SECTION III

Pulmonary Medicine
Introduction
With rapid industrialization, urbanization and smoking habits, prevalence of COPD is escalating. Today, it is the 12th most prevalent disease & 4th leading cause of death in the world, which by 2020 would acquire 5th & 3rd rank respectively. COPD incorporates chronic obstructive bronchitis & emphysema. Obstruction of small airways, loss of lung elasticity, enlargement of airspaces, & destruction of lung parenchyma with closure of small airways are some of the features.

Chronic bronchitis is defined by presence of cough with or without expectoration on most of the days of 3 months for 2 consecutive years, provided diagnosis of emphysema, lung abscess, bronchiectasis & tuberculosis are excluded. It is not necessarily accompanied by air ow limitation, however, excessive mucus secretion is associated with peripheral airway obstruction. Emphysema on the other hand is dilatation & distortion of lung distal to terminal bronchiole with destruction. An overlap of 10% between COPD and asthma is been noted.

There has been extensive research on asthma & revolution in asthma management. However, COPD is neglected with very little research and advances in therapy. It is increasingly appreciated that COPD is an important disease that is rising world over and that there is a need to develop new management profile to prevent progression of the disease. Financial viability, easy acceptability, availability and eectivity coupled with minimal untoward effect of expected out of the newer modalities.

Table 1 : Liability
- There are about 160 million smokers in India.
- Approximately 14 million Indians are currently suffering from COPD.
- One million Indians die in a year due to smoking related diseases.
- Would be fifth most prevalent disease by 2020.
- Expected to be the third leading cause of death by 2020.
- It is the only chronic disease that is showing progressive upward trend in both mortality and morbidity.
- Incidence is increasing in females across the world.
- More common in males. M:F ratio is 5:2.7 (in India).
Definition

COPD is progressive airflow limitation that is poorly reversible and is associated with abnormal inflammatory response of the lung to any noxious agents. It is considered in an individual having symptoms of chronic cough, sputum production &/or shortness of breath & history of exposure to risk factors. Diagnosis is confirmed by spirometry (Establishing airflow limitation that is poorly reversible). In situations where spirometry is not available, symptomatology, prolonged force expiratory time, a low peak ow, is consistent with COPD, though there is poor specificity.

Severity

Classification

Simple classification of disease severity for educational and management purpose is adopted. All FEV\textsubscript{1} values are post – bronchodilator ones. Respiratory failure means PaO\textsubscript{2} < 60 mm Hg (8kpa) with/without PaCO\textsubscript{2} > 50 mm Hg (6.7 kpa) while breathing room air. There is no perfect relationship between degree of airflow limitation & symptoms, through treatment of COPD is largely based on symptoms. This approach is aimed at practical implementation.

Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: At Risk</td>
<td>Chronic Symptoms (cough &amp; sputum production)</td>
</tr>
<tr>
<td></td>
<td>Normal spirometry</td>
</tr>
<tr>
<td>I: Mild COPD</td>
<td>With / without chronic symptoms (cough &amp; sputum production)</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} ≥ 80% of predicted</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} / FVC &lt; 70% Mild airflow limitation</td>
</tr>
<tr>
<td>II: Moderate COPD</td>
<td>Usually chronic symptoms (cough &amp; sputum production) with shortness of breath developing on exertion.</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} between 80% to 50% of predicted.</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} / FVC &lt; 70% Worsening airflow limitation</td>
</tr>
<tr>
<td>III: Severe COPD</td>
<td>Chronic symptoms (cough &amp; sputum production) with increased shortness of breath and repeated exacerbations.</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} between 50% to 30% of predicted.</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} / FVC &lt; 70% Further worsening airflow limitation</td>
</tr>
<tr>
<td>IV: Very Severe</td>
<td>Chronic symptoms (cough &amp; sputum production), Severe shortness of breath or Chronic respiratory failure.</td>
</tr>
<tr>
<td></td>
<td>Severe airflow limitation (FEV\textsubscript{1} may be ≤ 30% or even more)</td>
</tr>
</tbody>
</table>

Table 3

| Stage 0: At Risk | : Symptomatic, but lung function still normal.                                 |
| Stage 1: Mild   | : Lung function mildly abnormal, but individual not aware of the same.         |
| Stage 2: Moderate | : Deteriorating lung function, individual symptomatic, seeks medical attention due to exacerbation or breathlessness. |
| Stage 3: Severe | : Worsening of airflow limitation, aggravation of symptoms and recurrent exacerbations, affecting quality of life. |
Risk Factor

Environmental
- Tobacco smoking irrespective of the type remains the major risk factor. Cigarette, bidi, hukka, chillum, pipe, cigar are some of the types of smoking encountered in India.
- Occupational chemicals and dust – when exposure is prolonged and intense.
- Indoor air pollution – burning of biomass fuel for cooking and heating in poorly vented dwellings.
- Outdoor pollution – vehicular pollution constitute the main burden of inhale particle on lung. Industrial pollution is next in order.
- Passive smoking contributes to some extent.
- Recurrent respiratory infections in early childhood is associated with small lung and therefore, yearly declined in lung functions starts with low peak and developed in some percentage of cases into COPD.

Host
- Genes
  1) Normally there is decline of 15 to 30 ml in FEV₁ every year. In smokers it is accelerated 2 to 5 times the normal. But, such decline occurs only in 15% of whites and 5% of Asians. It suggests that genetic factor determines in which smokers airflow limitation would develop.
  2) Familial clustering of patients with early onset COPD.
  3) α₁ Anti-trypsin deficiency though occurs in < 1% of cases, the level below 10% of normal value may lead to early emphysema that is exacerbated by smoking indicating genetic predisposition.
  4) Reported risk of COPD is 10 times normal in Taiwanese population with polymorphism in gene associated with increased TNF-α production. However, in British population have same polymorphism do not have such increased risk.

These features clearly indicate genetic preponderance in certain cases.
- Hyper responsiveness
  Though uncertain, still hyper responsiveness of the airways is considered as risk factor for COPD.
- Low birth weight probably because of poor nutrition in foetal life, results in small lung and the decline in lung function starts with a low peak value.

Pathophysiology
There is chronic inflammatory process in COPD that differs from asthma with different in ammatory cells, mediators, effects & response to treatment.
- In ammatory Cells & Mediators: In ammation occurs in the peripheral airways & the lung parenchyma. Bronchioles obstructed by fibrosis & infiltration with macrophages & T – lymphocytes which are predominantly CD8 T – cells. Bronchial biopsy reveals infiltration of macrophages, CD8 T – cells, & increased number of neutrophils. In ammatory Mediators are less well defined. Leukotriene B4, cytokines TNF - α, Neutrophil – chemotactic chemokine, Interleukin – 8. There is probably a complex interaction between cells & mediators resulting in progressive obstructive changes in smaller airways, & destruction of lung parenchyma. Macrophages play a crucial role. Smoking & other irritants may activate macrophages to release neutrophil chemotactic factors like Leukotriene B4 & IL8. Neutrophils & macrophages release multiple proteinases that breakdown connective tissues resulting in emphysema. Mucus hypersecretion is also one of the results. Cytotoxic T – cells may be involved in destruction of
alveolar wall epithelial cell to the release of perforins & TNF - α.

- Protease & antiprotease interaction: Neutrophil elastase, proteinase 3 & cathepsins can produce emphysema in lab animals, evidenced by increased secretion of desmosin, & rapid decline in lung function. Neutrophil elastase is inhibited by α1-antitrypsin in the lung. In addition, serine proteases are stimulants of mucus secretions. Macrophage & neutrophil derived matrix metalloproteinases, 1(Collagenase), MM9(gelatinase b) activity of which is increased in patients with emphysema. In short, they are capable of inducing emphysema.

Normally all proteolytic enzymes are countered by anti – proteases like α1-antitrypsin & at least three tissue inhibitors of MMP (TIMP 1 – 3). They prevent parenchymal injury. Genetic polymorphism impairs the function or production of these proteins.

- Oxidative Stress: There is an increase in concentration of hydrogen peroxide, 8 – isoproston (marker of stress) in breath of patients with COPD. Oxidative damage of antiproteases enhances in ammation & proteolytic injury, by increasing production of IL8, TNF - α, & other in ammatory proteins.

- Systemic effects: There is increased release of reactive oxygen, circulating concentration of IL6 & C reactive proteins. They are further increased in exacerbations. Profound weight loss is a predictor of increased mortality independent of poor lung function. It is associated with increase

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Table 4: Protease – Antiprotease Imbalance in Chronic Obstructive Pulmonary Disease.

<table>
<thead>
<tr>
<th>Increase Imbalance</th>
<th>Decrease Imbalance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil elastase</td>
<td>α1-Antitrypsin</td>
</tr>
<tr>
<td>Proteinase 3</td>
<td>Secretory leukoprotease inhibitor</td>
</tr>
<tr>
<td>Cathepsins</td>
<td>Elafin</td>
</tr>
<tr>
<td>Matrix metalloproteinases (1, 2, 9, 12)</td>
<td>Tissue inhibitors of matrix metalloproteinases</td>
</tr>
</tbody>
</table>

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Fig. 1: Oxidative Stress in COPD (Barnes PJ. COPD. NEJM July 2000, vol 343 No. 4).
release of TNF - \( \alpha \) with leptin responsible for weight loss probably due to enhanced metabolism, important targets being skeletal & respiratory muscles. Improved nutrition & short course of anabolic steroids improve lung function.

- Amplifying mechanisms: Protease imbalance & in ammatory changes that occur in COPD are seen to occur in cigarette smokers without COPD, though to lesser extent. This indicates that accelerated decline in lung function may be due to amplification of response to irritants. It may be due to latent viral infection.

Though smoking is the prime cause of COPD, quitting smoking does not result in resolution of in ammatory process, suggesting perpetuating mechanisms, that may explain occurrence of COPD in individuals who have stopped smoking many years before their first symptom. An increase in exhaled NO\(_2\) & oxidative stress markers, presumably reflect increased in ammation that occurs in exacerbations.

Investigations
- Chest X-Ray – though reveal hardly any diagnostic features, it invariably excludes differential diagnosis like pulmonary tuberculosis.
- HRCT Thorax is also helpful in establishing hyper in ation and emphysematous bullaeas.
- Pulmonary function test – Obstructive ventilatory defect with bronchodilator reversibility test helps in excluding diagnosis of chronic asthma. Inhaled gluco-corticosteroid (ICS) reversibility test to identify patients having air ow limitations those respond to ICS treatment. Such test be perform after a trial of 6 to 12 weeks of ICS. If objective benefit is not achieved, ICS should be discontinued. Diffusion capacity of the lung is helpful in establishing diagnosis of emphysema.
- 6 Minute walk work helps in establishing incapacitating status. It gives an assessment of limitation of activities of daily life due to the disease.
- Arterial Blood gas Analysis – Invariably performed in patients having FEV\(_1\) < 40% and clinical science suggestive of respiratory failure or right heart failure. PaO\(_2\) < 60mm of Hg with/ without PaCO\(_2\) > 45 mm of Hg at sea level with room air breathing indicates respiratory failure, which may be associated with cyanosis.
- 2D Echo helps in establishing pulmonary hyper tension and also excludes diagnosis of cardiac failure.
- \( \alpha \)1 Anti-trypsin deficiency when COPD develops before 45 years or it develops in patients having strong family history, the deficiency screening be undertaken.
- Cadmium level interaction between host and environmental exposure to occupational chemicals like cadmium is vital. Hence its level helps in diagnosis.

Diagnosis
Diagnosis of COPD should be based on history of exposure to risk factors, characteristics symptoms of chronic cough, sputum production and/or breathlessness and spirometry.

- Chronic cough – present daily/intermittently, often through out the day seldom only at night time.
- Chronic sputum production – any pattern of sputum production i.e. persistent may indicate COPD.
- Acute bronchitis – repeated attacks may lead to COPD.
- Dyspnoea – progressive, persistent, worsening of exercise and during respiratory infection.
- The diagnosis should be confirmed on spirometry where invariably FEV\(_1\), FVC should be majored. If it is not available, then clinical symptoms stated above, signs of dyspnoea, increased forced expiratory time would help in diagnosis. A low peak ow though consistent with COPD, it has poor specificity.
Chronic cough and sputum production often precede the development of airflow limitation by many years in most of the cases, though all may not develop COPD.

**Differential Diagnosis**

**Table 5**

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Obliterative Bronchiolitis</td>
</tr>
<tr>
<td>Diffuse Panbronchiolitis</td>
<td></td>
</tr>
</tbody>
</table>

**Chronic Asthma**

Onset often in childhood, variably symptoms at night, early morning, history of rhinitis, allergy, eczema may be present. Strong family history may be given. But essentially markedly reversible airflow limitation present.

Salient features of differentiations are tabulated in Table No.5.

**Table 6**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Mild-life</td>
<td>Early in life (Often childhood)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Slowly progressive</td>
<td>Vary from day to day and peak in the night/early morning</td>
</tr>
<tr>
<td>History</td>
<td>Long smoking history or exposure to smoking and bio-mass fuel</td>
<td>History of allergy, rhinitis and/or eczema.</td>
</tr>
<tr>
<td>Inflammatory cells</td>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Airway hyper responsiveness</td>
<td>Poorly irreversible</td>
<td>Largely reversible</td>
</tr>
</tbody>
</table>

**Congestive Cardiac Failure**

In addition to clinical features fine crepitations in both infrascapular region, chest X-ray showing cadiomegaly, lung functions indicating no airflow limitation but restrictive ventilatory defects are some of the findings noted.

**Bronchiectasis**

Copious purulent expectoration, commonly associated with bacterial infection, presence of gross clubbing, coarse crepitations on auscultation, chest X-ray/HRCT thorax revealing bronchial dilation and thickening at times showing gross cystic changes are few of the features.

**Tuberculosis**

Tuberculosis occurs at any age in addition to the symptoms of chronic cough/expectoration, X-ray chest revealing lung infiltrates or cavitations, microscopic detection of AFB in high locally prevalent area suggest the diagnosis.

**Obliterative Bronchiolitis**

Onset in younger age non-smokers, there may be history of exposure to fumes or rheumatoid arthritis, C.T. Scan revealing hypo dense area on expiration are few of the findings encountered.

**Diffuse Panbronchiolitis**

Mostly male non-smokers practically all are having chronic sinusitis. Chest X-ray/HRCT thorax show diffuse small centrilobular nodular opacities with hyperinflation.
Management

Principles

- Cigarette smoking cessation
- Relieve symptoms
- Improve exercise tolerance
- Prevent disease progression
- Prevent / treat complications
- Prevent / treat exacerbations
- Reduce mortality
- Prevent / minimise untoward effects of treatment

Plan

- Assessment and monitoring
- Reduction in risk factors
- Management of stable COPD and exacerbations
- Hospitalisation

Assessment and Monitoring

- Medical history of exposure to risk factors – duration and intensity
- Past history of asthma, allergy and sinusitis or respiratory infections
- Family history of COPD
- Pattern of development of symptoms
- History of exacerbations / hospitalization
- Presence of Comorbidities like coronary artery disease / rheumatic heart disease
- Current medical treatment
- Impact of disease on patient’s life
- Familio-social support are to be addressed on priority.
- Investigations mentioned earlier can be performed for individual assessment.

Reduction in Risk Factors

- Tobacco smoking cessation is a single most effective and cost effective intervention to reduce the risk of development / progression of COPD. Unless there is high degree of motivation, no other means would be successful. Therefore, all efforts be made to motivate the smokers in quitting.
- Occupational Exposure primary prevention by elimination/ reduction of exposure to noxious agent at work place or secondary prevention by surveillance and early detection is paramount.
- Indoor air pollution – preventing burning of biomass fuel in poorly ventilated houses be done strictly.
- Outdoor air pollution – be achieved by implementing pollution under control legislation on war footing. Afflicted individuals are advised to stay indoor during pollution episodes and to avoid vigorous exercise in outdoor. Wherever available public announcement of air quality be followed religiously.

Management of Stable COPD and Exacerbations

A. Pharmacotherapy

It prevents & improves symptoms, reduces frequency & severity of exacerbations & improves exercise tolerance.

- Bronchodilators: These drugs have pivotal role to play. Used to relieve intermittent or worsening symptoms & also on regular basis to prevent or reduce persistent symptoms. Methylxanthines, short – or long – acting β2 agonist, & short – or long – acting anti
– cholinergics can be administered, singly or in combination. Tiotropium Bromide is long – acting anti – cholinergic drug of promise. It has revolutionized management of COPD, acting on M1 –, M2 –, M3 – receptors, dissociating quickly from M2 & blocking M1 & M3 for longer duration of time, has unique action based effects in reduction of cholinergic vagal tone of airways. The drug is safe, easy to administer, with minimal side – effects, good acceptance & affordability being some of the positive features.

Table 7

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral</th>
<th>Injectable</th>
<th>Nebulization</th>
<th>MDI</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylxanthines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Theophylline</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>b) Aminophylline</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>β2 agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Salbutamol</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>b) Terbutaline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>c) Formoterol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>d) Salmeterol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Ipratropium</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>b) Tiotropium</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- Glucocorticoids: It is preferable to administer inhaled glucocorticoids, that too only in patients showing improvement & documented spirometric response, & in those having FEV1 < 50% as well as repeated exacerbations. It should be advocated orally or parenterally in all exacerbations. It can be given by nebulization as well. Prolonged treatment may relieve symptoms in appropriate patients, however, does not modify long – term decline in FEV1. Long – term treatment with oral glucocorticoids is not recommended.

Table 8

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral</th>
<th>Injectable</th>
<th>Nebulization</th>
<th>MDI</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bectomethasone</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Budesonide</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mometasone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ciclisonide</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

- Vaccines: Pneumococcal & in uenza vaccines are available. In uenza vaccine is beneficial given once or twice in a year. It reduces serious illness & death in patients by 50%. However, general use of pneumococcal vaccine is not recommended due to lack of evidence.
- Antitussives, Mucolytic Agents: Patients having thick, tenacious sputum could be benefited, otherwise its regular use in stable patients is not recommended.
Antibiotics: Only to be used in infectious exacerbations & other bacterial infections.

Respiratory Stimulants: Irrespective of the type, regular use is not recommended.

### Hospitalization

Table 9: Indications

<table>
<thead>
<tr>
<th>Marked Increase in Intensity</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Disease</td>
<td>Diagnostic Uncertainty</td>
</tr>
<tr>
<td>New Signs</td>
<td>Older Age</td>
</tr>
<tr>
<td>New Arrhythmias</td>
<td>Home Support</td>
</tr>
<tr>
<td>Poor Initial Response</td>
<td>Facilities</td>
</tr>
</tbody>
</table>

Patients having severe form of background COPD developing new signs like cyanosis, having increase in intensity of symptoms like resting breathlessness, developing new arrhythmias, showing poor initial response to treatment, and having comorbidities like coronary artery disease should be admitted. Diagnostic uncertainty, older age, lack of facilities & home support are some of the other indications for hospitalization. Assessment of lung functions, ABG analysis, chest X-ray, ECG, other necessary biochemical tests to exclude diabetes, poor nutrition & electrolyte imbalance, & sputum/blood culture – susceptibility studies should be undertaken & appropriate treatment be executed.

Persistent risk factors, repeated exacerbations, cor pulmonale & comorbidities carry adverse prognosis. In End – stage COPD patients having exacerbations showing respiratory acidosis & need for ventilator support carry high risk of mortality.

### Non-pharmacotherapy

**Non-invasive ventilation:** Use of noninvasive positive pressure ventilation (NIPPV), which eliminates the necessity of intubation. NIPPV improves oxygenation & reduces work of breathing. The combination of oxygen therapy and NIPPV would be more effective. Controlled trials are now needed to quantify the benefits. There is no convincing evidence to the indication of ventilatory support in the routine management of stable COPD.

- **Pulmonary Rehabilitation:** Reduction in symptoms, improving quality of life and enhanced participation in day to day activities are some of the aims of the programme. Exercise training, nutritional counseling and education, are the main components. Patients at all stages of disease are benefited from the programme. Improvement in exercise tolerance, shortness of breath and fatigue are observed. The benefits are sustained even after a single programme of a period of two months. It can be conducted on inpatient, outpatient basis and even at home.

- **Patient education:** It helps to improve skills, ability to cope up with illness. It is effective way for smoking cessation. It improves responses to exacerbations, initiates discussion and understanding of advanced directives as well as end of life issues.

- **Long-term Oxygen Therapy (LTOT):** Patients with chronic respiratory failure can be administered oxygen for over fifteen hours per day. It has beneficial impact on pulmonary arterial pressure, polycythemia, exercise capacity, lung mechanics & mental status. Patients belonging to stage III & stage IV having PaO₂ < 55mmHg (7.3kPa) or SaO₂ < 88% with or without hypercapnia; or having PO₂ between 55mmHg (7.3kPa) to 60mmHg (8kPa) or SaO₂ of 89% with evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia, are incorporated.

- **Lung - Volume reduction surgery:** Removal of the most emphysematous part of the lung to improve ventilation by reduction in hyperin ation and thus enhancing mechanical efficiency of inspiratory muscles has generated considerable interest. Careful selection of the patient after initial period of pulmonary rehabilitation is rewarding. Patients with upper lobe emphysema do
the best. Results of a multicenter study i.e. National Emphysema Treatment Trial from USA to assess the efficiency & cost effectiveness would be helpful.

Newer Treatments
Apart from smoking cessation, no treatment slows the progression of COPD. This disease is still associated with active in ammation and progressive proteolytic injury to lung tissue. Suggesting pharmacologic intervention. A better understanding of cellular as well as molecular mechanism provides new molecular targets for the development of drugs.

- Mediator antagonists - Providing logical targets for the development of receptors antagonist is needed. 5 Lipoygenase inhibitors like zileuton, the leukotriene B$_4$ antagonist, interleukin-8 antagonists, TNF-α blockers and antioxidants are under development. But, it is not certain that antagonising a single mediator would have a substantial clinical effect. Since many a mediators with overlapping actions are involved in COPD.

- Protease inhibitors – Several inhibitors of neutrophil elastase are now in clinical development. The study shows no benefit with one that is tested. Several proteases are involved in COPD. Therefore, difficult to monitor with single inhibitor. Cathepsin inhibitors, Secretory leukoprotease inhibitor are a few. However, endogenous antiproteases such as α1 antitrypsin and elafin supplementation may be attempted.

- New Anti-in ammatory Drugs – Phosphodiesterase 4 inhibitor, one has been shown promising results in clinical trial. Other novel anti-in ammatory approaches underdevelopment include inhibitors of NF-kB, inhibitors though still a research tool.

Future
Further developments pertaining to high and increasing global prevalence of COPD and continued increase in morbidity and mortality as well as high cost, more attention needs to be focused on prevention and treatment of the disease. Positive approach to the management with several measures to improve quality of life with symptomatic disease. COPD may also be due to causes other than smoking. Why some are susceptible is not understood, but it is likely that advances and molecular genetics will provide the means to identify those at risk. It is likely that newer drugs will be effective in future. It is important to detect the disease at early stage before symptoms begin. To prevent the progression of the disease to the point which consumes a huge amount of medical resources.

References