoking cessation rates, and (b) early treatment might alter disease prognosis. However, there is no conclusive evidence for either. Evidence for the notion that a diagnosis of COPD promotes smoking cessation is equivocal.<sup>[109-111]</sup> Rather there is a conceivable risk that tobacco smokers informed to be having a normal lung function might be encouraged to continue smoking.<sup>[110]</sup>

There are no controlled trials comparing clinical outcomes between screened and non-screened populations. The US Preventive Services Task Force (USPSTF) summarized the evidence on spirometric screening for COPD in 2008,<sup>[112]</sup> that "screening for COPD using spirometry is likely to identify a predominance of patients with mild to moderate airflow obstruction, who would not experience additional health benefits if labeled as having COPD."<sup>[113]</sup> If screening spirometry is limited to smokers of more than 40 years of age, 833 individuals would need to be screened to prevent one exacerbation.<sup>[112]</sup> In the Indian setting, with a large "at risk" population, screening spirometry thus appears neither feasible nor cost-effective.

### **Recommendation**

1. Spirometry is not recommended as a screening tool in asymptomatic individuals to detect airflow obstruction. (2A)

### **What is the role of PEF measurement in diagnosis and monitoring of COPD?**

PEF measurement has often been advocated as a surrogate measure for FEV<sub>1</sub>. The PEF instrument is inexpensive, portable, and easy to operate and maintain.<sup>[114]</sup> It has been shown that PEF of less than 80% predicted has a sensitivity of 91% and a specificity of 82% in defining airflow obstruction, when using FEV<sub>1</sub>/FVC < 0.7 and FEV<sub>1</sub> < 80% as the gold standard.<sup>[115]</sup> However, this sensitivity value is rather low for a test to qualify as a good screening test. With a specificity of 82%, the PEF criterion fails to qualify as a good diagnostic test either. Numerous studies have shown absence of parity between PEF% and FEV<sub>1</sub>% values, with wide limits of agreement between the two measures.<sup>[114,116,117]</sup> PEF and change in PEF also cannot be used as a surrogate for standard spirometric criteria for bronchodilator reversibility assessment.<sup>[118]</sup> Although PEF has been used for the diagnosis, monitoring and prognostication in COPD, the supporting evidence is weak.<sup>[115,119,120]</sup>

### **Recommendation**

1. PEF should not be routinely used for screening, diagnosis or monitoring in COPD. (1A)

### **How should the severity of COPD be classified?**

Severity staging of COPD is important for disease prognostication as well as for treatment. GOLD guidelines classify COPD into mild (FEV<sub>1</sub> ≥ 80% predicted), moderate (50% ≤ FEV<sub>1</sub> < 80%), severe (30% ≤ FEV<sub>1</sub> < 50%), and very severe (FEV<sub>1</sub> < 30%) disease.<sup>[8]</sup> Most other guidelines follow the same classification system.<sup>[7,121]</sup> There is good quality evidence from large studies that worsening airflow limitation is associated with increasing mortality and hospitalization rates, as well as increased risk of exacerbations.<sup>[122-124]</sup> A measure like BODE index might offer additional prognostic information,<sup>[125]</sup> but there are no data whether treatment can be tailored according to the BODE index.

Most therapeutic considerations (derived from evidence available from large scale trials) differ only between the groups separated by a cutoff of above or below predicted FEV<sub>1</sub> of 50%. Evidence regarding treatment of patients having mild airflow obstruction (i.e., predicted FEV<sub>1</sub> > 80%) is scarce. Three broad groups based on spirometric severity can be formulated: Patients with FEV<sub>1</sub> ≥ 80%, those with FEV<sub>1</sub> between 50-79%, and those with FEV<sub>1</sub> < 50%. Only the prognostication varies significantly within the last group which, as has been pointed out earlier, has a continuous linear relationship with lung function.<sup>[91]</sup> An additional group with FEV<sub>1</sub> < 30% might be considered redundant.

The course of COPD is punctuated by exacerbations. An increase in frequency of exacerbations is associated with poorer quality of life (QoL), accelerated decline of lung function, and increased mortality.<sup>[126-128]</sup> A history of frequent exacerbations (more than one in a year) implies more severe disease and increased risk of future events.<sup>[122]</sup> The frequency of exacerbations also needs to be factored in for severity classification of the disease.

The assessment of patient's symptoms is extremely important in understanding the impact of the disease on patient's life. The mMRC questionnaire, as detailed above, helps to assess disability due to breathlessness and correlates well with other measures of health status and mortality risk.<sup>[129,130]</sup> The CAT is an eight-item questionnaire that comprehensively assesses the patient's symptoms and their impact on patient's life.<sup>[131]</sup> It is reliable and responsive, and correlates well with the St. George Respiratory Questionnaire (SGRQ) for health status assessment.<sup>[132]</sup> For simplicity and ease of use, mMRC questionnaire rather than CAT has been incorporated into our proposed classification as a measure of patient symptoms.

Finally, complications like respiratory failure, cor pulmonale, and secondary polycythemia (hematocrit > 55%) signify advanced disease, irrespective of other parameters.<sup>[133-135]</sup> Patients with any of these features should be placed in the category of severe disease. For evidence-based stratification of patients into treatment categories, FEV<sub>1</sub>, exacerbation frequency, mMRC grade, and presence of complications need to be considered. A proposed classification of severity of COPD is outlined in Table 9.

### Recommendations

1. Classification of severity of the disease should be done for all COPD patients based on the FEV<sub>1</sub> and exacerbation frequency. (1A)
2. Level of patient's disability due to symptoms should be assessed using mMRC Council dyspnea questionnaire or the CAT and recorded at each clinical visit. (1A)

### What is the role of additional investigations in COPD?

#### Sputum examination

Smoking increases the risk of both COPD and tuberculosis.<sup>[136-138]</sup> In a country with a high prevalence of tuberculosis, it would be prudent to screen a patient with chronic cough of more than 2 weeks duration for tuberculosis through sputum microscopy.

#### Pulse oximetry

Pulse oximetry can serve as a screening test for systemic hypoxemia during acute exacerbation of COPD, as well in patients with chronic respiratory failure. Studies have shown that a cutoff of 88-92% has an almost 100% sensitivity to predict hypoxemia during exacerbations.<sup>[139,140]</sup>

#### Chest radiography

The radiological abnormalities associated with COPD are nonspecific. Moreover, the sensitivity of chest radiography for the diagnosis of COPD is poor.<sup>[141-143]</sup> It is useful to exclude alternative diagnoses, and to identify other comorbidities and/or complications.<sup>[144]</sup>

#### Special investigations: HRCT, lung volumes, and diffusing capacity for carbon monoxide, exercise testing

Although HRCT can be useful in identification and quantification of early emphysematous changes, its clinical utility for this purpose is yet to be determined.<sup>[145]</sup> HRCT may

be useful in identifying other respiratory disorders in patients with symptoms suggestive of COPD. In one such study, among 516 patients with a pulmonary function test (PFT) suggestive of obstruction, HRCT was helpful in establishing an etiology other than COPD in 12.7% patients.<sup>[146]</sup>

Total lung capacity (TLC) is increased in COPD due to air trapping and emphysema. DLCO is decreased in emphysema due to reduction in the area of alveolar capillary membrane. The reduction in DLCO correlates well with pathological emphysema and emphysematous changes in HRCT.<sup>[147-149]</sup> A decreased DLCO may also help in predicting mortality in patients with COPD. There is no clear threshold value.<sup>[150,151]</sup> DLCO is typically within normal limits in COPD with a primarily chronic bronchitis phenotype.

Detailed cardiopulmonary exercise testing (CPET) is useful to assess functional status to establish exercise restrictions and to assess the impact of therapeutic interventions.<sup>[152-155]</sup> CPET has also been shown to be useful in patients with exertional dyspnea, out of proportion to their lung function abnormality, to assess additional contributing factors like myocardial ischemia.<sup>[156-158]</sup> Six-minute walk test (6MWT), a simpler surrogate for formal CPET, has also been found to be useful in assessment of functional status, effectiveness of therapy, and prognosis in COPD.<sup>[159-163]</sup>

#### AAT deficiency

Data on the prevalence of AAT in Indian patients with COPD is sparse.<sup>[164]</sup> Western data suggest that approximately 3% of patients with COPD might have AAT.<sup>[165]</sup> In the absence of an effective therapy for AAT, it would be prudent to restrict AAT testing for atypical cases of COPD with a high probability of AAT deficiency (such as a young patient with lower lobe emphysema).

### Recommendations

1. All new COPD suspects with cough of more than 2 weeks' duration should undergo sputum smear examination for acid fast bacilli to rule out pulmonary tuberculosis as per the standard practice of RNTCP. (UPP)
2. Pulse oximetry should be used to screen for hypoxemia in stable disease with FEV<sub>1</sub> < 50% and in the presence of clinical suspicion of hypoxemia. (3A)
3. An arterial blood gas analysis should be performed if arterial saturation by pulse oximetry is less than 90%. (2A)

**Table 9: Classification of severity of COPD**

Severity*	Postbronchodilator FEV <sub>1</sub> , % predicted	mMRC grade	Exacerbation frequency <sup>†</sup>	Complications <sup>‡</sup>
Mild	≥80	<2	<2	No
Moderate	50-79	≥2	<2	No
Severe	<50	≥2	≥2	Yes

\*The category with the worst value should be used for severity classification, <sup>†</sup>number of exacerbations in the last year, <sup>‡</sup>complications include respiratory failure (defined by pO<sub>2</sub> < 60 mmHg and/or SpO<sub>2</sub> < 88% and/or pCO<sub>2</sub> > 50 mmHg), cor pulmonale, and secondary polycythemia (hematocrit 55%); FEV<sub>1</sub>: Forced expiratory volume in first second, mMRC: Modified Medical Research Council questionnaire, COPD: Chronic obstructive pulmonary disease

4. Diagnosis of COPD should not be made on the basis of a chest radiograph. (2A)
5. Chest radiograph may be done during the initial evaluation of COPD to look for comorbidities, complications, and alternative diagnoses. (2B)
6. Special investigations like HRCT scan, lung volumes, DLCO, and exercise testing should be done in situations of diagnostic difficulty or whenever clinically indicated. (2A)
7. 6MWT may be used for monitoring of exercise capacity in COPD. (1A)
8. Testing for alpha-1 antitrypsin deficiency may be done in young patients with lower lobe emphysema. (UPP)

#### **What is the role of multidimensional assessment tools in COPD?**

Multidimensional assessment tools in COPD (such as BODE index, DOSE index, etc.) are useful in predicting mortality, exacerbations, and risk of hospitalizations.<sup>[166,167]</sup> Their predictive ability has been inconsistent when applied to different populations.<sup>[168]</sup>

#### **Recommendation**

1. Composite scores including BODE and DOSE should not be used to assess severity or prognosis in COPD unless they are validated in Indian patients. (2A)

#### **What are the differential diagnoses of COPD?**

The important differential diagnoses of COPD include asthma, congestive heart failure, bronchiectasis, tuberculosis, constrictive bronchiolitis, and diffuse panbronchiolitis [Table 10].

#### **What are the comorbidities associated with COPD?**

COPD is associated with many comorbid diseases, which may be pulmonary or extrapulmonary (coronary vascular disease, congestive heart failure, diabetes mellitus, metabolic syndrome, obstructive sleep apnea, skeletal muscle dysfunction, cachexia, osteoporosis, depression, lung cancer).<sup>[169-171]</sup> Comorbid diseases in COPD are independently associated with a higher risk of hospitalization and mortality.<sup>[172]</sup>

#### **Recommendation**

COPD patients should be routinely evaluated, and appropriately treated, for comorbid conditions. (2A)

#### **Management of stable COPD**

##### **What are the goals for the management of patients of stable COPD?**

The goals in managing stable COPD include reduction in current symptoms as well as future risk of disease progression, prevention of exacerbations, and reduction in mortality [Table 11].<sup>[8]</sup> It is also important to avoid treatment associated adverse effects while trying to achieve these goals. The goals should be individualized, and assessed and monitored objectively. For instance, breathlessness can be easily evaluated using the mMRC grading. Similarly, exercise tolerance can be assessed

through the 6MWT, and the QoL evaluated by using any one of the several validated questionnaires (such as SGRQ and others). Disease progression is measured by calculating the rate of decline in FEV<sub>1</sub>.

##### **What drugs are available for management of patients of stable COPD, and what are their recommended doses?**

The three main groups of drugs available for management of stable COPD include inhaled anticholinergics, inhaled beta2-agonists, and ICS. The currently available drugs and their commonly prescribed doses are summarized in Table 12. Other drugs which can also be used include the oral drugs-beta-agonists, methylxanthines, and selective phosphodiesterase-4 (PDE4) inhibitors.

##### **What is the ideal route and method of drug delivery?**

Inhaled therapy is now established as the mainstay of treatment for patients with stable COPD. It allows low doses of bronchodilators or corticosteroids to be delivered rapidly and directly into airways, thereby achieving high local concentrations at site of action, while significantly reducing systemic adverse effects as compared to oral or parenteral therapy. Several patients continue to receive oral agents, because of patient preferences, ignorance, financial constraints, and/or lack of availability or acceptance of inhaled drugs.

Three kinds of aerosol devices are available for treatment in COPD namely pressurized metered dose

**Table 10: Differential diagnoses of COPD**

Asthma
Early age of onset
Episodic symptoms with asymptomatic periods in between
Wide variation of symptoms day to day
Symptoms worse at night/early morning
Chronic productive cough is uncommon
History of atopy may be present
Family history of asthma may be present
Reversibility of airway obstruction
Increased diffusing capacity for carbon monoxide (DLCO)
Congestive heart failure
Cardiomegaly/pulmonary edema in chest X-ray
PFT suggestive of restrictive abnormality
Bronchiectasis
Copious purulent sputum
Clubbing, coarse crackles
HRCT shows bronchial dilatation and bronchial wall thickening
Tuberculosis
Fever, anorexia, weight loss
Chest X-ray opacity, fibrocavitary disease
Microbiological diagnosis
Constrictive bronchiolitis
Non-smoker, young age
History of rheumatoid arthritis, fume exposure, lung/bone marrow transplantation
HRCT shows mosaic attenuation
Diffuse panbronchiolitis
Non-smoker
Association with chronic sinusitis
HRCT shows centrilobular nodules, hyperinflation and air-trapping

COPD: Chronic obstructive pulmonary disease, PFT: Pulmonary function test, HRCT: High-resolution computed tomography

**Table 11: Treatment goals in a patient of stable COPD**

Reduction in current symptoms
Relief in breathlessness and other symptoms
Improvement in exercise tolerance
Improvement in overall health-related quality of life
Reduction of future risk
Prevention (or slowing down) of disease progression
Prevention of disease exacerbations
Reduction in disease-related mortality
Minimizing adverse effects from treatment

Adapted from GOLD guidelines. COPD: Chronic obstructive pulmonary disease, GOLD: Global initiative for chronic obstructive lung diseases

**Table 12: Commonly used drugs and dosages for pharmacotherapy of stable disease**

Drug category	Recommended dose
Inhaled agents*	
Anticholinergics	
Short acting	
Ipratropium bromide	20-40 µg as needed
Long acting	
Tiotropium	18 µg once daily
Beta-agonists	
Short acting	
Salbutamol	100-200 µg as needed
Levosalbutamol	45-90 µg as needed
Terbutaline	250-500 µg as needed
Long acting	
Salmeterol	25-50 µg twice daily
Formoterol	6-12 µg twice daily
Indacaterol	150-300 µg once daily
Corticosteroids	
Fluticasone	250-500 µg twice daily
Budesonide	100-400 µg twice daily
Beclomethasone	100-400 µg twice daily
Ciclesonide	80-160 µg twice daily
Mometasone	250-500 µg twice daily
Oral agents	
Beta-agonists	
Salbutamol	2-4 mg twice/thrice daily
Bambuterol	10-20 mg once daily
Terbutaline	2.5-5 mg thrice daily
Methylxanthines	
Sustained release theophylline	100-400 mg once daily
Doxophylline	400 mg twice/thrice daily
Selective PDE4 inhibitors	
Roflumilast	0.5 mg once daily

\*Recommended doses are those for a pressurized metered dose inhaler. These drugs are also available as dry powder inhalers and for nebulizer use, for which doses may vary; PDE4: Phosphodiesterase-4

inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers. pMDIs are commonly used, but many patients (especially elderly) find it difficult to use them correctly, often because of problems in actuation-inhalation coordination. pMDIs used with a valved spacer further improves drug delivery to airways and reduces oropharyngeal deposition. Breath-actuated pMDIs may also obviate some of these issues. A wide array of DPIs are available that vary significantly in generated particle size and airway delivery. DPIs are breath-actuated, so coordination issues are much less. Even then, many patients are unable to use these devices correctly as relatively higher airflows are required to generate good

aerosol. In an observational study of 3811 patients with COPD or asthma, critical errors in technique that potentially affected drug delivery were observed in 28% of pMDI users; and depending on the specific device, 11-32% of DPI users.<sup>[173]</sup> Another review found that 43, 55, and 59% patients could correctly use pMDI, pMDI with spacer, and DPI, respectively; and teaching substantially improved technique.<sup>[174]</sup> It is important to educate patients regarding correct inhaler technique, with regular monitoring of technique at follow-up visits. The correct technique of pMDI use is summarized in Table 13. Nebulizers use oxygen, compressed air, or ultrasonic power to generate fine aerosol from drug solutions or suspensions that is passively delivered to airways via mask or mouthpiece. However; they are bulky, much more expensive, require electrical power for operation, and need regular maintenance. Their overall dose delivery is largely comparable to pMDIs with spacer, or good quality DPIs.

Two large systematic reviews have concluded that the type of aerosol device has no effect on clinical outcomes in patients with COPD.<sup>[174,175]</sup> The American College of Chest Physicians and the American College of Asthma, Allergy, and Immunology have also recently concluded that when patients use these inhalation devices as prescribed, all of them work equally well.<sup>[175]</sup> In real-life clinical practice, selection of a delivery device ideal for a particular patient depends on several factors such as clinician and patient preference, availability, cost, patient age and dexterity, patient motivation and understanding, relative ease of device use, and others.

### ***What is the role of long acting antimuscarinic agents in the management of stable COPD?***

The most widely used inhaled LAMA for the management of stable COPD is tiotropium bromide. It has pharmacodynamic specificity for M1 and M3 receptors and has a half-life of more than 24 h, resulting in a convenient once daily dosing. The largest study till date on the use of tiotropium monotherapy in stable COPD is the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial.<sup>[176]</sup> There was no difference in the primary end point (rate of decline of lung function) between the two groups, although patients receiving tiotropium had better FEV<sub>1</sub> and FVC values at all-time points during the study period. Importantly, there was a significant decrease in the exacerbation rates and mortality with the use of tiotropium. Also, there was improvement in the QoL scores and lesser cardiac and respiratory adverse events in this group. A subgroup analysis of the UPLIFT trial focusing on the patients with moderate COPD (FEV<sub>1</sub> 50-70%), confirmed the benefits of tiotropium monotherapy in decreasing exacerbations and improving QoL and lung function, although there was no reduction in mortality.<sup>[123]</sup> Other subgroup analyses have also shown that the beneficial effects of tiotropium are observed in all patients of COPD; irrespective of their gender, ethnicity, or smoking status.<sup>[177-179]</sup> A recent

**Table 13: Correct technique for using pressurized metered dose inhaler**


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Steps for using pressurized metered dose inhaler

- Sit up straight, and remove inhaler cap
- Hold inhaler upright by placing index finger on top of the canister while providing support on the bottom of the device with the thumb, and shake well
- Take a few deep breaths and breathe out gently away from the device
- Put mouthpiece between teeth without biting and close lips to form good seal, keeping the tongue relaxed and not blocking the mouthpiece
- Start breathing in slowly through mouth, and simultaneously press down firmly on canister with the index finger, once only, to release one puff of medicine
- Continue to breathe in slowly, evenly and deeply over 5-7 s, till the lungs seem completely filled
- Hold breath for about 10 s, or as long as comfortable
- While holding breath, remove inhaler from mouth
- Breathe out slowly away from the device, and then inhale normally
- If an extra dose is needed, wait 30 s to a minute, and then repeat steps two to nine
- Replace inhaler cap

Steps for using pressurized metered dose inhaler with a spacer device

- Sit up straight, and assemble spacer device
- Remove inhaler cap
- Hold inhaler upright by placing index finger on top of the canister while providing support on the bottom of the device with the thumb, and shake well
- Insert inhaler upright into spacer
- Put mouthpiece between teeth without biting and close lips to form good seal, keeping the tongue relaxed and not blocking the mouthpiece
- Take a few deep breaths and breathe out gently away from the device
- Hold spacer horizontally at level of mouth, and press down firmly on canister with the index finger, once only, to release one puff of medicine
- Breathe in slowly, evenly and deeply, till the lungs seem completely filled, and then hold breath for about 10 s or as long as comfortable
- OR Breathe in and out normally for four breaths
- Remove spacer from mouth
- Breathe out gently away from the device, and then inhale normally
- Remove inhaler from spacer
- If an extra dose is needed, wait 30 s to a minute, and then repeat steps three to 11
- Replace inhaler cap and disassemble spacer device

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Cochrane review of 22 randomized controlled trials comparing tiotropium monotherapy with placebo also confirmed the beneficial effects of tiotropium.<sup>[180]</sup> In this meta-analysis, tiotropium use in stable COPD was associated with significant improvement in QoL and reduction in exacerbations (with a number needed to treat of 16 to prevent one exacerbation). A subgroup analysis based on FEV<sub>1</sub> (FEV<sub>1</sub> > 50% and FEV<sub>1</sub> < 50%) showed benefits of tiotropium in both the subgroups.

Aclidinium bromide is another LAMA used in some countries; it is however not available in India at present.<sup>[181]</sup> As compared to tiotropium, it possesses greater M3 muscarinic receptor selectivity.<sup>[182]</sup> Two large placebo-controlled randomized trials (Aclidinium in COPD 1 (ACCORD COPD 1) trial and Aclidinium To Treat Airway obstruction In COPD patients (ATTAIN) study) have shown that aclidinium bromide given twice daily improves dyspnea scores, lung function, and QoL.<sup>[183,184]</sup> The precise role of this new drug in the management of stable COPD is yet to be established.

### *What is the role of short acting antimuscarinic agent in the management of stable COPD?*

Prior to the introduction of tiotropium, short acting ipratropium was widely used for the management of stable COPD. Only a few short-term randomized controlled trials have compared ipratropium versus placebo.<sup>[103,185-187]</sup> These studies showed a consistent improvement in lung function and dyspnea scores in patients using ipratropium. None of these studies assessed exacerbation and mortality rates. No long-term studies have assessed regular ipratropium use in patients of stable COPD.

### *Is tiotropium better than ipratropium in pharmacotherapy of stable COPD?*

Numerous randomized controlled trials have compared tiotropium with ipratropium using clinical endpoints, and all have consistently shown better outcomes in patients using tiotropium, including prevention of exacerbations.<sup>[188-193]</sup> Tiotropium also results in better patient compliance due to its once daily dosing. In addition, several observational studies have reported increased cardiovascular adverse events with ipratropium use (see next section). Hence, tiotropium is a more effective and a safer alternative to ipratropium in the management of stable COPD. The current position of ipratropium is limited only to its use as a rescue medication for the relief of symptoms.

### *What are the possible adverse events with the use of inhaled antimuscarinic agents, and does their risk-benefit profile favor their use in COPD?*

Pooled analysis of 19 studies, as well as data from UPLIFT trial, shows that dryness of mouth is a significant adverse effect with tiotropium use.<sup>[176,194]</sup> Systemic side effects of inhaled anticholinergic agents are less common as their systemic absorption from respiratory and gastrointestinal tracts is poor. However, commonly reported minor side effects when using tiotropium include visual blurring, urinary retention, insomnia, and constipation.<sup>[176,194]</sup>

There has been a considerable debate on cardiovascular safety of inhaled antimuscarinics, especially ipratropium. In the Lung Health Study, mortality and hospitalization due to cardiovascular disease were highest among patients of mild-to-moderate COPD using ipratropium.<sup>[195]</sup> Two large retrospective observational studies have also shown that recent use of ipratropium is associated with an increased risk of cardiovascular events and mortality.<sup>[196,197]</sup> Ipratropium use has also been associated with higher risk of arrhythmias and stroke in large retrospective observational studies.<sup>[198,199]</sup>

In a meta-analysis of 17 studies, Singh *et al.*, concluded that inhaled anticholinergics increase risk of cardiovascular death, myocardial infarction, and stroke.<sup>[200]</sup> This meta-analysis clubbed trials of tiotropium and ipratropium, and also combined placebo-controlled and active-controlled trials. Further, the healthy survivor effect was not taken into consideration. Three other meta-analyses, and a Cochrane review that included only placebo controlled



trials of tiotropium, all concluded that use of tiotropium is not associated with an increased cardiovascular morbidity or mortality.<sup>[180,194,201,202]</sup> After the results of the UPLIFT study and a pooled analysis of 29 trials, the United States Food and Drug Administration (US-FDA) also concluded that the use of tiotropium was not associated with an increased risk of stroke, cardiovascular events, or death.<sup>[203]</sup> However, it is also important to note that the two largest trials evaluating tiotropium monotherapy (the UPLIFT trial and the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial) excluded patients with unstable coronary artery or decompensated cardiac diseases.<sup>[176,204]</sup> Hence, inhaled anticholinergics should be judiciously prescribed to patients with unstable cardiac diseases.

In contrast to tiotropium use by dry powder inhaler, the use of tiotropium by soft mist inhaler (Respimat device, currently not available in India) has been consistently shown to increase the risk of mortality.<sup>[205]</sup> Though the exact reason is not clear, it is postulated that this increase in adverse events could be due to higher drug deposition seen with soft mist inhalers.

### **Recommendations**

1. Short-acting antimuscarinic agent (SAMA) can be used as rescue medication to relieve patient symptoms. (1A)
2. Long-term SAMA monotherapy on regular basis is not recommended. (1A)
3. Long-acting antimuscarinic agents (LAMA) are useful in stable COPD ( $FEV_1 < 80\%$ ) to control symptoms and decrease the risk of exacerbations. (1A)
4. LAMA should be preferred over SAMA. (1A)
5. We suggest close monitoring of patients with coronary artery disease who are treated with LAMA. (UPP)

### **What is the role of long acting beta agonists in the management of stable COPD?**

The LABAs available for management of COPD are salmeterol, formoterol, and indacaterol. A Cochrane review of 23 studies concluded that the use of salmeterol 50  $\mu\text{g}$  twice daily was associated with better lung function and QoL scores, and lesser exacerbations (number needed to treat of 24), though there was no effect on mortality.<sup>[206]</sup> In the towards a revolution in COPD Health (TORCH) study, the use of salmeterol 50  $\mu\text{g}$  twice daily (vs placebo) decreased exacerbation rates and improved SGRQ scores and post bronchodilator  $FEV_1$  values.<sup>[207]</sup> There was however no mortality benefits. A more recent meta-analysis, that also included the results of TORCH trial, concluded that use of either salmeterol or formoterol led to better  $FEV_1$  values, better QoL scores, lesser exacerbations (number needed to treat of 30), and lesser use of reliever medication.<sup>[208]</sup> There is considerable evidence that LABA monotherapy leads to significantly improved lung function, better symptom relief, and lesser exacerbations in patients of stable COPD; but has no significant mortality benefit.

Indacaterol is a novel ultra-long acting selective beta-2 agonist with a half-life of more than 30 h, allowing

convenient once daily dosing at doses of 150-300  $\mu\text{g}$ .<sup>[209]</sup> This agent also has a rapid onset of action within 5 min (similar to salbutamol) because of its high intrinsic efficacy at the receptor level.<sup>[210]</sup> Although promising, the evidence base for this agent is still limited. Three randomized trials have compared indacaterol with salmeterol (INSIST and INLIGHT study) and formoterol (INVOLVE study) in patients with  $FEV_1$  between 30-80%.<sup>[211-213]</sup> Two other randomized trials (INHANCE<sup>[214]</sup> and INTENSITY<sup>[215]</sup>) have shown that indacaterol therapy results in better QoL scores and dyspnea relief as compared to tiotropium. A review of all placebo and active controlled trials of indacaterol concluded that indacaterol in daily doses up to 600  $\mu\text{g}$  was safe, with no increase in adverse vascular events or death.<sup>[216]</sup> Transient cough following inhalation is a common adverse reaction (14-18%) reported in all major trials.

### **What is the role of short acting beta-agonists in the management of stable COPD?**

A recent Cochrane review analyzed 13 short-term studies comparing use of SABA vs placebo in COPD.<sup>[217]</sup> Use of SABA led to better  $FEV_1$  values, better symptom relief, and lesser dropouts from trials. However, none of these studies assessed exacerbation or mortality rates. No long-term studies on SABA use in COPD are available. Similar to that of short acting anticholinergics, the current role of SABA is probably limited to use as rescue medication for symptom relief in patients already using LABA.

### **Does the risk-benefit ratio of inhaled beta-agonists favor their use in the management of COPD?**

Inhaled beta-agonists often lead to some common adverse events like tremors and palpitations, especially in high doses. They have also been shown to cause transient hypoxemia due to their vasodilatory effects on pulmonary vasculature which worsens ventilation-perfusion mismatch in areas of poor ventilation.<sup>[218]</sup> A single dose of beta-agonist increased the heart rate by 9 beats/min, and decreased serum potassium concentration by 0.36 mmol/L.<sup>[219]</sup> In the same meta-analysis it was also shown that long-term use of beta-agonists was associated with sinus tachycardia (OR 3.06) and an increase in major cardiovascular events (OR 2.54). A large retrospective cohort study of 76,661 patients has also shown that current use of SABA or LABA increase the risk of arrhythmias.<sup>[220]</sup> In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program, a large prospective observational study of patients with heart failure, use of bronchodilators was associated with poorer survival.<sup>[221]</sup> Another meta-analysis comparing the effects of beta-agonists and anticholinergics to placebo concluded that anticholinergics (but not beta-agonists) decrease the risk of COPD exacerbation, and that beta-agonists actually increase respiratory mortality.<sup>[222]</sup> The large TORCH study however did not show any increase in risk of cardiovascular adverse events with the use of salmeterol monotherapy.<sup>[223]</sup> A recent meta-analysis, that included the results of TORCH study, concluded that use of LABA

monotherapy decreases exacerbations, and that there was no increase in cardiovascular or respiratory mortality as previously suggested.<sup>[208]</sup>

### **Recommendations**

1. SABA can be used to relieve symptoms of dyspnea as and when needed. (1A)
2. Long-term SABA monotherapy on regular basis is not recommended. (2A)
3. LABA monotherapy can relieve symptoms and decrease the exacerbation rate in patients with stable COPD ( $FEV_1 < 80\%$ ). (1A)
4. Patients with symptomatic coronary artery disease receiving inhaled beta-agonists should be closely monitored. (UPP)

### **What is the role of ICS in the management of stable COPD?**

There are several long-term studies on the use of ICS in patients with COPD. Four of these studies (including the European Respiratory Society's study on COPD (EUROSCOP) study, the COPD on Primary Care Treatment (CO-OPT) study, and the Lung Health Study) included patients with relatively better lung function (mean  $FEV_1$  64-86%).<sup>[224-227]</sup> None of these studies showed any significant benefit of ICS use on  $FEV_1$  decline or reduction in exacerbations or mortality. Only in the Lung Health Study, the use of triamcinolone led to fewer respiratory symptoms and lesser healthcare visits.<sup>[227]</sup> Two other studies, the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study and the TORCH study, included patients with more severe COPD (mean  $FEV_1$  50% and 44%, respectively).<sup>[207,228]</sup> Both these studies showed that ICS use decreased the risk exacerbation, and led to better QoL scores and better  $FEV_1$  values. However, neither study demonstrated any mortality benefit with ICS use. A recent Cochrane review that analyzed 55 studies, concluded that ICS use in COPD decreases exacerbations, results in better QoL scores, and also slows  $FEV_1$  decline.<sup>[107]</sup> However, subgroup analysis based on  $FEV_1$  values was not performed in this review. A systematic review and meta-regression on the effect of ICS in preventing exacerbations also concluded that the modest effect of ICS in decreasing exacerbations was apparent only in a subset of patients with  $FEV_1 < 50\%$ .<sup>[229]</sup> From all these results, it appears that ICS use mainly benefits COPD patients with more severe disease ( $FEV_1 < 50\%$ ).

As opposed to bronchial asthma, ICS are believed to have only limited efficacy in COPD. This may partly be due to progressive reduction in histone deacetylase activity (particularly that of histone deacetylase 2), in lungs of patients with increasing severity of COPD.<sup>[230]</sup> Histone deacetylase 2 is required by corticosteroids to switch off activated inflammatory genes in COPD.

### **What are the adverse effects of ICS use, and does the risk-benefit ratio favor their use in COPD?**

Potential adverse effects of long-term ICS can be either local (oropharyngeal candidiasis, pneumonia, or

tuberculosis) or systemic (decreased bone mineral density and fractures, increased cataract and glaucoma, or possibly worsening diabetes control). Of these, the most worrisome are the increased risk of pneumonia and fractures.

Most studies on ICS use in COPD (including the TORCH study) have consistently revealed a higher risk of pneumonia (OR 1.60) as well as serious pneumonia (OR 1.71).<sup>[231]</sup> There was no increase in pneumonia-specific mortality. Two retrospective observational studies in patients with COPD admitted with pneumonia, have actually shown that ICS users have a lower mortality as compared to non-ICS users.<sup>[232,233]</sup> One of these studies also showed a decreased need for mechanical ventilation, even after adjustment for potential confounders.<sup>[232]</sup> Similarly, another prospective observational study of 460 patients of COPD with pneumonia showed that use of ICS did not lead to an increase in mortality.<sup>[234]</sup> It appears that although ICS use increases risk of developing pneumonia, this does not translate to worse clinical outcomes.

A meta-analysis that exclusively focused on the risk of fractures with ICS use showed a modest but statistically significant increase in the risk of fractures (number-needed-to-harm, 83).<sup>[235]</sup> This modest risk does not outweigh the beneficial effects of ICS in decreasing COPD exacerbations.

### **Recommendations**

1. ICS have a beneficial effect in subgroup of COPD patients with  $FEV_1 < 50\%$ . (1A)
2. ICS have a beneficial effect in subgroup of COPD patients with frequent exacerbations ( $\geq 2$  exacerbations/year). (1A)
3. The risk-benefit profile favors use of ICS in patients with severe COPD. (1A)

### **Which is better for the management of COPD: Tiotropium or LABA?**

The largest study comparing tiotropium with LABA (salmeterol) is the POET-COPD trial that randomized 7,376 patients of COPD ( $FEV_1 < 70\%$ ) and followed them for 1 year.<sup>[204]</sup> Tiotropium use was significantly better in decreasing the exacerbation rate in that study. Adverse reaction rates and mortality were similar. Subgroup analysis showed that beneficial effects of tiotropium in decreasing the exacerbations were uniformly seen in all the GOLD severity subgroups, including the GOLD stage 2 ( $FEV_1$  50-70%) subgroup.<sup>[236]</sup>

A recent Cochrane review analyzed six randomized trials comparing tiotropium with LABA monotherapy.<sup>[237]</sup> The LABA component was salmeterol in three studies, formoterol in one study, and indacaterol in two studies. Tiotropium was better than LABA in decreasing exacerbation rates (OR 0.86). Mortality rates, symptom scores, and QoL scores were similar. An economic evaluation as part of this review also concluded that tiotropium was more cost-effective than LABA monotherapy.

### **Can ICS monotherapy be an alternative to LABA/LAMA monotherapy?**

There is no study which directly compares ICS monotherapy with LAMA monotherapy. A recent review analyzed seven randomized trials that compared ICS/LABA combination with ICS and LABA monotherapy, and extracted data from these studies to compare ICS monotherapy with LABA monotherapy.<sup>[238]</sup> There was no difference in exacerbation rates, adverse events, or symptom scores between the two groups. Though the QoL score was better with ICS monotherapy, and FEV<sub>1</sub> values better with LABA monotherapy; both these differences were below the minimal clinically important threshold. Pneumonia occurred significantly more frequently among patients receiving ICS. The mortality rate was also higher (but not significantly so) with ICS monotherapy. Thus, ICS monotherapy did not confer any added advantage over LABA monotherapy, but increased the risk of pneumonia. Overall evidence therefore does not favor use of ICS monotherapy in management of stable COPD.

### **Which is better for the management of COPD: SAMA or SABA?**

The current role of short acting agents is only as a rescue medication and not as a standalone therapy for the management of stable COPD. A Cochrane review comparing SABA with SAMA concluded that the advantage of regular use of ipratropium over SABA is small if the aim is to improve symptom control, lung function, or exercise capacity.<sup>[239]</sup>

### **Recommendations**

1. LAMA is superior to LABA monotherapy. (1A)
2. ICS monotherapy should not be used. (1A)
3. SABA and SAMA are equally effective when used for COPD. (2A)

### **Is a combination of tiotropium plus LABA better than either of these agents used alone?**

A Cochrane review analyzed five randomized trials of at least 12 weeks duration, comparing LABA plus tiotropium therapy with LABA or tiotropium monotherapy.<sup>[240]</sup> All these studies included patients with FEV<sub>1</sub> < 70%. The combination therapy resulted in a slightly better QoL, symptom scores, and lung function as compared to monotherapy. There was however no difference in the exacerbation rates or the mortality rates. Another meta-analysis compared tiotropium plus formoterol combination to tiotropium alone, and included eight studies of at least 2 weeks duration.<sup>[241]</sup> This meta-analysis also concluded that the combination therapy improved lung function and symptom scores, but did not alter the exacerbation or mortality rates. Thus the combination of LABA and LAMA might benefit a subset of patients who continue to be symptomatic despite monotherapy. This combination does not decrease the exacerbation rates and may not be suitable for patients with frequent exacerbations.

### **What are the benefits of ICS plus LABA combination therapy over LABA monotherapy?**

The first landmark trial which assessed the ICS-LABA combination therapy was the TRial of Inhaled STeroids ANd long-acting  $\beta$ 2 agonists (TRISTAN) study.<sup>[242]</sup> This study randomized 1,465 patients and followed them for 1 year. The combination therapy led to better symptom scores, QoL scores, and lung function; as compared to LABA monotherapy. There was however no decrease in the exacerbation rates. The largest study on this issue till date is the TORCH study, which randomized and followed up 6,112 patients for 3 years.<sup>[207]</sup> The ICS/LABA combination decreased exacerbation rates and improved lung function and QoL when compared to LABA monotherapy. However, there was an increase in pneumonia rates. Also the ICS/LABA combination decreased the risk of cardiovascular adverse events, though the exact mechanism remains unexplained.<sup>[223]</sup>

A Cochrane review analyzing 14 studies (11,794 patients) compared ICS-LABA combination therapy to LABA monotherapy, and concluded that combination therapy decreased exacerbation rates and improved symptom scores, lung function, and QoL; without affecting mortality.<sup>[243]</sup> There was an increase in the incidence of pneumonia with the use of combination therapy. Two separate meta-analyses have also shown mortality benefit with use of ICS-LABA combination therapy.<sup>[208,244]</sup>

### **What are the benefits of ICS plus LABA combination over LAMA (tiotropium) monotherapy?**

The only large study comparing ICS-LABA combination therapy with tiotropium monotherapy is the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) study that randomized and followed 1,323 patients for 2 years.<sup>[245]</sup> Though the dropout rates were more in the tiotropium arm (34.5 vs 41.7%), the combination therapy was better than tiotropium in decreasing mortality and improving QoL. There was no difference in the exacerbations in this study. A Cochrane review also addressed this issue, but did not draw any conclusions due to lack of good quality randomized trials and a very high dropout rate in the inspire study.<sup>[246]</sup>

### **What are the benefits of triple therapy (ICS plus LABA plus LAMA)?**

A total of seven randomized trials and two observational studies (one retrospective and one prospective) have assessed the benefits of triple therapy. All seven randomized trials consistently showed improved lung function and QoL scores with the use of triple therapy.<sup>[220,247-252]</sup> Two of these studies have also shown a beneficial effect of triple therapy in decreasing exacerbations.<sup>[249,250]</sup> One retrospective observational study of 3,333 patients also showed a 33% decrease in risk of exacerbations.<sup>[253]</sup> Another small prospective observational study on 46 patients showed that triple therapy improved lung function and QoL scores.<sup>[254]</sup> A meta-analysis of four randomized trials of triple therapy concluded that such therapy improved the lung function,

dyspnea, and QoL scores; however the effect on decreasing exacerbations was not clear.<sup>[255]</sup>

### **Recommendations**

1. LAMA plus LABA may be used in patients who continue to have symptoms on monotherapy, except for those with frequent exacerbations. (1A)
2. LABA plus ICS should be preferred over LABA alone in patients with  $FEV_1 < 50\%$  or those having frequent exacerbations. (1A)
3. In patients of severe COPD ( $FEV_1 < 50\%$ ), triple therapy may be used in those who are symptomatic despite single or dual bronchodilator therapy. (1B)
4. There is lack of sufficient data to recommend ICS-LABA or ICS-LAMA combination over LAMA monotherapy.

### **Do oral theophyllines have a role in the management of COPD?**

Oral theophyllines have been extensively used in the past. With introduction of inhaled bronchodilators and corticosteroids, which are shown to be more effective, most international guidelines recommend the use of theophylline as a third-line option. Despite this, it is a common practice to prescribe theophyllines in our country due to its low cost.

The bronchodilator effect of theophylline is due to nonselective phosphodiesterase inhibition that occurs at plasma concentrations of 10-20 mg/L. These plasma levels are achieved at doses of 600-800 mg/day (standard dose). Theophyllines also antagonize adenosine receptors, which is responsible for serious adverse events such as seizures and arrhythmias. In view of the narrow therapeutic index, regular monitoring of serum theophylline levels is recommended for patients on long-term theophylline therapy. Such facilities are not routinely available in India. In recent years, theophyllines have also been shown to have a novel anti-inflammatory action related to histone deacetylase (HDAC) activation.<sup>[256]</sup> Airways of COPD patients have diminished HDAC activity. Corticosteroids act by recruiting HDAC to the transcription complex, leading to suppression of transcription of proinflammatory cytokines. Theophylline directly activates HDAC, independent of its binding to glucocorticoid receptors. Thus the anti-inflammatory action of both agents is synergistic. Theophylline induced HDAC activation occurs at plasma concentration  $< 10$  mg/L. These blood levels can be achieved at much lower doses of 300-400 mg/day (low dose) that cause negligible systemic adverse effects. The standard doses are generally recommended when theophyllines are used as a standalone therapy for their bronchodilating property. Low dose theophyllines can be used to potentiate anti-inflammatory action of steroids.

A systematic review of 22 randomized trials concluded that theophylline use improved lung function, increased  $PaO_2$ , and decreased  $PaCO_2$ , and was associated with a

higher patient preference as compared to placebo.<sup>[257]</sup> Low dose theophylline has been shown to improve lung function, QoL, and decrease exacerbations as compared to placebo.<sup>[258]</sup> A prospective observational study concluded that theophylline is well tolerated when used at doses below 400 mg/day, with nonserious adverse events reported in only 1.38% patients.<sup>[259]</sup> Adverse events were more common with concomitant use of macrolides.

Theophylline is shown to be inferior to salmeterol as well as formoterol, in improving lung function, QoL scores, or reducing rescue medication use.<sup>[260-263]</sup> When added to a combination of formoterol and tiotropium, theophylline failed to show any added advantage.<sup>[264]</sup> Hence, current evidence does not support the use of theophylline as a primary agent for pharmacotherapy of stable COPD.

Doxophylline, a newer theophylline analogue, may have a better safety profile, with fewer cardiac and neurologic side effects.<sup>[265]</sup> Doxophylline has not been shown to be superior to theophylline, and long-term studies assessing role of doxophylline in COPD are currently not available.

### **What is the role of selective phosphodiesterase-4 inhibitors in management of stable COPD?**

Roflumilast is an oral selective PDE4 inhibitor approved for the use in COPD at a dose of 500  $\mu$ g once daily. It is predominantly an anti-inflammatory agent rather than a bronchodilator, and should not be coadministered with theophyllines. The beneficial effects of roflumilast on lung function were initially demonstrated in patients with moderate-to-severe COPD and severe COPD.<sup>[266,267]</sup> Both studies showed a trend towards lesser exacerbations with the use of roflumilast. Following these early studies, four recent randomized trials confirmed the benefit of roflumilast in decreasing COPD exacerbations.<sup>[268,269]</sup> A post-hoc analysis of two trials showed that use of roflumilast shifts patients from a frequent to the more stable infrequent exacerbator phenotype.<sup>[270]</sup> A Cochrane review of 23 randomized trials with selective PDE4 inhibitors concluded that these agents offered benefit over placebo in improving lung function and reducing likelihood of exacerbations in patients of COPD.<sup>[271]</sup> They had little impact on QoL or symptoms. Gastrointestinal adverse effects and weight loss were also common. A recent study showed that roflumilast is effective and well-tolerated in the Asian population as well.<sup>[272]</sup> The optimum place of PDE4 inhibitors in COPD management still remains to be defined.

### **What is the role of oral beta-agonists in management of stable COPD?**

Oral beta-agonists are widely used in India as cheaper alternatives to inhaled beta-agonists. But, they need to be administered in much larger doses to achieve comparable bronchodilatation to inhaled agents. Such therapy is commonly associated with systemic adverse events like palpitations, tremors, and arrhythmias. As inhaled bronchodilators have a much better efficacy and safety

profile, oral beta-agonists cannot be recommended as a primary treatment for patients with stable COPD. Their use should be considered as a last resort only in situations where a patient does not wish to use inhaled bronchodilators, in the minimum possible doses that balance acceptable bronchodilatation with minimal side effects.

### Recommendations

1. Oral methylxanthines are not recommended as first line therapy in patients with COPD. (1A)
2. Oral methylxanthines can be used as
  - a. an alternative in patients not taking inhalers for any reason. (1B)
  - b. add-on therapy in patients continuing to have symptoms despite optimum inhaled therapy. (3A)
3. Patients on oral methylxanthines need to be monitored for side effects or drug interactions. (UPP)
4. Roflumilast may be used in frequent exacerbators as an add-on or substitute to ICS. (2B)

### What is the role of mucolytic agents?

Expectoration of sputum is a major bothersome symptom in COPD, and oral mucolytic agents are commonly prescribed for symptom relief. Traditional agents such as bromhexine and guaifenesin showed no significant change in lung function, sputum characteristics, or overall patient well-being.<sup>[273]</sup> The Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) study, a 3-year randomized, placebo-controlled trial using N-acetylcysteine in a dose of 600 mg/day in more than 500 patients, failed to show any decrease in rate of decline in FEV<sub>1</sub> or reduction in exacerbation rate.<sup>[274]</sup> A recent meta-analysis of 30 studies on patients with chronic bronchitis or COPD concluded that mucolytic therapy may result in minor reduction in acute exacerbation rates, but has negligible impact on lung function or overall QoL.<sup>[275]</sup> Quality of several included studies was poor with a high degree of heterogeneity.

### Recommendations

1. Routine use of mucolytic agents is not recommended in patients with COPD. (2A)

### What is the Indian strategy for the management of stable COPD?

When a patient initially presents to a physician with a diagnosis of COPD, he should be categorized into one of the three severity categories as per staging criteria described earlier [Table 9]. As initial therapy, physicians can prescribe a preferred treatment schedule, or an alternative schedule if the patient cannot take (or does not want to take) the preferred schedule for some reason [Table 3]. If a patient continues to be symptomatic despite such treatment, other drugs can be given as add-on therapy. During follow-up, if a patient shifts from one severity category to another, therapy should be accordingly modified. For example if a patient of mild COPD develops worsening symptoms, he would be labeled as moderate COPD and the treatment should be

changed accordingly. Similarly if a patient with mild or moderate COPD develops frequent exacerbations or FEV<sub>1</sub> falls below 50%, he would be categorized as severe COPD and treatment changed accordingly.

### Acute Exacerbations of COPD

#### What is the definition of AECOPD?

An exacerbation of COPD is an acute event characterized by a sustained worsening of any of the patient's respiratory symptoms (cough, sputum quantity and/or character, dyspnea) that is beyond the normal day-to-day variation and leads to a change in medication, and where other causes of acute breathlessness have been clinically excluded.<sup>[276-278]</sup>

#### What is the impact of exacerbation on patients?

COPD is a progressive disease with a gradual decline in lung function. The course of COPD is however punctuated by exacerbations, some of which may be severe enough to cause hospitalizations; this may not only lead to increase in mortality, but is also associated with increased cost of treatment.<sup>[279-282]</sup> Exacerbations are associated with a greater and irreversible decline in lung function.<sup>[282,283]</sup> The occurrence of a severe exacerbation requiring hospitalization increases the risk of further exacerbation. Patients have 25 times higher risk of readmission to hospital after the tenth hospitalization, as compared to the first hospitalization.<sup>[282]</sup> In fact, there is five-fold increase in risk of death after tenth hospitalization.<sup>[282]</sup> Exacerbations are associated with progression of emphysema measured on serial CT scans.<sup>[284]</sup> Moreover, exacerbations are associated with significant decline in QoL,<sup>[285,286]</sup> and add to the cumulative economic burden.<sup>[287]</sup> The mortality is 40% at 1 year in those requiring mechanical ventilation, and all-cause mortality may be as high as 49% at 3 years after hospitalization.<sup>[287,288]</sup>

#### What are the precipitating factors for exacerbation?

Several precipitating factors, both infectious and noninfectious, have been implicated in AECOPD [Table 14].<sup>[289,290]</sup> Infections are the most frequent cause of exacerbations, and both bacterial and viral infections have been detected during exacerbations.<sup>[291-294]</sup> Acquisition of a new strain of *Hemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, or *Pseudomonas aeruginosa* is strongly associated with the occurrence of an exacerbation.<sup>[295]</sup> A pooled analysis of studies utilizing bronchoscopic sampling with the use of a protected specimen brush revealed that bacteria were present in clinically significant concentrations in the airways of 4% of healthy adults, 29% of adults with stable COPD, and 54% of adults with COPD exacerbation.<sup>[295-298]</sup>

The noninfectious precipitants of acute exacerbations include nonadherence to medication, or inhalation of irritants like tobacco smoke or particles. Air pollution has been implicated in causing AECOPD. The effects of diesel particulates, sulfur dioxide (SO<sub>2</sub>), and others have been studied and potential mechanisms by

which airway inflammation is enhanced (increase in bronchial neutrophils and methyl histamine) have been proposed.<sup>[299,300]</sup> The role of air pollution in causing exacerbation is primarily based upon epidemiological studies implicating increased air levels of SO<sub>2</sub>, NO<sub>2</sub>, and black smoke particulate matter.<sup>[301,302]</sup>

Conditions like heart failure, pulmonary embolism, cardiac arrhythmias, pneumothorax, pleural effusion, and pneumonia can cause acute worsening of symptoms in patients with COPD and are considered COPD exacerbation mimics.<sup>[121,276,290,303,304]</sup>

#### **What is the differential diagnosis of AECOPD?**

The differential diagnosis of AECOPD includes the 6Ps; pneumonia, pulmonary embolism, pneumothorax, pleural effusion, pulmonary edema (heart failure), and paroxysmal atrial tachycardia (arrhythmias), and these need to be excluded in patients with acute worsening of breathlessness. Pulmonary embolism is especially difficult to differentiate from COPD exacerbation especially when dyspnea is the only symptom. The prevalence of pulmonary embolism in AECOPD was estimated to be about 19.9%.<sup>[305]</sup> Exacerbation *per se* may also increase the risk of deep venous thrombosis and pulmonary embolism due to diminution in physical activity.<sup>[306,307]</sup>

#### **How is an exacerbation of COPD diagnosed?**

The diagnosis of an exacerbation is primarily clinical, and is based upon of sudden change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation.<sup>[297,308]</sup> Worsening breathlessness is the cardinal symptom of an exacerbation and is usually accompanied by increased cough, fever, wheezing, chest tightness, and change in the color and/or volume of sputum. There may also be non-specific manifestations such as tachycardia, tachypnea, fever, malaise, insomnia, sleepiness, fatigue, depression, and confusion; these are more common in the elderly.

#### **How is the severity of an exacerbation assessed?**

**Table 14: Causes of exacerbation of COPD\***

Infectious (60-80% of all exacerbations)	Environmental factors
Frequent (70-85% of all infectious exacerbation)	Air pollution
Viruses (influenza and parainfluenza viruses, rhinoviruses, coronaviruses)	Non-adherence to respiratory medication
<i>Hemophilus influenzae</i>	Cold air
<i>Streptococcus pneumoniae</i>	Allergens
<i>Moraxella catarrhalis</i>	Tobacco smoking
Infrequent (15-30% of all infectious exacerbations)	
<i>Pseudomonas aeruginosa</i>	
Opportunistic gram-negative species	
<i>Staphylococcus aureus</i>	
<i>Chlamydia pneumoniae</i>	
<i>Mycoplasma pneumoniae</i>	

\*Modified from Papi et al.<sup>[289]</sup> COPD: Chronic obstructive pulmonary disease

The assessment of severity of an exacerbation is based upon patient's clinical status before exacerbation, symptoms, physical examination, comorbidities, arterial blood gas analysis, and other relevant laboratory tests [Table 15]. These parameters can help in categorizing the severity of an exacerbation and also help in deciding the place of management.

#### **How to investigate an exacerbation of COPD?**

The investigations that should be considered for evaluating an AECOPD are as follows:

- Pulse oximetry/Arterial blood gas analysis (wherever available) is helpful to confirm the diagnosis of acute, or acute on chronic, respiratory failure; and also assists in deciding supplemental oxygen therapy. As a general rule, a decline in PaO<sub>2</sub> value by 10-15 mmHg suggests an acute deterioration in a patient with chronic respiratory failure.
- Chest radiographs are worthwhile in excluding an alternative diagnosis like pneumonia, pneumothorax, pleural effusion, and others.
- An electrocardiogram facilitates identification of coexisting cardiac abnormalities.
- A complete blood count is useful in identifying anemia, polycythemia (hematocrit > 55%), and/or leukocytosis.
- Blood biochemical tests aid in identifying coexisting electrolyte abnormalities or hepatic or renal dysfunction. The use of spirometry during an exacerbation is not recommended, as it can be difficult to perform and the results are inaccurate.<sup>[121]</sup>
- Sputum cultures: *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the most common bacterial pathogens involved in an exacerbation. In severe exacerbations requiring invasive ventilation, *Pseudomonas aeruginosa* is an important consideration,<sup>[121,309]</sup> and sputum cultures may help in identifying the correct pathogen.

#### **Recommendations**

- No investigations apart from pulse oximetry are routinely required in patients with acute exacerbations managed in an outpatient setting. (IIA)
- In those hospitalized with AECOPD, serum electrolytes, liver and renal function tests, complete blood count, chest radiograph, electrocardiogram, and arterial blood gas analysis (if available) should be performed in all patients. (IA)
- If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiotic sensitivity test should be performed. (IIA)

#### **How to decide the site of management of a patient with COPD exacerbation?**

More than 80% of exacerbations can be managed on an outpatient basis.<sup>[122,176,310]</sup> The decision to hospitalize a patient is based on overall assessment [Table 15]. The presence of any one of the listed features may warrant hospitalization. Old age, poor nutritional status, presence of comorbidities, acidemia, altered mental status, and

**Table 15: Severity assessment (indications for hospitalization) of exacerbation of COPD\***

Symptoms
Marked reduction in activity of daily living due to dyspnea
Altered sensorium
New onset cyanosis
Signs
Use of accessory respiratory muscles
Paradoxical chest wall movements
Central cyanosis
Systolic blood pressure <90 mmHg
Respiratory rate 30/min
Heart rate >110/min
Asterixis
Altered mental status
Others
Presence of severe comorbid conditions
Lack of social support
Pulse oximetry
SpO <sub>2</sub> <90%

\*Presence of any of these qualifies a patient with need for admission; The ultimate decision to admit depends on the overall clinical assessment of the physician. COPD: Chronic obstructive pulmonary disease

hypotension are associated with poor outcomes in patients hospitalized with COPD.<sup>[311]</sup> A prospective study evaluating CURB65 scores in AECOPD reported 30-day mortality rates of 2.0, 6.7, and 21.3% respectively in low risk (scores 0-1), moderate risk (score 2), and high risk (scores 3-5) groups. It was concluded that CURB 65 score could be used for predicting early mortality in patients with AECOPD.<sup>[312]</sup> In another study; 88,704 patients with AECOPD were assessed for the purpose of stratifying in-hospital mortality. Three variables had high discrimination score of outcomes (blood urea nitrogen > 24 mg/dL, acute mental status change, and heart rate ≥ 110/min). The investigators used these three parameters along with age, and proposed a new score, that is, BAP-65. In those with all three factors, the mortality rates were 13.1 and 14.6% in the derivation and validation cohorts respectively, compared to 0.3% in both cohorts without any of the three factors and age < 65 years.<sup>[313]</sup> The BAP-65 score was further validated in a study across 177 US hospitals. Mortality increased with increasing BAP-65 class, ranging from 1% in subjects in class I (score of 0) to 25% in those meeting all BAP-65 criteria. The need for mechanical ventilation also increased with escalating score (2% in the lowest risk cohort vs 55% in the highest risk group).<sup>[314]</sup> In a recent study comparing CURB-65 score with BAP-65 score to evaluate the need for mechanical ventilation, it was concluded that BAP-65 identifies patients with AECOPD at high risk for need of mechanical ventilation more accurately than does CURB-65.<sup>[315]</sup>

### Recommendation

1. The decision to admit the patient can be made on the basis of level of severity as shown in Table 15 while BAP-65 score may help in deciding patients who need management in an intensive care unit [Figure 1]. (IIA)

### What are the treatment modalities?

The therapeutic components for acute exacerbation

include both pharmacological and nonpharmacological modalities. Three classes of medications are generally used in managing an acute exacerbation- bronchodilators, steroids, and antibiotics. The nonpharmacological strategies includes oxygen therapy and use of mechanical ventilation, both noninvasive and invasive.

### What is the role of short-acting bronchodilators in AECOPD?

SABA, with or without anticholinergic, are essential for symptomatic relief of airway obstruction, and constitute the first line of treatment.<sup>[121,316-319]</sup> Few studies have evaluated the use of bronchodilators in management of AECOPD. There were no significant differences in FEV<sub>1</sub> change in patients treated with beta-agonists or ipratropium bromide, and no additive benefit of adding ipratropium to beta-agonist.<sup>[320]</sup> Also, the optimal dosing and frequency of bronchodilators in AECOPD is not established. There was no difference in clinical outcomes in patients treated every 4 hours with either 2.5 or 5 mg of nebulized salbutamol.<sup>[321]</sup> There was also no significant difference in improvement in FEV<sub>1</sub> between hourly and 20-min dosing of salbutamol.<sup>[322]</sup> Post-hoc analysis however revealed significantly better improvement with the 20-min protocol in those with FEV<sub>1</sub> < 20%.<sup>[322]</sup> The drugs can be delivered by the inhaled route either using pMDI with spacer or nebulizer. There is no significant difference in outcomes based on either method of administration.<sup>[319,323]</sup> In severe exacerbations, altered mental status favors the use of nebulized bronchodilators, while in others pMDI with spacer is preferred due to lower costs and lesser chances of infection. In any case, the patient should be switched over to pMDIs with spacer at the earliest. Importantly, the drugs should not be nebulized using oxygen. Rather patients should receive supplemental oxygen separately through nasal prongs while nebulizing drugs using compressed air, with monitoring of oxygen saturation.

Intravenous or subcutaneous routes of administering beta-agonists are associated with significant adverse events without significant additional bronchodilatation. Intravenous methylxanthines (theophylline or aminophylline) are considered second-line therapy, to be used only in select cases when there is insufficient response to short-acting bronchodilators. Current evidence does not favor routine use of methylxanthines in AECOPD. In a recent systematic review, methylxanthines were found to have modest and inconsistent effects and significant adverse effects.<sup>[324,325]</sup> Two randomized controlled trials have compared intravenous magnesium sulfate (1.5 or 1.2 g) with placebo in patients with AECOPD, and have found modest improvements in lung function.<sup>[326,327]</sup>

### Recommendations

1. Inhaled route is the preferred route of administering bronchodilators. (IA)
2. Inhaled SABAs should be used for the first-line because of the quicker onset of action (IIIA), however SAMA are in no way inferior to SABAs.

3. Nebulized salbutamol at a dose of 2.5 mg every 20 min (or salbutamol pMDI 100 µg 2-4 puffs every 20 min) for 1 h can be given initially. (IIIA) Further dosing will depend on the clinical response, generally every 4-6 h. (IIIA)
4. If additional bronchodilatation is desired, a combination of ipratropium (500 µg nebulized or 20 µg 2-4 puffs with pMDI) and salbutamol (2.5 mg nebulized or salbutamol pMDI 100 µg 2-4 puffs) every 4-6 h can be used. (IIIA)
5. Nebulizer or pMDIs with spacer are equally effective. (IIA)
6. Patients should not be nebulized with oxygen but should receive oxygen separately through nasal prongs, with monitoring of oxygen saturation. (IIA)
7. Intravenous methylxanthines should not be routinely used. (IA)
8. The use of intravenous or subcutaneous route of administering bronchodilators should be reserved in the most seriously ill mechanically ventilated patient demonstrating inadequate response to inhaled therapy. (IIIB)

#### **What is the role of glucocorticoids in AECOPD?**

The pathophysiology of AECOPD is due to severe inflammation triggered by infective and/or noninfective causes, and thus systemic corticosteroids have a role in managing this condition. In a systematic review involving ten studies ( $n = 1051$ ), steroid use resulted in significantly fewer treatment failures (defined as the need to seek additional medical therapy within 30 days), shorter duration of hospitalization, improvement in breathlessness, and FEV<sub>1</sub>; but with no significant effect on mortality. There was an increased likelihood of an adverse event (hyperglycemia, weight gain, or insomnia) associated with corticosteroid treatment with a number needed to harm of any adverse event being 5 (95% CI 4-9).<sup>[328]</sup> In a study of approximately 80,000 hospitalizations for COPD, there was no advantage of high-dose corticosteroids over low-dose regimens; in fact lower-dose regimens actually improved outcomes.<sup>[329]</sup> The study of ICS has been restricted largely to its role as chronic therapy for the prevention of exacerbations.<sup>[229]</sup> Few studies have investigated the role of ICS in management of AECOPD.<sup>[330-332]</sup>

#### **Recommendations**

1. Systemic steroids shorten recovery time, improve lung function, oxygenation, reduce length of hospital stay, and are associated with fewer treatment failures. (IA)
2. A short course of oral prednisolone (or equivalent) at a dose of 30-40 mg/day is recommended for managing acute exacerbations. (IIA)
3. The duration of systemic steroid therapy should be 5-10 days. (IIA)
4. Intravenous steroids should be given in patients who are being mechanically ventilated or cannot tolerate oral medication. (UPP)
5. ICS are not routinely recommended in management of AECOPD. (IA)

#### **Should antibiotics be used in patients with acute exacerbations of COPD? What should be the dose and duration?**

The recommendation for prescribing antibiotics in AECOPD is based on the seminal study where 173 patients of AECOPD were randomly assigned to receive either antibiotics or placebo. Patients receiving antibiotics had a higher success rate in type I exacerbations (defined by increased dyspnea, increased sputum volume, and increased sputum purulence) compared to the placebo group; whereas those with only one or two cardinal symptoms did not benefit from antibiotic therapy.<sup>[308]</sup> In a systemic review of 16 trials ( $n = 2068$ ), there was evidence that antibiotics significantly reduce the risk of treatment failure; however hospitalized patients with severe exacerbations had a substantial benefit on treatment failure rates and mortality.<sup>[333]</sup> Antibiotics can effectively reduce treatment failure and mortality rates in COPD patients with severe exacerbations.<sup>[333,334]</sup> In a recent multicentric trial, treatment with antibiotics was associated with longer median time to next exacerbation even in those with nonsevere exacerbations.<sup>[335]</sup> The antibiotics that are used in managing AECOPD can be broadly classified as first-line (amoxicillin 500-1000 mg thrice a day for 5-7 days, doxycycline 100 mg twice a day for 5-7 days, azithromycin 500 mg once a day for 3 days) or second-line (amoxicillin/clavulanic acid 625 mg thrice a day for 5-7 days; second-generation or third-generation cephalosporins, e.g., cefixime 200 mg twice a day for 5-7 days).<sup>[336]</sup> A meta-analysis of seven randomized controlled trials comparing short (5 days) versus long (7-10 days) treatment with antibiotics (same dosage and same route of administration), revealed no difference in treatment success across the two groups. There were fewer adverse events in the short treatment duration group.<sup>[337]</sup> Fluoroquinolone use is associated with masking of tubercular infection and increased risk of drug resistance to *M. tuberculosis*,<sup>[338-342]</sup> its indiscriminate empirical use in India should be discouraged.<sup>[343]</sup>

#### **Recommendation**

1. Antibiotics should be prescribed for all exacerbations of COPD. (IIA)
2. The choice of antibiotics should be guided by local flora and sensitivity pattern. (IIA)
3. Fluoroquinolones should not be used routinely in treating AECOPD. (IA)
4. Patients with AECOPD being managed in the outpatient setting may be treated with first line antibiotics. (IIA)
5. Hospitalized patients or those requiring mechanical ventilation (noninvasive/invasive) should be treated with second line drugs. (IIA)
6. The duration of therapy should be 5-7 days. (IIA)

#### **What is the role of procalcitonin in deciding for antibiotic therapy?**

Several studies have evaluated the role of procalcitonin for initiating and stopping antibiotics in patients with respiratory tract infections. In a recent review evaluating 14 trials (4,221



participants), the authors concluded that procalcitonin can help in guiding the duration of antibiotic treatment in acute respiratory infections. There was significant decrease in total antibiotic exposure without increase in mortality.<sup>[344]</sup> But, procalcitonin use led to greater duration of antibiotics and mechanical ventilation, and overall increase in cost.<sup>[345]</sup> Moreover, there is no evidence on the use of procalcitonin to guide antibiotic therapy in AECOPD.

### **Recommendations**

1. Biomarkers do not have a role in management of acute exacerbation of COPD. (IIA)
2. Procalcitonin should not be used routinely in guiding antibiotic usage in COPD. (IIA)

### **When should oxygen be prescribed, and at what dose?**

The goal of inpatient oxygen therapy is to maintain  $\text{PaO}_2 \geq 8 \text{ kPa}$  ( $\geq 60 \text{ mmHg}$ ) or  $\text{SpO}_2 \geq 90\%$  in order to prevent tissue hypoxia and preserve cellular oxygenation. Because of the characteristics of the oxyhemoglobin dissociation curve, increasing the  $\text{PaO}_2$  to values greater than 60 mmHg confers little added benefit but significantly increases the risk of  $\text{CO}_2$  retention, which may lead to respiratory acidosis.<sup>[121]</sup> The choice of delivery devices depends on the patient's oxygen requirement, efficacy of the device, reliability, ease of therapeutic application, and patient acceptance. A Venturi air-entrainment mask mixes oxygen with room air, and provides an accurate and constant  $\text{FIO}_2$ . The Venturi mask is the oxygen delivery device of choice in AECOPD.<sup>[121]</sup> The nasal cannula delivers a variable  $\text{FIO}_2$  depending on the minute ventilation; the lower the minute volume the higher the  $\text{FIO}_2$ .<sup>[121]</sup> The nasal cannula can be used in AECOPD in those intolerant to Venturi mask, and after the acute phase of the exacerbation. An arterial blood gas analysis or oximetry is advised upon switching delivery devices. Frequent monitoring is advisable in the unstable patient.<sup>[346,347]</sup>

### **Recommendation**

1. Oxygen should be prescribed to hypoxemic patients with a target  $\text{SpO}_2$  between 88-92%. (IA)
2. Oxygen should be delivered preferably by a Venturi mask, and by nasal cannula upon recovery. (IIA)
3. Arterial blood gas monitoring is recommended in patients receiving oxygen therapy, wherever available. (IIA)

### **What is the indication of noninvasive ventilation during exacerbation of COPD?**

Noninvasive ventilation has revolutionized the management of AECOPD. Its use is associated with reduced rates of intubation, reduced length of hospital stay, and decline in mortality.<sup>[348-350]</sup> The benefit with NIV is observed even in those with hypercapnic encephalopathy, if it is used judiciously.<sup>[351,352]</sup> The patient needs to be closely monitored with facilities for intubation being readily available. NIV has also been demonstrated to be useful in weaning from invasive ventilation. In a review of 12 studies involving 530 patients, the use of NIV was associated with

significant reduction in mortality, ventilator associated pneumonia, and intensive care unit and hospital lengths of stay.<sup>[353,354]</sup> The indications and protocol of NIV are summarized in Table 16. Patients should be assessed at 1, 2, 3, 4, and 24 h after initiation of NIV; clinically and by monitoring arterial blood gases (or pulse oximetry).<sup>[348,355]</sup> The presence of any one factor listed in Table 16 should prompt consideration of invasive mechanical ventilation (Adapted from).<sup>[348,355]</sup>

NIV can be used even in settings where arterial blood gas monitoring is not routinely available in patients with acute onset of breathlessness with tachypnea ( $\text{RR} > 25\text{-}30/\text{min}$ ) and/or clinical signs of hypercapnia. Facilities for pulse oximetry, positive pressure ventilation, and intubation should be readily available. Patients not improving in 2-4 h should be promptly referred to a center with better facilities for further management.

### **Recommendations**

1. NIV should be used early in the management of respiratory failure due to AECOPD. (IA)
2. NIV can also be used in weaning from invasive mechanical ventilation. (IIA)
3. NIV can be used even in settings where arterial blood gas monitoring is not routinely available. (UPP)

### **What are the indications of invasive mechanical ventilation?**

With the advent of NIV, the need for invasive mechanical ventilation in management of AECOPD has significantly declined. The need for invasive mechanical ventilation is associated with poorer outcomes, the overall mortality among AECOPD patients is lower than mortality among patients ventilated for non-COPD causes.<sup>[356]</sup> There is evidence to suggest that patients likely to benefit with invasive ventilation are denied admission to intensive care units because of unwarranted prognostic pessimism.<sup>[357]</sup> The indications and ventilatory protocol of invasive mechanical ventilation are listed in Table 17. Adopted from.<sup>[348,355]</sup>

### **When should the patient be discharged from hospital?**

The decision to discharge a patient from the hospital is a clinical art, with scarce data to clearly define the optimal duration of hospitalization in AECOPD.<sup>[161,358,359]</sup> In general, the patient should be clinically stable for at least 24-48 h, should be able to eat and sleep comfortably, and should be ambulatory for activities of daily living. In addition, there should be minimal requirement of short-acting bronchodilators, and the patient should be able to use long-acting bronchodilators.

### **When should the patient be followed-up after the discharge from hospital?**

Patients should be followed-up 4-6 weeks after discharge from hospital. At every visit, due emphasis should be laid on smoking cessation, the inhaler technique checked, and the effectiveness of each medication monitored.<sup>[360]</sup>

**Table 16: Indications, protocol, and parameters of failure of noninvasive ventilation in acute exacerbation of COPD**

Indications	
Respiratory acidosis (arterial pH $\leq$ 7.35 and/or PaCO <sub>2</sub> 45 mmHg)	
Severe dyspnea	
Respiratory rate >30 breaths/min	
Use of accessory muscles of respiration	
Presence of paradoxical breathing	
Protocol	
Full face mask better tolerated in the acute setting	
Start with an inspiratory pressure support of 6-8 cm H <sub>2</sub> O and CPAP of 3-4 cm H <sub>2</sub> O	
Adjustments	
Increase inspiratory pressure and CPAP by 2 and 1 cm H <sub>2</sub> O, respectively	
Titrate to tidal volume (>5 mL/kg), respiratory rate (<35 breaths/min) and blood gases	
Maximum inspiratory pressure and CPAP generally used is 15-16 and 7-8 cm H <sub>2</sub> O, respectively	
Air leaks should be minimized	
Parameters for failure	
Failure in improvement of clinical parameters and gas exchange at 1 h	
Development of alteration in sensorium	
Hemodynamic instability	
Inability to tolerate oronasal mask	

COPD: Chronic obstructive pulmonary disease, CPAP: Continuous positive airway pressure

**Table 17: Indications and protocol of invasive mechanical ventilation**

Indications	
pH $\leq$ 7.25	
Unable to tolerate non-invasive ventilation or failure of noninvasive ventilation	
Respiratory or cardiac arrest	
Massive aspiration	
Diminished consciousness	
Failure to handle secretions	
Heart rate <50/min with loss of alertness	
Hemodynamic instability without fluid responsiveness	
Severe ventricular arrhythmias	
Life threatening hypoxia	
Protocol	
Mode	Volume-assist control mode
Initial tidal volume	4-6 mL/kg
Respiratory rate	8-12/min
PEEP	5-8 cm H <sub>2</sub> O
Inspiration: Expiration ratio	1:3-1:6
Flow waveform	Square waveform
Goals	
Plateau pressure	30 cm H <sub>2</sub> O
PaO <sub>2</sub>	55-60 mm Hg
pH	7.2-7.4

Modified from GOLD guidelines. PEEP: Positive-end expiratory pressure, GOLD: Global initiative for chronic obstructive lung diseases

For patients who are hypoxemic during an exacerbation, arterial blood gases, and/or pulse oximetry should be evaluated prior to hospital discharge and in the following 3-6 weeks. If the patient remains hypoxemic, long-term supplemental oxygen therapy may be required.

### Non-pharmacological management of COPD

#### *Should smoking cessation be advised? What are the methods of smoking cessation?*

Smoking cessation is without doubt the most effective

method to prevent COPD.<sup>[361]</sup> This has been established by a number of studies over the last several decades, and is recommended by all major guidelines.<sup>[7,8]</sup> In addition to a reduction in the rate of decline of FEV<sub>1</sub> in stable COPD, smoking cessation is also associated with reduction in the frequency of exacerbations.<sup>[362]</sup> Standard guidelines [Table 18] are available to both physicians and patients for quitting smoking; guidelines have also been made available by the National Tobacco Control Program under the MOHFW in India.<sup>[361,363,364]</sup>

A variety of pharmacotherapies have also become available. These include:

- Nicotine replacement therapies:** Act by the supplementation of nicotine during the period of abstinence and help to reduce withdrawal symptoms. Various forms are available including gums, tablets, patches, and inhalers. Use of nicotine replacement therapies has been shown to increase the quit rate by 50-70% compared to placebo.<sup>[365]</sup>
- Bupropion:** Acts by inhibiting the reuptake of both dopamine and norepinephrine in the brain; antagonism of the nicotine receptor has also been demonstrated.<sup>[366]</sup> There are higher odds (OR 2.12) for quitting smoking with the use of bupropion as compared to placebo.<sup>[367]</sup>
- Varenicline:** It is a partial agonist of the  $\alpha$ 4 $\beta$ 2 nicotinic receptor. It has a dual mechanism of action. It is both a partial agonist of the nicotinic receptor (wherein it provides some amount of stimulation) as well as simultaneously blocks the effect of nicotine on the receptor in case the patient smokes.<sup>[366]</sup> A meta-analysis of 69 trials showed that varenicline had the highest odds (2.55; 95% CI = 1.99-3.24) of smoking cessation out of all the available pharmacotherapies.<sup>[367]</sup>

There is no fixed protocol on the use of these agents. However, pharmacotherapy should be offered to all patients in view of the significantly increased quit rates with these modalities. The quit rate is even better if intensive counseling sessions are combined with pharmacotherapy.<sup>[365,368-370]</sup>

### Recommendations

- A smoking history, including pack years or smoking index (number of bidis/cigarettes smoked per day multiplied by number of years smoked; mild, moderate, and heavy smokers are defined as having a smoking index of < 100, 100-300, and > 300, respectively<sup>[371]</sup>) should be documented for all patients with COPD. (UPP)
- All COPD patients, regardless of age, should be encouraged to stop smoking, and offered help to do so, at every opportunity. (1A)
- Nicotine replacement therapies (varenicline or bupropion), combined with an appropriate support program, should be offered to people who are planning to stop smoking. (1A)

### *What is the role of health education in COPD?*

Intuitively, health education should improve the management

**Table 18: Simple steps in assisting patients on smoking cessation**


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Guidelines for physicians on tobacco cessation (the 5A strategy)

- ASK (about tobacco use)
- ASSESS (the status and severity of use)
- ADVISE (to stop)
- ASSIST (in smoking cessation)
- ARRANGE (follow-up program)

Guidelines for patients

- Review your tobacco use: Accept that smoking is a problem and harmful for your health
- Make a decision and determination to quit. Do not be over confident that you can quit any time you like
- Share your decision with family, friends, and doctor; and accept their help
- Fix a quit date, and do not postpone the set date
- Remove ashtrays and other objects that are reminders to the smoking habit
- Keep away from trigger situations
- Adopt healthy lifestyle such as relaxation, exercise, plenty of water, fruits, vegetables, and avoid tea/coffee/alcohol
- Take help from family, friends, and doctor.

First few steps of quitting tobacco smoking

- To reduce quantity
  - Change to nonpreferred brand
  - Keep a record of the amount and frequency of tobacco use
  - Decrease the number of puffs when smoking
  - Leave large stubs
  - Don't inhale deeply
- To deal with triggers when you have an urge to smoke (trigger coping)
  - For extraordinary urge to take tobacco, try alternatives (chewing gum, toffee, peppermint, cardamom)
  - Increase your water intake
  - Breathe deeply and quietly
  - Do some other work to engage your mind and to keep your mind off tobacco
  - Delay the act of smoking-count till 100 and think of pleasant situations
- Once you quit
  - Learn to say "no" to tobacco offers from others
  - Don't take even a single puff
  - Try to remain in smoke free areas
  - Avoid company of smokers and even tobacco chewers
  - Make a group of people who have quit tobacco-share their experiences
  - Collect the money saved from each pack of cigarette or "paan masala".
  - Buy a gift for your loved ones with that money
  - Try alternate ways to deal with mental stress and tension; such as relaxation, deep breathing, and listening to music
  - Remember there can be some withdrawal symptoms after quitting; such as headache, irritability, lack of concentration, etc., But bear with them. These are temporary and disappear in a few days
- Even if you fail in quitting smoking
  - Don't get disheartened, TRY AGAIN
  - Seek help of those who have quit smoking
  - Seek professional help and medical advise

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of patients with any disease, not only COPD. Health education may include informal out-patient discussions, didactic lectures, group sessions, and others. The role of multimedia, especially the role of the internet and online support groups should also be considered. However, modifying the habits of a lifetime is difficult. Various topics that may be covered in an educational program include:

1. Risks and benefits of stopping smoking and cessation strategies.
2. Avoidance of potential risk factors in nonsmokers.
3. The concept of normal lung function.
4. Inhaler use: It is important to check that the inhalers being used by the patient are the ones prescribed

- and that they are being used properly. The inhaler technique should be demonstrated to the patient and accompanying attendants and reinforced at every visit. The demonstration of the inhaler technique to the attendants is especially important in case of the elderly.
5. Use of other medications, including oxygen.
  6. Nutrition.
  7. Adequate physical exercise, especially if the patient is not enrolled in a pulmonary rehabilitation program.
  8. Breathing strategies.
  9. Advice related to travel and sexuality.
  10. End of life planning.

### **Recommendations**

1. Health education is an integral component of a COPD management program. Special importance should be given to inhaler technique, which should be demonstrated to the patient and accompanying attendants, and reinforced at every visit. This is particularly true for elderly patients. (UPP)
2. For COPD patients who are not active smokers, potential etiological exposures (environmental tobacco smoke, biomass fuel smoke, etc.) should be asked for and avoided. (UPP)

### **What are the components of nonpharmacological management of stable COPD?**

Various therapies are available for the management of stable COPD. Some of these modalities may be as good as or better than pharmacotherapy. These methods are meant to be applied to patients with stable COPD, that is, not during a period of acute exacerbations. They include pulmonary rehabilitation, oxygen therapy, noninvasive ventilation, bronchoscopic techniques, and surgery.

### **What is the role of pulmonary rehabilitation?**

The ATS and the European Respiratory Society have defined pulmonary rehabilitation as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce healthcare costs through stabilizing or reversing systemic manifestations of the disease".<sup>[372]</sup>

COPD is a multisystem disorder, affecting the skeletal muscles, bones, and other organs besides the lungs. In general, treatment is targeted to the respiratory system, ignoring the other organ systems involved. However, much of the morbidity of COPD is because of involvement of other organ systems. Pulmonary rehabilitation addresses these issues. Pulmonary rehabilitation has been used as a last resort for those failing medical management. However, this is not an optimal use of this strategy. In fact, patients should be integrated into rehabilitation programs from an early stage in the course of the disease.<sup>[372]</sup> The various components of pulmonary rehabilitation

include: (a) Patient selection and assessment; (b) exercise; (c) nutritional support; (d) psychosocial support; and (e) education.

The major component of pulmonary rehabilitation is exercise training. Exercise training is based on three major principles: Intensity (higher intensity producing greater results), specificity (only those muscles trained showing effect), and reversibility (cessation of regular exercise training resulting in decrease in the effect).<sup>[373]</sup> Regions to be included in exercise training include the upper limbs, lower limbs, and inspiratory muscles. The type of training also varies; it can either be continuous or interval, and strength or endurance based. The type of exercise sessions carried out is highly variable from center to center. The duration of each session can range from 15-45 min; the sessions can be carried out at intervals ranging from daily to once weekly. The intensity of each workout varies from 50% of the peak  $\text{VO}_2$  to the maximum tolerated. The duration of the program is also highly variable from 4 to 12 weeks, with greater benefits for longer programs.<sup>[8,372,373]</sup> A meta-analysis on the duration of pulmonary rehabilitation could not be carried out because of heterogeneity.<sup>[374]</sup>

Pulmonary rehabilitation has been proven to be effective in almost all aspects of management of COPD. A Cochrane review of 31 trials evaluated the effect of pulmonary rehabilitation on health-related QoL (HRQoL) and exercise capacity. The change in the QoL scores with pulmonary rehabilitation was above the minimal clinically important difference, while the change in exercise capacity was just below it.<sup>[375]</sup> A Cochrane review, which included nine trials with a total of 432 patients, found a significant improvement in both the QoL and exercise capacity, which was greater than the minimal clinically important difference.<sup>[376]</sup> The increase in HRQoL was greater with strength training as compared to endurance training; also, interval training was of similar benefit as compared to continuous training. Surprisingly, the evidence favoring high intensity exercise was weak.<sup>[377]</sup> Another analysis compared interval training to continuous training and found no difference on the QoL and exercise capacity between the two.<sup>[378]</sup> An advantage of inspiratory muscle training in addition to standard exercise was reported in another meta-analysis.<sup>[379]</sup> It is also suggested that starting pulmonary rehabilitation soon after an acute exacerbation leads to a reduction in future hospital admissions and mortality.<sup>[376]</sup>

Although the utility of structured rehabilitation programs is proven without doubt, it is often difficult to set up such programs in resource poor settings. A few small randomized clinical trials available from India have studied home-based rehabilitation and 'pranayama' breathing, and found positive results.<sup>[380-383]</sup> Exercise training options have also been detailed in resource poor settings.<sup>[384]</sup> Also, it is intuitive to advise patients to exercise daily as per their capacity because if the associated health benefits.

The use of nutritional therapy as part of structured rehabilitation programs has been the subject of much debate. The presence of malnutrition in patients presenting with COPD has been well-established. Various changes are noted in these patients, the prominent ones being loss of both total body fat mass as well as fat free mass.<sup>[372]</sup> Some of the methods available to assess the nutritional status of these patients include subjective assessment, assessment of BMI, skinfold anthropometry, bioimpedance analysis, and dual-energy X-ray absorptiometry.

The use of subjective assessment for nutritional status has been assessed in a resource poor setting for the initial evaluation of COPD patients.<sup>[385]</sup> The debate in this issue stems from the fact that most studies have found inconsistent benefits with nutritional supplementation in COPD.<sup>[386]</sup> However, a recent Cochrane meta-analysis of 17 studies with 632 participants, who received at least 2 weeks of nutritional support, reports a difference in the outcome parameters of respiratory muscle strength and QoL.<sup>[387]</sup> As of now, the role of nutritional supplementation should be decided on a case to case basis by a specialist.

### **Recommendations**

1. Structured pulmonary rehabilitation programs should be set up where feasible. (1A)
2. In the absence of structured programs, patients should be advised regarding unsupervised daily physical activity. (3A)
3. All patients should be assessed for nutritional status at least by BMI at the initial visit and followed-up by serial BMI estimation at every visit. Any patient found to be malnourished should be referred for nutritional advice to a specialist. (UPP)

### **What are the indications for oxygen therapy in stable COPD?**

The benefits of supplemental oxygen therapy were proven in two landmark trials carried out in the 1980s, that is, the Nocturnal Oxygen Therapy Trial (NOTT) and the MRC trials.<sup>[388-391]</sup> At present, supplemental oxygen is recommended in stable COPD for the following group of patients:<sup>[392]</sup>

- Those with severe daytime resting hypoxemia, that is,  $\text{PaO}_2$  of  $< 55$  mmHg (or pulse oxygen saturation of  $< 88\%$ ), or
- $\text{PaO}_2$  56-60 mmHg (or pulse oxygen saturation of 88-92%) with evidence of end-organ dysfunction including pulmonary hypertension, congestive cardiac failure, and erythrocytosis with hematocrit  $> 55\%$ .
- Additionally, hypoxia should be demonstrated on two occasions at least 3 weeks apart in the stable patient.

However, there are other patient groups in whom the evidence is not as clear as to the benefit of oxygen supplementation.<sup>[393-395]</sup> These include patients with moderate daytime hypoxemia, only nocturnal hypoxemia, and only exercise-induced hypoxemia. A recent analysis found no benefit of oxygen therapy in patients with

moderate daytime hypoxemia or nocturnal hypoxemia alone.<sup>[396]</sup> The ongoing Long-Term Oxygen Treatment Trial (LOTT) trial is likely to clarify some of these issues.

There have been numerous studies and meta-analyses evaluating the issue of supplemental oxygen therapy. One analysis included 31 studies with 534 participants and studied the effect of ambulatory oxygen in COPD. The authors concluded that ambulatory oxygen improved all pooled outcomes related to exercise capacity. However, the study was limited by heterogeneity, publication bias, and small sample size.<sup>[397]</sup> Another meta-analysis, which included only six trials, concluded that oxygen supplementation did not lead to an improvement in the mortality in patients with only nocturnal or mild daytime hypoxemia.<sup>[398]</sup> The most recent Cochrane review included 18 trials with 431 participants and reports that the use of supplemental oxygen relieved dyspnea in patients with mild or no hypoxemia. Interestingly, these patients were not eligible for oxygen therapy according to either absolute or relative indications.<sup>[396,399]</sup>

Oxygen therapy may be administered by various delivery devices such as oxygen cylinders, liquid oxygen systems, and oxygen concentrators. Patients should be advised regarding the various options available locally and the expenses involved. Patients should also be given advice regarding the proper use of oxygen, and especially to avoid smoking while receiving oxygen, because of the increased risk of fire and explosions. The prescription for oxygen should be written clearly, detailing all the technicalities involved. Advice should also be given regarding the target oxygen saturation, in order to avoid over-oxygenating the patient and precipitating hypercapnic respiratory failure.<sup>[400]</sup>

### Recommendations

1. Long-term supplemental oxygen therapy is indicated for those with severe daytime resting hypoxemia (1A) defined as:
  - a. PaO<sub>2</sub> of < 55 mmHg (or pulse oxygen saturation of < 88%), or
  - b. PaO<sub>2</sub> of 56-60 mmHg (or pulse oxygen saturation of 88-92%) with evidence of end-organ dysfunction such as pulmonary hypertension, congestive cardiac failure, and erythrocytosis with hematocrit > 55%.
  - c. Determined on two occasions at least 3 weeks apart in the stable patient.
2. The role of oxygen supplementation in other situations is currently not clear and should be decided on a case to case basis. (2B)
3. Supplemental oxygen should be titrated to achieve a pulse oximetric saturation of 90-92% or a PaO<sub>2</sub> of 60-65 mmHg. (3A)
4. Patients should breathe supplemental oxygen for at least 16 h a day. (1A)
5. Patients on long-term oxygen therapy should be reviewed at regular intervals with either pulse oximetry or arterial blood gas analysis as indicated. (UPP)
6. Patients should be warned about the risk of fire if

smoking is continued during the period of oxygen supplementation. (UPP)

### What is the role of noninvasive ventilation in stable COPD?

Although the use of NIV is well-established in the treatment of AECOPD,<sup>[401,402]</sup> its role in stable COPD is controversial.<sup>[7,8]</sup> There are many potential benefits, including improvement in respiratory muscle strength, maximum inspiratory pressure, gas exchange, and others.<sup>[403,404]</sup> A Cochrane review of four studies involving the use of nocturnal NIV for 3 months in hypercapnic patients found no consistent clinically or statistically significant effect on lung function, gas exchange, respiratory muscle strength, sleep efficiency, or exercise tolerance.<sup>[405]</sup> Another meta-analysis published in 2007 included 15 studies (six randomized control trials and nine non-randomized trials).<sup>[406]</sup> The randomized trials did not show any benefit in gas exchange or other parameters; while the non-randomized trials demonstrated benefit in QoL, exercise capacity, and lung hyperinflation. However, there was significant heterogeneity in this analysis.<sup>[406]</sup> A recent meta-analysis and review studied both the short- and long-term effects of NIV.<sup>[407]</sup> The results showed that there was a short-term benefit of NIV on gas exchange and exercise capacity which was not sustained over longer periods; there was no short- or long-term beneficial effect on FEV<sub>1</sub> or mortality. Additionally, there was an overall beneficial effect on breathlessness, but not on the rate of hospitalization.<sup>[407]</sup> The indications for NIV in stable COPD were laid out at a consensus conference in 1999,<sup>[408]</sup> and are still relevant and applicable:

1. Documentation of the diagnosis of COPD by a physician, optimization of other therapies, and exclusion of sleep apnea if required.
2. Presence of both symptoms (such as fatigue, dyspnea, morning headache, etc.) and physiologic criteria (one of the following):
  - a. PaCO<sub>2</sub> ≥ 55 mmHg or PaCO<sub>2</sub> of 50-54 mmHg and nocturnal desaturation (oxygen saturation by pulse oximeter ≤ 88% for continuous 5 min while receiving oxygen therapy at 2 L/min)
  - b. PaCO<sub>2</sub> of 50-54 mmHg and hospitalization related to recurrent (≥ 2 in a 12-month period) episodes of hypercapnic respiratory failure.

### Recommendations

1. Noninvasive ventilation may be used in patients with recurrent exacerbations who require frequent use of mechanical and noninvasive ventilation during the acute episodes; the patient should be referred to a specialist center for management. (3A)
2. The choice of the machine for NIV depends on the presence of coexistent sleep apnea syndromes. (UPP)

### What are the bronchoscopic techniques useful in stable COPD?

Also known as bronchoscopic lung volume reduction, the use of bronchoscopic techniques to achieve atelectasis of emphysematous lung areas has shown an expansion

in the past decade.<sup>[409]</sup> Various devices are available, ranging from spigots to endobronchial valves to extra anatomical bypass tracts.<sup>[410-414]</sup> At present, the field is still evolving and these treatments are best carried out in specialist centers.

### **Recommendation**

1. Bronchoscopic techniques are upcoming modalities of treatment, the data are too sparse to make an evidence-based recommendation.

### **What are the surgical treatments that can be offered for the treatment of COPD?**

There are three primary surgical modalities for the treatment of COPD. These are bullectomy, lung volume reduction surgery, and lung transplantation.

#### **Bullectomy**

The presence of large bullae is one of the common findings in patients with COPD. However, extensive data on the natural history of bullae is not available. Generally, enlargement of these bullae occurs with complications like dyspnea, hemoptysis, chest pain, and pneumothorax. Some of the accepted indications for bullectomy are the presence of single large bullae compressing the remaining lung, breathlessness due to the bullae, hemoptysis, and reduction in the FEV<sub>1</sub> to < 50%.

#### **LVRS**

Though the procedure was proposed a long while ago, LVRS came into vogue after results of the National Emphysema Treatment Trial (NETT) were published in 2003.<sup>[415]</sup> The proposed mechanisms of improvement of lung function include increased elastic recoil pressure, decrease in the degree of hyperinflation, and decreased regional ventilation perfusion mismatch.<sup>[416]</sup> The NETT trial divided patients of COPD into four groups, namely upper lobe predominant disease with either low or high exercise capacity and non-upper lobe predominant disease with low or high exercise capacity. There was unequivocal benefit for patients with both upper lobe predominant disease and low exercise capacity, and a clear increase in mortality for those with non-upper lobe predominant disease and high exercise capacity; the risk benefit ratio for the other two groups was equivocal.<sup>[415]</sup> A Cochrane review of eight trials, which was heavily dominated by the NETT trial, demonstrated almost similar results. In addition, there was an increase in 90-day mortality following LVRS; while long-term QoL, lung function, and exercise capacity were better.<sup>[416]</sup> The standard accepted indications and contraindications for LVRS are predominantly upper lobe emphysema and low post-rehabilitation exercise capacity.<sup>[7,8]</sup> The contraindications include FEV<sub>1</sub> < 20% predicted or either non-upper lobe predominant emphysema or a very low DLCO (< 20% predicted).

#### **Lung transplantation**

Lung transplantation has been carried out since the

1960s; however, it came into routine clinical practice only since the mid-1980s.<sup>[417]</sup> It is an accepted treatment for COPD, which is the most common indication for the procedure. It has been shown to improve the QoL and exercise capacity; however, survival benefit has not been shown consistently.<sup>[418]</sup> The accepted indications for lung transplantation include a BODE index of 7-10 with an FEV<sub>1</sub> < 20% predicted, or a DL<sub>CO</sub> < 20% and homogenous emphysema or cor pulmonale.<sup>[7,8]</sup>

### **Recommendation**

1. Bullectomy may be carried out in properly selected patients in appropriate centers. (3A)
2. LVRS may be offered to properly selected patients at centers capable of performing the procedure. (1A)
3. Lung transplantation may be offered to properly selected patients at centers capable of doing the procedure. (1A)

### **Are influenza and pneumococcal vaccinations useful in patients of COPD?**

Immunization with influenza and pneumococcal vaccines is generally considered to be useful. The data to support this practice are sparse. Pneumococcal vaccination has been shown to reduce the risk of pneumococcal bacteremia but not that of pneumonia.<sup>[419]</sup> Although there are data to support the use of influenza vaccination, it is based on the availability of surveillance data on the type of strains circulating in the community. As this data is lacking in this country, giving firm recommendations is difficult. The recent adult immunization guidelines promulgated by the Association of Physicians in India recommended against immunization for this reason.<sup>[420]</sup>

Two recent meta-analyses showed that influenza vaccination reduced the number of exacerbations in patients of COPD, especially in patients with severe disease; there was no difference in patients with less severe disease.<sup>[421,422]</sup> Regarding pneumococcal vaccination, there was a discrepancy between two recent meta-analyses. While a Cochrane review did not demonstrate any reduction in the rate of exacerbations, another meta-analysis showed a significant reduction in the rate of exacerbations of patients with severe COPD.<sup>[422,423]</sup>

### **Recommendations**

1. Influenza vaccination is likely to be beneficial in patients with severe COPD and/or frequent exacerbations. (UPP)
2. Pneumococcal vaccination is likely to be beneficial in patients with severe COPD and/or frequent exacerbations. (UPP)

### **What is the role of prophylactic antibiotics in COPD?**

Although prophylactic antibiotics have been used in COPD for at least 40 years, its benefit of use has only recently been demonstrated.<sup>[424]</sup> The postulated benefit is a decreased risk of exacerbations while the potential risks include adverse effects of the drugs used, development of

resistance, and increased cost. The largest trial available compared azithromycin 250 mg daily with placebo for 1 year. A significant decrease in the time to the first exacerbation as well as in the number of total exacerbations was noted.<sup>[425]</sup> There was increased risk of colonization with macrolide-resistant organisms and impaired hearing in some patients. Other randomized trials have also shown similar results; however, the numbers studied were not as large, except for one trial which used moxifloxacin.<sup>[426-428]</sup>

The data available are limited, though favorable. Further data would be needed, especially on the impact of the use of antibiotics in a high tuberculosis burden setting and also whether this would lead to increased antibiotic resistance in the community.

### Recommendation

1. Antibiotics should not be prescribed as a routine for the prevention of exacerbations of COPD. (2A)

### What should be the advice for patients of COPD regarding air travel?

Patients of COPD are liable to develop complications on exposure to high altitudes, including air travel. Though commercial airliners travel at altitudes varying from 25,000-45,000 feet above sea level; the cabin is usually pressurized to an altitude not above 8,000 feet above sea level. This is associated with a decrease in the partial pressure of oxygen in inspired air. COPD patients who require oxygen and those with borderline oxygen saturation at sea level may need additional oxygen during the flight.<sup>[429]</sup> Other risks include the expansion of air in large bullae because of the low pressure leading on to pneumothorax.

The methods of assessment of fitness for air travel include the hypoxia challenge test and the use of regression equations. Patients of severe COPD, especially those requiring long-term oxygen therapy and those with large bullae should be assessed by a specialist before air travel.<sup>[430]</sup> These patients may need additional oxygen during air travel; some airlines provide this facility if informed in advance. Otherwise, patients should be given general advice to carry all their medications and spacers with them.

### Recommendation

1. Patients with severe COPD and those on long-term oxygen therapy should be assessed before air travel by a specialist. (UPP)

### Vernacular term for COPD

In view of the common terminology, 'dama' used for both COPD and asthma in Indian vernacular languages, there has been a long-felt need to coin a separate identifying name for COPD. The point was discussed at length at the workshop. Of various suggestions, that were put forward the working group found the term 'kaladama' (black asthma) as an appropriate choice for COPD to distinguish

from dama (bronchial asthma). Similar terminology is in common use for some other diseases in India. The distinct terms will be helpful for patient-doctor interactions and public understanding of COPD as a progressive disease. The readers are welcome to offer suggestions and alternate terms with reasonable explanations. Those who agree with the terminology may also send their views (dr.skjindal@gmail.com).

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**How to cite this article:** Gupta D, Agarwal R, Aggarwal AN, Maturu VN, Dhooria S, Prasad KT, et al. Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint ICS/ NCCP (I) recommendations. *Lung India* 2013;30:228-67.

**Source of Support:** Indian Chest Society and National College of Chest Physicians (India), **Conflict of Interest:** None declared.