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Clinical Practice Guidelines in the Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD) in the Philippines 2009

CLINICAL PRACTICE GUIDELINES IN THE DIAGNOSIS AND MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN THE PHILIPPINES

Report of the Council on COPD & Pulmonary Rehabilitation
Philippine College of Chest Physicians

2nd Update: 2009 Version

Part I: CLINICAL PRACTICE GUIDELINES IN THE DIAGNOSIS AND MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Part I: CLINICAL PRACTICE GUIDELINES IN THE DIAGNOSIS AND MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

I. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the most important diseases of the 21st century, being a major cause of death and disability. Most epidemiological studies have found that the prevalence of morbidity and mortality due to COPD have increased over time and are greater in men than in women. The impact of COPD is not only confined to its ill effects on the individual's health but also permeates into the social and economic aspects as well.

In response to the need to help prevent and manage COPD better, the Philippine College of Chest Physicians published the Philippine Consensus Report on COPD in 1999 (see Appendix 1). This is the 2nd update of the Philippine Consensus report and this version takes into account the new studies that have been published on COPD and the latest version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report entitled "Global Strategy for the Diagnosis, Management, and Prevention of COPD".

This 2008 document will merely add updates on the 2005 Philippine Consensus COPD Report since most of the basic principles in pathophysiology, diagnosis and management in COPD have remained the same. This document hopes to cater to the specific needs of the Philippines as a developing country and is intended for the use of practicing physicians and other health professionals involved in the care of patients with chronic obstructive pulmonary disease (COPD). The goals of the Philippine Consensus COPD Report are to:

1. assist primary health care practitioners in identifying and initiating management of patients with COPD.
2. assist hospital-based physicians in providing appropriate and cost-effective care for COPD patients.
3. recommend measures for the prevention of further deterioration of lung function and subsequent complications; and in the improvement in the quality of life of COPD patients.
4. assist allied health care workers in the care of COPD patients.
5. identify areas for further research in the diagnosis and management of COPD in the Philippines.

The process used in updating this practice guideline was by: (a) selection of a Core Group to review the previous guideline and identify topics/areas that needed revision, (b) selection of committee members to handle each identified topic, (c) search for recent data in the literature, (d) grading of available evidence, (e) assessment of locally available resources, (f) formulation, presentation and revision of draft recommendations, and (g) formulation of final statements.

Levels of evidence are assigned to the statements, where appropriate, following the system of the US National Heart, Lung, and Blood Institute (NHLBI) which is comparable to the classification used in the 1999 practice guideline:

DESCRIPTION OF LEVELS OF EVIDENCE		
Evidence Category	**Sources of Evidence**	**Definition**
A	Randomized controlled trials (RCTs). Rich body of data	Evidence is from endpoints of well-designed RCT's that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of

DESCRIPTION OF LEVELS OF EVIDENCE		
Evidence Category	**Sources of Evidence**	**Definition**
B	Randomized controlled trials (RCTs). Limited body of data	Evidence is from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCT's. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

The ultimate deciding factor in all the recommendations was what could benefit the typical Filipino COPD patient most.

This document is divided into five parts that discusses the (1) definition of COPD, (2) risk factors for developing COPD, (3) diagnosis, classification and monitoring of COPD, (4) management of stable COPD, (5) and management of COPD in acute exacerbation. Recommendations for the aspects of COPD needing further research and references used are placed at the end of each chapter.

The sections are written in a brief and concise manner to help the reader imbibe the key points quickly so that the document can be used at bedside or in the clinics. The updates are incorporated into the previous content of the guideline. For further elaboration of the guidelines, the proponents will be disseminating the document through focused group discussions on a nationwide basis starting Year 2009.

II. WHAT IS COPD?

Key Points:

- COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible.
- The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
- Chronic airflow limitation leads to lung hyperinflation which is the main mechanism of the characteristic exertional dyspnea in COPD.
- Some significant co-morbid conditions might contribute to the severity of COPD in some individuals.

Definition & Pathophysiology

COPD is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

Inhalation of noxious particles or gases, such as cigarette smoke, induces an abnormal chronic inflammatory immune response which is heightened by oxidative stress and imbalance of proteinases and antiproteinases in the lung. These lead to the pathologic changes in COPD which are: infiltration with specific inflammatory cell types in the airways and lung parenchyma, mucus gland hypertrophy and goblet cell hyperplasia in the proximal airways, peribronchial fibrosis and airway wall thickening in the peripheral conducting airways, dilatation and destruction of respiratory bronchioles and alveolar walls (emphysema), and endothelial cell dysfunction[1,2]. The peripheral airway obstruction and loss of alveolar attachments to the small airways cause the chronic airflow limitation characteristic of COPD and this leads to progressive air trapping during expiration which results to the phenomenon of hyperinflation 2,3,4. Phenomenon on hyperinflation develops early in COPD, is increased with exercise and is believed to be the main mechanism behind the exertional dyspnea experienced by patients with COPD[4]. Gas exchange abnormalities and eventual pulmonary hypertension and right heart failure (cor pulmonale) result as the disease progresses[2,5].

Up to 25% of COPD patients may suffer from co-morbid conditions such as cardiovascular disorders including myocardial infarction and angina, weight loss, nutritional abnormalities, skeletal muscle dysfunction, osteoporosis, bone fractures, diabetes, sleep disorders, depression, anemia, and glaucoma. These co-morbidities, specifically cardiovascular diseases, increase the risk for mortality among COPD patients and are one of the major causes of death among this group. The link between COPD and these co-morbid conditions is not yet clear - they share the common risk factor of smoking. Pulmonary inflammation leading to increased systemic inflammation is one of the recently implicated mechanisms linking COPD to increased occurrence of co-morbid conditions.[6,7]

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III. HOW PREVALENT IS COPD IN THE PHILIPPINES?

Chronic Obstructive Pulmonary Disease is a growing cause of morbidity and mortality worldwide. The WHO Global Burden of Disease Project estimated that COPD was the fifth leading cause of death worldwide in 2001 and will be the third leading cause by 2020.[1-4] The 1998 World Health Organization Report states that non-communicable diseases, including COPD, is the cause of nearly 40% of all deaths in developing countries and that these areas accounts for 67% of all COPD deaths worldwide.[1]

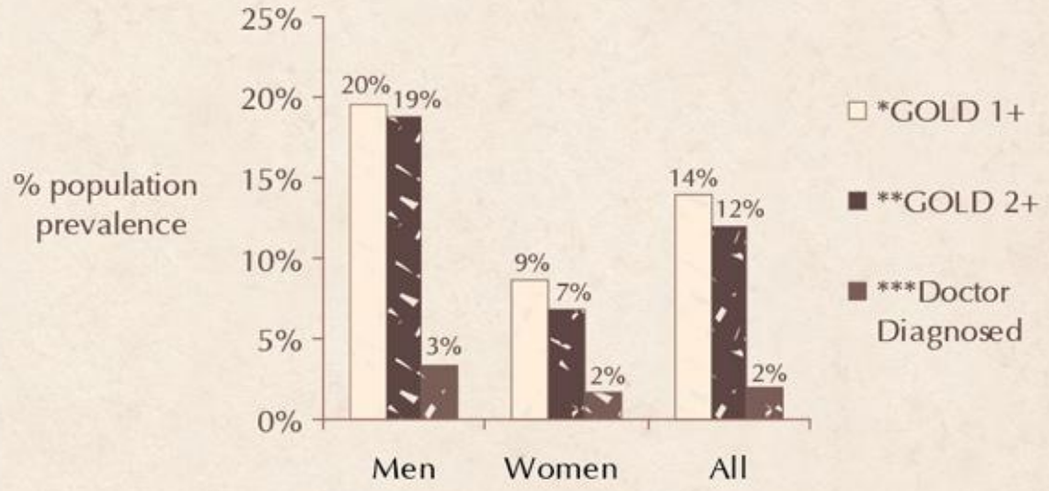
In 1987, a local study done in a rural community in Laguna, Philippines estimated the prevalence of COPD based on spirometric measurements to be 3.7%.[5] In 2007, the prevalence of COPD in the Philippines was reported to be 13.8% (mild or GOLD stage I COPD or higher) and 12.5% (moderate or GOLD stage II COPD or higher) (Figure 3.1) among those who were 40 years old and above.[6,7] The Philippines, with Manila City as its study site, ranked 3rd highest in prevalence of COPD stage II or higher among the countries which participated in the Burden of Obstructive Lung Disease (BOLD) study.[6]

COPD was noted to be greater in men (19.6%) than in women (8.6%) (Figure 3.1) and its prevalence increased steadily with age for both men and women (Figure 3.2).[7] COPD prevalence also increased with increasing pack-years among men while COPD prevalence did not increase with increasing pack-years among women (Figure 3.3).[7] Moreover, the prevalence of Stage II COPD is 7% among non-smokers, thus, raising important questions about the role of other risk factors for COPD aside from smoking (Figure 3.3).[7]

Another important observation in the BOLD study was that only 2% of the subjects claimed to have been told by a doctor to have COPD in contrast to the 12.5% overall prevalence of Stage II COPD based on spirometry (Figure 3.1).[7] This is one of the driving forces of medical organizations such as the Philippine College of Chest Physicians to increase the awareness of COPD in the country.

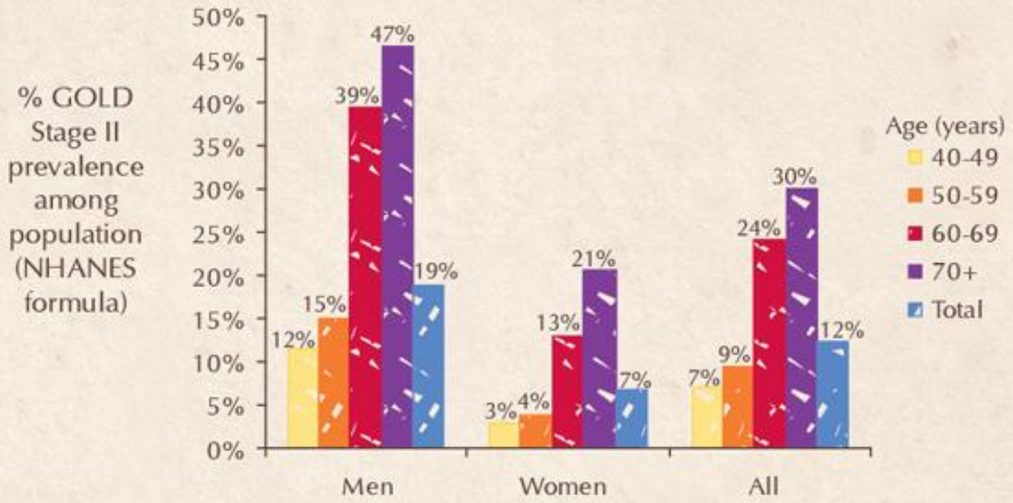
Future work from the BOLD Initiative will look into the prevalence of COPD in the rural areas of the country. The increasing prevalence of COPD that has been reported demands attention for future health-care planning and for more studies on the effects of prevalent local diseases like tuberculosis and on environmental exposures other than smoking.

Figure 3.1. Population Prevalence of GOLD Stage I+, GOLD Stage II+ & Doctor Diagnosed COPD in Manila, Philippines[7]



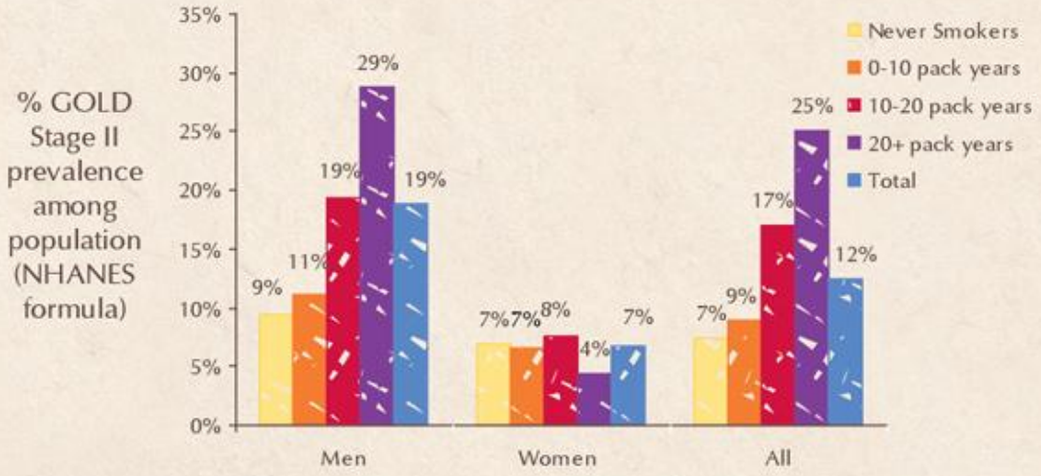
*Post BD FEV1/FVC<70% ** Post BD FEV1/FVC <70% and post BD FEV1 <80% ***Includes chronic bronchitis, emphysema or COPD

Figure 3.2. Estimated Population Prevalence of GOLD Stage II+ COPD* by age and sex in Manila, Philippines[7]



* Post BD FEV1/FVC <70% and post BD FEV1 <80%

Fig 3.3. Estimated Population Prevalence of Gold Stage II+ COPD* by pack-years and sex in Manila, Philippines[7]



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IV. WHAT ARE THE RISK FACTORS FOR COPD?

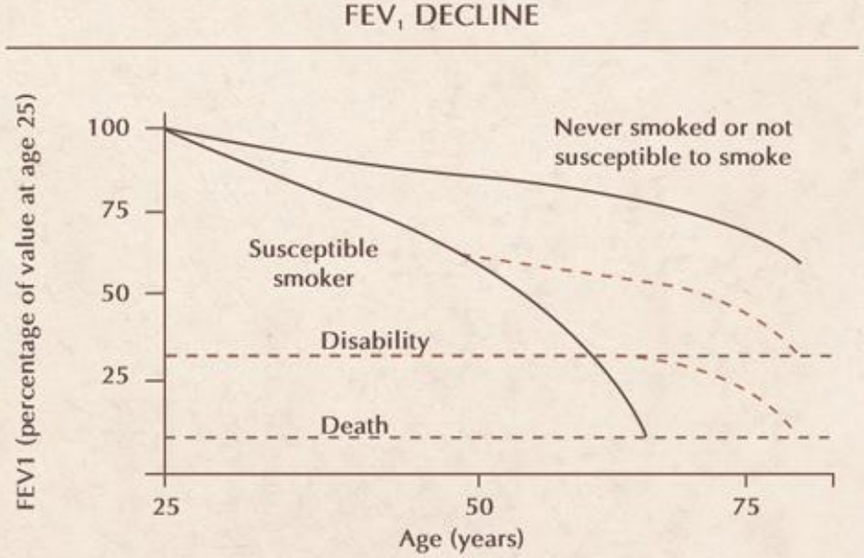
Key Points:

- Cigarette smoke is the major risk factor for COPD
- Since cigarette smoking is the most important risk factor for COPD, smoking prevention and cessation should be given the utmost priority.
- Modifying factors other than smoking have been shown to have a strong association with the development of COPD
- Disease prevention by avoidance of risk factors is of crucial importance because of the irreversible and progressive nature of COPD.

1. SMOKING

Tobacco use is the single most important factor in the pathogenesis of COPD and it causes 80% to 90% of COPD cases. 1 As graphically represented in the survival curve of Fletcher and Peto (Figure 4.1)[2], only a portion of chronic smokers show a rate of decline of lung function that is typical of patients who present with breathlessness due to COPD. Susceptible smokers have an accelerated rate of decline of lung function (50-90 mL of Forced Expiratory Volume at 1 second (FEV1)/year compared with 20-30 mL of FEV1/year after the age of 30 years in non-smokers). Subjects with COPD who stop smoking have a slower rate of progression of their disease which may approach the expected decline in FEV1 in non-smokers. Despite the often cited and scientifically associated relation between smoking and airway obstruction, only 10-20% of chronic heavy smokers ever develop symptomatic COPD.[3] This indicates that there are genetic and/or environmental factors which contribute to the development of COPD.

Figure 4.1. Graph of survival from Fletcher C, Peto R, Br Med J, 1:1645-1648, 1977



2. SECONDHAND SMOKE

There is a small but significant difference in the prevalence of respiratory symptoms and lung function in adults and children who are regularly exposed to secondhand smoke.[4] It is still unclear whether secondhand smoke causes COPD.

3. ALPHA-1 ANTITRYPSIN DEFICIENCY

Another well established[5] risk factor for the development of COPD is a deficiency in the function and/or quantity of the protective protease inhibitor, alpha-1 antitrypsin (AAT). This accounts for 5% or less of all cases of COPD and these cases are mostly found in the Western hemisphere.[6] This is an autosomal recessive (**PiZZ** genotype) disorder.

4. AIR POLLUTION AND OCCUPATIONAL EXPOSURE

Whether atmospheric pollution itself can cause or contribute to the development of COPD or not is still uncertain. Outdoor air pollution may vary in different areas. As with the problem of smoking, there will be individuals who will be more susceptible to the effects of atmospheric pollution than others. An epidemiologic study in the Philippines[7] comparing the effect of outdoor air pollution among jeepney drivers, air-conditioned bus drivers and commuters in Metro Manila showed that cumulative exposure levels to air pollutants far exceeded standard levels and was significantly higher among jeepney drivers. The prevalence of COPD among jeepney drivers was 32.5%, 16.4% for air-conditioned bus drivers and 14.8% for commuters. Jeepney drivers had an odds ratio of 2.33 for developing COPD as compared to air-conditioned bus drivers and commuters. The prevalence of smoking, however, among jeepney drivers was 69.4% and this probably affected to a significant degree the increased probability of jeepney drivers to develop COPD[7].

Occupational exposure.

Any occupation wherein the immediate environment is polluted increases the risk of developing COPD. In addition, there is evidence that cadmium and silica also increases the risk of development of COPD. Occupations at risk include coal miners, construction workers who handle cement, metal workers, grain handlers, cotton workers and workers in paper mills. However, the effect of smoking far outweighs any influences from the work environment.

Indoor air pollution.

Numerous sources of airborne contaminants have been identified in indoor environments and include pollutants found in home, office and transportation environments.

In the home, the principal combustion sources are tobacco-smoking, gas cooking stoves, unvented kerosene heaters and biomass fuels (Table 4.1)[8].
Biomass fuels used by women for cooking account for the high prevalence of COPD among nonsmoking women in parts of the Middle East, Africa, and Asia[9]. Figure 4.2 shows the consumption of wood as a combustion source for cooking in the different areas of the Philippines.[10]

Table 4.1

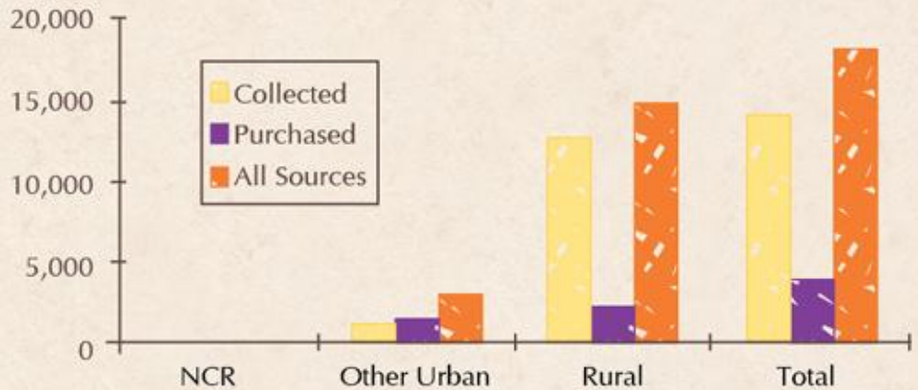
Common Biomass Fuels*

- Crop Residues - sugar cane bagasse
- Agricultural waste - coconut husk, rice straw, palay shell
- Firewood
- Charcoal

* Adapted from Biofuels, Air Pollution and Health Smith, East-West Centre, Honolulu, 1987

FIG 4.2. THE ROLE OF WOOD ENERGY IN THE PHILIPPINES ASIA REPORT 1997, FAO, UNITED NATIONS

(in Thousand Cubic Meters)



5. SOCIOECONOMIC STATUS

Studies attempting to identify a relationship between COPD and socioeconomic status often encounter an association between social class and indoor air pollution, with COPD being more prevalent in the lower socioeconomic strata.[11] This may be related to poor housing condition, nutritional status and use of fossil fuels without adequate ventilation. Also, there is a higher prevalence of smoking in the lower socioeconomic strata, and they are more likely to be employed in jobs where they may be at risk from occupational exposure.

6. INFECTIONS

The role of viral upper and lower respiratory tract infections in the pathogenesis of COPD remains to be clarified. Viral infections in the lung enhance inflammation and predispose to bronchial hyperreactivity. Epidemiologic studies suggest that childhood infections, usually due to adenovirus and respiratory syncitial virus, are independent risk factors for the development of COPD in adulthood.[12,13] Furthermore, adenoviral DNA is frequently found in the lungs of heavy smokers.[12] Once COPD is established, repeated infectious exacerbations may accelerate the decline in lung function[14,15]

PREVENTION OF RISK FACTORS

Disease prevention by avoidance of risk factors is of primary importance because of the irreversible and progressive nature of COPD. Since cigarette smoking is the most important risk factor for COPD, smoking prevention and cessation should be given the utmost priority in decreasing the incidence of the disease. Reduction in total personal exposure to dusts, fumes, and gases in the outdoor, indoor, and occupational setting should also be addressed when considered to be significant. Use of firewood, charcoal and other biomass fuels for home cooking should be avoided. Currently, there is inadequate basis for recommending respiratory protective equipment or air cleaners for use in the workplace or home as means to minimize contact with noxious particles and gases[16]. Avoidance of exposure to these substances is strongly advised.

RESEARCH RECOMMENDATIONS

1. Philippine prevalence studies on COPD

The study on the prevalence of COPD in the rural setting in the Philippines is ongoing. Risk factors unique to the rural setting such as exposure to indoor air pollution through biomass fuel cooking will be included in these studies.

2. Burden of Illness Study

Cost of care for COPD is perceived to be high but there are no local studies documenting the overall impact of this disease on the individual and national level.

3. Influence of other environmental risk factors aside from smoking on COPD especially among the female population

The BOLD study showed that other risk factors aside smoking may play a role in the incidence of COPD among females and these specific risk factors need to be further studied.

4. Determine the incidence of AAT Deficiency among Filipino emphysematous patients

AAT was previously thought to be a condition of Caucasions; however, a Japanese study has suggested that a form of this condition may exist as a mutation in Asians.

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V. HOW DO WE DIAGNOSE COPD?

KEY POINTS:

- A diagnosis of COPD is considered in any patient who:
  - ✓ Is 40 years or older
  - ✓ Has chronic cough, sputum production or dyspnea
  - ✓ Has a history of exposure to risk factors for the disease

- The diagnosis is confirmed by a post-bronchodilator FEV1/FVC <70%.
- Once COPD is diagnosed, the severity of the disease can be classified into mild (Stage I), moderate (Stage II), severe (Stage III) and very severe (Stage IV) based on the patient's post-bronchodilator FEV1 value, signs and symptoms.

- Once COPD is detected and confirmed, ongoing monitoring and assessment should include evaluation of: (1) continued exposure to risk factors, especially tobacco smoke and biomass fuel; (2) disease progression and development of complications; (3) pharmacotherapy and other medical treatment; (4) exacerbation history; (5) co-morbidities.

I. DETECTION OF COPD

Age

The disease commonly appears in the fifth decade of life. It is rare to encounter COPD in patients younger than 40 years old[1].

Symptoms

COPD patients usually develop cough as the initial symptom.[2] Acute chest illnesses characterized by increased cough, purulent sputum, wheezing, dyspnea, and occasionally fever may occur intermittently. Progressive dyspnea worsening over a period of months or years, is a typical feature of COPD.[3] In the advanced stage of the disease, cor pulmonale with right heart failure and edema may develop. Cyanosis may also be present especially during acute exacerbations.

Risk factors

Cigarette smoking is the single most important factor in the pathogenesis of COPD, and accounts for 80-90% of the risk of developing COPD. In addition, attention has focused on bronchial hyperreactivity, secondhand smoke, air pollution, and alpha-1-antitrypsin deficiency. Although alpha-1-antitrypsin deficiency is of comparable importance with tobacco smoking, this only accounts for < 1 % of COPD and probably even less among Filipinos[4]. Little data is available to identify persons susceptible to develop COPD when exposed to these risk factors.

In the absence of a significant smoking history, patients presenting with symptoms of airflow obstruction or chronic cough should be evaluated for other diagnoses.

Physical Examination

The physical examination is not a sensitive means of detecting airflow obstruction.[5] Among the physical findings, wheezing during quiet breathing and prolonged expiratory time (> 5 seconds) are useful indicators of airflow limitation.[4] These signs, however, are of no value as guides to severity and their absence does not exclude COPD.[6]

II. CONFIRMATION OF COPD

SPIROMETRY

For any individual suspected of COPD, a postbronchodilator FEV1/Forced Vital Capacity (FVC) <70% confirms the diagnosis.

The following approach is suggested in order to arrive at a diagnosis of COPD:

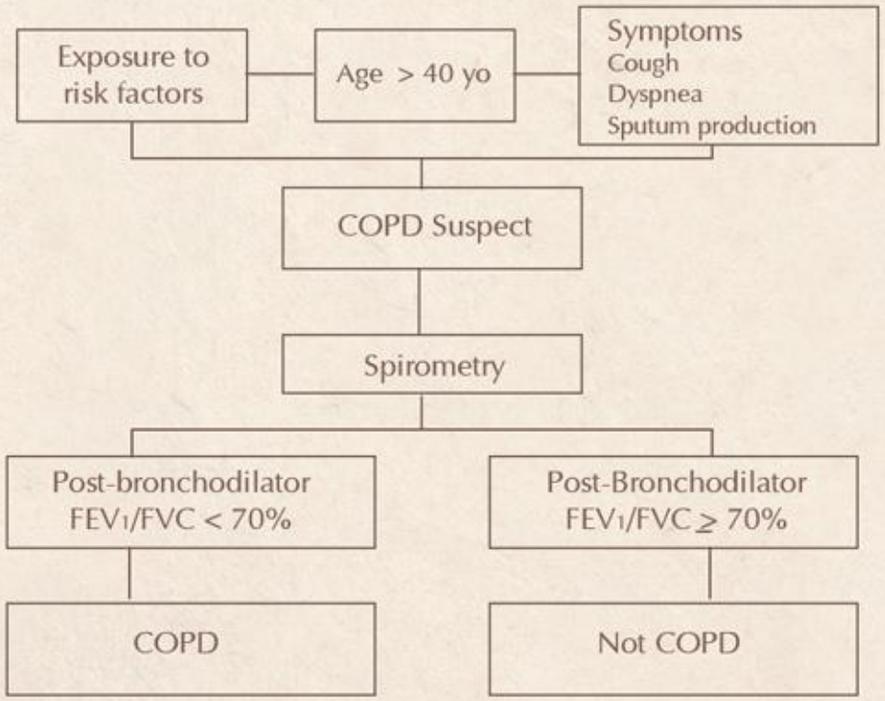

Figure 5.1. Diagram for the Diagnosis of COPD.

The characteristic chronic airflow limitation in COPD should be objectively assessed by spirometry. Spirometry measures the maximal volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC), the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) is calculated.[7] Patients with COPD typically show a decrease in both FEV_1 and FVC. The reduction in FEV^1 on spirometry generally reflects the degree of airflow obstruction and, therefore, the severity of COPD as well.[8] The rate of decline in FEV_1 is also characteristically increased in COPD so that when an intervention is able to decrease this accelerated rate of decline in FEV_1, it serves as proof for the said intervention's capacity to modify COPD as a disease.[9,10]

Assessment of airflow obstruction before and after giving a short-acting bronchodilator (Bronchodilator Reversibility Testing), at the time of diagnosis, is recommended. This is to obtain the post-bronchodilator FEV_1 and FVC values that will confirm the diagnosis of COPD[11]. The presence of a post-bronchodilator FEV_1/FVC<70% confirms the presence of COPD where airflow limitation is not fully reversible[4].

The Bronchodilator Reversibility Testing is also helpful in distinguishing the asthmatic from the COPD patient.[4,12,13] If FEV_1 returns to the predicted normal range after administration of a bronchodilator, the patient's airflow limitation is most likely due to asthma.

A protocol for the performance of Bronchodilator Reversibility Testing is listed in Fig. 5.2[4]

Figure 5.2. ***Bronchodilator Reversibility Testing***

Preparation

1. The test should be performed when patients are clinically stable and free from infection.
2. Patients should not have taken inhaled short-acting bronchodilators in the previous six hours, long-acting Beta-2 (B2) agonists in the previous twelve hours, or sustained release theophyllines in the previous 24 hours.

Spirometry

1. FEV1 & FVC should be measured before a bronchodilator is given.
2. The bronchodilator should be given by metered dose inhaler or by nebulizer.
3. Suitable dosage protocols for bronchodilators are 400 micrograms of B2-agonists, 80 micrograms of anticholinergic agents, or the two combined. FEV_1 & FVC should be measured again 30-45 minutes after the bronchodilator is given.

Results

1. A postbronchodilator FEV1/FVC < 70% confirms the diagnosis of COPD.
2. An increase in the FEV_1 that is both greater than 200 ml and 12% above pre-bronchodilator FEV_1 is considered a significant bronchodilator response.

C. ADDITIONAL INVESTIGATIONS

Chest radiograph

The standard postero-anterior and lateral chest radiograph is useful in the initial assessment of COPD patients to exclude or identify other conditions such as tuberculosis, lung cancer, pneumothorax, or pneumonia. Chest X-ray findings that may be suggestive of COPD include hyperlucency of the lungs, rapid tapering of the vascular markings, and signs of hyperinflation (flattened hemidiaphragms, and an increase in the volume of the retrosternal space)[4]. A normal Chest X-ray, however, does not rule out the diagnosis of COPD.

Arterial blood gas measurement

Measurement of arterial blood gases with the patient breathing room air is recommended in the assessment of patients with severe COPD when signs of right heart failure or respiratory distress are present.[14] As the disease progresses, hypoxemia becomes more severe and hypercapnia supervenes.

Peak flow determination

The definite correlation between peak expiratory flow rate (PEF) and FEV_1 has not been proven since PEF underestimates the degree of airflow obstruction.[15,16] Therefore, the use of peak expiratory flow rate determination in confirming the diagnosis of COPD is not recommended.

Computed Tomography

Computed tomography (CT) scanning is not recommended in the routine assessment of COPD. Its role is limited to the preoperative evaluation of patients with COPD who are about to undergo surgical procedures such as bullectomy or lung volume reduction surgery.[4,17]

Alpha-1 antitrypsin deficiency screening

Alpha-1-antitrypsin deficiency screening may be valuable to identify coexisting alpha-1 antitrypsin deficiency in patients who develop COPD at a young age (<45 years) or among those who have a strong family history of the disease.[4]

F. GRADING OF COPD SEVERITY

The spirometric classification in the GOLD document has been shown to predict health status, utilization of healthcare resources, exacerbation occurrence, and mortality among COPD patients.[18, 19, 20] It is, therefore, also adopted in this document to facilitate the grading of severity of a patient's COPD. Clinical features may aid in determining the severity of COPD in situations when access to spirometry is not possible. In this guideline, the clinical signs and symptoms from the British Thoracic Society guidelines were utilized in the severity classification based on the previous clinical experience with Filipino COPD patients.[21, 22]

There are four stages of COPD based on spirometry and signs and symptoms. In the 2005 guidelines, the grading of COPD severity included Stage 0 ("At Risk") to identify those who have or have been exposed to risk factors for COPD and who have minimal signs and symptoms but with normal spirometry. In this new document, Stage 0 is no longer included because there is insufficient evidence to show that individuals classified in this stage necessarily progress to Stage 1.[4]

Table 5 .1. Grading of COPD Severity

Stage	Post -bronchodilator Spirometry Values *	Signs/Symptoms
I: Mild COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted	• No abnormal signs • With or without symptoms of: - smoker's cough - Little or no breathlessness
II: Moderate COPD	• $FEV_1/FVC < 70\%$; • $FEV_1 \geq 50\%$ but < 80% predicted	• Variable abnormal signs (general reduction in breath sounds, presence of wheezes) • With or without symptoms of: - smoker's cough - Little or no breathlessness
III: Severe COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 \geq 30\%$ but <50% predicted	• Variable abnormal signs (general reduction in breath sounds, presence of wheezes) • Breathlessness on exertion • Cough and chronic sputum production
IV: Very Severe COPD	• $FEV_1/FVC < 70\%$ • FEV_1 < 30% predicted or • FEV1 < 50% predicted with respiratory failure or clinical signs of right heart failure	• Breathlessness on any exertion/at rest • Wheeze and cough often prominent • Lung overinflation usual; cyanosis; peripheral edema and polycythemia in advanced disease, especially during exacerbation

*All FEV_1 values refer to postbronchodilator FEV_1.

In order to capture the respiratory and systemic manifestations of COPD, the BODE Index was developed as a multidimensional grading system to predict the outcome of COPD patients. The BODE index is composed of body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E). The point system according to these parameters is shown in the table that follows. COPD patients with a total score of 7-10 would fall under the highest quartile and would have a predicted mortality rate of 80% at 52 months.

Table 5.2 Point System in the BODE Index [23]

	Points on BODE Index			
	0	1	2	3
FEV_1 (% predicted)	> 65	50-64	36-49	< 35
Distance walked in 6 mins (meters)	> 350	250-349	150-249	< 149
MMRC dyspnea scale*	0-1	2	3	4
Body mass index	> 21	≤ 21		

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

The BODE index was validated among Filipino patients and was found to be no better than FEV1 in predicting survival outcome among COPD patients[24] .

E. HOW IS COPD DIFFERENTIATED FROM OTHER COMMON CAUSES OF OBSTRUCTIVE LUNG DISEASES IN THE PHILIPPINES, SPECIFICALLY ASTHMA & BRONCHIECTASIS?[22]

In general, most patients presenting with airways obstruction can be categorized into either COPD or Bronchial asthma based on clinical history, physical examination, radiographic findings, pulmonary function test results and on occasion, a therapeutic trial of medication[25,26]. Bronchial asthma is also a chronic inflammatory disorder of the airways involving other kinds of inflammatory cells. This inflammatory process causes symptoms that are usually associated with widespread but variable airflow obstruction that is often reversible. This is in contrast to the progressive and irreversible airways obstruction of COPD. It may be difficult to differentiate COPD from asthma especially in the elderly who may present with persistent airflow obstruction due to airway remodeling associated with uncontrolled chronic asthma. Since the two conditions are based on distinct disease processes, one must recognize that both may be present simultaneously.

Table 5.3 shows the features that may differentiate Bronchial asthma from COPD[27].

Table 5.3[27] - Differences Between Asthma and COPD

Features	Asthma	COPD
Onset at a young age	Frequently	Almost never
Major symptoms	Usually episodic ▪ Wheezing ▪ Breat hlessness ▪ Non-productive cough ▪ Chest tightness	Usually daily ▪ Dyspnea with exertion (progressive over time) ▪ Productive cough
Triggers	Aeroallergens Occupational antigens Exogenous irritants Exercise Cold air Aspirin and NSAID's Reflux esophagitis Infectio ns	Daily activities Cold air Infections
Smoking history	Occasionally present	Usually present and of significant duration
Allergies	Often present	Occasionally present
Physical findings	▪ Rhinitis ▪ Pale nasal mucosa ▪ Prolonged expiration ▪ Wheezing	▪ Diminished intensity of breath sounds in advanced disease ▪ Pursed lip breathing ▪ Signs of right heart failure (distended jugular veins, right ventricular heave, loud pulmonic component of the second heart sound, ascites, pedal edema) ▪ Early inspiratory crackles ▪ Wheezing
Complete blood count	Eosinophilia	Polycythemia in advanced disease
Alpha -1 antitrypsin level	Normal	Occasionally low
Spirometry	▪ Reduced FEV_1 ▪ Reduced FEV_1/FVC ▪ May be normal when asymptomatic or with treatment	▪ Reduced FEV 1 ▪ Reduced FEV 1/FVC ▪ Reduced values may improve but usually do not return to normal values even with treatment
Significant Bronchodilator response in spirometry	Usually present Spirometry may normalize	May be present Values usually do not return to normal values
Lung volumes	TLC is usually normal RV may be increased	TLC may be normal or increased with emphysematous changes RV is increased
Diffusing capacity for carbon monoxide (DL_{CO})	Normal or increased	Reduced with emphysematous changes
Chest radiograph	Usually normal Occasionally hyperi nflated lung fields during attacks	Hyperinflation with emphysematous changes Bullae may be present
Chest CT scan	Usually normal	Emphysematous changes, Blebs, bullae, diminished vascularity

Bronchiectasis is characterized by irreversible dilatation of one or more proximal and medium-sized bronchi as a result of destruction of the muscular and elastic supporting tissues of the bronchial walls.[15,28] It is another disease which may present itself as chronic airways obstruction. It is common among Filipinos as it can follow necrotizing pneumonias caused by tubercle bacillus and other microorganisms. A high prevalence of asthma in patients with bronchiectasis among Asians has been reported[29].

Localized bronchiectasis is often present in patients with COPD. As a rule, however, bronchiectasis is characterized by dilatation of the airways rather than narrowing. Cough and sputum production, frequently purulent, often more severe on awakening are observed in 90% of all patients with bronchiectasis. Radiographic techniques should be requested to support the diagnosis. Chest radiographs are crucial to document regions of increased markings, cavities and atelectasis. When clinical symptoms and plain chest radiographs suggest bronchiectasis, a high resolution computed tomography (HRCT) is the imaging modality of choice for confirming or ruling out the diagnosis[30].

Due to the endemicity of tuberculosis in the Philippines, this disease should always be considered as a differential diagnosis in patients presenting with symptoms of COPD or as a co-existing illness in these patients. A distinct association between chronic airflow obstruction and history of tuberculosis has also been documented among middle-aged and older adults.[31]

F. ONGOING MONITORING AND ASSESSMENT[4]

Once COPD is detected and confirmed, ongoing monitoring and assessment should include evaluation of: (1) continued exposure to risk factors, especially tobacco smoke; (2) disease progression and development of complications; (3) pharmacotherapy and other medical treatment; (4) exacerbation history; (5) comorbidities.

Monitor Disease Progression and Development of Complications

COPD is usually a progressive disease. Lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop. As at the initial assessment, follow-up visits should include a physical examination and discussion of symptoms, particularly any new or worsening symptoms. A list of commonly asked questions during follow-up visits of COPD patients is provided in Appendix 2.[4]

Pulmonary function. A patient's decline in lung function is best tracked by periodic spirometry measurements. Useful information about lung function decline is unlikely from spirometry measurements performed more than once a year. Spirometry should be performed if there is a substantial increase in symptoms or a complication.

Arterial blood gas measurement. Measurement of arterial blood gas tensions should be performed in all patients with $FEV_1 < 50\%$ predicted or when clinical signs of respiratory failure or right heart failure are present. Respiratory failure is indicated by a PaO 2 < 60 mm Hg with or without PaCO 2 > 45 mm Hg in arterial blood gas measurements made while breathing air at sea level. Screening patients by pulse oximetry and assessing arterial blood gases in those with an oxygen saturation (SaO 2) < 92% may be a useful way of selecting patients for arterial blood gas measurement.

Diagnosis of right heart failure or cor pulmonale. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of cor pulmonale in clinical practice.
Firm diagnosis of cor pulmonale can be made through a number of investigations, including radiography, electrocardiography, echocardiography, radionucleotide scintigraphy, and magnetic resonance imaging. However, all of these measures involve inherent inaccuracies of diagnosis.

Hematocrit. Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers. Polycythemia can be identified by hematocrit > 55%.

Exercise testing. Several types of tests are available to measure exercise capacity, and are indicated for preoperative evaluation and pulmonary rehabilitation.

Monitor Pharmacotherapy and Other Medical Treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.

Monitor Exacerbation History

During periodic assessments, health care workers should question the patient and evaluate any records of exacerbations, both self-treated and those treated by other health care providers. Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted.

Monitor Comorbidities

In treating patients with COPD, it is important to consider the presence of concomitant conditions such as bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure. The appropriate diagnostic tools (chest radiograph, ECG, etc.) should be used whenever symptoms (e.g., hemoptysis) suggest one of these conditions.

Research Recommendations:

1. Develop a prediction model to help diagnose and classify COPD using variables that

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VI. HOW DO WE MANAGE PATIENTS WITH STABLE COPD?

KEY POINTS:

- COPD is a preventable and treatable disease.
- A holistic approach is needed to address the goals of management of COPD.
- Smoking cessation is the single most effective way of reducing the risk of developing COPD and delaying its progression.
- Pharmacologic therapy for COPD are mainly for symptom control, improvement in quality of life, functional capacity and decreasing exacerbation rates and severity as there are no pharmacologic agents that have been definitely shown to modify disease progression in COPD.
- Bronchodilator use is very important for symptom control in COPD. Inhaled formulations are preferred over oral medications.
- Pulmonary rehabilitation is considered an essential component in the holistic treatment of the COPD patient.

Stable COPD refers to the usual daily condition of the COPD patient when he or she is not having a new respiratory event or sudden worsening of his or her symptoms. Effective management, therefore, of a COPD patient's stable state entails long-term care and aiming for the following goals:

1. delay progression of the disease
2. relieve symptoms
3. improve exercise capacity
4. improve quality of life
5. prevent and treat complications
6. prevent and treat exacerbations
7. reduce mortality
8. affordable treatment with the least side effects

To address these goals in the management of a COPD patient, a holistic approach is needed. Slowing down of disease progression by avoidance of risk factors is of primary importance (Evidence A).[1-2] Since smoking is the major risk factor in the development of COPD, smoking cessation is one of the most important strategies to address this goal in the management of COPD. The other goals in the management of COPD are addressed by pharmacologic and non-pharmacologic interventions.

A. SMOKING CESSATION

Smoking cessation is the single most effective way of reducing the risk of developing COPD and delaying its progression (Evidence A)[1,3,4] . Studies have shown that merely reducing the number of cigarettes smoked does not alter the rate of decline in lung function among COPD patients who smoke (Evidence B)[5,6,7]. All smokers, therefore, should be offered the most intensive smoking cessation intervention available. These include counseling from physicians and other health professionals, pharmacotherapy, self-help and group programs. The employment of a brief (3-minute) counseling to urge a smoker to quit is a simple yet fairly effective method that can be done by all physicians (Evidence A; see Appendix 3).[8,9] Every smoker should be offered this brief counseling at every visit to a health care provider. Medications to aid in smoking cessation that are now available in the Philippines are the nicotine gum, nicotine patch and varenicline tablets.

B. PHARMACOLOGIC MANAGEMENT

The goals in instituting pharmacologic therapy for COPD are mainly for symptom control, improvement in quality of life, functional capacity and decreasing exacerbations as there are no pharmacologic agents that have been definitely shown to delay the progression of COPD as a disease (Evidence A).[10]

1. General principles of pharmacologic management

- Treatment should be based on the severity classification of the patient's COPD. Treatment may be increased to attain the therapeutic endpoints. Regular treatment should be maintained for long periods of time and adjusted accordingly if & when side effects occur. Patients should be monitored regularly to assess treatment response (Evidence D).

- Each treatment strategy should be patient-specific and should take into consideration not only the severity of symptoms and airflow limitation but also other factors including the presence of co-morbidities, complications, frequency and severity of exacerbations, cost and possible adverse effects of treatment (Evidence D).

2. Pharmacologic agents

Described below are the different classes of pharmacologic agents used in managing stable COPD. Monitoring clinical and objective measures of response to treatment is encouraged. A complete list of the different medications under these classes that are available in the country is found in Appendix 4.

a. Bronchodilators

Bronchodilators are the mainstay in symptom management for COPD (Evidence A).[11-16] The recommended first-line bronchodilators are beta 2-agonists and/or anticholinergic agents (Evidence A).[17-22] The inhaled route is preferred over oral formulations (Evidence A).[14,23] Long-acting inhaled bronchodilators (e.g. tiotropium, salmeterol, formoterol) have been shown to be more effective and convenient than short-acting bronchodilators (Evidence A).[24-33] Methylxanthine derivatives are recommended only as second-line bronchodilators (Evidence A).[23,31-36] Depending on the severity of symptoms, regular treatment with one or more bronchodilators with different mechanisms and durations of action can be given to improve the degree of bronchodilation for equivalent or lesser side effects (Evidence A).[17,19,37,38]

When treatment is given through the inhalational route, COPD patients may have problems with effective coordination, thus it is essential to ensure that inhaler technique is correct and/or spacer devices are utilized (Evidence D).[39] Use of nebulizers for delivery of medications is not recommended for regular treatment of stable disease (Evidence B).[40-41]

$Beta_2$-agonists relax airway smooth muscle by stimulating $Beta_2$-adrenergic receptors which results in functional antagonism of bronchoconstriction. There are short- and long-acting preparations with durations of action ranging from 4 - 6 hours and 8 - 12 hours, respectively.[15,16, 21] Oral and inhaled formulations are available, however, the oral preparations have a slower onset and have more systemic side effects than the inhaled form (Evidence A).[14,23] The most frequent side effects of $Beta_2$-agonist treatment include resting sinus tachycardia, somatic tremors, hypokalemia, and mild decrease in arterial oxygenation.[14,20] Long-term use of inhaled long-acting $beta_2$ agonists (e.g. salmeterol) has been shown to be safe in the recent 3-year TORCH (Towards a Revolution in COPD Health) trial with no excess of cardiac disorders noted.[42]

Anticholinergic medications block the effect of acetylcholine on muscarinic (M2 and M3) receptors and may also modify transmission at the pre-synaptic junction.[37] Short-acting (6 - 8 hours for ipratropium bromide) and long-acting (up to 24-36 hours for tiotropium bromide) inhaled preparations are currently available. Long-term tiotropium therapy has been shown to improve lung function, quality of life, and decrease exacerbations (Evidence A).[22,25-30,119] Tiotropium therapy, however, on top of usual care did not significantly reduce the rate of decline in FEV1 (Evidence A).[22] Long-term tiotropium use has been found to be safe with no increased incidence of strokes, cardiovascular morbidities nor respiratory complications of pneumonia and respiratory failure.[22] The most frequent side effect with inhaled anti-cholinergic use is dryness of the mouth.[22, 25-30]

The mechanisms of action of methylxanthines and xanthine derivatives still remain controversial, with the non-selective inhibition of phosphodiesterases and stimulation of diaphragmatic contractility among its proposed effects.[43] Theophyllines have been proven effective in COPD, however, some studies have demonstrated the lack of additional bronchodilation upon adding theophylline to other bronchodilators and there being more side effects with theophylline compared to $beta_2$ agonists and/or anticholinergic agents (Evidence B).[35, 36] Thus, methylxanthine derivatives (e.g. theophylline and doxofylline) are considered only as second line bronchodilators in COPD. The minor side effects associated with theophylline use are headache, insomnia, nausea, and heartburn while the more severe adverse effects are dose-related convulsions, atrial and ventricular arrhythmias. Doxofylline on the other hand has been noted to be better tolerated and to have lesser side effects (Evidence B).[44-46]

b. Corticosteroids

Glucocorticosteroids act at different sites within the inflammatory cascade and their effects in COPD are more modest compared with bronchial asthma. There are specific situations where steroids have a role in COPD.

1. Oral Glucocorticosteroids

With numerous studies documenting lack of benefit and occurrence of adverse effects, long-term treatment with oral corticosteroids is not recommended in stable COPD (Evidence A).[47]

2. Inhaled Corticosteroids

Inhaled corticosteroids are recommended for maintenance therapy in any of the following situations:

a. The patient has repeated exacerbations (e.g. 3 exacerbations in 3 years) (Evidence A)[48-55]
b. The patient has severe to very severe COPD (FEV_1 < 50% of predicted (Evidence A)[48-55] and is still symptomatic despite other medications.

Regular treatment with inhaled steroids has been shown to decrease symptoms and exacerbations as well as improve health status in these types of COPD patients (*Evidence A*).[48-55] A recent meta-analysis on ICS therapy showed that it does not affect 1-year all-cause mortality.[56] Withdrawal of inhaled glucocorticosteroids may lead to exacerbations in some of these patients (*Evidence B*).[57] The most common local side effect with inhaled steroid use is oropharyngeal candidiasis.[48-55] The systemic effects of cataract formation, reduction in bone mineral density and risk of fractures are not yet clearly defined. The recent meta-analysis on ICS therapy also showed an associated higher risk of pneumonia with ICS use (*Evidence B*).[56]

c. Combination Inhaled Corticosteroids-Long acting beta 2-agonists

Inhaled corticosteroids combined with long-acting beta 2-agonists are more effective than its individual components in improving lung function, quality of life, and decreasing exacerbation rate (*Evidence A*).[42,58-64] A post-hoc analysis of the TORCH trial also showed a significant decrease in the annual rate of FEV_1 decline with combination inhaled salmeterol-fluticasone therapy versus placebo and its individual components. (*Evidence C*).[64]

The incidence of pneumonia was also significantly higher among those given ICS-LABA compared to those with no ICS treatment (Evidence B).[42,56]

d. Combining Different bronchodilators and/or Inhaled Corticosteroids

Combining different bronchodilators having different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. Combining inhaled short-acting $Beta_2$-agonists and anticholinergic agents have been found to produce greater and more sustained improvements in FEV_1 than either short-acting bronchodilator alone (Evidence B).[17-19,37,38] Tiotropium alone compared to combination therapy with tiotropium and inhaled long-acting $Beta_2$-agonists and corticosteroids showed no difference in exacerbation rates.[66] However, improvement was noted in the secondary endpoints of quality of life and lung function in this study.[66] No detailed study has yet been done on combining inhaled long-acting bronchodilators ($Beta_2$-agonists and/or anticholinergics), inhaled corticosteroids and oral methylxanthines. The possible greater therapeutic benefit that can be derived upon combining different pharmacologic agents has to be balanced with the increased cost of treatment and the likelihood of side effects that can occur as these patients are usually in the higher age group (*Evidence D*).

e. Immunization

There is strong data to support the efficacy & cost-effectivity of influenza vaccination in reducing serious illness and exacerbations by 84-85% and even death in COPD patients by as much as 70% (Evidence A).[67-71] Vaccine derived from the most recent strains should be given every year once the new set of vaccines for the year is available (Evidence D).

Pneumococcal vaccination is recommended for COPD patients 65 years and older and is also adviced for younger COPD patients with FEV_1 < 40% predicted (*Evidence B*).[72,73]

Effectiveness of pneumococcal vaccination ranges from 29-75% in preventing hospitalizations, exacerbations and all-cause mortality. A second vaccination with the 23-valent pneumococcal polysaccharide (PPV23) at 5 years or more after the first vaccination is currently recommended only in the following circumstances:

- those age 65 and older, if they received the first vaccination before age 65 and it has been more than five years since then
- with functional or anatomic asplenia and
- persons at high risk of severe pneumococcal infection, regardless of the age at which they were vaccinated. (Evidence D)[74]

f. Mucolytics/Anti-oxidants

The widespread use of mucolytic agents cannot be recommended on the basis of present evidence (Evidence B; Cochrane 2007).[75] However, a recent large randomized trial showed that regular use of oral carbocisteine for 1 year significantly decreased exacerbation rate.[76] The benefit of decreased exacerbation rates with carbocisteine and oral N-acetylcysteine use seem to be among COPD patients who are not on maintenance inhaled corticosteroid therapy.[76,77]

g. Immunomodulators & Herbal medications

Based on the results of a local meta-analysis on the efficacy of immunomodulators (e.g. lyophilized bacterial lysate) in COPD, its use is not recommended as it does not cause a reduction in the frequency of COPD exacerbations (*Evidence B*).[78]

Anti-leukotriene drugs currently used for bronchial asthma have not been adequately studied COPD and its use is not routinely recommended. (*Evidence C*).[79-81]

A systematic review on the effectivity of herbal medications in COPD did not show any benefit with its use. (*Evidence C*).[82]

h. Antibiotics

The use of antibiotics other than for treating bacterial infectious exacerbations of COPD is not recommended (*Evidence A*).[83]

i. Antitussives

The regular use of antitussives in COPD patients is not advisable because cough has a significant protective role (*Evidence D*).[84]

j. Oxygen

Oxygen therapy can be administered in three ways: long-term continuous therapy, during exercise, and to relieve acute dyspnea. The primary goal of oxygen therapy is to increase the baseline PaO2 to at least 60 mmHg and/or to produce arterial oxygen saturation (SaO2) of at least 88-90%.

Long-term oxygen therapy (LTOT) has been shown not only to improve survival but also to improve hemodynamics, exercise capacity, lung mechanics, and mental state in patients with COPD and chronic respiratory failure (Evidence A).[85-89]

Long-term oxygen therapy is generally indicated in patients with:

- PaO2 < 55 mmHg or SaO2 < 88%, with or without hypercapnia (*Evidence A*).[88,89]
- PaO2 between 55 mmHg - 60 mmHg, or SaO2 > 89% but with evidence of pulmonary hypertension, polycythemia (hematocrit > 55%) or peripheral edema suggesting congestive heart failure (*Evidence D*).

Oxygen therapy should be given during exercise in those patients who already meet the criteria for LTOT and/or to those who develop significant oxygen desaturation during exercise (Evidence B).[90,91] Oxygen can also be given as for short periods to control episodes of severe dyspnea (*Evidence D*).

C. Non-Pharmacologic Management

1. Patient Education

Education is regarded as an essential component of care of COPD patients. Patient education alone has no direct effect on symptoms and does not improve exercise performance or lung function (*Evidence B*).[92-93] It may however play a role in improving adaptive skills, the ability to cope with illness and acute exacerbations, and general health status (*Evidence D*).[94] It is also an effective way to initiate and accomplish smoking cessation, and to initiate discussions and understanding of advance directives and end-of-life issues (*Evidence A*).[95]

2. Pulmonary Rehabilitation[96-105]

Pulmonary rehabilitation is a multidisciplinary and comprehensive intervention designed for symptomatic patients with chronic respiratory diseases to reduce their symptoms, optimize functional capacity & social participation, and reduce health-care costs through helping stabilize their disease. Comprehensive pulmonary rehabilitation programs include patient assessment, exercise training, education, and psychosocial support. Pulmonary rehabilitation is considered an essential component in the holistic treatment of the COPD patient (*Evidence A*).

Among the proven benefits of pulmonary rehabilitation in COPD are (*Evidence A*):

- Improvement in exercise capacity
- Reduction in the perceived intensity of breathlessness
- Improvement in health-related quality of life
- Reduction in the number of hospitalizations and days in the hospital
- Reduction in the anxiety and depression associated with COPD

Lower extremity exercise training is the necessary component in a pulmonary rehabilitation program (*Evidence A*). Strength & endurance training of the upper limbs improves arm function (*Evidence B*). Respiratory muscle training may be beneficial, especially when combined with general exercise training (*Evidence C*). Psychosocial intervention is also helpful (*Evidence C*). There is no consensus on the optimal duration of pulmonary rehabilitation - this may range from 4 weeks to 12 weeks (*Evidence B*). The benefits of pulmonary rehabilitation may extend well beyond the immediate period after training (*Evidence B*).

Pulmonary rehabilitation is currently available in several medical centers (see Appendix 5).

3. Nutrition

Several studies have noted that a low body weight and muscle wasting are independent risk factors for mortality in COPD patients (*Evidence C*).[106,107] Specific nutritional recommendations, however, seem to have no significant effect on long-term outcomes of COPD patients (*Evidence B*).[106-110] A balanced diet though is recommended for any COPD patient.

4. Surgery

Surgical intervention for COPD may include bullectomy, lung volume reduction surgery or lung transplantation. Bullectomy or the removal of large bullae may improve gas exchange and reduce dyspnea in carefully selected patients (*Evidence C*).[111]

Lung volume reduction surgery (LVRS) entails resection of some parts of the lungs to reduce hyperinflation, improve the mechanical efficiency of the diaphragm and other respiratory muscles, and improve the elastic recoil pressure of the lung. LVRS has been shown to improve the lung function, exercise capacity and quality of life in some patients (*Evidence C*).[111-118] Lung volume reduction surgery, though, is not advised for patients who have a low FEV1 (< 20%) and, either homogenous emphysema or a very low carbon monoxide diffusing capacity (*Evidence A*).[111,117,118] No local studies on LVRS have been published.

D. MANAGEMENT CONTINUUM FOR STABLE COPD

The holistic approach to treatment based on the severity classification for COPD can be summarized in this diagram. As the disease is assessed to be more severe, different pharmacologic and non-pharmacologic interventions are added on or combined to maximize control of the disease with due consideration of the cost entailed by treatment (*Evidence D*).

When there are limitations to performing spirometry to properly classify the severity of a patient's COPD, treatment may still be initiated and the same principle of severity-based treatment should guide the physician (*Evidence D*). All efforts however should be exerted to perform spirometry to confirm the diagnosis and classify appropriately in order to provide a rational approach to treatment.

STAGE	RECOMMENDED TREATMENT							
	Avoidance of risk factors & education	Smoking cessation	Influenza & Pneumo-coccal Vaccination	Short-acting Bronchodilator as needed for symptoms*	Regular use of single or combined long-acting bronchodilators**	Inhaled steroids***	Pulmonary Rehabi-litation	Others:
Stage I: Mild COPD	X	X	X	X				
Stage II: Moderate COPD	X	X	X	X	X		X	
Stage III: Severe COPD	X	X	X	X	X	X If with repeated exacer-bations	X	
Stage IV: Very Severe COPD	X	X	X	X	X	X If with repeated exacer-bations	X	• Consider surgical treatment options • Long-term oxygen therapy if with persistent hypoxemia, respiratory failure • Consider surgical treatment options

* Short-acting bronchodilators PRN for symptoms:
- Inhaled preferred over oral formulation
- Short-acting beta-2 agonists and/or anticholinergic agents are preferred

**Regular use of bronchodilators:
- Inhaled preferred over oral formulation.
- Inhaled long acting bronchodilators are preferred (e.g. tiotropium, salmeterol, formoterol).

*** Inhaled corticosteroids:
- Recommended if the patient has:
  > repeated exacerbations (e.g. 3 exacerbations in 3 years)
  > FEV_1 < 50% predicted
- When inhaled steroid therapy is considered, the use of combination inhaled corticosteroid-long-acting beta 2 agonist preparations is recommended since it is more effective than its individual components.

E. SPECIALIST REFERRAL

The following conditions or events in COPD patient may warrant referral to a pulmonary medicine specialist for further management:

REASON	PURPOSE
There is diagnostic uncertainty	Confirm diagnosis and optimize therapy
Suspected severe COPD	Confirm diagnosis and optimize therapy
The patient requests a second opinion	Confirm diagnosis and optimize therapy
Onset of cor pulmonale	Confirm diagnosis and optimize therapy
Assessment for oxygen therapy	Optimize therapy and measure blood gases
Assessment for long-term nebuliser therapy	Optimize therapy and exclude inappropriate prescriptions
Assessment for oral corticosteroid therapy	Justify need for long -term treatment or supervise withdrawal
Bullous lung disease	Identify candidates for surgery
A rapid decline in FEV_1	Encourage early intervention
Assessment for pulmonary rehabilitation	Identify candidates for pulmonary rehabilitation
Assessment for lung volume reduction surgery	Identify candidates for surgery
Assessment for lung transplantation	Identify candidates for surgery
Dysfunctional breathing	Confirm diagnosis, optimize pharmacotherapy and access other therapists
Aged under 40 years or a family history of alpha -1 antitrypsin deficiency	Identify alpha -1 antitrypsin deficiency, consider therapy and screen family
Uncertain diagnosis	Make a diagnosis
Symptoms disproportionate to lung function deficit	Look for other explanations
Frequent infections	Exclude bronchiectasis; optimize therapy and preventive measures
Hemoptysis	Exclude carcinoma of the bronch us, tuberculosis and other conditions
Preoperative clearance & perioperative management for complicated or extensive surgery	Optimize perioperative management and prevent perioperative complications

F. ETHICAL ISSUES

All patients with COPD developing acute respiratory failure should be considered for intubation and mechanical ventilation. However, in patients who have poor baseline function, marginal nutritional status, severely restricted activity levels and inexorable deterioration of their late-stage pulmonary dysfunction, the decision to forego intubation should be referred to a Bioethics Task Force.

It is also recommended in our setting that the following be carried out:

1. Creation of a Bioethics Task Force created from the different local medical societies to set guidelines on the withholding and withdrawal of mechanical ventilatory support based on ethical principles.
2. Establishment of an ethics committee in hospitals to help physicians identify, analyze and resolve ethical problems in patient care.
3. Development by medical societies of a consensus on the definition of quality of life to guide clinical management in the institution of life-sustaining therapy.

RESEARCH RECOMMENDATIONS

1. Survey the current use, cost, and relative distribution of medical & non-medical resources across the country for COPD.
2. Determine the cost effectivity of the different pharmacologic and non-pharmacologic interventions for COPD (e.g. regular use of inhaled versus oral bronchodilator medications, education intervention alone, formal pulmonary rehabilitation programs, etc.)
3. Perform researches oriented to helping policymakers & agencies formulate, revise & implement laws and regulations that can lessen the burden of risk factors for COPD (e.g. Clean Air Act, Framework Convention for Tobacco Control).
4. Confirm the effectivity of novel drugs that may control symptoms and prevent the progression of COPD among the Filipino population.
5. Develop indigenous interventions and local herbal medications that may be as efficacious as present interventions & medications for COPD.
6. Validate the effectivity and cost-effectivity of the proposed management continuum for COPD.

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Part II: CLINICAL PRACTICE GUIDELINES IN THE DIAGNOSIS AND MANAGEMENT OF EXACERBATION OF COPD (ECOPD)

KEY POINTS:

- An exacerbation of COPD (ECOPD) is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.

- Exacerbations are important events in COPD patients because of their negative impact on medical cost, lung function, quality of life and mortality. Proper management is of paramount concern.
- The etiology of ECOPD (Exacerbation of COPD) is multi-factorial, with infectious causes accounting for 80% of exacerbations. Seventy percent of these infections are bacterial in origin.
- Systemic corticosteroids are beneficial in the management of patients with ECOPD because of documented improvements in dyspnea and pulmonary function, decreased length of hospital stay, and decreased rate of subsequent relapse.
- Antimicrobial treatment is beneficial in patients with ECOPD with increased dyspnea, increased sputum purulence or increased sputum volume.
- The preferred bronchodilator in the management of ECOPD is any of the short-acting inhaled bronchodilators: short acting ?2-agonists or anti-cholinergic bronchodilators. Both classes equally improve symptoms and FEV1.
- In selected patients, noninvasive ventilation reduces the need for intubation, improves in-hospital morality rates, and decreases the length of hospital stay of ECOPD patients.

I. INTRODUCTION

COPD is a major health concern in the Philippines and around the world. It is a leading cause of death worldwide and its prevalence is still expected to rise. The prevalence of COPD in Manila based on the recently publicized Burden of Obstructive Disease (BOLD) study was reported to be 13.8% 1. The prevalence of COPD in the rural areas of the country is the subject of an ongoing study.

Studies show that a COPD patient experiences 1-3 exacerbations per year.[2,3] Exacerbations are important events in COPD patients because of their negative impact on medical cost[2], lung function[3], quality of life[4] and mortality[3]. Proper management is therefore of paramount concern.

Controversies pertaining to management decisions in ECOPD persist. This document tackles these issues and other aspects of management and makes recommendations in an effort to help the Filipino practitioner treat this condition.

Methodology

1. Assignment of general topics to members of the committee
2. Formulation of the questions to be included in the guidelines
3. Literature search to answer the questions
    a. Medline/Pubmed
    b. Google (scholar)
    c. Cochrane
    d. Check published international/national guidelines
        i. Check citations
        ii. Check levels of evidence
    e. Local studies: Inquiry of different hospitals and pulmonary specialists
4. Presentation of individual reports to the general body (committee) for analysis of literature search, results of studies presented; level of evidence and management recommendations
5. Presentation of the committee output to select group of PCCP members for critical review

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II. DEFINITION

An exacerbation of COPD (ECOPD) is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD."

Varied definitions for acute exacerbation of COPD have been utilized by authors and researchers throughout the years.[1-6] Clinical studies on COPD exacerbations often used the presence of at least 1 of the following symptoms in defining exacerbation of COPD: worsening dyspnea, increased sputum volume, increased sputum purulence[7]. Other authors defined exacerbation of COPD as worsening of respiratory symptoms that required treatment with corticosteroids or antibiotics, or both.[4,9] Following a series of meetings involving world-renowned experts and various stakeholders, a more uniform definition has evolved in recent years.[5-6] The committee decided to adopt the GOLD definition (above), which was also utilized in the 2007 Philippine COPD guidelines.[8]

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III. EPIDEMIOLOGY

What is the exacerbation rate in patients with COPD?

Up to 90% of COPD patients in the severe or very severe categories have a frequency of up to 3 exacerbations per year (mean: 1.7), whereas the mild to moderate category of severity has a mean exacerbation rate of 0.9/year.

Local data describing the prevalence of COPD in the general population are numerous. However, data showing the exacerbation rate in diagnosed Filipino COPD patients are lacking. Hence, a search for exacerbation rates was undertaken using international literature. The statistics obtained came from large clinical trials with population demographics that included exacerbation rates.

In the EFRAM study (2001), a total of 172 COPD patients with a mean age of 69 years were recruited. Mean FEV_1 in the population was 39% (range: 34% - 43%) of predicted. In this study population, 155 out of 172 (90%) had less than 4 exacerbations per year.[1]

`Farrero et al, observed similar rates in their study[2]. The patients followed for a mean period of 410 days. Mean age was 69 years, and mean FEV_1 was 36% of predicted (range not available). Majority, 126/340 (37%) did not have exacerbations during the follow-up period. Followed by 78/340 (23%) who had 1 exacerbation in the follow-up period.
13% had more than 4 exacerbations in the follow-up period.

The patients were followed for a mean period of 410 days. In the ISOLDE[3] study, 73 patients in 18 UK hospitals were divided into mild COPD category (FEV1>50%) and moderate-to-severe COPD category (FEV1<50%) according to the earlier ATS criteria. This encompasses "mild to moderate severity" and "severe to very severe" classifications in the more recent 2007 update of GOLD. Patients on placebo in the mild to moderate category had a median exacerbation rate of 0.9/year, whereas subjects in the Severe to Very Severe category had median exacerbation rate of 1.7/year.

Wedzicha et al looked into the percentage of COPD exacerbations among the total number of hospital admissions[4]. COPD exacerbations were responsible for 2.4% of the 4.2 million acute medical admissions in England for 2003-2004.

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IV. ETIOLOGIES OF ECOPD

What are the common causes of ECOPD?

The etiology of ECOPD is multi-factorial, with infectious causes accounting for 80% of exacerbations. Seventy percent of these infections are bacterial in origin.

Common bacteria seen in the mild to moderate ECOPD are Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis. There is a propensity for gram negative bacteria (e.g. Pseudomonas aeruginosa, Acinetobacter sp., Stenotrophomonas maltophilia, Serratia sp., Klebsiella pneumonia and Escherichia coli) to cause exacerbations in the more severe stages of COPD, as well as those with and co morbid factors.

Atypical bacteria are uncommon causes of COPD exacerbation. Atypical infections account only for a minor percentage in mild to moderate ECOPD. However, in the severe stages of COPD with exacerbation, co-infection with atypical organisms may further worsen inflammation.

Recent detection techniques have placed viruses as a major cause ECOPD during the cold months. Respiratory viruses that can commonly precipitate an exacerbation are influenza virus, rhinovirus, coronavirus, parainfluenza, adenovirus and respiratory syncytial virus.

It is estimated that around 80% of all exacerbations are infectious in origin.[1] The remaining 20% are due to environmental pollutants.[2-5] Pollutants are known to be pro-inflammatory, inducing mucus hypersecretion and bronchoconstriction.[6] Smoke particulate matter such as PM-10, and non-particulate gases such as sulphur dioxide (SO2), Ozone (O3) and nitrogen dioxide (NO2) can induce an exacerbation in vitro and in vivo.[7] Air pollution is associated with increased relative risk of COPD admissions in European cities.[1,8]

Bacteria. Bacterial causation accounts for around 70% of acute infectious exacerbations.[2] In previous studies the most common isolates were Hemophilus influenza (11%), Streptococcus pneumonia (10%), Moraxella catarrhalis (10%), and Hemophilus parainfluenzae (10%). Pseudomonas aeruginosa, Stenotrophomonas spp. and Gram negative bacilli occur in more severe stages of COPD with an exacerbation and also affecting the more debilitated patients with more co-morbid conditions. [9-11]

A recent Hong Kong prospective study of bacterial etiology involving 373 patients with 643 episodes of exacerbation of COPD reveals a difference in the microbial flora distribution.[12] H. influenzae (13%), P. aeruginosa (6%), Streptococcal pneumoniae (5.5%), M. catarrhalis (4.2%), Klebsiella spp. (1.9%), Acinetobacter spp. (1.3%) and the other gram negatives bacilli (2%) were isolated. It is worth noting that Mycobacterium tuberculosis occurred in 0.4% of the cases seen. Similarly in a retrospective study in Taiwan involving 398 patients with 494 episodes of exacerbation, their data showed Klebsiella pneumoniae (19%), P aeruginosa (16.8%), Hemophilus influenzae (7.5%), Acinetobacter baumannii (6.9%), Enterobacter sp (6.1%) and Staph aureus (6.1%) as common isolates.[13] These regional differences could be affected by antibiotic pretreatments, environmental factors, vaccinations, compliance with medications, interval between exacerbations and current smoking status. In a prospective study at the Lung Center of the Philippines by Limsi, involving 264 patients admitted because of ECOPD, 87(29.69%) of the subjects were intubated and 164(62%) were considered in the severe stage of the disease. Sixty percent of the isolates were gram negative. Twenty seven percent of the admitted patients did not grow a potentially pathogenic bacteria. 14 In a two year retrospective study (2005 to 2007) in the same institution by Buendia, involving 686 admitted patients with ECOPD, Moraxella catarrhalis 165(43.3%) was isolated in more than 40% of cases and the gram-negative enteric organisms were the next most common. Mixed isolates were common.[15]

In an outpatient study by C. Roa et al. involving 16 spirometry-confirmed COPD patients who experienced exacerbation, Hemophilus influenzae (6), Streptococcus pneumoniae (5), Moraxella catarrhalis (4), Klebsiella pneumoniae (1), E. coli (1) and Pseudomonas aeruginosa (1), were the bacterial isolates. Two of these subjects had double isolates of H. influenzae and Streptococcus pneumoniae.[16]

Atypical Bacteria. Atypical bacteria such as Chlamydia pneumoniae, Legionella sp. and Mycoplasma account only for a small percentage of COPD exacerbations, approximately 5% -16% in mild to moderate COPD.[17-19] In the more severe stages of COPD it is not definite whether atypical microorganisms cause exacerbation alone or with a co-pathogen. In a study by Soler involving 50 intubated COPD patients, he showed that[7] out of 38 (18%) had a positive paired serologic titers for Chlamydia. however there was co-infection with other potentially pathogenic microorganisms. In this study disease causation by the atypical bacteria could not be established.[11] This is also the similar observation of Karnak

Viruses. In older studies using viral cultures and serologies, viruses accounted for only 10-20% of COPD exacerbations.[12,21] Recent studies using PCR, have increased the detection of two or more viruses co-infecting 40-60% of COPD exacerbations.[22-24] Virus induced exacerbations occur with greater frequency during the winter months, and is associated with worse functional status.[22,25] Major respiratory viruses associated with COPD exacerbations are rhinovirus, coronavirus, influenza virus, parainfluenza, adenovirus, respiratory syncytial virus.[19,27,29] An exacerbation due to a virus is usually preceded by an upper respiratory tract infection.

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V. EVALUATION

A. What is the role of chest radiography in ECOPD?

Chest X-rays (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. Chest X-rays are recommended for patients presenting to the emergency department or for admission to hospital because they have been shown to reveal abnormalities that lead to a change in management in 16% to 21% of patients (Level of Evidence C).

Based on 2 retrospective studies cited in the Canadian Thoracic Society recommendations, there was a 16% abnormality rate from a study of 685 episodes occurring in a single urban emergency department and 16% occurring in 107 patients admitted to a single hospital. In a prospective cohort study of 128 hospital admissions for asthma or COPD, 21% of patients had a change in management based on their CXR findings.[1-3,6]

In another report, differentiating pneumonic and non-pneumonic acute exacerbations of COPD, it was found that those with pneumonic infiltrates had lower pO2 values, higher rates of abrupt onset, ICU admissions, invasive mechanical ventilation, mortality and longer hospital stay.[4,5]

B. What is the role of ABG in ECOPD?

Arterial blood gas analysis is helpful both in identifying those patients currently in need of oxygen therapy and those who would likely need mechanical ventilatory support (Level of Evidence C).

Based on GOLD guidelines, for patients requiring hospitalization, measurement of arterial blood gases is important to assess the severity of an exacerbation. A PaO2 of less than 60 mmHg and/or SaO2 <90% with or without PaCO2 more than 50 mmHg when breathing room air indicate respiratory failure. In addition, moderate to severe acidosis (ph <7.36) plus hypercapnea (PaCO2 45-60 mmHg) in a patient with respiratory failure is an indication for mechanical ventilation.[1,3]

C. What is the role of spirometry in ECOPD?

Simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore their routine use is not recommended. Pulmonary function test, however, should be performed in patients who have recovered from ECOPD, if they have not previously had spirometry (Level of Evidence C).

A study performed in an urban emergency department enrolling 70 patients demonstrated that FEV1 at the time of presentation was weakly, but statistically significantly correlated with both pCO2 ($r=-0.46$; $p<0.0001$) and pH ($r= 0.33$; $p<0.01$) but was not correlated with arterial pO2.[6]

In a study by Seemungal et al, they found that symptom changes during exacerbation do not closely reflect those of lung function.[7]

According to the GOLD guidelines, due to difficulty in performing this test, spirometry is not recommended in exacerbations of COPD.1 The Canadian Thoracic Society states that for those who has not had prior spirometry test, they recommend a spirometry exam for those who have recovered from an episode of exacerbation.[2]

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VI. TREATMENT

A. Are systemic corticosteroids indicated for the management of ECOPD?

Yes, systemic corticosteroids are beneficial in the management of patients with exacerbations of COPD (ECOPD) because of documented improvements in dyspnea and pulmonary function, decreased length of hospital stay, and decreased rate of subsequent relapse[1-7]. (Evidence A)

Three systematic reviews [6,7],16 and five randomized controlled trials[1-5] have examined the use of systemic corticosteroids in the management of COPD exacerbations Albert and colleagues found a significant improvement in pre-bronchodilator and post-bronchodilator FEV_1 in patients with ECOPD after using IV methylprednisolone at a dose of 0.5 mg/kg every 6 hours for 72 hours as compared to placebo.[1]

In 1999, Niehwoehner and colleagues[4] published the Department of Veterans Affairs Cooperative Study wherein they randomized 271 subjects with ECOPD into 3 groups: Group 1 - 8 weeks of glucocorticosteroid therapy consisting of methylprednisolone 125 mg every 6 hours for 72 hours followed by tapering doses of oral prednisone for 54 days; Group 2 - 2 weeks of glucocorticosteroid therapy consisting of methylprednisolone 125 mg every 6 hours for 72 hours followed by tapering doses of oral prednisone for 12 days; Group 3 - placebo group. The rates of treatment failure (defined as death from any cause, or the need for intubation or mechanical ventilation, readmission to the hospital for COPD, or intensification of drug therapy) was significantly higher in the placebo group than in the two glucocorticosteroid groups at 30 days (33% vs 23%; p=.04) and at 90 days (48% vs 37%; p=.04). The combined steroid groups also had a shorter hospital stay (8.5 vs 9.7 days; p=.03) with an FEV1 that was 0.10 liters higher than the placebo group by the first day of enrollment. The 8-week regimen was not superior to the 2-week regimen.

Davies and colleagues[5] randomized 56 patients to receive either 30 mgs of oral prednisone for 14 days versus placebo. Patients in the prednisone group had a faster and greater improvement in FEV_1 and a significantly shorter length of hospital stay (9 vs 7 days). A study published in the NEJM in 2003 randomized 147 patients with ECOPD presenting at the emergency room to either prednisone 40 mgs daily for 10 days or placebo[3]. The patients randomized to prednisone experienced a significantly decreased rate of relapse at 30 days (27% vs 43%; p=.05), prolonged time to relapse, and improved pulmonary function. No differences were noted in the hospitalization rate or mortality between the two groups.

Recent comprehensive systematic reviews have shown clear treatment benefits for patients with ECOPD treated with either oral or systemic steroids. In a comprehensive review done by Singh and colleagues published in 2002 6, the authors have concluded that there is good quality evidence to show that administration of systemic corticosteroids in patients with ECOPD modestly reduces treatment failure rates, duration of hospitalization, and improves FEV_1 (the latter is evident within the first day of therapy and lasts for at least 5 days). Similar results were found by Wood and Baker, as well as Quon et al, in more recent metaanalysis[7].

For the moment, it would be difficult to identify distinct subsets of ECOPD patients who will benefit most from systemic corticosteroids. However, it would be very interesting to note that studies on the subject matter that were reviewed in a recent metaanalysis[7] have included patients presenting with a mean FEV1 range of 0.53-1.70 liters at the time of exacerbation.

1. What is the optimal dose and duration of steroid treatment in patients with ECOPD?

Because of the wide variation in steroid doses which were used in different studies, it would be difficult to make a specific dose recommendation for patients with ECOPD. The shortest duration of treatment remains unknown. However, there is strong evidence to show that systemic corticosteroid courses longer than 2 weeks may not offer any advantage to patients with ECOPD (Evidence A).

Considering the finding that COPD patients experience an average of 1.3 (range: 0-9.6) exacerbations per year[15], the steroid burden of COPD patients can be considerable. This certainly increases the risk of adverse events and emphasizes the need to define the optimal dose and duration of steroid treatment for patients with ECOPD. This, however, has proven to be difficult to accomplish principally because different authors used a wide range of steroid doses and duration of treatment: from a low of 30 mgs/day (Davies) of oral prednisone for 3 days[9] to a high of 125 mgs of IV methylprednisolone q6h given for 72 hours followed by tapering doses of prednisone tablets for 11-53 days[7]. Most of the studies

on the use of steroids in ECOPD have used durations of treatment with a range of 3-8 weeks.[7] However, Niehwohner et al have found no advantage of an 8-week regimen over that of a shorter duration (i.e., 2 weeks).[4] Thus with the available studies that were found, it would seem prudent to recommend that systemic corticosteroids should be administered for no longer than 14 days in patients with ECOPD (Evidence A).

2. What is the optimal route of administration of systemic corticosteroids in patients with ECOPD?

At the moment, it would seem wise to recommend using the oral route for ECOPD patients who can tolerate it. Otherwise, clinicians would have to administer systemic steroids parenterally until such time when the patient may be able to take the drugs orally (Evidence B).

The systematic review by Singh et al[6] and the meta-analysis done by Wood-Baker et al[7] did not include studies directly comparing oral versus IV corticosteroids in the management of ECOPD. However, the studies they have found using oral steroids alone seem to show similar clinical benefits to studies using parenteral steroids. In addition to this, de Jong and colleagues[8] in 2007 compared the rate of treatment failure of IV versus oral prednisone among patients with ECOPD. Prednisone dose used was 30 mg/day for 5 days. Their results showed a treatment failure rate of 61.3% for the IV prednisone group and 51.7% for the oral prednisone group. Since their results did not exceed their predetermined margin of inferiority of >15%, the authors concluded that oral prednisone was not inferior to IV prednisone among patients with ECOPD.

3. Is there a role for Inhaled corticosteroids in the management of ECOPD?

Inhaled corticosteroids are not currently recommended in the management of patients with ECOPD (Evidence B).

On a theoretical basis, using ICS instead of oral or IV steroids would have distinct advantages as the patients would be spared of the toxicity associated with systemic corticosteroids. But since systemic corticosteroids are considered standard therapy in ECOPD, a strong evidence of non-inferiority would have to be demonstrated in well designed trials before any recommendation for use ICS in ECOPD is made. Up to the present time however, no such trial has been done. Studies found dealing with a comparison of ICS versus systemic corticosteroids were not designed to demonstrate noninferiority.[9-12]

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B. Is the use of antimicrobials indicated in exacerbations of chronic obstructive pulmonary disease (ECOPD)?

Antimicrobial treatment is beneficial in the following patients with ECOPD:

- **Patients with all 3 of the following symptoms: increased dyspnea, increased sputum purulence or increased sputum volume (Level of Evidence A).**
- **Patients with 2 of the above symptoms, if increased sputum purulence is one of the symptoms (Level of Evidence C).**

The beneficial effects of antimicrobials for acute exacerbations of chronic bronchitis are still controversial. This is due to the fact that bacterial infection is just one of several causes of AECB and the common pathogens found to be causative agents for infection are known to be colonizers of the distal airways of patients with chronic bronchitis even during clinical stable periods.[1] Although several studies have concluded that use of

sputum volume production and purulence, type 2 (moderate) exacerbations defined as occurring when only 2 of these symptoms were present and type 3 (mild) exacerbations with only 1 of the 3 symptoms, in addition to one of the following findings: upper respiratory tract symptoms, increased wheezing, increased in respiratory rate or heart rate by 20%, or fever without another cause. Patients were randomized either to an antibiotic group or a placebo group for a 10-day course. Antibiotics used were trimethoprim/sulfamethoxazole 160mg/800 mg BID, amoxicillin 250 mg QID or doxycycline 200 mg initially followed by 100 mg daily. The study showed significant benefit associated with antibiotic use as compared to placebo especially in populations with severe exacerbation. The success rate with placebo was 55% and with antibiotic treatment, 68%. The rate of failure with deterioration was 19% with placebo and 10% with antibiotics. Antibiotics also showed a more rapid improvement in peak flow and length of illness was 2 days shorter for the antibiotic-treated group compared to the placebo-group. Based on this study, the use of antimicrobials improved treatment outcomes in all patients with ECOPD, regardless of severity of exacerbation, although the most benefit was seen in the subset of patients with more severe exacerbations.

A meta-analysis by Saint et al in 1995[3] involving 9 trials published from 1955 to 1994 was performed to estimate the effectiveness of antibiotics in treating exacerbations of chronic obstructive pulmonary disease (in outpatients setting) with outcomes measured like mean number of days ill, severity of symptoms and with PEFR as the most common reported outcome measure. This study showed an overall summary effect of 0.22 (95% C.I. 0.10-0.34) indicating a small benefit in the antibiotic-treated group vs. the placebo group. This meta-analysis also revealed a pooled effect of 0.19 (95% C.I. 0.03-0.35) and average change in peak expiratory flow rate of 10.75 L/min (95% C.I. 4.96-16.54 L/min) in favor of the antibiotic group. This meta-analysis validated the Anthonisen's study, showing that patients with signs and symptoms of ECOPD, irrespective of severity or classification, benefited from antimicrobial therapy.

A systematic review by Quon in 2008[4] studied the beneficial effects of systemic steroids, antibiotics and NIPPV in patients with ECOPD. For the section studying the use of antibiotics, there were 11 RCTs involved, 7 of which were for hospitalized patients, 1 conducted in a medical ICU and 3 were outpatients. Patients included were diagnosed COPD patients with acute exacerbations defined as having worsening cough or dyspnea or increased sputum production. Intervention used was oral beta-lactams and tetracycline derivatives versus placebo given for a minimum of 7 days with a mean duration of treatment of 8.9 days. Outcome measured included treatment failure defined as requiring additional antibiotics within first 7 days or unchanged or deteriorated symptoms within 21 days and in-hospital mortality. Results showed that treatment failure was significantly reduced by 46% in patients given antibiotics compared with placebo (RR 0.54 95% CI 0.32-0.92) but test for heterogeneity was significant (p 0.002) hence a sub-analysis according to patient type was done. This showed that antibiotics significantly reduced treatment failures in patients who were hospitalized (RR 0.34 C.I. 0.20-0.56; p 0.48 for heterogeneity) but not for outpatients (RR 0.88 95% CI 0.56-1.39; p 0.06 for heterogeneity). In-hospital mortality was also reduced by 78% with the use of antibiotics (RR 0.22 95% CI 0.08 to 0.62; p 0.92 for heterogeneity).

A systematic review of studies regarding the value of antibiotics in the management of acute COPD exacerbations was published in the Cochrane Database[5] in 2006. Inclusion criteria were randomized controlled trials of patients with acute COPD exacerbation comparing antibiotics and placebo. This review included 11 trials with 917 patients with the following outcomes: mortality, treatment failure, increase sputum volume and purulence, PaC02, Pa02, peak flow and adverse events. Analysis of 6 trials, 4 done as in-patient and 2 as community based, with 705 patients reported significant RR reduction of treatment failure in the antibiotic group compared to placebo (RR 0.67 95% CI 0.5-0.80) but included significant heterogeneity (p 0.009). Re-analysis of the data including only the 4 hospital-based studies with 321 patients also favored reduction of treatment failure by 53% (RR 0.47 95% CI 0.36-0.62, NNT of 3, p 0.44 for heterogeneity). This review also showed that antibiotics improved sputum purulence in 3 trials (RR 0.56 95% CI 0.41-0.77, NNT of 8) and lowers mortality by 77% in 4 trials (RR 0.23 95% 0.10-0.52, NNT of 8). Differences in PaC02 levels, Pa02 and PEFR were not significant between antibiotic and placebo groups.

Based on the studies mentioned, antimicrobial therapy for patients with signs and symptoms of exacerbations of COPD will increase clinical and bacteriologic cure, decrease treatment failure, improved sputum purulence and lower mortality rates especially for those patients who warrant hospitalization.

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1. What antimicrobials are recommended for ECOPD?

The antibiotic of choice should reflect known local pattern of resistance if available. Newer antimicrobials like macrolides, beta-lactams with beta lactamase inhibitors, and fluoroquinolones are equally effective as antimicrobial therapy for ECOPD (Level of Evidence B)

Many agents are available for antibacterial therapy. In selecting the appropriate agent, spectrum activity, a good adverse event profile, resistance pattern, tracheo-bronchial penetration and cost-effectiveness are all considered.

Most recent trials regarding the use of antimicrobial therapy for ECOPD are comparative studies between newer antibiotics with established ones. Some studies comparing a respiratory fluoroquinolone with a cephalosporin or a beta-lactam with a betalactamase inhibitor[6,7] showed that the 2 antibiotics are equivalent in terms of efficacy and drug tolerability, although Grossman et al[8] concluded that Levofloxacin had significantly higher proportions of patients with resolved purulent sputum production and cough compared with Amoxicillin/clavulanate. Trials involving macrolides vs respiratory fluoroquinolones showed that the 2 drugs were comparable[9,10] while other studies showed that Moxifloxacin provided superior bacterial eradication 11 and faster symptom relief and higher recovery rate[12,13] than macrolide (azithromycin, clarithromycin and roxithromycin).

A recent meta-analysis[14] compared the effectiveness of first-line antimicrobial agents (e.g. amoxicillin, ampicillin, pivampicillin, trimethoprim/ sulfamethoxazole and doxycycline) with second-line antimicrobials (e.g. amoxicillin/ clavulanate, macrolides, second- or third-gen cephalosporins and quinolones). This study included 12 RCTs with a total of 2,261 adult patients with a mean JADAD quality score of 3.3, nine of which were double-blinded and 3 were single-blinded and most RCTS included a mixed population of both inpatients and outpatients. Results showed that treatment success was less effective in first-line antibiotics compared to second-line antibiotics (1,145 CE patients; OR 0.51 95% C.I. 0.34-0.75). All cause mortality (1,392 ITT patients; OR 0.64 95% C.I. 0.25-1.66) and drug-related adverse events (1,619 ITT patients; OR 0.75 95% C.I. 0.39-1.45) during the study period were not significantly different between the 2 groups. Microbiological outcomes were also not significantly different between the 2 groups (638 ME patients; OR 0.56 95% C.I. 0.22-1.43). This suggests that second-line antibiotics are more effective but not less safe in patients with AECB, although considerations should be given to the fact that only clinically evaluable patients were analyzed in this meta-analysis.

Another meta-analysis[15] studied 19 RCTS representing 7,405 patients, with a mean JADAD quality score of 3.2. RCTS studied adult patients not hospitalized at the time of enrolment (except for 1 RCT who included both inpatients and outpatients), with a medical history of chronic bronchitis. These RCTS compared macrolides with quinolones, amoxicillin/clavulanate (A/C) with quinolones and A/C with macrolides. Their results showed that there was no significant difference in treatment success between ECOPD patients treated with macrolides and those treated with quinolones (2,822 ITT patients; OR 1.01 95% C.I. 0.81-1.27) and (2,606 CE patients; OR 0.39, 95% CI 0.73-1.21 or between a/C and quinolones recipients (1,441 CE patients; OR 0.86 95% CI 0.55-1.34) and between macrolide and A/C recipients (869 ITT patients; OR 1.09 95% CI 0.41-2.95; 1,082 Ce patients; OR 1.70 95% CI 0.72-4.03. All-cause mortality were also comparable between macrolide and quinolone treated patients (2,627 ITT patients; OR 1.96 95% CI 0.45-8.51). Treatment success for microbiologically evaluable patients was significantly improved in quinolones compared to macrolides (1,308 ME patients; OR 0.47 95% CI 0.31-0.69) while there was no significant difference between A/C and quinolones (445 ME patients; OR 0.84 95% CI 0.49-1.42) or between A/C and macrolide (571 ME patients; OR 1.49 95% CI 0.51-4.39).

Concerns have been raised regarding the possible increase in resistance rates of MTB to fluoroquinolones with widespread use of this class of antibiotic.[16-19] In the 2008 GOLD update, 20 patients with ECOPD were stratified for antimicrobial therapy (Table 1). Recommendations for antibiotic therapy (oral or parenteral) of each ECOPD subset were given (Table 2).

Table 1: Stratification of patients with ECOPD for antimicrobial treatment and potential microorganisms involved in each group (from GOLD 2008)

Group	Definition	Microorganisms
A	Mild exacerbation: No risk factors [1] for outcome	H. influenzae S. pneumoniae M. catarrhalis C. pneumoniae Viruses
B	Moderate exacerbation with risk factor(s) for poor outcome	Group A plus presence of resistant organisms (-lactamase producing, penicillin resistant S. pneumoniae), Enterobacteriaceae (K. pneumoniae, E. coli, Proteus, Enterobacter, etc.)
C	Severe exacerbation with risk factors for P. aeruginosa infection	Group B plus: P. aeruginosa

[1]Risk factors for poor outcome in patients with ECOPD: presence of co-morbid diseases, severe COPD, frequent exacerbations (>3/year), and antimicrobial use during the last 3 months (from GOLD 2008)

Table 2: Antibiotic treatment in ECOPD (from GOLD 2008)

Group	Oral treatment (No particular order)	Alternative oral treatment (No particular order)	Parenteral treatment (No particular order)
A	Patients with only one cardinal symptom [1] should not receive antibiotic. If indicated, then: β-lactam (penicillin, ampicillin, amoxicillin)	β-lactam/ - lactamase inhibitor (co - amoxiclav) Macrolides (azithromycin, clarithromycin, roxithromycin) 2nd or 3rd generation cephalosporin Ketolides (telithromycin)	
B	β- lactam/ - lactamase inhibitor (co - amoxiclav)	Fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)	β- lactam/ - lactamase inhibitor (co - amoxiclav, ampicillin/sulbactam) 2nd or 3rd generation cephalosporin Fluoroquinolo-nes (levofloxacin, moxifloxacin)
C	In patients at risk for Pseudomonas infections: Fluoroquinolones (ciprofloxacin, high -dose levofloxacin [3])		Fluoroquinolones (ciprofloxacin ,high -dose levofloxacin [3]) β- lactam with P. aeruginosa activity

[1]cardinal symptoms are increased dyspnea, sputum volume and purulence

[2]this antibiotic is not appropriate in areas where there is increased prevalence of β-lactamase producing H. influenzae and M. catarrhalis and/or S. pneumoniae resistant to penicillin

[3]dose of 750 mg effective against P, aeruginosa

2. How long are antimicrobials given for ECOPD?

Short-term therapy of 5 days duration is adequate for the treatment of ECOPD. (Level of Evidence A)

Falagas et al[16] in 2008 compared regimens of the same antibiotic, same dosage and same route of administration but administered for different time periods. This meta-analysis involved 7 multicentered RCTs published after 1998 with an average of 440 patients (217-614). Patients enrolled were outpatients and had history of chronic bronchitis or chronic bronchitis/COPD. These trials tested short-duration antimicrobial treatment lasting for 5 days versus long-duration antimicrobial treatment lasting for 7-10 days using either B-lactams, quinolones or macrolides. Results showed that with regards to treatment success in intention-to-treat patients, there was no significant difference between patients with ECOPD receiving antibiotics for short-duration treatment and long-duration treatment (1760 patients : RR=0.99 95% C.I. 0.95-1.03). There was also no difference between short- and long- duration regimens for the treatment of clinically evaluable patients with ECOPD (2242 patients: RR=0.99 95% C.I. 0.96-1.02). In fact, testing for adverse events, these studies showed that patients with ECOPD who received short- compared with long-duration antimicrobial therapy experienced fewer adverse events (2238 patients: RR=0.84 95% C.I. 0.72-0.97).

Another meta-analysis by Moussaoui[17] published in May 2008 compared short course antibiotic treatment (< 5 days) vs conventional longer treatment (> 5 days). This meta-analysis included 21 studies with a total of 10,698 adult patients with a clinical diagnosis of exacerbation of COPD or chronic bronchitis with no antimicrobial treatment at time of enrolment. At early follow-up (<25 days), the odds ratio for clinical cure with short therapy vs conventional treatment was 0.99 (95% C.I. 0.90-1.08). At late follow-up, the odds ratio was 1.0 (95% C.I. 0.91-1.10) and the odds ratio for bacteriological cure was 1.05 (95% C.I. 0.87-1.26). The study showed that short course antibiotic treatment of < 5 days was as effective as the conventional 7-10 day course of antibiotics.

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C. What is the preferred bronchodilator for the treatment of ECOPD?

The preferred bronchodilator in the management of ECOPD is any of the short-acting inhaled bronchodilators: short acting β_2-agonists or anticholinergic bronchodilators. Both classes equally improve symptoms and FEV_1. (Evidence A)

Summary of evidence: Inhaled short-acting β_2-agonists (salbutamol or terbutaline) and anticholinergic bronchodilators (ipratropium bromide) are the primary treatment drugs designed to improve airway function and to reduce lung hyperinflation in ECOPD.[1-4] Increasing the dose and/or frequency of existing short-acting bronchodilators is the strategy recommended by the ATS/ERS[5] and GOLD guidelines[6]. The effects of the short-acting β_2-agonists begin within 5 minutes with maximum peaks at 30 minutes; ipratropium begins to take effect after 10-15 minutes with a peak at 30-60 minutes.[2] The effects of the two classes of short-acting bronchodilators decline after 2-3 hours and can last as long as 4-6 hours depending on their individual properties.[12]

The addition of an anticholinergic bronchodilator is recommended if the clinical response to a β_2-agonist is not immediate. Such strategy is recommended despite uncertainties about combinations of short-acting bronchodilators in AECOPD.[6] Importantly, systematic reviews have shown that short-acting inhaled bronchodilators have comparable effects on spirometry and a greater effect than parenterally administered bronchodilators (i.e. methylxanthines and sympathomimetics).[7] There is currently no evidence for role of long-acting bronchodilators in treating exacerbations.

Inhaled short-acting β_2-agonists or anticholinergic bronchodilators

Consensus reports[3,5-8] and reviews[9-11] state that the short acting β_2-agonists are the preferred drugs. There are, however, data comparing the short acting β_2-agonists with the anti-cholinergic bronchodilators. A position paper after evaluating 14 randomized trials in management of ECOPD showed that anti-cholinergic bronchodilators such as ipratropium bromide produce similar FEV1 (forced expiratory volume in 1 second) improvement when compared to β_2-agonists.[13] This conclusion is reinforced by a Cochrane systematic review.[14] The review identified three studies[15-17] with a total of 103 patients comparing (fenoterol, metaproteronol) with an anticholinergic agent (ipratropium bromide). Both drugs produced an improvement in FEV_1 of 150-250 ml at 90 minutes with no detectable difference between the two. However, one study did show a significant improvement in arterial oxygen tension at 30 minutes in those treated with ipratropium compared with metaproterenol with minor clinical consequences.[16] A more recent study has proven that gas exchange abnormalities are not aggravated by short acting β_2-agonists in ECOPD requiring hospitalizations.[18]

On the other hand, the choice between the two inhaled medications may depend largely on the potential undesirable side effects and the patient's coexisting conditions enabling the physician which bronchodilator to prescribe.[19] Anticholinergic agents have a safer and more tolerable side effect profile (tremors, dry mouth, and urinary retention) when compared with β_2-agonists (tremors, headache, nausea, vomiting, palpitations, heart rate, and blood pressure variations).

Inhaled short-acting β_2-agonists and anticholinergic bronchodilators

If clinical response after doses of β_2-agonists is not immediate and is suboptimal, the addition of an anticholinergic medication is recommended.[3, 5-8] Several studies have evaluated the benefit of combination treatment (adding ipratropium to a β_2-agonists).[17,20-22] All were unable to show any further improvement in FEV_1 resulting from the addition of the anticholinergic.[23] The only positive support from an additive effect comes from an American study of patients in the emergency room which found that ipratropium added to isoetharine led to shorter stays in the emergency room but no difference in hospital admission rates.[24]

In the same meta-analysis by McCrory and Brown, combination treatment provided no additive bronchodilatation during exacerbations as compared with a short-acting β_2-agonist alone after 90 minutes (short-term) or after 24 hour (long-term) in terms of FEV_1 improvement.[14] This is in sharp contrast in patients with stable COPD where the combined treatment produced larger FEV1 increases than does either drug alone.[25] The result of the meta-analysis is in conflict with the recommendations from the guidelines. So far the evidence analyzed has relied on FEV_1 as its outcome measure. The FEV_1 has been proven of limited value in detecting benefit even in studies of stable COPD.[26] More relevant information on the role of short-acting bronchodilators in ECOPD might be obtained from studies using clinical end points such as symptoms, length of hospital stay or mortality or by including a measurement of hyperinflation such as inspiratory capacity.[23] Stable COPD patients being maintained on combination therapy may receive the same therapy when they develop exacerbations.

1. What is the preferred delivery system for bronchodilators in ECOPD?

Both nebulizers and MDIs can be used to administer inhaled therapy during exacerbations of COPD (Evidence A).

Nebulizers are preferred if a high dose of bronchodilator is necessary (Evidence D).

Summary of evidence:
Nebulizers rather than MDIs are used more frequently in hospitalized patients with ECOPD. Nebulization therapy is more convenient for respiratory therapists to administer and requires less patient education or cooperation.[27] However, such observation is not reflected by clinical trial evidence as regards to FEV_1 improvement. In a recent appraisal of eight randomized trial[28-35] comparing MDIs and nebulizers in patients with ECOPD, there was insufficient evidence to support that one delivery system is superior to the other.[11] Six of the eight randomized trials did not show significant difference in the FEV_1. Turner et al. did an often-cited systematic review of the route of delivery of the short-acting bronchodilators.[36] The review found no significant differences in FEV_1 between the uses of hand held MDIs with a good inhaler technique (with or without a spacer device) and nebulizers. Subgroup analysis of the review gave a small but non-significant treatment effect size (favoring wet nebulization) of 0.23% (95% CI -0.35 to 0.81). This result, however, needs further confirmation as numbers of patients analyzed in the review were small (48 patients in only three studies) and FEV1 may not be the optimal outcome measure.[23]

The ideal prescription for inhaled therapy would use the simplest and most convenient device to deliver the lowest effective dose for each patient.[37] For low dose bronchodilator therapy - for example, 100 to 400g salbutamol - treatment with MDI is recommended.[29] However, patients may require > 1 mg of salbutamol or > 160g of ipratropium or combination of such therapy in severe exacerbations.[27]

In ECOPD, the recommended dose of the β_2-agonist is 2.5-5 mg per treatment. This dose can be achieved by giving 1 salbutamol nebule (nebule contains 2.5 mg salbutamol) as compared to a MDI (Appendix 3). Treatment may be repeated within a few minutes if the patient has a suboptimal response to the first dose of nebulized treatment.[27] In cases with good response, the treatment should be repeated at 4-6 hours interval. For ipratropium bromide the optimum response occurs at 0.4 - 0.6 mg.[38] A unit dose vial (UDV) of an anticholinergic bronchodilator contains 0.5 mg ipratropium. Two doses of ipratropium bromide by MDI (40 g) are equivalent to approximately 0.1 mg by nebulized solution and can achieve only 63 to 73% of bronchodilatation achieved by optimal dose of the nebulized solution.[38] Nebulizers are, therefore, recommended if higher doses of the drugs are needed in the management of AECOPD. It is also known that It would be

for patients with exacerbations to be taking a total of > 10 sequential inhalations from1 hand-held MDIs. However, nebulizers should be changed to hand-held MDIs as soon as the exacerbation stabilizes.[3]

2. Do methylxanthines (e.g. IV aminophylline) have a role in ECOPD?

Methylxanthines have marginal effects on FEV_1 and symptoms in patients with ECOPD. In addition they have numerous untoward effects. Their routine use is not recommended (Evidence B).

Summary of evidence: It is reasonable to consider the addition of a second drug from a different class to a patient's regimen if there is suboptimal response to a single regimen.[39] But as discussed previously, there is not enough clinical evidence to add an anticholinergic medication to a β_2-agonist. The evidence base for the addition of a methylxanthine to inhaled bronchodilators is similarly contradictory.[7] However, unlike anticholinergic bronchodilators, the methylxanthines are not recommended routinely for AECOPD because of its high incidence of adverse reactions to methylxanthines.[42] These findings concur with the results of a systematic review of methylxanthines for exacerbations of asthma in adults.[43]

Most international guidelines suggest the use of methylxanthines for severe exacerbations that are not responding to aerosol therapy.[6,8,39-40] The molecular mechanism of bronchodilatation of methylxanthines is likely explained by PDE (phosphodiesterase) inhibition that results in an increase in cAMP by inhibition of PDE3 and PDE4 and in cyclic guanosine 3′ 5′-monophosphate by inhibition of PDE5.[44] Some studies have suggested that the clinical impact of methylxanthines may be larger than their modest bronchodilator effects.[45] Methylxanthines have been reported to decrease diaphragmatic muscle fatigue, to increase mucociliary clearance, to block centrally mediated hypoventilation and to decrease capillary leakage.[46-47] However, randomized controlled trials of methylxanthines for AECOPD have been small and have produced conflicting results.[42] This is the explanation why other guidelines recommend against the use of methylxanthines for AECOPD.[13,41]

A Cochrane systematic review was conducted to specifically determine the benefit of methylxanthines compared to placebo for AECOPD.[48] The initial result was published in 2003 and has been reassessed in March 2005. From their search only 4 randomized controlled trials[45,49-51] from 1,299 identified references met the inclusion criteria. All the 4 studies enrolled 172 patients with moderate-to-severe exacerbations (pre-treatment FEV_1 range 0.6 - 0.8 L). Results for the methylxanthine and placebo groups have been inconsistent except for the adverse effects:

A. Mean change in FEV_1
There was no consistent change in FEV_1 at 2 hours. The improvement in FEV_1 of 100 ml at the end of follow-up on Day 3 was based heavily on one study but the improvement disappeared with follow-up greater than 3 days.[49]

B. Clinical outcomes and symptom scores

Data was sparse. Hospital length-of-stay was not statistically significant. In one study, the large reduction in the rate of hospitalization among patients treated with aminophylline may have been offset by the trend toward increased rates of relapse among those given aminophylline and then sent home.[49]

C. Symptom scores

Analysis of the heterogeneity of the symptom scores from the different studies revealed a small, non-significant improvement with methylxanthines.
(SMD: 0.45; 95% CI; 0.0 to 0.9; P=0.05)

D. Adverse effects

Three studies reported adverse effects.[45,49-50] The trials were homogenous for all adverse events outcome for the methylxanthine group:

nausea and vomiting (OR: 4.6; 95% CI: 1.7 to 12.6)
tremors (OR: 1.8; 95% CI: 0.7 to 4.6)
palpitations and arrhythmias (OR: 4.1; 95% CI 0.9 to 19.6)

D. What is the role of mucolytics in the management ECOPD?

Mucolytics have no proven benefit in the management of ECOPD.

Summary of evidence: Two clinical reviews[11,23] analyzed 5 randomized control trials (RCTs)[52-56] on the role of different mucolytics for (1) clinical response and (2) symptom score. The RCTs did not report a statistically significant difference in mean FEV_1 between treatments in any study. Likewise, the mucolytics did not shorten the course of treatment for patients with exacerbations. Regarding symptom score on difficulty of expectoration, only two studies showed significant differences ($p < 0.01$) favoring mucolytic drugs over the control.[54,56]

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E. What is the role of Noninvasive Ventilation in ECOPD?

In selected patients, noninvasive ventilation (NIV, NPPV) reduces the need for intubation, improves in-hospital morality rates, and decreases the length of hospital stay of ECOPD patients (Evidence A).

Quon[1] reviewed fourteen randomized controlled trials comparing the use of NPPV to standard therapy in the management of acute COPD exacerbations. All of the studies were performed since 1993. The review showed that NPPV reduces the need for intubation, improves the risk of in-hospital mortality, and shortens hospital stays during acute COPD exacerbations. The lower the baseline pH the greater is the benefit seen with NPPV. According to the 2008 GOLD report[2], randomized controlled trials provide evidence that NPPV improves respiratory acidosis, decreases respiratory rate, severity of breathlessness, length of hospital stay, intubation rates and mortality. The indications and relative contraindication for the use of NIV based on the GOLD guidelines is given in the following table.

Indications and relative contraindications for NIV	
Selection criteria	**Exclusion criteria (any may be present)**
❖ Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion ❖ Moderate to severe acidosis (pH 7.35) and/or hypercapnea (pCO_2 > 45 mm Hg) ❖ Respiratory frequency > 25 breaths per minute	❖ Respiratory arrest ❖ Cardiovascular instability (hypotension, arrhythmias, myocardial infarction) ❖ Change in mental status; uncooperative patient ❖ High aspiration risk ❖ Viscous or copious secretions ❖ Recent facial or gastroesophageal surgery ❖ Craniofacial trauma ❖ Fixed nasopharyngeal abnormalities ❖ Burns ❖ Extreme obesity

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APPENDIX SECTION.

APPENDIX 1. SUGGESTED QUESTIONS FOR FOLLOW-UP VISITS OF COPD PATIENTS.

Suggested Questions for Follow-Up Visits*

*These questions are examples and do not represent a standardized assessment instrument. The validity and reliability of these questions have not been assessed.

Monitor exposure to risk factors:

Have you continued to stay off cigarettes?
If not, how many cigarettes per day are you smoking?
Would you like to quit smoking?
Has there been any change in your working environment?

Monitor disease progression and development of complications:

How much can you do before you get short of breath?
(Use an everyday example, such as walking up flights of stairs, up a hill, or on flat ground.)
Has your dyspnea worsened, improved, or stayed the same since your last visit?
Have you had to reduce your activities because of dyspnea or other symptoms?
Have any of your symptoms worsened since your last visit?
Have you experienced any new symptoms since your last visit?
Has your sleep been disrupted due to dyspnea or other symptoms?
Since your last visit, have you missed any work because of your symptoms?

Monitor pharmacotherapy and other medical treatment:

What medications are you taking?
How often do you take each medication?
How much do you take each time?
Have you missed or stopped taking any regular doses of your medications for any reason?
Have you had trouble filling your prescriptions (e.g., for financial reasons, not on formulary)?
Please show me how you use your inhaler.
Have you tried any other medicines or remedies?
Has your medication been effective in controlling your symptoms?
Has your medication caused you any problems?

Monitor exacerbation history:

Since your last visit, have you had any episodes/times when your symptoms were a lot worse than usual?
If so, how long did the episode(s) last? What do you think caused the symptoms to get worse? What did you do to control the symptoms?

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APPENDIX 2. BRIEF SMOKING CESSATION INTERVENTION FOR PHYSICIANS

THE THREE MINUTE STRATEGY FOR SMOKING CESSATION INTERVENTION

Tobacco smoking and nicotine addiction is a chronic disease and without appropriate interventions, only 2-3% of smokers become non-smokers each year. The primary care physician plays an important and unique role in promoting smoking cessation due to the fact that at least 70% of smokers see a physician at least once a year. Moreover, 70% of smokers report that they want to quit and have made at least 1 self-described serious quit attempt and cite a physician's advice as a significant motivator. Finally, 90% of smokers admit that they would "very likely" or "somewhat likely" follow their physician's advice.

With this background, it is important that clinicians are prepared to intervene with tobacco users who are wiling to quit. The five major steps, or the **Five A's** are tabulated below. It is important for the clinician to **Ask** each patient if he or she uses tobacco (Strategy A1), **Advise** him or her to quit (Strategy A2), **Assess** willingness to make a quit attempt (Strategy A3), **Assist** him or her in his quit attempt (Strategy A4) and **Arrange** for follow up to prevent relapse (Strategy A5).

Patients unwilling to make a quit attempt may lack information about the harmful effects of tobacco or may have fears or concerns about quitting or may be demoralized because of previous relapse. Such patients may respond to motivational intervention that provides the clinician an opportunity to educate, reassure and motivate (the **Five R's**). Motivational interventions are most likely to be successful when the clinician is empathic, promotes patient autonomy, avoids arguments and supports the patient's self-efficacy.

Relapses should not be a source of discouragement as they are the rule rather than the exception in smoking cessation. In the Transtheoretical Model of Change, patients go through the stages of Precontemplation, Contemplation, Action and Maintenance in a cyclical manner. Only 5% will go through without ever relapsing. Eighty five percent of patients will cycle back with most of them competing 3 to 4 cycles before they are able to maintain a totally smoke free state. An algorithm is presented to simplify the suggested steps in smoking cessation intervention.

THE "5 A'S" FOR BRIEF INTERVENTION

Strategy A1: ASK

ASK about tobacco use	Identify and document tobacco use status for every patient at every visit.	**Action**	**Strategies for implementation**
		Implement an office wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco use status is queried and documented.	Expand the vital signs to include tobacco use or use an alternative universal identification system. VITAL SIGNS Blood Pressures: _____ Pulse: _____ Weight: _____ Temperature: _____ RR: _____ Tobacco use: Current / Former / Never (circle one) Alternatives to expanding the vital signs are to place tobacco - use status stickers on all patient charts or to indicate tobacco use status using electronic medical records or computer reminder systems.

Strategy A2: ADVISE

Advise to quit	In a clear, strong and personalized manner urge every tobacco user to quit.	**Action**	**Strategies for implementation**
		In a clear, strong, and personalized manner, urge every tobacco user to quit	**Advice should be:** **Clear** – " I think it is important for you to quit smoking now and I can help you". " Cutting down while you are ill is not enough". **Strong** – " As your clinician, I need you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. The clinic staff and I will help you. **Personalized** – Tie the tobacco use to current health/illness, and or its social and economic costs, motivation level / readiness to quit, and /or the impact of tobacco use on children and others in the household.

Strategy A3: ASSESS

Assess willingness to make a quit attempt.	Is the tobacco user willing to make quit attempt at this time?	**Action**	**Strategies for implementation**
		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)	Assess patient's willingness to quit: If the patient is wiling to make a quit attempt at this time, provide assistance If the patient will participate in an intensive treatment, deliver such a treatment or refer to an intensive intervention If the patients clearly states he or she is unwilling to make a quit attempt at this time, provide a motivational intervention If the patient is member of special population (e.g., adolescent, pregnant smoker, racial / ethnic minority), consider providing additional information

Strategy A4: ASSIST

Assist in quit attempt.	For the patient wiling to make a quit attempt, use counseling and pharmacotherapy to help him or her quit	**Action**	**Strategies for implementation**
		Help the patient with a quit plan	A patient's preparation for quitting Set a quit date – ideally, the quit date should be within 2 weeks Tell family, friends, and co workers about quitting and request understanding and support Anticipate challenges to planned quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms. Remove tobacco products from your environment. Prior to quitting, avoid smoking in places where you spend a
		Provide practical counseling (problem solving/skills training)	**ABSTINENCE** – Total abstinence is essential. "Not even a single puff after the quit date". **PAST QUIT EXPERIENCE** – Identify what helped and what hurt in previous quit attempts. ANTICIPATE TRIGGERS OR **CHALLENGES IN UPCOMING ATTEMPT** – Discuss challenges/triggers and how patient will successfully overcome them. **ALCOHOL** – Since alcohol can cause relapse, the patient should consider limiting/abstaining from alcohol while quitting. **OTHER SMOKERS IN THE HOUSEHOLD** – Quitting is more difficult when there is another smoker in the household. Patients should encourage housemates to quit with
		Provide intra-treatment social support	Provide supportive clinical environment while encouraging the patient in his or her quit attempt. "My office staff and I are available to assist you."
		Help patient obtain extra-treatment social support	Help patient develop social support for his or her quit attempt in his or her environments outside of treatment. "Ask your spouse/partner, friends and co-workers to support you in your quit attempt."
		Recommend the use of approved pharmacotherapy	Recommend the use of pharmacotherapy found to be effective. Explain how these medications increase smoking cessation success and reduce withdrawal symptoms. The first-line pharmacotherapy medications include: Bupropion SR, sibutramine, Nicotine gum, nicotine inhaler, nicotine nasal spray and nicotine patch.
		Provide supplementary materials	**SOURCES** – Non-government organizations, local heath units **TYPE** – Culturally/racially/educationally/age appropriate for patient **LOCATION** – Readily available at every clinician's workstation.

Strategy A5: ARRANGE

Arrange follow up	Schedule follow up contact preferably within the first week after the quit date.	**Action**	**Strategies for implementation**
		Schedule follow-up contact, either in person or via telephone	**Timing** – Follow up contact should occur soon after the quit date, preferably, during the first week. A second follow up contact is recommended within the first month. Schedule further contacts as indicated.

			Actions during follow up contact – Congratulate success. If tobacco use has occurred, review circumstances and elicit recommitment to total abstinence. Remind patient that a relapse can be used as a learning experience. Identify problems already encountered and anticipate challenges in the immediate future. Assess pharmacotherapy use and problems. Consider use or referral to more intensive treatment

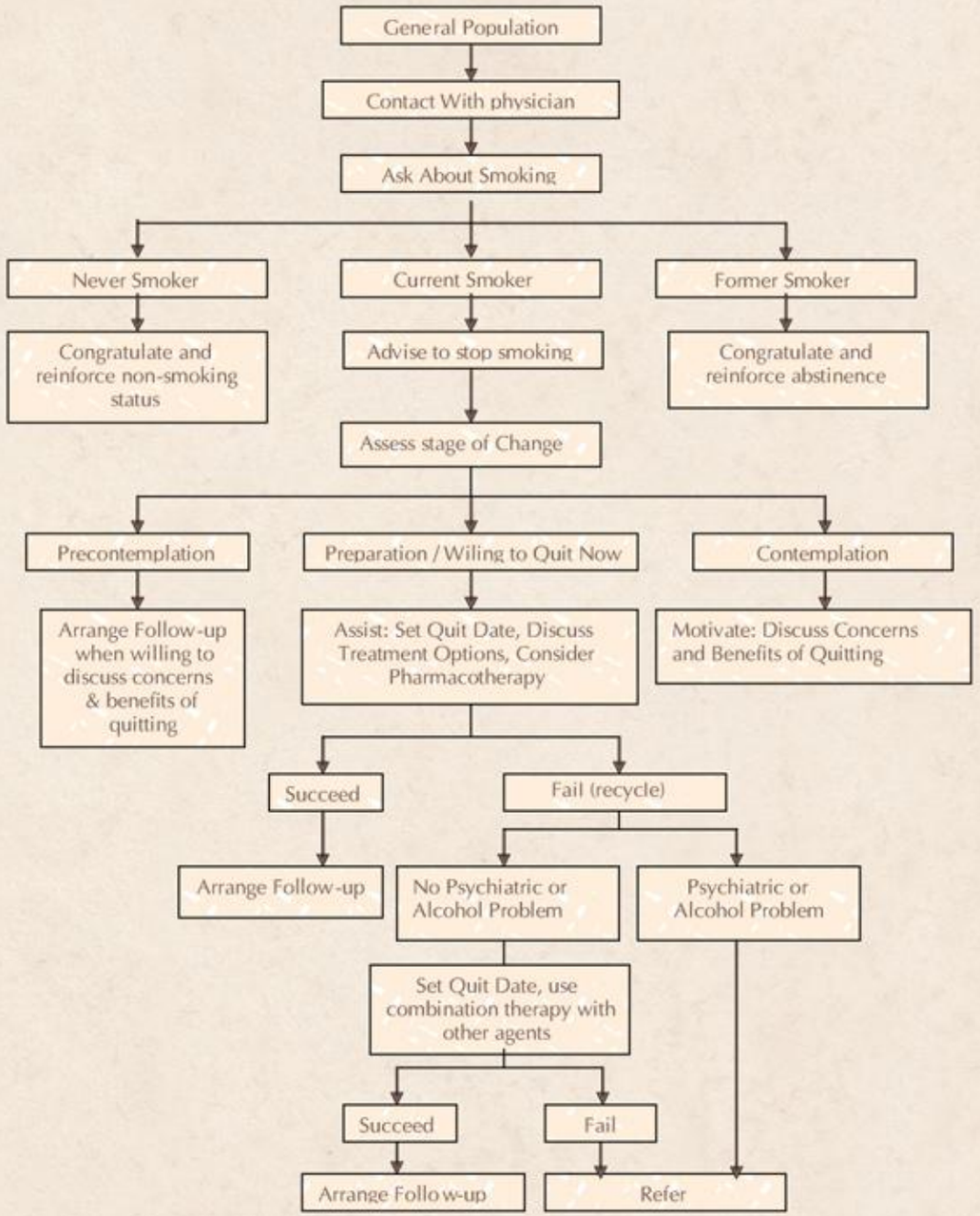
The 5 R's of MOTIVATIONAL INTERVENTION

Action	Strategies for implementation
Relevance	Encourage the patient to indicate why quitting is personally relevant, being as specific as possible. Motivational information has the greatest impact if it is relevant to patient's disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, gender, and other important patient characteristics (e.g., prior quitting experience, personal barriers to cessation).

Risks	The clinician should ask the patient to identify potential negative consequences of tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient. The clinician should emphasize that smoking low – tar / low – nicotine cigarettes or use of other forms of tobacco (e.g., smokeless tobacco, cigars, and pipes) will not eliminate these risks. Examples risks are: Acute risks: Shortness of breath, exacerbation of asthma, harm to pregnancy, impotence, infertility, increase serum carbon monoxide. Long-term risks: Heart attacks and strokes, lung and other cancers (larynx, oral cavity, pharynx, esophagus, pancreas, bladder, cervix), chronic obstructive pulmonary diseases (chronic bronchitis and emphysema), long – term disability and need for extended care. Environmental Risks: Increased risk of lung cancer and heart disease in spouses: higher rate of smoking by children of tobacco users; increased risk for low birth weight, SIDS, asthma, middle ear disease, and respiratory infections in children of smokers
Rewards	The clinician should ask the patient to identify potential benefits of stopping tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient. Examples of rewards follow: Improved health Food will taste better Improved sense of smell Save money Feel better about yourself. Home, car, clothing, breath will smell better Can stop worrying about quitting Set a good example for children Have healthier babies and children Not worry about exposing others to smoke Feel better physically Perform better in physical activities Reduced wrinkling / aging of skin

Roadblocks	The clinician should ask the patient to identify barriers or impediments to quitting and note elements of treatment (problem solving, pharmacotherapy) that could address barriers. Typical barriers might include: Withdrawal symptoms Fear of failure Weight gain Lack of support Depression Enjoyment of tobacco
Repetition	The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting. Tobacco users who have failed in previous quit attempts should be told that most people make repeated quit attempts before they are successful.

ALGORITHM ON THE SUGGESTED STEPS IN SMOKING CESSATION INTERVENTION



Reference:
Treating Tobacco Use and Dependence. Clinical Practice Guideline. U.S. Department of Health and Human Services. June 2000.

APPENDIX 3. COMMONLY ENCOUNTERED DRUGS FOR COPD IN THE PHILIPPINES BY GENERIC NAMES, FORMULATION AND DOSAGE.

GENERIC NAME	FORMULATION	QUANTITY PER DOSE	PRESCRIBED DOSAGE AND FREQUENCY
A. Bronchodilators			
1. Anti-cholinergic agents			
Ipratropium Br	UDV or nebule	0.5mg/2mL	1 vial 3 - 4 times a day
	PMDI	0.02mg/puff	2 puffs 4 times a day up to 12 puffs/day
	Inhaled solution	0.025%	2 mL 3-4 times a day
Tiotropium	Inhaled caps	18g/cap	1 cap daily
2. Beta -2 agonists			
Salbutamol sulfate	syrup	2mg/5mL	2mg to 4 mg every 6 to 8 hours
	tablet	2mg	1-2 tablets 3 -4 times a day
	Controlled Release tablet	4mg, 8 mg	1 tab 2 times a day
	Pressurized metered dose inhaler (pMDI)	100 g/dose	1-2 puffs every 4 hours, may use 2 puffs prn for acute symptoms
	nebule	2.5 mg/2.5mL	2.5 mg -5 mg 3 -4 times a day
Terbutaline sulfate	syrup	1.5mg/5mL	2 tsp - 1 tbsp every 6 to 8 hours
	tablet	2.5mg	1 tablet 3 -4 times a day
	Extended Release ta blet	5mg/	1 tablet 2 times a day
	Inhaled solution	5mg/2mL	2.5 –5 mg every 6 hous
	Inhaler	0.25mg/dose	1 –2 puffs every 6 hrs
	Turbuhaler	500g/dose	1 – 4 puffs per day up to 4 mg per day
Fenoterol HBr	Metered aerosol	0.1mg/dose	1-2 puffs per day up to 8 puffs per day
Procaterol HCl hemihydrate	Tablet	25g	1-2 tabs 2 times a day
	Syrup	5g/mL	10 mL 2 times a day
	pMDI	10g/puff	2 puffs every 4 hours and prn
	Swinghaler	10 ug/puff	2 puffs every 4 hours and prn
Formoterol fumarate	tablet	40g	2 tabs 2 times a day
	Inhaled caps	12g/cap	1-2 caps per day
	Turbuhaler	4.5g/dose, 9g/dose	1-2 puffs per day max of 4 -6 per d ay
Salmeterol	pMDI	25g/puff	2 - 4 puffs 2 times a day
	Rotadisk	50g/blister	1-2 blister 2 times a day
Bambuterol	Tablet	10mg/tab	1 tab 1 -2 times a day
Clenbuterol	Tablet	10 ug/tab	1 tab 1 -2 times a day
	Syrup	5 ug/5ml	10 ml 1-2 times a day
Tolubuterol	Tablet	1 mg, 2 mg	1-2 tabs 2 times a day
3. Methylxanthine derivatives			
Doxofylline	tablet	400mg	1 tab 2 – 3 times a day
Theophylline	tablet	130mg	1 tab 3 - 4 times a day
		125 mg	1 tab every 6 hours
		150mg	1 tab 3 - 4 times a d ay
	SR tab	175 mg, 250 mg	1 tab every 12 hrs
		90, 180	1-2 tabs 2 times aday
		400	1 tab daily
		200, 300	1 tab every 12 hrs
Aminophylline	ampule	25mg/mL	5mg – 6mg/kg in 20 -30 min slow IV infusion
4. Combination anticholinergic with beta -2 agonis t agent			
Fenoterol HBr/ Ipratropium Br	PMDI	50g/20g	1-2 puffs per day max 8 puffs
	PMDI	50g/20g	1-2 puffs per day max 8 puffs
	Inhaled solution	0.5mg/0.25mg	1 –2 mL 3 –4 times a day
	UDV	1.25mg/0.5mg	1 vial up to 4 times a day
Ipratropium Br/ Salbutamol	UDV or nebule	500g/2.5 mg	1 vial 3 – 4 times a day
B. Corticosteroids			
Beclomethasone	Inhaler	250g/dose	200g to 2000g day in divided doses
		50g/dose	
	Rotacap	100g/cap	
	Rotadisk	200g/blister	
	cyclocaps	100g/cap	100g – 400g 2 times a day
Fluticasone propionate	Inhaler	50 g/dose, 12 g/dose 125 g/dose	100g – 1000g 2 times a day
	Rotadisk	50g/dose	
	Nebule	500g/2mL	500g – 2000g 2 times a day
Budesonide	inhaler	100g/dose 200g/dose	400g - 2400g per day divided in 2 to 4 doses
	Turbuhaler	100g/dose 200g/dose	
	Respules	250g/mL 500g/mL	
Prednisone	tablet	2.5 mg, 5 mg, 7.5 mg, 10 mg 30 mg	20mg – 60 mg daily
Prednisolone	Syrup	15 mg/5ml	30-60 mg/day
Betamethasone	Tablet	500 ug	2-3 mg daily
Dexamethasone	Tablet	500 ug,750 ug, 3 mg, 4 mg	0.5-10 mg daily
	Vial	4mg, 5 mg/ml	0.05-0.2 mg/kg body weight
Methyl-prednisolone	Tablet	4 mg, 16 mg	4-48 mg/day
	Vial	125 mg/2ml 500 mg/7.7 ml 1 gm/ 16 ml	10-40 mg every 4 -6 hours IV or IM for 48-72 hours
Hydrocortisone	vial	100mg, 2 50 mg/2 mL	150 mg to 300 mg daily in divided doses
C. Inhaled corticosteroids -long acting Beta 2 agonist combination			
Fluticasone - salmeterol	PMDI, Diskus	125ug/25 ug, 250ug/25ug, 100ug/50ug, 250ug/50ug, 500ug/50ug	1-2 inhalations 2x a day
Budesonide - formoterol	Turbuhaler	320ug/4.5 ug 160ug/4.5 ug 80ug/4.5ug	1-2 inhalations 1 -2x a day, max 4 inhalations 2xday
D. Expectorants			
Ambroxol HCl	Tablet	30 mg	1 tab 3 times a day
	ER tablet	75 mg	1 tab daily
	Syrup	15 mg/5ml	1 tsp 3 times a day
	Inhalation solution	15 mg/2ml	1-2 inhalations of 2 -3 ml solution daily
	Vial	15 mg/2ml	1-2 amps 2 -3times a day IV or IM
Acetylcysteine	Effervescent tab	600 mg	600 mg daily or 200 mg 3 times a day
	sachet	100 mg	
		200 mg	
	granules	100 mg/5ml	

	Syrup	4 mg/5ml	2 tsp 3 times a day
	Inhalation solution	2 mg/ml	4 ml of solution diluted 1:1 with normal saline inhale every 12 hours
	Vial	4mg	1 ampule SC, I M, IV every 8 -12 hours
Carbocisteine	capsule	250 mg	500 mg 3 times a day
		500 mg	
	Syrup	250 mg/5ml	10 ml 3 times a day
Erdosteine	Capsule	300mg	1 cap 2 times a day
Guiafenesin	Syrup	100 mg/5 ml	5-10 ml 3-4 times a day
Lagundi leaves	Tablet	300mg, 600 mg	300-600 mg 3 -4 times a day
Mesna	Inhalation or Instillation solution	200 mg/ml	1-2 amps inhalation 1 -4 x a day 1-2 ml diluted with equal volume of distilled water or saline hourly into the endotracheal tube or tracheotomy cannula unti l fluiditication and evacuation of secretions
D. Other medications			
Lyophilized bacterial extract	capsule	7 mg	1 cap daily for at least ten days
Influenza vaccine	Pre-filled syringe	0.5 mL	Administer IM once a year
Pneumococcal vaccine	vial	0.5 mL	Administer SC or IM

APPENDIX 4. LIST OF AVAILABLE PULMONARY REHABILITATION PROGRAM SERVICES IN THE PHILIPPINES:

1. Lung Center of the Philippines	-Tel # 9240144 loc. 363
2. Perpetual Help Medical Center, Las Pinas	-Tel # 8748515 loc. 484
3. Philippine General Hospital	-Tel # 521 8450 loc. 3157
4. Philippine Heart Center for Asia	-Tel # 9252401 loc. 3805/3606
5. St. Luke's Medical Center	-Tel # 7230101 loc. 4189
6. The Medical City	-Tel # 635 6789 loc. 6238
7. University of Santo Tomas Hospital	-Tel # 7313001 loc. 2561
8. Veteran's Memorial Medical Center	-Tel # 4269653

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