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Indian College of Physicians

Monograph on

Indian Perspective

Chief Editor :

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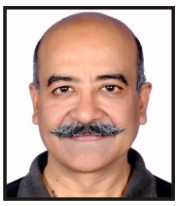

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Association of Physicians of India
Indian College of Physicians

This book is dedicated to

My grand father

Late Mahashya Kishori Ram

(1895 - 1960)

For setting all the moral, ethical,
social and academic values for our family,

This book is dedicated to

My parents

Com. Ved Parkash Gupta and Prof. Santosh Gupta

Who are my role models

My wife and son

Dr. Sonia Gupta and Dr. Varun Gupta

Who are my greatest support,

My friend and mentor

Dr. Gurpreet S. Wander

Without whose sustained and continuous support

I could not have achieved much academically

My fellow editors

Dr. M. Sabir, Dr. Vishal Chopra and Dr. Akashdeep Singh

This book would not have been possible without their whole hearted support

My colleagues of

Association of Physicians of India (Malwa Branch)

Who always extend unconditional support for every academic activity in the region

My batchmates of GOMCO 1978 (Patiala)

Dr. Shardaindu Sharma, Dr. Tajinder Singh Goindi, Dr. Berinder S. Mangat & many more

Whose company influenced my personality to become a better person

Most importantly my daughter

Dr. Meghna Gupta

Who is my strongest critic and influences every aspect of my life

Last of all my teachers, patients and friends

Who taught me medicine and how to enjoy life

FOREWORD

It is a privilege and a honor to write a foreword for the API-ICP monograph on “COPD : Indian Perspective” edited by Chief Editor Dr Vitull K Gupta and his team comprising of Dr. M Sabir, Dr. Vishal Chopra, Dr. Akashdeep Singh and Dr. Meghna Gupta. Chronic obstructive pulmonary disease is not only common but also causes significant morbidity and mortality world over. In our country the pattern of COPD is changing with the increasing environmental pollution adding up to the known risk factors. Smoking continues to be common in some parts of the country inspite of the government’s initiative to have caution labeling on cigarettes and bidi packings which has been made very prominent with the recent legislation. Also, it is important to have our own monograph on this since tobacco chewing is unique and very common to India and contributes to the increasing risk. The topic has been covered very well in the 18 chapters by the eminent faculty in this field. Newer modalities of diagnosis and management have been discussed thread bear and the protocols for handling different clinical scenarios have been delineated in a very simplistic and practical manner. I am sure this monograph will be widely followed by physicians in this country for the next few years due to the high academic input that has been put in a very readable and practical manner in the monograph. The writing, expression and discussion skills of the editorial board specially the chief editor are well seen in the chapters of this book. I hope you will all enjoy reading this book and then translate it into better management of patients with COPD which is the main aim of this monograph.

Wishing you all the best.
Jai Hind !

Dr Gurpreet S Wander
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President, Association of Physicians of India
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FOREWORD

COPD is a common disorder which is gradually but relentlessly progressive in nature. COPD is not only a disease of the lungs but is also a systemic inflammatory disorder and the rising trend in prevalence and burden of COPD poses threat of an epidemic magnitude which is more dangerous than that of an infectious disease since COPD is a chronic and progressive condition. COPD has lacked a uniform definition and a recognizable terminology. It is difficult for the people and the policy-makers to distinguish COPD from other causes of cough and breathlessness particularly from bronchial asthma. In India, both asthma and COPD continue to be recognized by the single vernacular term of 'dama'. This monograph "COPD: Indian Perspective" edited by Dr. Vitull K. Gupta and his team comprising of Dr. M. Sabir, Dr. Vishal Chopra, Dr. Akashdeep Singh and Dr. Meghna Gupta has presented comprehensive information about COPD and expressed it in a simplified text with emphasising on Indian perspective that will benefit Indian doctors at large. It gives me immense pleasure to write the foreword for this unique monograph which will be very very useful to doctors in daily practice and managing COPD. This monograph contains 18 chapters contributed by eminent faculty. I congratulate Dr. Vitull K. Gupta, his editorial colleagues and all the contributors for their efforts to bring out this valuable text on COPD.

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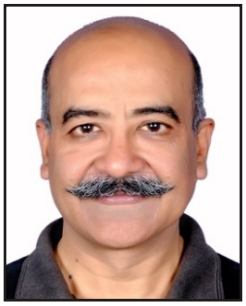
PERFACE



This monograph “COPD: Indian Perspective” is published with the objective of presenting comprehensive information about COPD in a simplified form with an emphasis on Indian perspective that will benefit Indian doctors at large. COPD is becoming increasingly common and is progressive in nature. More over COPD is not only a disease of the lungs but is also a systemic inflammatory disorder and the rising trend in prevalence and burden of COPD poses threat of a great magnitude which is more dangerous than that of an infectious disease. I feel short of words while thanking Dr. Gurpreet S. Wander, President, Association of Physicians of India, Dr. Sidharath N. Shah, Dr. Shashank Joshi, Dr. Rajinder Bansal, Jt. Sec. API and Dr. A Muruganathan, Dean, Indian College of Physicians for guiding me and authorizing the publication of this prestigious monograph. I greatly appreciate the team work shown by the editorial team of Dr. M. Sabir, Dr. Vishal Chopra, Dr. Akashdeep Singh and Dr. Meghna Gupta in developing the scientific agenda of this book and selecting extremely distinguished faculty for contributing various chapters. I am indebted immensely to the talented and eminent contributors, who have put in great efforts and written excellent and informative chapters detailing all aspects of COPD in Indian context. Each chapter comprises of latest information expressed in simple text, which will enable readers to have detailed insight of the subject easily and in less time. I am very proud to have extremely talented, intelligent, ethical and academic seniors like Dr. Paramjeet Singh Aulakh, Dr. Hem Raj Goyal, Dr. Sanjeev Uppal, Dr. Sudhir Verma, Dr. Ashwani Maheshwari, Dr. Vinay Jindal, Dr. Bimal Garg, Dr. Karamveer Goyal and Dr. U. P. Singh, who polished my academic skills. I wish to express my gratitude to all members of the Association of Physicians of India (Malwa Branch) for their unconditional moral and financial support for the publication of this monograph. I am thankful to Dr. Naresh Goyal, Dr. G.S. Gill, Dr. Sharad Gupta, Dr. B.B. Jindal & many other friends for financially supporting academic activities of API (Malwa Branch). I will be failing in my duty, if I do not mention my childhood friends Mr. Surinder Katia, Mr. Anil Garg, Mr. Sat Dev Dharni and Mr. Ashwani Malhotra for their unconditional support and on whom I can rely through the thick and thin of my life. It gives me immense pleasure to dedicate this unique monogram to all my doctor colleagues of India. I am sure that this monogram will be very very useful to all the doctors in understanding and managing COPD.

Dr. Vitull K. Gupta

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INDEX

S.NO.	TOPIC		PAGE
1.	Introduction:- Need Attention from All	Dr. M. Sabir	1
2.	COPD: The Unrecognized Epidemic in India	Dr. S. K. Jindal	3
3.	COPD: Etiopathogenesis	Dr. Lalita Fernandez	10
4.	COPD: Clinical Presentation, Diagnosis and Assessment of Disease Severity	Dr. M. Sabir	16
5.	Management of Stable COPD: Non-pharmacological Management. Identify And Reduce Exposure to Risk Factors	Dr. Vishal Chopra	27
6.	Management of Stable COPD: Non-pharmacological Management- Physical exercises & Rehabilitation	Dr. Virendra Singh	33
7.	Emerging therapies for COPD	Dr. Raja Dhar	39
8.	Pharmacological Management of Stable COPD	Dr. Akashdeep Singh	50
9.	COPD: Acute Exacerbation	Dr. Ajay Handa	58
10.	COPD: Critical care	Dr. Amol Hartalkar	66
11.	COPD: Oxygen Therapy.	Dr. Sanjay Kochar	76
12.	Pitfalls in Diagnosis and Management of COPD	Dr. Angira Dasgupta	86
13.	COPD - A Systemic Disease	Dr. Parvaiz A. Koul	92
14.	Cor-Pulmonale- Misdiagnosed & Mismanaged Entity	Dr. G. S. Wander	100
15.	COPD: Prognosis	Dr. Sunil kumar Gothwal	111
16.	COPD- Prevention	Dr. Surendra Verma	116
17.	Asthma-COPD Overlap Syndrome (ACOS) : a New Entity?	Dr. Vitull K. Gupta	122
18.	Indian COPD Guidelines: What is Different from GOLD Guideline	Dr. Mahesh PA	130

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1

COPD - Need attention from all

Dr. M. Sabir

Introduction:

Chronic obstructive pulmonary disease (COPD) is a progressive chronic inflammatory disorder, having poorly reversible chronic airway obstruction accompanied by many systemic manifestations responsible for significant disability and premature deaths. Global burden of COPD cases has been estimated to be more than 384 million (global prevalence 11.7%), resulted in more than 3 million deaths annually, around the world. The global burden of COPD continues to grow, more so amongst people of low socioeconomic status (SES) living mostly in developing & underdeveloped countries. This difference is mostly because of health disparities related to level of education, general awareness about health and hygiene, housing, work place, availability of cocking fuel, religious belief, social customs, taboos, quality of environment and socio-political factors. Respiratory system is more likely to be affected by health disparities as compared to other organs, because of vast variation in environment in different locations where people are breathing. Exposure to polluted air because of tobacco smoke, biomass fuel, occupational hazards and other pollutants (indoor as well as outdoor) is more prevalent amongst people from low SES & ethnic minority.

It has been reported that lowest social groups are up to 14 times more likely to have respiratory diseases than people of highest SES. According to the World Health Organization (WHO), more than 90% of COPD deaths occur in low-income and middle-income countries, where higher number of population belongs to low SES. The menace is further added by the fact that, treatment outcome of COPD patients from low SES group has been observed to be poor as compared to high SES group. It can be attributed to disparities in availability of health care facilities and lack of awareness. Studies suggest that in India prevalence of COPD has grown in an epidemic form with cumulative prevalence rising every year, causing significant disability, loss of man hours and working capacity putting serious burden on health care infrastructure and exchequer. Impact of burden of COPD in India is expected to be further enhanced by the fact that a large section of our population can be categorized as low SES group.

In India different studies adopting different methods from different parts, reported prevalence of Chronic Bronchitis/COPD to be ranging from 3.49% to 7.7%, estimating more than 22 million COPD patients in India. It is also estimated that more than Rs. 48,000 crore will be spent by the patients and their families in India on the treatment of COPD alone in the year 2016. More comprehensive and broad based studies are required to evaluate real burden of COPD in India.

In devoloping countries in additoion to direct cost of treatment; indirect loss of productivity

and social burden incurred because of incapicated COPD patients is more important for overall ecconomic loss, as manpower is the biggest asset for devoloping countries like India.

Awareness in terms of its burden, immediate & long term social & economic impacts, and affordable methods of prevention and treatment are important for better care and control of a disease. It is a fact that COPD is comparatively less known diseases amongst patients, general public, healthcare - provider, planner & executors, media and doctors also. It has been observed that better understanding of COPD among general practitioners, physicians, and pulmonologists in India is needed to overcome the prevalent under-diagnosis and under-treatment of COPD.

This monograph is a humble effort in this direction to increase awareness about COPD amongst physicians specially working in India. All the authors in this monograph have not only judiciously covered the the subject but have given due importance to Indian aspects of COPD.

Suggested Readings:

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"When you can't breathe, nothing else matters"
– Canadian Lung association

2

COPD - The Rising Epidemic in India

Dr. S. K. Jindal

Abstract:

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disorder of airways characterized by airflow limitation which is poorly reversible with treatment. It is one of the four major groups of chronic non-communicable diseases responsible for significant respiratory disability and premature mortality. It is often accompanied with several systemic co-morbidities. COPD results from chronic and persistent exposures to tobacco smoke and/or other noxious air pollutants. Globally, it is the third most common cause of death and 5th leading cause of morbidity measured in terms of disability-adjusted life-years. COPD in India has grown in an epidemic proportion with the cumulative prevalence rising every year. In the nation-wide Indian Study on Epidemiology of Asthma, Respiratory symptoms and Chronic bronchitis, the field prevalence of the disease was found as 3.49% of adult population on an average. It poses an enormous burden on health-care infrastructure and economics in being an important cause of work-loss, loss of wages and increased expenditure.

Introduction:

COPD is a common disorder which is gradually but relentlessly progressive in nature. It is characterized by poorly reversible airflow limitation. The disease commonly occurs in response to tobacco smoke and/or other harmful inhalational exposures, hence preventable if the exposures are avoided. A large number of systemic manifestations and other co-morbidities are also associated with COPD. There is good evidence to suggest that COPD is the most important and common chronic disease which is increasing in prevalence and associated morbidity the world over.

COPD is a chronic inflammatory disease as a result of immune responses to long term exposure to noxious particles and gases, particularly cigarette smoke. All cigarette smokers have some inflammation in their lungs, but those who develop COPD have an enhanced or abnormal response to inhaling toxic agents. COPD is characterized by increased numbers of neutrophils, macrophages and T lymphocytes (CD8 more than CD4) in the lungs. These inflammatory cells release a variety of cytokines and mediators which in turn are responsible for pathophysiological abnormalities such as mucous hypersecretion and ciliary dysfunction. These changes lead to physiological dysfunction including airflow obstruction, lung hyperinflation, gas exchange abnormalities and pulmonary hypertension. Pulmonary hypertension occurs later in the disease course due to pulmonary arterial constriction, endothelial dysfunction, remodelling of the pulmonary arteries (i.e. smooth muscle hypertrophy and hyperplasia) and destruction of the pulmonary capillary bed. In addition,

there occur structural changes in the pulmonary arterioles which may also result in persistent pulmonary hypertension and right ventricular hypertrophy or enlargement and dysfunction (cor-pulmonale).

COPD is not only a disease of the lungs but is also a systemic inflammatory disorder. Muscular weakness and weight loss, increased risk for atherosclerotic vascular disease particularly involving the coronary and cerebral vessels, depression, osteoporosis and abnormalities in fluids and electrolyte balance are important and frequently serious consequences of COPD adding to the disease morbidity and mortality.

Epidemiology:

The rising trend in prevalence and burden of COPD poses threat of an epidemic magnitude.[1] The threat is even more sinister than that of an infectious disease since COPD is a chronic and progressive condition. The number of cases of COPD and therefore the health-care burden keeps an adding every year. Chronic respiratory disease along with cardiovascular disease, diabetes and cancers, is indentified by the United Nations General Assembly as one of the four most important chronic and 'life-style related' diseases needing global attention.[2] COPD in fact, has been reported as the only leading cause of death that is increasing in prevalence. The UN General Assembly had called upon all its member-countries to take suitable action for control of all these non communicable disease (NCDs).[2]

In the past, there has been a general lack of focus on chronic respiratory disease, commonly identified by COPD. The neglect can be attributed to several different reasons. Most importantly, COPD has lacked a uniform definition and a recognizable terminology. It is difficult for the people and the policy-makers to distinguish COPD from other causes of cough and breathlessness particularly from bronchial asthma. Even today in India, both asthma and COPD continue to be recognized by the single vernacular term of 'dama'. Further, cough and exertional breathlessness are often ignored as non-specific or 'nuisance symptom' rather than as indicators of a serious disease.

Global burden:

COPD is a widely prevalent disease among adults all over the world. Various investigators have studied the COPD prevalence and burden in different countries.[3-5] For example in USA, COPD is recognised as the fifth leading cause of deaths, fourth leading cause of years of life lost from premature deaths and second most common cause for disability adjusted life years.[6] According to WHO estimates, 65 million people have moderate to severe COPD.[4] More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally.

Some of the larger initiatives include the Burden of Obstructive Lung Disease (BOLD) and Chronic Obstructive Pulmonary Disease in five Latin American cities (PLATINO).[7, 8] It was seen in the BOLD study, that the average prevalence of COPD based on questionnaires and spirometry was 10.1% at 12 different sites with wide regional variations.[7] Most of the information available on COPD prevalence, morbidity and mortality comes from high-income countries. Even in those countries, accurate epidemiologic data on COPD are difficult and expensive to collect. It is known that almost 90% of COPD deaths occur in low- and middle-income countries. COPD is now the third most common cause of death in the world.[9] The COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.[10]

The data reported in different studies have significantly varied. A systematic review and

meta-analysis of studies from 28 countries reports that less that 6% of adults have been told to suffer from COPD.[3] On the other hand, PLANTINO study reported a high prevalence from 7.8% to about 20% in different Latin American regions.[8]

Burden of COPD is even more alarming. The high disease- prevalence accounts for a significant burden measured in terms of loss of work, Disability Adjusted Life Years (DALYs), premature mortality, loss of income and disease-management costs. It therefore results in a huge financial burden on the patients' families as well as the health-care system due to both direct and indirect losses. Globally, COPD was listed as the 5th most common cause of death in the Global Burden of Disease Study (GBDS) in 1997, predicted to become the 3rd leading cause of death by 2020. According to latest reports it is already the 3rd most common cause in the GBDS 2010.[9] COPD is also the 5th most common cause of disease morbidity measured with DALYs.

COPD in India:

A. Prevalence:

A number of prevalence studies which had been undertaken in the past were limited to small populations or clusters. In an earlier analysis, we had collated the field studies from India and reported a median prevalence of 5% in male and 2.7% in female population; the prevalence of COPD and its smoking association in studies of three time-periods (before 1970; between 1970- 1990 and after 1990) were nearly similar.[11]

More concise data from larger studies have become available in the last 10-15 years. A large, Indian Council of Medical Research (ICMR) sponsored population study, the Indian study on Epidemiology of Asthma, Respiratory symptoms and Chronic Bronchitis (INSEARCH) was undertaken at 16 different sites in two different phases with same methodology. The 1st phase covered 35295 adults from 4 centres while the 2nd phase covered 169575 adults of over 35 years of age at 12 other centres.[12,13] The INSEARCH study employed a standardized questionnaire validated for diagnosis of COPD before its use in field. Uniform methodology was followed at all sites. The overall prevalence of chronic bronchitis (CB) was 3.49% while one or the other respiratory symptom was reported in 8.5% of subjects.[13]

The INSEARCH study did not employ spirometry for assessment of airway limitation even though the questionnaire validation was done for COPD diagnosis made on spirometric criteria. Spirometry was not used for field prevalence to avoid the technical errors of biases with such measurement in the field in diverse regions.

There have been a few other studies on COPD prevalence during this period.[14] A field study in Bangalore in a cluster population of 44387 subjects reported a prevalence of 4.36% in a rural area.[15] In another study using BOLD questionnaire for the prevalence of CB among smokers, significant differences were reported in male population in Karnataka.[16] In another report from South India, the overall prevalence of COPD in rural women of Tamil Nadu, was found to be 2.44% which was higher among biomass fuel users (odds Ratio 1.94; 95% CI, 0.36-6.64).[17]

A systematic review of 16 papers identified out of 351 studies was published almost at the same time as the INSEARCH report.[18] The authors who had found the data unsuitable for meta-analysis in view of the great heterogeneity of different studies, reported an average estimated prevalence of CB between 6.5% and 7.7% in the rural areas. Most of these reports from rural areas have specifically pointed to the role of exposure to biomass smoke amongst these populations.[16-18]

A number of factors have been blamed for the marked difference in prevalence rates several of which relate to the methodology employed for the study.[13] It is also likely that the use of spirometry in the COPD prevalence studies is likely to detect asymptomatic and early COPD, thus providing higher figures for the disease- prevalence.[18,19]

B. Risk factors

Tobacco smoke: Tobacco smoking of all kinds as well as the passive or second hand smoking i.e. environmental tobacco smoke (ETS) exposure is the most important cause of COPD the world over as well as in India.[8,13] In the systematic review of studies from 28 countries, COPD was most common in men amongst smokers and ex smokers than in non smokers.[8]

Smoking is by far recognized to be the most important risk factor for development of COPD. Smoking behaviours in India are also peculiar with a large number of people using non conventional form of tobacco in hookah, bidi or chillum. Bidi and other indigenous forms of tobacco smoking are at least as (or even more) harmful than cigarette smoking.[13] Low tar or filtered cigarettes are similarly harmful though there is evidence that their effect on COPD is inconsistent. Passive exposure to cigarette smoke (also known as environmental tobacco smoke) may also contribute to respiratory symptoms and development of COPD.[13,20]

COPD in non-smokers: In India and in many other developing or third world countries, COPD prevalence is high in non smoking people of both sexes.[13,21,22] A number of risk factors, other than tobacco smoking have been found as responsible for COPD in non-smoking populations.[21,22] Exposure to solid biomass domestic fuel combustion is the most significant factor for COPD in non-smokers, especially amongst women.[21-23] The risk of development of COPD due to house-hold air pollution (HAP) from biomass fuel combustion is about double the risk among non HAP exposed population.[23] Exposure to domestic combustion of biomass fuels like dried animal dung, crop residues and forest woods is widely prevalent especially in rural and semi-urban areas. More than one-half of the world's households use biomass fuels and a significant proportion of this activity takes place in conditions where much of the effluent is released into the indoor living area. Women, who do most of the cooking for households are the most affected. Biomass fuels are now considered as one of the major cause of COPD.

In India, majority of the homes use biomass fuel for cooking and heating purposes in poorly ventilated kitchens and the amount of particulate matter generated by the burning of biomass fuel is extremely high. 90% of rural households and 32% of urban households cook their food on a biomass stove with only 25% of the cooking being done with cleaner gases.[24,25] There are a few studies that show that other indoor air pollutants such as those produced during the burning of mosquito coils and incense sticks may also be associated with respiratory morbidity.[26,27] However, the evidence is limited at present.

Outdoor air pollution: Outdoor air pollution mainly from emission of pollutants from motor vehicles and industries is an important public health problem.[28] In a community-based study, it has been observed that higher traffic density was significantly associated with lower FEV1 and FVC in women.[29] In the Danish Diet, Cancer and Health cohort study involving 57,053 participants, it has been shown that COPD incidence was significantly associated with nitrogen dioxide levels.[30] Particulate pollutants, ozone and nitrogen dioxide can produce bronchial hyper reactivity, airway oxidative stress, pulmonary and systemic inflammation.[28]

Occupational exposures: Occupational exposures ambient air pollution, other indoor

pollutants and respiratory infections have been also blamed for non-smoking COPD. Chronic asthma due to persistent inflammation and airway remodelling is increasingly recognized as an important cause of COPD in both smokers and non-smokers.

C. Burden of COPD in India:

Burden of COPD is measured in terms of morbidity indices, mortality rates and economic costs. A large body of data is available on various indicators of COPD burden from western countries. However, the data from India is rather sparse. COPD is reported as one of the important causes of burden from NCDs which along with injuries, account for 52% of deaths in India.[31] There is little quantitative data on morbidity from COPD. The earlier estimates therefore appear to reflect a gross under-assessment. In view of the enormity of disease prevalence for which adequate information is now available, the burden requires to be reassessed.[33, 32] It is also known that the morbidity from COPD is not restricted due only to respiratory disability from airflow limitation. There are several systemic diseases which are frequently associated with COPD due to shared risk factors and mechanisms of pathogenesis. Enhanced atherosclerosis seen in these patients causes higher incidence of cardio- and cerebro-vascular diseases. Other systemic co-morbidities such as osteopenia, depression and metabolic diseases significantly add to disease-morbidity and mortality.

There is limited factual data on COPD mortality. Bronchitis and asthma were reported as the most common causes of death in both men and women in multiple surveys conducted by different agencies such as the Survey of Causes of Death, Annual Reports of Registrar General of India, Census of India I and NFHSI I and II.[33-35]

Exacerbations of COPD multiply the disease burden by several folds both in term of disease related indices and economic costs. Health care utilization due to COPD exacerbations has been recently assessed in India with predication modelling, several discriminators have been reported to predict 'prolonged hospital stay' and 'prolonged intensive care'.[36] Similarly, a systematic review of humanistic and economic burden reported substantial economic burden and impairment of health related quality of life (HRQoL) due to symptomatic COPD.[37] Reduced HRQoL in India COPD patients has been also reported in an earlier study.[37]

Economic burden: COPD has severe economic implications. Estimates of costs and other economic losses have been made in a few studies. In an indirect assessment study for expenditure on health care, we have found significantly higher direct and indirect fiscal losses in families with one or more smokers than non-smoker families.[38] The direct costs on COPD was assessed in an earlier ICMR task force study and found to be significantly burdensome.[33,39] The total fiscal burden will obviously depend upon the current disease prevalence and management costs. In an earlier assessment in 2011, the estimated economic loss in India due to COPD was about Rs. 350,000 million for that year, was predicted to exceed Rs. 480,000 million for year 2016. It was also calculated that proper 'program based' or 'guideline based' management of COPD could significantly reduce these costs by approximately 70%.[40]

Summary:

COPD is a major cause of burden on health-care infrastructure and health-care costs. The burden keeps on adding every year with mounting disability and numbers of new patients added to the existing load. Besides the stress on pharmacotherapy and disease-management therefore, preventive and rehabilitative steps are important to minimize the disease prevalence and burden.

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"Always go too far, because that's where you'll find the truth"
–Albert Camus

3

Etiopathogenesis of Chronic Obstructive Pulmonary Disease

Dr. Lalita Fernandes, Dr. A. M. Mesquita

Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is defined as a common preventable and treatable disease characterised by a persistent airflow limitation that is usually progressive and associated with an enhanced inflammatory response in airways and the lung to noxious particles and gases.[1] Pathologically COPD is characterised by two distinct and frequently coexisting components namely small airway abnormalities and parenchymal destruction. It has been reported that cigarette smoke can induce pathological changes in the small airways of smokers who have not developed COPD.[2] Hogg et al demonstrated that the peripheral airways is the major site of increased resistance in smokers and that significant increases in the airway can be present without changes in total airway resistance.[3] Thus understanding the pathophysiology in COPD is of utmost importance for better diagnosis and management of this important non communicable disease which is currently the third commonest cause of death.[4]

Risk Factors for Chronic Obstructive Pulmonary Disease:

A) Host factors:

1. Genetic predisposition: The best documented genetic risk factor is a severe hereditary deficiency of alpha-1 antitrypsin which leads to a premature and accelerated development of panlobular emphysema. In this condition there is perturbation of SERPINA gene which codes for serine protease inhibitor.[5] Another risk factor is polymorphism in the gene for enzyme microsomal epoxide hydrolase responsible for the metabolism of reactive epoxide intermediates generated by tobacco smoke. This polymorphism is shown to be associated with a 4-5 fold increase in COPD risk.[6,7] Polymorphism in matrix metalloproteinase MMPI and MMPI2 and antioxidant glutathione-S-transferase individually has been associated with rapid decline in lung function.[8,9] There are also associations for polymorphism reported in genome wide association (GWA) studies in COPD identified susceptible loci. A GWA study was conducted in Norway and top 100 single nucleotide polymorphisms (SNPs) were followed up in the family based International COPD Genetics Network (ICGN). The most definitive evidence of association was found on two SNPs at the nicotinic acetylcholine receptor locus on chromosome 15q 25, the same locus implicated in risk of lung cancer.[10,11]

2. Nutrition and lung growth: Early nutrition is important and small for dates babies have an increased risk of development of COPD in later life.[12] Low dietary intake of antioxidant vitamins A, C, E are found to be associated with increased risk of COPD.[13] Poverty can predispose to COPD and so also physiological lung function decline in old age.[14]

B) Environmental factors:

1. Tobacco smoke:

Tobacco smoking is the most common risk factor for COPD. Each puff of cigarette contains more than 2000 xenobiotic compounds and 10^5 free radicals. The gaseous phase components are carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, volatile nitrosamines, hydrogen cyanide, volatile sulphur containing compounds, volatile hydrocarbons, aldehydes and ketones. There are carcinogens namely nitrosamines, hydrazines and vinyl chloride, ciliotoxins and irritants like hydrogen chloride, formaldehyde, acetone, ammonia, acrolein and oxides of nitrogen. Carbon monoxide forms carboxyhaemoglobin which interferes with oxygen transport while pharmacologically active nicotine stimulates acetylcholine receptors at autonomic ganglia of sympathetic and parasympathetic system, stimulates neuromuscular receptor sites and the central nervous system. COPD results from a gene-environment reaction. People with same smoking history, not all will develop COPD due to differences in genetic predisposition to the disease. Passive smoking is also associated with COPD.

2. Air pollution:

a) **Indoor air pollution by biomass fuel smoke:** Around three billion people (half the world's population) cook using biomass fuel (wood, animal dung and crop residue) and coal in poorly ventilated kitchens. Even homes are heated using this fuel leading to indoor air pollution. Both men and women exposed to heavy indoor smoke are 2-3 times more likely to develop COPD. Due to inefficient combustion, the wood smoke contains volatile and particulate substances derived from wood polymers and resins. 90% of these are in the respirable range.[15,16] Substances found in biomass smoke include particulate matter < 10 microns (PM10), carbon monoxide, nitrogen dioxide, sulphur dioxide, formaldehyde, benzopyrene, volatile organic compounds, chlorinated dioxins and free radicals.

b) **Outdoor air pollution:** Air pollution due to burning of low quality (sulphurous) coal in industries and fossil fuel combustion from vehicles releasing hydrocarbons and nitrogen dioxides in air.

3. Occupational dust and chemicals exposures:

These include organic and inorganic dusts (coal, quartz, silica) chemicals and fumes. It is estimated that approximately 15% of COPD may be attributable to work place exposures. [17]

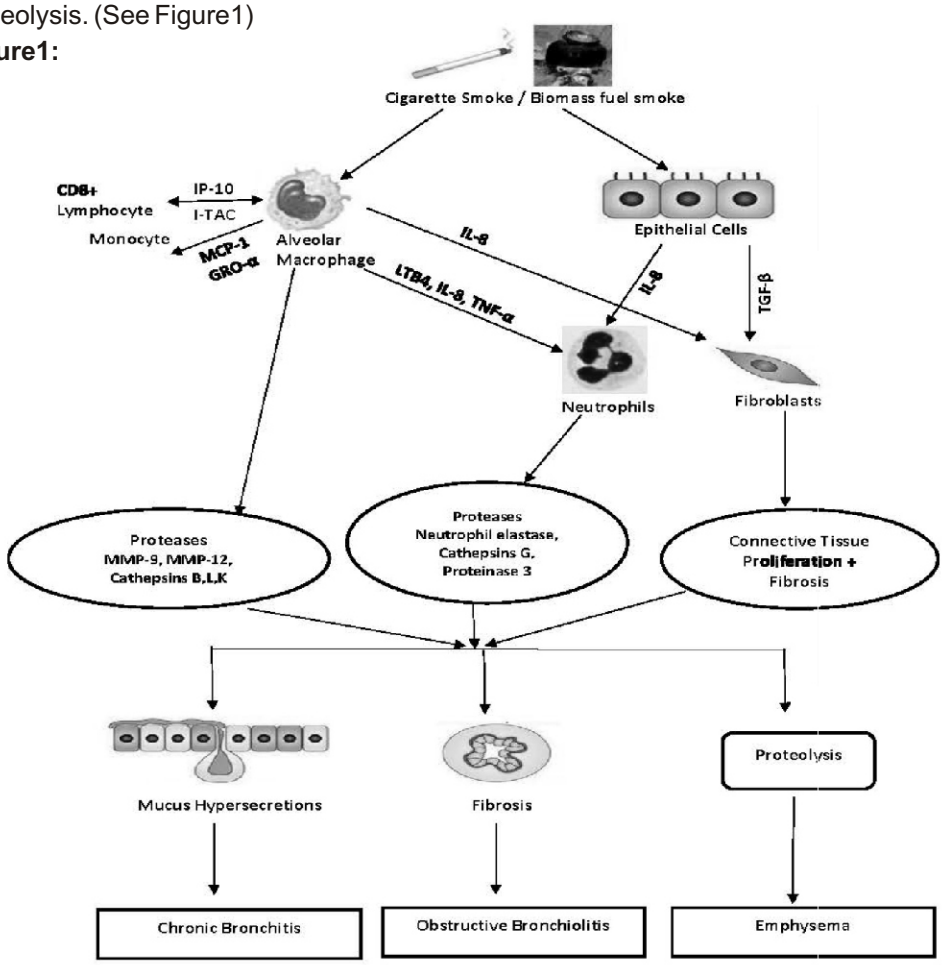
Pathophysiology of COPD:

Cigarette smoke constituents activate alveolar macrophages and epithelial cells in the respiratory tract to release neutrophil chemotactic factors like interleukin-8 (IL-8) and leukotriene B4 (LTB4). Neutrophils release proteases (neutrophil elastase, cathepsin G, proteinase 3) in excess of protease inhibitors. The inflammation leads to mucus hypersecretion in large airways leading to chronic bronchitis, the inflammation in small airways with remodelling leads to obstructive bronchiolitis while proteolysis of connective tissue leads to emphysema. Inflammation of pulmonary arterial vessels also contributes to the pathogenesis of COPD. MCP-1 Monocyte Chemotactic Protein-1, GRO-α Growth related oncogene α, IP-10 interferon-inducible protein -10, I-TAC, interferon inducible T cell alpha, chemo-attractant.

Inflammation in COPD: Cigarette smoke triggers inflammatory response that involves innate immune mechanism while adaptive immune response evolving into an autoimmune

reaction that destroys the lung occurs in susceptible individuals. Smoking and other inhaled irritants cause inflammation with macrophages, CD4+, CD8+ T lymphocyte, B lymphocytes, fibroblasts and neutrophils. These cells release various mediators responsible for inflammation which can either resolve or become associated with fibrosis, remodelling and proteolysis. (See Figure1)

Figure1:



A. The cellular involvement in COPD:

1. **Alveolar macrophages:** Alveolar macrophages are activated and are concentrated in the airways and centriacinar zones. These activated macrophages release inflammatory mediators like tumor necrosis factor α (TNF-α), interleukin-8 (IL-8), leukotriene B4(LTB4), reactive oxygen species(ROS), proteases (matrix metalloproteinases MMP9, MMP12) and elastolytic cysteine proteinases such as cathepsin B,L,K. Macrophages in the lung are recruited from the circulating monocytes by chemotactic factors like CXCLI (chemokines) and CCL2.[19]
2. **CD8+ lymphocytes:** CD8+ (cytotoxic/suppressor) lymphocytes are found in the mucosa and submucosa of central and peripheral airways, mucus secreting glands and lung parenchyma. They release enzymes such as perforins, TNF-α and granzyme B which cause apoptosis of epithelial cells and alveolar epithelial cells. [20]

3. **Neutrophils:** Neutrophils are circulating leucocytes that are attracted into the tissue sites by LTB4, IL-8 and growth related oncogene-α (GRO-α). Neutrophils themselves produce LTB4, IL-8, superoxide anion (O2-), myeloperoxidases (MPO) and serine proteases namely neutrophil elastase, cathepsin-G and proteinase-3.
4. **Epithelial cells:** The epithelial cell integrity is crucial for normal function of the airways. It acts as a physical barrier and a regulator of immune responses. Injury due to smoking causes increased epithelial thickness which contributes to airway wall thickness, production of TNF-α, IL-8 and transforming growth factor (TGF)-β. TGF-β is responsible for peribronchiolar fibrosis and secretion of epithelial mucin.
5. **Fibroblasts:** Fibroblasts cause excessive production of extracellular proteins in small airways and fibrosis

B. Inflammatory mediators:

Leukotriene B4: is a potent neutrophil chemo-attractant derived from alveolar macrophages and neutrophils.

IL-8 and chemokines: IL-8 is a neutrophil chemo-attractant secreted by macrophages, neutrophils and airway epithelial cells.[21] IL-8 is found in induced sputum of patients of COPD and correlates to the number of neutrophils and degree of airway obstruction.

TNF–α: is released by alveolar macrophages and may activate the transcription of NF-KB (Nuclear Factor Kappa Beta) which switches on the transcription of inflammatory genes. TNF-α inhibits expression of skeletal muscle protein via activation of NF-KB. [22]

TGF-β1: Transforming growth factor β1 participates in the fibrotic processes in the small airways.

C. Oxidative stress:

Oxidative stress is an important component in COPD. Each puff of cigarette smoke contains 10 reactive oxygen species (ROS) molecules[17] and ROS are also produced by activated macrophages and neutrophils. Oxidative stress occurs when ROS are produced in excess of antioxidant defence mechanisms resulting in damage to lipids, proteins and DNA.

Protease-antiprotease imbalance: Emphysema occurs due to imbalance between proteases which digest elastin and other structural proteins in the alveolar wall and antiproteases. Various proteases involved are neutrophil elastase, proteinase 3, cathepsin, MMP. The MMPs are produced by neutrophils, alveolar macrophages and airway epithelial cells and they degrade the elastin, collagen, proteoglycans, laminin and fibronectin. MMP9 is a major elastolytic enzyme in emphysema. The antiprotease that counter balance the proteases are α1 antitrypsin, α1 antichymotrypsin, secretory leukocyte protease inhibitor (SLPI) derived from airway epithelial cells and tissue inhibitors of metalloproteinases(TIMPS) which counteracts the effects of MMP. Cystatins act against cathepsins.

Cells	Mediators	Proteinases	Effects
Macrophage	LTB4	Neutrophil Elastase	Mucus Hypersecretion
Neutrophil	IL8, GRO-α	Proteinase 3	Fibrosis
CD8+ T lymphocyte	MCP1	Cathepsins	Smooth muscle hypertrophy
Epithelium	TNF-α	MMPs	Alveolar wall destruction
Eosinophil	GM-CSF		
Smooth Muscle	ROS		
Endothelial cells	NO		
Fibroblast	TGF-β1		
	Endothelin		

Pathology of COPD:

1. **Chronic bronchitis:** There is chronic inflammation in the central cartilaginous airways mucosa, smooth muscle and sub mucosal glands. Goblet cell hyperplasia, increased proportion of goblet cells and enlarged mucus glands leads to excess mucus production and luminal obstruction. There is also increase in smooth muscle mass leading to airway wall thickening. The airways react to non – specific stimuli resulting in increased airway resistance. Ciliary abnormalities are also present.[23]
2. **Obstructive bronchiolitis:** Inflammation involves small and peripheral airways < 2 mm in diameter. The lumen is collapsed and there is increased mucus in lumen. The replacement of normal surfactant with mucus predisposes to early closure of airways during expiration. The increased number of fibroblasts initiates a process of repair leading to increased extracellular matrix deposition. The injury and resolution process results in structural remodelling of airway wall with increased collagen content and scar formation. This further narrows the lumen and produces fixed airway obstruction. There is smooth muscle hypertrophy which is most predominant in small bronchi and bronchioles. Fibrosis along with increased smooth muscle and other inflammatory cells increase the airway wall thickness and decrease luminal diameter. It is found that the wall thickness of membranous and respiratory bronchioles for each bronchiolar diameter is increased in almost all size range in smokers compared to lifetime non-smokers.[24] There is also loss of alveolar attachments that provide support to the bronchiole. Due to loss of this support, the bronchiole perimeter contributes to early closure of bronchioles during expiration.
3. **Emphysema:** There is permanent enlargement of air spaces distal to the terminal bronchioles accompanied by destruction of the alveolar walls. In centrilobular emphysema, the respiratory bronchioles are enlarged while panacinar emphysema involves dilatation and destruction of respiratory bronchioles, alveolar duct and alveolar sacs. In emphysema there is implication of premature cellular senescence,[25] increased apoptosis [26]and auto immunity.[2]
4. **Pulmonary vascular disease and cor-pulmonale:** Small arteries with diameter < 500µ are affected. There is destruction of pulmonary capillary bed, pulmonary arterial vessel inflammation and vascular smooth muscle hypertrophy giving rise to pulmonary hypertension and right sided heart failure. Hypoxic pulmonary vasoconstriction also contributes to pulmonary hypertension.
5. **Systemic disease:** Extrapulmonary inflammatory disease occurs due to passage of oxidants into the bloodstream causing cachexia, increased respiratory and skeletal muscle fatigue with wasting, osteoporosis, depression, peptic ulceration, metabolic syndrome and acute coronary syndrome. Studies have shown raised level of myocardial biomarkers such as NT pro BNP (N-terminal pro-brain natriuretic peptide), troponin-T and platelet – monocyte aggregates in COPD patients during acute exacerbations. [27]

Conclusion:

COPD is a systemic disease and its pathophysiology is complex. Pathologically it causes chronic bronchitis, obstructive bronchiolitis, emphysema and pulmonary vascular involvement. Understanding the amplified inflammatory response will go a long way in better management of the various COPD phenotypes.

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"The fundamental activity of medical science is to determine the ultimate causation of disease"
–Wilfred Trotter

4

COPD: Clinical Presentation, Diagnosis and Assessment of Disease Severity

Dr. M. SABIR

Chronic Obstructive Pulmonary Disease (COPD) is the widely accepted term used for chronic inflammatory persistent airway obstruction with varying presentation of productive cough, dyspnea, and many other pulmonary and extra pulmonary manifestations. Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD as "Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/ or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1]

Indian guidelines jointly prepared by Indian Chest Society and National College Of Chest Physicians of India define it as "Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable disorder which is characterized by progressive, poorly reversible airflow limitation and systemic manifestations, in response to tobacco smoke and/or other harmful inhalational exposures."[2] This definition and previous GOLD definitions includes systemic manifestations also. Comorbidities and other extra pulmonary manifestations have major impact on prognosis and management of the disease, and should be given due consideration while making diagnosis of COPD and assessing disease severity.

According to guidelines, COPD should be suspected in any ageing individual with symptoms of cough, sputum production or breathlessness and/or a history of exposure to risk factors, in particular smoking.[1,2] Smoking is well known for causing COPD, but the lists of risk factors for developing COPD is long and include both host factors and environmental exposures e.g. active and passive smoking, use of biomass fuel, occupational pollutions, ageing, inactivity and diet in developing countries. These factors are most often interacting (Table 2).[3-6]

Many previous definitions included terms 'chronic bronchitis' and 'emphysema'. Chronic bronchitis has been described as presence of cough and sputum production for at least 3 months for two consecutive years, remains a clinically and epidemiologically useful term. Chronic respiratory symptoms may precede the development of airway obstruction and spirometric abnormalities especially amongst smokers. It has been observed that significant number of smokers with ought airflow limitations have varying structural changes suggestive of emphysema, air wall thickening and gas trapping.[1] Emphysema denotes destruction of alveoli leading to decrease in gas exchanging surfaces of lungs is a pathological term, often wrongly used clinically. It may not present in all patients of COPD.

Clinical presentation:

Cough, sputum production and exertional dyspnea are the common symptoms of COPD. Many patients have such symptoms, especially chronic cough with or without sputum

production for months or years before seeking medical consultation, as most of them to relate it to smoking habit. Many patients correlate their illness with an episode of acute exacerbation but a carefully taken history reveals presence of symptoms prior to acute exacerbation.

Symptoms:

Dyspnea: Progressive persistent breathlessness or dyspnea worse with exercise and time is a cardinal symptom of COPD and is an important cause of disability and anxiety for which usually patient seek medical advice. Dyspnea does not have a well defined or universally accepted definition. Breathlessness is defined as an undue awareness of increased or inappropriate respiratory effort and assumed to relate to an awareness of the motor command to breathe. The American Thoracic Society defines dyspnea as ''the subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.''[5-7] Terms used for describing dyspnea by patients vary individually and culturally. COPD patients describe it as difficulty in breathing, more so during inspiration, chest heaviness, air hunger or gasping. In early stages patient usually reduce his daily activity to overcome his dyspnea. Breathlessness on exertion is best elicited by changes in performance of physical activities. It has been observed that activities involving arm work especially above shoulder are particularly difficult for COPD patients.[8]

Cough: Chronic cough is another most common symptom of COPD, generally precedes breathlessness. Chronic cough is often the first symptom of COPD and is frequently not taken seriously by the patient and their relatives, usually considered as the usual consequence of smoking or other exposures to environmental pollutants. Initially cough is intermittent but gradually increases in frequency and duration to become more persistent. It is usually worse in the morning and usually disturbs the patient sleep. It can be disabling because of the embarrassment felt by many patients when they have bursts of productive cough on social occasions and may contribute to the isolation often imposed on patients due to breathlessness. In patient with severe COPD sometimes cough syncope is seen due to increased intrathoracic pressure while coughing causing reduce venous return and cardiac output. Spells of severe cough can cause fracture of rib, may produce severe chest pain and discomfort and sometimes may be asymptomatic. Chronic cough may be intermittent, productive or unproductive.

Sputum Production: Sputum production in COPD patients is usually in small quantity and is tenacious and mucoid in nature, but its frequency, amount, consistency and nature changes with intermittent exacerbations and remissions. Change in color and amount of sputum production invariably indicate acute exacerbation of COPD. Patients producing large amount of sputum may have associated underlying bronchiectasis.

Fatigue, anorexia and weight reduction: Fatigue, anorexia and weight reduction are common and multifactorial problems of COPD. They have prognostic importance and are also present in other diseases like tuberculosis and lung cancer. Fatigue in COPD is generally due to undue awareness of decrease mental and physical activity. It should not be confused with decrease activity due to breathlessness.

Wheezing and chest tightness: Wheezing and chest tightness are the symptoms varies with days and time. Widespread inspiratory and expiratory wheezes are heard on auscultation in many patients. Chest tightness is poorly localized, may arise from the isometric contraction of intercostal muscles. Absence of wheezing and chest tightness does not rule out the possibility of diagnosis of COPD, nor does their presence confirm diagnosis

of asthma.

Other symptoms:

- o Pedal edema is usually resulting from right ventricular failure (cor-pulmonale).
- o Gastro- esophageal Reflux Disease (GERD) is also common among COPD patients.
- o Psychiatric morbidity is high in COPD, reflecting the social isolation, the neurological effects of hypoxemia and possibly the effects of systemic inflammation.
- o Sleep quality is impaired in advanced disease and this may contribute to neuropsychiatric comorbidities.
- o Chest pain in COPD usually muscular but risk of IHD is also more than general population.

History taking:

History taking is important aspect of assessment of disease severity of COPD patient and for excluding possibilities of other diseases having similar clinical presentation. It should include:

- Detailed history related to production and progression of symptoms related to pulmonary and extrapulmonary part of COPD.
- Detailed history related to patient's exposure to risk factors, such as smoking (active and passive) and occupational or environmental exposures (indoor as well as outdoor pollutants), especially for biomass and other cocking fuel.
- Smoking history should be well defined in pack-year and smoking index. (1 pack-year is equivalent to 20 cigarettes smoked per day for 1 year). Smoking habits of the family may determine the outcome of smoking cessation intervention. Possibilities for reducing risk factors, especially smoking cessation should be evaluated.
- Past medical history, including tuberculosis, asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood; and other respiratory diseases should be recorded.
- Family history of COPD, tuberculosis or other chronic diseases.
- Hospitalization if required in the past especially for respiratory diseases. Patients may be aware of periodic worsening of symptoms in the past, even if these episodes have not been identified as exacerbations of COPD.
- Presence of systemic manifestations /comorbidities of COPD, such as heart disease, osteoporosis, musculoskeletal disorders and malignancies that may also contribute to restriction of activity.
- Impact of disease on patient's life, including limitation of activity, decrease in working capacity and missed work and economic impact, effect on family routines, feelings of depression or anxiety, well being and sexual activity.
- Social and family support available to the patient.

Physical examination:

The physical signs in patients with COPD will invariably depend on the severity of disease. A physical examination will in general be a poor tool for detecting mild or moderate COPD and the reproducibility of physical signs have been shown to be very variable. In contrast, physical signs are more specific and sensitive for severe COPD. Raised JVP, hepatomegaly and pedal edema suggest cor-pulmonale.

The mild to moderate form of COPD usually don't show any physical sign. Many patient often use pursed-lip-breathing, to avoid small airway collapse. Patients will often sit leaning

forward with their arms resting on a table in front of them or on some other stationary object in order to use the rib cage and larger muscles to function as inspiratory muscles. The general stature of the patients should be observed. Weight loss, especially when there is clear muscle atrophy, can be a sign of severe COPD specially patients having predominantly emphysema, and likely a systemic effect of COPD, possibly due to systemic inflammation. These patients often have "barrel shaped chest" result from hyperinflation of lung. Percussion of lung although insignificant but show tympanic note due to hyperinflation of lung. On auscultation of lung breath sound are diminished and sometimes adventitious sounds like wheeze and crackles are present. Cardiac auscultation shows tachycardia and signs of atrial fibrillation, ventricular gallop, loud pulmonary second sound and tri-cupid insufficiency.

Investigations:

Lung Function Test: Spirometry although not easily accessible to deprived population, but still remains the most reproducible and objective measurement of airflow limitation available. Peak expiratory flow (PEFR) measurement although have good sensitivity but because of weak specificity, it alone cannot be reliably used as the only diagnostic test.

Spirometry measures:

- FVC (Forced vital capacity): Maximum volume of air forcibly exhaled from the point of maximum inspiration.
- FEV1 (Forced expiratory volume in one second): Volume of air exhaled during first one second.
- FEV1/FVC: Ratio of Forced expiratory volume in one second and forced vital capacity

The ratio between FEV1 and slow vital capacity (VC), FEV1/VC, is sometimes measured instead of the FEV1/FVC ratio. This will often lead to lower values of the ratio, especially in pronounced airflow limitation, however, the cut-off point of 0.7 should still be applied. Spirometry measurements are evaluated by comparison with reference values based on age, height, sex and race. Lung function test is not only the important tool to confirm the diagnosis of COPD, but also a valuable tool for assessing severity and prognosis of disease and for monitoring the treatment and course of disease. Guidelines usually state that a suspected diagnosis of COPD is confirmed by presence of post-bronchodilator ratio of FEV1/FVC of <0.7.

Lung Volumes and Diffusing Capacity: Help to characterize severity, but not essential to management. With worsening disease severity, lung volumes may increase, resulting in an increase in total lung capacity, functional residual capacity and residual volume. In patients with emphysema, the diffusing capacity may be reduced, reflecting the lung parenchymal destruction characteristic of the disease.

Oximetry and Arterial Blood Gas analysis (ABG): Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. Partial pressure of oxygen (paO2) is generally reduced as FEV1 reduces while paCO2 remain normal in initial and stable condition. In severe condition or later stages paCO2 started to rise, leading to type 2 respiratory failure. Initial measurement of oxygen saturation is recommended and if it is found to <92%, than ABG is recommended.

Blood Investigations: Blood investigation generally have no role in diagnosis of COPD. It might show polycythaemia. Anemia can be seen in COPD as with in other chronic systemic

diseases generally a marker of poor prognosis.

Imaging: Although, X-ray chest is not useful to establish a diagnosis of COPD, but it is valuable in excluding diseases having similar clinical presentation and also diagnoses and establishing the presence of systemic manifestations of COPD and comorbidities such as concomitant respiratory (tuberculosis, pulmonary fibrosis, bronchiectasis, pleural diseases), skeletal (e.g., kyphoscoliosis) and cardiac (e.g., cardiomegaly) diseases.

Over inflation of the lungs results in low diaphragms, an increase in the retrosternal airspace and an obtuse costophrenic angle on the postero-anterior or lateral chest radiograph. The vascular changes associated with emphysema can often be seen on a plain chest radiograph by a reduction in the size and number of pulmonary vessels, particularly at the periphery of the lung, vessel distortion and areas of transradiancy, however, assessment of vascular loss in emphysema is very dependent on the quality of the radiograph.

Computed tomography (CT) can be used for the detection and quantification of emphysema, either using semi-quantitative visual assessment of low-density areas on the CT scan or by using measures of lung density to quantify areas of low x-ray attenuation. CT-scan is used as a densitometer. As emphysema develops, alveolar wall mass decreases and this leads to a decreased CT lung density. Initial experiences suggest that this can be used to measure progression of emphysema, although the radiation involved precludes its use as a frequent measure of disease progression. Magnetic resonance (MR) scanning using hyperpolarised gases such as Helium is still in its pioneering phase.

ECG and 2D Echocardiography: ECG may show atrial fibrillation or P pulmonale. ECG is not a good test to diagnose cor-pumonale. Cor-pulmonale is diagnosed via 2D Echo. 2D Echo can access associate cardiac abnormality as well as right ventricular function.

Alpha-1 Antitrypsin Deficiency Screening: Perform when COPD develops in patients of Caucasian descent under 45 years or with a strong family history of COPD.

Exercise Testing & assessment of Physical activity: Objective measurement of impairment in capacity to perform exercise is powerful indicator of health status impairment and predictor of prognosis. Six minute walk test (6MWT) is easy to perform and low cost and the maximal walked distance represents high prognostic value in several cardiopulmonary disorders. This test is also widely used to assess exercise capacity before and after an intervention, such as an exercise-training program. Patients are instructed to walk both ways for six minutes on a corridor around 30 meters, which is delimited by two cones. The maximum walked distance is the main outcome in the 6MWT.[9]

Laboratory testing using cycle or treadmill ergometry can assist in identifying co-existing or alternative conditions e.g., cardiac diseases. In parallel with exercise testing, tests of muscle strength may be applied. Simple measures, e.g., quadriceps muscle strength, have been shown to be of value in COPD.[10]

Differential Diagnosis:

Most important differential diagnosis of COPD are bronchial asthma, bronchiectasis, obliterative bronchitis, tuberculosis, congestive heart failure and cystic fibrosis. The most difficult clinical problem will often be distinguishing COPD from persistent poorly reversible asthma, especially in older patients. In specialist clinics exhaled air NO measurement, cell differential and mediators in sputum and mucosal biopsy assessment can be done to overcome this problem. Spirometry and imaging (HRCT) are also used to differentiate from other respiratory diseases having similar clinical presentation. (Table 1)

Table 1

Diagnosis	Characteristics	Clinical Presentation	Pulmonary Function Tests	Chest Imaging	Other tests recommended
COPD	Onset in mid-life or later; steadily progressive with exacerbations; long history of tobacco smoking	Chronic productive cough, dyspnea and wheezing	Partially reversible/ or fixed airflow limitation decreased DLC	Hyperinflation increased BV markings, bronchial thickening	A-1 antitrypsin testing, ABG testing, & chest CT in selected patients
Asthma	Onset early in life, episodic; associated with other allergic disorders & family history, symptoms at night/early morning;	Episodic wheezing dyspnea, and cough	Reversible airflow limitation spontaneously or after treatment, normal DLCO	Normal between episodes	Allergy testing, peak-flow monitoring
Bronchiectasis	Usually early-life onset; progressive with exacerbations; large volumes of purulent sputum/ commonly associated with bacterial infection	Productive cough with thick, purulent sputum; dyspnea; wheezing; digital clubbing; coarse crackles on auscultation	Obstructive airflow limitation, both fixed and reversible	Focal pneumonia, atelectasis; dilated, thickened airway (ring shadow); CT shows bronchial dilation, bronchial wall thickening	Bacterial and fungal sputum culture; chest CT
Bronchiolitis obliterans	Relatively common in younger age; may be associated with history of flu-like illness, collagen vascular disease, toxic exposure; rheumatoid arthritis; usually in nonsmokers	Often sub-acute presentations with dyspnea, cough, and fever	Decreased vital capacity, decreased DLCO, usually no obstructive component	Multifocal, bilateral. alveolar infiltrates, CT on expiration s hypodense areas	High resolution CT lung biopsy
Congestive heart failure	Midlife to late-life onset; associated with risk factors e.g. CAD, hypertension. Chest X-ray-dilated heart, pulmonary edema. PFT-volume restriction, no airflow limitation	Fatigue, exertional & paroxysmal nocturnal dyspnea, & peripheral edema	Decreased DLCO, predominantly used to exclude other diagnosis	Increased heart size, pulmonary vascular congestion, pleural effusions	Echo, BNP measurement, ECG; cardiac catheterization in selected patients.
Tuberculosis	Onset at any age; associated with history of exposure	Cough >2 wks, fever, wt. loss & hemoptysis	Not used for diagnosis	Infiltrate, fibro-cavitary lesions, hilar lymph-adenopathy in children	Sputum microscopy for Z N staining: AFB culture
Cystic Fibrosis	Usually early life onset; progressive with exacerbations; associated with pancreatic disease, failure to thrive, intestinal obstruction, cirrhosis, and steatorrhea	Productive cough with purulent sputum, dyspnea & wheezing	Predominantly fixed airflow obstruction	Bronchiectasis frequent in upper lobes	Sweat chloride test (diagnostic), bacterial sputum culture

COPD = Chronic Obstructive Pulmonary Disease; DLCO = Carbon monoxide diffusion in the lung; ABG = arterial blood gas; CT = computed tomography; BNP = brain natriuretic peptide; AFB = acid-fast bacillus.PFT = Pulmonary Function Test, CAD = Coronary Artery Disease, BV=Broncho vascular

Diagnosis:

Diagnosis of COPD should be suspected when a patient: (Figure 1)

1. Complains of shortness of breath (breathlessness/ dyspnea), cough, sputum production or symptoms suggestive of recurrent lower respiratory infections.
2. Reports risk factors, host and environmental exposures (Table 1) specially ageing, exposure to tobacco smoke and biomass fuel.

These symptoms of COPD generally do not correlate with disease severity.

Additional medical history is obtained for:

1. Symptoms related to comorbidities/systemic manifestation of COPD e.g. oedema, palpitation, cyanosis, decrease urine output, fatigue, loss of appetite, weight loss, psychiatric symptoms and joint pains.
2. Evidences of other conditions present with similar symptoms specially tuberculosis.
3. Ability to perform day to day activities.[3]

Figure 1- Diagnosis of COPD

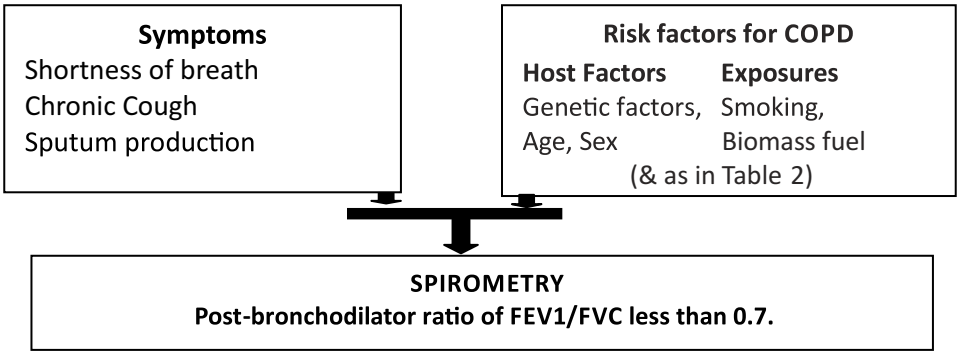

Table 2- Risk factors for COPD.[2]

Established	Probable
• Tobacco smoking • Environmental tobacco smoke • Exposure to biomass fuel smoke • Occupational exposure • α-1-antitrypsin deficiency	• Outdoor air pollution • Pulmonary tuberculosis • Poorly treated asthma • Intrauterine growth retardation • Poor nourishment • Repeated LRTI during childhood Others: 1. Age 2. Male gender 3. Low socioeconomic status

Assessment of disease severity of COPD:

COPD assessment is done to determine levels of airflow limitation, assess its impact on health status, predict risk of future exacerbation, hospital admission and death and plan preventive and therapeutic strategies.

To achieve these goals assessment of following aspect of the disease is recommended.[1]

- Airflow limitation using spirometry.
- Symptoms.
- Risk of exacerbations.
- Comorbidities.

Assessment of severity of airflow limitation:

Most accepted spirometric criterion for airflow limitation remains a post-bronchodilator fixed ratio of FEV1/FVC < 0.70. This criterion is simple and independent of reference values and has been used in numerous clinical trials that form the evidence base from which most of treatment recommendations are drawn (GOLD 2017).[1]

Classification of severity of air flow limitation in patients with FEV1/FVC < 0.70:

GOLD 1: Mild	FEV1 ≥ 80% predicted
GOLD 2: Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3: Severe	30% ≤ FEV1 < 50% predicted
GOLD 4: Very Severe	FEV1 < 30% predicted

*Based on Post-Bronchodilator FEV1

It has been observed that there is a weak correlation between FEV1, symptoms and impairment of patient's health status. For this reason, symptomatic assessment is required.

Assessment of symptoms:

Degree of breathlessness can be measured by various scales and questionnaire. The simple MRC dyspnea scale[12] is a useful tool but as it was originally developed for assessing breathlessness in epidemiological surveys in the workplace, it is relatively insensitive to changes. However, a slightly modified version of the MRC Questionnaire is a good measure of health status.[13]

The Modified Medical Research Council dyspnea scale (mMRC).

Grade Description:

0 Not troubled with breathlessness except with strenuous exercise.

1 Troubled by shortness of breath when hurrying or walking up a slight hill.

2 Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on the level.

3 Stops for breath after walking 100 m or after a few minutes on the level.

4 Too breathless to leave the house or breathless when dressing or undressing.

In recent past it is considered that in addition to breathlessness, other impact of COPD e.g. other symptoms and health status should also be considered while assessing COPD. Assessing a patient's health-related quality of life (HRQoL) allows clinicians to make individualized patient management decisions.

There are several health-related quality of life (HRQoL) questionnaire based assessment tools are available.[1]

- Chronic Respiratory Questionnaire (CRQ).
- St. George's Respiratory Questionnaire (SGRQ).
- COPD Assessment Test (CAT).
- COPD Control Questionnaire (CCQ).

The CAT is considered to be more practical, was created using COPD patients' input and then developed using modern questionnaire methodology: psychometric analysis and item

response theory using Rasch analysis identified items with the best fit to form a unidimensional instrument. Self-administered questionnaire consists of 8 items assessing various manifestations of COPD aiming to provide a simple quantified measure of HRQoL.[11,12]

Assessment of risk of exacerbations:

History of exacerbations and spirometry are considered to be the good predictor to assess risk of future exacerbations and mortality:

- Two or more exacerbations within the last year or an FEV1 < 50 % of predicted value are indicators of high risk.[15]
- One or more hospitalizations for COPD exacerbation should be considered high risk.[16]
- Blood eosinophil count. Clinical trials in COPD patients with an exacerbation history showed that higher blood eosinophil counts may predict increased exacerbation rates in patients treated with long acting beta agonists without inhaled corticosteroid (ICS). and ICS can have preventive role in COPD exacerbation.[17,18]

Assessment of extrapulmonary (systemic)/ concomitant chronic illnesses (comorbidities):

Patients with COPD often have important associated chronic illnesses at the time of diagnosis. Aging, smoking, alcohol, diet and inactivity are some common risk factors for development of COPD and its systemic manifestations e.g. weight loss, nutritional abnormalities and skeletal muscle dysfunction and comorbidities including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer. All these manifestations affect patient's capability of doing physical activity and quality of life and they have significant impact on prognosis, exacerbation, hospitalization and mortality.[18-22]

Revised combined COPD assessment:

Recent GOLD guidelines have revised its previous scheme of comprehensive assessment module, evaluating COPD through assessment of:[1]

- Severity of airflow limitation by spirometry (i.e., spirometric grade).
- Dyspnea using mMRC scale.
- Symptoms using CAT.
- History of exacerbations (including prior hospitalizations).

For a practicing clinician still this tool of COPD assessment needs more simplification.

BODE index: Patients with COPD have systemic manifestations that are not reflected by the FEV1 measurement. Computation of the Body-Mass Index, Degree of Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) is a multidimensional grading system that assessed the respiratory and systemic manifestations of COPD. It is simple grading system, better than the FEV1 alone in predicting the risk of death from any cause including from respiratory causes among patients with COPD.[24]

Table 3- Variables and Point Values Used for the Computation for BODE Index.[24]

Variables	Points on Bode SCALE			
	0	1	2	3
FEV_1 % Predicted after bronchodilatation*	≥65	50-64	36-49	≤35
6 Minute Walk Distance in Meters	≥350	250-349	150-249	≤149
mMRC Dyspnea Scale**	0-1	2	3	4
Body Mass Index***	<21	≤21		

+The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV1- Forced Expiratory Volume in one second.

*The FEV1 categories are based on stages identified by the American Thoracic Society.

**Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

***The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

Celli, B R et el J Med 2004;350:1005-12.

DOSE Index: DOSE Index (MRC dyspnea scale, airflow obstruction, smoking status and exacerbation frequency) is a multi-component assessment tool of COPD severity that is applicable to all patients and healthcare settings. The DOSE index was derived in primary care populations as a measure of health status, but has also been shown to reflect current and future exacerbations and admissions and mortality.[25]

Most of the scoring systems especially the composite scores including BODE and DOSE should not be used to assess severity or prognosis in COPD unless they are validated in Indian patients.[2]

Assessment of severity as per Indian Guidelines:

Indian guidelines recommend classification of severity of the disease to be done for all COPD patients based on the FEV1, exacerbation frequency, level of patient's disability due to symptoms (as assessed using modified Medical Research Council (mMRC) dyspnea questionnaire or the COPD assessment test (CAT).

Table 4 - Classification of severity of COPD (Indian Guidelines).[2]

Severity*	Post-bronchodilator FEV_1 % Predicted	mMRC grade	Exacerbation Frequency†	Complications‡
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, †number of exacerbations in the last year, ‡complications include respiratory failure (defined by pO_2 <60 mmHg and/or SpO_2<88% and/or pCO_2>50 mmHg), cor-pulmonale and secondary polycythemia (hematocrit >55%); FEV1: Forced expiratory volume in first second, mMRC: Modified medical research council questionnaire, COPD: Chronic obstructive pulmonary disease

In Indian set up it is recommended that 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 Revised National Tuberculosis Control Program (RNTCP).

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"There are things known and there are things unknown, and in between are the doors of perception"
–Aldous Huxley

5

Non-pharmacological Management of Stable COPD: Identify and Reduce Exposure to Risk Factors

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Introduction:

COPD is currently the fourth leading cause of death in the world and is expected to third leading cause by 2020.[1] It is a condition with high and continually increasing mortality. Approximately 7% of all individuals have COPD including 10% >65 years of age or older.[2] This disease has a high economic, social and personal burden. The most important factor to decrease the burden is the modification of environmental exposure. The management of COPD can be divided into pharmacological and non-pharmacological. The non-pharmacological component is at least as important as the pharmacological component and the non-pharmacological component can be applied to patients with stable COPD and acute exacerbations.[3] The role of non-pharmacological therapies remains commanding though underutilized in our settings and it must not be forgotten as it provides symptomatic improvement and better quality of life.[4] These also improve life expectancy, which is not done by pharmacological therapy.[4] The management can be divided into educational interventions encouraging self-management to medical interventions. These interventions include smoking cessation, reduction of other risk factors, oxygen therapy, vaccinations, surgical/ bronchoscopic procedures and pulmonary rehabilitation. As per the Gold guidelines the therapies of COPD are guided by disease severity and aim to control symptoms, decrease exacerbations and improve patient function and quality of life.[5]

Education:

It is a well-known fact that education is the key to self-management programme of any disease. Educating the patients about their disease, interventions and teaching inhaler techniques has shown to improve lung function. Patients should be taught about rationale of treatment, smoking cessation (the single most effective intervention), effective inhaler techniques and how to recognize acute exacerbations. Educating the patients and relatives can decrease the health care utilization. A proper action plan told the patient can also reduce emergency room visits.[3]

Smoking cessation:

Smoking cessation is the most important step in management of all patients with COPD but is very poorly documented. This intervention is known to decrease the rate of decline of FEV1 in smokers with COPD. A decline in post-bronchodilator FEV1 of 54.2 and 66.1 ml in women and men respectively who continued to smoke over 11 ten year period has been reported in the Lung Health study.[6] Complete, sustained cessation and abstinence have shown a decrease in the rate of decline in FEV1 but the reduction in the amount of cigarettes did not get the same results unless the reduction was >85%.[7]

Indian guidelines advise smoking history including pack years and smoking index should be documented for all patients of COPD and all patients should be encouraged to stop smoking and offered all help.[8] Patient education, clinician advice and encouragement, nicotine replacement therapy, behavioral counseling and medications as bupropion and varenicline are the various interventions that help in smoking cessation.[9] Counseling and medication for smoking cessation when combined together have shown to give best cessation rates.[10] Legal ban on smoking in public places is in place in India but often not adequately implemented.[11] Medications should be advised to the patients who are planning to stop smoking.

Though the benefits of smoking cessation are very clear and known to the patients but the success rate is low among smokers and even the large proportion of moderate to severe COPD patients still continue to smoke in-spite of the symptoms. Nicotine in tobacco is attributed for this failure as it being an addictive drug leading to release of dopamine which is a reason of addiction. Smoking is also being done socially which also needs to be addressed for quitting. When the physicians are dealing with this intervention it is best to consider it as a chronic disease as the goal is quitting with many relapses on the way.[4]

Communication: At each visit the physician should ask the patient about their smoking habits and willingness to stop smoking and also should advise them to quit smoking. The risk of smoking, the advantages of quitting and the methods available should be told to the all the smokers at each visit. Counseling and close follow up remain an important part of the cessation process.

Nicotine Replacement Therapy (NRT): NRT has a two fold increase in smoking cessation rates as compared to placebo.[12] By proving only nicotine which is considered to be the basis of addiction, the harmful effects of tobacco can be avoided. Various preparations like gums, lozenges, transdermal patch, inhaler and nasal spray are available. In India however, the general availability of NRT is limited to chewing gums and patches. Side effects of all forms of NRT include insomnia and disturbing dreams. Combination of short and long acting NRT is associated with higher abstinence rate as compared to single NRT.

Chewing gum releases nicotine which is absorbed through the lining of the cheek and is good for smokers who require a flexible administration of NRT as it controls the amount of nicotine and occasion of use. Nicotine gum should be used in a 'chew and park' technique to get best results. The gum should be chewed slowly until the taste becomes strong, for about one minute, which should be followed by resting the gum between the cheek and gum and chewing it again as the taste fades.

Transdermal patch is a discreet, easy-to-use, once-a-day solution and preferred as it helps tobacco users deal with the cravings and withdrawal symptoms associated with quitting smoking. It has most reliable and steady delivery of nicotine which is released through the skin over 16 hours once the patch is applied. It can lead to higher craving in the morning. Dosage depends on the kind of smoker you are. Smokers who smoke more than twenty cigarettes a day, or who smoke their first cigarette in less than 30 minutes after waking up, are classified as heavy smokers. Smokers having lesser intensity of tobacco intake than this can be termed as light smokers. For light smokers one should use nicotine 2 mg gum, whereas for heavy smokers one should start with nicotine 4 mg gum. There is also evidence that combining a nicotine patch with a nicotine gum or inhaler is more effective than using a single type of an NRT product.[13]

Standard guidelines [Table 1] 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.[14,15]

Bupropion: This antidepressant has been shown to nearly double the quit rates when compared to placebo.[13] It effects by potentiating dopaminergic and noradrenergic signaling which reduces the craving and decreases withdrawal symptoms. The dose is 150mg bid. Insomnia is the greatest side effect and it reduces the seizure threshold thus contraindicated in patients with seizure history. It is more effective in combination with NRT.

Varenicline: It is a partial agonist of nicotine receptors and is one of the more effective agents. It reduces withdrawal symptoms and also reduces the rewarding and reinforcement effects of nicotine. The side effects associated with its use are GI intolerance, insomnia, visual disturbances and also has possibility of neuropsychiatric symptoms including depression and suicidal thoughts.[16]

E-cigarettes: These are battery powered devices that deliver nicotine in aerosolized form and come in variety of brands. These are claimed to be less harmful can be used where one cannot smoke and are effective in quitting smoking.[17] However these are largely unregulated and at present are of unknown safety and there role in smoking cessation has not yet been determined.[18] The forum on International Respiratory Societies (FIRS) has issued a statement that E-cigarettes should be restricted or banned until more data is available.[19] At present it is recommended to use FDA approved therapies.

Immunization: Influenza vaccine has resulted in significant reduction in exacerbations compared to placebo. Indian guidelines recommend that Influenza and pneumococcal vaccination is likely to be beneficial in patients with severe COPD and/or frequent exacerbations.[8]

Smoking Cessation Therapies

	Benefits vs Placebo	Optimal Dose	Side Effects	Combination vs Single Agent Therapy
Nicotine Replacement Therapy (NRT)	2 fold increase in smoking cessation compared to placebo	Depends on amount of cigarettes smoked /day at quit date	Insomnia, disturbed dreams, nasal irritation (for nicotine nasal spray)	Combination long and short acting NRT more successful than single agent
Bupropion	2 fold increase in smoking cessation compared to placebo	150mg po bid X 7-12 weeks	Insomnia, lowers seizure threshold, suicidal thoughts/ actions	Bupropion + NRT more successful than either agent alone.
Varenicline	2-4 fold increase in smoking cessation compared to placebo	1mg po bid X 12 weeks	Insomnia,depression, suicidal thoughts/ actions, disturbing dreams, GI side effects	Conflicting data on superiority of varenicline + NRT vs varenicline alone
E- cigarettes	Unclear at present times, further studies required	N/A	Unregulated	N/A

Pulmonary Rehabilitation:

It is a multi-disciplinary program of care designed to optimize physical and social performance and autonomy.[20] It includes exercise training, psychosocial and behavioural interventions and nutritional therapy.[3] This topic is discussed in detail as a separate chapter in this book.

Oxygen therapy:

Long term oxygen therapy is recommended for patients with PaO2 ≤ 7.3kPa or a PaO2 between 7.3 and 8 kPa with signs of peripheral edema, polycythemia (hematocrit >55%) or pulmonary hypertension. It is known to improve cardiac output, exercise tolerance and

quality of life. This topic is discussed in detail as a separate chapter in this book.

Comprehensive care plans:

Comprehensive care management programmes have grown not only in COPD but in management of other chronic diseases. It consists of self-management, streamlining access to health care, decision support and clinical information system. These strategies have shown to decrease rates of hospitalizations and emergency/unscheduled visits and a shorter length of stay compared with control groups.[21] It has also shown to improve the symptoms and quality of life of the patients.[22] One education session is very important for patients to understand his own disease and to own it. This results in improved medical compliance and health status.[21] Non-compliance with the medications especially inhaler techniques have shown to be a big problem. It has been shown that 45% of the admissions for COPD could have been prevented with proper inhalation techniques.[23]

Surgery in COPD:

Surgical intervention in management of COPD has not been developed in India to it's full potential.[11] Lung volume reduction surgery (LVRS) and unidirectional endo-bronchial valve (EBV) technique are the techniques which can be used in patients with advanced COPD. New surgical technique of LVRS was introduced in mid 1990s. [24] In this procedure 20-30% of emphysematous lung is removed which lets the other lung to expand leading to increased vital capacity, improving elastic recoil and expiratory flow thus improving V/Q matching.[25] National Emphysema treatment Trial (NETT) a prospective multi-centric trial was conducted which enrolled >1200 patients to study this procedure. Though the mortality was higher in patients undergoing this procedure but a survival benefit was shown in patients with upper lobe emphysema and this procedure also showed increase in exercise capacity and improvement in dyspnea.[26]

Minimal invasive surgical technique of EBV includes putting one way valves bronchoscopically which blocks the inspiratory flow in lobar bronchus causing atelectasis which decreases the dead space ventilation and hyperinflation which improves the vital capacity.[27] A largest RCT including 220 patients showed that EBV treatment for advanced heterogeneous emphysema induced modest improvements in lung function, exercise tolerance, and symptoms at the cost of more frequent exacerbations of COPD, pneumonia, and hemoptysis after implantation.[28] In a recent study EBV treatment significantly improved pulmonary function and exercise capacity in patients with severe emphysema characterized by an absence of inter lobar collateral ventilation.[29] None of the EB valves are yet approved by Indian FDA and are not available for treatment.[11]

Nutrition in COPD:

More than 30% of patients with severe COPD have protein-calorie malnutrition which is associated with increased mortality, decreased respiratory muscle function and diminished immune competence. It has been shown that low BMI and low body weight and obesity have been shown to be independent risk factors of mortality in COPD.[30,31] It has also been shown that negative effects of low body weight can be reversed by appropriate therapy in few of the patients of COPD. Nutritional depletion has been shown to be an independent risk factor for mortality and hospitalization in these patients. European Society for Parenteral and Enteral Nutrition (ESPN) guidelines state that enteral nutrition (EN) in combination with exercise and anabolic pharmacotherapy has the potential to improve nutritional status and function in COPD patients and frequent small amounts of oral nutritional supplements are preferred in

order to avoid postprandial dyspnoea and satiety as well as to improve compliance.[32] For maintenance of muscle and bone tissue, appropriately timed, high-quality protein intake and addressing vitamin D deficiency must be considered. Specific nutrients (e.g., n-3 polyunsaturated fatty acids and polyphenolic compounds) may have the pharmacologic potential to boost decreased muscle mitochondrial metabolism and enhance impaired physical performance, particularly when the metabolic stimulus of physical activity alone is limited.[33]

Most of the studies have shown inconsistent benefit of nutritional supplementation in COPD.[34] Recent Cochrane review found moderate-quality evidence that nutritional supplementation promotes significant weight gain among patients with COPD, especially if malnourished.[35] Indian guidelines suggest that the role of nutritional supplementation should be decided on a case to case basis by a specialist.[8]

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"Your genetics load the gun. Your lifestyle pulls the trigger"
-Mehmetoz

6

Management of Stable COPD: Non-Pharmacological Management– Physical Exercises and Rehabilitation

Dr. Sheetu Singh, Dr. Virendra Singh

Introduction:

Human beings have tremendous power of acquiring skills. By doing proper set of exercises an athlete can train his body to run for 20 miles while a sedentary worker can hardly run even for a mile. With exercise training the body and lungs of an athlete to perform 20 time more. Therefore it is logical to explore possibility of making lungs of Chronic Obstructive Pulmonary Disease (COPD) patients so efficient as to perform 20 times more physical activity. If we translate it in to distance a COPD patient walking 50 meters, after training patient may be able to walk 1km and earn improvement in quality of life. Exercise training and rehabilitation have been shown to reduce disability in many chronic respiratory diseases.[1,2] COPD is progressive disease[3] with poor prognosis. In severe COPD patients treatment options are limited and oxygen is the only modality that prolongs survival.[4] With disease advancement, co-morbidities and recurrent exacerbations a patient becomes disabled. Disability is a cause of decreased activity, social isolation and depression. Further, decreased activity is an independent predictor of mortality in COPD.[5] The aim of pulmonary rehabilitation is to break this vicious cycle and help the COPD patients to participate in daily activities. It is known to improve quality of life and exercise tolerance in COPD.[6]

Why COPD patient develop dyspnoea?

Dyspnoea and exercise intolerance in COPD are due to multiple factors. Expiratory airflow obstruction[7] is an important cause but not the only one. Inspiratory muscle dysfunction[8], gas exchange abnormalities[9] and cardiac dysfunction[10] are other causes. Exercise intolerance can be best explained by the concept of dynamic hyperinflation.[11] The motion of thorax is restricted due to hyperinflation and thereby capacity to increase tidal volume during exercise is limited. Hyperinflation also compromises the ability of inspiratory muscles to generate pressure[12] and weakens them.

Pulmonary Rehabilitation:

American thoracic society and European respiratory society proposed the most acceptable definition in 2006. It states “Pulmonary rehabilitation is 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 health care costs through stabilizing or reversing systemic manifestations of the disease.[9]

A lot of research has been done in various aspects of pulmonary rehabilitation in patients

with COPD. This review analyzes the methods of pulmonary rehabilitation and various aspects as follows:

1. Smoking cessation.
2. Clearing of airway secretions.
3. Breathing techniques.
4. Exercises.
5. Energy conservation and fatigue obviation.
6. Patient education.

1. Smoking cessation:

With age lung functions decline and usually forced expiratory volume one second (FEV1) declines 20 ml every year after 20 years of age. In smokers annual decline in FEV1 is 35 to 40 ml. None of the existing medicines can reduce the faster rate of decline in lung functions in a smoker. Only strategy to prevent faster rate of decline is cessation of smoking. Therefore cessation of smoking should be emphasised at the time of every medical consultation.

2. Clearing of secretions:

Cough and sputum production are key symptoms of COPD. Traditional definition of chronic bronchitis is also based on chronic production of sputum. Presence of secretions in airways not only interferes in ventilation but also in physical capacity. Therefore clearing of airways from secretions is an important step before performing exercises. Good hydration, smoking cessation, avoidance of irritants and bronchodilator therapy are prerequisites. Chest physiotherapy is helpful in clearing secretions and subsequently preventing sequelae like dyspnoea and hypoxemia. Controlled cough and forced expiration are two techniques found useful.[13] Patients with severe COPD may tolerate the latter technique better. The techniques should be practised every morning for ten minutes after the dose of short acting bronchodilator. They may be practised more frequently in patients with problem of copious sputum.

3. Breathing techniques:

Some breathing techniques are useful in providing relief in dyspnoea in patients with severe COPD. The patient is advised to breathe slowly and deeply to reduce dead space and improve carbon dioxide elimination. This pattern of breathing reduces physiological dead space, improves carbon dioxide removal and consequently ventilation.

a) **Pursed lip breathing:** A patient take a slow and deep breath through nose and exhale slowly through mouth providing resistance. It is assumed by some COPD patients instinctively during an exacerbation. Pursed lip breathing involves active expiration against resistance.[14] Resistance may be provided at level of lips or tongue and a whistling is produced during expiration.[15] It is called as pursed lip breathing. When resistance imposed at level of vocal cords it is called as grunting. This procedure reduces the respiratory rate and improves tidal volume and therefore provides relief in dyspnoea.[16] Other theories to explain improvement in ventilation with pursed lip breathing are alteration in respiratory muscle recruitment[17] and development of positive pressure in the airways during breathing thereby preventing dynamic airway collapse.[18]

b) **Diaphragmatic breathing:** It is another pattern of breathing which distracts the patient from the distress of dyspnoea and alleviates the anxiety.[19] This form of

breathing is practised when patient is comparatively less distressed. One hand is kept on the chest and another on the abdomen. Patient is instructed to take abdominal breathing by taking a deep slow inspiration and allow the abdominal wall to move outward. The possible mechanism of action of this method is altered respiratory muscle recruitment and reduction in respiratory frequency.[20]

c) **Huffing:** This technique helps in clearing tracheobronchial secretions. Patient takes a deep breath and then exhale in three even forceful breaths. A sound of Ha Ha Ha is made during forceful exhalations. It is less tiring method of expelling sputum.

d) **Deep breathing:** It is an age old method in which a patient inhales a deep breath by nose and then holds the breath for a count of.[5] Then patient exhales slowly and completely. It is usually done for 10 minutes.

4. Exercises:

Exercise improves vigour, health status[13] and life expectancy[21] in normal healthy individuals. A number of studies and meta-analysis have been performed to decide the indications, intensity, duration and long term effects of exercise. It has been observed that around 30% of muscle mass gets wasted in an average COPD patient.[22] Poor muscle mass leads to early fatigue and decreased exercise tolerance. Thus, exercise training builds up muscle mass and strength. It has been known to increase exercise capacity, improve health related quality of life measures and reduces symptoms of dyspnoea. Exercise also has psycho-social benefits with reduced prevalence of depression.[23] However, there is inadequate evidence that indicate improvement in survival in COPD patients.

a) **Type of exercises:** The muscle strength and endurance are increased for the specific group of muscle trained. Thus, both upper limb and lower limb exercise training are advised.[23] Lower limb training includes treadmill, cycle ergometry and corridor walking.[9] Various studies have reported an increase in peak exercise capacity, walking distance and endurance.[24] Many COPD patients have difficulty in performing activities involving use of upper limbs. Upper extremity training is required in these cases and it includes ergometry, throwing and weights.[9] Unsupported weights have been found superior to supported exercises in form of ergometry. Similar to lower limb muscle training arm endurance and strength are increased by upper limb muscle training.

b) **Who should undertake exercises of pulmonary rehabilitation?** Usually patient of COPD with severe dyspnoea interfering with lifestyle, reduced tolerance to exercise and patients in pre-operative period are suitable candidates for a rehabilitation program. Some guidelines refer patients with medical research council (MRC) dyspnoea scale of more that III-IV.[23]

c) **Patients with recent myocardial infarction (past three months),** unstable angina, uncontrolled blood pressure, debilitating arthritis, congestive heart failure, dementia, neurological and peripheral vascular disease are not prescribed pulmonary rehabilitation.[25]

d) **Intensity and duration of exercise:** Depending on the underlying COPD, co-morbidities and muscle wasting patients are assigned either high or moderate intensities of exercises. High intensities of exercise include training at 90-100% of maximum exercise capacity[25] or heart rate. Performing high intensity exercise for short interval increases the strength of the muscles and performing less intense

exercise for a longer interval increases the endurance. Moderate intensity of exercise includes training at 60-80% of maximum exercise capacity.[25]

e) **Outcome measures:** The outcome can be measured by subjective and objective methods. Since most patients are referred for pulmonary rehabilitation due to decreased exercise tolerance, poor quality of life and increased dyspnoea, the assessment of outcome by the patient is important.

- Subjective methods: These include symptom improvement in terms of questionnaires like chronic respiratory disease questionnaire[26] and St George's respiratory questionnaire.[27] Borg scale[28] and visual analogue scale[29] can also be used to assess the degree of breathlessness.
- Objective methods: These include cardiopulmonary exercise testing (CPET), six minute walk test (6MWD),[30] incremental shuttle walk test (ISWT) and endurance shuttle walk test.[31] CPET is the gold standard as it measures maximal exercise capacity. However it is expensive and not easily available. 6MWT is a simple test and can be used to evaluate distance walked in six minutes. The results of 6MWT can be an alternative.

f) **Maintenance exercises:** The benefits of exercise programme after stopping wanes with time. Various maintenance programmes have been studied with variable results. Foglio et al[32] had studied the effect of pulmonary rehabilitation programme held yearly. They found gains similar to the standard eight week programme. Similarly other studies have found modest effects of maintenance programmes on long term results. Further research is needed to decide the duration, type and intensity of maintenance programmes.

g) **Adjuncts to exercise training:**

i. Nutrition: Caloric supplementation to meet increased energy requirements has to be done. Adequate carbohydrates have to be provided in COPD patients with a BMI of less than 21kg/m2 or loss of more than 10% body weight in past six months.[9] Proteins are also required to build fat free mass. Anabolic hormones including growth hormone[33] and testosterone have also shown increase in muscle mass; however the transformation of increased muscle mass in increased exercise tolerance is uncertain.

ii. Oxygen therapy: It has been known to improve survival in COPD patients. COPD patients already on domiciliary oxygen require it during exercise at higher flow rates.[9] Oxygen is also indicated in patients with normal oxygen saturation at rest but also with exercise induced hypoxemia. Oxygen leads to increase in the exercise capacity, intensities and endurance.[34] However the long term benefits are not known. Carrying an oxygen cylinder during exercise is also cumbersome and may discourage the patient.

iii. Non invasive ventilation (NIV): NIV during exercise acts by unloading of the respiratory muscles thereby reducing the work of breathing. The results of various trials are ambiguous regarding the role of NIV during exercise. However it can be recommended that NIV provides benefit in exercise tolerance in patients with advanced COPD.[34]

iv. Inspiratory muscle training: It is another pulmonary rehabilitation strategy with

equivocal results. It is indicated in patients with inspiratory muscle weakness.[9] There are three types of inspiratory muscle training namely voluntary isocapnic hyperventilation, inspiratory threshold loading and inspiratory resistive loading. Results of various studies with the above three techniques are inconclusive with no distinct advantage of one technique over the other.

5. Energy conservation and fatigue obviation:

COPD patients have impaired lung functions, co-morbidities and muscle weakness due to which they have fatigue and dyspnoea on performing routine day to day activities. To overcome the airway obstruction and structural lung changes these patients have to spend more energy on the work of breathing. The anaerobic threshold is reduced in these patients, with glycolysis occurring in the muscles sooner than that in a healthy individual thereby restricting exercise. Earlier studies have shown that leg fatigue and dyspnoea are the major limiting factors restricting exercise.[35] Difficulty in carrying out daily activities leads to withdrawal of the patient and depression. The degree of restriction of day to day activities has to be assessed and management has to be planned accordingly. Learning new behaviour strategies forms the integral component of conserving energy. Patient should manage time accordingly with proper hours of rest so that fatigue does not occur. The pace of performing activities should be slowed down with rest of about 30 minutes after every meal and proper rest during night. Similarly work should be performed in such a way that it consumes less energy. Unsupported arm movements consume more energy and should be avoided. In breathing energy is spent less during expiration than inspiration. Therefore exertional activities should be coordinated and performed during expiration.

6. Patient education:

Patient education also requires a multidisciplinary approach and includes information on exercise, diet, energy conservation, drugs and inhaler device technique. It starts with diagnosis, smoking cessation and extends up to end-of-life discussions. Educating the patient regarding the premonitory signs of an exacerbation may help patient in identifying the signs early and avoiding severe exacerbations. Psycho-social support is also required because of chronic and progressive nature of the disease.

Conclusion:

Pulmonary rehabilitation is a multidisciplinary approach which requires active participation of the patient as well as the physician. It has been known to improve exercise capacity, dyspnoea and health related quality of life index in COPD. However further research is required to establish exercise regimes which will benefit all the patients.

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7

Emerging therapies for COPD

Dr. Raja Dhar, Dr. Tarang Kulkarni

Introduction:

COPD continues to be an ever increasing global problem. While the incidence of other chronic diseases is plateauing off or actually reducing, the sharp increase in the COPD cases continues unabated especially in the developing world. We, in India contribute significantly to the global burden of COPD and this is now the second commonest cause of mortality in our country. Looking forward we are going to look into what all is going to be available to us to treat this dreaded disease in the future. We are briefly going to look into different pharmacological and non-pharmacological entities which are on the anvil and then discuss in some details about Endoscopic Lung volume reduction and the options available therein. No effective anti-inflammatory treatment now exists for COPD. The focus thus is on bronchodilators and a lot of new drugs are hence in various stages of development. The newer crops of drugs are called Ultra Long Acting Beta Agonists (Ultra LABA) and Long Acting Muscarinic Antagonists (LAMAs) because of their long duration of action. They can thus be used on a 'once daily' basis. The chart below gives a comparative analysis of the newer Ultra LABAs and their comparative advantages and disadvantages.

Molecule	GOLD category	FEV1 improvement	Exercise	Exacerbations	Health status & symptoms	Safety & adverse effects	General comments
Indacaterol	B, C, D	+++	++	++	++	Cough (6.5%), headache (5.1%) nausea (2.4%)	Improved CV safety profile & lung function compared to salmeterol
Vilanterol	B, C, D	++	++ *	++ *	++	Nasopharyngitis (10%), headache (9%), dry mouth (<10%)	
Olodaterol	B,C,D	++	++	-	++	Dizziness (>2%) rash (>2%) arthralgia (>2%)	
Abediterol		+++					Better lung function impact compared to indacaterol

- No improvement, + NS, ++ significantly improved compared to placebo, +++ significantly improved to other drugs of the same class. * in combination therapy

The newer LAMAs are even greater in number and are now considered the most powerful agents for bronchodilation in patients with stable COPD. Comparative studies between LABAs and LAMAs show that the latter agents are more efficacious when used as 'single agents' in patients with COPD.

The chart below again shows a comparative assessment of the newer LAMAs which are already available or going to become available in the near future.

Molecule	Gold category	FEV1 improvement	Exercise	Exacerbations	Health status & symptoms	Safety & adverse effects	General comments
Aclidinium	B,C,D	++	+–	++	++	Bronchospasm, nasopharyngitis (6%) headache (5%) dry mouth (<2%)	Faster onset of action to tiotropium, better night time FEV1, BID dosing
Glycopyrronium	B,C,D	+++	+–	++	++	Antimuscarinic & cardiac side effects similar to placebo	Rapid onset, very good safety profile
Umeclidinium	B,C,D	++	+–*	++*	++*	Minimal antimuscarinic side effects	Combined with vilanterol

However maximal bronchodilatation is now obtained by combining an Ultra LABA with a LAMA and is considered the most efficacious treatment in GOLD B, C and D. The recent publication of the FLAME study also suggests that this combination is also the most effective method of preventing exacerbations of the disease. A comparative analysis of the LABA LAMA combinations is outlined in the chart below:

Molecule	Gold category	FEV1 improvement	Exacerbations	Health status & symptoms	Safety & adverse effects	General comments
Umeclidinium & vianfreol	C,D	+++	++	++	No increase in adverse events compared to placebo	First LABA- LAMA approved by the US FDA for maintenance Rx
Glycopyrronium & indacaterol	C,D	! ! !	! ! !	! ! !	No increase in adverse events compared to tiotropium glycopyrronium alone	Significantly better FEV1 and SGRQ compared to tiotropium & or glycopyrronium alone
Tiotropium & olodaterol	C,D	+++	+	+++	No significant difference in adverse events compared to monocomponen ts	Significant improvement in SGRQ score was only seen in the 5/5 mcg dosing
Aclidinium and formoterol	C,D	+++	-	-/–+	nasopharyngitis (7.8%) headache (7.5%0	Significant improvement in FEV1 1-hour post dosing compared to monocomponents
Glycopyrrolate & formoterol	+++					improvement in FEV1 from 0 hours to 12 hours versus monotherapy with glycopyrrolate, formoterol or tiotropium

-No improvement, + NS, ++ significantly improved compared to placebo, +++ significantly improved to other drugs of the same class. * in combination therapy

The use of inhaled steroids in patients with COPD is now very controversial. It is now accepted that its use should be restricted in the exacerbation prone phenotype of COPD belonging to GOLD C and D classes. This has also got be balanced against the risk of developing Pneumonia as a result of using inhaled steroids as has been evidenced in the TORCH study and many other subsequent studies. However, this has not really stalled research in this area and a plethora of ICS LABA combinations are now undergoing trials in COPD. A comparative analysis of these agents is given in the chart below:

Molecule	Gold category	FEV1 improvement	Exacerbations	Health status & symptoms	Safety & adverse effects	General comments
Vilanterol & fluticasone	C,D	+	+++		Compared to vilanterol alone, fdc leads to an increased risk of pneumonia	Once daily fdc of LABA - ICS
Indacaterol & mometasone	C,D	++		++		Non-inferiority comparison To combined fluticasone propionate /salmeterol in asthma
Formoterol & ciclesonide		++			Oral candidiasis was the most common adverse event	
Formoterol & fluticasone	C,D	+++		++	approved for asthma but in phase III clinical trials for moderate to serve COPD	more rapid bronchodilator effect than fluticasone propionate/ salmeterol

- No improvement, + NS, ++ significantly improved compared to placebo, +++ significantly improved to other drugs of the same class. * in combination therapy

Pulmonary rehabilitation is one evidenced based management option for COPD which hardly gets practised in India because it is expensive, requires a lot of equipment and a facility to accommodate these and it is difficult for patients to reach these centres especially in the large metropolitan cities in India. There is emerging data about the role of home based pulmonary rehabilitation from Japan and this would be a game changer for the management of COPD in India.

Nicotine vaccination as a smoking cessation technique is also undergoing a lot of research. The working mechanism for this is to develop antibodies to nicotine which then prevents nicotine from entering the brain. Hence they abolish the rewarding properties of smoking. Even though the initial trials have not been as successful as anticipated this is certainly going to be something which will generate a lot of interest in the future.

Endoscopic Lung Volume Reduction (ELVR):

Emphysema is characterised by lung parenchymal destruction leading to reduction of surfaces for effective gas exchange. Disruption of alveolar integrity and loss of structural elements lead to decrease in the elastic recoil and narrowing of airways resulting from decreased outward tension that maintains their patency. In presence of higher intra thoracic

pressures, diseased airways are compressed thereby leading to progressive air trapping and the resultant phenomenon of 'dynamic hyperinflation'. Dynamic hyperinflation plays an important role in progression of chronic airflow limitation and exertional dyspnoea. Reducing the volume of the hyperinflated lung is practical, especially if the most diseased portions of the lung contributing the least to gas exchange are removed.

Surgical and non-surgical approaches have been implied in lung volume reduction (LVR) to reduce dynamic hyperinflation.

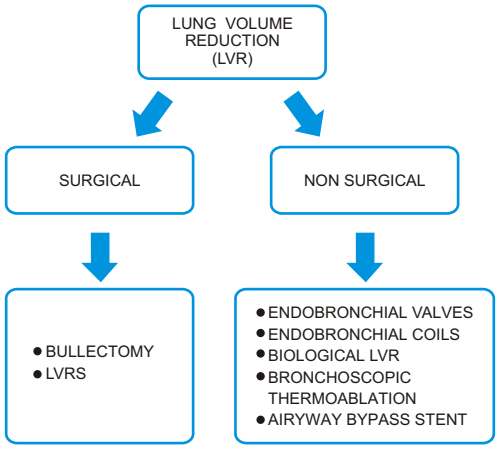


Table 1: Effects of Lung Volume Reduction

Physiological Effects of Lung Volume Reduction.[1,2]
1. Matching between the size of lungs and the capacity of thoracic cavity resulting in an improvement of expiratory airflow by re tensioning effect.
2. Reduction of functional residual capacity (FRC) leads the diaphragm to return to its original curved shaped leading to an improvement in its mechanical function
3. Reduction of dead space by reflation of previously compressed parenchyma leading to improved matching of ventilation and perfusion.
4. Improved left ventricular filling, end diastolic dimension and cardiac index due to decreased intra thoracic pressure.

Baseline CT scan is important in patients considered for LVR not only to determine the nature of emphysema but also to exclude co-morbidities like bronchiectasis and to rule out lung nodules and lung cancer which has a high incidence in these groups of patients. Nature of emphysema is extremely crucial to determine the modality of ELVR to be used. Based on CT, emphysema can be broadly characterised into homogenous and heterogenous emphysema. Most clinical trials are being performed on patients with heterogenous emphysema, as homogenous emphysema has a greater presence of collateral ventilation making LVR difficult in these cases.[3]

I. Surgical Lung Volume Reduction:

A) Bullectomy: Surgical resection of giant bullae (bullae occupying more than 30% of hemi thorax) has been achieved through lateral thoracotomy or video assisted thoracoscopic surgery. Symptomatic patients with a FEV1 of >50% are associated

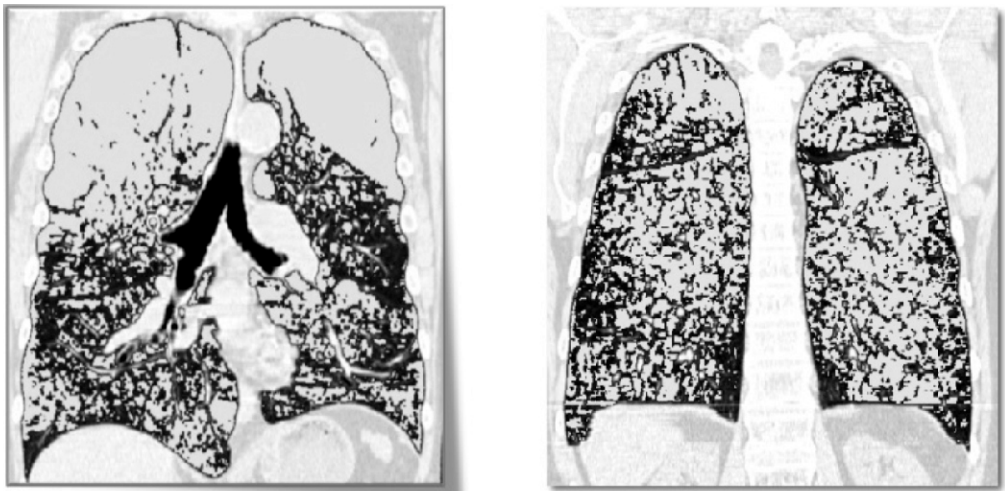


fig 1. Representation of parenchymal damage in homogenous (left) and heterogenous emphysema (right).

with a better outcome post-surgery. Staple excision of the bulla is the most commonly used technique and other techniques like plication, ablation techniques like laser; radiofrequency energy etc. and modified Monaldi procedure have also been employed. Modified Monaldi Procedure involves a limited thoracotomy to visualize the bulla, insufflation of the bulla with iodized talc and drainage of the bulla with a Foley catheter under water seal to collapse the bulla.[4]

B) Lung Volume Reduction Surgery (LVRS): LVRS also sometimes referred to reduction pneumoplasty or bilateral pneumectomy, involves resection of the most diseased portion of the emphysematous lung coupled with denervation. Patient selection is extremely crucial for LVRS procedure. Patients with heterogeneous emphysematous changes on computerised tomography with an upper lobe predominance having FEV1 <45% and DLCO >20% are appropriate candidates for LVRS.[5] National Emphysema Treatment Trial (NETT) was one of the largest trials conducted on 1218 patients comparing efficacy of LVRS to standard medical management. The trial concluded that LVRS does not improve survival but improves exercise tolerance when compared to standard medical management alone. Low risk and moderate risk patients showed a survival benefit with upper lobe emphysema and low exercise capacity.[6]

II. Non-surgical Lung Volume Reduction:

Non-surgical LVR includes techniques like endobronchial coils, endobronchial and intrabronchial valves, biologic LVR, thermal ablation techniques and airway bypass techniques. The rationale for non-surgical LVR is that the use of endoscopic methods to collapse areas of diseased emphysematous lung would have a beneficial effect similar to resecting these areas during LVRS, but without the morbidity of surgery. Thus, patients who are not good surgical candidates might be able to undergo non-surgical LVR. Several non-surgical LVR techniques are reversible, which may contribute to increased safety. Non-surgical LVR techniques can be divided in 4 major groups based on their approach for LVR.

1. Devices occluding airways.
2. Agents inducing an inflammatory response.
3. Airway bypass techniques.
4. Devices leading to mechanical compression.

Table 2: Indications and contraindication of Endoscopic Lung Volume Reduction

Indications for Endoscopic Lung Volume Reduction.[7]
1. 40-75 years 2. Dyspnoea despite maximal medical therapy and pulmonary rehabilitation. 3. FEV1 15-45% 4. Hyperinflation with TLC >100% and RV > 150-175% 5. PaCO2 <6.7 kPa (50mmHg) 6. PaO2 >6 kPa (45 mmHg) while breathing ambient air 7. 6MWD ≥140m (after rehabilitation)
Contraindications for Endoscopic Lung Volume Reduction.
1. Current smoker (previous 6 months) 2. Giant bullae (1/3rd of hemithorax) 3. α-1 antitrypsin deficiency 4. Previous thoracotomy, pleurodesis or chest wall 5. Severe pulmonary hypertension 6. Active infection 7. Unstable cardiac condition 8. Excessive sputum 9. DLCO <20% (relative contraindication)

1. Devices occluding airways:

This approach involves placement of unidirectional valves into segmental airways allowing air to escape thereby causing lobar atelectasis. The resultant atelectasis leads to decrease in the functional residual capacity (FRC) thus reducing the work of breathing, improving respiratory mechanics, reduction of dynamic hyperinflation thereby improving exercise tolerance. One way valves allows air and secretions to escape the concerned segment of the lung while preventing air from re-entering causing atelectasis. Two types of unidirectional valves are under investigation: duck billed shaped endo bronchial valves and umbrella shaped intra bronchial valves.

a) **Endobronchial valves:** Endobronchial valves or 'duck-billed' shaped valves are composed of a nitinol skeleton and silicon body with a duckbill valve on the proximal end. These valves are deployed using a special catheter which can be inserted through the working channel of a bronchoscope. Three sizes of the valve are currently available (4.0 low profile, 4.0 and 5.5) according to the size of the sub segment which has to be occluded. The Endobronchial Valve for Emphysema Palliation Trial (VENT) was conducted on 321 randomly assigned patients with severe heterogeneous emphysema (FEV1 15-45%) to endobronchial valve placement and standard medical care. At the end of six months, the mean between group difference for FEV1 was 6.8% and for six minute walk distance (6MWD) 5.8% in favour of the endobronchial valves. Modest

improvements in dyspnoea and quality of life were also evident. The frequency of adverse events like pneumonia, haemoptysis, pneumothorax, and exacerbations of COPD requiring hospitalization in the endobronchial valve group were also noted.[8] (fig.2)

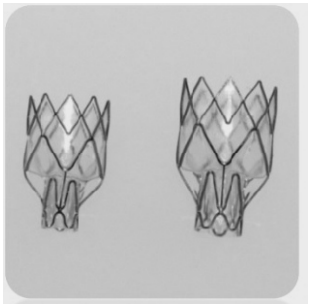


fig 2. Endobronchial valve

fig 3. Intrabronchial umbrella shaped valve

b) Intra-bronchial valves: Intra bronchial valve is an umbrella shaped nitinol framed prosthesis with a synthetic polymer cover. These valves to maintain contact with the airway wall and prevent air from entering the concerned segment while allowing for mucus and air to escape.This one way valve effect with the intent of redirecting airflow to more normal areas inducesatelectasis of the emphysematous area blocked by the valve. Intra bronchial valves are deployed under direct bronchoscopic guidance using special deployment devices passed through the working channel of a bronchoscope. These valves are then reposition using standard biopsy forceps. Greater improvement was observed in complete unilateral occlusion group confirming that complete lobar isolation as an independent predictor for success of intra bronchial valves.[9] (fig.3)

2. Devices leading to mechanical compression:

Endo bronchial LVR coil is an implantable coil composed of a biocompatible super elsatic alloy nitinol. These coils are placed bronchoscopically under fluoroscopic guidance into the intended airways, with the removal of the primary sheath the coil springs back to its original

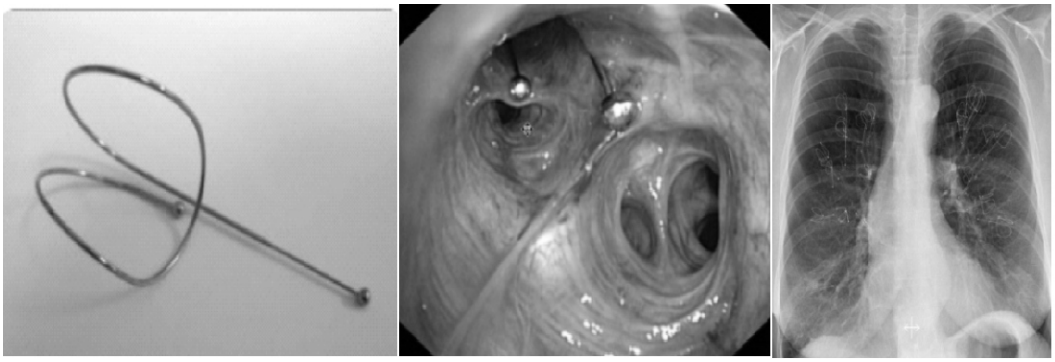


Fig.4, 5 & 6- Intrabronchial placement of endobronchial coils as seen bronchoscopically and on chest X ray.

shape thereby reducing lung volume. These coils internally compress the treated segments of the lung and increase lung recoil thereby reducing gas trapping and resultant dynamic hyperinflation in both heterogeneous and homogenous emphysematous lungs. Collateral circulation has no impact on the working of these valves as opposed to the previously described airway occluding devices. A large multicentre RENEW trial compared efficacy of standard COPD management with pulmonary rehabilitation with bilateral placement of endobronchial coils in patients with predominantly homogenous emphysema. Clinically significant differences were observed in favour of endobronchial coils in terms of six minute walk distance and FEV1.[10]

3. Agents inducing inflammatory response:

This approach is intended to reduce lung volume by tissue remodelling, through induction of an inflammatory reaction that leads to a scar formation and hence contraction of the treated lung segment and reducing collateral ventilation.

a) **Polymeric LVR:** Polymeric LVR (PLVR) involves bronchoscopic deployment of a biodegradable gel into the sub segmental bronchi. The solution creates hydrogel foam which is distributed to the distal airways. As gas within the foam (which fills damaged alveoli) is absorbed, the foam adherent to the alveolar tissue collapses and it reduces lung volume and hyperinflation.[11] Benefits are not achieved for several weeks because of the time taken for scar formation and increased incidence of COPD exacerbations was observed accompanied with a flu-like reaction due to the primary inflammatory reaction.

b) **Bronchoscopic thermal vapour ablation:** Thermal airway ablation involves using a specialized catheter via a flexible bronchoscope to administer steam vapour into the targeted segmental airway. During the procedure, a vapour occlusion balloon is inflated to protect other airwaysfrom the heated vapour.[12] An inflammatory response is induced that results in occlusion and atelectasis of the concerned segment. Bronchial thermal ablation was performed in an observational study on 44 patients with predominantly upper lobe emphysema. Improvements were seen in the FEV1 (141 +/- 26ml over baseline), exercise tolerance and quality of life. Higher incidence of COPD exacerbations, pneumonia and haemoptysis in this group were also observed.[12,13]

c) **Bronchoscopic intra-bullous blood instillation:** Bronchoscopically instilled autologous blood induces an inflammatory response leading to inflammation and scarring and contraction of giant bulla. Although not many studies have demonstrated effect of this technique, it is thought that presence of blood in the airways post procedure invariably would increase the risk of infection.[14]

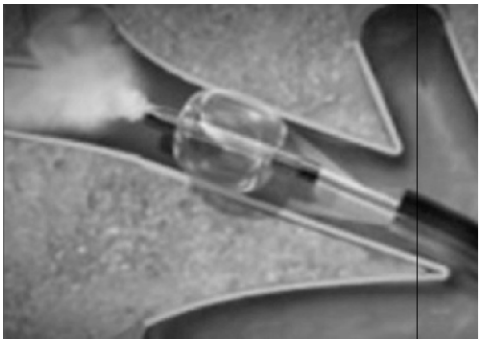


fig 7. Bronchoscopic thermal ablation: a balloon catheter is used to seal off the targeted segment and steam is released causing inflammation & scarring.

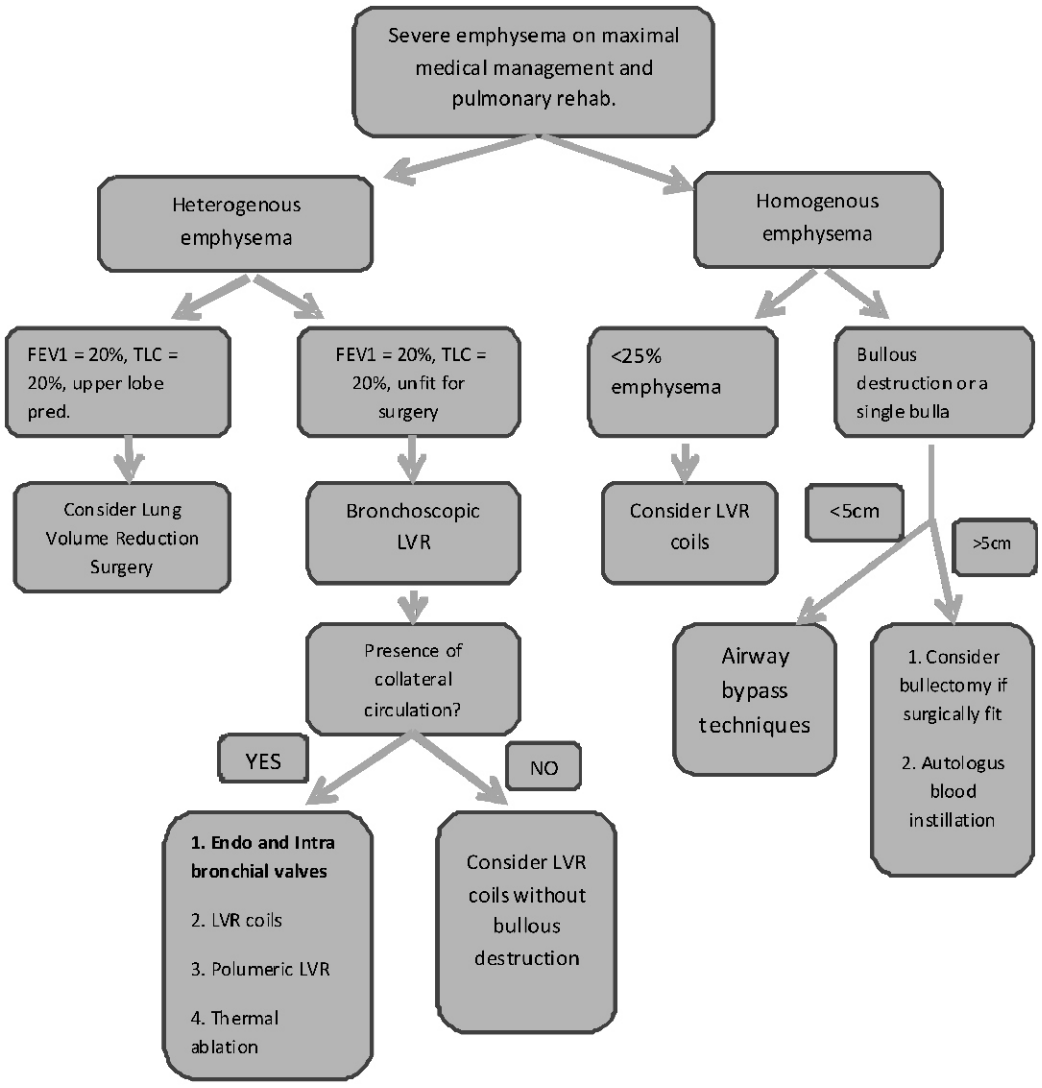
4. Airway bypass techniques:

Airway bypass technique also known as extra bronchial fenestration involves placement of drug eluting stents through the bronchial wall into an area with severe emphysematous disease thereby decompressing areas of severe emphysema. Decompression of emphysematous segments leads to reduction of dynamic hyperinflation allowing chest to return to the normal shape increasing exercise tolerance and decreasing dyspnoea. Paclitaxel is the most commonly used drug in drug eluting stents. Despite favourable evidences in the preliminary studies, large multicentre Exhale Airway Stent for Emphysema (EASE trial) trial which included 208 patients with severe homogenous emphysema did not demonstrate any benefit in terms of dyspnoea and improvements in FVC.[15, 16]

Table 3: Comparison of various modalities of ELVR

	Intrabronchial and endobronchial coils	Endobronchial coils	Polymeric LVR/ BioLVR	Thermal ablation	Intrabullous blood instillation	Airway bypass technique.
Mechanism of Action	Valves allow escape of air & secretions causing atelectasis of affected segment.	Coils internally compress lung segments resulting into ↑ recoil and ↓gas trapping.	the polymer adherent to the alveolar tissue collapses and it ↓ lung volume and hyperinflation by inflammation and scarring	Steam induces an inflammatory response resulting in occlusion and atelectasis of the segment	Scarring, inflammation and contraction of bulla dueto instillation of autologous blood	Drug eluting stents connect bronchial wall with emphysematous areas reducing dynamic hyperinflation.
Emphysema distribution	Heterogenous	Heterogenous and homogenous, RV >200%, without bullous destruction.	Heterogenous	Heterogenous	Giant bulla	Homogenous
Effect of Collateral circulation	Collateral ventilation prevents atelectasis, limits success	No effect	No effect	No effect	No effect	Enhances effect; collateral ventilation allows trapped gas to escape from a wider area
Complications and Limitations	Risk of pneumothorax	Procedure irreversible, coils difficult to trace	Increased risk of COPD exacerbation and pneumonia	Increased risk of COPD exacerbation and pneumonia	Blood in airways increase risk of infection	High chances of stent occlusion.

Table 4: Algorithmic approach towards Endoscopic Lung Volume Reduction.



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"Half of what you are taught as medical students will in 10 years have been shown to be wrong. And the trouble is none of your teachers know which half"

-Sydney Burwell

8

Management of Stable COPD: Pharmacological Management

Dr. Akashdeep Singh

Abstract:

Chronic obstructive pulmonary disease (COPD) is a common problem. All COPD patients who smoke should be counseled about smoking cessation. Influenza and pneumococcal vaccinations are now the standard of care for all patients with COPD. The Global Initiative for Chronic Obstructive Lung Disease assigns patients with COPD into four groups based on the degree of airflow restriction, symptom score, and number of exacerbations in one year. Pulmonary rehabilitation is recommended for patients in groups B, C, and D. Those in group A should receive a short-acting anticholinergic or short-acting beta2 agonist for mild intermittent symptoms. For patients in group B, long-acting anticholinergics or long-acting beta2 agonists should be added. Patients in group C or D are at high risk of exacerbations and should receive a long-acting anticholinergic or a combination of an inhaled corticosteroid and a long-acting beta2 agonist. For patients whose symptoms are not controlled with one of these regimens, triple therapy with an inhaled corticosteroid, long-acting beta2 agonist and anticholinergic should be considered. Prophylactic antibiotics and oral corticosteroids are not recommended for prevention of COPD exacerbations.

Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease, in response to tobacco smoke and/or other harmful inhalational exposures is characterized by persistent airflow limitation that is usually progressive and often associated systemic manifestations. COPD is a leading cause of morbidity and mortality worldwide. Globally it is estimated that approximately 8% of all individuals have COPD.[1] The estimated burden of COPD in India is about 15 million cases (males and females contributing to 9.02 and 5.75 million, respectively).[2] However, these figures underestimate the true burden of the disease as it is both under-recognized and under-diagnosed.

Goals for the management of stable COPD patient:

The goals in managing stable COPD patients include reducing the existing symptoms as well as risk of disease progression, prevention of exacerbations and reduction in mortality. The goals should be individualized and assessed and monitored objectively. It is important to prevent treatment associated adverse effects while trying to achieve the above goals.

Route and method of drug delivery:

Inhaled therapy is the mainstay of treatment for patients with stable COPD. It allows low doses of the drug to be delivered rapidly and directly into airways while significantly reducing systemic adverse effects as compared to oral or parenteral therapy. Three kinds of aerosol devices are available namely pressurized metered dose inhalers (pMDIs), dry powder

inhalers (DPIs) and nebulizers. pMDIs used with a valved spacer improves the drug delivery to airways, reduces the oropharyngeal deposition and obviates the problems of actuation-inhalation coordination. DPIs are breath-actuated, thus coordination issues are less often.[3] The critical errors in the inhalational technique that potentially affects the drug delivery have been observed in 28% with pMDI users and 11-32% of DPI users.[4] Nebulizers (driven either by oxygen, compressed air or ultrasonic power) generate fine aerosol from drug solutions or suspensions that is passively delivered to airways via mask or mouthpiece. Nebulizers may have theoretical advantage in patients who have low inspiratory flow rates and overinflated lungs. However, they are bulky, more expensive, require electrical power for operation and require regular maintenance. There is little evidence for their benefit over other devices. Nebulized treatment should only be continued if the patient reports obvious symptomatic benefit that cannot be achieved by simpler, cheaper and more portable devices. The selection of an optimal delivery device 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.

Various classes of drugs used in the management of stable COPD patient:

Bronchodilators (beta agonists and anticholinergics) and inhaled glucocorticoids given alone or in combination are the mainstays of drug therapy of stable symptomatic COPD. The currently available drugs and their commonly prescribed doses are summarized in Table1. Other drugs which can also be used include the oral drugs-beta-agonists, methylxanthines and selective phosphodiesterase-4 (PDE4) inhibitors. The initial pharmacological management of COPD as proposed by GOLD 2016 is based according to the individualized assessment of symptoms and exacerbation risk is shown in Table 2.

Bronchodilators:

Bronchodilators are central to symptom management in COPD. They increase the FEV1 or change spirometric variables by altering the airway smooth muscle tone. They improve emptying of the lungs, tend to reduce dynamic hyperinflation and improve exercise performance.[5] The extent of these changes, especially in severe and very severe patients, is not easily predictable from the improvement in FEV1. Dose-response relationships using FEV1 as the outcome are relatively flat with all classes of bronchodilators. Toxicity is also dose-related. Inhaled therapy is preferred over oral or parentral therapy.

The choice between beta2-agonist, anticholinergic, theophylline or combination therapy depends on availability and individual patient response in terms of symptom relief and side effects. Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms. Long-acting inhaled bronchodilators are convenient and more effective in producing sustained symptomatic relief than short-acting bronchodilators. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single agent.

Beta2-agonists: The beta2-agonists relax the airway smooth muscle by stimulating beta2-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Short-acting beta agonists (SABAs) include salbutamol and levosalbutamol. They improve symptoms and lung function. The bronchodilator effects of SABAs usually last for 4 to 6 hours. In general, SABAs are prescribed on an as-needed basis, rather than regularly scheduled. The use of high doses of SABAs on an as-needed basis in patients already treated with long-acting bronchodilators is not advisable.[6]

The long-acting beta agonists (LABAs) include salmeterol, formoterol, arformoterol, indacaterol, vilanterol and olodaterol. Multiple studies have demonstrated the benefit of LABAs in patients with stable COPD including improvement in FEV1 and lung volumes, dyspnea, health-related quality of life and exacerbation rate[7-10], but have no effect on mortality and rate of decline of lung function. Indacaterol is a once-daily LABA that is approved for the treatment of COPD. It has a rapid onset and a long duration (~24 hours) of action.[11] Adverse effects of beta agonists include tremor, reflex tachycardia, potential to precipitate cardiac rhythm disturbances in susceptible patients and hypokalemia.

Anticholinergics: The mechanism of action of anticholinergic medications appears to be blockage of acetylcholine's effect on muscarinic receptors. The short-acting drugs, such as ipratropium and oxitropium block M2 and M3 receptors and modify transmission at the pre-ganglionic junction.[12] The bronchodilating effect of short-acting inhaled anticholinergics generally lasts up to 8 hours after administration. The role of short acting anticholinergic agents is only as a rescue medication and not as a stand alone therapy for the management of stable COPD. The long-acting anticholinergic, tiotropium has a pharmacokinetic selectivity for the M3 and M1 receptors. Among long-acting anticholinergics, aclidinium has duration of at least 12 hours whereas tiotropium and glycopyrronium have duration of action of more than 24 hours. Tiotropium reduces exacerbations and related hospitalizations, improves symptoms and health status[13,14] and improves the effectiveness of pulmonary rehabilitation.[15]

The POET COPD trial, comparing tiotropium with salmeterol clearly demonstrated that tiotropium was significantly better in decreasing the exacerbation rate. Adverse reaction and mortality were similar to salmeterol.[16] The long-acting anticholinergics aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium. The main side effect is dryness of the mouth, occasional prostatic symptoms, bitter & metallic taste and an unexpected small increase in cardiovascular events which requires further investigation.[17] Use of solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye.

Methylxanthines: Theophylline is the most commonly used methylxanthine. The bronchodilator effect of theophylline is due to nonselective phosphodiesterase inhibition that occurs at plasma concentrations of 10-20 mg/L. Such plasma levels are achieved at doses of 600-800 mg/ day (standard dose). Theophyllines can potentiate the anti inflammatory action of steroids by histone deacetylase (HDAC) activation. Theophylline induced HDAC activation occurs at plasma concentration < 10 mg/L which can be achieved at much lower doses of 300-400 mg/day. A systematic review concluded that theophylline use improved lung function, increased PaO2 and decreased PaCO2 and was associated with a higher patient preference as compared to placebo.[18] Low dose theophylline improves lung function, QoL, and decrease exacerbations as compared to placebo.[19]

Theophylline is inferior to salmeterol, in improving lung function, QoL scores or reducing rescue medication use.[20] Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if these drugs are available and affordable. The toxicity of xanthine derivatives is dose-related, because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Adverse effects include the development of arrhythmias and convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea and heartburn and these may occur within the therapeutic range of serum

theophylline. They have significant interactions with commonly used medications such as digitalis, coumadin, etc.

Combination Bronchodilator Therapy: Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a SABA and an anticholinergic produces greater and more sustained improvements in FEV1 than either drug alone.[21] The combination of a beta2-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function and health status.[21-22] The combination therapy using formoterol and tiotropium has been shown to have a better impact on FEV1 than the single component.[23]

Corticosteroids:

Inhaled Corticosteroids (ICS): ICS have limited efficacy in COPD which may partly be due to progressive reduction in histone deacetylase activity in lungs of patients with COPD.[24] Several studies failed to show any significant benefit of ICS use on FEV1 decline or reduction in exacerbations or mortality.[25-26] The ISOLDE study and the TORCH study showed that ICS use decreased the risk exacerbation, and led to better QoL scores and better FEV1 values [9,27] However, neither study demonstrated any mortality benefit with ICS use. The adverse effects of long term ICS can be either local (hoarse voice, oropharyngeal candidiasis, pneumonia or tuberculosis) or systemic (skin bruising, 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.

Combination Inhaled Corticosteroid/Bronchodilator Therapy: An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD.[9,28-29] Combination therapy is associated with an increased risk of pneumonia,[30] but no other significant side effect. The addition of a LABA/ICS combination to tiotropium improves lung function and quality of life [31] and may further reduce exacerbations but more studies of triple therapy are needed.

Oral Corticosteroids: Oral corticosteroids have numerous side effects. An important side effect of long-term treatment of COPD with systemic corticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality and respiratory failure in subjects with very severe COPD. However, systemic corticosteroids for treating acute exacerbations have been shown to improve symptoms, lung function, reduce rate of treatment failure, and shorten length of hospital stay.

Phosphodiesterase-4 Inhibitors:

The mechanism of action of phosphodiesterase-4 inhibitors is to reduce inflammation by inhibiting of the breakdown of intracellular cyclic AMP. Roflumilast is an oral selective PDE4 inhibitor which has predominant anti inflammatory rather than a bronchodilator action. Roflumilast shifts patients from a frequent to the more stable infrequent exacerbator phenotype. [32] Phosphodiesterase-4 inhibitors should always be used in combination with at least one long-acting bronchodilator. The most frequent adverse effects are nausea, reduced appetite, abdominal pain, diarrhea, sleep disturbances and headache. Roflumilast should be used with caution in patients with depression. Roflumilast and theophylline should not be given together

Table 1: Formulations and Typical Doses of COPD Medications					
Drug	**Inhaler (mcg)**	**Nebulizer Solution (mg/ml)**	**Oral**	**Injection Vial (mg)**	**Duration of Action (hr.)**
Beta2-agonists					
Short-acting Beta2-agonists					
Fenoterol	100-200 (MDI)	1	0.05% (Syrup)		4-6
Levalbuterol	45-90 (MDI)	0.21, 0.42			6-8
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5 mg (Pill), .024%(Syrup)	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)		2.5, 5 mg (Pill)		4-6
Long-acting Beta2-agonists					
Formoterol	4.5-12 (MDI & DPI)	0.01			12
Arformoterol		0.0075			12
Indacaterol	75-300 (DPI)				24
Olodaterol	5 (SMI)				24
Salmeterol	25-50 (MDI & DPI)				12
Tulobuterol			2mg (transdermal)		24
Anticholinergics					
Short-acting Anticholinergics					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6-8
Oxitropium bromide	100 (MDI)	1.5			7-9
Long-acting Anticholinergics					
Aclidinium bromide	322 (DPI)				12
Glycopyrronium bromide	44 (DPI)				24
Tiotropium	18 (DPI), 5 (SMI)				24
Umeclidinium	62.5 (DPI)				24
Combination short-acting beta2-agonist plus anticholinergic in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	100/20 (SMI)				6-8
Combination long-acting beta2-agonist plus anticholinergic in one inhaler					
Formoterol/aclidinium	12/340 (DPI)				12
Indacaterol/ glycopyrronium	85/43 (DPI)				24
Olodaterol/tiotropium	5/5 (SMI				24
Vilanterol/umeclidinium	25/62.5 (DPI)				24
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240	Variable, up to 24
Theophylline SR			100-600 mg (Pill)		Variable, up to 24
Inhaled corticosteroid					
Beclomethasone	50-400 (MDI & DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20. 0.25, 0.5			
Fluticasone	50-500 (MDI & DPI)				
Combination long-acting beta2-agonists plus corticosteroids in one inhaler					
Formoterol/beclometasone	6/100 (MDI & DPI)				
Formoterol/budesonide	4.5/160 (MDI) 9/320 (DPI)				
Formoterol/mometasone	10/200, 10/400 (MDI)				
Salmeterol/Fluticasone	50/100,250,500(DPI)				
Vilanterol/Fluticasone furoate	25/100 (DPI)				
Systemic corticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone			4, 8, 16 mg (Pill)		
Phosphodiesterase-4 inhibitors					
Roflumilast			500 mcg (Pill)		24

Abbreviations: MDI=metered dose inhaler; DPI=dry powder inhaler; SMI=soft mist inhaler

Table 2 : Pharmacologic management of Stable COPD based on combined assessment of airflow limitation, symptoms and exacerbations adapted from GOLD

Category	Symptoms	Risk	Suggested treatment
A	**Less symptomatic** Mild or infrequent symptoms (mMRC 0-1) or CAT <10	**Low risk** FEV_1 /FVC ratio <0.7 and an FEV_1 ≥50% predicted (GOLD I, II) & 0 or 1 exacerbations in the past year	**First choice:** SABA or SAMA prn **Second choice:** LABA or LAMA or SABA and SAMA **Alternative:** Theophylline
B	**More symptomatic** Moderate to severe symptoms (mMRC > 2) or CAT ≥10	**Low risk** FEV_1 /FVC ratio <0.7 and an FEV_1 ≥50% predicted (GOLD I, II) & 0 or 1 exacerbations in the past year	**First choice:** LABA or LAMA **Second choice:** LABA and LAMA **Alternative:** SABA and/or SAMA theophylline
C	**Less symptomatic** Mild or infrequent symptoms (mMRC 0-1) or CAT <10	**High risk** FEV_1/FVC ratio <0.7 and an FEV_1 <50% predicted (GOLD III, IV) OR ≥2 exacerbations per year or one hospitalization for an exacerbation	**First choice:** LABA +ICS or LAMA **Second choice:** LABA + LAMA **Alternative:** PDE4-I, SABA and/or SAMA, theophylline
D	**More symptomatic** Moderate to severe symptoms (mMRC > 2) or CAT ≥10	**High risk** FEV_1/FVC ratio <0.7 and an FEV_1 <50% predicted (GOLD III, IV) OR ≥2 exacerbations per year or one hospitalization for an exacerbation	**First choice:** LABA +ICS or LAMA **Second choice:** LABA + ICS+ LAMA or LABA + ICS+ PDE4-I or LABA + LAMA or LAMA + ICS or LAMA + PDE4-I **Alternative:** Carbocysteine, SABA and/or SAMA, theophylline

Other Pharmacologic Treatments:

Vaccines: Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization and death) in COPD patients. The strains are adjusted each year for appropriate effectiveness and should be given once each year. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older, and also in younger patients with significant comorbid conditions and FEV1 < 40% predicted.[33]

Alpha-1 Antitrypsin Augmentation Therapy: Younger patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for patients with COPD that is unrelated to alpha-1 antitrypsin deficiency.

Antibiotics: In various studies the prophylactic, continuous use of antibiotics was shown to have no effect on the frequency of exacerbations in COPD and a study that examined the efficacy of chemoprophylaxis undertaken in winter months over a period of 5 years concluded that there was no benefit . The use of antibiotics, other than for treating infectious exacerbations of COPD is currently not indicated.[34]

Mucolytic (mucokinetic, mucoregulator) and Antioxidant Agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol, N-acetylcysteine):

The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results. Although a few patients with viscous sputum may benefit from

mucolytics, the overall benefits seem to be very small and the widespread use of these agents is not recommended. N-acetylcysteine has antioxidant effects and may have a role in the treatment of patients with recurrent exacerbations. In patients treated with and without ICS, high doses of N-acetylcysteine significantly reduced exacerbation rates, but only in GOLD stage 2 patients. 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.[35]

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; LABA, long-acting β2-agonist; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; PDE4-inh, phosphodiesterase-4inhibitor; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist; prn, (as needed); mMRC, modified Medical Research Council; CAT, COPD Assessment Test

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"There is always going to be need for new medications, better medications:

- Anthony Fauci

9

COPD Acute Exacerbation: Early Diagnosis, Prevention and Management

Gp Capt Ajay Handa

Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide and acute exacerbations of the disease account for bulk of the deaths and for health care related expenditure in western countries.[1] During acute exacerbation of COPD (AECOPD) there is increased inflammation and airway obstruction which imposes excessive work of breathing and worsens ventilation perfusion relationships precipitating acute hypercapnic respiratory failure.[2] Acute exacerbations lead to irreversible decline in lung functions in COPD patients. Therefore frequency of exacerbations is the most important determinant of quality of life and survival in COPD. Severe exacerbations requiring mechanical ventilation are associated with significant mortality 34-65%. Physicians must be aware of risks factors for COPD exacerbation and effort must be directed towards early diagnosis and prevention of AECOPD for better long term health in these patients.[3]

Definition:

Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) are characterized by sustained worsening of symptoms (lasting greater than 24 hours) beyond the day to day for the individual which necessitates change in treatment with or without need for hospitalization provided other causes of acute breathlessness are clinically ruled out. [2]

Presence of new onset respiratory symptoms should lead to suspicion of AECOPD. Anthonisen's triad includes three cardinal symptoms which must be elicited:[4,5]

1. Increased sputum volume.
2. Increased sputum purulence.
3. Increased dyspnea with or without wheezing.

Differential Diagnosis:

The presence of COPD in a smoker predisposes these patients to diseases such as coronary artery disease (CAD) which can present with acute onset breathlessness and mimic acute exacerbation of COPD. These conditions need to be ruled out at the bedside as the management is totally different. At times, focussed investigations with chest radiograph, serum N-terminal pro b-type natriuretic peptide (NT pro BNP) and ECG may be required to rule out these differentials in appropriate clinical settings [(6)]. The mimickers of AECOPD are given below.

1. Pneumothorax,
2. Pneumonia,
3. Pulmonary thromboembolism,

4. Paroxysmal atrial tachycardia or fibrillation,
5. Pulmonary edema (left heart failure),
6. Pleural effusion.

Pulmonary embolism in particular poses special challenges as it has been found to be coexisting in AECOPD in almost 20% cases,[7] moreover AECOPD increases the risk for deep vein thrombosis and pulmonary embolism due to immobility and need for ventilatory support and patients need to be started on venous thrombosis prophylaxis.

Etiology of AECOPD:

AECOPD is characterized by worsening airway inflammation which can be precipitated by respiratory infections and other non-infective triggers or environmental factors including air pollution. However in some cases no specific trigger can be found.These patients without obvious precipitating factor for AECOPD probably are clinical phenotype of COPD with tendency for exacerbations and have rapid progression of COPD over time.[3] Combined assessment of COPD is concept based on severity of dyspnea (m MRC scale), GOLD stage of airflow obstruction (FEV1 % predicted) and frequency of exacerbation to classify into GOLD class A, B, C and D. This classification helps to optimize medications for those patients who are at risk of exacerbations.[2] Increase in ambient air pollution levels especially during winter months and fire crackers displays during festivals are known triggers for exacerbations of COPD.[1] Other factors could be poor compliance with medications, tobacco smoking and exposure to cold air or allergens.[5]

Infective triggers account for 60-80% of all exacerbations. Large majority of these are viral in origin, influenza, parainfluenza, rhinovirus, corona virus and respiratory syncytial virus are the usual isolates. Bacterial infections account for remaining cases, common organisms isolated include Streptococcus Pneumoniae, Moraxella Catarrhalis and Hemophilus Influenza.[5] Patients with advanced COPD (stage III or IV) are at risk for Pseudomonas Aeruginosa colonization. The other bacteria known to cause AECOPD include gram negative bacilli, Staphylococcus Aureus, Chlamydia Pneumonia and Mycoplasma Pneumoniae in 15-30% cases. These bugs can lead to pneumonia in those requiring mechanical ventilation for severe hypercapnic respiratory failure and broad spectrum antimicrobial coverage must be given in such cases.[5]

Pathogenesis:

Stable COPD has two major phenotypes, chronic airway inflammation with goblet cell hyperplasia and mucus production in chronic bronchitis and alveolar destruction with loss of alveolar septal attachments on terminal airways leading to expiratory collapse in predominant emphysema.[2] The vast majorities of COPD patients have features of both these phenotypes and behave according to the dominant pattern. The respiratory drive is heightened in those with emphysema and is blunted in those with chronic bronchitis and hence patients with chronic bronchitis are more prone for recurrent acute respiratory failure and pulmonary hypertension and cor pulmonale (blue bloaters) as compared to emphysema predominant COPD (pink puffers).

In stable COPD, there is chronic inflammation with increased number of macrophages and CD8 T lymphocytes in the mucosal and submucosal layers of airways. During exacerbations there is change in the inflammatory cellular pattern with increase of eosinophils and/or neutrophils in the airway walls. These cells release various inflammatory cytokines as tumour necrosis factor-alpha (TNF), regulated upon activation normal T cell expressed and

secreted (RANTES) and numerous chemokines which lead to further cellular infiltration and airways mucosal edema, bronchial smooth muscle spasm and excessive mucus production leading to acute worsening of COPD.[3] During acute exacerbation, there is further worsening of airway obstruction due to increased inflammation leading to bronchial wall edema, excess mucus production and increased bronchial smooth muscle tone. These lead to increased resistive work of breathing with worsening ventilation perfusion status and thus precipitate hypercapnic respiratory failure. The airflow obstruction aggravates the hyperinflation which worsens the diaphragmatic contractility and by leading to respiratory muscle fatigue can cause respiratory arrest.[5]

Clinical Features:

The diagnosis is mainly clinical based on history of worsening respiratory symptoms which are beyond the day to day for the patient. Increased breathlessness is the cardinal symptom of AECOPD and may be associated with cough, sputum, fever, wheezing and chest tightness. Other symptoms as new onset cyanosis, marked reduction in activity due to dyspnea, malaise, insomnia, sleepiness, fatigue, depression and confusion are more commonly seen in elderly patients.[5]

The clinical signs in AECOPD patients include tachypnea (respiratory rate >30/min), signs of respiratory distress, accessory muscle use, tachycardia (HR>110/min), hypotension and central cyanosis, altered sensorium and asterixes. The presence of the above signs indicates need for hospitalization. Pulse oximeter is a valuable tool at bedside for assessment of severity of respiratory failure (SpO2< 90%) and can help in decision making.[5] Presence of paradoxical respiration, shallow respiratory efforts, diaphoresis and hypotension indicates imminent respiratory arrest and need for emergent tracheal intubation to save the life.[2]

Investigations:

Investigations are not required in patients of mild AECOPD who can be managed on outpatient basis. In patients requiring hospitalization, full blood counts, serum chemistry, ECG, chest radiographs and arterial blood gas (ABG) analysis should be done. Polymorphonuclear leucocytosis suggests presence of bacterial infection or pneumonia. Chest radiography is required to exclude mimics of AECOPD in certain cases. ABG analysis must be done in all cases with SpO2<90% to confirm diagnosis of acute/acute on chronic respiratory failure. Serial ABG are recommended during use of non- invasive or invasive mechanical ventilation.The routine use of sputum gram stain & culture is not recommended but must be considered in patients not responding to initial antibiotics. Role of biomarkers as serum procalcitonin assay in AECOPD for decisions regarding initiation of antibiotics are based on few studies and evidence is not conclusive. They add on to the cost of care and cost benefits analysis does not justify their routine use in AECOPD.[5]

Assessment of Severity:

Vast majority of patients can be managed on outpatient basis and only 20% require hospitalization.[8] Various scoring systems have been studied to assist clinical decision making in AECOPD. CURB 65 (C-confusion, U- BUN>25 mg/dl, Respiratory rate>30/min, B-systolic BP <90 mmHg, age > 65years) has been use in pneumonias for many years. CURB 65 score was a good tool to predict of mortality of AECOPD. The study showed 30 days mortality in low risk (scores 0-1), moderate risk (score 2) and high risk (scores 3-5) groups was found to be 2%, 6.7% and 21.3% respectively.[9] New scoring system, BAP- 65 (B-

BUN>25mg/dl, A-acute mental status change, P-heart rate>110/min) has been validated in large cohort of AECOPD.[10] The mortality increased from 1% with score of 0 to 25% with all four criteria. In another study, BAP 65 score was superior to CURB-65 in predicting need for need of mechanical ventilation in AECOPD.[11] Physicians must use the CURB-65 or BAP-65 score in these cases to decide if to ICU care is required. The mortality of AECOPD requiring hospitalization is 10% and goes up to 34-65 % in those requiring ventilatory support therefore aggressive treatment is advocated.[6]

Indications for hospital admission in AECOPD are mentioned below:[5]

Symptoms:

1. Increased dyspnea with marked limitation of activities,
2. Altered consciousness,
3. New onset cyanosis.

Signs:

1. Use of accessory respiratory muscles,
2. Paradoxical chest wall movements,
3. Central cyanosis,
4. Systolic blood pressure <90mmHg,
5. Respiratory rate >30 per minute,
6. Heart rate >110 per minute,
7. Asterixes,
8. Altered mental status,
9. Room air SpO2< 90%.

Treatment of AECOPD:

The pharmacological treatment of AECOPD rests on the use of short acting bronchodilators, systemic steroids and antibiotics in all the cases. The non-pharmacological strategies include controlled oxygen supplementation, ventilatory support, smoking cessation and pulmonary rehabilitation.[5] All AECOPD patients must be managed energetically with timely institution of treatment and non-invasive ventilatory support under close clinical monitoring to prevent adverse outcomes.

a) **Oxygen:** In patient with AECOPD, controlled oxygen therapy is used to correct the hypoxemia with targets SpO2 of 90-92% and PaO2 of 55-60 mmHg. Risk of uncontrolled oxygen in these patients is abolition of hypoxic drive leads to worsening hypercapnia with CO2 narcosis.[5] Venturi mask is the most suitable device for oxygen therapy in acute phase with reliable FiO2 and high flow rates to meet the respiratory demands of the patient. During recovery nasal cannula can be used when flow rates are less than 6L/min. Serial ABG must be monitored for adequacy of oxygenation and ruling out respiratory acidosis during oxygen therapy.

b) **Bronchodilators:** Short acting beta agonists (SABA) salbutamol or levo-salbutamol are first line drugs to achieve reversal of airway obstruction and must be administered immediately along with oxygen therapy. Metered dose Inhaler with spacer device is as effective in mild to moderate exacerbations (salbutamol 100ug 4 puffs every 20 mins initially). However in severe exacerbation with respiratory distress and/ or altered sensorium nebulized salbutamol 2.5 mg every 15 mins continuously for first hour and then every 4-6 hourly. If there is inadequate response with salbutamol alone,

ipratropium (500 µg) nebulised can be used in combination every 4-6 hourly till airway obstruction is reversed. Nebulisation must be given using nebulizer and never with high flow oxygen with close monitoring of oxygen saturation to prevent CO2 narcosis. Parenteral beta-2 agonists (salbutamol/ terbutaline) and methylxanthines (aminophylline infusion) are not recommended for routine use as they have significant toxicity and their use must be strictly reserved for patients on mechanical ventilation showing inadequate response to first line bronchodilators (salbutamol ± ipratropium).

c) **Systemic steroids:** They are indicated in all except the mild cases of AECOPD as the increased airway inflammation is the main problem. Use of systemic steroids is associated with improvement in lung functions, shorter duration of hospitalization and less treatment failure, but has no significant effect on mortality.[12] Oral prednisolone in 30-40 mg once daily for 5-10 days is recommended. Intravenous steroids (Hydrocortisone 100 mg 6 hourly) are required to be used in critically ill patients on mechanical ventilation or those cannot take orally till patient recovers. There is no role for using nebulized steroids in patients on systemic steroids.

d) **Antibiotics:** Antibiotics should be prescribed to all cases of AECOPD and should be based on local microbial flora and antibiotic sensitivity pattern.[5] Antibiotics reduce the incidence of treatment failure in AECOPD, especially in hospitalized patients where they also afford mortality benefit.[13] In non-severe exacerbations, antibiotic use delays time to next exacerbation. As per the recent Indian COPD treatment guidelines, first-line drugs should be used in most cases include Tab Amoxicillin 500-1000 mg TDS or Tab Doxycycline 100 mg OD or Tab Azithromycin 500 mg OD. Second-line antibiotics should be used in hospitalized cases of AECOPD and include Cap Amoxicillin+ Clavulanic acid 625 mg TDS or Tab Cefuroxime 250-500 mg BD or Tab Cefixime 200 mg BD. The duration of antibiotics is for 5-7 days in most cases. Use of respiratory fluoroquinolones should be avoided as indiscriminate use promotes resistance of Mycobacterium Tuberculosis in those with occult pulmonary tuberculosis.

e) **Non-invasive ventilation (NIV):** In AECOPD with hypercapnic respiratory failure use of NIV has dramatic results. The benefit is by achieved by reduction in rates of tracheal intubation and nosocomial pneumonias, hence the length of hospital stay and mortality are reduced significantly.[14] NIV is usually contraindicated in patients with altered sensorium, but hypercapnic encephalopathy due to AECOPD is an exception where a trial of NIV under close monitoring can be given for 2-3 hours. Many patients show good recovery with NIV trial, however facilities for intubation readily available in view of poor sensorium. NIV is labour intensive and requires close team work of physician, trained nurses or respiratory therapists as the patients need close monitoring for improvement in respiratory parameters and hemodynamic status. Hourly ABG analysis for first four hours after initiation NIV should be done to document improvement in respiratory acidosis. Thereafter ABG can be repeated every 8 hours in the first 24 hours and then once daily till recovery. NIV support is given continuously for first 12-24 hours and after clinical recovery and resolution of respiratory acidosis the support is reduced gradually and patient is maintained on Venturi mask when off NIV support. In addition, NIV has also been found to be useful in weaning from invasive ventilation especially in patients with underlying COPD.[5]

f) **Mechanical ventilation (MV):** There is ample evidence to demonstrate that patient with AECOPD requiring MV have good outcomes and lower mortality than patients ventilated

for non COPD causes of respiratory failure.[5] The pessimistic attitude of the physicians and health care workers are unfounded and their mindset needs to be changed to save more patients with AECOPD. NIV Failures and/or contraindications to NIV are indications of initiating MV in AECOPD with respiratory failure are given below:

Indications of Mechanical Ventilation:

1. Unable to tolerate NIV or failure of NIV,
2. pH <7.25 and PaCO2> 90 mmHg,
3. Respiratory or cardiac arrest,
4. Massive aspiration,
5. Diminished consciousness,
6. Poor cough: unable to clear respiratory secretions,
7. Hypotension requiring vasopressors,
8. Severe ventricular arrhythmias,
9. Life-threatening hypoxemia despite high Fio2 (PaO2<40 mmHg on FiO2=0.5)

Physicians need to be aware that patients of AECOPD are prone for dynamic hyperinflation and barotraumas with worsening on initiating MV. Utmost care must be exercised in initial ventilator settings using volume assist controlled mode (ACMV) with low tidal volumes (4-6ml/Kg predicted body weight), low rates 8-10/min and inspiratory to expiratory ratio at 1:3 to 1:6, keeping low PEEP of 5-8 cm H2O. The targets are achieving safe oxygenation (PaO2 of 55-60mmHg) with gradual reduction of CO2 levels (pH 7.20-7.40 rather than specific of level of PaCO2) always keeping plateau pressure less than 30 cm H2O to avoid barotrauma. Patient must be closely monitored with serial ABG and attempts to wean must be started as soon as clinical stability is achieved.[5]

g) Decision for discharge: Once patient is clinically stable for 24-48 hours and maintains stable oxygenation and does not need nebulized salbutamol and is able to take the inhalers with ease they can be discharged from hospital.

Prevention of AECOPD:

AECOPD leads to irreversible decline in lung functions and is associated with increased morbidity and mortality despite treatment, hence prevention of these episodes should be given priority.[6] Various strategies for preventing exacerbations of COPD have been tried and include smoking cessation, pharmacologic therapy, long term oxygen therapy, pulmonary rehabilitation, vaccinations, home non-invasive ventilatory support and self management plans after health education.[5,6]

(a) Smoking cessation: This is the most effective method to prevent COPD and is endorsed by most guidelines. It is known to reduce the decline of lung functions and reduce exacerbation in stable COPD and provides mortality benefits.[2,5] Every patient of AECOPD should be offered counselling and assistance for nicotine deaddiction at the time of discharge from hospital as they are most receptive at this time and succeed in quitting tobacco smoking.

(b) Pharmacological treatment: Use of regular inhaled combination of corticosteroids and long acting beta agonists (ICS-LABA) in severe COPD (FEV1<50% predicted or those having frequent exacerbations) is known to reduce acute exacerbations. Severe COPD (FEV1<50%) who are symptomatic despite ICS- LABA dual therapy, inhaled long acting

anti-muscarinic can be added. Care must be taken to explain use of the device and proper inhalation technique. The use of inhaler medication must be checked at regular intervals to improve the inhalation technique and ensure better compliance. Oral Roflumilast (Phosphodiesterase 4 inhibitor) has been shown to reduce exacerbations as add on agent in severe COPD with recurrent exacerbation.[5] FLAME trial compared combination of Indacaterol and Glycopyrronium once daily with salmeterol–fluticasone twice daily and showed Indacaterol and Glycopyrronium was more effective in preventing exacerbations in COPD patients with history of exacerbation in previous year,[15] however the drug is expensive and considering the burden of disease in our country these results need to be assessed in Indian COPD patients.

(c) Long term domiciliary oxygen therapy (LTOT): The benefits of LTOT are well established in advanced COPD with severe hypoxemia. It reduces exacerbations, mortality and improves quality of life in these patients. Indications for LTOT are presence of severe daytime resting hypoxemia (PaO2< 55mmHg) or PaO2 of 55-60 mmHg with evidence of end organ dysfunction as pulmonary hypertension, congestive heart failure or haematocrit >55%. The patients must be advised to use oxygen regularly at 1-2 L/min for at least 16 hours /day using oxygen concentrator or oxygen cylinder based system. The target should be to keep SpO2 between 90-92% and PaO2 between 60-65 mmHg and patients must be told to avoid over oxygenation. Also the risk of fire hazard needs to be clearly explained to current smokers.[5]

(d) Pulmonary rehabilitation (PR): Pulmonary rehabilitation is a multi-disciplinary activity which involves exercise training, nutritional supplementation, health education and psychological counselling. The benefits of PR in COPD are improvement in quality of life and exercise capacity. PR in patients discharged after acute exacerbation of COPD has shown to have reduction of future hospitalization and mortality.[2,5] This strategy is under-utilized in clinical practice and needs to be included in care of patients with COPD. Every patient should be advised doing regular physical activities and ensuring good balanced diet in addition to drug therapy.

(e) Vaccinations: As per the national COPD guidelines, Pneumococcal and Influenza vaccination are likely to be beneficial in patients with severe COPD and/or frequent exacerbations (level of evidence to support this recommendation was weak and hence as useful practice point).

(f) Self-management plans (SMP): This concept is well established in severe asthma and has been tried in patients with advanced COPD and results were encouraging. Patients of severe COPD with at least one exacerbation in the previous year were put on SMP after training for 2 months. Patients were asked to start prescribed antibiotics promptly and take oral steroids for 10-14 days at onset of infective exacerbation (based on presence of 2 or more of symptom changes including increased dyspnea, sputum volume and sputum purulence). When compared with usual care group they had 39.8% reduction in hospital admissions (p=0.01), emergency department visits were reduced by 41% (p=0.02) and unscheduled physician visits were reduced by 57% (p=0.003). There were significant improvement in quality of life scores at 4 months and benefit lasted for one year.[16] This strategy holds promise in advanced COPD with recurrent exacerbations who are well educated to recognize the symptoms and have adequate social/family support system in place.

(g) Domiciliary non-invasive ventilation: In advanced COPD with symptomatic chronic hypercapnia despite optimal medical treatment and LTOT, after optimizing all therapeutic efforts and excluding sleep apnea syndrome, selected patients may be considered for home NIV therapy.[17] The patient must be assessed by experienced pulmonologist for presence of symptoms of hypoventilation (fatigue, headache, somnolence and dyspnea) with any one of the following physiologic derangements:

(i) PaCO2 > 55mmHg or PaCO2 of 50-54 mmHg with nocturnal desaturation (SpO2 by oximetery <88% for 5 minutes on LTOT 2 Litres/min)

(ii) PaCO2 of 50-54 mmHg with two or more hospitalization due to hypercapnic respiratory failure in one year.

Conclusion:

Acute exacerbation of COPD are events which cause increase in airway obstruction and worsening of ventilation perfusion relationships leading to acute hypercapnic respiratory failure which are associated with high mortality by causing irreversible decline in lung functions. They determine quality of life and survival in these patients. All physicians must be aware of risks factors for exacerbation so as to make early diagnosis and prevent future episodes to avoid adverse outcomes.

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10

COPD: Critical Care

Dr. Amol Hartalkar

Introduction:

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive, persistent, expiratory airflow limitation that is not fully reversible.[1,2] In the United States, COPD annually accounts for $29.5 billion in direct health care costs,[3] 750,000 hospitalizations, and 1.5 million emergency visits.[4] Globally it is now ranked as the fifth leading cause of death.[1,3,4] COPD is generally described as a progressive disease; however, there is considerable variability among patients.[5] Exacerbations are often the cause of morbidity and mortality in COPD patients.[1,2,6] An exacerbation of COPD is characterized by an acute worsening of a patient's respiratory symptoms that results in change in treatment and increased utilization of health care resources. Most exacerbations can be managed in the outpatient setting; however, patients with more severe underlying disease or exacerbation may require hospitalization. Acute exacerbations in patients with moderate to severe COPD can cause respiratory failure and a possible need for ventilatory support. Patients with acute exacerbation of COPD causing acute respiratory failure with severe hypoxia or persistent or severe respiratory acidosis, altered mental status or hemodynamic instability require admission to an intensive care unit (ICU) for management.

The objective of this review is to briefly elucidate the clinical features of COPD and management of exacerbations and provide a detailed description of management of COPD in the ICU, including indications for admission to ICU and treatment of acute respiratory failure in COPD in the ICU, in terms of pharmacologic and ventilatory therapy. Advance care planning, rehabilitation and palliative care are necessary components for comprehensive critical care of these patients.

Clinical features of COPD:

COPD is a preventable and treatable disease. COPD is preventable because the majority of cases are the result of cigarette smoking. It is treatable because maintenance with long-term bronchodilators has been shown to improve lung function and reduce the frequency of exacerbations. The expiratory airflow limitation that characterizes COPD is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, mainly cigarette smoking. Diagnosis of COPD should be considered in any patient with chronic cough or sputum production, dyspnea, and/or a history of exposure to risk factors for the disease. Physical examination in a patient with COPD may be normal, especially in mild stages of the disease. Diminished breath sounds with prolonged expiratory phase (>4 seconds) are usually found in patients with symptomatic disease. Rhonchi and wheezes indicate bronchospasm and may be heard on

lung auscultation but are not consistent findings. They are more likely to be heard with exacerbations. In severe disease, characteristic physical signs such as increased accessory muscle use, pursed lip breathing to facilitate exhalation and signs of pulmonary hypertension and right heart failure may be apparent. Although COPD affects the lungs, it also produces significant extrapulmonary effects such as cor pulmonale, osteoporosis, skeletal muscle dysfunction, weight loss and depression. Systemic co-morbidities of COPD include myocardial infarction, congestive heart failure (CHF), arrhythmia and venous thromboembolism (VTE).[7]

Diagnosis:

The diagnosis of COPD is made by spirometry, demonstrating the presence of airflow limitation that is not fully reversible with a post-bronchodilator FEV1/FVC (forced expiratory volume in 1 second over the forced vital capacity) ratio less than 0.70.[1,2] Diffusion capacity may be decreased in COPD due to destruction of alveoli and loss of alveolar capillary basement membrane. Due to loss of elastic recoil of the lung, hyperinflation occurs with an increase in total lung capacity (TLC). Increase in residual volume (RV) may also be seen and reflects air trapping. Spirometric classification is useful in guiding care and monitoring the progression of disease.

While the presence of airway obstruction is determined by a ratio of FEV1 to forced vital capacity of less than 0.07, the severity of COPD is based on the post-bronchodilator FEV1 as follows[1,2,8:]

- Stage 1: Mild FEV1/FVC <0.7; FEV1 ≥ 80% predicted
- Stage 2: Moderate FEV1/FVC <0.7; FEV1 ≥ 50% predicted to < 80% predicted
- Stage 3: Severe FEV1/FVC <0.7; FEV1 ≥ 30% predicted to < 50% predicted
- Stage 4: Very severe FEV1/FVC <0.7; FEV1 < 30% predicted.

In addition to FEV1, exercise capacity and dyspnea have proven to be useful in predicting outcomes such as survival in large cohorts of patients. Celli and colleagues[9] reported on four factors: the body mass index (B) obtained by dividing the weight (in kg) over the square of the height (in m2); the degree of airflow obstruction (O) measured by FEV1; dyspnea (D) measured by the Modified Medical Research Council (MMRC) Scale; and exercise capacity (E), measured by the 6-minute–walk test predictive of mortality. These variables were used to generate the BODE index, a multidimensional 10-point scale, based on points ranging from 0 to 3 for severity of each variable. This study established that higher scores indicate a higher risk of death in patients with COPD. This index has been found to be a much better predictor of mortality than FEV1 alone. BMI values less than 21 kg/m2 are also associated with increased mortality.

Management of stable COPD:

Treatment of COPD is aimed at (1) improving airflow obstruction, (2) providing symptomatic relief, (3) modifying or preventing exacerbations and (4) altering disease progression. Treatment modalities of stable COPD are shown in Box 1.

Box 1: Treatment modalities of stable COPD
· Bronchodilators a) Short-acting bronchodilators such as albuterol, ipratropium b) Long-acting bronchodilators such as salmeterol, tiotropium
· Inhaled corticosteroids
· Supplemental oxygen therapy if hypoxia present
· Pulmonary rehabilitation

Bronchodilators are used in COPD for prevention of symptoms (maintenance therapy) as well as to acutely relieve symptoms (rescue inhalers). Bronchodilators act by altering the bronchial smooth muscle tone and reducing dynamic hyperinflation (air trapping) at rest and with exertion. Maintenance medications include long-acting β2-agonists (LABAs) such as salmeterol and formoterol and long-acting anticholinergics such as tiotropium for prevention of symptoms. Short-acting bronchodilators are used for the acute relief of symptoms, including the short acting β2-agonist (SABAs) albuterol and anticholinergics such as ipratropium. The preferred mode of administration of these bronchodilators is by metered dose inhaler (MDI) or dry powder inhaler (DPI).[1,2]

Inhaled corticosteroids (ICS) provide anti-inflammatory therapy. Because patients with COPD often have an underlying inflammatory process, ICS are sometimes used to stabilize the inflammatory process as well as to reduce the frequency of exacerbations.

Supplemental oxygen therapy is indicated in patients with COPD with resting PaO2 of 55 mm Hg or lower on room air or PaO2 of 56 mm Hg or greater and 59 mm Hg or lower in conjunction with cor pulmonale or erythocytosis (haematocrit 55%).[1,2] A decrease in oxygen saturation (SaO2) to less than 88% with normal walking is an indication for supplemental O2 with activity.[1] Pulmonary rehabilitation has become an established mode of treatment to improve functional capacity and reduce symptoms of dyspnea in patients with COPD.[1,2]

Acute Exacerbations of COPD (AECOPD): An exacerbation of COPD is an "event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variations."[1] The variability is sufficient to warrant a change in management. Though the majority of exacerbations can be managed in an outpatient setting, despite aggressive medical treatment, approximately one third of patients discharged from the emergency department with acute exacerbations have a recurrence within 14 days,[1,10] and 17% relapse and require hospitalization.[11] Mortality for exacerbations requiring hospitalizations are approximately 2%, increasing to 20% if the patient requires mechanical ventilation.[12] In addition, although most exacerbations are related to a bacterial or viral infection, the causes of a third of cases are never identified. The cost of an exacerbation is substantial. In 2006, more than a million hospitalizations occurred at a cost of $11.9 billion.[12] The best predictor of an exacerbation is a history of a prior exacerbation, irrespective of severity of COPD.[13]

Patients with an exacerbation of COPD require hospitalization in the following settings:[1]

1. Frequent exacerbations.
2. Worsening hypoxemia or hypercapnia.
3. Changes in mental status.
4. Concomitant presence of any of these comorbid conditions: CHF, cardiac arrhythmia, diabetes mellitus, renal or liver failure, and pneumonia.
5. Inadequate response to outpatient management.
6. Inability of the patient to be cared for and/or to care for her- or himself at home.
7. Advancing age.

Treatment for a hospitalized patient with AECOPD includes bronchodilator therapy with SABAs (albuterol, salbutamol) and/or ipratropium, administered via spacer or nebulizer as

needed.[14,15] Corticosteroids therapy should be started in these patients: oral prednisone 30 to 40 mg/day or intravenous equivalent dose if the patient cannot tolerate oral intake with subsequent transition to oral. Steroids should be tapered over 10 to 14 days.[16,17] Supplemental oxygen should be administered for O2 saturation of less than 90%. Antibiotics[18,19] should be initiated in patients who have a change in their sputum characteristics (purulence and/or increased volume) or obvious radiographic or microbiological evidence of respiratory tract infection. Choice of antibiotic should be based on local bacteria resistance patterns. As per the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines, macrolides, amoxicillin/clavulanate or respiratory fluoroquinolones may be options for use in an acute exacerbation.[1,2] If infection with Pseudomonas and/or other Enterobacteriaceae species is suspected, combination therapy should be considered.

Management of COPD patients in the ICU:

The need for admission to an ICU is based on the severity of respiratory failure. Patients with severe exacerbations of COPD may be admitted to intermediate care units if skilled and experienced personnel and equipment are available to provide appropriate care and manage acute respiratory failure successfully. The indications for admission to an ICU or a special respiratory care unit are summarized in Box 2.[1]

Box 2: Indications for ICU admission
· Acute respiratory failure, actual or impending.
· Hemodynamic instability.
· Altered mental status/inability to protect airways.

COPD negatively impacts long-term survival. Specific factors, including advanced age and cardiovascular, neurologic or renal dysfunction increase morbidity and mortality. Length of stay and invasive mechanical ventilation are also associated with an increase in mortality.[20] Treatment of patients in a special unit or ICU is similar to treatment of hospitalized non-ICU patients in terms of pharmacologic therapy with nebulized bronchodilators, corticosteroids and antibiotics. Patients with respiratory failure require ventilatory support, which may be either invasive or noninvasive.

Ventilatory support of COPD patients: Mechanical ventilation in COPD patients in the ICU aims at providing supportive therapy while underlying AECOPD and the consequent acute respiratory failure are reversed with medical therapy.[21,22] Mechanical ventilation should be instituted when, despite appropriate medical therapy and oxygen administration, there is no significant improvement in moderate to severe respiratory acidosis (pH <7.36) and the work of breathing.

Modes of mechanical ventilation: Mechanical ventilation can be delivered through an endotracheal or tracheostomy tube (invasive mechanical ventilation) or through the use of a mask, without the use of an endotracheal tube (noninvasive mechanical ventilation), which is also known as noninvasive positive pressure ventilation (NPPV).

NPPV: NPPV represents a major advancement in the treatment of AECOPD in the ICU. NPPV has resulted in lesser number of intubations and invasive mechanical ventilation being performed, and has also significantly reduced mortality for severe COPD exacerbations. NPPV is by far the most commonly used mode of providing noninvasive ventilation.[22,23] Commonly used modes of NPPV include continuous positive airway pressure

(CPAP) plus pressure support ventilation (PSV) or bilevel positive airway pressure (BIPAP).

NPPV should be administered to patients with exacerbations when, after optimal medical therapy and oxygenation, respiratory acidosis (pH <7.36) and or respiratory distress persists. For pH less than 7.30, NPPV should be delivered under controlled environments such as intermediate care units or high-dependency respiratory units (in institutions where they exist) where close monitoring of patients can be performed, with facilities for rapid endotracheal intubation and institution of conventional mechanical ventilation promptly available. If pH is less than 7.25, NPPV should be administered in the ICU with intubation being readily available. Settings of BIPAP with inspiratory positive airway pressure (IPAP) of 10 to 15 and expiratory positive airway pressure (EPAP) of 4 to 6 or the combination of pressure support (PS) of 10 to 15 cm H2O and CPAP of 4 to 8 cm H2O provides an effective mode of NPPV. Contraindications to the use of NPPV are shown in Box 3. Patients with contraindications to NPPV or failing therapy with NPPV should be intubated and placed on invasive mechanical ventilation.

Box 3: Contraindications to NPPV.

- Respiratory or cardiac arrest.
- Hemodynamic instability (hypotension, arrhythmias).
- Myocardial infarction.
- Impaired mental status, inability to cooperate.
- Excessive airway secretions.
- Inability to use mask due to recent facial surgery or trauma.
- Upper airway obstruction.

Several controlled trials have shown that NPPV is effective in the treatment of acute respiratory failure with COPD exacerbation.[24] In addition to randomized clinical trials, high quality meta-analyses have shown that NPPV is very effective and safe in exacerbations of COPD[25] with respiratory acidosis.[26] The patients most likely to benefit from NPPV are those with elevated arterial carbon dioxide, who are able to cooperate with the caregivers and with no coexisting comorbid problems such as sepsis, severe pneumonia, cardiovascular instability and arrhythmias.

In patients with severe respiratory acidosis (pH <7.25), NPPV may be as effective as conventional mechanical ventilation to reverse acute respiratory failure due to COPD.[27,28] One-year mortality was reported to be lower in patients receiving NPPV for exacerbations of COPD, compared to both patients receiving optimal medical therapy alone[29] and those receiving conventional mechanical ventilation.[30] NPPV should be considered as the first-line intervention, in addition to optimal medical therapy, for the management of patients with respiratory failure due to exacerbation of COPD.[25] In the first few hours of initiation, NPPV requires the same level of assistance as conventional mechanical ventilation.

Studies have shown that NPPV is highly cost effective in exacerbation of COPD complicated by acute respiratory failure.[31] In patients on invasive ventilation, with weaning failure, NPPV can be used successfully for weaning.[32,33] Factors associated with successful outcome with NPPV include younger age, ability to cooperate, lower acuity of illness, experienced caregivers, and availability of resources for monitoring.[1,2]

Invasive ventilation/conventional mechanical ventilation: Intubation and institution of conventional mechanical ventilation should be considered in patients in the following situations:

1. When NPPV fails: worsening of arterial blood gases and or pH in 1–2 h; lack of improvement in arterial blood gases and/or pH after 4 h.
2. Severe respiratory acidosis (pH <7.25) despite use of NPPV.
3. Life-threatening hypoxia (PaO2 <50 mm Hg).
4. Severe respiratory distress with increased work of breathing and respiratory rate greater than 35 breaths/min.
5. Hemodynamic instability.
6. When NPPV is contraindicated, not tolerated or in cases of impending respiratory arrest.

Usually patients with COPD with acute respiratory failure are started on assist control (AC) mode of ventilation. Low tidal volumes of 6 mL/kg as are used in acute respiratory distress syndrome (ARDS) patients are not mandatory but may be required to reduce auto positive end-expiratory pressure (PEEP). Initial ventilator settings in these patients may be AC at a rate of 10 to 12 breaths/min, tidal volume of 8 to 10 mL/kg of predicted body weight, FiO2 as required to maintain oxygen saturation at greater than 90% and PEEP of 0 to 5. Based on adequacy of oxygenation and ventilation as evidenced on arterial blood gas as well as patients response to mechanical ventilation, ventilator parameters may be further modified. It is important to remember that the goal of ventilation is to achieve pO2 of 60 mm Hg or greater and a pCO2 that is the patient's baseline value with a normal or near normal pH. Patients with COPD may have chronic hypercapnia and should not be ventilated to achieve a normal pCO2.[1]

Mechanical ventilation in patients with COPD can present certain challenges. Due to increased airway resistance and air trapping in these patients, patients are prone to develop intrinsic PEEP or auto PEEP.[30] Auto PEEP can have adverse hemodynamic consequences that can be life-threatening. To reduce auto PEEP, exhalation time should be prolonged by either reducing rate or tidal volume and/or applying extrinsic PEEP. Aggressive inhaled bronchodilator therapy should be administered to reduce airway resistance. Ventilator dysynchrony should be prevented with adequate sedation. In some cases, neuromuscular blockade may be required to counter patient–ventilator dysynchrony.

If respiratory acidosis persists on AC with pH less than 7.30, minute ventilation should be increased. If the patient's plateau pressure (Ppl) is greater than 30 cm H20, tidal volume may be increased. If Ppl is greater than 30 cm H20, respiratory rate may be increased or mild to moderate elevated levels of CO2 with consequent respiratory acidosis may be tolerated (permissive hypercapnia). An important point to remember is that ventilation in respiratory failure in COPD should be directed at normalizing the pH and not the pCO2.[34]

Medical therapy of the exacerbation of COPD, including bronchodilators, systemic steroids, and antibiotics should continue concomitantly. Patients require sedation, nutritional support, and gastrointestinal and deep venous thrombosis prophylaxis while on ventilator support. Because of the administration of systemic steroids, they are likely to develop hyperglycemia. Blood glucose levels should be periodically checked and corrected with insulin therapy to maintain blood glucose levels of less than 180 g/dL. All metabolic and electrolyte derangements should be corrected if present. Daily sedation holidays are also important, as in any critically ill patient in the ICU, to optimize sedation and reduce the risk of oversedation causing increased duration of ventilator support.

Once patients show clinical improvement, usually in 48 to 72 hours, spontaneous breathing

trials should be attempted. Weaning trial should be performed once the patient's FiO2 requirement is 50% or less, the patient is hemodynamically stable, awake enough to protect his or her airway and does not have copious secretions requiring frequent pulmonary toilet. On pressure support weaning mode, which is the more commonly used spontaneous breathing trial (SBT) in ICUs, lung mechanics and extubation parameters are determined. If these are satisfactory (Box 4), the patient can be extubated. In patients who fail weaning, tracheostomy for prolonged mechanical ventilation will be necessary. In patients with severe disease and/or multiple comorbidities, palliative care should be considered.

Box 4: Extubation parameters for patients with COPD with acute respiratory failure
1. Respiratory rate ≤30 breaths/min.
2. Spontaneous tidal volume ≥5 mL/kg.
3. Minute ventilation <10 L/min.
4. Rapid shallow breathing index <105.
5. Negative inspiratory force > -30 cm H2O.
6. PaO2 > 58 – 60 mm Hg.
7. pH normal.
8. pCO2 at patient's baseline.

Pulmonary rehabilitation:

Pulmonary rehabilitation is an effective and safe intervention for impacting hospital admissions and mortality.[35] Pulmonary rehabilitation is designed to reduce symptoms, optimize function and improve quality of life. The program should be multidisciplinary and include activity, educational, nutritional and psychosocial support. Complementary measures to relieve dyspnea and address and improve quality of life and functional capacity should include not only exercise, oxygen, and pharmacotherapeutics but also relaxation techniques, walking aids, sleep aids and other symptomatic treatments.[36]

Nursing interventions for breathlessness have been tested with mixed effect. The acronym BREATH AIR[36] has been developed to help bedside nurses identify causes and treatments for dyspnea: Bronchospasm, Rales, Effusions, Airway obstruction, Thick secretions, Hemoglobin low, Anxiety, Interpersonal issues and Religious concerns have been identified as causes for dyspnea. Appropriate interventions should include pharmacotherapeutics such as steroids and bronchodilators, diuretics, thoracentesis, cough assist devices, mucolytics, suction techniques, transfusions, position and opioids for physical symptoms. Nursing interventions with emphasis on social, spiritual and financial support needs to be included in the care planning for effective rehabilitation.[36]

For patients successfully treated and discharged from the ICU, discharge planning should involve a comprehensive evidence-based program. Collaboration with the primary care provider is of utmost importance here. Hopkinson and colleagues[37] developed and piloted a promising care bundle for COPD discharge planning. The program had six components including a referral to a clinical nurse specialist; smoking cessation; rehabilitation referral; demonstration of inhaler use; a follow-up appointment; and information regarding COPD self-management, oxygen therapy, and support groups. The 30-day readmission rate for those receiving the bundle interventions was encouraging with a downward trend, although not statistically significant.[37]

Palliative and advanced care planning:

When NPPV or an attempt at weaning from mechanical ventilation fail or intubation is not an

option (for reasons such as patient's wishes, terminal condition), comfort care should be instituted. The progressive nature of the disease and its multisystem effects increase the risk for respiratory failure and death. Patients who refuse life supportive care or request to have it withdrawn require expert delivery of palliative care with interventions, such as dyspnea management and terminal sedation.[1] Discussion of advance directives and advanced care planning (ACP) and referral to the palliative care team assist in decisions regarding supportive care at the end of life (EOL) in patients with COPD admitted to the ICU in acute respiratory failure.

The high burden of the symptoms with COPD, especially dyspnea, reduces overall functional capacity. Discussion of palliative care, symptom relief, quality of life and improving function should be considered, preferably before requiring ICU admission with ongoing discussion during the ICU admission. Discussion of EOL wishes and advanced directives is imperative as a major element in the comprehensive care of the COPD patient. Curative and restorative care must include palliative care. The American Thoracic Society published an official statement that endorses the concepts of palliative care for respiratory disease in critical illness. The statement applies to all stages of COPD and provides recommendations for incorporation of palliative care into treatment, suggested competencies for decision making as well as relationship and communication competencies of health care providers.[38]

ACP, with inclusion of the patient's primary care providers, the patient, and family and/or care givers, is necessary with disease progression of COPD. The aim of ACP should be to increase discussion and increase communication of understanding of the patient's values and goals related to his or her disease. Measures of quality of life and care goals should focus on symptoms including fatigue and dyspnea, activity alterations, emotional function, social isolation and the patient's perception of the degree of control over the disease.[36]

Heffner[39] discusses the need for ACP and the lack of ACP with COPD patients. Patients with COPD have worse health status, higher functional dependence and higher levels of anxiety and depression than patients with lung cancer and yet receive less direction and management of EOL care or palliative management.[39] Evaluation of ACP in COPD patients reveals that COPD patients receive insufficient integration of palliative care with disease-directed treatments, which could improve the quality of life.[39] Practitioner reluctance and skill in conducting ACP as well as patient denial, poor understanding of his or her disease and misperceptions of ACP are barriers to development of EOL care in COPD patients.

Models for implementation of palliative care have suggested that the discussion concerning palliative care occur upon diagnosis or early identification of the disease and well before admission to ICU. Disease-directed treatments with patient-centered goals are identified in these models.[39,40] Multiple diagnostic criteria and clinical prediction instruments have been developed with some promise for tools that will aid practitioners in prognostication. No clear-cut guidelines or measurements have shown consistent outcomes and all need additional testing. Instruments such as the early incorporation of palliative care teams may aid in overcoming barriers to disease management and improved quality of life. Further research is necessary to improve the incorporation of palliative care, identifying triggers in the patient's disease progress that would prompt the practitioner to initiate the discussion.

Summary:

AECOPD resulting in acute respiratory failure is commonly encountered in the ICU. In conjunction with medical therapy, ventilatory support, both noninvasive and invasive, can be

lifesaving. However, mechanical ventilation in these patients can be associated with significant adverse consequences, for example, pneumonia, barotrauma and deconditioning. It is important for caregivers in the ICU to be familiar with the respiratory mechanics in COPD so that appropriate ventilatory settings can be applied for optimal treatment of the respiratory failure. Quality of life and palliative care must be integrated into the care of all COPD patients to address the symptomatic needs of these complex patients.

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"Extraordinary claims require extraordinary evidence"
– Carl Sagan

11

Oxygen Therapy in COPD Patients

Dr. Sanjay Kumar Kochar

Abstract:

Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and disability. Hypoxemia associated with COPD contributes to reduced quality of life, diminished exercise tolerance, reduced skeletal muscle function and ultimately increased risk of death. On the other hand, treatment of severe hypoxemia with long-term oxygen therapy (LTOT) is one of the few interventions shown to prolong life in hypoxemic COPD patients. Although LTOT prescribed to patients with lung diseases proven to be safe but there are some concerns about worsening carbon dioxide retention and increased oxidant injury.

Introduction:

Oxygen therapy is the administration of oxygen as a medical intervention. Normal air is composed of 20.947% oxygen by volume.[1] Oxygen is essential for the cell metabolism, and thus, tissue oxygenation is essential for all normal physiological functions.[2] Oxygen, as a therapeutic agent, has been introduced several decades ago, but much has been learned regarding the detrimental effects of hypoxemia and the beneficial impact of oxygen therapy. The large numbers of patients receiving supplemental oxygen as treatment and the high costs incurred in providing oxygen therapy necessitate the practitioner to know the indications for LTOT as well its effects on survival, pulmonary hemodynamic, sleep and exercise capacity. Oxygen saturation, ‘‘the fifth vital sign’’, should be checked by pulse oximetry in all breathless and acutely ill patients (supplemented by blood gases when necessary) and the inspired oxygen concentration should be recorded on the observation chart with the oximetry result. Although LTOT prescribed to patients with lung diseases proven to be safe but there are some concerns about worsening carbon dioxide retention and increased oxidant injury.

COPD is a leading cause of global morbidity and disability and by 2020 is predicted to become the third greatest cause of death worldwide.[3] As pulmonary function deteriorates and as the disease progresses, the risk of alveolar hypoxia and consequent hypoxemia increases.[4] Hypoxemia associated with COPD contributes to reduced quality of life, diminished exercise tolerance, reduced skeletal muscle function and ultimately increased risk of death.[5] On the other hand, treatment of severe hypoxemia with LTOT is one of the few interventions shown to prolong life in hypoxemic COPD patients.[5]

Medical uses of oxygen therapy:

Oxygen is used as a medical treatment, can be used in hospital, pre-hospital or entirely out of hospital, dependent on the needs of the patient.

Indication of long-term oxygen therapy: [6]

1. **Chronic obstructive pulmonary disease (COPD):**
   - Patients with stable COPD and a resting PaO2 ≤7[3] kPa should be assessed for LTOT which offers survival benefit and improves pulmonary hemodynamic. (Grade A)
   - LTOT should be ordered for patients with stable COPD with a resting PaO2 ≤8 kPa with evidence of peripheral edema, polycythemia (hematocrit ≥55%) or pulmonary hypertension (PHT). (Grade A)
   - LTOT should be ordered for patients with resting hypercapnia if they fulfil all other criteriafor LTOT. (Grade B)
2. **Interstitial lung disease (ILD):**
   - Resting PaO2 ≤7.3 kPa. (Grade D)
   - Resting PaO2 ≤8 kPa in the presence of peripheral edema, polycythemia (hematocrit≥55%) or evidence of PHT.(Grade D)
3. **Cystic fibrosis:**
   - Resting PaO2 ≤7.3 kPa. (Grade D)
   - Resting PaO2 ≤8 kPa in the presence of peripheral edema, polycythemia (hematocrit ≥55%) or evidence of PHT. (Grade D)
4. **Pulmonary hypertension:**
   - LTOT should be ordered for patients with PHT, including idiopathic PHT, when the PaO2 is ≤8 kPa. (Grade D)
5. **Neuromuscular or chest wall disorders:**
   - Non-invasive ventilation (NIV) should be the treatment of choice for patients with chest wall or neuromuscular disease causing type 2 respiratory failure. Additional LTOT may be required in case of hypoxemia not corrected with NIV. (Grade D)
6. **Advanced cardiac failure:**
   - Resting PaO2 ≤7.3 kPa. (Grade D)
   - Resting PaO2 ≤8 kPa in the presence of peripheral edema, polycythemia (hematocrit ≥55%) or evidence of PHT on ECG or echocardiograph. (Grade D)

Indication of oxygen therapy in other conditions:

1. Oxygen can be prescribed in advanced cancer or neurodegenerative disease despite having relatively normal blood oxygen levels.
2. High concentration oxygen is used as home therapy to abort cluster headache attacks due to its vaso-constrictive effects.[7]
3. It is also used in resuscitation, major trauma, anaphylaxis, major hemorrhage, shock, active convulsions and hypothermia.[8]
4. It may also be indicated for any other patient where their injury or illness has caused hypoxemia, although in this case oxygen flow should be moderated to achieve target oxygen saturation levels, based on pulse oximetry (with a target level of 94–98% in most patients, or 88–92% in COPD patients).[2]

Patients who are receiving oxygen therapy for hypoxemia following an acute illness or hospitalization should not routinely have a prescription renewal for continued oxygen therapy without a physician's re-assessment of the patient's condition. If the person has

recovered from the illness, then the hypoxemia is expected to resolve and additional care would be unnecessary and a waste of resources.[8]

Supplemental oxygen therapy in non-hypoxemic patients:

- Oxygen therapy is useful in carbon monoxide poisoning.
- Hyperoxemia may also be used to accelerate the resolution of pneumothorax in patients who do not require a chest drain.[9]
- Short-term postoperative oxygen therapy (for 2 h) has been shown to reduce the risk of surgical wound infections in double blind trials of patients having bowel surgery but not in general surgery.[10,11]
- Oxygen therapy has potential benefit in human anastomotic surgery.[12]
- Hyperbaric oxygen reduced the risk of amputation in patients with chronic diabetic foot ulcersand may improve the chance of healing over 1 year, but the Cochrane reviewers had concerns about the size and quality of existing studies and recommended further trials.[13] It is not known if conventional oxygen therapy has any effect on wound healing.[14]
- Although some reports have suggested that oxygen may have a specific antiemetic effect during ambulance transfers and in the postoperative state, subsequent studies reported no effect on motion sickness and no anti-emetic effect in postoperative patients.[15]

Hypoxemia in COPD:

The major consequence of COPD is hypoxemia. Ventilation/perfusion mismatch resulting from progressive airflow limitation and emphysema is the key driver of this hypoxia, which may be exacerbated by sleep and exercise.[16] When PaO2 level remain above 55-60 mmHg, there is no significant increase in ventilation, but as PaO2 falls below 55 mmHg, there is a marked rise in minute ventilation (VE), with a subsequent fall in PaCO2.

Effect of hypoxemia:[6]

- Hypoxemia causes peripheral vasodilation, which induces a compensatory tachycardia and a subsequent increase in cardiac output to improve oxygen delivery.
- Alveolar hypoxia causes pulmonary vasoconstriction in an effort to match ventilation and perfusion and thus PHT.
- Long term effect of PHT causes signs of right ventricular failure (cor-pulmonale) such as elevated jugular venous pressure (JVP), pedal edema, hepatomegaly, ascites, etc.
- Erythrocytosis occurs due to increase in erythropoietin secretion, thereby increasing oxygen carrying capacity. These compensatory mechanisms can cause detrimental long-term effects, such as polycythemia.
- Hypoxia can cause coronary vasodilation, decreased systemic vascular resistance (transient) which results in myocardial ischemia/infarction, ischemia/infarction of other critically perfused organs, hypotension and arrhythmias.
- On a cellular level, mitochondrial function declines, anaerobic glycolysis occurs and lactate/pyruvate ratio increases.
- Hypoxia can activate renin-angiotensin axis, which increases the risk of acute tubular necrosis.

- Patients may have impaired judgment at low levels of hypoxemia with progressive loss of cognitive and motor functions and eventually loss of consciousness as severe hypoxemia ensues.
- Other nonspecific symptoms like headache, breathlessness, restlessness and tremor can be found in patients with hypoxemia.

A combination of these factors leads to diminished quality of life, reduced exercise tolerance, increased risk of cardiovascular morbidity and greater risk of death. Concomitant sleep-disordered breathing may place a small but significant subset of COPD patients at increased risk of these complications.[16]

Oxygen therapy in COPD:

There is strong evidence of survival benefit of LTOT in patients with COPD and severe chronic hypoxemia when used for at least 15 hours daily.[6] Therefore, oxygen therapy in COPD must be used with care in the acute setting but it can have distinct benefits in the long term.

Oxygen therapy in the acute setting (in hospital):[8]

- Oxygen therapy will have to be complemented with other interventions for any acute exacerbation of COPD.
- For most COPD patients, target SaO2 should be 88-92%, (compared with 94-98% for most acutely ill patients NOT at risk of hypercapnic respiratory failure). Mark the target saturation clearly on the drug chart.
- The aim of (controlled) oxygen therapy is to raise the PaO2 without worsening the acidosis. Therefore, give oxygen at no more than 28% (via venturi mask, 4 L/minute) or no more than 2 L/minute (via nasal prongs) and aim for oxygen saturation 88-92% for patients with a history of COPD until arterial blood gases (ABGs) have been checked.[17]
- If the saturation remains below 88% despite a 28% venturi mask, change to nasal cannula at 2–6 l/min or a simple mask at 5 l/min with target saturation of 88–92%.
- Measure ABGs within 60 minutes of starting supplemental oxygen or changing its concentration. If PaO2 improves with an associated drop in PaCO2 and the pH is relatively unaffected (pH >7.26) then the concentration of the supplemental oxygen may be increased to maintain PaO2 >7.5 kPa.
- If the PaCO2 is raised but pH is ≥7.35 ([H+] ≤45 nmol/l), the patient probably has long-standing hypercapnia; maintain target range of 88–92% for these patients. ABGs should be repeated at 30–60 min to check for rising PaCO2 or falling pH.
- If acidosis (pH <7.35 or [H+] >45 nmol/l) develops with a rising PaCO2 (>6 kPa or 45 mmHg), other therapeutic interventions need to be discussed with the acute medical team; the intensive treatment unit (ITU) may need to be involved and decisions regarding ceiling of care have to take place at this point. Non-invasive positive pressure ventilation (NIPPV), intermittent positive pressure ventilation (IPPV) and doxapram are all options.

Long-term oxygen therapy (LTOT):[6]

- LTOT can be defined as oxygen used for at least 15 h per day in chronically hypoxemic patients. Chronic hypoxemia is defined as a PaO2 ≤7.3 kPa or, in certain clinical situations, PaO2 ≤8.0 kPa.

- Consider assessment for people with severe airflow obstruction (FEV1 30-49% predicted).
- Offer LTOT to people with PaO2 <7.3 kPa when stable (or <8 kPa when stable and with peripheral edema, polycythemia (hematocrit ≥55%) or PHT).
- Patients potentially requiring LTOT should not be assessed using pulse oximetry alone. Assess by measuring ABGs on two occasions at least three weeks apart in people with confirmed stable COPD who are receiving optimum medical management.
- Patients who develop a respiratory acidosis and/or a rise in PaCO2 of >1 kPa (7.5 mmHg) during an LTOT assessment may have clinically unstable disease. These patients should undergo further medical optimization and be reassessed after 4 weeks.
- When patient has respiratory acidosis and/or a rise in PaCO2 of >1 kPa (7.5 mmHg) two repeated occasions, while apparently clinically stable, should only have domiciliary oxygen ordered in conjunction with nocturnal ventilatory support.
- LTOT should be given over a minimum of 15 hours a day, and up to 24 h per day may be of additional benefit.
- **LTOT flow rates:**
  - Patients eligible for LTOT should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until SpO2 >90%. An ABG should then be performed to confirm that a target PaO2 ≥8 kPa (60 mm Hg) at rest has been achieved.
  - Non-hypercapnic patients initiated on LTOT should increase their flow rate by 1 L/min during sleep in the absence of any contraindications.
  - Ambulatory and nocturnal oximetry may be performed to allow more accurate flow rates to be ordered for exercise and sleep, respectively.
- If LTOT is ordered for patients who are continuing to smoke, the potential for more limited clinical benefit should be discussed with the patient.
- If they smoke, warn them about the risk of fire and explosion.
- Be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression.
- Refer people who are hypercapnic or acidotic on LTOT to a specialist center for consideration of long-term NIV.
- NIV should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations not responding to medical therapy.

Ambulatory oxygen therapy (AOT):

- AOT assessment should only be offered to patients already on LTOT if they are mobile outdoors.
- AOT should be offered to patients for use during exercise in a pulmonary rehabilitation program or during an exercise program following a formal assessment demonstrating improvement in exercise endurance.
- It is recognized that there may be some patients, for example with ILD and disabling breathlessness, who do not qualify for LTOT but who do desaturate on exercise who may benefit from AOT.

- **Oxygen delivery:**
  - Use oxygen concentrators to provide the fixed supply for LTOT at home.
  - Nasal cannula should be considered as the first choice of delivery device for patients requiring home oxygen therapy.
  - Venturi masks should be considered in patients in whom there are concerns about existing or developing hypercapnic respiratory failure, those with a high resting respiratory rateor those with cognitive problems.
  - Oxygen-conserving devices should be considered in patients who are active outside the home following an ambulatory oxygen assessment.

Effect of oxygen administration: [5]

Effects of oxygen therapy are divided into short-term effect and long-term effect.

Short-term effect:

- Relieving arterial hypoxemia
- Improves breathlessness in both normal subjects and in those with COPD during exercise.[18,19]
- Exercise tolerance is improved in those who develop significant hypoxemia as well as in those with only mild to moderate hypoxemia.[20]

In COPD, the perceived decrease in breathlessness and improvement in exercise capacity may be due to:

- Decreased VE (minute ventilation).[19]
- A decrease in dynamic hyperinflation.[21]
- Alleviation of hypoxic pulmonary vasoconstriction and improved hemodynamics (e.g., decrease in pulmonary vascular resistance and increase in cardiac output).[22]
- Increased oxygen delivery.[23]
- Improvement in ventilatory muscle function24 and altered ventilatory muscle recruitment.[25]
- Oxygen flow may also stimulate upper airway and facial receptors of the trigeminal nerve and reflexively inhibit central ventilatory drive.[26]
- There also appears to be a direct effect of oxygen administration on the perception of dyspnea independent of any changes in VE.

Long-term effect:

Chronic hypoxemia leading to the development of cor-pulmonale portends a poor prognosis, with mortality ranging anywhere from 32 to 100%.[27] Early non-controlled studies showed a reduction in mortality in patients with COPD, cor-pulmonale and severe hypoxemia with the use of continuous oxygen therapy for 7 to 41 months.[28] LTOT improves survival in patients with severe hypoxemia (arterial PaO2 <8 kPa) but has no effect in patients desaturating only at night or in patients with moderate hypoxemia.[29]

Effect of sleep in COPD: [5]

Sleep disturbance is common in patients with COPD. Increased sleep latency, decreased total sleep time, decreased slow-wave sleep and decreased REM sleep have been noted in many polysomnographic studies of patients with COPD.[30,31] Approximately 30 to 70% of patients with COPD complain of insomnia, early morning awakenings, morning tiredness or

daytime sleepiness.[31,32] Common reasons include medication side effects, airflow obstruction and hypercapnia, but perhaps the most important is nocturnal oxygen desaturation (NOD). NOD may lead to the development of PHT and cor-pulmonale in patients with COPD. Oxygen therapy during sleep may prevent nocturnal hypoxemia and possibly the development of PHT. However, two clinical studies examining normoxemic patients with COPD with evidence of nocturnal desaturation found neither an improvement in survival with nocturnal oxygen despite a reduction in pulmonary artery pressures nor a delay in the time to prescription of continuous oxygen therapy.[33,34] Given the lack of survival advantage, screening for nocturnal desaturation in normoxemic patients with COPD should probably be reserved for those with hypercapnia, erythrocytosis or evidence of PHT.

Effect of air travel:

Hypobaric conditions develop when ascent to high altitude via air travel which increases risk of hypoxemia. Pressurizing the aircraft cabin limits the fall in atmospheric pressure. Commercial air travel is generally safe for patients with COPD when their disease is stable.[35] Oxygen supplementation is indicated if the predicted PaO2 at 8,000 ft. is <50 mmHg. Those with an SpO2 >95% or a PaO2 >72 mmHg while breathing ambient air at sea level will most likely not require oxygen supplementation.

Source of oxygen therapy:

Oxygen can be separated by a number of methods, including chemical reaction and fractional distillation and then either used immediately or stored for future use. The main types of sources for oxygen therapy are:

1. **Liquid storage:** Liquid oxygen is stored in chilled tanks until required and then allowed to boil to release oxygen as a gas.
2. **Compressed gas storage:** Oxygen gas is compressed in a gas cylinder, which provides a convenient storage without the requirement for refrigeration found with liquid storage.
3. **Instant usage:** Use of an electrically powered oxygen concentrator or a chemical reaction based unit can create sufficient oxygen for a patient to use immediately with the advantage of being continuous supply without the need for additional deliveries of bulky cylinders.

Delivery of oxygen:

Various devices are used for administration of oxygen. In most cases, the oxygen will first pass through a pressure regulator used to control the high pressure of oxygen delivered from a cylinder (or other source) to a lower pressure. This lower pressure is then controlled by a flowmeter and this controls the flow in a measure such as liters per minute (lpm).

Supplemental oxygen:

Many patients require only a supplementary level of oxygen in the room air they are breathing rather than pure or near pure oxygen and this can be delivered through a number of devices dependent on the situation:

1. Nasal cannula (NC): It is a thin tube with two small nozzles that protrude into the nostrils. It can only comfortably provide oxygen at low flow rates, 2–6 liters per minute (lpm), delivering a concentration of 24–40%.
2. Simple face mask: It often used at between 5 and 8 lpm, with a concentration of oxygen to the patient of between 28% and 50%.

3. Venturi mask: It is more controlled air-entrainment mask, which can accurately deliver a predetermined oxygen concentration to the trachea.
4. Partial rebreathing mask: It is based on a simple mask, but featuring a reservoir bag, which increases the provided oxygen concentration to 40–70% oxygen at 5 to 15 lpm.
5. Non-rebreather masks draw oxygen from attached reservoir bags with one-way valves that direct exhaled air out of the mask. When properly fitted and used at flow rates of 8-10 lpm or higher, they deliver close to 100% oxygen. This type of mask is indicated for acute medical emergencies.
6. Demand oxygen delivery systems (DODS) or oxygen resuscitators deliver oxygen only when the person inhales or in the case of a non-breathing people, the caregiver presses a button on the mask. These systems greatly conserve oxygen compared to steady-flow masks, which is useful in emergency situations when a limited supply of oxygen is available.

High flow oxygen delivery:

In cases where the patient requires a high concentration of up to 100% oxygen, a number of devices are available:

1. Non-rebreather mask (or reservoir mask): It is similar to the partial rebreathing mask except it has a series of one-way valves preventing exhaled air from returning to the bag.
2. Humidified high flow nasal cannula, which enables flows exceeding a patient's peak inspiratory flow demand to be delivered via nasal cannula.
3. Tight fitting masks.
4. Trans-tracheal oxygen: Oxygen is delivered via a catheter inserted percutaneously between the second and third tracheal rings.
5. Positive pressure ventilation delivery mask.
6. Filtered oxygen masks: These masks have the ability to prevent exhaled potentially infectious particles from being released into the surrounding environment. These are normally of a closed design such that leaks are minimized and breathing of room air is controlled through a series of one-way valves.

Adverse effect of oxygen supplementation: [8]

The most significant effect of excess oxygen on the respiratory system is hypercapnic respiratory failure in a population of vulnerable patients especially in COPD patients. This does not occur in the absence of significant pulmonary disease or musculoskeletal disease affecting the thorax and it occurs while the PaO2 is still within the normal range or slightly below normal.

There are at least five mechanisms responsible for this:

- V/Q mismatch,
- Ventilatory drive,
- Haldane effect,
- Absorption atelectasis,
- Higher density of oxygen compared with air.

Adverse effects can be:

1. Rebound hypoxemia following sudden cessation of supplementary oxygen therapy.
2. Coronary and cerebral vasoconstriction.
3. Reduced cardiac output.

4. Damage from oxygen free radicals.
5. Increased systemic vascular resistance.
6. Delay in recognition of physiological deterioration.
7. High levels of oxygen given to infants causes blindness by promoting overgrowth of new blood vessels in the eye obstructing sight. This is retinopathy of prematurity (ROP).
8. In rare instances, hyperbaric oxygen therapy patients have had seizures
9. Fire risk: Oxygen itself is not flammable but the addition of concentrated oxygen to a fire greatly increases its intensity.

Conclusion:

Oxygen therapy offers significant short and long-term benefits in those with COPD. Immediate benefits include alleviation of hypoxemia and its sequelae, reduction of dyspnea, improvement in exercise capacity and possibly sleep physiology. The eligible patients for LTOT are those who, in the steady state, present with severe hypoxemia (arterial oxygen tension PaO2 ≤7.3 kPa). Patients with a PaO2 of 7.4-8 kPa are also eligible if such hypoxemia is accompanied by an elevated hematocrit and clinical signs of cor pulmonale. Long-term use has been shown to improve survival in severely hypoxemic patients with COPD and cause a slight reduction in pulmonary artery pressure.

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"True ignorance is not the absence of knowledge, but the refusal to aquire it"

– Karl Popper

12

Pitfalls in Diagnosis and Management of COPD

Dr. Angira Dasgupta

Abstract:

There are many international and country specific guidelines for diagnosis and management of COPD. All these guidelines consider spirometry as the only diagnostic tool for COPD diagnosis. They do not emphasize need for other tests for assessment of small airway function to detect early disease. The use of fixed FEV1/FVC ratio has its limitations. Further, the grading (A, B, C and D) approach to management does not consider the presence of any underlying uncontrolled airway inflammation. This chapter discusses the pitfalls in spirometry diagnosis of COPD and discusses use of measures of airway inflammation by sputum quantitative assay in COPD management.

Introduction:

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lung and one of the leading causes of mortality and morbidity worldwide.[1] Several guidelines, including country specific guidelines, on COPD exist which are updated regularly.[2-5] But, the main issue is with the evidences used to form these COPD guidelines. Even though the number of publications on COPD has increased enormously in recent years, most are observational studies making their results difficult to translate into specific recommendations.[6]

COPD has been defined as a common treatable and preventable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response of the airways and the lung to noxious particles or gases.[2] The diagnosis of COPD is based primarily on demonstration of irreversible airflow obstruction by spirometry. However, presence of irreversible airflow obstruction forms only part of the disease definition. The measurement of airway inflammation has been traditionally ignored in the various global recommendations. Yet, airway inflammation forms the central component of airway diseases[7] and treatment strategies guided by optimizing airway inflammation reduces hospitalizations by 62% compared to guideline-based approaches.[8] This chapter will describe the pitfalls in COPD diagnosis and management with special emphasis on the limitations of using spirometry as the only tool for measuring airflow obstruction and discuss various of measures of airway inflammation in COPD management.

Pulmonary Function Tests:

COPD is a disease which is diagnosed primarily by spirometry. Clinical symptoms are nonspecific. However, using spirometry alone for diagnosing COPD may not be appropriate.The reasons for this are manifold; the commonest reason being technical issues

such as inability of COPD patients to perform the forced expiratory maneuver adequately especially those with severe disease. This may result in poorer airflows leading to inaccuracies in consequent management. The use of sound technique and appropriate reference equations are other things that needs to be taken care of and lacks emphasis in most guidelines. There is a primary disagreement between the GOLD and the ATS/ERS recommendations for defining airflow limitation. The former regards post-bronchodilator FEV1//FVC ratio of <0.7 as the presence of significant airflow limitation while the latter supports use of population specific lower limit of normal (LLN) criterion. Such disagreements stem from the fact that aging may cause indolent decline in lung function which is reflected in spirometry by an FEV1/FVC ratio <0.7 even in the absence of pathological airflow limitation irrespective of the smoking status. Hence, it is likely to lead to over diagnosis of disease in the elderly.[9] In a study in the general population comparing use of the fixed ratio with the LLN criterion, the proportion of subjects over 50 years of age who was incorrectly identified as having airway obstruction was at an alarmingly high of 68%. The concept of using the LLN method is based on the traditional understanding that for most physiological and biochemical variables is traditionally defined so that 5% of healthy subjects fall below the LLN and this is applicable for the FEV1/FVC ratio too. Hence use of the fixed ratio definition will under diagnose disease in adults <45 years.[10] The advantages of using a fixed ratio are that it is simple to apply in busy clinics, independent of reference values and has been used in clinical trials thus far. The major disadvantage of using the LLN method is that it has not yet been validated in clinical trials and longitudinal studies are lacking.[11]

It has been long since we have known that COPD starts with small airways dysfunction.[2] The COPD inflammation causes increased airflow resistance decreased expiratory flow and loss of elastic recoil of the lungs. Thus more effort is required to exhale air from the lungs which in turn leads to early closure of small airways and air trapping. Therefore; it is intuitive that assessment of small airway function is necessary for early diagnosis of COPD. However, spirometry which is the only recommended diagnostic test for COPD is not a very accurate tool for measuring small airway function.[12,13] Although, FEF25 has been held to be more sensitive in assessment of small airway function, its variability precludes use of such measures. Lung volume estimation by body plethysmography gives more information on small airway function and air trapping by measuring residual volume and total lung capacity which may be the only treatment responsive measures in some patients. Recently, impulse oscillometry has been proclaimed as a tool that gives accurate measurements of small airway dysfunction[14] and has been found to correlate well with quality of life scores such as St George's Questionnaires.[15] It is yet to find a place in guidelines mostly due to availability issues and non availability of reference equations.

Measurement of airway inflammation:

Although, by definition, COPD is a chronic 'inflammatory' disease of the airways, the measurement of airway inflammation has always been ignored in almost all diagnosis and management guidelines of COPD.[2-5] Airway inflammation forms the central component of airway diseases including COPD and is responsible for the various pathophysiological consequences.[16] Airway inflammation cannot be estimated by measuring airflow by spirometry. In fact, only a weak association between airway inflammation and spirometry has been observed.[17] Neither can ongoing inflammation be assessed clinically as it may be present even in the absence of clinical symptoms.[18] These observations suggest that airway

inflammation needs to be measured directly and objectively and one way to achieve this is to utilize sputum quantitative assays. It is a specific, sensitive, repeatable and valid method of measuring sputum cell counts noninvasively[19] and the normal values have also been well established.[20] When patients cannot produce sputum spontaneously it can be safely induced with increasing concentrations of hypertonic saline (3%, 4% and 5%) or with isotonic saline even in patients with severe airflow limitation.[21] The measurement properties and validation are beyond the scope of this chapter. There is limited experience in use of other tools for measuring airway inflammation such as fraction of NO in exhaled breath (FeNO) or analysis of other substances in breath condensates in COPD management. Sputum quantitative assay entails selection of a small quantity of sputum from either a spontaneous or induced sample, treatment with a sputolysin (dithiothreitol) or subsequent filtering to obtain a homogenous suspension of cells. The total cell count and viability are determined in a haemocytometer, while differential counts are obtained from Wright stained cytospins.[19]
According to the cellular nature, inflammation can be of four main types namely:
(i) eosinophilic, (ii) neutrophilic, (iii) combined eosinophilic and neutrophilic and
(iv) paucigranulocytic.
The causes of the different types of bronchitis are summarized in Table 1.

Table 1: Causes of various types of bronchitis.[23]

I. Eosinophilic bronchitis:

- Allergies/Atopy
- Parasitic infestations
- Eosinophilicvasculitis
- Chronic eosinophilic pneumonias
- Hypereosinophilic syndromes
- Haematological disorders and Solid organ malignancies

II. Neutrophilic bronchitis:

- Infections
- Smoke
- Occupational exposures
- Diesel exposure
- Pollution
- Ozone exposure

III. Combined eosinophilic and neutrophilic bronchitis

IV. Paucigranulocytic

Although it is important to know the stimuli, but identification of the nature of bronchitis is crucial as this is what predicts response to a particular therapeutic agent by providing a reasonable understanding of the chemical mediators involved in the pathogenesis. The presence of a clinically relevant eosinophilic bronchitis is indicated by a sputum eosinophil differential count of more than 3% and it is usually associated with a normal total cell count. The importance of recognizing an eosinophilic bronchitis is that it is a steroid responsive condition and treatment is targeted at achieving and maintaining a count of less than 3%.[22] A neutrophilic bronchitis is considered to be present when there are more than 65% neutrophils on a sputum differential cell count.[23] This indicates a non-eosinophil driven

mechanism and is a steroid non responsive condition. A neutrophilic bronchitis with a raised total cell count can be arbitrarily graded as “mild” if the total count is > 9.7 million cells/g but <20, “moderate” if 20 to <50, and “intense” if <50 million cells/g.[24] An infective bronchitis of viral origin is milder with only a modest elevation of total cell count and neutrophil differential of <80% while bacterial bronchitis has neutrophilia of >80% with the total count raised to the “intense” range.[21] This however requires further validation. If the total count is only mildly elevated with a neutrophilia, non infective causes should be considered. These include smoker’s bronchitis, exposure to ozone, diesel exhaust particles, endotoxins[25] and contaminated metal working fluids or inflammatory bowel disease.[26] The clinical implication of an isolated rise in neutrophil count has not yet been fully realized. It may be an effect of corticosteroid treatment which is known to be anti-apoptotic to neutrophils.[27] A paucigranulocytic or normal sputum indicates absence or controlled airway inflammation and addition of steroids or antibiotics is not indicated. There is ongoing research to understand the importance of the other cells in sputum such as lymphocytes and macrophages in obstructive lung diseases.

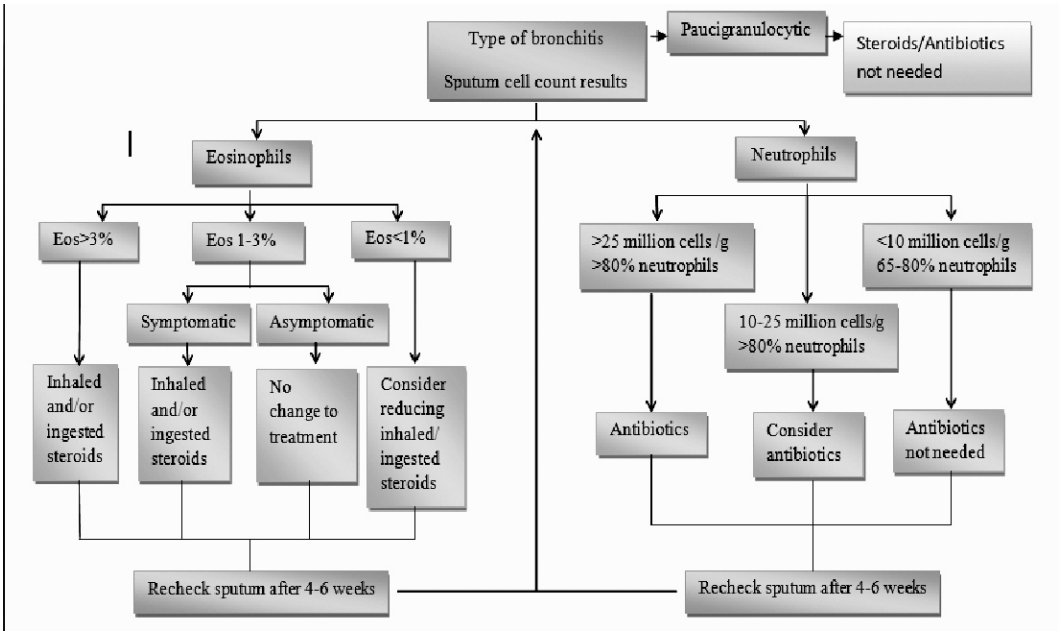
It might be relevant to suggest here that some of these patients may have a systemic inflammation (CRP >3ng/l) component only that needs attention. This subgroup of patients may benefit from statin therapy. Statins have been shown to reduce number of COPD exacerbations, reduce lung function decline,[28,29] improve exercise capacity and reduce mortality.[30] The major limitation of sputum quantitative assay is its limited availability and need for specialized training. Thus there is ongoing research to identify surrogates for sputum inflammatory markers which would be easy to perform even in busy clinics. One such surrogate biomarker that has been researched in COPD patients is blood eosinophils in lieu of sputum eosinophils. Treatment decisions guided by blood eosinophil count, although a poor surrogate of airway eosinophilia, may lead to better outcomes than clinical decisions.[31] Patients with blood eosinophil counts >0.2 seem to respond more favorably to corticosteroids than patients with normal eosinophil counts.[32,33] More importantly, patients with normal blood eosinophil counts have a poor response when administered corticosteroids.[32]

Use of inflammometry in treatment of COPD:

The recent COPD management guideline is based on characterization of patients into one of four grades (A to D) based on their spirometry values, functional class and risk of exacerbation.[2] It involves using short-acting bronchodilators and active reduction of risk factors (smoking cessation and vaccinations) across all COPD severity classifications in addition to the other grade specific pharmacotherapies.[2] Accordingly, patients in the milder two grades (A and B) are treated with long acting bronchodilators (beta-agonists alone or with anti-muscarinics) only whereas patients in the other two groups (C and D) who are regarded to be at high risk of exacerbations are prescribed additional corticosteroids. The presence and nature of any ongoing airway inflammation is not considered. The problem with treating with only bronchodilators is that if these patients have an underlying ongoing inflammation which if not identified and treated may end up in an exacerbation and decline in lung function. Further, use of steroids (inhaled or ingested) as a standard antiinflammatory agent may worsen neutrophilic airway inflammation[34] if present and when applied generally in COPD has a risk for pneumonia.[35] Such an approach would have been successful if all patients in Grade C and D had associated eosinophilic bronchitis. But in reality it is not so.

Only one third of stable COPD patients and 1 in 5 COPD exacerbations are associated with eosinophilic bronchitis.[36]

Figure 1: Titration of treatment based on sputum quantitative assay (Adapted from Ref [23])



An additional thing to consider while treating COPD patients is the heterogeneity of the disease especially in the nature of inflammation. Although cluster analysis has been used to identify repeatable biological clusters and seems to suggest that the nature of exacerbations is predictable from the stable state, this is not always true. Heterogeneity is present in both stable disease and during exacerbations and not only between patients but also in longitudinal follow up of individual patients.[37] This makes it necessary to repeat measuring inflammation during each exacerbation and whenever considering change of therapy. A one-off sputum quantitative assay during exacerbations or in stable state is not enough to phenotype COPD patients.

Conclusion:

COPD therapy needs to be individualized and this is best done by inflammometry guided intervention. Patients with eosinophilic inflammation benefit from corticosteroids in addition to bronchodilators while neutrophilic inflammatory pathways are addressed using macrolide antibiotics. Systemic inflammation represents a further pathway that when identified by a raised CRP level is treated with statins.

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13

COPD: A systemic Disease

Dr. Parvaiz A. Koul, Hyder Mir

Chronic obstructive pulmonary disease (COPD), as per the Global Initiative for Obstructive Lung Disease (GOLD), is defined as a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases, particularly inhaled cigarette smoke. Initially thought to affect the lungs alone, COPD is increasingly been now recognized as a systemic disease complicated with various comorbidities including lung cancer, atherosclerosis, muscle wasting, osteoporosis, diabetes and anxiety/depression. To add on to the direct burden of systemic disease as a result of COPD, is the presence of smoking, increasing age, physical inactivity and comorbidities (diseases coexisting with COPD without necessarily a cause and effect relationship). The awareness of these systemic manifestations and comorbidities is crucial not only for prevention and management of COPD but also for reduction of the burden on the health-care system. Figure 1 depicts the commonly seen comorbidities in COPD.

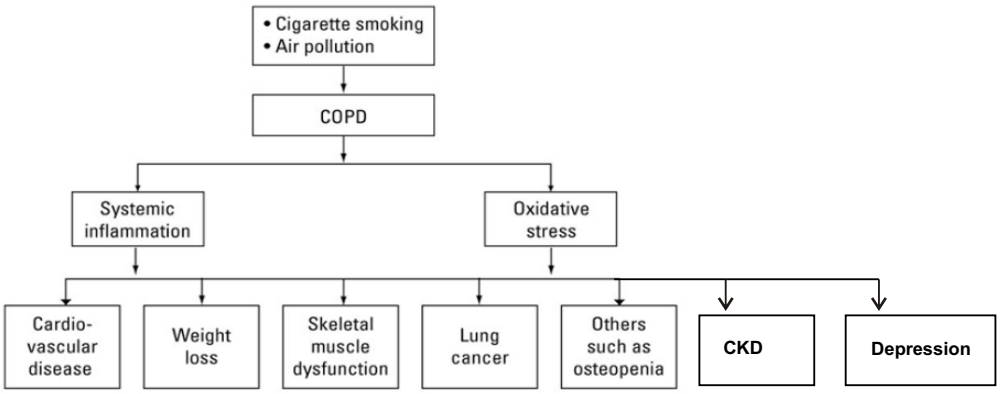

Figure1. Systemic effects of COPD

Systemic inflammation in COPD:

Patients with COPD, particularly when the disease is severe and during exacerbations, have evidence of systemic inflammation. Systemic inflammation appears to relate to an accelerated decline in lung function and is increased during exacerbations. Patients with stable COPD have a heightened cellular as well as cytokine response. Increased numbers of leukocytes (lymphocytes, neutrophils, natural killer cells) and increased levels of cytokines and acute phase reactants have been demonstrated in cases with COPD. Circulatory inflammatory markers such as TNF-α, CRP, lipopolysaccharide-binding protein, lipid

peroxidation products, inflammatory cells, markers of neutrophilic inflammation (matrix metalloproteinase-9 [MMP-9], elastase, calprotectin, MMP-9/tissue inhibitor of metalloproteinase-1 ratio, IL-6, BAL neutrophils), and proinflammatory markers (IL-6, IL-β, IFN-α, I, monokine induced by gamma interferon and macrophage inflammatory protein 1 alpha) are found to be significantly elevated in patients with COPD. Chemokines like IL-8, adipokines (Leptin) and ghrelin have also been found to be dysregulated in stable COPD patients. Inflammatory biomarkers in respiratory specimens such as sputum, BAL and endobronchial biopsy have also been found to demonstrate a heightened expression in COPD. It is still unclear whether the systemic markers of inflammation represent a spill-over of the inflammation from that in the peripheral lung, a parallel abnormality or are related to some comorbid disease which then affects the lung. The inflammation may in part be attributable to smoking which is an invariable component of many forms of COPD. However, the degree of systemic inflammation in COPD is greater. Other potential origins of systemic inflammation in COPD include lung hyperinflation, tissue hypoxia, skeletal muscle dysfunction and the bone marrow. Whatever the origin, the heightened inflammatory milieu is believed to account for various systemic manifestations of COPD and may help predict clinical outcomes and responses to therapy as well as aid in the identification of new targets for therapy. This inflammation is similar to other chronic illnesses such as chronic heart failure, obesity, diabetes and even the normal process of aging.

Systemic manifestations and comorbidities:

1. Cardiovascular system: The close association between the pulmonary and the cardiovascular system is such that any abnormality in one will reflect on the other. A number of cardiovascular comorbidities have been described in patients with COPD and are discussed in detail elsewhere in this monograph.

2. Malnutrition and skeletal muscle wasting: Skeletal muscle wasting and loss of lean body mass is a common and serious problem for patients with COPD, especially those with the emphysema phenotype. Unexplained weight loss occurs in about 50% of patients with severe COPD, but it can also be seen in about 10 to 15% of patients with mild to moderate disease. Skeletal muscle weakness associated with wasting of fat-free mass (FFM) of the extremity, is independent of airflow obstruction and COPD subtype.

Patients with low body weights have greater gas trapping, lower diffusing capacity and less exercise capacity than to persons with similar respiratory mechanics but normal body weights. Loss of body cell mass is associated with a reduction in the mass of the diaphragm and of the respiratory muscles, resulting in decline in strength and endurance. A malnutrition-related decline in immune status may further blunt airway defenses. These effects can contribute to undesirable clinical sequelae that include hypercapnic respiratory failure, difficulty with weaning from mechanical ventilation and nosocomial lung infections. Body weight and BMI have been identified as independent risk factors for mortality in COPD patients.

Weight loss in COPD is mostly due to skeletal muscle atrophy. Further, the remaining muscle mass is often dysfunctional. This combination contributes significantly to reduce the exercise capacity (and thus, the health status) of patients with COPD. Physical inactivity, oxidative stress, systemic inflammation and negative protein balance lead to muscle atrophy. Moreover, reduced intake due to dyspnea and impaired leptin regulation, increased work of breathing, hypoxia and endocrine changes disrupts the fine balance of energy intake and consumption.

The mechanisms underlying skeletal muscle abnormalities in COPD are not precisely defined, but they are probably multiple and interdependent. Systemic inflammation is a likely contributor to muscle proteolysis. For instance cytokines, particularly TNF-α, activate the transcription factor nuclear factor (NF)-κB, up-regulate the inducible form of the nitric oxide synthase and facilitate the degradation of myosin heavy chains through the ubiquitin–proteasome complex. Cytokines also promote apoptosis in skeletal muscle cells, as has recently been shown to occur in patients with COPD and low body weight. Disturbances in energy balance occur in patients with COPD that may reflect both the mechanical inefficiency of breathing and the reduced dietary energy intakes of these patients. In COPD patients, resting energy expenditure (REE) has been reported to be 15–20% above predicted values and the increased energy required for breathing has been suspected to account for the difference. Complex changes in metabolism are ultimately the result of inflammation, hypoxia, hypercapnia, nutritional deprivation and pharmacologic therapy. Stressors like nosocomial infection may exacerbate the situation by promoting hypermetabolism. The ubiquitin-proteasome pathway is activated in catabolic states to accelerate the breakdown of muscle proteins. Cytokine-mediated cachexia, similar to other end-stage organ failure syndromes, is also possible in COPD patients. Elevated concentrations of soluble tumor necrosis factor receptors and acute phase proteins have been observed and anorexia and decreased dietary intakes are common. Steroid therapy may further stimulate proteolysis and promote gluconeogenesis through inhibition of both protein synthesis and the transport of amino acids into muscle. Patients with severe parenchymal destruction tend to be the most malnourished and the least responsive to nutritional intervention. It is likely that COPD patients with macroscopic emphysema manifest the sequela of both the inflammatory process and semi-starvation. The result may be a combination of alterations in intermediary metabolism and negative energy balance that culminate in loss of body cell mass.

The poor prognosis due to low BMI in COPD is independent of other, more traditional indices, such as FEV1 or PaO2. Thus weight loss identifies a new systemic domain of COPD that needs a careful consideration in the clinical management of patients with COPD and the recently proposed BODE (body mass index; airflow obstruction; dyspnea; exercise capacity) index, as a multi-domain approach to prognosticate COPD is a step forward in this direction. Better understanding of the mechanisms leading to malnutrition in COPD patients should guide the development of improved interventions and help clinicians learn who should be targeted.

3. Osteoporosis: Osteoporosis is among the major systemic comorbidities of COPD. Although the causal relationship and molecular link between COPD and osteoporosis remain to be established, recent epidemiological data clearly indicate that osteoporosis is highly prevalent in COPD patients. The National Health and Nutrition Examination Survey (NHANES) demonstrated a 16.9% prevalence of osteoporosis in 995 COPD subjects and 8.9% prevalence in 14,828 non-COPD subjects aged 45 years or older. Other cross-sectional studies comparing COPD patients with controls and population-based cohort studies have also estimated the COPD-associated risk of osteoporosis at approximately 1.5–2-fold. A large case-control study (108,754 cases) using UK general practice research database reported that crude OR (95% CI) for osteoporotic fractures was 1.61 (1.52–1.71) in COPD/asthma patients when compared with controls. Another more recent cohort study in UK estimated fracture risk in 3,142,673 primary care patients with various comorbidities and

reported that adjusted hazard ratio (95% CI) of COPD for hip fracture was 1.23 (1.16–1.31) in women and 1.34 (1.22–1.48) in men. Vertebral compression fractures were found in 41% of ambulatory patients with COPD.

COPD patients have several risk factors for osteoporosis, including advanced age, poor mobility, smoking, poor nutrition, low BMI and high doses of inhaled corticosteroids as well as courses of oral steroids. Systemic inflammation has also been proposed to underlie the causation of osteoporosis in COPD (Figure 2). There is a significant correlation between CT-measured emphysema and bone density, supporting the view that osteoporosis is related to emphysema. There is some evidence that osteoporosis is also associated with an increased risk of atherosclerosis and heart disease in patients without COPD. The association between osteoporosis and increased arterial wall stiffness as well as between these variables and the systemic level of IL-6 suggests a common association with the degree of systemic inflammation. Indeed, several inflammatory mediators, including TNF-α, IL-1β and IL-6 act as stimulants of osteoclasts, which cause bone resorption. Osteoclasts are regulated by a receptor activator of NF-κB (RANK) and the TNF-like RANK ligand, which synergize with TNF-α and are inhibited by osteoprotogerin, another TNF-like cytokine, which is regulated by TGF-β. Pro-inflammatory cytokines, IL-1β, IL-6 and TNF α, poor nutrition, vitamin D deficiency and oral steroid therapy add on to the risk of osteoporosis in COPD patients.

Osteoporosis results in further restriction of movement and increases the risk of vertebral compression fractures that could further compromise respiratory function. An additional contribution to the development of pulmogenic osteopenia comes from the body mass deficit, myopathy, organic physical activity and smoking. Vitamin D supplementation and calcium has been found to be effective in reducing fracture risk; the role of vitamin D as an immunomodulator is being investigated extensively for several respiratory disorders. Although some studies show benefits using bisphosphonates and the use of teriparatide is well established for glucocorticoid induced osteoporosis, there is a dearth of studies related specifically to COPD.

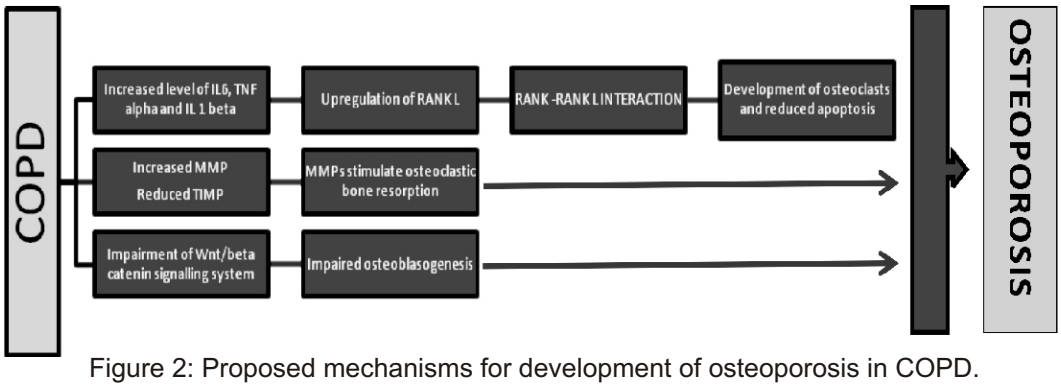

Figure 2: Proposed mechanisms for development of osteoporosis in COPD.

4. Diabetes and metabolic syndrome: A link between metabolic syndrome (MetS) and COPD has been observed in several cross-sectional and longitudinal studies and the syndrome has been identified as an independent risk factor for worsening respiratory symptoms, increasing lung function impairment, pulmonary hypertension and asthma. In a recent meta-analysis of 19 studies involving 4208 COPD patients, the pooled prevalence of MetS was 34%. Patients with MetS and COPD had higher body mass index (BMI), had

higher forced expiratory volume in one second (FEV1%) predicted and were more frequently females compared to controls. The prevalence of diabetes, a frequent accompaniment of MetS, in various studies in COPD ranges from 3 to 12%. Indian data are scant, with the prevalence ranging from 40 to 70% in few reported studies. A large, recent study involving more than 121,000 adult participants showed that MetS was associated with lower FEV1 or FVC when adjusted for confounding factors such as smoking, age/sex, education, physical activity or BMI.

The individual components of MetS, i.e., obesity, dyslipidemia, fasting hyperglycemia and hypertension were independently associated with impairment of lung function too, abdominal obesity having the strongest association. Obesity is associated with a decrease in expiratory reserve volume and functional, residual capacity due to its extrapulmonary restrictive component. Obesity can also perpetuate both systemic and pulmonary inflammation since excessive adipose tissue is able to produce various proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). There is a higher expression of inflammatory markers and adipokines such as leptin and adiponectin 3 in visceral fat. Dysregulation of adipokines, through their effects on bronchial hyper-reactivity and effect on airway epithelial cell receptors, is a potential mechanism for obesity-mediated airway changes in airway disease.

Adipokines could also play a role in MetS-mediated effects in lung function. Leptin may propagate pulmonary as well as systemic inflammation and together with resistin contribute to the pathogenesis of related dysglycemia. Fatty acid accumulation in MetS leads to potentiated inflammation that could prove to cause lung function impairment. Circulating levels of fatty acids are regulated by insulin-stimulated uptake and release of triglycerides and free fatty acids by adipocytes.

COPD is also associated with an increased risk of hyperglycemia. In the Nurses' Health Study that was conducted prospectively over an 8-year period, COPD patients had a 1.8 times risk of developing diabetes. Markers of inflammation such as IL-6, TNF-α and C-reactive protein (CRP) are elevated in both COPD and diabetes and these markers are elevated to a greater extent in overweight and obese COPD patients. Mannino et al. showed that cases with stage 3-4 COPD had a higher risk for developing diabetes with an odds ratio of 1.5. MetS may also increase the risk of COPD exacerbation with associated hyperglycemia, hypertriglyceridemia and CRP elevation.

Hypoxia may also modulate insulin resistance (IR) and detrimental effects on glucose metabolism in COPD cases through alterations in the hypoxia-inducible factor family. MetS also represents a risk factor for the development of all forms of pulmonary vascular disease and right ventricular (RV) dysfunction. Patients with pulmonary arterial hypertension exhibit an increased prevalence of glucose intolerance and IR, which is associated with changes in RV structure and function. The potential mechanisms by which MetS causes RV dysfunction include mitochondrial dysfunction with a shift in cardiomyocyte energy utilization from fatty acid oxidation to glucose which reduces the mitochondrial use of lipids, leading to cytoplasmic accumulation and deposition of lipid intermediaries, a condition known as "lipotoxic cardiomyopathy."

The pathogenesis of lung disease and MetS is multifactorial. The two share a number of risk factors including smoking, genetics, obesity, physical inactivity and airflow limitation. Systemic inflammation may probably be the common pathogenic mechanism responsible for genesis of COPD and its other comorbidities such as the MetS. However, recent data

from the ECLIPSE study showed a poor correlation between sputum neutrophils and severity of COPD; thus, there was no significant association with the severity of inflammation and the exacerbation rate of COPD. Even intervention studies in COPD-like monoclonal antibodies against IL-8 and anti-TNF-α antibodies - infliximab - do not significantly modify the local or systemic inflammatory mediators. These observations further shroud our understanding of the underlying pathogenetic mechanisms responsible for the development of MetS in COPD.

5. Lung Cancer: The annual risk of development of lung cancer is about 2-5 fold times higher in patients with COPD than in smokers with normal lung function. This risk is for development as well as poor outcome of the management of lung cancer. COPD is also found in about 40-70% of patients with lung cancer. The association between COPD is notably independent of patient age or extent of tobacco exposure. Although all lung cancer cell types occur in the setting of COPD, airflow obstruction has been specifically associated with increased risk for squamous cell carcinoma.

Chronic inflammation associated with COPD seems to play a seminal role in the pathogenesis of lung cancer. COPD and lung cancer both share common genetic risk factors and susceptibility genes shared by both diseases have been identified. Chronic inflammation may result in repeated airway epithelial injury and accompanying high cell turnover rates and propagation of DNA errors resulting in amplification of the carcinogenic effects of cigarette smoke. Others have postulated that impaired mucociliary clearance of carcinogenic substances from cigarette smoke, as a result of chronic airflow obstruction, increases exposure of the bronchial epithelium to these carcinogens and promotes pathologic changes leading to squamous cell neoplasia. Pro-inflammatory mediators and the gene regulating transcription factor nuclear factor (NF)-κB have also been implicated in tumor development and metastasis. Figure 3 depicts some of the hypothesized mechanisms of the association between COPD and lung cancer, highlighting the role of underlying genetic predisposition and environmental influences of smoking, recurrent infections, oxidative stress and chronic inflammation.

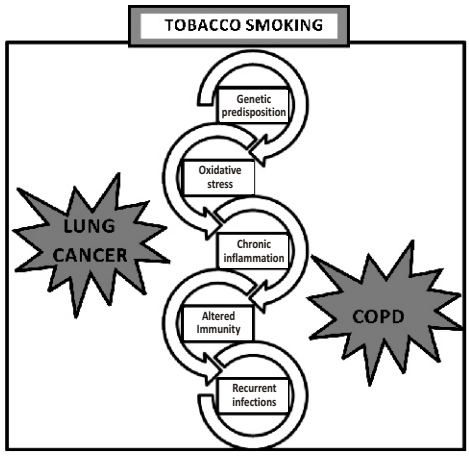

Figure 3. Complex interplay of hypothesized factors in the causation of lung cancer in COPD

Although, no specific recommendations exist for screening for lung cancer in COPD patients, lung function tests are routinely recommended at the time of diagnosis of lung

cancer in order to plan further management. As a result of the impairment of lung function, patients with COPD often do not meet traditional criteria for tolerance of definitive surgical lung cancer therapy. Emerging information regarding the physiology of lung resection in COPD indicates that post-operative decrements in lung function may be less than anticipated by traditional prediction tools. In patients with COPD, more inclusive consideration for surgical resection with curative intent may be appropriate as limited surgical resections or non-surgical therapeutic options provide inferior survival. Cessation of tobacco smoking remains a powerful intervention for preventing both the maladies, even as COPD has been increasingly reported among non-smoking individuals.

6. Anxiety and depression: Anxiety and depression significantly contribute to morbidity associated with COPD, primarily by impairing quality of life and reducing adherence to treatment. The incidence of depression in a longitudinal study involving 35,000 patients with COPD was 16.2 cases per 1000 person-years in the COPD group compared with 9.4 cases per 1000 person-years in the non-COPD control group. Those with severe COPD were twice as likely to develop depression compared to patients with mild COPD. The prevalence of clinical anxiety in COPD outpatients has been reported variously between 13% and 46%. The relationship between COPD and depression is likely to be bi-directional, as depression may be both a cause and a consequence of COPD. Depression and anxiety may lead to fear, panic and hopelessness, low self-esteem, social isolation and dependence on caregivers. Dyspnea, muscle weakness, increased dependency along with social isolation might be some of the factors that cause depression. This results in the initiation of a vicious circle that perpetuates anxiety and depression.

The exact mechanisms linking smoking and COPD with depression and anxiety have, however, not been identified. Low-grade chronic inflammation is believed to play a major role in the pathogenesis as increased inflammatory markers have been documented in both late-life depression as well as COPD. Left untreated comorbid anxiety and depression in patients with COPD have devastating consequences, overwhelm their coping strategies their caregivers and increase healthcare utilization. Recent data have emerged that have shown promise in reducing anxiety and depressive symptoms in COPD by employing pulmonary rehabilitation, smoking cessation, and psychological and antidepressant drug therapy.

7. Sleep disturbance and obstructive sleep apnea syndrome (OSAS): Sleep disturbance in COPD patients has been a cause of concern since a long time. It has been found by means of sleep questionnaires with or without polysomnographic evaluation that subjects with COPD sleep poorly. Impaired quality of sleep was observed in some studies that showed a decrease in total sleep time, reduced efficacy and reduced REM sleep, leading to more anxiety and depression. It would be interesting to note that daytime sleepiness was not as common in COPD. OSA was found in 10% of people with COPD while COPD was present in about 20% of the OSA cohort. OSAS in COPD causes nocturnal hypoxia and nocturnal desaturation leading to development of pulmonary hypertension and more frequent heart failure. It is thus responsible for frequent hospitalizations, increased morbidity and mortality. COPD may coexist with OSA (overlap syndrome). Patients with overlap syndrome have a higher risk of cardiopulmonary disease, and OSA may contribute to the development of IR and hyperglycemia. Several mechanisms are believed to contribute to the pathogenesis of OSA-related IR: sleep fragmentation and intermittent hypoxia, inflammation and oxidative stress and enhanced sympathetic output. Even as the understanding of how OSA might lead to IR and overt type 2 diabetes mellitus (DM) are far

from complete, OSA should be considered as an independent risk factor for the development of type 2 DM and when coexisting with COPD, the risks are likely to be higher. In this regard, a recent meta-analysis performed by Yang et al. supported the beneficial effects of CPAP on the glucose metabolism.

8. Anemia: Anemia is found to be present in about 15- 30 % of cases of COPD, especially in the severe disease group as opposed to polycythemia which is found only in 6%. Anemia contributes significantly to functional impairment and reduced exercise capacity. In some reports, anemia has also been a predictor of mortality in patients with COPD. Malnutrition, age and cardiovascular disease are confounding factors for the development of anemia. The anemia is usually normochromic and normocytic type that is characteristic chronic disease and appears to be due to resistance to the effects of erythropoietin, the concentration of which is elevated in these patients. It is unclear if the treatment of anemia will result in improvement in functional outcome measures. Treatment with erythropoietin is likely to be little benefit due to end organ resistance and as such blood transfusion may be necessary. Indeed a small study in anemic COPD patients showed that blood transfusion improved exercise performance.

9. Chronic kidney disease: Patients with COPD and chronic kidney disease (CKD) share common risk factors. However, there is limited information about COPD and CKD. In a recent case control study using the Taiwanese National Health Insurance Research Database, the overall incidence of CKD was higher in the COPD group (470.9 per 10(4) person-years) than in the non-COPD group (287.52 per 10(4) person-years). The adjusted hazard ratio of case was 1.61 (P□<□0.0001) times that of control. These findings suggest that patients with COPD should also be monitored for renal disease.

Conclusion:

COPD is a complex disorder caused by the complex interplay of chronic inflammatory processes initiated by tobacco smoke or biomass fuel exposure. The presence of comorbidities and other systemic effects results in a poor quality of life, exacerbations and mortality. The intensity and repetition of exacerbations of health related events adds to the financial burden of the patient and the health care system. Apart from smoking cessation and physical exercise, observational and epidemiological studies have suggested that some treatments directed at inflammation, such as statins and angiotensin converting enzyme (ACE) inhibitors, used for comorbid diseases, may apparently benefit COPD, with a reduction in exacerbations and mortality. Several alternative anti-inflammatory approaches are currently being investigated. These drugs have largely been developed as systemic treatments and would therefore be expected to reduce systemic inflammation and perhaps treat systemic manifestations of COPD, such as skeletal muscle weakness and osteoporosis. Newer targets aimed at various components of the inflammatory cascade in COPD are being investigated for potential benefits in this exorable progressive disease.

Further reading:

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14

Cor- Pulmonale: Misdiagnosed and Mismanaged Entity

Dr. Mridul Mahanta, Dr. Gurpreet Singh Wander

Introduction:

Cor Pulmonale (CP) is the alteration of right ventricular structure and or function that is due to pulmonary hypertension (PHTn) caused by diseases affecting the lung or its vasculature. It excludes right-sided heart disease from primary disease of the left side of the heart or congenital heart disease.[1] It is often seen in clinical practice to misdiagnose CP and treating right heart failure without entertaining the underlying cause, causing mismanagement leading to ineffective treatment and even undue side effect and mortality in this common cardiovascular disease. This article stresses upon proper diagnosis and management of CP and highlights the probable mistakes in these two aspects.

Table I : Major causes of cor-pulmonale

Lung disease • Chronic obstructive pulmonary disease • Cystic fibrosis • Interstitial lung diseases
Disorders of the pulmonary circulation • Pulmonary thromboembolism • Primary pulmonary hypertension • Tumour emboli • Sickle cell anaemia • Schistosomiasis • Pulmonary veno-occlusive disease
Neuromuscular diseases • Amyotrophic lateral sclerosis • Myasthenia gravis • Poliomyelitis • Guillain-Barre syndrome • Spinal cord lesions • Bilateral diaphragmatic paralysis
Thoracic cage deformities • Kyphoscoliosis
Disorders of ventilatory control • Primary central hypoventilation • Sleep apnea syndromes

Pathophysiology:

CP is a state of cardiopulmonary dysfunction that may result from several different aetiologies and pathophysiologic mechanisms (table I):

1) Pulmonary vasoconstriction (secondary to alveolar hypoxia or blood acidosis).
2) Anatomic reduction of the pulmonary vascular bed (emphysema, idiopathic pulmonary fibrosis, pulmonary emboli, etc.).
3) Increased blood viscosity (polycythaemia, sickle-cell disease, etc.).
4) Increased pulmonary blood flow.

Diagnosis:

Symptoms of CP:

• Directly attributable to PHTn:
  – Dyspnea on exertion, fatigue, lethargy.
  – Chest pain, syncope with exertion.
• Typical exertional angina:
  – Occurs in patients with primary or secondary PHTn even in absence of epicardial CAD.
  – Subendocardial RV ischemia induced by hypoxemia and increased transmural wall tension.
  – Dynamic compression of left main coronary by enlarged PA.
• Less common:
  – Cough, hemoptysis, hoarseness.
• With severe right ventricular (RV) failure:
  – Passive hepatic congestion.
  – Anorexia, right upper quadrant discomfort.

Physical findings:

• Cardiac findings:
  - RVH.
  - Prominent A wave in the jugular venous pulse (JVP) with right sided 4th heart sound.
  - RV failure leads to systemic venous HTn.
  - Elevated JVP with a prominent V wave, RV S3, high pitched tricuspid regurgitant (TR) murmur.
• Extra cardiac changes:
  - Hepatomegaly, pulsatile liver, peripheral edema often related to hypercarbia and passive Na+ and water retention.
• Other areas of fluid retention:
  - Pleural effusion, often bilateral.
  - Engorged inferior vena cava.
  - Hepatic congestion.
  - Ascites.
  - Anasarca.
• Jugular pulsations:
  - May also be elevated in heart failure and renal failure, but not cirrhosis.
  - Hepatojugular Reflux.
  - In RHF sustained elevation.
- Low specificity and sensitivity

Table 2:

Disorder	Pulmonary edema	Central venous pressure	Ascites and/or pedal edema
Left-sided heart failure	+	Variable	-
Right-sided heart failure	-	Variable	+
Cirrhosis	-	Normal	+
Renal disease	Variable		+
Nephrotic sysndrome	-	Variable	+
Idiopathic edeme	-	-Normal	+
Venous insufficiency	-	Normal	+ edema may be asymmetric

Symptoms & Signs – Acute cor pulmonale:

- Sudden onset of severe dyspnea and cardiovascular collapse.
- Occurs in the setting of massive pulmonary embolism (PE).
- Pallor.
- Sweating.
- Hypotension.
- Rapid pulse of small amplitude.
- Neck vein distention.
- Pulsatile distended, tender liver.
- Systolic murmur of tricuspid regurgitation along the left sternal border.
- Presystolic (S4) gallop.

Evaluation of cor pulmonale: [2]

- Laboratory CBC, chem. test, LFT's, BNP.
- Chest radiograph.
- Electrocardiogram.
- Two D and Doppler echocardiography.
- Pulmonary function tests.
- Radionuclide ventriculography.
- Magnetic resonance imaging.
- Right heart catheterization.
- Lung biopsy.

Radiograph and cor pulmonale:

- Enlargement of Central PA's.
- In 95% of Pts with PHTn from COPD the diameter of the descending branch of the right PA is > 20 mm in width.
- Peripheral vessels are attenuated leading to peripheral oligemia.

RV failure may result in RV and right atrial (RA) dilatation on chest radiography. RV enlargement can also lead to a decrease in the retrosternal space. However, these findings may be obscured in the presence of kyphoscoliosis, hyperinflated lungs, left ventricular enlargement or interstitial lung disease (ILD).

Electrocardiogram:

May demonstrate signs of RV hypertrophy or strain. Findings that may be seen in chronic RV overload include:

- Right axis deviation and R/S ratio greater than 1 in lead V1.
- Increased P wave amplitude in lead II (P pulmonale) due to RA enlargement.
- Incomplete or complete right bundle branch block (RBBB).
- In acute cor pulmonale, such as occurs with acute PE, a classic pattern of an S wave in lead I with a Q and inverted T wave in lead III may be seen.

Most electrocardiographic criteria show a high specificity (i.e., the findings are absent in patients without the disease) but a low sensitivity (i.e., the findings are present in patients with the disease) for the detection of RVH. The sensitivity of the electrocardiogram is even worse in patients with biventricular hypertrophy or COPD, but the presence of electrocardiographic changes of CP in these settings connotes a poor prognosis.[3]

2D and Doppler Echocardiography:

It is the most reliable noninvasive estimate of the Pulmonary Artery Pressure (PAP), more sensitive as PAP increases. The elevation in pressure leads to increased thickness of the RV with paradoxical bulging of the septum into the LV during systole. At a later stage, RV dilatation occurs, and the septum shows abnormal diastolic flattening.

The efficacy of doppler echocardiography may be limited by the ability to identify an adequate tricuspid regurgitant jet. It may also be less sensitive because of alterations induced by the underlying disease. For example, acoustic windows in patients with COPD may be limited by the increased antero-posterior diameter of the chest. Echocardiographic CP was said to be present when the RV free wall thickness was > 0.6 cm in the sub-xiphoid view, PA systolic pressure was greater than 40 mmHg by tricuspid jet Doppler with saline contrast, and the RV/LV ratio was increased. CP was identified by clinical criteria in only 39% of patients versus 75% with echocardiography. The use of saline contrast significantly enhanced the sensitivity of Doppler ultrasound in detecting tricuspid regurgitation.

Table 3

RHF without pulmonary hypertension	Cor pulmonale/pulmonary hypertension present
Chest x-ray: Enlargement of pulmonary arteries (uncommon), olligemic peripheral lung fields (rare) Echocardiography: No evidence of increaased pulmonary pressure. Septal flattening during diastole but not systole	Chest x-ray: Right-sided cardiac enlargement, enlargement of pulmonary arteries, oligemic peripheral lung fields Echocardiography: Evidence of increases pulmonary pressure. Septal flattening during systole Physical examination: Evidence of underlying pulmonary pathology if cor pulmonale present (but not in primary PAH)
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Right sided cardiac catheterization:

Right sided cardiac catheterization is the gold standard for the diagnosis of CP.

Indications includes:

- When echo does not permit measurement of TR,
- When symptoms are exertional and left sided pressures are unremarkable,
- When therapy will be determined by precise measurement of pulmonary vascular resistance (PVR) and the response to vasodilators,
- When left heart catheterization is also required (patients > 40 y/o and or with CAD).

Misdiagnosis:

1) Clinical detection and assessment of CP are difficult due to the subtle and often non-specific signs and symptoms. The development of peripheral oedema in COPD is not necessarily a reliable marker of PTHn and CP. Hypoxia, hypercarbia and compensatory increase in bicarbonate level can cause salt and water retention causing edema. CP leading to right heart failure occurs late in age and in these older patients ankle edema frequently results from decreased cardiac output with subsequent salt and water retention rather than from increased venous pressure secondary to right heart failure.
2) Left sided heart diseases causing PHTn can be misinterpreted. They are:
   - Left ventricular systolic dysfunction,
   - Left ventricular diastolic dysfunction,
   - Valvular diseases,
   - Congenital/acquired left sided heart inflow/outflow tract obstruction.

PHTn as a consequence of left ventricular systolic dysfunction, aortic and mitral valve disease and cor triatriatum is often recognized because of the distinct clinical and echocardiographic patterns of these phenotypes. Recognition of PHTn as a result of HFpEF is more challenging and HFpEF is commonly mistaken for IPAH. Table 4 highlights some of the features that can help distinguish PHTn caused by HFpEF from group 1 PAH.

Table 4

Characteristic	PAH more likely	HFPEF more likely
Age	Younger	Older
Comorbid conditions- DM, HTN, CAD, obesity (metabolic syndrome)	Often absent	Often multiple present
Symptoms-PND, orthopnea	Often absent	Often present
Cardiac examination	RV heave, loud P2, TR murmur	Sustained LV implulse, LS4
CXR	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	RAD, RVE	LAE, LVE, atrial fibrillatilon, no RAD
Natriuretic peptides	Often elevated	Often elvated
Echo-LAE, LVH	Absent	Often present
Echo-diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echo-right ventricle	Often enlarged, may share the apex	Often normal, mildly enlarged
Echo-pericardial effusion	Sometimes	Rare

3) Nephrotic syndrome, cirrhosis of liver and renal failure can cause significant fluid overload and should be excluded by careful clinical history, ECG, echocardiography and other diagnostic tools.
4) In the patient with obvious failure of the right side of the heart in whom edema, distended neck veins, ascites, hepatomegaly and cyanosis are present-the diagnosis of CP is made without hesitation. However, enlargement of the RV is often a late sign in patients with CP. In the absence of heart failure the heart size is likely to be normal; even if present, enlargement of the various cardiac chambers cannot be determined by physical examination in the patient with severe chronic pulmonary disease. The presence of an accentuated pulmonary second sound and a forceful subxiphoid pulse should be viewed with suspicion.[2] Probably the most important clinical symptom of PHTn is fatigability; the most characteristic symptom of heart failure and COPD without PHTn itself. In this situation CP may be under-diagnosed.
5) In patients with COPD, pulmonary hypertension may not be present at rest but right ventricular dysfunction is there which can be explained by increased pulmonary pressure during exercise and nocturnal hypoxia common in these patients. So, patients with mean PAP between 15 to 25 mm HG should be treated to prevent right heart failure.[4]

Management:

Management of CP depends upon management of underlying cause of PHTn. Mismanagement occurs if we don't identify or treat the underlying cause and mechanism. Management revolves around following factors:

1) Identification of underlying cause.
2) Relief of pulmonary vasoconstriction.
3) Decongestive therapy.
4) Vasodilators.

Modern concepts of therapy in chronic CP or heart disease secondary to lung disease have developed largely as a result of increased knowledge of the physiologic disturbances in pulmonary function which give rise to the circulatory sequelae in these diseases. Since the cardio circulatory complications spring from the underlying pulmonary dysfunction, therapy, if it is to be successful, must be directed at the former as well as at the latter. The older pessimistic attitude concerning therapy in these patients resulted from attacking exclusively or primarily the cardiac insufficiency to the neglect of the parent entity, pulmonary insufficiency.

Hence one can say that treatment of chronic CP really begins with a correct diagnosis of the lung disease causing it. Prognosis of the ultimate outcome is also dependent upon accurate diagnosis. One cannot outline the same therapy for a patient with pulmonary fibrosis as for one with pulmonary emphysema as far as improvement of pulmonary function is concerned. On the other hand the treatment of right heart failure consists of much the same regimen in both cases.

Although there are many forms of lung disease which can secondarily compromise the circulation and produce chronic CP, the commonest include chronic obstructive pulmonary emphysema, different types of pulmonary fibrosis and granulomatous lesions which may eventually result in fibrosis. Rarer types of chronic pulmonary hypertension such as those due to pulmonary emboli or secondary to pulmonary metastases when diagnosed are treated with strategy for each disease.

Chronic cor-pulmonale due to chronic pulmonary emphysema:

There are three fundamental disturbances in pulmonary function in chronic pulmonary emphysema:

(1) There is gross impedance to air flow in and out of the lungs,

(2) The air is unevenly distributed to the alveoli,

(3) The blood returning to the lungs is similarly unevenly distributed to the alveoli.[5-7]

At the present time it is not possible to attack the latter dysfunction therapeutically. Means are available, however, which permit us to remedy the first two abnormalities. The inadequate air flow is caused not only by loss of elasticity of the lung tissue, but also by bronchiolar spasm and mucosal edema and by obstruction resulting from secretions and exudates. Vaporized bronchodilators are often quite effective in alleviating the symptoms due to bronchial obstruction. Bothersome secretions and exudates so often encountered in the patient with emphysema generally result from either acute or chronic pulmonary infections and may be combated by the intensive use of antibiotics given in a variety of ways. In these patients they do not tolerate well any further encroachment upon their pulmonary reserve. The loss of even a small area of functioning lung tissue as a result of bronchial or pulmonary infection may be sufficient to precipitate severe pulmonary insufficiency.

The majority of patients with emphysema, however, do not present only simple ventilator insufficiency. At some time in their disease more severe ventilatory dysfunction, coupled with gross disturbance in distribution of air and blood to the alveoli, leads to alterations in gas exchange, with resulting anoxia and hypercapnia. In some individuals, anoxia with or without carbon dioxide retention is only seen with acute pulmonary infections and subsides with the alleviation of the infection. In others, of course, the disease process itself is more advanced or is associated with frequent and severe attacks of bronchiolar spasm; hence anoxia and hypercapnia of varying degree are constantly present. It is when anoxia and hypercapnia becomes a dominant feature of emphysema that the circulatory complications may appear, i.e., PHTn, hypervolemia with polycythemia and right heart failure.

Unfortunately many of the patients with chronic pulmonary emphysema and CP are not seen by a physician until heart failure is present. Then one is faced with a most difficult therapeutic problem, namely, the management of the patient with advanced pulmonary emphysema who enters the hospital acutely ill, intensely cyanotic, coughing ineffectively, bringing up with difficulty thick tenacious sputum, oxygen must be supplied. In a certain group of these subjects whose interference with gas exchange has produced anoxia without hypercapnia, this is not hazardous and administration of oxygen by mask, tent or nasal catheter rapidly alleviates the symptoms and signs of oxygen want.[8] In others, however, where alveolar hypoventilation is marked and carbon dioxide retention is present in addition to anoxia, the respiratory response to carbon dioxide is known to be diminished and anoxia, operating through the carotid body chemoreceptors, remains the primary stimulus to breathing. The increase in arterial blood oxygen tension following oxygen therapy results in a further marked reduction in alveolar ventilation and hence a further rise in carbon dioxide tension and bicarbonate levels in the blood. Eventually the carbon dioxide retention may lead to narcosis and even death. Thus in all emphysematous patients one should always determine the carbon dioxide content of the arterial blood before starting oxygen therapy and if there is hypercapnia, employ some mechanical means mostly non invasive ventilation to maintain adequate alveolar ventilation while oxygen is being supplied.

During the acute episodes of cardiac and pulmonary insufficiency the patient should use these mechanical ventilatory aids as much as 18 to 20 hours a day. The use of vaporized bronchodilators make these aids more effective. It generally requires 10 days to 2 weeks of intensive treatment to achieve a state in which the respiratory aids are no longer essential. Since every effort is being made to improve ventilation and to clear the respiratory passages of secretions in the presence of a poor cough mechanism, it is obvious that the use of morphine, codeine and barbiturates is contraindicated and if used in some subjects may be fatal. The anatomic restriction of the pulmonary vascular bed is, of itself, generally not sufficient to produce anything but minimal PHTn at rest in the emphysematous patient. When anoxia and hypercapnia appear there evolves the classic picture of CP, severe PHTn, polycythemia, high cardiac output and ultimately right heart failure.[8,9]

The specific cardiac therapy of the patient in failure with chronic CP is the same as would be used in heart failure due to other forms of heart disease, that is low salt diet and, when necessary, diuretics. The polycythemic state of these patients is disadvantageous because it promotes an increased venous return to a failing RV and also plays a role in maintaining and exaggerating PHTn. In these patients, when the lesser circulation becomes abnormal, an increased blood flow and polycythemia cannot be considered as advantageous homeostatic responses directed towards the satisfaction of tissue oxygen needs in the presence of anoxia, as they are in normal man. Therefore, it is imperative to reduce blood flow and blood volume by means of phlebotomies.

If pursued unremittingly, all these measures will result in improved pulmonary function, reduction in and even abolition of PHTn at rest and relief of the right heart failure. In fact the problem of heart failure, per se, can almost invariably be resolved in these subjects. When heart failure persists despite the measures discussed above, one should reconsider the diagnosis as it is unlikely that emphysema alone is the primary cause of the difficulties.

Maintenance Therapy:

Once the patient has recovered from the acute episode of cardiopulmonary insufficiency, all efforts are directed at maintaining him free of circulatory complications and in as optimal a state of pulmonary function as is possible with modern methods. These patients should be followed regularly and at frequent intervals.

One can obtain essential information concerning pulmonary function from analysis of the arterial blood for its oxygen saturation and carbon dioxide content, associated, if possible, with a determination of arterial pH, so that carbon dioxide tension can also be calculated. If the emphysematous patient with CP is doing well, there are only minor fluctuations in arterial blood oxygen saturation and carbon dioxide content as determined at rest under basal conditions. The frequency with which these determination is need to be made depends upon many factors and may vary from every two to six months depending upon the severity of the individual patient's disease and the occurrence of complications. The oxygen saturation may vary as much as 10% on repeated monthly samplings but is usually found to be above 80%, the carbon dioxide tension generally lies in the range of 45 to 55 mmHg when the patient is well controlled. Variations in carbon dioxide tension are much smaller than variations in arterial oxygen saturation and hence a change of 5 mmHg or more in this measurement in the individual patient is highly significant. It is necessary to obtain such data because it is often difficult to demonstrate changes in the patient's condition by clinical examination alone. The acute respiratory infection may be clinically imperceptible and gradual change which is uncovered only by serial laboratory determinations. The gradual decline in pulmonary

function is reversible by an intensification of the therapeutic pulmonary regime. These individuals, who are already using nebulizer regularly, are advised to use it frequently. Antibiotics are used vigorously even if the subject is afebrile.

Chronic cor-pulmonale due to pulmonary fibrosis:

The location and distribution of anatomic lesions in all the various forms of pulmonary fibrosis determine in large measure the degree of circulatory involvement to be expected. The process must be generalized and located in such a way as to encroach upon all the pulmonary vasculature either by restricting its expansibility by collar like perivascular lesions or by actual reduction in the number of the functioning vessels.

1) In silicosis it has long been known that the pulmonary dysfunction may remain one of ventilatory insufficiency without arterial anoxia for long periods of time. Anoxia is seldom severe in silicosis unless the disease is far-advanced or associated with emphysema.
2) In that group of rarer diseases which produce pulmonary lesions located in the pulmonary alveolar-capillary membrane and which are characterized by difficulty of oxygen diffusion the term "syndrome of alveolar-capillary block" has been proposed which include various granulomas of the lung (due to exposure to beryllium, Boeck's sarcoid and of undetermined origin), scleroderma and the diffuse reticular pulmonary fibroses. In these patients mild PHTn is due to anatomic restriction of the vascular bed and not to anoxia, is common at rest, increases with exertion, and in some instances may even be progressive. Hence in the patient presenting this syndrome the anatomic lesion is the fixed and dominant factor and the compromising of the right heart at first minimal, later in the disease severe is irreversible.

It is obvious then that therapy in cardiac failure due to chronic pulmonary fibrosis or pulmonary granulomas, with their irreversible PHTn, cannot be expected to be as beneficial or successful as in CP due to emphysema. Polycythemia is not a frequent complication but if present should be relieved. Obviously attention to pulmonary infection is of great importance.The use of oxygen by the usual clinical means is satisfactory as long as there is no complicating pulmonary emphysema with its dangerous hypercapnia.

There is as yet little direct therapy for the primary pulmonary disease in patients with some form of fibrosis. It is reasonable to suggest that until better circulatory studies are available in all forms of pulmonary fibrosis physical exertion should be curtailed, as it is only by maintaining as low a level of pulmonary artery pressures as possible that right heart strain can be minimized.

To summarize, the prognosis in a patient with chronic CP due to some form of pulmonary fibrosis or granulomas is poor as compared with the subject with pulmonary emphysema as his primary disease.

Diuretics:

If right ventricular filling volume is markedly elevated, diuretic therapy could improve the function of both RV and LV the latter effect being achieved as left ventricular diastolic filling is enhanced through reduction in dilation of the RV. As a result, diuretic therapy could improve cardiovascular performance in some patients with significant volume overload of the RV. However, excessive volume depletion must be avoided, since a drop in cardiac output may result if right ventricular filling volume and pressure are reduced too dramatically in PHTn. A

simple method to assess volume status is to monitor the BUN and plasma creatinine concentration. As long as these parameters remain stable, it could be assumed that renal perfusion and therefore flow to other organs are being maintained. Another potentially important complication of diuretic therapy in CP is the development of metabolic alkalosis. Alkalosis suppresses ventilation, which can have important implications in severe lung disease, e.g., leading to difficulty in weaning from a ventilator.

Digoxin:

Except in cases of co-existent left ventricular failure, clinical studies do not support the use of digitalis in patients with CP. Specifically, the use of digoxin in COPD patients with normal left ventricular function does not improve right ventricular ejection fraction at rest or during exercise, nor does it increase maximal exercise performance.

Vasodilators:

Several vasodilator agents (including hydralazine, nitrates, nifedipine, verapamil and ACE inhibitors) have been utilized in an attempt to ameliorate PHTn. In some studies, short-term but modest reductions in pulmonary artery pressure have been documented. However, vasodilators generally do not result in sustained or significant improvement and maybe associated with adverse side effects. The use of vasodilators in patients with COPD can be associated with worsening of arterial oxygenation and/or systemic hypotension, although these effects usually are not severe. Overall, therefore, the use of vasodilator medications for patients with COPD has generally dropped from routine clinical practice. Nevertheless, patients with severe and persistent PHTn despite oxygen and bronchodilator therapy may be candidates for a trial of vasodilator therapy. In this setting, right heart catheterization is recommended during the initial administration of the vasodilator either sustained release nifedipine (30 to 240 mg/d orally, sustained release) or diltiazem (120 to 720 mg/d orally, sustained release) is recommended in order to objectively assess efficacy and detect possible adverse haemodynamic consequences. A reduction in pulmonary vascular resistance of more than 20 % (provided that cardiac output does not decrease and pulmonary artery pressure does not increase) is a reasonable criterion that has been suggested as evidence of efficacy.

Theophylline and sympathomimetic amines:

Theophylline and sympathomimetic amines (terbutaline) may have salutary effects not related to bronchodilation.

These agents may:

1) Improve myocardial contractility.
2) Provide some degree of pulmonary vasodilation.
3) Enhance diaphragm endurance.

Such effects may explain why some patients treated with theophylline, for example, experience a reduction in dyspnoea (as documented in at least one double-blind trial) even without a reduction in airflow obstruction.

Mismanagement:

The major areas of mismanagement are –

1) Improper diagnosis.
2) Not treating the primary cause.
3) Injudicious use of oxygen, diuretic, vasodilators and digoxin.

Summary:

To summarize, we have to remember that major contributor to CP is COPD followed by pulmonary fibrosis. But major cause of right ventricular failure is due to left sided heart diseases. Hence the later should be excluded first to confirm the diagnosis. PHTn and acute PE accounts for lesser no of CP but by consideration of their high incidence in population should be taken into account in evaluating cause of CP.

In emphysema, we are fortunately able to reverse two features of the pulmonary insufficiency, anoxia and carbon dioxide retention, which are of paramount importance in producing the salient circulatory complications, that is PHTn, hypervolemia, right heart failure. By vigorously combating anoxia and hypercapnia, it is possible to reverse these circulatory abnormalities and prevent their recurrence. If the premonitory signs of increasing anoxia and hypervolemia are present and proper therapy instituted, it may even be possible to prevent an initial episode of heart failure in the emphysematous subject.

In patients with pulmonary fibrosis as well as those with granulomas of the lung the anatomic lesions are for the most part irreversible, so is the PHTn. This has limited our therapeutic approach in this form of chronic CP to rigorous restriction of physical activity directed at minimizing exacerbations of PHTn.

While emphasis has been placed upon the difference in management of the patient with emphysema or fibrosis and CP, nonetheless it should be remembered that in any individual patient these two conditions may coexist. In that event, intensive therapy directed at the sequelae of emphysema maybe very rewarding.

In acute CP due to PE and chronic CP due to Primary PAH management is specific and chance of being mismanaged is not there if guidelines are followed. So, understanding the pathophysiology of CP, proper diagnosis is the cornerstone in preventing mismanagement if this disease.

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"Don't die by your weaknesses, live through your strengths"
– Marl S. Kerr

15

COPD Prognostic Factors and Prognostic Indices

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Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease, with high impact on health care system in terms of mortality and morbidity. It is characterized by progressive decline in lung function and progressive airway inflammation, degree of airflow obstruction is generally considered to be the key factor for staging COPD severity and to guide and monitor treatment.[1] However, (pharmacological) interventions to both stabilize the progression of airflow obstruction and reduce premature mortality are disappointing.[2-4] Currently, there is a growing recognition that COPD should no longer be regarded as a synonym for airflow obstruction alone, but instead as a multidimensional condition that comprises several phenotypes.[1,5-8] In addition, patients tend to die from other diseases than COPD.[9]

Thus there are other factors other than airflow limitation having high impact on COPD outcome, identified and used in prognostic indices, include age, gender, degree of dyspnea, body mass index, exercise capacity, hypercapnea, bronchodilator response, cardiovascular comorbidity, acute exacerbations and airway bacterial load . C-reactive protein is a strong and independent predictor of future COPD outcome in individual with airway obstruction.

Pulmonary function test:

Since several decades natural history of COPD have been studied to identify prognostic factors, majority of them found that pulmonary function test is best predictor for prognosis. Most studies confirmed that FEV1 is strong predictor of survival. In a sentinel study, Burrows and Earle examined long-term survival in 200 patients with an initial FEV1 < 60% predicted.[11] Indices of ventilatory capacity were the most predictive of survival.

A longer-term follow-up of the same patients and an additional 100 patients confirmed that the FEV1 percent predicted after the administration of a bronchodilator was the best predictor of long-term survival.[12] Two large North American studies [the Nocturnal Oxygen Therapy Trial (NOTT) and the Intermittent Positive Pressure Breathing Trial (IPPB)][13,14] also suggest that FEV1 is good predictor.

Diffusing capacity:

A decreased diffusing capacity (DLCO) has been suggestive of a decreased survival in some studies.[12,15-17] in the early Chicago series of Burrows and colleagues a decreased DLCO was weakly predictive of mortality in univariate but not multivariate analysis.[11] In contrast, Boushy et al noted that those patients with a DLCO < 3 mL/min/mm Hg had significantly worse 3 and 5-year survival.[16] In multiple regression analysis, DLCO remained a predictor of mortality after adjusting for FEV1. In an analysis of 140 patients with chronic airflow limitation (CAL) (76% with a DLCO >80% predicted), a decreased DLCO was predictive of worsened survival

in multivariate analysis.[17] In contrast, analysis of the large IPPB trial database (mean DLCO 49% predicted) did not identify DLCO as a predictor of mortality in stepwise, multivariate analysis. As such, a decreased DLCO may be an additional predictor of mortality in patients with severe chronic airflow obstruction, although a clear threshold value for individual patients is difficult to establish.

Arterial Blood Gases:

In numerous investigators have confirmed that a low paO2 is associated with decreased survival in COPD.[10,18] The difference in survival between various cohorts of COPD patients has been attributed, in part, to the negative effects of hypoxemia, particularly in early studies where LTOT was not routinely employed.[10,14] According to Anthonisen, if hypoxemia is treated with continuous oxygen therapy, the outlook of these patients appears to be no different from those with similar obstruction, but without baseline hypoxemia.[14] This argument has been supported by an analysis of the Association Nationale pour le Traitement a Domicile de 1'Insuffisance Respiratoire (ANTADIR) Observatory where long-term survival in patients with a paO2 >60 mm Hg was not different than those patients with more severe hypoxemia treated with LTOT. Importantly, those patients with the worst initial paO2 (<50 mm Hg) had a significantly worse prognosis despite LTOT. As such, hypoxemia is likely a weak predictor of mortality, particularly in those with more severe baseline hypoxemia, although much of the detrimental impact can be abrogated by the use of LTOT.

A stronger argument can be made that an elevated paCOa is an independent predictor of mortality in COPD.[10] "CO2 retention" was noted to be an independent predictor of mortality by one group.[17] Similarly, a worse prognosis was noted in COPD patients with a paCOa >48 mm Hg.[16] This persisted in patients with an FEV1 above or below 0.75 liter. In addition, patients presenting with hypercarbia (paCO2 >50 mm Hg) during an exacerbation experience significant mortality during long-term follow-up (11% hospital, 20% 60-day, 43% 1-year, and 49% 2-year).[19]

Exercise capacity:

Overall impairment in functional status has been associated with impaired survival in COPD. Several investigators have noted worse survival in COPD patients with a lesser exercise capacity.[10] This has been recently confirmed by Strom who noted an increased mortality in those patients with a poor overall performance status.[20] Petty and Bliss analyzed pedometer data quantifying the daily exercise capacity during the initial 3-week stabilization period prior to randomization in the NOTT.[21] Those patients classified as achieving a "low" walk distance (< 3950 feet/day) had a worse survival than those classified as the "high walking group."

In multivariable analysis that included demographic features, body mass index (BMI) and pulmonary function, a longer post rehabilitation 6-minute walk distance and higher post rehabilitation functional activity were strongly predictive of improved survival. As such, impaired exercise capacity despite maximal pulmonary rehabilitation is independent of factors associated with poor survival. A value of 300 to 500 feet during a 6-minute walk test may be an appropriate threshold.[22]

The prognosis of COPD associated with alpha1-antitrypsin deficiency (alpha 1-ATD) has been examined in great detail. In an early study from Sweden, Wu and Eriksson analyzed mortality in 158 adults with severe alpha 1-ATD (mean FEV1 50.3% predicted).[23] Three-year mortality was 40% in those with an initial FEV1 <30% predicted compared to 93% when the FEV1 was between 30 and 65% predicted.

Recent data suggest that females with COPD may have a better prognosis than males.[24] In addition, comorbidities strongly influences survival in COPD patients. Incaizi et al described survival in consecutive patients discharged after an acute exacerbation of COPD.[25] The most common comorbidities included hypertension (28%), diabetes mellitus (14%), and ischemic heart disease (10%). The nutritional status has been demonstrated to strongly influence COPD prognosis.[26,27] Most recently, in a population-based study of COPD patients identified in the Copenhagen City Heart Study, BMI was an independent predictor of mortality.[27] This association was particularly strong in those patients with the most severe COPD. As such, a low BMI appears to be an independent feature negatively affecting prognosis in COPD.

Several among these prognostic factors are combined in prognostic indices and used to assess the severity, monitoring, decision making and risk stratification. To date, 15 prognostic indices for COPD patients have been reported since the publication of the BODE (body mass index, obstruction, dyspnea and exercise) index in 2004. All indices except one were developed or enhanced for clinical use. However, in current COPD guidelines, airflow obstruction is still the only structured measure that guides clinicians on treatment decisions, along with information on patients' subjective wellbeing at the time of their visit. COPD stages by GOLD guidelines stratify patients with chronic obstructive pulmonary disease according to the severity of dyspnea and FEV1 levels. There are five stages numbered in Roman numerals with 0 being the least severe and stage IV being the most severe with predominant dyspnea and chronic respiratory failure:

- Stage 0: no diagnosis but at risk with chronic cough and sputum production present but with normal spirometry.
- Stage I: mild COPD characterized by mild airflow limitation (FEV1/FVC less than 70% but FEV1 80% or more than predicted).
- Stage II: moderate COPD, indicated by worsening airflow limitation (FEV1 50-79% predicted) and usually progression of symptoms, with shortness of breath on exertion.
- Stage III: severe COPD characterized by further worsening of airflow limitation (FEV1 30-50% predicted), increased shortness of breath and repeated exacerbations.
- Stage IV: very severe COPD with severe airflow limitation (FEV1 less than 30% predicted) or the presence of chronic respiratory failure.

Besides its excellent predictive power with regard to outcome, the BODE index is simple to calculate and requires no special equipment. The score comprises body mass index (BMI), post-bronchodilator FEV1 predicted, grade of dyspnea (measured by the modified Medical Research Council dyspnea scale, MMRC) and the six-minute-walking-distance.

Table 1: Variables & Point Values Used for Computation of Body Mass Index, Degree of Airflow Obstruction & Dyspnea, & Exercise Capacity (BODE) Index

Variable	Points on the BODE Index			
	0	1	2	3
FEV1 % predicted †	≥ 65	50 – 64	36 – 49	≤ 35
Distance walked in 6 min (m)	≥ 350	250 –349	150 –249	≤ 149
MMRC dyspnoea scale‡	0 –1	2	3	4
Body mass index§	>21	≤ 21		

* The cut-off values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV1 % predicted denotes forced expiratory volume in one second as a percentage of the predicted value.

† The FEV1 % predicted categories are based on stages identified by the American Thoracic Society.

‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4;

0 – "Not troubled with breathlessness except with strenuous exercise";

1 – "Troubled by shortness of breath when hurrying on the level or walking up a slight hill";

2 – "Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level";

3 – "Stops for breath after walking about 100 yards or after a few minutes on the level";

4 – "Too breathless to leave the house or breathless when dressing or undressing"

§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

Approximate 4 Year Survival Interpretation 0-2 points 80%, 3-4 points 67%, 5-6 points 57%, 7-10 points 18%.

The British Medical Journal has previously published a series on prognosis studies, with an emphasis on the need for impact studies that demonstrate improvement of decision making and patient outcome when using an index to guide patient management . Despite various validation methods of the still growing number of COPD prognostic indices, none of these indices has revealed its impact in daily practice yet.

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"Education is the most powerful weapon which you can use to change the world"
– Nelson Mandela

16

Chronic Obstructive Pulmonary Disease: Prevention

Dr. Surendra Verma

Introduction:

Chronic obstructive pulmonary disease (COPD) is the result of complex interplay between clinical and molecular (i.e., genetic) risk factors.[1] These interactions are the reason that two individuals may have identical clinical risk factors, but only one will develop COPD. Identifying risk factors for COPD and understanding their interactions may lead to strategies that reduce the prevalence of COPD.

Risk factors:

Definite risk factors for COPD include smoking and increased airway responsiveness.[2] Environmental exposures may also be risk factors.

Smoking: Numerous epidemiologic studies indicate that tobacco smoking is overwhelmingly the most important risk factor for COPD.[3] As an example, a retrospective cohort study (n = 8045) found that subjects who smoked cigarettes throughout a 25 year observation period were more likely than never smokers to develop COPD (36 versus 8 percent).[3] Genetic influences may enhance an individual's susceptibility to the detrimental effects of cigarette smoke. This is supported by an observational study that found that bronchodilator responsiveness was increased among current or former smokers who had a first-degree relative with severe early-onset COPD, compared to current or former smokers who did not have such a relative.[4] Smoking both tobacco and marijuana synergistically increases the risk of COPD and respiratory symptoms.[5]

Airway responsiveness: According to observational studies, increased airway responsiveness to allergens or other external triggers is a risk factor for COPD.[7] As an example, one retrospective cohort study (n = 9651) found that the incidence of COPD over 11 years was higher among individuals with increased airway responsiveness, compared to those without increased airway responsiveness (OR 4.5, 95% CI 3.3-6.0).[7]

While it is certain that both airway responsiveness and smoking are independent risk factors for COPD, conflicting data make it unclear whether they interact. While several studies suggest that cigarette smoking increases the effect of airway responsiveness on the development of COPD[8], other studies do not.[6]

Environmental exposure: Studies indicate that environmental exposure to particulate matter, dusts, gases, fumes or organic antigens may also be a risk factor for COPD.[9] As an example, a population-based sample (n = 8515) found that COPD was more common among those exposed to occupational dust than those who were unexposed (OR 1.5, 95% CI 1.17-2.08).[9] COPD is also more common in women exposed to indoor biomass smoke.[10]

Sex: Women appear to be more susceptible to developing COPD and emphysema than men.[11] In a study that assessed the amount of emphysema by measuring lung attenuation on computed tomography, men and women had a similar amount of emphysema overall, but women had smoked a substantially lower number of pack years.[11]

Atopy: Atopy may increase an individual's risk for COPD, according to an observational study of 1025 older men (mean age 61 years) without asthma who underwent baseline skin prick and pulmonary function testing and were then followed for a median of three years.[12] Atopy was considered present when there was a mean wheal size ≥2 mm in response to four antigens: house dust, mixed grasses, mixed trees and ragweed. Atopy predicted an excess annual rate of decline of the FEV1 (9.5 mL per year) and the FEV1/FVC (0.3 percent per year), compared with non-atopic patients.

Antioxidant deficiency: There are limited data suggesting that a deficiency of antioxidant vitamins (e.g., vitamins C and E) may be a risk factor for COPD.[13] In theory, a deficiency of antioxidant vitamins leaves the host unable to defend itself against the destructive effects of oxidative radicals, which derive from both exogenous sources and endogenous sources.

Bronchopulmonary Dysplasia: Bronchopulmonary dysplasia, also known as neonatal chronic lung disease (CLD), is a consequence of preterm birth that is defined by dependence on supplemental oxygen for more than 28 days post-partum. Radiographic emphysema and evidence of airflow limitation on pulmonary function testing have been noted in young adult survivors of moderate and severe bronchopulmonary dysplasia.[14]

Tuberculosis: Pulmonary tuberculosis may contribute to airflow obstruction via endobronchial infection and subsequent bronchostenosis or via lung parenchymal destruction with loss of airway tethering. In a study of 8784 Chinese subjects aged 50 or older, radiographic evidence of prior pulmonary tuberculosis was associated with an increased risk for airflow obstruction, independent of cigarette smoking, biomass fuel exposure and prior diagnosis of asthma.[15]

Molecular risk factors: Observational studies indicate that molecular risk factors for COPD exist.[4,16] As an example, one observational study found that the risk of COPD was approximately three times higher among the first-degree relatives of patients who had severe premature COPD unrelated to alpha-1 antitrypsin deficiency.[16] Molecular risk factors for COPD have been assessed using several different methods which are described below.

Gene polymorphisms: Several gene polymorphisms (SNPs) have been identified that may increase the risk of COPD.[17-21] The functions of many of these genes are still unknown. Some examples are listed here:

1. Transforming growth factor beta: Transforming growth factor beta is a member of a large superfamily of polypeptides involved in cellular growth, differentiation, and activation. SNPs of the gene encoding transforming growth factor beta-1 have been associated with development of COPD in smokers.[17]
2. Serpine2: Serpine2, also known as serpin peptidase inhibitor, was initially identified based on mouse and human fetal lung gene expression and then assessed in a case control study.[22] Serpine2 appears to be a COPD susceptibility gene that may be influenced by gene-by-smoking interaction.
3. Genome wide association studies (GWAS): GWAS have identified five separate loci as being associated with COPD: 15q25 locus (CHRNA3/CHRN5/IREB2),[19] 4q31 (near HHIP).[20] Two additional loci have been identified at 19q13 (near CYPA6)21, a

locus also associated with cigarette smoking, and 5q32 (near the gene for 5-hydroxytryptamine receptor 4, HTR4)[18], a locus also associated with lung function in the general population. This is a smaller number of loci than have been identified for asthma. The reasons for this are unclear. In addition, genes related to alpha-mannosidase appeared to be associated with the ratio of upper to lower lobe emphysema in some ethnic groups.

Antioxidant related enzymes: Genetic variation in antioxidant enzyme function or regulation may affect risk for COPD. In particular, the genes for glutathione S-transferases P1 and M1, glutamate cysteine ligase, and superoxide dismutase appear to be involved. Gene association studies are not available for some other antioxidant enzymes (e.g., thioredoxin, gamma-glutamyltransferase) that may turn out to be important.

Glutathione S-transferases: Glutathione S-transferase P1 (GSTP1) aids in the detoxification of a number of substances that are found in cigarette smoke. Decreased glutathione S-transferase P1 activity due to genetic polymorphisms may increase the frequency of COPD.[23] Several case-control studies have identified a specific polymorphism in exon 5 (Ile105Val) that is more common among persons with COPD than controls.[23,24] Homozygous deletion of glutathione S-transferase M1 (GSTM1) has been associated with increased COPD risk in some, but not all studies.[17,24]

Glutamate cysteine ligase: Glutamate cysteine ligase (GCL) is one of the three enzymes that relate to glutathione synthesis. Genetic variants in the promoter region and in the catalytic subunit that cause decreased glutathione levels have been associated with and increase risk of COPD.[25]

Metalloproteinase dysregulation: Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that degrade extracellular matrix proteins. The activity of MMPs is regulated by tissue inhibitors of metalloproteinase (TIMPs). Numerous observational studies have demonstrated an association between COPD and abnormal activity of certain MMP or TIMP subtypes.[26, 27] A case-control study compared the bronchoalveolar lavage fluid of patients with emphysema to normal controls.[26] Patients with emphysema had increased MMP-1 (collagenase-1) expression and absent MMP-12 (macrophage elastase) activity.[26] Sputum from patients with asthma and COPD has increased MMP-2 (gelatinase A), MMP-9 (gelatinase B), MMP-8 (Collagenase 2) and TIMP-1 activity, compared to controls.[27] In addition, patients with stable COPD have an increased concentration of serum TIMP-1, compared to controls and patients with stable asthma.[28] MMP 12 has been identified as a gene associated with reduced lung function in asthma and early decline in lung function in COPD.[29]

Excess Elastase: Premature emphysema is associated with deficiency of alpha-1 antitrypsin, an inhibitor of neutrophil elastase. This is true even if excess inflammatory cells are attracted to the lung with exogenously administered monocyte chemo-attractant protein-1.

Risk reduction:

Most of the clinical risk factors for COPD can be modified. However, it is difficult to directly measure the impact of risk factor modification on the incidence of COPD because of the extended duration between exposure to the risk factor and the onset of measurable airway obstruction. As an alternative approach, most studies determine the rate of lung function decline and use it as an indirect measure of the risk of developing COPD. The goal of risk factor modification is to mitigate lung function decline, since patients with increased lung

function decline are more likely to develop COPD. Indirect evidence suggests that smoking cessation has the greatest impact on preventing COPD. Physical activity and avoidance of inhalational exposures may also reduce the incidence of COPD. Anti-inflammatory therapy and antioxidant therapy have been studied, but appear to have minimal impact on the development of COPD.

Smoking cessation: Smoking cessation reduces the accelerated decline in lung function that is associated with smoking, which decreases the likelihood that COPD will develop.[3]

This was illustrated by a retrospective cohort study (n = 8045) that found the incidence of COPD over 25 years was less among patients who had never smoked or quit smoking than among patients who continued to smoke.[3] Specifically, the incidence of COPD among never smokers, smokers who quit prior to the study, smokers who quit during the initial five years of the study, smokers who quit 5 to 15 years into the study, smokers who quit 15 to 25 years into the study and those who continued to smoke was 4,12,5,14, 24, and 41 percent, respectively among men. The incidence was 9,11,20,25,29, and 31 percent, respectively, among women.

One approach to smoking cessation is the five-step algorithm called the "5 A" (Ask, Advise, Assess, Assist, Arrange). Patients who wish to quit smoking be managed with a combination of behavioural and pharmacologic treatments. Most studies demonstrate increasing quit rates with increasing behavioural support. Other behavioural counselling options include computer programs, text messaging, web-based interventions and phone apps. Pharmacological therapies for smokers are combination nicotine replacement therapy (NRT) or the centrally acting medications varenicline or bupropion. Each of these medications has proven efficacy for smoking cessation. Acupuncture and hypnosis can also be tried but there are no proven benefits for the same.

Exposure avoidance: Reduction of environmental exposure is associated with slower lung function decline, but to a much smaller degree than smoking cessation. This was demonstrated by a retrospective cohort study (n = 9651), which found that decreased particulate matter concentration was associated with a small reduction of the annual rate of decline of the forced expiratory volume in one second (FEV1) over 11 years.[30] Specifically, a 10 mcg per m3 annual decrease in the concentration of particulate matter was associated with a 3 mL reduction of the annual decrease of FEV1. This effect is small and of limited clinical relevance to individual patients, but may have public health relevance.[31]

In a nine-year prospective cohort study, improved kitchen ventilation and/or use of biogas instead of biomass fuel were associated with a reduced decline in FEV1.[32] When both interventions were utilized, the decline in FEV1 was decreased by 16 mL/year (95% CI 9-23 mL/year). A variety of strategies are available to reduce the burden of inhaled particles and gases.[32]

Implement, monitor and enforce strict control of airborne exposure in the workplace. Initiate intensive and continuing education of workers, managers, clinicians and legislators. Promote smoking cessation since smoking aggravates exposure to other particles and gases. Improve ventilation in areas where biomass fuels are used for cooking and promote use of clean fuels.

Physical activity: Physical activity may mitigate lung function decline in active smokers. In a retrospective cohort study, 6790 volunteers were followed for a median duration of 11years.[33] Active smokers with a moderate to high level of physical activity were less likely to develop COPD than active smokers with a low level of physical activity (OR 0.77, 95% CI 0.61-0.97).

Additional studies are necessary to validate this fact.

Anti-inflammatory therapy: The observation that increased airway responsiveness is a risk factor for COPD led to the hypothesis that anti-inflammatory therapy may mitigate accelerated lung function decline.

1. **Inhaled glucocorticoids:** The use of inhaled glucocorticoids in young adults to prevent the onset of COPD has not been studied.
2. **Statins:** In observational study of COPD,[34] statins have been associated with a lower rate of decline in pulmonary function, reduced rate and severity of exacerbations, rate of hospitalizations, and mortality. However, in a randomized trial that compared simvastatin with placebo in 885 patients with COPD, simvastatin did not attenuate lung function decline or reduce exacerbations. These studies are described in greater detail separately. The effect of other anti-inflammatory therapies (e.g., nonsteroidal anti-inflammatory drugs, systemic glucocorticoids) has not been studied in relevant patient populations.
3. **(N) acetylcysteine:** (N) acetylcysteine is a thiol derivative that has potential antioxidant and mucoactive effects. Conflicting results regarding its usage in COPD patients have been noticed. A trial that randomly assigned 50 patients with COPD to receive (N) acetylcysteine (600 mg/day) or placebo for three years found no between group difference in the annual rate of lung function decline.[35] Similarly, in a study that used a higher dose of (N) acetylcysteine (1200 mg/day) in 120 patients with COPD, no difference was found in the rate of decline in FEV1, although a slight reduction in the rate of exacerbations was noted in the (N) acetylcysteine group.[36]

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"Student: Dr Einstein, Aren't these are the same questions as last year's final exam?
Dr Einstein: Yes, but this year the answers are different"
-Albert Einstein

17

Asthma-COPD Overlap Syndrome: A New Entity?

Dr. Vitull K. Gupta, Dr. Meghna Gupta

Introduction:

Asthma and chronic obstructive pulmonary disease (COPD) are chronic airway obstructive diseases and the two most common respiratory diseases worldwide with millions of patients suffering from these syndromes. The chronic airway syndromes of asthma and COPD are diseases where the environment, genetics and epigenetics contribute to a wide spectrum of phenotypes[1] suggesting that probability of patients having elements of both asthma and COPD is quite high. COPD and asthma were regarded as two distinct disease entities, but these two conditions are now increasingly being recognized as heterogeneous and often overlapping conditions as some patients may present with a mixture of both diseases, which is being termed as "asthma–COPD overlap syndrome" (ACOS). It was observed that in clinical practice it was common to see patients with asthma that also showed COPD-like phenotypes and vice versa and adult patients with active asthma were 12 times more likely to acquire COPD over time than patients without active asthma. More over epidemiological studies have shown that about half of the older patients with obstructive airway disease have overlapping diagnoses of both asthma and COPD. Several diagnostic terms most including the term 'overlap' has been applied to such patients, however there is no agreed term or defining features for this category of patients. Asthma and COPD are representative chronic inflammatory lung diseases and ACOS may be a manifestation of characteristics of both asthma and COPD.

Is ACOS a new entity?

No, ACOS is not a new entity as in 1961, a "Dutch hypothesis," sighted frequent problems in differentiating asthma from COPD and suggested that asthma and COPD may differ in their extremes, but in adults, the clinical expression may depends on age, sex and environmental factors and ACOS patients demonstrate significant heterogeneity.[8] ACOS is common and has been reported worldwide and is being increasingly recognized similar to asthma and COPD as no single phenotype or endo-type defines all ACOS patients. International guidelines for management of COPD and asthma have included recommendations for treatment of ACOS[5,6] and consensus document and review on ACOS has also been published.

Asthma:

Global Initiative for Asthma (GINA) defines asthma as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[5]

COPD:

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)[6] defines COPD as, a common preventable and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Many previous definitions of COPD have emphasized the terms "emphysema" and "chronic bronchitis".

Chronic bronchitis: Chronic bronchitis is defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough (e.g., bronchiectasis) have been excluded. It may precede or follow development of airflow limitation and may be associated with development and/or acceleration of fixed airflow limitation. Chronic bronchitis also exists in patients with normal spirometry. This definition has been used in many studies, despite the arbitrarily selected symptom duration but is clinically and epidemiologically useful term.

Emphysema: Emphysema is a pathological term that describes abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles that is accompanied by destruction of the airspace walls, without obvious fibrosis (i.e., there is no fibrosis visible to the naked eye).[14] Emphysema can exist without airflow obstruction and is more common in moderate or severe airflow obstruction.[6]

Both of these pulmonary disorders are characterized by various degrees of airflow limitation, inflammation and tissue remodeling. Classical definitions of two disorders describe the physiological and anatomic extremes of asthma and COPD and allow them to be recognized as distinct disease entities. Asthma has been differentiated from pure COPD through several condition described like onset in younger age, non-smokers, episodic and completely reversible airway obstruction and airway hyperresponsiveness and history of allergic including the association with rhinitis. Pathologically airway inflammation in asthma differs from that in COPD. Asthma is characterized predominantly by eosinophilic inflammation and inflammation involving type 2 helper T (Th2) lymphocytes, whereas COPD is characterized predominantly by neutrophilic inflammation and inflammation involving CD8 lymphocytes.[5,6]

Irreversible airway obstruction develops over time in some patients with asthma owing to airway remodeling with the result that these patients with asthma resemble those with COPD. In contrast, reversible airway obstruction can occur in patients with COPD with the result these patients with COPD resemble those with asthma. However, each disorder has a very wide spectrum of clinical and patho-biological phenotypes thereby in considerable patients the diagnosis becomes vague, confusing and being overlapped. Even as asthma and COPD are defined as distinct clinical syndromes, the distinction in clinical practice is not as easy and clear and a number of patients exhibit features of both the disorders. Generally, if three or more features of either asthma or COPD are present than diagnosis of asthma or COPD is considered and if equal numbers of features are present, than diagnosis of ACOS should be considered. The important variables are age at onset, pattern and time course of symptoms, personal history or family history, variable or persistent airflow limitation, lung function between symptoms and severe hyperinflation.

Asthma-COPD overlap syndrome:

Definition and Diagnosis: The definition of ACOS has been a source of debate and no definite consensus has been reached. ACOS has been recognized as a phenotype of both

asthma and COPD.[16] A number of diagnostic criteria have been proposed for ACOS, but a specific formal definition of ACOS has yet to be determined. The importance of identifying patients with features of ACOS is underlined by evidence demonstrating more symptoms, exacerbations, hospitalizations, lower health-related quality of life and higher mortality in ACOS than patients with COPD or asthma alone.[17, 18, 19, 20]

GINA and GOLD guidelines stated that distinguishing asthma from COPD can be problematic, particularly in smokers and older adults and issued a descriptive definition of ACOS for clinical use, that ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD. Broadly, ACOS can be described as an obstructive airflow condition or a set of clinical characteristics where aspects of both asthma and COPD are present, such as FEV1/FVC < 0.70 and evidence of airflow reversibility (post-bronchodilator FEV1 increase of >12% and >0.200 L). A stepwise approach to diagnosis is advised, comprising recognition of the presence of a chronic airways disease, syndromic categorization as asthma, COPD or ACOS.

The Spanish guidelines of COPD identify ACOS patients based on following criteria:

A) Major criteria:

1. Very positive bronchodilator response (>400 ml and >15 % in FEV1),
2. Sputum eosinophilia or previous diagnosis of asthma.

B) Minor criteria:

1. Increased total serum IgE,
2. Previous history of atopy or positive bronchodilator test (>200 mL and >12 % in FEV1) on at least two occasions.[11,21]

For diagnosis of ACOS, a patient must fulfill two major or one major and two minor criteria.

The Czech Republic diagnostic guidelines are:

Major criteria:

1. Strong bronchodilator test positivity (FEV1 > 15 % and > 400 ml),
2. Positive bronchial challenge test,
3. Fraction of NO in exhaled breath (FeNO) > 45–50ppb and/ or sputum eosinophilia ≥3 %
4. Previous history of asthma.

Minor criteria:

1. Mild chbronodilator test positivity (FEV1 > 12 % and > 200 ml),
2. Increased total IgE,
3. History of atopy.

The Finnish diagnostic criteria states:

Major criteria:

1. Significant bronchodilatory effect (FEV1 > 15 % and > 400 ml),
2. Sputum eosinophilia or elevated FeNO (>50 ppb),
3. Previous asthma symptoms (starting before the age of 40).

Additional criteria:

1. Elevated total IgE,

2. Atopy,
3. Repeated significant bronchodilatory response (FEV1 > 12 % and >200 ml), APEF-follow up typical of asthma.

For both Czech Republic diagnostic guidelines and the Finnish diagnostic criteria, a patient must fulfill two major (or main) criteria or one major and two minor (or additional) criteria. But these criteria for diagnosis of ACOS are neither specific nor sensitive because airway eosinophilia is not exclusive to asthma and is present in COPD patients and a clinically significant bronchodilator response (≥15%) can be elicited in COPD patients.

The Australian Asthma Management Handbook recommends pooling of features corresponding to asthma and COPD in order to make a diagnosis of ACOS. Even though asthma and COPD differ in onset, history of smoking, course and response to steroids, but in clinical practice, differentiating these two diseases may pose difficulties because of overlapping features.

The absence of ACOS-specific pathological definitions and the variability of ACOS criteria across the literature present challenges for conducting studies to add to the available evidence

Prevalence of ACOS:

There is paucity of reliable epidemiological data of ACOS, partly due to a historical insistence on a clear separation between COPD and asthma and partly due to clinical trial exclusion criteria, which have excluded patients with COPD from asthma trials and vice versa.[11,24] Estimates of the population prevalence of ACOS ranged from 1.6% to 4.5% from various studies.[19,25] In a study the prevalence of ACOS varied with the definition of ACOS and is estimated to be present in 15 to 45% of the population with obstructive airway disease showing that the prevalence increases with age.[8,25] In a study conducted in general population, the prevalence of overlapping asthma and COPD was 1.6%, 2.1% and 4.5% in the age groups of 20–44 years, 45–64 years and 65–84 years, respectively.[25] Data derived from large population studies have revealed that a high proportion of adult patients with respiratory symptoms are commonly diagnosed with more than one obstructive lung disease, especially elderly individuals.[25] Using the Spanish criteria, 5% prevalence of ACOS was observed and using the same criteria another study observed a prevalence of 3.9% which increased to 15.9 % when criterion of a previous diagnosis of asthma was used. In a retrospective observational study of COPD patients 5% prevalence of ACOS was observed in smoking-related COPD and a higher prevalence of 21.2% was observed in biomass smoke related COPD. In the Spanish EPISCAN epidemiological study, including patients with COPD and previous diagnosis of asthma before the age of 40, a prevalence of 17.4 % of ACOS was observed among COPD patient population.

Pathophysiology:

Whether ACOS is simply the coexistence of asthma and COPD or a distinct phenotype related to fundamental pathogenic mechanisms of asthma and COPD remains to be determined and the mechanisms underlying the overlap between asthma and COPD remain controversial. Two hypotheses for underlying disease mechanisms are popular: the “Dutch hypothesis” proposes that asthma and COPD are manifestations of the same basic disease process, with asthma predisposing to the COPD during the aging process,[9] whereas the “British hypothesis” suggests that asthma and COPD are distinct entities generated by different mechanisms. In asthma, the “typical” pathogenic processes are known to include

mast cell-mediated bronchoconstriction, inflammation due to local antibody production, and eosinophilic inflammation, mediated by a number of different messenger molecules, including histamine, cysteinyl leukotrienes, prostaglandin D2, interleukins (ILs) and chemokines. The airflow limitation is usually reversible; a diagnosis of persistent airflow limitation is usually only characteristic of patients with severe asthma.[5]

In patients with COPD, the typical pathogenic mechanisms include mucus hypersecretion, alveolar wall destruction and fibrosis orchestrated by various cells and messenger molecules, including epithelial cells, macrophages, chemokines, monocytes, neutrophils, T-helper cells and type 1 cytotoxic cells.[31] Airflow limitation in patients with COPD is not generally reversible by short-acting β2-agonists alone.[5] In patients with overlap between asthma and COPD, the extent of the contribution of the underlying mechanisms of the two diseases may differ significantly between individuals, influenced by genetic predisposition, environmental exposure, the initiating condition and the evolution of the natural history of each patient. Different studies classify ACOS as a sub-phenotype of COPD[2] whereas other studies treat ACOS as a phenotype distinct from either COPD or asthma.[20] Clinically asthma and COPD can be distinct disorders, but more frequently the distinction is not clear which is expressed in the overlap of the biochemical, pathological, structural and inflammatory processes like various types of cells involved and the cytokines.

Management of ACOS:

The identification of the predominant diagnosis and the potential underlying inflammatory pattern remains central to the proper management of all patients with airways disease. Asthma and COPD are both complex heterogeneous disorders with distinct risk factors, pathophysiological processes, natural history and treatment responses, whereas ACOS represents an overlap of both of these heterogeneous disorders. The management of the majority of patients with "pure" COPD or asthma may not present major challenges. In some patients with more severe or difficult-to-treat forms of either disease, experienced clinicians have little difficulty in incorporating additional treatment options based on specific characteristics, which permit classification into different phenotypes or endotypes. The current treatment guidelines for COPD and asthma are based on treatment responses studied in highly selected subgroups of patients that represent the typical phenotype of asthma and COPD. GINA and GOLD guidelines provide well-defined treatment and management plans for clear cases of asthma and COPD, respectively.[5,6]

Asthma: A stepwise approach is recommended on the basis of disease severity with focus on inhaled corticosteroids (ICS) in combination with bronchodilator drugs especially short-acting beta-agonists (SABA) and long-acting beta-agonists (LABAs). Leukotriene-receptor antagonists are an alternative choice in milder disease. For severe allergic asthma with appropriate IgE levels, anti-IgE treatment is an approved option; long-acting muscarinic antagonists (LAMAs) have been shown to work in controlled trials and are now included in the treatment of severe asthma.[5] The use of "triple" therapy (LAMA, LABA and ICS) may be considered as an appropriate option in patients with more severe symptoms, especially in the presence of frequent exacerbations. Theophylline may be of benefit in some patients.

COPD: A stepwise treatment approach is also recommended, with a focus on reduction of symptoms, exacerbations and management of comorbid conditions. The main emphasis is on smoking cessation and the use of LABAs and LAMAs. The role of ICS has been debated for years and is limited to patients with more severe disease and those with frequent

exacerbations.[6]

Patients with asthma and signs of concomitant COPD: Given the lack of randomized intervention studies of ACOS, it is difficult to provide firm treatment guidance for patients with the syndrome. Treatment with ICS should be continued in patients with long-standing asthma even if a component of irreversible airway obstruction develops. Leukotriene modifiers may be of value in those with atopy. Combination therapy with a LAMA and a LABA is a well-established treatment and is a reasonable approach for patients with more severe asthma or COPD or with overlapping conditions.

Patients with COPD and signs of concomitant asthma: Traditionally, COPD is characterized by a relevant smoking history, persistent and progressive airway obstruction, lack of reversibility of airway obstruction and neutrophil infiltration in the airways. But reversibility, eosinophilia and bronchial hyperresponsiveness may be present in patients with COPD, that is asthma like features which might benefit from ICS added to use of LABAs and LAMAs. Patients with COPD and concomitant signs of asthma may not have easily measured changes in FEV1 in response to treatment especially over a short period of time.[31]

GOLD and GINA guidelines has recommended treatment of ACOS according to the predominant features of asthma or COPD. If differential diagnosis is equally balanced between asthma and COPD, then treatment should be accordingly for asthma that is pivotal role of ICS.[32] If assessment suggests asthma or ACOS or there is significant uncertainty about the diagnosis of COPD, it is prudent to start treatment as for asthma until further investigation has been performed to confirm or refute this initial position. Treatments will include an ICS (in a low or moderate dose, depending on level of symptoms) and LABA should be continued (if already prescribed), or added but should not be given alone without an ICS (often called LABA monotherapy). If assessment suggests COPD, appropriate symptomatic treatment with bronchodilators or combination therapy should be commenced, but not ICS alone (as monotherapy).[33] Treatment of ACOS should also include advice about other therapeutic strategies[34] including: smoking cessation, pulmonary rehabilitation, vaccinations and treatment of co-morbidities, as advised in the respective GINA and GOLD guidelines.

In a majority of patients, the initial management of asthma and COPD can be satisfactorily carried out at primary care level. But further diagnostic evaluation is necessary in the following contexts:

- Patients with persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty, especially if an alternative diagnosis is suspected (e.g. bronchiectasis, post-tuberculous scarring, bronchiolitis, pulmonary fibrosis, pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Patients with suspected asthma or COPD in whom atypical or additional symptoms or signs (e.g. haemoptysis, significant weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease) suggest an additional pulmonary diagnosis.
- When chronic airways disease is suspected but features of both asthma and COPD are few.
- Patients with co-morbidities that may interfere with the assessment and management of their airways disease.

To make it simple, a potential four-step algorithmic approach for patients with ACOS is suggested:

1. Identification of patients with airway disease, symptoms and signs.
2. Evaluation of eosinophilic airways inflammation (e.g., by increased sputum eosinophils or FeNO) or other asthma characteristics (e.g., very positive bronchodilator reversibility), which may represent an indication for ICS use and dose optimization.
3. Evaluation of presence of persistent airflow obstruction (as expressed by the absence of complete reversibility after bronchodilator reversibility testing and/or treatment) may represent an indication for optimization (or maximization) of bronchodilation in appropriate patients (i.e., via combination therapy of LAMA and LABA).
4. Evaluation of exacerbation history leads to the selection of the most appropriate treatment for exacerbation reduction, according to the predominant disease characteristics.

Conclusion:

ACOS is not a new entity but represents revival of old concept of overlap between COPD and asthma. In clinical practice physicians have been facing the problem of asthma presenting with COPD-like features and vice versa. Review of literature suggests that it is premature to recommend the designation of ACOS as a disease entity as more research is needed to better characterize patients to obtain a standardized definition of ACOS. Guidelines recommend treatment of ACOS according to the predominant features of asthma or COPD. If differential diagnosis is equally balanced between asthma and COPD, then treatment should be accordingly for asthma that is pivotal role of ICS. Strategies to prevent development of obstructive airway disease include risk factor management and adequate treatment include early initiation of appropriate drugs like ICS/LABA and prevention of exacerbations by measure like vaccination must be integral part of obstructive airway disease management whether asthma, COPD or ACOS.

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"A wise man proportions his belief to evidence"
-David Hume

18

Indian COPD Guidelines: What is different from GOLD Guideline

Dr. Mahesh PA

Introduction:

Genesis of the Indian COPD guidelines: The Indian COPD guidelines was published in Lung India in the July-September issue, 2013 for the first time and was a joint effort between the two societies, Indian Chest Society (ICS) and the National College of Chest Physicians (NCCP). The Department of Pulmonary Medicine, PGI, Chandigarh was the main coordinator and included eminent respiratory physicians from ICS, NCCP and other medical colleges in India as its members. Leading members from other allied departments such as internal medicine, radiology, pharmacology, microbiology and community medicine were also included as members to develop this guideline. The Indian guidelines is very well written, easy to read, has extensively used a question and answer style and has given clear recommendations based on evidence with emphasis on the Indian scenario.

The group was involved in extensive literature search of various databases including the Pubmed, GOLD website, American Thoracic Society (ATS) documents, National Institute of Clinical Excellence (NICE) documents and relevant information was collated. This was followed by a joint workshop to give shape to the final guideline manuscript. The group developed the guidelines under five main headings.

1. Definition, epidemiology and disease burden.
2. Disease assessment and diagnosis.
3. Pharmacologic management of stable COPD.
4. Management of acute exacerbations of COPD.
5. Nonpharmacologic and preventive measures.

Importance was given to issues and evidence relevant to the Indian context. The final document including references runs into close to 40 pages.

Genesis of GOLD guidelines: The Global Initiative for Chronic Obstructive Lung Disease (Gold) was developed in 1998 as a collaborative effort between the National Heart Lung and Blood Institute (NHLBI), The National Institute of Health (NIH) and the World Health Organization (WHO). The first guideline document was published in 2001. The follow-up modifications have been published again in 2006 and 2011. Updates with minor changes were released in 2013, 2014, 2015 and 2016. The GOLD guidelines have a full version (111 pages) and a pocket version (32 pages). The basis for the guidelines has been an extensive literature search of all documents related to COPD published or translated to English. If the publication has been in peer-reviewed journals that are not in Pubmed, copy of the abstract and the full paper can be submitted to the Chair, Scientific Committee of the GOLD for consideration.

The key information in the GOLD guidelines include information on Introduction to COPD with definition and overview, diagnosis and assessment, therapeutic options, management of stable COPD, management of exacerbations of COPD, COPD and co-morbidities with extensive references, figures and tables. A separate section on Asthma COPD Overlap Syndrome (ACOS) is included recently since the last few years developed in collaboration with the Global Initiative on Asthma (GINA).

Grading of published literature:

There are some differences in the grading of the published literature used as evidence to develop the guidelines as listed below in Table 1. The Indian guidelines used a modified grade system for classifying evidence and gave a grading of recommendation with Grade A meaning recommended and Grade B meaning suggested. The Indian working group considered important factors such as costs, feasibility and practicality and availability of healthcare in India when grading the recommendations (Table 1).

Table 1: Strength of evidence used in guideline formulation.

Indian Guidelines		GOLD guidelines	
Level 1	High quality evidence. Consistent results. Guidelines have included well conducted both: a. Randomized control trials, b. Observational studies.	A	Randomized control trials. Consistent results. Adequate number of studies with adequate patients.
Level 2	Moderate quality evidence. Randomized control trials with some limitations.	B	Randomized control trials. Inconsistent results. Inadequate number of studies with smaller number of patients.
Level 3	Low quality evidence: a. Observational studies. b. Randomized control trials with serious limitations.	C	Observational studies. Studies that are not Randomized control trials.
Useful practice point	Consensus by the group.	D	Panel judgment for issues that are deemed useful.
Grade A	Strong recommendation. Benefits clearly outweigh the risks.	Not used in GOLD guidelines.	
Grade B	Weaker recommendation. Risk benefit ratio not clear.		

Definition of COPD and overview:

There are minor differences in the definition of COPD adopted by the Indian guidelines, which has made the definition simpler. The Indian definition does not consider the effect of exacerbations or other comorbidities on disease progression. Both the definitions are given below for comparison.

Indian Guidelines: "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."

GOLD guidelines: Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

The Indian guideline provides emphasis on certain risk factors that are relevant to the Indian context. Importance is given especially to biomass fuel exposure, which is very important in Indian women as risk factor for COPD. Evidence regarding the association of pulmonary tuberculosis with COPD is presented. The key risk factors such as tobacco smoking, air pollution and occupation are discussed with relevance to data from the Indian population and the table on risk factors is useful. The Indian guidelines have a subsection on graded recommendations that are very useful to the reader. One of the most common methods of tobacco smoking in India is bidis, which are similar or more harmful than cigarette smoking (IA). There is also mention of adverse effects of consumption of smokeless tobacco. The GOLD guidelines places equal importance on most of these risk factors along with additional emphasis on lung growth and development. The chapter on definition and overview also includes a section on current views on pathology and pathogenesis of COPD.

Diagnosis of COPD:

Both the Indian and the GOLD guidelines are similar in their recommendation on when to suspect COPD. A patient who has chronic symptoms of cough, sputum production, wheeze and shortness of breath, especially when they have a prolonged exposure to risk factors such as tobacco smoking or biomass exposure. GOLD guidelines specify that the age should be above 40 years in the appropriate clinical context to consider COPD, but the Indian guidelines do not specify the age limit. The GOLD guidelines does not place any emphasis on physical examination, whereas the Indian guidelines has placed major emphasis on physical examination and signs with a long list of signs classified under inspection, palpation, percussion, auscultation and special maneuvers such as Forced Expiratory Time and Snider's match test. List of differential diagnosis are similar in both the guidelines.

Both the guidelines recommend that spirometry according to ATS standards be used to confirm airflow obstruction. Both discuss the details of the spirometry equipment, calibration, technique of spirometry, reversibility testing and acceptable test results. The key difference between the two guidelines is that the Indian guidelines recommend that a post bronchodilator FEV1/FVC below the Lower Limit of Normal (LLN) be considered in situations where these reference values are available for the population. Only in the absence of availability of reference equations for LLN, a post bronchodilator FEV1/FVC <0.7 should be

used to diagnose COPD. The Indian guidelines discusses their arguments for choosing LLN over FEV1/FVC <0.7 for the diagnosis of COPD. The GOLD guidelines does not recommend the use of LLN but has recommended a FEV1/FVC <0.7 to diagnose COPD. GOLD guidelines enumerate their reasons why they prefer a fixed value of FEV1/FVC <0.7 to diagnose COPD.

Severity assessment:

The GOLD guidelines use the post bronchodilator FEV1 to classify COPD into four groups as mild (FEV1 ≥ 80% predicted), moderate (FEV1 <80% and ≥50%), severe (FEV1 <50% and ≥30%), and very severe (FEV1 < 30%) disease. It also recommends use of combined scores to assess the impact of COPD on the individual utilizing a combined COPD assessment by evaluating symptoms mMRC grade or CAT score, GOLD category of severity of obstruction and exacerbation frequency to classify the patient into four groups (categories A, B, C or D). The Indian guidelines classify COPD severity as mild, moderate or severe based on post bronchodilator FEV1 (≥80%, 50-79%, <50% respectively), mMRC grade (<2, ≥ 2 and ≥ 2 respectively), exacerbation frequency (<2, <2 and ≥ 2 respectively) and presence of complications (No, No and Yes respectively).

The Indian guidelines severity classification is more broad-based and the category with the worst value should be the classification the patient should be placed into. The complications evaluated are respiratory failure (pO_2 < 60 mmHg or SpO_2 < 88% and/or pCO_2 > 50 mmHg), cor-pulmonale and secondary polycythemia (hematocrit >55%). If any of these complications are present, the patient falls into the severe category. The Indian guidelines recommends not to use composite scores such as BODE or DOSE in assessing the severity of COPD or to predict prognosis unless they are validated in the Indian population.

Screening for COPD:

The Indian guidelines recommends against the use of spirometry to screen for COPD in asymptomatic individuals to detect airflow obstruction. It also recommends against the use of PEFR for the screening, diagnosis or monitoring of COPD. The GOLD guideline does not discuss spirometry for screening for COPD or use of PEFR.

Management of stable COPD:

In previous reports, the GOLD guidelines recommended treatment of stable COPD based on severity classification, which included only spirometry (FEV1). The present GOLD guideline (2016 update) includes a more comprehensive assessment of the patient and classifies the patient as belonging to Group A (Low risk and Less symptoms), Group B (Low risk and More symptoms), Group C (High risk and Less symptoms) and Group D (High risk and More symptoms). Various therapeutic options and the management of stable COPD are discussed in separate chapters.

Treatment goals for COPD:

Both the Indian and the GOLD guidelines emphasize on reduction of current symptoms and prevention of future risk. In reducing current symptoms, both the guidelines discuss reducing dyspnea, improving exercise tolerance and health status/health related quality of life. In prevention of future risk, both the guidelines discuss reducing/slowing disease progression, reduce exacerbations and mortality. The Indian guideline in addition discusses the need for reducing the medication adverse events. The list of the drugs used in the management of COPD is similar in both the groups. The GOLD guidelines in addition mention long acting beta- agonists (LABA) formoterol, olodaterol and tulobuterol, short acting antimuscarinic

agents (SAMA) such as oxitropium bromide, long-acting antimuscarinic agents (LAMA) such as aclidnium bromide, umeclidinium, glycopyrronium bromide, combination of LABA + LAMA such as formoterol+aclidinium, Indacaterol+ glycopyrronium, Olodaterol+ tiotropium and Vilanterol+umeclidinium. Some of these combinations have recently become available in the Indian market, though they were not available at the time of writing the Indian guidelines. It also mentions different formulations and its doses classified as inhalation, nebulization and oral along with the duration of action of each drug. The Indian guidelines mention two oral drugs Bambuterol and Doxophylline commonly used by physicians in India.

There are differences between the treatment recommendations of GOLD guidelines and the Indian COPD guidelines based on the severity of COPD as well as the treatment options recommended (Table 2). The Indian guidelines have discussed the key evidences for each specific issue in an easy to read question and answer format. Since many of the primary care physicians are still prescribing oral medications, the Indian guideline enumerates the correct technique for using a pressurized metered dose inhaler with or without a spacer.

Table 2: Recommendations for treatment of COPD

Recommendations for first choice treatment of COPD			
GOLD guidelines	Recommendation	Indian Guidelines	Recommendation
A	SABA or SAMA	Mild	SABA or SAMA
B	LAMA or LABA	Moderate	LAMA
C	ICS + LABA ICS + LAMA	Severe	ICS+ LABA
D	ICS + LABA and or LAMA		
Recommendations for alternate choice treatment of COPD			
A	LAMA or LABA or SABA+SAMA	Mild	Methylxanthines
B	LABA+LAMA	Moderate	LABA
C	LABA + LAMA or LABA + PDE4 inh or LAMA + PDE4 inh	Severe	LAMA
D	ICS+LABA+LAMA ICS + LABA + PDE4 inh LAMA + LABA LAMA + PDE4 inh		

Non-Pharmacological management of COPD:

Both the guidelines emphasize on the importance of smoking cessation and pulmonary rehabilitation. The Indian and the GOLD guidelines recommends the 5A strategy for guidelines for doctors; Ask, Assess, Advice, Assist and Arrange. The Indian guidelines include detailed steps for doctors on how to advise their patients, initial counseling, first few steps of quitting tobacco smoking, to deal with triggers when there is an urge (trigger coping) and how to handle the urge once they quit, which are not discussed in the GOLD guidelines. The GOLD guidelines summarize the major clinical findings and recommendations of the treatment of tobacco dependence clinical practice guidelines succinctly in a table. While the

Indian guidelines recommends nicotine replacement therapies, either varenicline or bupropion along with appropriate support program should be offered to people who wish to stop smoking, the GOLD guidelines recommend that first line pharmacotherapy for tobacco dependence varenicline, bupropion SR, nicotine in the form of gum, inhaler, spray or patch are clinically effective and at least one of them should be prescribed in the absence of contraindications.

The Indian guideline discusses the ten topics for health education in COPD patients, which are very relevant to the Indian population. Both the guidelines discuss the importance of pulmonary rehabilitation and both are similar in their recommendations.The GOLD guideline enumerates the benefits of pulmonary rehabilitation with grading of available evidence. Nutritional supplementation is a useful adjunct to exercise training according to GOLD guidelines with a low to moderate quality of evidence.

The Indian guideline does not recommend nutritional supplementation for all patients with COPD, but any patient who is malnourished should be referred for nutritional advice to a specialist. The recommendations on initiation of long-term oxygen therapy are similar in both the guidelines.

The Indian guideline recommends use of oxygen for at least 16 hours per day. The GOLD guideline describes long-term oxygen therapy as more than 15 hours per day. The Indian guidelines recommend that doctors warn the patients of a fire hazard if patients continue to smoke during oxygen supplementation.

The Indian guidelines have clearly mentioned the indications for use of noninvasive ventilation in stable COPD. In the background of a confirmed diagnosis of COPD by a physician, optimization of other treatment and in the absence of sleep apnea, presence of both symptoms such as fatigue, dyspnea or morning headache and one of the physiologic abnormalities:

a. PaCO2 ≥55 mmHg.
b. PaCO2 of 50-54 mmHg and nocturnal desaturation (SaO2 ≤ 88% for 5 minutes continuously while on oxygen therapy of 2L/min).
c. PaCO2 of 50-54 mmHg and two or more admissions to the hospital due to recurrent hypercapnic respiratory failure.

The choice of the model for NIV depends on the choice of the clinician and the patient and whether the patient also has sleep apnea. The GOLD guidelines do not offer such clear cut guidelines, but recommends NIV for stable COPD when there is both sleep apnea and hypercapnic respiratory failure. The recommendations of both the guidelines regarding bullectomy, bronchoscopic lung volume reduction, surgical lung volume reduction and lung transplantation are similar. GOLD guidelines give a clear recommendation in favor of use of both influenza and pneumococcal vaccinations. The Indian guidelines recommend both these vaccinations are likely to be beneficial in COPD patients, but since surveillance data of influenza strains are sparse in India, it would be difficult to give a firm favorable recommendation.

Acute exacerbations of COPD (AECOPD):

The Indian guidelines give a more detailed definition of AECOPD. It includes Anthonisen's criteria as well as requires the clinician to evaluate for other causes for acute breathlessness.

Indian guideline definition: 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

GOLD definition: An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication

The Indian guideline lists the various causes of exacerbation of COPD, both infectious and environmental factors. The infectious agents are further classified as frequent (70-85% of all infectious exacerbations) and infrequent. Severity assessments including clinical, radiological as well as laboratory are similar in both the guidelines with minor variations. The choices of drugs are similar though the Indian guideline gives a step-by-step recommendation on the dose and frequency and duration of use of bronchodilators and steroids. The indications for hospital admission are similar with the Indian guideline recommending the use of BAP-65 scores to decide on whether the patient should be admitted to the ICU. The GOLD guideline has a different set of indications for admission to the ICU. Dyspnea that does not respond adequately to emergency room management, hypoxia with PaO2 of 40 or less, worsening acidosis with a pH of 7.25 or less in spite of management, need for mechanical ventilation, changes in mental status and hemodynamic instability with need for vasopressors would mandate that the patient is treated in the ICU. Both the guidelines give the indications for both non-invasive and invasive ventilation in a table and the Indian guidelines in addition mention the protocols to be followed in application of non-invasive and invasive ventilation. The GOLD guideline gives a more detailed recommendation on when to discharge the patient, itemized checklist on discharge and on follow-up. The GOLD guideline also discusses home management of AECOPD and prevention of AECOPD.

COPD and comorbidities:

GOLD guideline has a separate chapter on comorbidities, which are not discussed in the Indian guidelines. The need to evaluate for cardiac comorbidities such as IHD, heart failure, atrial fibrillation, hypertension and how to manage COPD in the presence of these conditions are discussed. In addition emphasis in given to osteoporosis, lung cancer, bronchiectasis, anxiety, depression, impaired cognitive function, Infections, metabolic syndrome and diabetes.

Recommended reading:

1. Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint ICS/NCCP (I) recommendations. Lung India, Volume 30, issue 3, July-Sep 2013, 228-267
2. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016). www.goldcopd.org

"Research is creating new knowledge"
-Neil Armstrong

4th Annual Conference of the Association of Physicians of India

(MALWA BRANCH)

MAPICON

Bathinda 2017

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Conference Secretariat :

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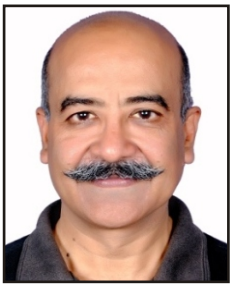
Monograph
on
"COPD: Indian Perspective"

Salient Features:

- This monograph is published with the aim of presenting comprehensive information about COPD in a simplified form with an emphasis on Indian perspective for the benefit of primary care physicians, undergraduates, post graduates as well as physicians including pulmonologists.
- It contains 18 chapters by eminent faculty who have done original work in field of COPD.
- Monograph incorporate chapters pertaining to Epidemiology, Etiopathogenesis, Clinical features, Diagnosis, Management, Prognosis, Prevention, ACOS and comparison to GOLD Guidelines.



Dr. Vitull K. Gupta
Chief Editor

Dr. Vitull K. Gupta MD (Medicine), FICP, FCSI is an active health & human rights activist. He is Consultant Physician at Kishori Ram Hospital and Diabetes Care Centre and Associate Professor at Adesh Institute of Medical Sciences and Research, Bathinda. He did his MBBS from GMC, Patiala (1982) and MD in Medicine from GMC, Amritsar (1998). Dr. Vitull K. Gupta was awarded Fellow of Indian College of Physicians and Fellow of Cardiological Society of India for his academic achievements. Dr. Vitull has delivered several guest lectures, chaired sessions, presented several study papers at national and international conferences (Airway Vista, APICON, CSI, RSSDI, DIPSI, IRA, IMA). He has 21 publications, 20 chapters and has 10 international abstract publications to his credit. He was a member of expert committee for DIPSI-JAPI guidelines for GDM, Chairperson, Organizing Committee, APICON 2014, Ludhiana, Member Scientific Committee, APICON 2016, Hyderabad, Sub Editor Medicine Update 2016 and Organizing Secretary, MAPICON Bathinda 2014, 2015 and 2016. He is Chairman, Association of Physicians of India (Malwa Branch), Press Secretary, Cardiological Society of India (Punjab Chapter), Member, Editorial Advisory Board, Indian Heart Journal, Member Advisory Board, DIPSI and CSI. He is principal investigator from India in multinational trial on COPD being undertaken by Asian Network on Obstructive Lung Diseases (ANOLD), South Korea. He has organized several state and local conferences for the benefit of primary care physicians, post graduate and under graduate students. He has documented, reported and published several human rights violations cases. He was awarded Roll of Honor in sports, table tennis, lawn tennis, badminton and swimming during this graduation.

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