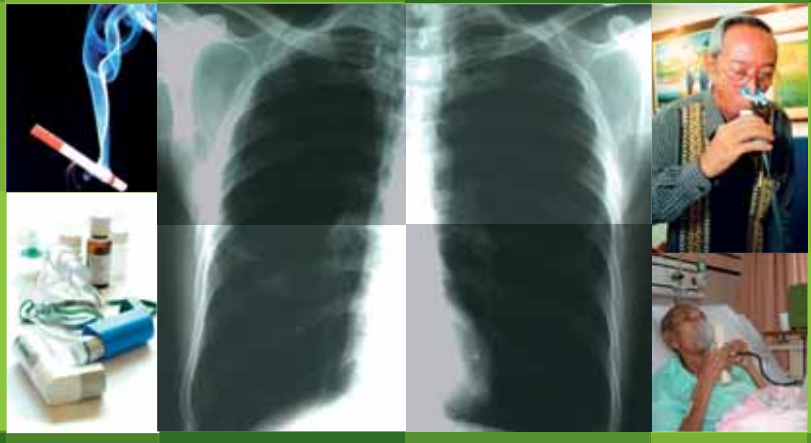
CLINICAL PRACTICE GUIDELINES

November 2009 MOH/X/XXX/XXXX

MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

[2nd Edition]



Ministry of Health Malaysia

Academy of Medicine Malaysia

Malaysian Thoracic Society

This is a revised and updated Clinical Practice Guideline (CPG) on the Management of Chronic Obstructive Pulmonary Disease (COPD). This CPG supersedes the previous CPG on Management of COPD (1998).

STATEMENT OF INTENT

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical presentation of the patient and the management options available locally.

REVIEW OF THE GUIDELINE

This guideline was issued in November 2009 and will be reviewed in November 2013 or sooner if new evidence becomes available.

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The electronic version is available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
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PREFACE

Chronic Obstructive Pulmonary Disease (COPD) is a common illness associated with major morbidity and high mortality throughout the world. It is the fourth leading cause of death in the United States[1] and is projected to rank fifth 2020 in terms of burden of disease worldwide, according to a study by the World Bank and World Health Organization.[2] Yet COPD is relatively unknown to the public and often ignored by health policy makers and government officials.

In 1998, the Malaysian Thoracic Society with the support of the Academy of Medicine of Malaysia and Ministry of Health of Malaysia in their efforts to create awareness about the disease and improve patient care, initiated the publication of COPD management guidelines to be used as a reference for medical practitioners.[3] The working group comprised 10 respiratory specialists who were working in government hospitals, teaching institutions and private medical facilities. The recommendations made were mainly based on the published literature available at the time after thorough assessment by the assigned member or members of the working group and discussion at several face-to-face meetings. The evidence used for the recommendations then was not graded according to its level of strength with some recommendations made based on the consensus agreement of members of the working group. Notwithstanding, the concept of evidence-based medicine was just emerging at that time. After more than a decade, with advancement of care made and with the publication of many important large-scale, randomised studies which had added new dimension to the management of COPD, the time had come for the guidelines to be reviewed and updated. An updated CPG will ensure that the recommendations for the management of COPD in Malaysia are current. We would like to emphasise the importance of (1) early diagnosis through targeted spirometry and early intervention including smoking cessation even in mild COPD; (2) improving dyspnoea and activity limitation in stable COPD using up-to-date evidence-based treatment algorithms; and (3) preventing and managing acute exacerbations, particularly in more severe COPD.

I sincerely hope this revised edition of the CPG for the Management of COPD will be fully utilised by all relevant health care professionals and will benefit patients suffering from COPD. I would like to express my heartfelt gratitude to everyone who was involved in the development of this guideline and especially to the working group members for their enthusiasm, relentless effort and immense contribution.

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References:

1. National Heart, Lung, And Blood Institute. Morbidity And Mortality Chartbook On Cardiovascular, Lung And Blood Diseases. Bethesda, Maryland: Us Department Of Health And Human Services, Public Health Service, National Institute Of Health. Accessed At:http://Www.Nhlbi.Nih.Gov/Resources/Docs/Cht-Book.Htm; 2004.
2. Lopez Ad,Shibuya K, Rao C, Et Al. Chronic Obstructive Pulmonary Disease: Current burden and future projections. Eur Respir J 2006; 27:397-412.
3. Guidelines In The Management Of Chronic Obstructive PUlmonary Disease-A Consensus Statement Of The Ministry Of Health Of Malaysia, Academy Of Medicine Of Malaysia And Malaysian Thoracic Society. Med J Malaysia 1999; 54:387-400.

GUIDELINE DEVELOPMENT AND OBJECTIVES

Guideline Development

Respiratory physicians working in government hospitals, academic institutions and private medical facilities; an emergency medicine physician and primary care physicians from a government health clinic, an academic institution and private general practice were invited to be members of the guidelines development working group.

The previous edition of the CPG on the Management of COPD (1998) was used as the basis for the development of this present set of guidelines. Members of the working group were divided into smaller groups comprising 2 to 5 members who were assigned to prepare documents on the following sections: (1) definition, classification of severity and mechanism of COPD; (2) burden of COPD; (3) risk factors; (4) assessment and monitoring of disease; (5) reducing risk factors; (6) managing stable COPD - pharmacological treatments; (7) managing stable COPD - non-pharmacological treatments; (8) managing exacerbations; and (9) translating guideline recommendations to the context of primary care.

Members responsible for each section were tasked to ensure that the relevant literature was adequately searched, retrieved, critically appraised and accurately presented. Literature search was carried out at electronic databases which included PUBMED, Medline and Cochrane Database of Systemic Reviews. The full text of reference articles quoted in the guidelines was carefully studied. In addition, the reference lists of relevant articles retrieved were searched to identify other studies. Other guidelines on the management of COPD that were referred to included the "Guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease" (2008) and the "Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease"(2007).

Each section leader presented his/her section of the proposed guidelines at several meetings where all members of the working group met and participated in the discussion. The final draft of the guidelines inclusive of recommendations was the result of agreement by the majority, if not all, members of the working group at such meetings as well as through e-mail discussions in between the meetings. Throughout the development of the guidelines, a total of six meetings were held from 10 January 2009. In situations where the evidence was insufficient or lacking, the recommendations made were by consensus of the working group.

In the guidelines, statements are supported by evidence which is graded using the United States/ Canadian Preventive Services Task Force level of evidence scale with the level of evidence indicated in parentheses after the relevant statement, while the grading of recommendations was modified from the Scottish Intercollegiate Guidelines Network (SIGN) which is also shown in parentheses. In this CPG, the final recommendations made by the Guideline Development Group have not been influenced by the views or interests of any funding body.

The draft guideline was sent for external review. The draft guideline will be posted on the Ministry of Health Malaysia website for comments and feedback. This guideline will be presented to the Technical Advisory Committee for Clinical Practice Guidelines and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

Objectives

The main objective of the guideline is to provide up-to-date evidence-based recommendations to assist health care providers in the identification, diagnosis and optimal management of people with COPD.

Clinical Questions

The clinical questions of these guidelines are:

1. How can COPD be prevented?
2. How is COPD diagnosed?
3. How can people with COPD be optimally managed?

Target Population

This guideline is applicable to adults with COPD.

Target Groups/Users

This guideline is intended for all health care professionals involved in managing patients with COPD who include: medical officers, family medicine specialists, general practitioners, public health personnel, general physicians, respiratory physicians, geriatricians, emergency medicine physicians, nurses, physiotherapists, pharmacists, as well as respiratory nurse educators.

CLINICAL INDICATORS FOR QUALITY MANAGEMENT

Proportion of people with COPD treated for acute exacerbation (with antibiotics and/or systemic corticosteroids and/or requiring hospitalisation)

Numerator : Number of episodes of acute exacerbation treated in one year[#]

Denominator : Total number of patients with COPD on treatment in one year[#]

([#]It is necessary to distinguish patients with moderate stable COPD from those with severe or very severe stable COPD)

The optimum achievable standard:

For patients with

- Moderate COPD : $\leq$1 exacerbation per patient per year
- Severe or very severe COPD: $\leq$ 1.5 exacerbations per patient per year

These standards are arrived at based on the results of several recent large randomised controlled trials. In the INSPIRE study in patients with severe and very severe COPD (i.e., FEV_1 <50% predicted), the exacerbations rates were 1.28 per year in patients treated with salmeterol/fluticasone combination and 1.32 per year in patients on tiotropium.[1] (Level 1) In the TORCH study involving patients with moderate to very severe COPD (FEV_1 <60% predicted), treatment with salmeterol, fluticasone and salmeterol/fluticasone combination was associated with exacerbation rates of 0.97, 0.93 and 0.85, respectively compared to 1.13 in patients on placebo.[2] (Level 1) In the UPLIFT study involving patients with moderate to very severe COPD (FEV_1 $\leq$70% predicted) already on a regular β_2-agonist with or without inhaled corticosteroids, treatment with tiotropium or placebo was associated with exacerbation rates of 0.73 and 0.85 per patient-year, respectively.[3] (Level 1)

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SECTION 1 DEFINITION, CLASSIFICATION OF SEVERITY AND PATHOPHYSIOLOGY

1.1 Definition

Chronic obstructive pulmonary disease (COPD), a preventable and treatable respiratory disorder largely caused by smoking, is characterised by progressive, partially reversible airflow obstruction and lung hyperinflation with significant extrapulmonary (systemic) manifestations[1 (Level II-2)] and co-morbid conditions[2 (Level II-3)] all of which may contribute to the severity of the disease in individual patients.

The co-morbid conditions associated with COPD include ischaemic heart disease; osteopenia, osteoporosis and bone fractures; cachexia and malnutrition; normochromic normocytic anaemia; skeletal muscle wasting and peripheral muscle dysfunction; diabetes mellitus; sleep disorders; cataracts and glaucoma; lung cancer; and anxiety and depression both of which increase in incidence with disease severity.[1-9 (Level II-2)]

1.2 Airflow Limitation in COPD

The chronic airflow limitation in COPD is due to a mixture of small airway disease (obstructive bronchiolitis) and lung parenchymal destruction (emphysema), the relative contributions of which vary from individual to individual. Airflow limitation, associated with an abnormal inflammatory reaction of the lung to noxious particles or gases, the most common of which worldwide is cigarette smoke, is usually progressive, especially if exposure to the noxious agents persists.

Airflow limitation is best measured by spirometry, the most widely available and reproducible test of lung function.

1.3 Spirometric Classification of COPD Severity

Objective demonstration of airflow obstruction by spirometry is essential for the diagnosis of COPD. Spirometry also provides an assessment of the severity of pathological changes in COPD. Spirometry should be performed after an adequate dose of an inhaled bronchodilator (e.g., 400 µg of salbutamol)[10 (Level III)] in order to minimise variability.

For diagnosis and severity assessment of COPD, a post-bronchodilator FEV_1 /FVC ratio of <0.70 and post-bronchodilator FEV_1 measurement, respectively are recommended.[11 (Level III)] A simple but yet to be clinically validated classification of COPD severity into four stages based on spirometric cut-points ($FEV_1 < 80$, 50, or 30% predicted) is recommended **(Table 1-1)**.[11 (Level III)]

Table 1-1 Classification of COPD Severity[11] (Level III)

COPD stage	Severity	Post-bronchodilator spirometric values[11] (Level III)	Symptoms that may be present
I	Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	Chronic cough and sputum production may be present. At this stage, the individual is usually unaware that his or her lung function is abnormal.
II	Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted	Dyspnoea typically on exertion, cough and sputum production sometimes also present. This is the stage at which patients usually seek medical attention because of chronic respiratory symptoms or an exacerbation of COPD.
III	Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted	Greater dyspnoea, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on the patient's quality of life.
IV	Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure	Respiratory failure may lead to cor pulmonale with signs which include elevation of the jugular venous pressure and pitting ankle oedema. At this stage, quality of life is markedly impaired and exacerbations may be life-threatening.

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

1.4 Assessment of COPD Severity

The relationship between the degree of airflow limitation based on spirometry and COPD symptoms is not perfect. The impact of COPD on an individual patient depends not just on the degree of airflow limitation, but also on the severity of symptoms - especially breathlessness and decreased exercise capacity. COPD management decisions for the individual patient should therefore not be based solely on spirometry results, but also on the severity of dyspnoea and disability[12 (Level III)] which can be assessed using the modified Medical Research Council (MMRC) dyspnoea scale **(Table 1-2)**[13 (Level III)] which reflects overall disease impact among COPD patients than FEV_1.

A multidimensional grading system of disease severity, the BODE index [body mass index (BMI), airflow obstruction, dyspnoea and exercise capacity], better predicts survival in COPD patients than FEV_1.[14 (Level II-2)] A simple but yet to be validated classification of COPD severity can be based on both spirometry and symptoms **(Table 1-3)** bearing in mind that there may be poor correlation between spirometric measures of lung function and symptoms in individual patients.

Table 1-2 The Modified Medical Research Council (MMRC) Dyspnoea Scale[13 (Level III)]

Grade of dyspnoea	Description
0	Not troubled by breathlessness except on strenuous exercise
1	Short 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 m *or* after a few minutes on the level
4	Too breathless to leave the house *or* breathless when dressing or undressing

To determine the appropriate treatment, a comprehensive assessment of COPD severity should take into account the patient's level of symptoms and the severity of the spirometric abnormality; the presence of complications such as respiratory failure, cor pulmonale and weight loss; as well as the presence of extrapulmonary effects of COPD and co-morbidities. Besides spirometry, the overall assessment of a COPD patient should also include the assessment of the patient's BMI, the patient's dyspnoea (such as using the MMRC dyspnoea scale),[13 (Level III)] exercise capacity (such as using the 6-minute walk test), [15 (Level III)]and co-morbidities.

Table 1-3 Classification of COPD Severity Based on Spirometric Impairment and Symptoms
(adapted from references 11 and 12)[Level III]

COPD stage	Severity	Classification by post-bronchodilator spirometric values	Classification by symptoms and disability
I	Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	Short of breath when hurrying on the level *or* walking up a slight hill (MMRC 1)
II	Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted	Walks slower than people of the same age on the level because of breathlessness; *or* stops for breath after walking about 100 m or after a few minutes at own pace on the level (MMRC 2 to 3)
III	Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted	Too breathless to leave the house *or* breathless when dressing or undressing (MMRC 4)
IV	Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure	Presence of chronic respiratory failure *or* clinical signs of right heart failure

FEV_1: forced expiratory volume in one second; FVC:forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

After confirmation of diagnosis by spirometry, the treatment for the individual patient may be based on symptoms with the recognition that symptoms may be made worse by co-morbid conditions which should also be appropriately treated if present.

1.5 Pathology, Pathogenesis and Pathophysiology

The pathological changes in COPD, which include chronic inflammation and structural changes resulting from repeated injury and repair due to inhaled cigarette smoke and other noxious particles, are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature.[16 (Level II-2)] The chronic inflammation in COPD is characterised by an increase in the numbers of neutrophils (in the airway lumen), macrophages (in the airway lumen, airway wall, and parenchyma), and CD8+ lymphocytes (in the airway wall and parenchyma).[17 (Level II-2)] The cells and mediators involved in the inflammatory processes in COPD and in asthma are different which explains the differences in physiological changes, symptoms and response to treatment in these two diseases.

These pathological changes lead to mucus hypersecretion,[18 (Level II-2)] expiratory airflow limitation with dynamic small airway collapse causing air trapping and lung hyperinflation, gas exchange abnormalities, and progressive pulmonary hypertension that may lead to cor pulmonale.[19 (Level II-2)]

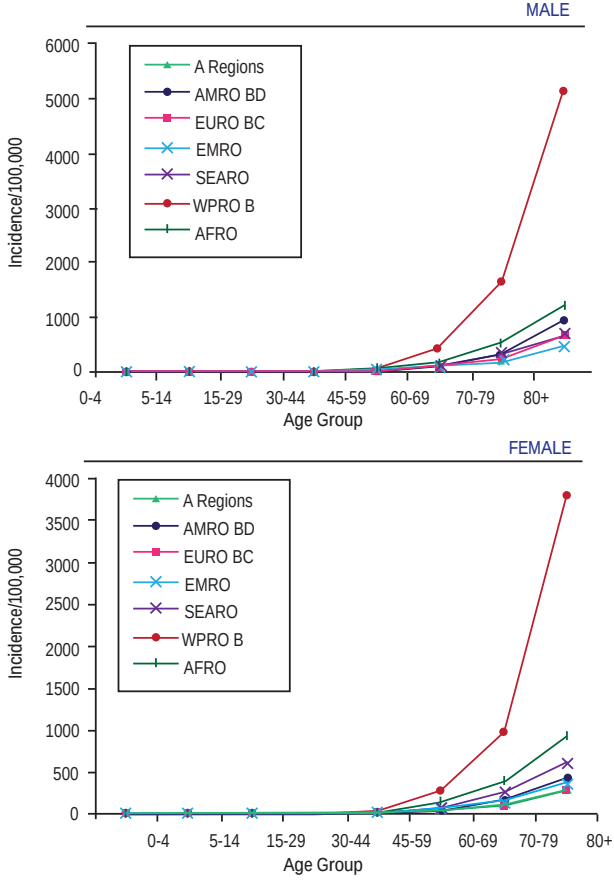
There is further amplification of the inflammatory response in the airways during exacerbations, which may be triggered by bacterial or viral infections or by environmental pollutants.

In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation.

Recommendations: Diagnosis and Assessment of Severity
1. Spirometry is essential for the diagnosis of COPD and is useful for assessment of the severity of airflow obstruction. *[Grade C]*
2. Management decisions should be guided by overall assessment of the patient which besides spirometry, should also include the patient's symptoms, exercise capacity and the presence of co-morbidities and complications. *[Grade C]*

SECTION 2 COPD : EPIDEMIOLOGY AND DISEASE BURDEN

COPD prevalence, morbidity, and mortality vary across the world and across different ethnic groups within countries. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population.[20-22 (Level II-3)] According to WHO estimates in 2007, 210 million people have COPD worldwide with 80 million of them experiencing moderate to severe chronic disease.[23 (Level II-3)] COPD was ranked as the twelfth leading cause of disability in 1990, but it is projected to rank fifth in 2020, behind ischaemic heart disease, major depression, traffic accidents and cerebrovascular disease as leading causes of disability.[24 (Level II-3)] It is second only to heart disease as a cause of disability that forces people to stop working.[25 (Level II-3)] The number of deaths from COPD have increased more than 60% over the last 20 years, and more than 95% of all COPD-related deaths occur in people older than age 55 **(Figure 2-1)**.[26] COPD will become the third leading cause of death worldwide by 2030.[27 (Level III)]



A regions: developed countries in North America, Western Europe, Japan, Australia, and New Zealand; **AMRO BD**: developing countries in the Americas; **EURO BC**: developing countries in Europe; **EMRO**: Eastern Mediterranean and north Africa; **SEARO**: South-east Asia; **WPRO**: Western Pacific; **AFRO**: sub-Saharan Africa.

Figure 2-1: Age Standardised COPD Mortality Rate by WHO Region

These statistics are likely to underestimate COPD as a cause of death due to the imprecise and variable definitions of COPD that complicate the quantification of its mortality and morbidity.[28-29] In addition, COPD is more likely to be reported as a contributory rather than underlying cause of death or morbidity, or may not be reported at all.[30-31 (Level III)] In Asia-Pacific countries where tobacco smoking and indoor air pollution are highly prevalent the rise of COPD incidence is particularly dramatic contributing to a significant disease burden.[32] Data from a WHO/ World Bank study were used to extrapolate a COPD prevalence figure of 3.8% for the entire Asian population,[24 (Level III)] but recent studies suggest that COPD is a more significant problem in the region than has been previously realised.

Two major studies conducted in Japan[33 (Level II-2)] and Korea[34 (Level II-2)] more recently showed a COPD prevalence of 8.55% and 7.5% respectively. The prevalence of COPD in Asia-Pacific has been estimated indirectly through a risk factor prevalence model, which was mainly driven by varying smoking rates and levels of air pollution.[32] The prevalence of moderate to severe COPD in adults aged 30 years or above in the Asia-Pacific region was estimated to be at approximately 6.3% and for Malaysia at 4.55% **(Figure 2-2)**.

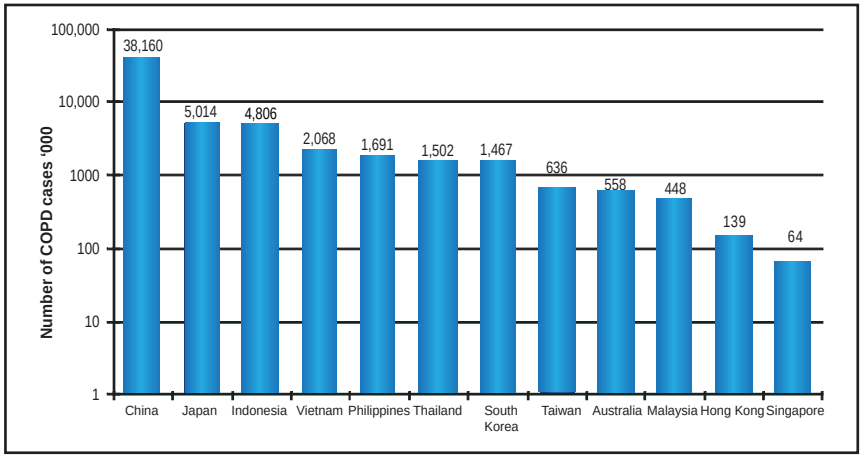


Figure 2-2: Model Projections of Moderate-Severe COPD in Population Aged ≥ 30 Years

Consistent with the WHO Global Burden of Disease study,[24] both mortality and morbidity rates for COPD were reported to be higher for men than for women and increased with increasing age.[35 (Level III)] COPD-related illness was higher in men, with rates of 32.6 to 334.[26] per 10,000 people, compared with rates of 21.2 to 129 per 10,000 for women.[36] Chronic respiratory disease including COPD was responsible for 7% of the total Disability-Adjusted Life Years (DALYs) in Malaysia and was ranked fifth as the leading cause disease burden.[37 (Level III)] The burden of COPD in males is almost three times that of females. The per capita burden of disease increases with age both in males and females where it is predominantly due to COPD in males, while in females it is related to other respiratory diseases.[37 (Level III)] In a survey by the South East Asia Tobacco Association (SEATCA) in Malaysia in 2006, 77% of the health economy burden with the highest growth projected health care cost (2004-2010) among the three major tobacco-related diseases in Malaysia is contributed by COPD.[37]

SECTION 3 RISK FACTORS

3.1 Introduction

Cigarette smoking is the best known and most studied risk factor for COPD. About 15% of smokers develop COPD.[38(Level II-2)] However, tobacco smoke is the risk factor for as much as 90% of the cases of COPD.[39(Level III)] Understandably, tobacco smoke cannot be the only risk factor for COPD as non-smokers may also develop the disease. Other risk factors for COPD are varied and are listed in Table 3-1.

Table 3-1 Risk Factors for COPD

Genes
Exposure to particles
- Tobacco smoke
- Occupational dust, organic and inorganic
- Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings
- Outdoor air pollution

Lung growth and development
Oxidative stress
Gender
Age
Respiratory infections
Socioeconomic status

3.2 Genes

Severe alpha-1 antitrypsin enzyme deficiency causes panlobular emphysema in both smokers and non-smokers. This rare hereditary disease is most commonly seen in individuals of Northern European origin.[40 (Level II-2)] There have been inconsistent reports on the familial risk of airflow obstruction in smoking siblings of patients with severe COPD.[41 (Level II-2)]

3.3 Exposure to Particles

- Tobacco smoke

Cigarette smoke causes COPD in susceptible individuals. The risk of COPD in smokers in dose-related.[42] Pipe and cigar smokers have greater COPD morbidity and mortality rates than non-smokers, although their rates are lower than those for cigarette smokers.[43 (Level III)] Environmental tobacco smoke also contributes to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particles and gases.[44,45 (Level II-2)] Pregnant women are advised to stop smoking as tobacco smoke poses a risk for the foetus by affecting lung growth and development in utero.[46 (Level II-3)]

- Occupational dusts and chemicals

Occupational exposures are independently associated with the severity of airflow limitation, respiratory symptoms, and employment status in patients with COPD.[47 (Level II-3)] These exposures include organic and inorganic dusts, chemical agents and fumes. Livestock farmers have an increased risk of chronic bronchitis, COPD and reduced FEV_1. Ammonia, hydrogen sulfide, inorganic dust and organic dust may be causally involved, but a role for specific biological agents cannot be excluded. Atopic farmers appear more susceptible to develop farming-related COPD.[48 (Level II-3)]

- **Indoor air pollution**

Biomass and coal are the main sources of energy for cooking and heating in many communities in the Middle East, Africa and Asia.[49,50 (Level III)] Wood, animal dung, crop residues and coal are burned in poorly functioning stoves, in poorly ventilated rooms and lead to very high levels of indoor air pollution, a well established risk factor of COPD in women.[51-54 (Level II-2)]

- **Outdoor air pollution**

The role of outdoor air pollution in causing COPD is unclear, but appears to be small when compared with cigarette smoking. However, air pollution from motor vehicle emissions in cities is associated with a decrease in lung function.[55 (Level II-3)]

3.4 Lung growth and development

Any factor that affects lung growth during gestation and childhood has the potential for increasing an individual's risk of developing COPD. A large study and meta-analysis confirmed a positive association between birth weight and FEV_1 in adulthood.[56 (Level III)]

3.5 Oxidative stress

Oxidative stress results from an imbalance between oxidants (generated by phagocytes during mitochondrial electron transport, air pollutants, cigarette smoke, etc.) and antioxidants. Oxidative stress directly injures the lungs and initiates lung inflammation which plays a role in the pathogenesis of COPD.[57 (Level III)]

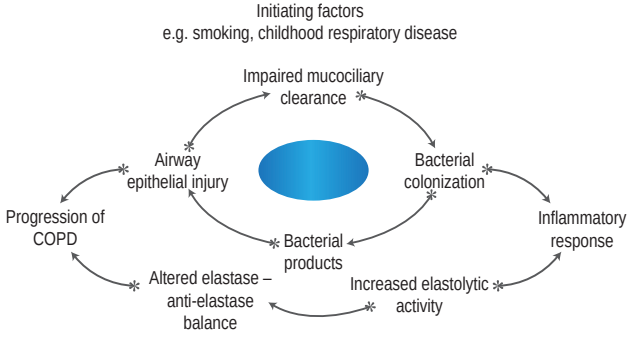
3.6 Gender

The role of gender in determining COPD risk remains unclear. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men and raise concerns on the increasing number of female smokers in both developed and developing countries.[58 (Level II-3)]

3.7 Infection

Infections both viral and bacterial may contribute to the pathogenesis, progression of COPD[57,59] and the bacterial colonization associated with airway inflammation.[60 (Level II-1)] Infection also plays a significant role in exacerbations associated with deterioration in lung function.[61(Level II-2)] **Figure 3-2** is a schematic diagram of the vicious circle hypothesis of the role of bacterial colonization in the progression of COPD.[62 (Level III)]

Figure 3-2: Vicious Circle Hypothesis



3.8 Socio-economic status

There is evidence that the risk of developing COPD is inversely related to socioeconomic status.[63] (Level II-2) It is not clear whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, or other factors that are related to low socioeconomic status.[64,65] (Level III)

SECTION 4 ASSESSMENT AND MONITORING

4.1 Initial Diagnosis

COPD is significantly underdiagnosed worldwide, including Malaysia.[35,66] (Level III) Many COPD patients present to their doctors with advanced disease at the time of diagnosis. Early diagnosis with successful smoking cessation interventions reduce the decline in lung function, and early intervention with effective treatment improves symptoms and health status.[67,68] (Level II-2)

A clinical diagnosis of COPD should be considered in any patient with a history of exposure to risk factors for the disease with symptoms of chronic cough, sputum production or dyspnoea.

The diagnosis should be confirmed by spirometry. A post-bronchodilator FEV_1/FVC ratio of less than 0.7 confirms the presence of airflow limitation that is not fully reversible and is currently widely accepted as the diagnosis criteria for COPD.[69] (Level III)

If spirometry is unavailable, clinical signs and symptoms, such as progressive shortness of breath and chronic cough with low peak expiratory flow rate, can be used to help with the diagnosis. [70] (Level III) Since peak expiratory flow readings have poor specificity,[71] (Level II-2) every effort should be made to refer the patient for spirometry to confirm the diagnosis.

4.2 Assessment of Symptoms

Dyspnoea is the hallmark symptom of COPD and is the main reason most patients seek medical attention. The dyspnoea is progressive over months or years and is persistent. As lung function deteriorates, the breathlessness interferes with patients' daily activities.

Cough is often the first symptom of COPD which may initially be intermittent but later present daily, often with chronic sputum production. Wheezing and chest tightness may also be present. Extrapulmonary effects such as weight loss, signs of cor pulmonale and other co-morbid conditions should also be identified and assessed.[72] (Level III) Psychiatric morbidity is common in advanced COPD.[73] (Level III)

COPD patients experience fluctuations in symptoms and general feelings of well being - these can vary from one day to the next.

4.3 Medical History

A thorough medical history should include the following:

- Current symptoms and the pattern of symptom development including severity of breathlessness, for example using the modified Medical Research Council (MMRC) dyspnoea scale **(Table 1-2)**[13]
- Exposure to risk factors and possibilities for eliminating or reducing exposure
  - Smoking history
    - Quantification of tobacco consumption: total pack years = (number of cigarettes smoked per day ÷ 20) x number of years of smoking
  - Occupational and environmental exposures to other lung irritants

- Impact of disease on psychosocial well being
- Past medical history including exacerbations and admissions for respiratory illnesses
- Family history of any respiratory disorder
- Presence of other co-morbidities such as cardiovascular disease, psychiatric illness, malignancy, osteoporosis and musculoskeletal disorders
- All current medical therapy and its appropriateness
- Social and family support available to the patient.

4.4 Physical Examination

Physical examination is not usually diagnostic of COPD but is an important part of patient care. Physical signs of airflow limitation and air trapping (barrel chest, loss of cardiac and liver dullness, prolonged expiration, reduced breath sounds) are not usually present until the disease is already at an advanced stage. Physical examination may detect co-morbidities or other illnesses and detect the development of complications of COPD such as malnourishment and cor pulmonale.

4.5 Measurement of Lung Function

Spirometry is required to confirm the diagnosis of COPD and to assess the severity of the disease. Spirometry should be performed in people with exposure to risk factors who have chronic cough and sputum production even without dyspnoea as it may help identify patients earlier in the course of the disease.[13, 74 (Level III)] Peak flow measurements can detect airflow limitation but has poor specificity. The relationship between peak expiratory flow and FEV_1 is poor in COPD.[75 (Level II-2)]

4.6 Bronchodilator Reversibility Testing:

Bronchodilator testing is required to establish the best attainable lung function at that point of time. Response to a bronchodilator is considered significant if the change in FEV_1 is both at least 200 mls and 12% above the pre-bronchodilator FEV_1.[76 (Level III)] If there is a marked response to bronchodilators, asthma should be considered. A proportion of COPD patients may show significant response to bronchodilators.[77 (Level III)]

4.7 Assessment of COPD Severity

COPD severity is based on the patient's level of symptoms, the severity of spirometric abnormality based on FEV_1 and the presence of complications such as respiratory failure and cor pulmonale **(Table 1-3)**.[78 (Level III)] Multidimensional assessment of severity includes the BODE index[79 (Level II-2)] and the locally developed SAFE index.[80 (Level II-2)]

4.8 Additional Investigations

i. Six Minute Walk Test (6MWT)[81 (Level III)]:

This test measures the distance covered during six minutes and is a useful test of exercise capacity and provides prognostic information.[82 (Level II-2)] Arterial oxygen desaturation can be measured with a pulse oximeter during walking.

ii. Chest Radiograph:

A chest radiograph is valuable in excluding other diagnoses such as lung cancer, heart failure, bronchiectasis and tuberculosis. Radiological changes associated with COPD include the presence of hyperinflation (flattened diaphragm and increase in lung volume), bullae and hyperlucency of the lungs. High resolution computed tomography scanning is not routinely recommended unless there is diagnostic uncertainty.

iii. Arterial Blood Gas Analysis:

This should be performed in patients with $FEV_1 < 40\%$ predicted if they have low arterial oxygen saturation (less than 92% on pulse oximetry) or with clinical signs of respiratory failure or cor pulmonale as these patients may benefit from long term oxygen therapy at home.[83] (Level III)

iv. Full Blood Count:

This detects underlying anaemia of chronic diseases. Polycythaemia can develop with arterial hypoxemia.

v. Electrocardiography (ECG):

ECG is useful in detecting pulmonary hypertension in advanced disease and concurrent ischaemic heart disease.

vi. Alpha-1 Antitrypsin Deficiency Screening:

This should be performed in young COPD patients (<45 years old) or who have a strong family history of the disease.

Other suggested investigations include fasting plasma glucose, serum albumin and serum fasting lipids to detect other common co-morbidities

4.9 Differential Diagnoses

Other potential diagnoses in older patients presenting with progressive breathlessness are listed in **(Table 4-1)**. The major differential diagnosis is chronic asthma. In most instances, the diagnosis can be easily made **(Table 4-2)** but occasionally a clear distinction between asthma and COPD may not be possible clinically and physiologically, and it is assumed that both conditions co-exist in these patients.

Table 4-1 Main Differential Diagnoses of COPD

Bronchial asthma	Bronchiectasis
Congestive heart failure	Diffuse parenchymal lung disease
Pulmonary tuberculosis	Pulmonary vascular disease

Table 4-2 Clinical Differences Between Asthma and COPD

Clinical features	Asthma	COPD
Age of onset	Usually early childhood, but may have onset at any age	Usually > 40 years old
Smoking history	May be non-, ex- or current smoker	Usually > 10 pack-years
Atopy	Often	Infrequent
Family history	Asthma or other atopic disorders commonly present	Not a usual feature
Clinical symptoms	Intermittent and variable	Persistent and gradually progressive worsening
Cough	Nocturnal cough or on exertion	Morning cough with sputum
Sputum production	Infrequent	Often
Reversibility of airflow obstruction	Characteristic of asthma	Airflow limitation may improve but never normalises
Exacerbations	Common at all levels of severity except in mild disease	Increase in frequency with increasing severity of disease

4.10 Ongoing Monitoring and Assessment

COPD patients should be followed up regularly as COPD is usually a progressive disease with deterioration in clinical symptoms and lung function over time. Ongoing monitoring and assessment in COPD is vital to ensure that the goals of treatment are being met.

Follow up visits should include evaluation of:

- Exposure to risk factors especially tobacco smoke. Ask about smoking and their willingness to stop (Refer to Section 5).
- Current symptoms and any new or worsening symptoms to suggest deterioration in lung function or development of complications. Consider the presence of concomitant conditions or co-morbidities.
- Physical examination to detect complications such as respiratory failure or cor pulmonale and other co-morbidities. Body weight and body mass index provide information on the nutritional status of the patient.
- Spirometry measurement especially if symptoms worsen. Active smokers and patients with frequent exacerbations are at risk of faster decline in lung function.
- Pharmacotherapy and other medical treatment. Assess the effectiveness of current regimen in controlling symptoms and any side effects from the medications. Ensure that patients are taking their medication at the right dose and frequency and inhaler techniques are correct. Issues regarding non-compliance to medications should be addressed.

- Exacerbation history. The frequency, severity and causes of exacerbations should be recorded. Severity can be estimated by the increased need for bronchodilator medication or systemic glucocorticosteroid requirements. Hospitalisations should be documented including the duration of stay and any use of invasive and non-invasive ventilation.
- Patient education. It is important for patients with COPD to understand the nature of their disease, risk factors for progression and strategies to help minimise symptoms.

Recommendations: Diagnosis and Assessment of Severity

1. The diagnosis of COPD should be confirmed by spirometry showing a post-bronchodilator FEV_1/FVC ratio of less than 0.7. *[Grade C]*
2. Assessment of COPD severity should be based on the severity of spirometric abnormality, the patient's symptoms, exercise capacity and the presence of co-morbidities and complications. *[Grade C]*

SECTION 5 REDUCING RISK FACTORS

5.1 Introduction

Identification, reduction, control and elimination of risk factors are important steps toward effective prevention and management of any disease. For COPD, these risk factors include tobacco smoke, occupational exposures, indoor and outdoor air pollution and irritants. Since cigarette smoking is the most commonly encountered risk factor for COPD worldwide, priority must be given to tobacco control programme, where amongst others smoking prevention strategies and availability of smoking cessation services should be emphasised to encourage smoke-free lifestyles.

5.2 Smoking Prevention

Smoking prevention is the single most effective intervention to reduce the risk of developing COPD and stop its progression.[68 (Level I)] This is endorsed by the international community with the establishment of the WHO Framework Convention on Tobacco Control (WHO FCTC) in 2005.

- Comprehensive tobacco control policies and programmmes with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel, including health care providers; community activities; schools; and radio, television, and the print media. Mandatory legal provision for pictorial health warnings on cigarette packs and packages is an efficient way to deliver clear truthful anti-smoking messages directly to smokers.
- National and local campaigns should be undertaken to reduce exposure to tobacco smoke in public places. Such bans are proven to work, resulting in measurable gains in respiratory health.[84(Level I)]
- Smoking prevention programmes should target all ages, including young children, adolescents, young adults, and pregnant women.
- Interventions to prevent smoking uptake and maximise cessation should be implemented at every level of the health care system.
- Doctors and public health officials should encourage smoke-free environments, including smoke-free homes.

Second-hand smoke exposure is also an important cause of respiratory symptoms and increased risk for COPD, especially in partners and offspring of smokers.[85(Level I)] Long-term indoor exposure, combined with crowded living conditions in poorly ventilated homes, adds to the total burden of particulate exposure and increases the risk of developing COPD.[86 (Level I)] Adults should not smoke in the immediate vicinity of non-smokers, especially children, nor in enclosed spaces such as cars and poorly ventilated rooms that expose others to increased risk. Children less than two years old who are passively exposed to cigarette smoke have an increased prevalence of respiratory infections, and are at a greater risk of developing chronic respiratory symptoms later in life.[87.88 (Level I)]

5.3 Smoking Cessation

Quitting smoking can prevent or delay the development of airflow limitation, or reduce its progression,[88 (Level I)] and can have a substantial effect on subsequent mortality.[89 (Level I)] All smokers – including those who may be at risk for COPD as well as those who already have the disease – should be offered the most intensive smoking cessation intervention available .

Smoking cessation interventions are effective in both sexes, in all racial and ethnic groups, and in pregnant women. Age influences quit rates, with young people less likely to quit. Nevertheless, smoking cessation programmes can be effective in all age groups. Effective interventions include individual as well as group programmes such as community-based stop-smoking challenges. The essential approaches are:

1. Pharmacotherapy
   - Nicotine replacement therapy (NRT) in the form of transdermal patches, gums, and nasal sprays
   - Varenicline
   - Bupropion
   - Nortriptyline
2. Counseling from doctors and other health professionals, given either by individual face-to-face interactions, group interactions or through telephone or web-based quit smoking services
3. Combination of counseling and pharmacotherapy

A successful smoking cessation strategy requires a multifaceted approach that includes sustained escalation in tobacco taxation, coherent government policies and legislations to reduce tobacco demands and production as well as health education and frequent dissemination of consistent anti-tobacco messages through the media and settings such as schools.[90,91(Level I)] However, health care providers, including doctors, nurses, dentists, psychologists, pharmacists, and others, are key to the delivery of smoking cessation messages and interventions. Involving as many of these individuals as possible will help. Health care workers should encourage all patients who smoke to quit, even those patients who come to the health care provider for unrelated reasons and do not have symptoms of COPD, evidence of airflow limitation, or other smoking related disease.[92 (Level I)]

5.4 Five Step Programme for Intervention (5A)[91(Level I)]

1. ASK: Systematically identify all tobacco users at every visit.

Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.

2. ADVISE: Strongly urge all tobacco users to quit in a clear, strong, and personalised manner.

3. ASSESS: Determine willingness to make a quit attempt.

Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).

4. ASSIST: Aid the patient in quitting.

a. Help the patient with a quit plan
b. Provide practical counseling
c. Provide intra-treatment social support
d. Help the patient obtain extra-treatment social support
e. Recommend use of approved pharmacotherapy except in special circumstances
f. Provide supplementary materials.

5. ARRANGE: Schedule follow-up contact, either in person or via telephone.

5.5 Counseling

Counseling delivered by doctors and other healthcare professionals significantly increases quit rates over self-initiated strategies.[93 (Level I)] Even a brief (three-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5-10%.[94 (Level I)] At the very least, this should be done for every smoker at every health care provider visit.[95 (Level I)]

5.6 Pharmacotherapy

Numerous effective pharmacotherapies for smoking cessation now exist,[96 (Level I)] and pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Special consideration should be given before using pharmacotherapy in selected populations:

- People with medical contraindications
- Light smokers (fewer than 10 cigarettes/day)
- Smokers who are pregnant
- Adolescent smokers

All forms of nicotine replacement therapy are significantly more effective than placebo.[96 (Level I)] Every effort should be made to tailor the choice of replacement therapy to the individual's culture and lifestyle to improve adherence. Other pharmacotherapy, like bupropion[97 (Level I)] and nortriptyline have also been shown to increase long term quit rates,[98,99 (Level I)] but should always be used as one element in a supportive intervention programme rather than on their own. Varenicline, a nicotinic acetylcholine receptor partial agonist that aids smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine has been demonstrated to be safe and efficacious.[100 (Level I)] The main adverse effect of varenicline is nausea, mostly mild or moderate which usually subsides over time. There are recent concerns that varenicline may be linked with depressed mood, agitation or suicidal thinking and behaviour in some smokers.[101 (Level I)]

5.7 Occupational Exposure

Many occupations have been shown to be associated with increased risk of developing COPD, particularly those that involve exposure to fumes and mineral and biological dusts. Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures, many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases.[102-104 (Level I)]

The main emphasis should be on primary prevention, which is best achieved by the elimination or reduction of exposures to various substances in the workplace. Secondary prevention, achieved through surveillance and early case detection, is also of great importance. Both approaches are necessary to improve the present situation and to reduce the burden of lung disease.

5.8 Indoor and Outdoor Air Pollution

Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants and particulates that cause adverse effects on lung function.[104 (Level I)]

Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients. Reduction of exposure to smoke from biomass fuel, particularly among women and children, is a crucial goal to reduce the prevalence of COPD.

5.9 Steps for Health Care Providers/Patients

The health care provider should consider COPD risk factors including smoking history, family history, exposure to indoor/outdoor pollution and socioeconomic status for each individual patient. Some steps to consider are:

- Individuals at risk for COPD should be counseled concerning the nature and degree of their risk for COPD.
- If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged.
- Respiratory protective equipment has been developed for use in the workplace in order to minimise exposure to toxic gases and particles.
- Ventilation and interventions to meet safe air quality standards in the workplace offer the greatest opportunity to reduce worker exposure to known atmospheric pollutants and reduce the risk of developing COPD.

In patients who have been diagnosed with COPD:

- Persons with advanced COPD should monitor public announcements of air quality and be aware that staying indoors when air quality is poor may help reduce their symptoms.
- The use of medication should follow the usual clinical indications; therapeutic regimens should not be adjusted because of the occurrence of a pollution episode without evidence of worsening of symptoms or lung function.

Recommendation: Smoking Cessation
1. Smoking cessation is the single most effective and cost effective intervention in most people to reduce the risk of developing COPD and stop its progression. All smokers should be offered smoking cessation interventions. *[Grade A]*

SECTION 6 MANAGING STABLE COPD

6.1 Objectives of Managing Stable COPD

These include:

1. Preventing disease progression
2. Reducing frequency and severity of exacerbation
3. Improving exercise tolerance
4. Improving lung function and general health
5. Improving patient's symptoms, e.g. dyspnoea, cough and tiredness.
6. Improving quality of life
7. Reducing mortality.

6.2 Patient Education

Patient education, essential in any chronic illness, should be individualised to address the cause, disease severity, specific symptoms, response to therapy and other co-morbidities. It is aimed to improve their quality of life.

Topics for patient education may include:

- A brief explanation on the aetiologies, pathogenesis and pathophysiology of the illness
  - o Understanding the aetiologies of COPD will enable patients to take necessary steps toward avoiding these risk factors.
  - o Patients may be enlightened on how the pathophysiological changes of COPD have contributed to their symptoms.
  - o As many patients still think that they have some form of asthma-related disease, explanation should be given to differentiate COPD from asthma **(Table 4-2)**.
- Information about the natural course of the illness.
  - o COPD is a progressive disease
  - o Smoking cessation has the most significant effect on modifying the course of disease progression.
  - o COPD exacerbation accelerates disease progression. Education has been shown to improve patients' response to exacerbations and health outcomes.[106,107 (Level I)]
- Patients should be counseled on their roles in optimising treatment and health outcomes. Studies have shown that education plays a role in improving patient skills, ability to cope with illness and health status.[108-111]
- Instruction on how to use an inhaler, assessing inhaler technique (consider recommending a holding-chamber if technique is unsatisfactory) and other treatment.
- Self-management plan in acute situation (e.g., recognition of a COPD exacerbation, treatment intervention; and, when to seek medical help).
- Strategies on minimising dyspnoea.
- Information on proper nutrition intake, exercise and pulmonary rehabilitation.
- Roles of vaccination.
- For patients with more severe disease, counseling may include:
  - o Information about complications of COPD
  - o information about long-term oxygen therapy
  - o Advanced directive and end-of-life decisions. Prospective end-of-life discussion can lead

to better understanding of advanced directives and effective therapeutic decision at end of life.[112 (Level II-1)]

Limited published data exist evaluating the efficacy of the chronic care model in COPD management.[113 (Level I)] However, COPD patients recruited to a comprehensive COPD education programme in Canada had significantly fewer exacerbations and hospitalisations. They also utilised less health care resources.[114 (Level I)] These results may encourage adoption of similar programmes locally.

6.3 Influenza Vaccination

- Reduces the risk of COPD exacerbation
- COPD patients infected with influenza have a significant risk of requiring hospitalisation.
- An annual influenza vaccination reduces morbidity and mortality from the disease by as much as 50% in the elderly and reduces the incidence of hospitalisation by as much as 39% in patients with chronic respiratory conditions.[115-116 (Level II-1)]

6.4 Pneumococcal Vaccination

- The benefit of pneumococcal vaccination in COPD is less well established. Some reports state that the vaccine has up to a 65% efficacy in COPD patients,[117] although an effect on reducing the frequency of COPD exacerbation has yet to be established.
- A recent report demonstrated a reduction in the prevalence of community-acquired pneumonia following pneumococcal vaccination in a subgroup of COPD patients younger than 65 years with an $FEV_1 < 40\%$ predicted.[118 (Level I)]
- Hence, a 23-valent polysaccharide vaccine (PPV23) is recommended for patients who are younger than 65 years but with a $FEV_1 < 40$ % predicted (irrespective of age)
- Even though the vaccination of PPV23 remains controversial, the panels support the WHO position stand to vaccinate all COPD patients at least once in their lifetime and have it repeated $\geq$ 5 years (with a maximum of two doses in one's lifetime).[119 (Level III)]

6.5 Treatment Strategy: Consisting of Pharmacological and Non-pharmacological Interventions

6.5.1 Pharmacological Therapy

- Bronchodilators remain the mainstay of pharmacological therapy
  - o They reduce airway smooth muscle tone, improve expiratory flow rate, reduce air-trapping and hyperinflation of the lung.
  - o They also improve the patients' dyspnoea scores, increase exercise tolerance, reduce disability in daily living and improve overall health status.
  - o Optimal pharmacotherapy should be guided by the patients' symptoms, level of activity and frequency of COPD exacerbation.

Inhaled short-acting bronchodilators

- These include inhaled short-acting β_2-agonists (SABAs) and inhaled short-acting anticholinergics (SAACs).

Inhaled SABAs

(Example: MDI salbutamol 200 µg, fenoterol 200 µg or terbutaline 200 µg PRN or 4 to 6 hourly)

- They have been shown to improve lung function, dyspnoea and exercise tolerance.
  - o A systematic review of 13 randomised controlled trials (RCTs) showed that inhaling SABAs on a regular basis for at least 7 days in patients with various stages of COPD (FEV_1 of <70% predicted) is associated with improvements in post-bronchodilator lung function and a decrease in both breathlessness and treatment failure. Nonetheless, they have not been shown to have a consistent impact on quality of life.[120 (Level I)]

Inhaled SAACs

(Example: MDI ipratropium bromide 40 µg 6 hourly)

- Inhaled SAACs act on the muscarinic receptors by blocking their bronchoconstrictor effects and reducing mucus secretions. An increase in FEV_1 was observed with anticholinergics compared to the placebo.[121-124(Level I)] Some studies also found that the inhalation of SAACs is associated with an improvement in dyspnoea, a reduction in the need for rescue medications,[122-123 (Level I)] and an improvement in the quality of life.[124] The combination of inhaled SABA and SAAC achieves a greater bronchodilator effect than either one alone.[122,126 (Level II-1)] However, there was no data to show that either SAAC or SABA reduces exacerbation.

Inhaled long-acting bronchodilators

- Consist of long-acting β_2-agonists (LABAs) and long-acting anticholinergics (LAACs)
- Offer a more sustained relief of symptoms and improvement of lung function
- Also improve patients' compliance to treatment.

Inhaled LABA

Examples: salmeterol 50 µg twice a day or formoterol 9-12 µg twice a day.

- The duration of action of LABAs is 12 hours or longer as compared to 4 hours in SABAs.
- A review of 23 randomised controlled trials showed that the treatment of patients with COPD (FEV_1<75% predicted) using LABA as compared to placebo produces modest increases in lung function, and improves health-related quality of life and symptoms.[126 (Level I)] In this review, LABA was also associated with a significant reduction in COPD exacerbations. [126 (Level I)]
- The results of this systematic review were further supported by the TORCH study, a 3-year randomised controlled study, which showed that salmeterol significantly reduced exacerbations, improved lung function and improved health-related quality of life as compared with placebo in patients with COPD of FEV_1 < 60% predicted.[127 (Level I)]

Inhaled LAAC

- Tiotropium is the only LAAC currently in the market. The dose is 18 µg once daily administered through a Handihaler®.
- It is effective for at least 24 hours in patients with airflow limitation and dynamic hyperinflation.
- Several clinical trials using tiotropium for 6 weeks to 12 months showed improvement in exercise tolerance, quality of life and dyspnoea as well as reduction in exacerbation as compared to the placebo.[128-131 (Level II-1)]
- This is further supported by a 4-year prospective study, the UPLIFT trial, which demonstrated that the use of tiotropium in patients with FEV_1 of less than 70% predicted, was associated

with a reduction in exacerbation and hospitalisation due to exacerbation but was not associated with a reduction in the rate of decline in FEV_1 when compared to placebo.[132 (Level I)]

- A few studies have suggested that tiotropium produces superior bronchodilation as compared to the LABAs.[133-134 (Level I)]

Inhaled LAAC and Inhaled LABA

Two small short-term studies showed that the combination of tiotropium and formoterol may have an additive effect on lung function and may reduce the use of rescue medication.[134-135 (Level II-1)] However, in a larger and longer study on patients with moderate to severe COPD, the OPTIMAL study, the addition of salmeterol to tiotropium did not show any improvement in lung function or a reduction in exacerbation compared to tiotropium alone.[136 (Level I)] Nonetheless, this combination did improve the health-related quality of life.

Inhaled LABA and inhaled corticosteroid (ICS) combination

The combination of LABA/ICS has been shown to improve lung function, quality of life and reduce exacerbations compared with placebo in COPD patients with FEV_1 <65% predicted.[127, 137-139 (Level I)] In the TORCH study, there was a trend towards a reduction in mortality in patients taking LABA/ICS compared to placebo, though the reduction was not statistically significant.[127 (Level I)] In the same study, the decline in lung function in the patients taking LABA/ICS (39 mL/year) was also slower compared with placebo (55 ml/year).[140 (Level II-1)] When ICS/LABA was compared with LAAC in the INSPIRE study among patients with severe and very severe COPD with a history of exacerbation, there was no difference in exacerbation rate but the former was associated with better health related quality of life and lower mortality.[141 (Level I)] However, this study was not statistically powered to study the mortality outcome.

Inhaled LAAC and inhaled LABA/ICS combination

In the UPLIFT study, where 53% of the study patients had severe to very severe COPD and 46% of them were on ICS/LABA, the addition of tiotropium was associated with a significant improvement in lung function, a significant delay in time to first exacerbation, significant reduction in number of exacerbations and significant improvement in health-related quality of life.[132 (Level I)] Thus, in patients who are already on a LABA/ICS combination, but still have persistent symptoms, addition of a LAAC should be considered. On the other hand, the OPTIMAL study showed that adding ICS/LABA to tiotropium significantly improved lung function, improved quality of life and reduced hospitalisation but did not reduce exacerbation rates.[136 (Level II-2)]

ICS

(Example: fluticasone 500 µg twice daily, budesonide 800 µg twice daily, beclomethasone 1000 µg twice daily)

- The trial outcomes using ICS on COPD are rather conflicting. The EUROSCOP trial[142] and the Copenhagen Lung Health Study[143] showed the use of ICS in mild COPD does not slow the rate of decline of FEV_1. However, the ISOLDE trial[144] and and the study by Paggiarro PL et al[145] showed that treatment with high dose ICS, in this case, fluticasone 1000 µg a day, in moderate to severe COPD decreases exacerbations and modestly slows the progression of respiratory symptoms, but has minimal or no impact on lung function.[(Level I)] Two recent multi-centre randomised controlled studies confirmed that ICS alone improves FEV_1 and health-related quality of life, and reduces moderate to severe exacerbations.[127,139] Furthermore, the TORCH study showed a slower rate of decline in lung function in patients taking high dose ICS alone (42 ml/year) as compared with placebo (55 ml/year).[140 (Level II-1)]

Oral Corticosteroids[142,144,146,147]

- About 10% of COPD patients will have 20% improvement in FEV_1 after oral corticosteroid administration.
- However, chronic systemic corticosteroid usage is known to be associated with potentially serious side-effects such as osteoporosis, premature cataract, muscle weakness, diabetes mellitus and hypertension.
- Indeed, one study showed that in severe COPD patients, maintenance treatment with oral glucocorticoids is associated with increased mortality in a dose-dependent manner. Hence, prolonged courses of systemic corticosteroids for the treatment of COPD should be discouraged.(Level II-2)

Combination of LAAC and ICS

There is no data to support the use of this combination.

Methylxanthines

(Example: oral theophylline 100-300 mg twice daily)

- Theophylline is a weak bronchodilator, hence offering only a modest improvement in symptoms and exercise tolerance.
- This drug should be relegated to third line therapy. It should only be added if inhaled long-acting bronchodilators and ICS do not achieve the desirable control of symptoms.
- It may be added to bronchodilator treatment if patients still have persistent symptoms despite LABA.[148 (Level II-1)]
- This potential benefit should be weighed against its side-effects, such as nausea, abdominal discomfort, diarrhoea and risk of cardiac arrhythmias.
- In view of the narrow therapeutic window and significant toxicity, monitoring of drug levels is desirable. The therapeutic range is 10 – 20 mg/L.[149]
- Some recent studies suggest that it has an anti-inflammatory effect.[150,151 (Level I)] In one study, COPD patients treated with low doses of theophylline (with concentration < 10 mg/L) were noted to have reduced neutrophil counts, interleukin (IL)-8 concentration and myeloperoxidase levels, as well as reduced neutrophil chemotactic responses in induced sputum.[150] In another placebo-controlled study, a significant reduction in myeloperoxidase and neutrophil elastase was noted after four weeks of treatment with theophylline.[151]
- Corticosteroids suppress the inflammatory genes through deacetylation of core histone by histone deacetylase (HDAC). It has been found that HDAC activity is reduced in cells of cigarette smokers possibly due to increased oxidative stress.[152,153 (Level II-1)] There is some evidence to suggest that low doses of theophylline restore steroid responsiveness in COPD patient by increasing the HDAC activity.[154 (Level II-1)]

Phosphodiesterase-4 (PDE4) inhibitors

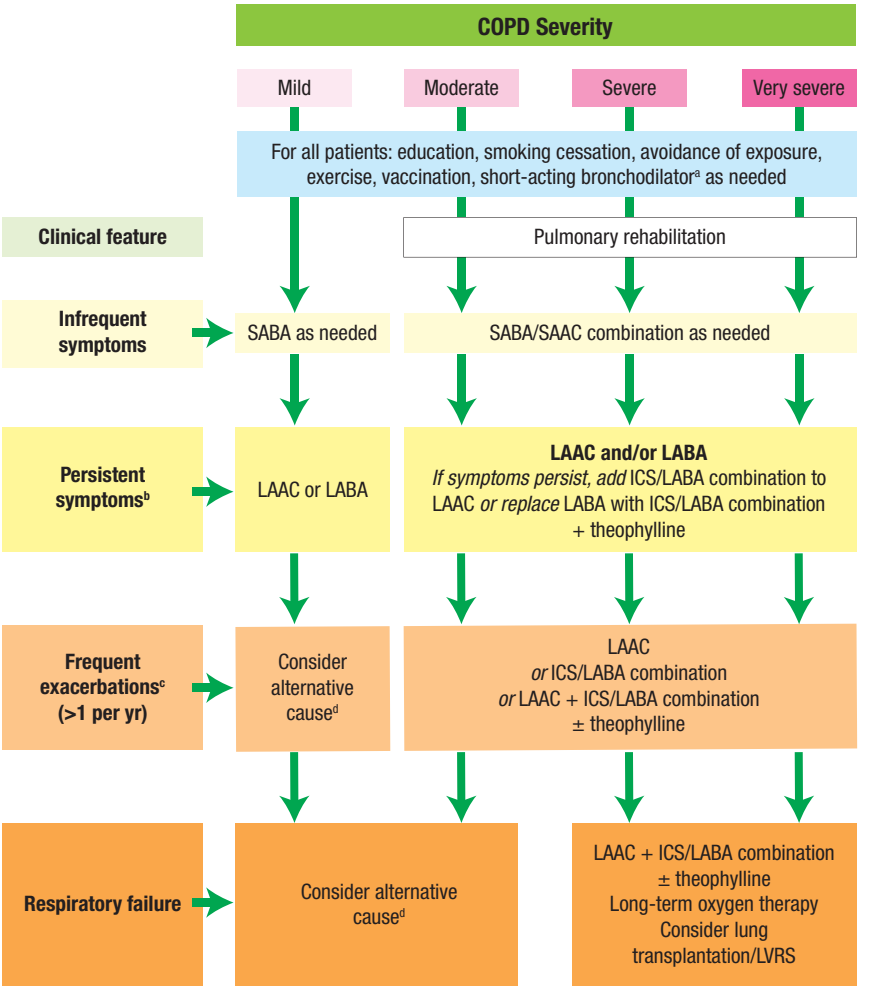
(e.g. oral roflumilast 500 mg once daily, cilomilast 15 mg twice daily)

- Recently, treatment with PDE4 inhibitors have been studied in COPD patients.
- The results of four phase III clinical studies have been recently published on roflumilast. Two 12-month studies of patients with severe COPD and bronchitic symptoms demonstrated that roflumilast produced a statistically significant and clinically relevant reduction in exacerbations, 17% per patient per year (rate of 1.14 events per year with roflumilast vs. 1.37 per year with placebo, $p<0.001$).[155 (Level I)] This reduction in exacerbations occurred even in patients treated with concomitant LABA. The other two studies involving patients with moderate-to-severe COPD showed roflumilast improved patients' pre-bronchodilator FEV1 beyond long-acting bronchodilators (salmeterol or tiotropium). However, in the latter study, it did not lead to a statistically significant reduction in COPD exacerbations.[156 (Level I)] Across the studies, roflumilast demonstrated a statistically significant improvement in pre-bronchodilator FEV_1, in the range of 48 to 80 mL.
- One 24-week, randomised, placebo-controlled study of COPD patients treated with cilomilast showed quite similar result. A difference of 40ml of pre-bronchodilator FEV1 was detected, favouring cilomilast. There was a clinically significant mean reduction by 4.1 in the total St George's Respiratory Questionnaire score in subjects receiving cilomilast therapy compared with those on placebo. A higher proportion of subjects in the cilomilast group were exacerbation-free at 24 weeks compared with those on placebo (74% versus 62%).[157 (Level I)]
- Significant adverse effects in subjects treated with PDE4 inhibitors include nausea, diarrhoea, weight loss and headache.
- PDE4 inhibitors maybe an important treatment for patients with COPD, particularly those with bronchitic symptoms, in the future.

Recommendations: Managing Stable COPD

1. Treatment recommendation should be based on disease severity, symptoms and frequency of COPD exacerbations ***(Figure 6.1)***. *[Grade C]*
2. COPD patients at any stage of disease severity should be advised to quit smoking if they still smoke. *[Grade A]*
3. In patients with mild COPD who are symptomatic, SABA or SAAC or a combination of both may be prescribed. *[Grade C]*
4. In patients with moderate to very severe COPD with persistent symptoms, but without frequent COPD exacerbations, either a LAAC or LABA may be initiated. If symptoms persist despite this treatment, an ICS/LABA combination should be added; and vice versa. *[Grade A]*
5. Theophylline can be added to patients who are symptomatic despite maximum inhaled therapy. *[Grade C]*
6. In resource limited settings, alternative treatment may be used ***(Figure 6.2).*** *[Grade C]*

Figure 6.1: Algorithm for Managing Stable COPD

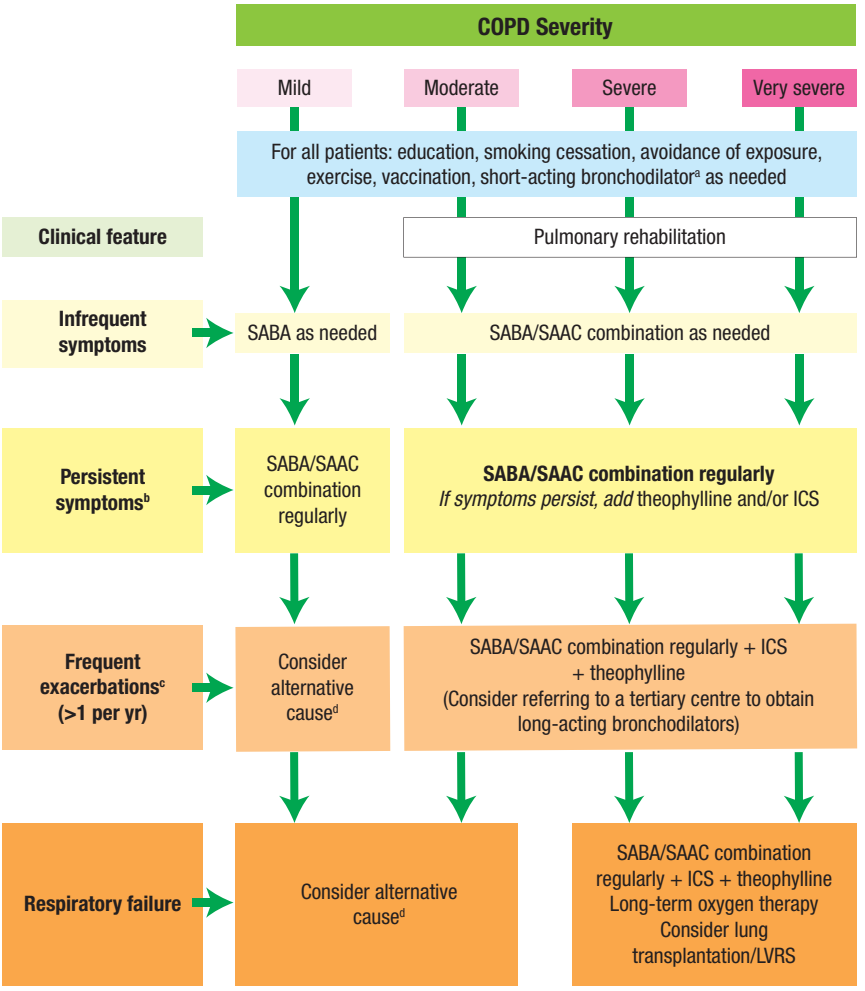


Notes:

1. SABA – Short-acting ß2 agonist; SAAC – Short-acting anticholinergic; LAAC – Long-acting anticholinergic; LABA – Long-acting ß2 agonist; ICS – Inhaled corticosteroid; LVRS – lung volume reduction surgery
2. ICS dose per day should be at least 1000 µg of fluticasone or 1600µg of budesonide or beclomethasone

a. All COPD patients, irrespective of disease severity, should be prescribed SABA or SABA/SAAC combination (Berodual®/Combivent®) as needed. SABA has a more rapid onset of bronchodilatation than SAAC.
b. Defined as need for rescue bronchodilators more than twice a week.
c. Frequent exacerbation is defined as one or more episodes of COPD exacerbation requiring systemic corticosteroids ± antibiotics and/or hospitalisation over the past one year
d. Consider alternative causes - it is less common for patients with mild COPD to have frequent exacerbations; similarly, respiratory failure is uncommon in patients with mild to moderate COPD severity. Hence, in such patients, an alternative cause should be explored even if the COPD diagnosis is firmly established.

Figure 6.2: Algorithm for Managing Stable COPD in Resource-Limited Settings



Notes:

1. SABA – Short-acting ß2 agonist; SAAC – Short-acting anticholinergic; LAAC – Long-acting anticholinergic; LABA – Long-acting ß2 agonist; ICS – Inhaled corticosteroid; LVRS – lung volume reduction surgery
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d. Consider alternative causes - it is less common for patients with mild COPD to have frequent exacerbations; similarly, respiratory failure is uncommon in patients with mild to moderate COPD severity. Hence, in such patients, an alternative cause should be explored even if the COPD diagnosis is firmly established.

SECTION 7 MANAGING STABLE COPD: NON-PHARMACOLOGICAL TREATMENTS

7.1 Pulmonary Rehabilitation in COPD

Pulmonary rehabilitation aims to reduce symptoms, decrease disability, increase participation in physical and social activities, and improve the overall quality of life (QoL) for patients with chronic respiratory diseases. It includes exercise, education, psychosocial and behavioural intervention by an interdisciplinary team of specialists.[158 (Level III)]

Most structured pulmonary rehabilitation programmes last between 6 and 12 weeks[159-160(Level III)] They have been demonstrated to produce benefits that last between 12 and 18 months. There is no consensus on the optimal duration of pulmonary rehabilitation programmes. An exercise programme can be helpful in the home, in the hospital, or in institutional settings.[161-167 (Level I)] In Malaysia, only a small fraction of patients with COPD are able to get exercise training as only a few hospitals have programmes that provide closely supervised exercise training and access to these programs is limited.

General aerobic conditioning is more helpful than specific training of respiratory muscles.[159,160,168 (Level III, Level I)] The muscles of ambulation should be a focus of pulmonary rehabilitation, emphasising endurance and strength training. Benefit is seen even in irreversible pulmonary disorders, since much of the disability and handicap results not just from the respiratory disorder per se but from secondary morbidities that often are treatable. Although the degree of airway obstruction or lung hyperinflation does not change much with pulmonary rehabilitation, reversal of muscle deconditioning and better pacing enables patients to walk further with less dyspnoea.

Benefits of pulmonary rehabilitation include: [159,160,169,170 (Level III, Level I)]

- Improvement in exercise tolerance
- Reduction in the sensation of dyspnoea
- Improvement in health-related quality of life (HRQoL).
- Improvement in peripheral muscle strength and mass
- Reduction in number of days spent in hospital
- Cost effectiveness
- Improvement in the ability to perform routine activities of daily living
- Reduction in exacerbations
- Reduction in anxiety and depression

Improvements in exercise tolerance are maintained for 6 to 12 months. Improvements in HRQoL may be maintained for longer periods.

There is insufficient evidence to determine if pulmonary rehabilitation improves survival among patients with COPD.

Recommendations: Pulmonary Rehabilitation

1. Pulmonary rehabilitation should be considered as an addition to medication therapy for symptomatic patients who have GOLD Stage II, III, or IV COPD. *[Grade A]*
2. Efforts should be directed towards the setting up of both hospital and home-based programmes locally. *[Grade A]*

7.2 Domiciliary Oxygen Therapy for COPD

Long-term administration of oxygen of >15 hours per day to patients with chronic respiratory failure has been shown to increase survival.[171-172 (Level I)] Home oxygen therapy did not appear to improve survival in patients with mild to moderate hypoxaemia or in those with only oxygen desaturation at night.[173 (Level I)] The goal of long-term oxygen therapy is to increase the baseline PaO_2 to at least 60 mm Hg (or 8.0 kPa) at rest, and/or produce an SaO_2 of at least 90%.

Indications for long-term oxygen therapy:[69 (Level III)]

- $PaO_2 \leq 7.3$ kPa (55 mmHg) or $SaO_2 \leq 88\%$, with or without hypercapnia; or
- PaO_2 between 7.3 and 8.0 kPa (55-60 mm Hg) or SaO_2 of 89%, if there is evidence of pulmonary hypertension, peripheral oedema suggesting congestive heart failure, or polycythemia (haematocrit > 55%).

Arterial blood gas measurements should be made on two occasions when the patient is in a stable condition and on optimal treatment.[69 (Level III)]

Oxygen therapy is not indicated for patients

- with severe airflow limitation whose main complaint is dyspnoea but who maintain a PaO_2 >8 kPa (60 mm Hg) and who show no secondary effects of chronic hypoxia;
- who continue to smoke cigarettes
- who have not received adequate therapy of other kinds (eg, inhaled and oral bronchodilators and corticosteroids, treatment for right ventricular failure or for any respiratory infection)
- who are not sufficiently motivated to undertake the discipline required for oxygen therapy.

Domiciliary oxygen therapy is available in Malaysia from a variety of providers. Oxygen concentrators are generally regarded more cost-effective. It should be prescribed by a qualified medical practitioner and titrated carefully due to concerns of carbon dioxide retention. Patients should be reassessed 1–2 months after starting continuous or nocturnal oxygen therapy, both clinically and by measurement of PaO_2 and $PaCO_2$.[174 (Level I)] Subsequent review should be undertaken at least annually, or more often, according to the clinical situation.

Recommendations: Long-term Oxygen Therapy (LTOT)

1. LTOT should be prescribed for all patients with COPD who have chronic hypoxemia. *[Grade A]*
2. LTOT is best delivered via an oxygen concentrator. *[Grade A]*

7.3 Nutrition in COPD

Cachexia is an important systemic manifestation in COPD.[175,176] (Level III, Level II-2) Weight loss is a marker of disease severity in advanced COPD and it is associated with adverse outcomes independent of lung function. Low BMI is associated with higher mortality. Weight loss may further exacerbate decreased respiratory muscle strength and increase dyspnoea and impair immunity.[177,178] (Level II-2, Level I) The general assessment of patients with COPD should include weight and the calculation of BMI at each visit. The goal is to try to maintain a reasonable body weight and BMI (between 22 and 27 kg/m2) and keep serum albumin levels above 35 g/L.[178] (Level I) A balanced diet with adequate caloric intake in conjunction with exercise to prevent or reverse malnutrition and muscle atrophy is prudent. (Level II-2) However, excessive weight gain should be avoided, and obese patients should strive to gradually reduce body fat. Studies of nutritional supplementation alone have not shown improvement in pulmonary function or exercise capacity. Trials of anabolic steroids, growth hormone supplementation, and tumour necrosis factor-□ (TNF) antagonists in reversing malnutrition and improving functional status and prognosis in COPD have been disappointing.[178,179] (Level I, III)

The role of pulmonary rehabilitation is now well-recognised in COPD. Ongoing research is currently exploring how nutritional support can enhance exercise training and optimise the effects of pulmonary rehabilitation.[180] (Level III)

Recommendation: Nutrition in COPD
1. A balanced diet with adequate caloric intake in conjunction with exercise is recommended in patients with COPD. *[Grade B]*

7.4 Lung Volume Reduction for COPD

7.4.1 Lung Volume Reduction Surgery (LVRS)

Lung volume reduction by resection of non-functioning emphysematous areas improves exercise tolerance and decreases 2-year mortality in patients with severe, predominantly upper-lung emphysema who have low baseline exercise capacity after pulmonary rehabilitation.[181,182] (Level I) However, to date, LVRS has not been performed in Malaysia.

7.4.2 Bullectomy

Bullectomy has been reported to improve lung function and dyspnoea in selected patients by removal of large bullae compressing on adjacent lung parenchyma.[183] (Level III) Health-related quality of life was maintained three years post-bullectomy. Surgical techniques used have included thoracotomy, video-assisted thoracoscopy and stapled wedge resection.

7.4.3 Minimally-Invasive Lung Volume Reduction Procedures

Newer minimally-invasive techniques of lung volume reduction such as endoscopic bronchial valve placement await the results of large scale randomised studies.[184,185] (Level III)

7.5 Lung Transplantation

Lung transplantation is available in Malaysia. However, at the present time it is limited to younger patients with other chronic lung diseases. Patients with COPD are considered for lung transplantation when[186 (Level III)]:

- life expectancy is not predicted to exceed 24-36 months despite optimal and maximal medical management
- they have class III or IV New York Heart Association (NYHA) symptoms.
- < 60 yrs old with an FEV_1 < 25% predicted after bronchodilator therapy or with severe pulmonary hypertension.

The 5-year survival after transplantation for emphysema is 45 to 60% in Western series.[187,188 (Level III)] Lifelong immunosuppressive therapy is required.

Recommendation: Surgical Treatment for COPD
1. COPD patients who continue to deteriorate despite optimal medical therapy may be considered for surgical therapy. *[Grade A]*

7.6 COPD and Surgery

A careful evaluation of patients with COPD undergoing surgery should include identification of high-risk patients and aggressive treatment. Elective surgery should be deferred in patients who are symptomatic, have poor exercise capacity, or have acute exacerbation.

Patients with COPD are several times more likely to have a major postoperative complication.[189-192 (Level I, Level II-2)] Similarly, an FEV_1 <60% predicted was found to be an independent predictor of increased mortality in patients undergoing coronary artery bypass graft procedures.[193 (Level III)] In general, the incidence of postoperative pulmonary complications is inversely related to the distance of the surgical incision from the diaphragm.[193 (Level III)]

The risk of respiratory failure is increased in patients undergoing pneumonectomy with a preoperative FEV_1 of < 2L or <50% predicted and/or DLCO <50% predicted.[194] High risk patients should undergo further testing such as lung perfusion and exercise capacity tests.[194] Benefits of surgery must be weighed against known risks.

Patients with COPD should be treated aggressively to achieve the best possible baseline function. Bronchodilators, smoking cessation (at least 4-8 weeks preoperatively is optimal), antibiotics, and chest physical therapy may help significantly reduce pulmonary complications.[194-196 (Level III)] The role of pre-operative steroids is uncertain although smaller studies have indicated reduction of postoperative pulmonary and non-pulmonary complications in COPD patients undergoing CABG.[197,198 (Level I, Level II-2)] Consider postponing elective surgery if improvement of pulmonary function is possible and requires more time. The patient should be educated regarding early postoperative deep breathing and incentive spirometry.

Regional anaesthesia and laparoscopic techniques and limited duration of surgery should be considered where feasible.[199,200(Level III)] Careful and vigilant use of muscle relaxants is advisable to avoid postoperative muscle weakness. Adequate hydration should be maintained to allow mobilisation of airway secretions. Postoperatively, early ambulation should be encouraged and the use of opioids that may depress ventilation should be minimised.

Recommendations: Surgery in COPD Patients

The following measures help minimise pulmonary complications in at-risk patients: [200-202 (Level I, Level III)] *[Grade B]*

Preoperative

- Smoking cessation
- Antibiotics for acute bronchitis
- Optimise COPD treatment regimens
- Educate patient on lung expansion manoeuvres
- Consider inspiratory muscle training or pulmonary rehabilitation in high-risk patients

Postoperative

- Early mobilisation
- Lung expansion manoeuvres
  - consider CPAP in high-risk patients
- Adequate pain control
  - consider epidural analgesia in at-risk patients
  - avoid opiates
- Selective use of nasogastric decompression and total parenteral nutrition
- DVT prophylaxis

SECTION 8 MANAGING EXACERBATION OF COPD

8.1 Introduction

The natural course of COPD is of gradual decline in lung function with episodes of exacerbations.

8.2 Definition of Acute Exacerbation of COPD

Exacerbation is defined as an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication.[69 (Level III)]

8.3 Morbidity and Mortality Associated with Acute Exacerbations of COPD

Acute exacerbation of COPD (AECOPD) is a major cause of morbidity and mortality[203 (Level III)] and incurs huge cost in terms of healthcare resource utilisation.[204 (Level II-2)] Exacerbations impact negatively on lung function[205 (Level II-2)] and health-related quality of life.[206 (Level III)] The impact is significant and patients may take a long time to recover.[207 (Level II-2)] Some patients never recover fully and have repeated exacerbations.[207 (Level II-2)]

Measures to prevent AECOPDs are important to reduce morbidity and mortality. They must be put in place either when patients are seen in clinic or when they present with an exacerbation to the general practitioner or government health clinics or emergency departments with/without hospitalisation. AECOPD should be suspected if smokers present with symptoms of chest infection.

8.4 Causes of Acute Exacerbations of COPD

Exacerbations are associated with an increase in airway inflammation and caused mainly by lower respiratory tract infections and inhalation of pollutants. Cigarette smoking is a major cause of COPD and smoking cessation is effective in reducing risk of exacerbation[208 (Level II-2)] and reduces risk of hospitalisation.[209 (Level II-2)] Most (50 to 60%) exacerbations are caused by bacterial or viral respiratory infections,[210,211 (Level III, Level II-2)] while 10 to 20% are due to environmental factors[212 (Level II-2)] and non-compliance to medications, and 30% are of unknown aetiology.[213-215 (Level III)] Bacterial organisms that have been isolated in various studies of AECOPDs include *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Staphylococcus aureus.*[215 (Level III), 216-217 (Level II-3)] Other precipitating factors include congestive heart failure, cold air and pulmonary embolism.[218 (Level III), 219 (Level II-2)]

8.5 Diagnosis and Assessment of Severity

Exacerbation of COPD is a clinical diagnosis which is supported by physical examination and investigations. Usual symptoms are increased dyspnoea, cough and production of sputum which may become purulent. Non-specific symptoms may be present such as lethargy, insomnia, sleepiness, depression and confusion. Patients tend to underestimate their symptoms and underreport exacerbations[220 (Level III)] probably because they have poor understanding of their disease and the term "exacerbation".[206 (Level III)]

Assessment of severity is based on history, physical examination and investigation findings.

8.5.1 History and Physical Examination

It is important to ascertain patient's baseline condition before the exacerbaton and the development of any new symptoms, severity of COPD [FEV_1, previous exacerbations, hospital admissions especially history of admission into intensive care unit (ICU) and receiving invasive or non-invasive ventilation], co-morbidities and previous and current medications. The history may help reveal possible cause(s) of and precipitating factors for the exacerbation and concomitant medical illnesses. It is worth noting that anxiety and depression are common in COPD patients and in those with exacerbations.[221 (Level II-2), 222 (Level III-3)] History can also help rule out other differential diagnoses (see **8.6**).

Physical examination includes checking vital signs (temperature, respiratory rate, pulse rate and rhythm, and blood pressure), signs of poorer prognosis (confusion, reduced conscious level, cachexia, respiratory distress, cyanosis and evidence of cor-pulmonale) and evidence of co-morbid conditions such as cardiovascular and neurovascular diseases, diabetes mellitus and lung cancer.

8.5.2 Spirometry and Peak Flow Readings

These tests are difficult to be performed by sick patients and to be interpreted by doctors during AECOPD. The measurements are not accurate and therefore their routine testing during the acute phase of AECOPD is not recommended. However, spirometry may be performed after the patient has recovered either before hospital discharge or on a following clinic visit especially if they have not done it before.

8.5.3 Pulse Oximetry

Pulse oximetry is used to evaluate the patient's oxygen saturation (SpO_2), need for supplemental oxygen and response to treatment and to guide further management. Oxygen supplementation should be given if SpO_2 <90%.[69 (Level III)] If arterial blood gas results are not readily available, controlled oxygen therapy using Venturi mask is recommended to avoid CO_2 narcosis, aiming for $SpO_2 \geq 90\%$. Morbidity and mortality are increased in patients with hypercapnic respiratory failure when the SpO_2 is increased to above 93-95%.[223 (Level III)] However, pulse oximetry does not provide information about CO_2 levels.

8.5.4 Arterial Blood Gas Measurement

Arterial blood gas measurement is useful as a tool to assess the severity of AECOPD. It is recommended for patients attending the accident and emergency department and also in those who are hospitalised. It should be performed in unwell patients despite them having good SpO_2 levels. In patients who are breathing room air, respiratory failure is defined as PaO_2 <8.0 kPa (60 mmHg) and / or SaO_2 < 90% with or without $PaCO_2$ > 6.7 kPa (50 mmHg). The respiratory failure and exacerbation is worse if there is respiratory acidosis pH < 7.36 with hypercapnia pCO_2 6 - 8 kPa (45 – 60 mmHg) and is an indication for assisted (non-invasive or invasive ventilation) ventilation.[69 (Level III)] It should also be considered in patients who do not respond to initial medical treatment.

8.5.5 Sputum Gram Stain and Culture

If an AECOPD is infectious in nature and does not respond to initial antibiotic therapy, sputum culture and sensitivity should be performed.[69 (Level III)] Sputum examination should also be performed on patients who are hospitalised [224(Level II-3)] or whose chest radiographs show changes suggestive of pneumonia.

8.5.6 Chest Radiograph

A chest radiograph is useful to identify possible causes of the AECOPD (for example, pneumonia), alternative diagnoses that may mimic features of COPD (for example, heart failure and bronchiectasis) and possible complications (for example, lung cancer and pneumothorax).

8.5.7 Electrocardiogram (ECG)

An ECG is a valuable tool for the diagnosis of tachyarrhythmias, myocardial ischaemia and right ventricular hypertrophy.

8.5.8 Other Laboratory Tests

Full blood count:

A raised total white blood cell count may indicate underlying sepsis but a normal count does not rule it out. The presence of purulent sputum in AECOPD is enough to commence empirical antibiotic therapy.[225 (Level III)] Polycythaemia and raised haematocrit levels suggest cor pulmonale. Anaemia could be due to underlying chronic disease, malnutrition or blood loss.

Renal profile, blood glucose and liver function test:

Biochemical abnormalities may be present during AECOPD. These additional tests may reveal the presence of co-morbid conditions such as renal impairment, uncontrolled diabetes and malnutrition.

8.6 Differential Diagnoses

Non-compliance to medications may mimic an exacerbation, therefore careful history taking is necessary. If patients do not respond to standard therapy, they need to be reassessed to determine if they have other diagnoses that may imitate or aggravate their AECOPD such as:

- Asthma (may co-exist with COPD)
- Bronchiectasis
- Diffuse parenchymal lung disease
- Lung cancer
- Pulmonary embolism
- Pneumothorax
- Heart failure

Patients with advanced COPD often have several co-morbid conditions[218 (Level III), 127(Level I)]

8.7 Managing Acute Exacerbations of COPD

The aims of management in exacerbations of COPD are to:

1. Relieve symptoms and airflow obstruction
2. Maintain adequate oxygenation
3. Treat any co-morbid conditions that may contribute to the respiratory deterioration or treat any precipitating factor such as infection.

Most patients with AECOPD are treated in the primary care setting but a minority of patients will require hospital assessment or admissions. Indications for hospital assessment or admissions for AECOPD are shown in **Table 8-1.**

Table 8-1: Indications for Hospital Assessment or Admission for Acute Exacerbations of COPD

- Marked increase in intensity of symptoms such as sudden development of dyspnoea
- Underlying severe COPD
- Development of new physical signs e.g., cyanosis, peripheral oedema
- Failure of exacerbation to respond to initial medical management
- Significant co-morbidities
- Newly occurring cardiac arrhythmias
- Older age
- Insufficient home support

8.8 Home Management (Refer Figure 8-1)

8.8.1 Bronchodilator Therapy

Inhaled bronchodilators improve airflow obstruction and reduce lung hyperinflation, thereby improving dyspnoea. Short-acting inhaled β_2-agonists are preferred for treating AECOPD.[76,195, (Level III), 226 (Level I)] The dosage and frequency of existing short-acting β_2-agonists therapy should be increased, or example, salbutamol 200-400 µg or terbutaline 500 µg every 3-4 hours. Anticholinergic therapy (ipratropium bromide 40 µg 6 hourly) may be added, if not yet in use until the symptoms improve.

8.8.2 Systemic Corticosteroids

Systemic corticosteroids should be used in addition to existing bronchodilator therapy in an AECOPD with significant increase in dyspnoea or if the patient's baseline FEV_1 is <50% predicted. Systemic corticosteroids have been shown to shorten recovery time, improve oxygenation and lung function and reduce treatment failure.[227 (Level I)] A dose of 30-40 mg prednisolone per day for 7-14 days is appropriate for most patients. There is no advantage in prolonged corticosteroid therapy as the risk of side effects is significant.

8.8.3 Antibiotics

The use of antibiotics is discussed in **8.9.4** under hospital management.

8.9 Hospital Management (Refer Figure 8-2)

The initial management of a patient with an AECOPD in the emergency department is to provide controlled oxygen therapy and assessing the severity of the exacerbation to determine if the patient can be treated in the emergency department or in the general ward. If the exacerbation is life threatening, the patient should be admitted to a high dependency unit or the ICU.

8.9.1 Controlled Oxygen Therapy

Supplemental oxygen therapy is considered the cornerstone of hospital treatment for an AECOPD. Oxygen therapy is given to maintain adequate oxygenation ($PaO_2 \geq 8$ kPa or ≥ 60 mm Hg or $SpO_2 \geq 90\%$) without precipitating acidosis or worsening hypercapnia. Controlled oxygen therapy should be given in the form of 24-28% oxygen via Venturi mask if available to ensure accurate delivery of oxygen or 1-2 litres of oxygen via nasal prongs.[76,195 (Level III)] Arterial blood gases should be checked 30-60 minutes later to ensure adequate oxygenation without CO_2 retention or acidosis. Arterial blood gases should be monitored regularly depending on the clinical state of the patient **(Figure 8-3)**.

Figure 8-1: Algorithm for Managing Acute Exacerbation of COPD: Home Management

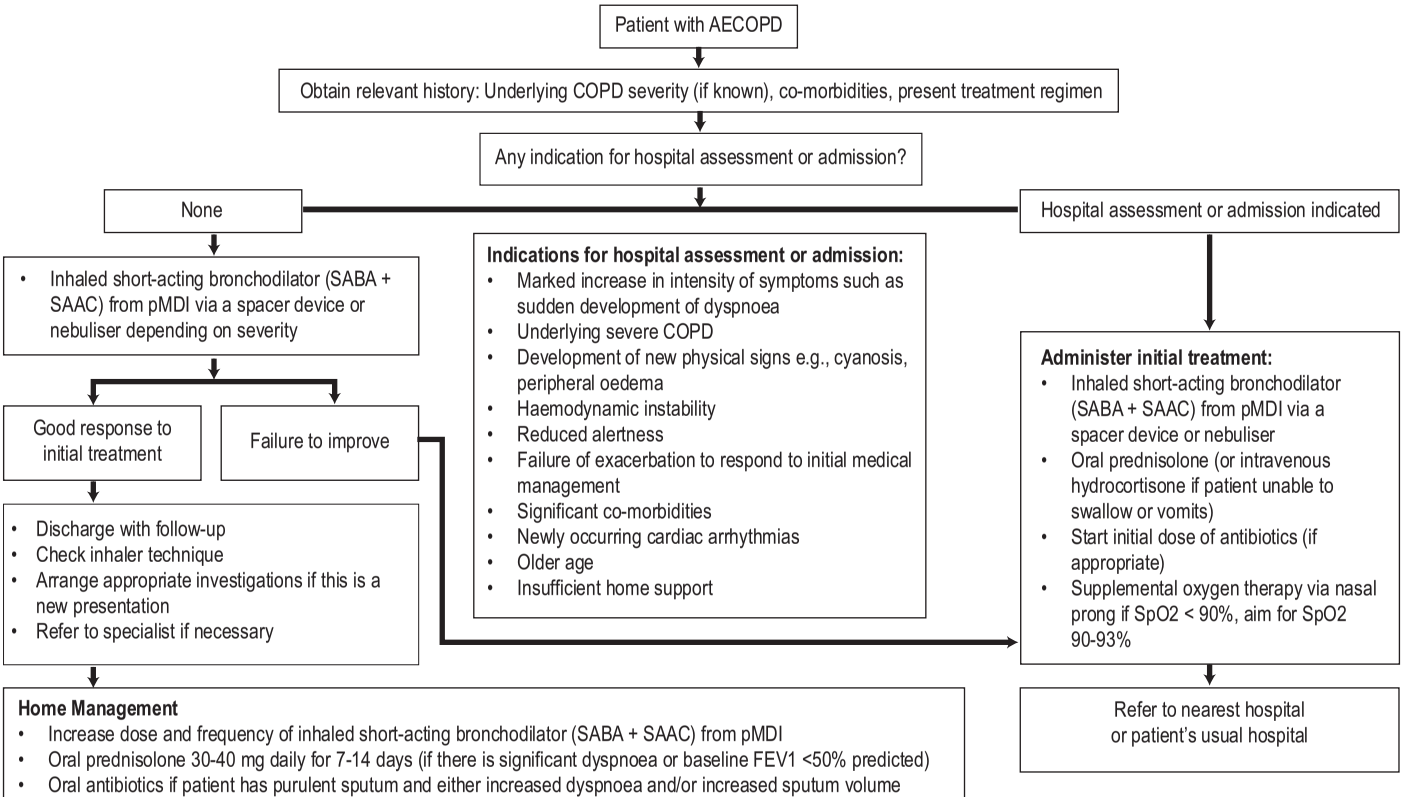


Figure 8-2: Algorithm for Managing Acute Exacerbation of COPD: Hospital Management

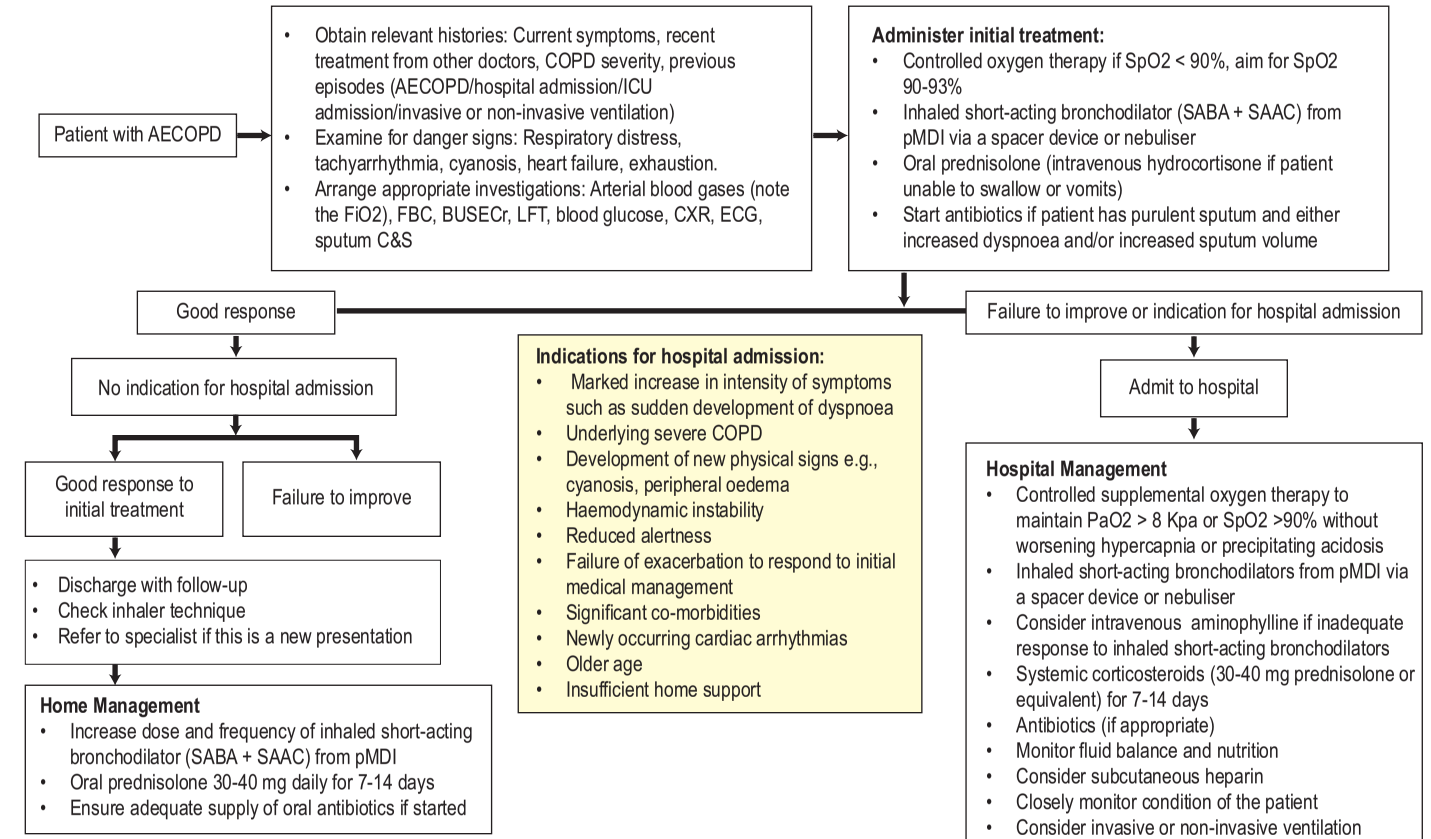
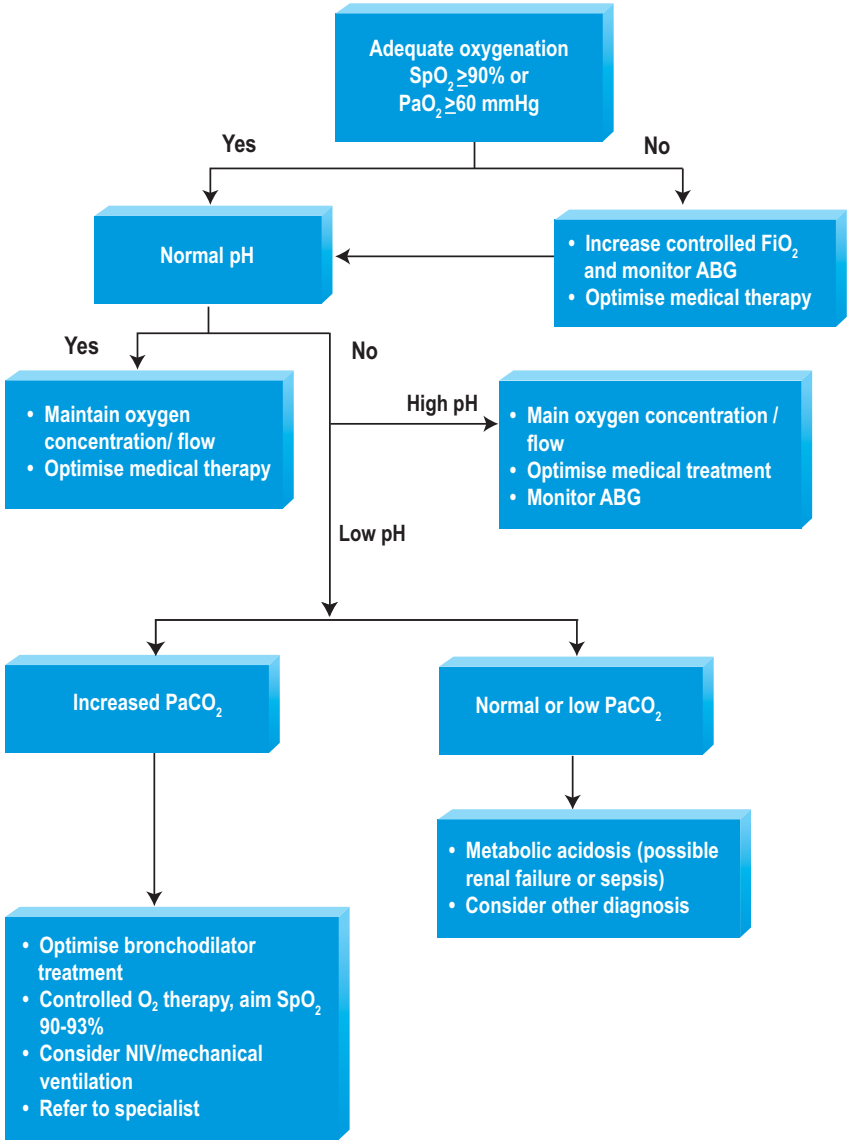


Figure 8-3: Algorithm for adjustment of oxygen setting based on arterial blood gases



8.9.2 Bronchodilator Therapy

The relief of airflow obstruction by bronchodilator therapy is the major goal in the treatment of AECOPD. Short-acting inhaled β_2-agonists is usually given in the nebulised form although there is evidence that administration of short-acting inhaled β_2-agonists via a metered dose inhaler (10 to 20 puffs via a spacer device) has equal efficacy to nebulised treatment.[76,195 (Level III), 226 (Level III)] The use of nebulisers poses a risk of nosocomial infection to healthcare workers and other patients.[228 (Level III)] Extra precautions should be taken to reduce the risk of transmitting respiratory infections such as Influenza A (H1N1). In severe exacerbation, nebulised short-acting β_2-agonists can be combined with a short-acting anticholinergic, for example, Combivent® nebuliser solution 2.5 mls (ipratropium bromide 500 µg, salbutamol 2.5 mg) 6 hourly or Duovent® nebuliser solution 4 mls (ipratropium bromide 500 µg, fenoterol 1.25 mg) 6 hourly.

In severe exacerbations, intravenous methylxanthines can be considered if there is inadequate response to short-acting inhaled β_2-agonists and anticholinergic.[229 (Level II-1)] The recommended loading dose of intravenous aminophylline is 250-500 mg (5 mg/kg) over 20 minutes followed by a maintenance dose of 500 µg/kg/hour, adjusted according to plasma theophylline concentration (10–20 mg/L or 55–110 µmol/L). Patients already on maintenance theophylline treatment should not be given a loading dose. Doctors need to be aware of interaction between aminophylline with various other drugs.

8.9.3 Systemic Corticosteroids

Corticosteroids are effective treatments for AECOPD and are recommended as an addition to other therapies in the hospital management of exacerbations of all COPD patients in the absence of significant contraindications. Systemic corticosteroids improve lung function over the first 72 hours, shorten hospital stay and reduce treatment failure over the subsequent 30 days.[230,231 (Level I)] A dose of 30-40 mg of oral prednisolone daily for 7-14 days appears to be safe and effective. A study has shown that nebulised corticosteroids may also be beneficial during AECOPD as an alternative to oral prednisolone in the treatment of non-acidotic exacerbations of COPD.[232 (Level I)] Systemic corticosteroids should be discontinued after the acute episode as they are associated with significant side-effects.

8.9.4 Antibiotics

Bacterial lower respiratory tract infections either primary or secondary following an initial viral infection is a common cause of AECOPD. Antibiotics are beneficial during AECOPDs but have no proven benefit to prevent exacerbations.[233 (Level I), 234 (Level III)]

Antibiotics should be given to patients with AECOPD having purulent sputum and either increased dyspnoea and/or increased sputum volume.[225 (Level III)] Patients with a severe AECOPD that requires invasive or non-invasive ventilation should also be covered with antibiotics.[235 (Level I)] The choice of antibiotics depends on the local antibiotic policy **(Table 8-2)**.

Table 8-2: Antibiotic Treatment for Acute Exacerbation of COPD
(Adapted from the National Antibiotic Guideline 2008, Ministry of Health of Malaysia[236]**)**

Stable clinical state	Symptoms of exacerbation and risk factors	Probable bacterial pathogen	Suggested treatment
Simple COPD (without risk factors)	Increased cough and sputum volume, purulent sputum and increased dyspnoea	*Haemophilus influenza, Moraxella catarrhalis, Streptococcus pneumonia,* Atypical respiratory pathogens	**Preferred** Extended spectrum macrolide e.g., azithromycin 500 mg once daily for 3 days, clarithromycin 250 mg twice daily for 7 days OR 2nd or 3rd generation cephalosporin e.g., cefuroxime 250-500 mg twice daily for 7 days **Alternative** β-lactam/β-lactamase inhibitor e.g., amoxycillin/clavulanate 625 mg twice daily for 1 week OR Erythromycin 800 mg twice daily for 7 days OR Doxycycline 100 mg twice daily for 7 days OR Moxifloxacin 400 mg once daily for 5-7 days
Complicated COPD (with risk factors) *	As in COPD without risk factors plus at least one of the following: • FEV_1<50% predicted • >4 exacerbations/ year • >65 years • Significant co-morbidity (especially heart disease) • Use of home oxygen • Chronic oral corticosteroid use • Antibiotic use in the past 3 months	*Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumonia,* Atypical respiratory pathogens, *Klebsiella spp,* Other Gram-negatives	**Preferred** β-lactam ± β-lactamase inhibitor e.g. amoxicillin 1 g three times a day or amoxycillin/clavulanate 2 g twice daily for 7 days OR 2nd or 3rd generation cephalosporin e.g., cefuroxime 500 mg twice daily, ceftriaxone 1 g once daily for 7 days OR/AND Extended spectrum macrolide e.g., azithromycin 500 mg once daily for 3-5 days **Alternative** Fluoroquinolone e.g., levofloxacin 750 mg once daily for 5 days, moxifloxacin 400 mg once daily for 5-7 days, ciprofloxacin 250-500 mg twice daily for 5-7 days

* May require parenteral therapy. Consider referral to hospital.

8.9.5 Other Measures

Further hospital management include:

- monitoring of fluid balance
- deep vein thrombosis prophylaxis with subcutaneous heparin especially in immobile patients and those with acute on chronic respiratory failure[237 (Level III), 238 (Level II-2)]
- supplementary nutrition[239 (Level II-2)]
- sputum clearance[239]

There is no convincing evidence to support the routine use of pharmacological mucus clearance strategies. Chest physiotherapy has no proven value during exacerbations unless a large amount of sputum is produced (>25 mLs per day) or there is mucus plugging with lobar atelectasis.

Diuretics are indicated if there is evidence of peripheral oedema.

8.10 Management of Severe But Not Life Threatening Exacerbations of COPD in the Emergency Department or the Hospital

- Assess severity of symptoms, blood gases, chest radiograph
- Administer controlled oxygen therapy, repeat arterial blood gas measurements after 30 minutes
- Bronchodilators
    - o Increase dose frequency
    - o Combine short-acting inhaled β_2-agonist and anticholinergic agent
    - o Use spacers or air-driven nebulisers
    - o Consider adding intravenous aminophylline, if needed
- Oral or intravenous glucocorticosteroids
- Antibiotics when signs of bacterial infection are present
- Consider non-invasive mechanical ventilation if patient's condition deteriorates
- At all times:
    - o Monitor fluid balance and nutrition
    - o Consider subcutaneous heparin
    - o Identify and treat associated conditions (e.g. heart failure, arrhythmias)
    - o Closely monitor patient's condition

Recommendations: Drug Treatment for AECOPD
1. Inhaled bronchodilators and systemic corticosteroids are effective treatments for exacerbations of COPD. *[Grade A]*
2. Antibiotics should be used in patients with signs of airway infection (i.e., increased dyspnoea, increased sputum volume and change of colour of sputum). *[Grade A]*

8.11 Non-invasive Ventilation

In patients with COPD and acute respiratory failure, the use of non-invasive ventilation (NIV) results in less frequent intubation, decreased complications and mortality, and a shorter hospital stay[240] (Level I)

The primary indication is persistent hypercapnoeic respiratory failure despite optimal medical therapy.[241] It is recommended that NIV should be delivered in a dedicated setting with staff who have been trained in its application, who are experienced in its use and who are aware of its limitations. When patients are started on NIV there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed.[242] (Level III)

Indications for Non-Invasive Ventilation[69] (Level III):

- Moderate to severe dyspnoea with use of accessory muscles and paradoxical abdominal motion.
- Moderate to severe acidosis (pH 7.25 - 7.35) and/or hypercapnia ($PaCO_2$ >6.0 kPa [45 mmHg])
- Respiratory rate >25 breaths per minute.

Contraindications for Non-Invasive Ventilation[69] (Level III):

- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- At high risk for aspiration
- Impaired mental status; uncooperative patient
- Significant facial injury
- Viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity
- Underlying intestinal obstruction

8.12 Invasive Mechanical Ventilation

The use of invasive ventilation is influenced by the likely reversibility of the precipitating event, the patient's wishes (or advance directive) and the availability of intensive care facilities.

Indications for Invasive Mechanical Ventilation[69] (Level III):

- Unable to tolerate NIV or NIV failure
- Severe dyspnoea with use of accessory muscles and paradoxical abdominal motion.
- Respiratory rate >35 breaths per minute
- Severe acidosis (pH < 7.25) and/or hypercapnia ($PaCO_2$ > 8.0 kPa, [60 mmHg])
- Respiratory arrest
- Impaired mental status; somnolence
- Cardiovascular instability (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

Recommendations: Ventilatory Support

1. NIV should be considered for AECOPD patients with hypercapnoeic respiratory failure despite optimal medical therapy. *[Grade A]*
2. Patients with severe AECOPD requiring NIV should be monitored in wards with dedicated staff that have been trained in NIV, high dependency unit or intensive care unit. *[Grade C]*

8.13 Hospital Discharge

Patients with AECOPD can be discharged when:

- Inhaled β_2-agonist therapy is required no more frequently than every 4 hours
- Patient, if previously ambulatory, is able to walk across the room
- Patient is able to eat and sleep without frequent awakening by dyspnoea
- Patient has been clinically stable for 12-24 hours
- Arterial blood gases or oxygen saturation have been stable for at least 12-24 hours
- Patient (or home caregiver) understands the disease and its management at home
- Follow-up has been organised

A copy of discharge summary should be given to the patient. A close working relationship between hospital and primary care doctors is desirable.

8.14 Follow Up

Patients should be reviewed within 8 weeks after discharge. The following should be assessed[243 (Level II-2)]:

- Ability to cope in the patient's usual environment
- Spirometry measurement
- Inhaler technique
- Understanding of recommended treatment regimen
- Smoking status and cessation
- Needs for long-term oxygen therapy and/or home nebuliser (for patient with stage IV [very severe] COPD)
- Suitability for pulmonary rehabilitation
- Vaccination with influenza with or without pneumococcal vaccines
- Self-management plans and future monitoring

SECTION 9 TRANSLATING GUIDELINE RECOMMENDATIONS TO THE CONTEXT OF PRIMARY CARE

9.1 Introduction

Primary care provides the first point of contact for medical care delivery. Most patients with COPD are seen in primary care and it is therefore paramount that primary care physicians are adept in identifying, managing and preventing COPD. The best practice recommendations are detailed in Sections 1 to 8, and require effective translation of such recommendations to individual circumstances in the primary care setting. In Malaysia, the main providers of primary care are the public health centres, hospital-based primary care outpatient clinics and private general practice. The factors that are particularly pertinent in this context are described in this section.

9.2 Early Diagnosis

Early identification of patients at high risk is an important role for primary care doctors. Such identification allows intervention to be taken such as smoking cessation, reduction of exposure to tobacco smoke as well as other risk factors such as occupational dusts, indoor and outdoor pollution.

Diagnosis should be made based on at risk individuals with symptoms of chronic cough, increased sputum production, or breathlessness, confirmed by spirometry. However, it is not recommended to use spirometry for the purpose of screening all adults for COPD. Therefore spirometry should be used as a diagnostic test for patients identified as at risk.[244] (Level I)

9.3 Smoking Cessation

To date, smoking cessation is the only effective way of preventing the development and reducing the progression of COPD. Smoking cessation interventions, which include brief behavioural sessions and pharmacotherapy, are effective in making patients quit smoking.[245] (Level I) All individuals with COPD who still smoke will benefit from smoking cessation.

9.4 Spirometry

In primary care, COPD is diagnosed mainly on clinical grounds alone. However, the diagnosis can be easily overlooked and the condition therefore is frequently under-diagnosed.

Spirometry is strongly advocated for the confirmation of diagnosis and the assessment of COPD severity. The training in execution and correct interpretation of the spirometry is therefore necessary. In sites where spirometry is not available, referral to other centres where this test can be performed should be arranged. Peak expiratory flow measurement may be considered where spirometry is not available.[246] (Level III) However, while low peak expiratory flow rates (PEFR) with little or no bronchodilator reversibility are consistent with COPD, but such findings can also be due to other lung diseases. Furthermore, PEFR is only reduced in advanced COPD. Therefore, it is important to realise that spirometry is now the choice investigation for diagnosis and assessing severity.

9.5 Long Term Management

COPD is a chronic disease. The role of primary care doctors include the following:

- Education and counseling on COPD, and how it is different from asthma.
- Raising awareness of COPD and that cigarette smoking cessation and avoidance of other risk factors can help to prevent the development and progression of COPD.

- Preventing exacerbations, such as by risk factor avoidance, vaccination, and appropriate pharmacotherapy.
- Coordinating care with hospital-based specialists in issues of selection of therapies, prevention and treatment of exacerbations, treatment of co-morbidities and complications such as cor pulmonale. Of particular relevance are the awareness of availability of pulmonary rehabilitation, and the assessment of the need for and prescribing of domiciliary oxygen.
- Dealing with problems in relation to home caregivers, such as coping with the disease, provision of support and dealing with end-of-life issues, especially relevant when the disease is advanced.

9.6 When to Refer to Hospital-Based Specialists?

Referral to a hospital-based specialist should be considered in the following situations:

- When the diagnosis is in doubt
- For spirometry testing when such a facility is not available on site
- Onset of cor pulmonale
- Assessment and prescribing of domiciliary oxygen therapy
- When there is a rapid decline of FEV_1 indicating severity of the disease
- Patient aged <40 years in whom an underlying genetic predisposition such as alpha-1 antitrypsin deficiency is suspected
- When access to certain drugs is a problem.

Recommendations: Translating Guideline Recommendations to the Context of Primary Care
1. Early identification of patients at risk for COPD and smoking cessation is important in primary care. *[Grade A]*
2. Spirometry is now strongly advocated for the confirmation of diagnosis and the assessment of COPD severity. *[Grade A]*
3. All COPD patients who smoke should be advised and assisted to stop smoking. *[Grade A]*
4. COPD is a chronic disease that should be jointly managed whenever necessary between primary and hospital-based doctors. This includes managing exacerbations and prescribing long term oxygen therapy. *[Grade A]*

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LEVELS OF EVIDENCE SCALE

The definition of levels of evidence and the grading of recommendations used in this guideline are shown in the following tables:

I	Evidence obtained from at least one properly randomized controlled trial
II - 1	Evidence obtained from well-designed controlled trials without randomization
II - 2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II - 3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: U.S / CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

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