Essence Series

Essential information in brief

A Cipla initiative

COPD

FOREWORD

Recent years have witnessed an explosion of knowledge in almost all the fields of medicine. Developments in one medical arena often have a significant impact on other disciplines.

Patients often have several coexisting conditions; hence, knowledge of diseases not directly related to one's area of expertise has assumed considerable importance.

Cipla, as part of its commitment to provide user-friendly scientific information, presents the **ESSENCE SERIES.** *A series of booklets that provide concise, updated and relevant information on important disease conditions.*

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INTRODUCTION

Though Chronic Obstructive Pulmonary Disease (COPD) has been recognized for a long time, it has not received the attention it deserves for many decades. It was believed that little could be done for these patients and management remained stagnant.

The prevalence of this disease has been on the rise all over the world. It is now a leading cause of morbidity and mortality. The increasing burden has stimulated global interest in COPD, leading to better understanding of the disease and its effective management.

COPD is no longer considered a progressive, relentless disease. Scientific research has now shown that it is preventable and treatable. We have entered a new era where novel effective pharmacological and non-pharmacological therapies are available for managing COPD. These can provide considerable benefit to these patients and improve quality of life.

The purpose of this booklet is to update medical professionals on various aspects of COPD.

February 2005

WHAT IS CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)?

Chronic obstructive pulmonary disease (COPD) is a **preventable and treatable** disease state characterized by **airflow limitation** that is **not fully reversible**. The airflow limitation is usually **progressive** and is associated with an **abnormal inflammatory response** of the lungs to noxious particles or gases, primarily caused by **cigarette smoking**. Although COPD affects the lungs, it also produces significant **systemic consequences**.

WHAT IS THE MAGNITUDE OF THIS PROBLEM?

The global scenario of COPD

COPD is presently ranked fourth among the leading causes of mortality worldwide. By the year 2020, it is expected to rank among the first three diseases to claim the maximum number of lives. According to recent estimates, 600 million people suffer from COPD all over the world. The disease claims 2.75 million lives every year.

The Indian scenario of COPD

The Journal of the Association of Physicians of India 2004, reports that 65 million Indians suffer from various chronic respiratory diseases excluding tuberculosis. While current prevalence figures for COPD are not available, in 2001, *the Indian Journal of Chest Diseases and Allied Sciences* reported that close to 13 million Indians suffered from COPD. About 62 percent of these were men and the remaining women.

WHAT CAUSES COPD?

The aetiology of COPD is multi-factorial, but tobacco smoking, active (cigarette, bidi, cigar, pipe, etc) and passive, is unquestionably the major causative factor. It accounts for approximately 80% of the attributable risk.

Other risk factors, which can cause COPD, are:

- Occupational exposure to coal, silica and gold
- Environmental pollution due to exhaust from vehicles and industries
- Indoor pollution due to smoke from wood fire

- Premature birth and recurrent childhood infections impair lung growth and may lead to lower maximally attained lung function in adulthood
- Genetic predisposition i.e. alpha-1 antitrypsin deficiency: Alpha-1 antitrypsin is a protective enzyme, which protects the lung parenchyma against the destructive activity of the proteases

COPD – A MULTISYSTEM DISEASE

In COPD pathological changes occur in the airways, lung parenchyma and pulmonary vessels. Besides these, COPD also affects other organs, particularly skeletal and respiratory muscles, and produces systemic and metabolic effects leading to weight loss.

Pathophysiological changes in patients with COPD

There are various processes contributing to the pathological changes in COPD.

Cigarette smoke and other irritants stimulate the alveolar macrophages and epithelial cells to produce interleukin-8 (IL-8) and leukotriene-B4 (LTB4) which stimulate the neutrophils to produce enzymes called proteases. These cause mucus hypersecretion leading to chronic cough and breakdown of elastin in the alveolar walls resulting in emphysema, which results in abnormalities in gas exchange.

IL-8 stimulates fibroblasts to divide and redivide to produce connective tissue proliferation and fibrosis, causing airway obstruction and hyperinflation.

The irritants also lead to protease-antiprotease imbalance leading to increased activity of proteases.

These irritants can also lead to thickening of the walls of the pulmonary blood vessels, thereby resulting in pulmonary hypertension. This causes enlargement of the right ventricle due to back pressure called cor pulmonale, which can lead to right sided heart failure.

There is also release of tumour necrosis factor-alpha (TNF-alpha), which causes pathological changes in the muscles, leading to muscle weakness.

In contrast to COPD there is no airway hyper-responsiveness in asthma. Unlike COPD where neutrophils are the main inflammatory cells found in the respiratory tract, eosinophils are found in the respiratory tract of asthmatics.

DIAGNOSING COPD

A diagnosis of COPD should be considered in any smoker or ex-smoker over the age of 35 who has one or more of the characteristic symptoms listed in Table 1 and a history of exposure to risk factors for the disease.

Table 1: Key Indicators for Considering a COPD Diagnosis

• **Chronic cough:**	• Present intermittently or every day • Often present throughout the day; • Seldom only nocturnal
• **Chronic sputum production:**	• Any pattern of chronic sputum • production may indicate COPD
• **Dyspnoea that is:**	• Progressive (worsens over time) • Persistent (present every day) • Worse on exercise • Worse during respiratory infections

Reference: *Global Initiative for Chronic Obstructive Lung Disease (GOLD Guidelines), update 2003.*

WHAT ARE THE FINDINGS ON EXAMINATION?

The findings on clinical examination in patients with COPD are variable. The examination may be normal during early stages of the disease. As the disease advances following clinical signs may be found:

- Increased respiratory rate usually > 18/minute
- Thin patients with low body mass index (BMI)
- Pursed-lip breathing which helps to keep the airways open, thereby increasing lung emptying and reducing the air trapping
- Use of accessory respiratory muscles due to increased effort of breathing
- Barrel chest deformity due to air trapping and hyperinflation
- Raised jugular venous pressure (JVP)
- Rhonchi because of airway obstruction

CONFIRMATION OF DIAGNOSIS OF COPD

In a patient with symptoms and signs suggestive of COPD, investigations are required to confirm the presence of airflow obstruction and to assess the patient for complications and associated conditions. Complete blood count, ECG, chest X-ray and arterial blood gas measurements should be done. Diagnosis of COPD should always be confirmed with spirometry.

WHAT IS SPIROMETRY?

Spirometry is a simple test to measure the amount of air a person can breathe in and out, and the amount of time taken to do so. Spirometry is needed to make a firm diagnosis of COPD, to stage the severity of the disease, and to monitor disease progression.

Fig. 1: Spirometer

Important parameters in COPD measured with the spirometer are:

- ***Forced vital capacity (FVC):*** Total amount of air exhaled when the patient inhales maximally and then exhales as forcefully and deeply as possible. It is measured in litres.
- ***Forced expiratory volume in one second (FEV_1):*** Volume of air exhaled in the first second of maximal expiration after a maximal inspiration. It is measured in litres.
- ***FEV_1/ FVC:*** FEV_1 expressed as a percentage of FVC gives a clinically useful index of airflow limitation.

By comparing these volumes with those predicted for the patient's age, sex and height, and computing the ratio of FEV_1 to FVC, it is possible to diagnose airflow obstruction with confidence. It is also possible to diagnose mild airflow obstruction and to assess the severity of airflow obstruction.

Post bronchodilator FEV_1/FVC less than 70% and FEV_1 less than 80% confirms the presence of airflow limitation that is not fully reversible i.e. COPD.

Other important parameters in COPD are:

Total Lung Capacity (TLC): Total lung capacity is the volume of air in the lungs at the end of maximum inspiration. It is measured by multiple breath helium dilution method and body plethysmography.

Normal range is 5 – 6 L.

It is increased in COPD because of air trapping.

Residual Volume (RV): Residual volume is the volume of air remaining in the lungs at the end of maximum expiration.

Normal range is 1.2 L.

It is increased in COPD because of air trapping.

Functional Residual Capacity (FRC): Functional Residual Capacity is the volume of air in the lungs at the end of a normal expiration.

The normal range is 2.5 – 3 L.

The functional residual capacity is increased in COPD because of air trapping.

Inspiratory Capacity (IC): The maximum volume of air that can be inspired into the lungs from the end of a quiet expiration up to total lung capacity is the inspiratory capacity.

IC is decreased as COPD advances in severity.

HOW CAN PATIENTS WITH COPD BE DIFFERENTIATED FROM OTHER DISEASES?

A major differential diagnosis of COPD is asthma. In most cases, the history, examination and investigations clearly differentiate these two chronic respiratory diseases (Table 2). Sometimes the two conditions may coexist.

Table 2: Differentiating Features Between COPD and Asthma

	COPD	Asthma
Onset	Mid-life	Early in life (often childhood)
Smoker or ex-smoker	Nearly all	Possibly
Symptoms below 35 years	Uncommon	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Winter bronchitis	Common	Uncommon
Night-time waking with dyspnoea	Uncommon	Common
Diurnal variability	Uncommon	Common
Airflow limitation	Largely irreversible	Largely reversible
First line therapy	Inhaled Bronchodilators	Inhaled Corticosteroids

Characteristic features of other diseases that need to be differentiated from COPD are indicated in Table 3.

Table 3: Differential diagnosis of COPD

Congestive Heart Failure	• Fine basilar crackles on auscultation • Chest X-ray shows dilated heart, pulmonary edema • Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	• Large volumes of purulent sputum • Commonly associated with bacterial infection • Coarse crackles on auscultation • Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	• Onset at any age • Chest X-ray shows lung infiltrate or nodular lesions • Microbiological confirmation • High local prevalence of tuberculosis
Obliterative bronchiolitis	• Younger onset and in nonsmokers • History of rheumatoid arthritis/ fume exposure • Hypodense areas on expiration on CT suggestive of bronchiolitis
Diffuse panbronchiolitis	• Affects mostly male nonsmokers • Almost all have chronic sinusitis • Diffuse small centrilobular nodular opacities and hyperinflation on chest radiography and HRCT
Interstitial Lung Disease	• Can be a younger patient • Dry cough, exertional dyspnea, fine crepitations on ausculation • Restrictive loop on Spirometry • Chest X-ray: Often reticulonodular pattern • HRCT: Usually diagnostic

WHAT IS THE COURSE OF COPD?

Since COPD typically results from irreversible damage to the alveoli and smaller airways it usually follows a slow but progressive downhill course over many years. If the patient stops smoking, the rate of decline of lung function is substantially slowed.

The typical course of untreated COPD is characterized by:

- Breathlessness initially on exercise but later at rest
- Cough and sputum initially in the morning but later all day
- Acute respiratory infections with increasing frequency, especially in winter
- Hypoxia initially on exercise but later during sleep and even at rest by day
- Chronic respiratory failure and cor pulmonale
- Terminal acute respiratory failure

MANAGEMENT OF COPD

The goals of COPD management include:

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality
- Prevent or minimise side effects from treatment

These goals can be achieved through implementation of a COPD management program with the following components:

1. Assess the Disease
2. Reduce Risk Factors
3. Manage Stable COPD
4. Manage Exacerbations
5. Monitoring the Disease

ASSESS THE DISEASE

A detailed medical history of the patient should be taken to assess exposure to risk factors, pattern of symptom development, history of exacerbations, previous hospitalisation for respiratory disorders, presence of comorbidities and impact of disease on patient's life. To assess severity, the disease should be graded as suggested in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines-2003 (Table 4).

REDUCE RISK FACTORS

Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and slow its progression. Avoiding home and workplace air pollutants, and other risk factors are key to preventing the initial development of COPD.

MANAGE STABLE COPD

The GOLD guidelines offer a valuable framework for COPD management. Table 4 depicts a step-wise approach to COPD treatment.

Table 4: COPD Management According To Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines-2003

Stage	At Risk	Mild	Moderate	Severe	Very Severe
Post-bronchodilator FEV$_1$ (% predicted)	Normal	>80%	50-80%	30-50%	<30%
	• Avoidance of risk factors – **SMOKING CESSATION** • Influenza vaccination				
		Add short-acting bronchodilator when needed			
			• *Add* regular treatment with one or more long-acting bronchodilators; including tiotropium • *Add* rehabilitation		
				Add inhaled corticosteroids if repeated exacerbations	
					• *Add* long-term oxygen therapy if chronic respiratory failure • Consider surgical options

PHARMACOLOGICAL TREATMENT

Role of bronchodilators:

"Bronchodilator medications are central to the symptomatic management of COPD"
– GOLD report 2003.

Impaired lung function in COPD is caused by structural narrowing of the airways, combined with the effect of cholinergic vagal bronchoconstrictive tone and decreased elastic lung recoil.

Bronchodilators improve the airflow limitation in patients with COPD by producing airway smooth - muscle relaxation and improved lung emptying during tidal breathing. The resultant increase in FEV_1 may be relatively small but is often accompanied by larger changes in lung volumes with a reduction in residual volume and/ or delay of the onset of dynamic hyperinflation during exercise. Both of these changes contribute to a reduction in perceived breathlessness.

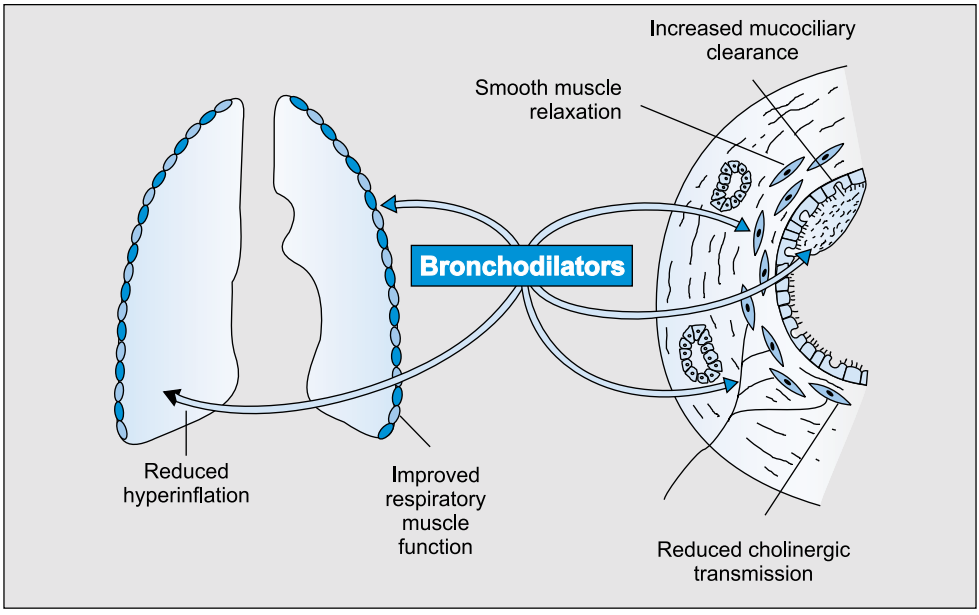
β_2-agonists, anticholinergics and xanthines are all effective bronchodilators in COPD. β_2-agonists act directly on bronchial smooth muscles to cause bronchodilation, whereas anticholinergics act by inhibiting resting bronchomotor tone. Both classes of drugs act synergistically to reduce airway resistance and reduce hyperinflation. Mechanism of action of xanthines is uncertain. The narrow therapeutic range of methylxanthines and their relatively weak bronchodilator effect makes them a less attractive initial therapeutic option. Bronchodilators also increase mucociliary clearance and improve respiratory muscle function.

The use of short-acting bronchodilators should be restricted to symptomatic relief for patients with infrequent, intermittent symptoms. Patients whose symptoms are not adequately controlled with short-acting bronchodilators, or whose use of relief medication becomes more frequent or regular, rather than intermittent, should be given a long-acting bronchodilator.

Evidence suggests that, of the long acting bronchodilators, the newly introduced anticholinergic, tiotropium is the drug of first choice. Tiotropium is given once daily and it provides most consistent improvements on important clinical outcomes like FEV_1, lung volume, dyspnoea, health-related quality of life, exacerbations of COPD and exercise endurance.

Interestingly viral infections increase cholinergic tone, an effect that may be directly counteracted by anticholinergics.

Fig. 2: Diagram showing the effects of bronchodilators on airways and respiratory mechanics in patients with COPD



Benefits of bronchodilators need to be assessed by measures other than improvement in spirometry, such as better exercise tolerance, less breathlessness and fewer symptoms.

Frequently used bronchodilators are shown below in Table 5.

Table 5: Commonly used bronchodilators

Short-acting β_2-agonist	Long-acting β_2-agonist (LABA)	Short-acting Anticholinergic	Long-acting Anticholinergic	Xanthines
Salbutamol (Asthalin)	*Salmeterol* (Serobid) *Formoterol* (Foratec) *Bambuterol* (Bambudil)	*Ipratropium* (Ipravent)	*Tiotropium* (Tiova)	*Theophylline* (Theobid/ Theoday)

Combining bronchodilators :

"Patients with moderate to severe symptoms of COPD require combination of bronchodilators"

"Combining bronchodilators with different mechanisms and durations of actions may increase the degree of bronchodilation for equivalent or lesser side effects"
– GOLD report 2003.

GOLD 2003 guidelines recommend regular treatment with one or more long-acting bronchodilators (e.g. tiotropium + LABA) for patients with moderate COPD. Bronchodilation produced by two bronchodilators of different classes is of greater magnitude than that of either component alone. This effect is mainly due to:

Possible synergistic and/or additive activity: Bronchodilators improve airflow limitation by producing airway smooth muscle relaxation. β_2-agonists induce bronchodilation through stimulation of β_2-receptors whereas anticholinergics relax airway smooth muscle through antagonism of acetylcholine at muscarinic receptors.

Different sites of action: Greatest density of muscarinic receptors is in the large central airways, and a higher density of β_2-receptors is in the small peripheral bronchioles. Therefore, anticholinergics relax central airways and β_2-agonists relax those peripherally.

Effects on mucus hypersecretion: Anticholinergics reduce neurogenic control on mucus hypersecretion and β_2-agonists increase mucociliary clearance and ciliary beat frequency.

Enhanced patient compliance: Combination treatment is more convenient to the patient therefore compliance is enhanced.

Frequently used combinations are shown below.

Short-acting β_2-agonist (*Salbutamol*) + Short-acting Anticholinergic (*Ipratropium*) (**DUOLIN**) $\rightarrow$ gives relief for a short duration of time.

Long-acting β_2-agonist (*Formoterol*) + Long-acting Anticholinergic (*Tiotropium*) **(DUOVA)** $\rightarrow$ provides bronchodilation for a long duration of time and is recommended to be given just once daily.

Role of corticosteroids: Although inflammatory changes are present in the airways of patients with COPD, the role of corticosteroids remains controversial.

The role of oral and inhaled corticosteroids in COPD is much less dramatic than in asthma, and their role in the management of COPD is limited to very specific indications.

Patients with very severe COPD or frequent exacerbations or a significant asthmatic component may benefit from inhaled corticosteroids. Oral/systemic corticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time and help restore lung function more quickly.

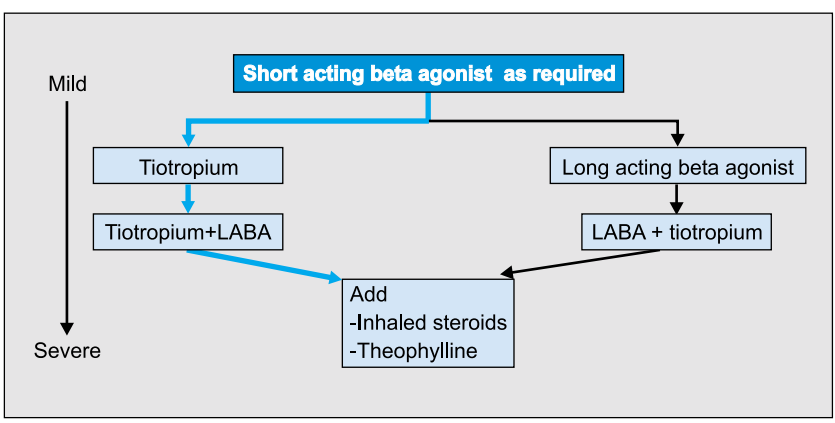
Combination Therapy: Combining long-acting inhaled β_2-agonists and inhaled corticosteroids show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its individual components.

Effect of steroids on β receptor numbers or post-receptor mechanism is the most plausible mechanism of the apparent synergy between long-acting inhaled β_2-agonists and inhaled corticosteroids. Some data suggest that long-acting inhaled β_2-agonists may have synergistic effects with steroids on inflammatory cells.

Proposed algorithm for COPD management:

Figure 3 illustrates two alternative pathways for the staged introduction of long acting bronchodilator therapy with increasing COPD severity. Available evidence suggests certain advantages in choosing the right-hand pathway (in bold in figure) in less severe disease (stage II).

Fig. 3: The proposed three-step algorithm based on GOLD



Role of Vaccines: Pneumococcal vaccine has been shown to reduce the incidence of invasive pneumococcal disease in patients with chronic lung disease. Influenza vaccine reduces serious illness and death in COPD. It can be given once a year.

Note: Mucolytics, antitussives and respiratory stimulants are not recommended for regular use.

NON-PHARMACOLOGICAL TREATMENT

Pulmonary rehabilitation: A typical program incorporates physical training, disease education, and nutritional advice, psychological and behaviour intervention. The goals are to reduce symptoms, improve quality of life and increase participation in everyday activity. This should be offered to all patients who consider themselves functionally disabled by COPD.

Oxygen therapy: Supplemental long term oxygen therapy (LTOT) improves survival, exercise, sleep and cognitive performance in hypoxemic patients. LTOT is the only intervention known to increase life expectancy in such patients. When used in conjunction with pulmonary rehabilitation, it also improves quality of life. Specific benefits include amelioration of cor pulmonale, enhanced cardiac function, increased body weight, reversal of polycythemia, improved neuropsychiatric function and exercise performance, reduced pulmonary hypertension, improved skeletal-muscle metabolism. Active patients require portable oxygen.

Surgery: Bullectomy, lung volume reduction surgery (LVRS) and lung transplantation may result in improved spirometry, lung volumes, exercise capacity, dyspnoea, health related quality of life and possibly survival in highly selected patients.

LVRS removes functionless areas of lung in patients with COPD. It works by improving the mechanics of breathing by reducing thoracic volumes.

Lung transplantation has been used successfully in COPD but availability of organs has seriously limited its application.

MANAGEMENT OF EXACERBATIONS

An exacerbation of COPD is an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum beyond day to day variability sufficient to warrant a change in management.

Many exacerbations are caused by infection of the tracheobronchial tree or an increase in air pollution, but the cause of about one-third of severe exacerbations cannot be identified.

Acute exacerbation is a determinant of disease progression in COPD. It is likely that exacerbation accelerates decline of pulmonary function and health status. Its occurrence has been related to lower survival rates. Acute exacerbation is also an important cause of health expenditure, due to hospitalization, outpatient care and drug consumption. Therefore, prevention of exacerbation of COPD is a very important aspect of COPD management.

The decision to treat at home or hospital essentially depends on the severity of symptoms (particularly the degree of breathlessness, the presence of cyanosis or peripheral edema and the level of consciousness), the presence of comorbidities, whether or not the patient is already receiving long term oxygen therapy, the level of physical functioning, and the patient's ability to cope at home.

The pharmacological treatment of patients with an exacerbation of COPD is based on the same medications utilised in the management of the stable patient. However, the evidence supports the use of systemic glucocorticoids.

Use of antibiotics in exacerbations of COPD is controversial. The British Thoracic Society Guidelines on COPD recommend that antibiotics should be given if two of the following three features are present:

- increased breathlessness,
- increased sputum volume or
- increased sputum purulence.

Amoxicillin, cephalosporins, quinolones, and macrolides are effective in these cases.

Among the quinolones, moxifloxacin is the drug of choice because it produces

faster relief of symptoms and prolongs the time free from exacerbations, which in turn reduces the decline in lung function and improves quality of life. The unique pharmacological features of moxifloxacin maintain the concentration of the drug well above the concentration which prevents the growth of resistant mutant strains for a total period of 24 hours.

Mechanical ventilation should be considered when despite optimal medical therapy there is acidosis, hypercapnia and increased respiratory rate. It is not a therapy, but a form of life support until the cause underlying the acute respiratory failure is reversed with medical therapy.

Mechanical ventilation can be delivered as follows:

- Conventional or invasive mechanical ventilation: Through an endotracheal tube, bypassing the upper airway.
- Noninvasive mechanical ventilation (NIMV): It refers to the technique of providing ventilatory support without a direct conduit to the airway, thereby eliminating the need for intubation or tracheostomy. The most popular mode is noninvasive positive pressure ventilation (NPPV).

  NPPV is delivered by a nasal or facemask. NPPV can be given by a volume ventilator, a pressure controlled ventilator, a bilevel positive airway pressure (BiPAP) device, or a continuous positive airway pressure (CPAP) device.

  BiPAP ventilators provide continuous high flow positive airway pressure that cycles between a high positive pressure and a lower positive pressure.

MONITORING THE DISEASE

COPD is usually a progressive disease. Lung function can be expected to worsen over time, even with the best available care. Symptoms and lung function should be monitored to follow the development of complications, to guide treatment, and to facilitate discussion of management options with patients.

FURTHER INFORMATION FROM CIPLA ON COPD

Physician Resources

- COPD – Successful Management In Primary Practice
- SPIROMETRY Made Easy
- COPD – A Clinician's Guide
- COPD Today – Justified Optimism. Speaker: Dr Bartolome Celli (on CD)
- COPD Today: Easier to Understand. Easier to Manage (on CD)

Patient Resources

- How To Live Better With COPD (Chronic Obstructive Pulmonary Disease) [Available in nine languages]
- Breathing Exercises For COPD – poster (Available in two languages) and leaflet (Available in nine languages)

Additional information can also be accessed at :

http://www. cipladoc.com/respiratoryupdate.htm and

http://www.cipladoc.com/html/eom/eom.htm

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Notes

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