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Review Article

Chronic Obstructive Pulmonary Disease (COPD): A Practical Approach for General Practitioners

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Received: August 01, 2019; **Published:** September 11, 2019

Abstract

The increased prevalence of chronic obstructive pulmonary disease (COPD) poses a significant medical concern worldwide. COPD, a complex, heterogeneous, and progressive lung disease characterized by persistent respiratory symptoms and airflow limitation, is associated with rapid deterioration in quality of life, high exacerbation and hospitalization rates. Early diagnosis and treatment is essential to slow disease progression and improve patient treatment outcomes. COPD is generally underdiagnosed or misdiagnosed and subsequently under or delayed treatments are of major concern in general practice. In about 52 - 91% of individuals with airflow limitation, COPD remains undetected. There are several guidelines that offer strategies for diagnosis and treatment of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines are used for worldwide COPD management, however, implementation and adherence to these guidelines clinically are limited. This can be attributed to lack of understanding or awareness of guidelines among physicians. Around 24% of general practitioners have reported that they are not familiar with the GOLD strategy. Current guidelines are large and complex and a concise guidance document is needed to further enhance utility and adoption of guidelines by physicians. We present a simplified, practical and accurate COPD guide outlining key diagnostic, assessment and treatment approaches in COPD. This document can serve as a practical guide to physicians, especially general practitioners, encompassing key aspects of the GOLD strategy. Furthermore, we also include much simplified and consolidated checklists for COPD screening and assessment of COPD comorbidities.

Keywords: *Chronic Obstructive Pulmonary Disease; Primary Care; Screening; Assessment; Diagnosis; Treatment; Comorbidities*

Introduction

Chronic obstructive pulmonary disease (COPD) represents a significant healthcare concern with increased prevalence and morality rates globally. Approximately 3 million deaths every year are attributed to COPD, and the disease is expected to become the third leading cause of mortality by 2030 [1]. COPD is a complex, heterogeneous, debilitating and progressive disease characterized by persistent respiratory symptoms and airflow limitation [2]. It is a common lung disorder in an aging population with systemic features that contribute to morbidity and mortality in all stages of severity [3,4].

COPD begins with an asymptomatic phase where lung function deterioration is not associated with clinically relevant symptoms, eventually progressing to a symptomatic phase which is clinically evident only when the values of forced expiratory volume in 1 second (FEV_1) decrease substantially [5]. Common symptoms of COPD include dyspnea, chronic cough, wheezing, and regular sputum production. Dyspnea is the most prominent and distressing clinical symptom of COPD that results in exercise intolerance and physical decline in patients. As the disease progresses, symptoms worsen with an increase in exacerbation rate and deterioration of health status, further increasing the risk of hospitalization and mortality [6]. COPD often coexists with comorbidities that may have a significant impact on the disease

prognosis. COPD patients are found to have up to a median of nine comorbidities, including cardiovascular disease, osteoporosis, anxiety, depression, infection, cognitive impairment and lung cancer [7].

There is an increasing need for early diagnosis and treatment of COPD to slow disease progression and improve patient treatment outcomes. It is important to make a correct diagnosis and tailor treatment strategies appropriately in order to meet management goals at an individual level. Although there are several tools available to support the diagnosis of COPD, the disease is generally underdiagnosed or misdiagnosed and thus undertreated. This continues to be a major problem in general practice. In about 52 - 91% of individuals with airflow limitation, COPD remains undetected [6]. Up to 80% of COPD cases remain undiagnosed until the disease is advanced and substantial end-organ damage is present [8]. There are more than 50 guidelines for diagnosis and management of COPD published worldwide. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline is used for COPD diagnosis and management globally [9]. Current guidelines are large and complex and familiarity amongst general practitioners is suboptimal. Around 24% of general practitioners have reported that they are not familiar with the GOLD strategy [10].

Clinical practice has been shown to deviate significantly from COPD guidelines [11]. A cross-sectional Swiss study showed that during diagnosis of COPD, only 55% of physicians used spirometry and amongst them only one-third had knowledge of the GOLD diagnostic criteria [12]. A retrospective study of stable COPD in the US found that 56% of patients received treatment in accordance with GOLD guidelines. Patients that received treatment in accordance with guidelines had significantly fewer (approximately half) the number of reported exacerbations compared to patients that received treatment which differed from guidelines [13]. A US COPD study found that 27%, 25% and 32% of patients had spirometry recorded in the previous year, comorbidities appropriately managed, and risk reductions measures put in place, respectively [14]. Prescription of long-acting bronchodilators or inhaled steroids has been shown to be in accordance with guidelines in 20% of mild to moderately severe COPD patients (GOLD stage I or II). In more severe COPD patients (GOLD III or IV), 64% received treatment in accordance with guidelines [15]. A retrospective study found that patients receiving suboptimal treatment management in respect to guidelines, more often died during treatment than patients with optimal treatment management [16]. These studies highlight the importance of guidelines-based treatment in the management of COPD.

From this perspective, a standardized, practical and accurate guidance document that outlines the key diagnostic and treatment approaches in COPD would serve as a simple and usable reference for physicians. We present a comprehensive and simplified guide, based on the GOLD strategy, which addresses multiple aspects of the screening, diagnosis and treatment of COPD.

COPD screening

Accurate screening of COPD in patients presenting with risk factors is essential for timely diagnosis and effective treatment. Table 1 presents a screening checklist including all key risk factors/symptoms for COPD. The importance of each checklist item is explained below.

COPD Screening Checklist		
• Age more than 35 years • Smoker (current, ex or passive) • Professional exposure to noxious gases, smoke or particles	> 35 years and any of the other two indicators present	High clinical suspicion of COPD
• Recurrent respiratory infections (from childhood, or more than 2 times usage of antibiotics per year) • Drug or alcohol abuse • Dyspnea during exercise • Chronic cough and/or expectoration (for more than 3 months in two consecutive years) • Chronic fatigue (without known disease, or exaggerated degree according to the disease severity) • Anxiety/depression • Body Mass Index (BMI) < 20	Plus any single indicator present	Refer of chest x-ray and spirometry for final diagnosis

Table 1: *Checklist for COPD screening.*

Why is age greater than 35 years important?

Age of onset is an important factor that can be used to characterize a population with chronic disease [17]. An increase is observed in the prevalence rate of COPD with age. The prevalence of COPD in the general population is 2.1%, while in very old persons (≥ 85 years) it is 44% [18]. Patients who are diagnosed with airflow limitation at a younger age (< 35 years) are more likely to have asthma, alpha1-antitrypsin deficiency (AATD), cystic fibrosis or other rarer diseases. In general, half of COPD patients are less than 65 years and are often undiagnosed and may not be treated appropriately. This can delay the opportunity to slow disease progression and improve work ability, productivity and quality of life.

Why are smokers in danger?

Smoking is the most important risk factor in developing COPD. In adolescence, smoking reduces the rate of lung function growth and the predicted value of forced expiratory volume in one second is not achieved [19]. Exposure to tobacco smoke is an important factor for predicting the risk of developing the disease. Pack-years, an index of total exposure to tobacco smoke, is a useful parameter to determine the risk for COPD. Pack-years is calculated using the following formula [20]:

$$Pack - years = \frac{Number\ of\ cigarettes\ per\ day}{20} X\ years\ of\ smoking$$

Tobacco smoke contains oxygen radicals and each radical is an unstable molecule. Oxidants and free radicals cause sequestration and accumulation of neutrophils in pulmonary microcirculation, as well as accumulation of macrophages in the respiratory bronchiole which creates a potential reservoir for new oxidants. Alternative tobacco products, such as electronic cigarettes, smokeless tobacco, and water pipes also cause serious potential health problems, including cancer [21]. Passive smoking may also cause COPD as well as other respiratory diseases [22].

Why is professional exposure to noxious gases, smoke or particles an issue?

COPD is an inflammatory disease of the airways. Inflammation is triggered by long-term inhalation of different irritant particles, usually from tobacco combust, and also from exposure to noxious gases and particles. The inflammatory cells and mediators involved in COPD are different than in asthma, and particularly different than to those involved in bacterial inflammation. Neutrophils and cluster of differentiation 8 (CD8) T lymphocytes are the predominant inflammatory cells that trigger protease imbalance in COPD patients [2,23].

Why are recurrent respiratory infections a matter of concern?

Lung infection is the most common cause of acute exacerbations. Recurrent respiratory infections in childhood can damage bronchial airways (bronchial deformations and bronchiectasis) and increase susceptibility to pollution and other irritants, causing impaired mucociliary clearance, increased sputum production and reduced lung function. Any COPD exacerbation, whether triggered due to air pollution or any other cause including infection, will have symptoms of increased intensity of cough, sputum and dyspnea. Usually, there is fever if there is infection.

Why is drug or alcohol abuse of concern in COPD?

Cannabis, also known as marijuana, is mostly abused through smoking [24]. Marijuana smoke inhalation has similar effects as tobacco smoke, causing cough, sputum production and upper lobe emphysematous changes. Smoking cannabis can be expressed as joint-years which is similar to pack-years in the case of tobacco smoking. Each additional joint-year of cannabis smoking is associated with a 0.3% increase in prevalence of COPD [25]. Alcohol is also a well-known etiological cause for COPD [26].

Why is dyspnea during exercise important in COPD?

Dyspnea during exercise is the most common reason for a patient to visit a doctor. However, dyspnea remains mostly unidentified in the early stages of COPD. Many patients think that dyspnea is common with aging. Patients tend to attribute dyspnea to obesity or lack of regular training. In such situations, active screening can be very useful in identifying symptoms earlier in the course of the disease.

Why are chronic cough and/or sputum important respiratory symptoms?

More than half of COPD patients have cough and/or sputum as major respiratory symptoms. Inflamed airways produce more sputum. There are two different types of sputum: mucoid and purulent. During stable COPD, sputum is usually mucoid, white or light yellow color. During COPD exacerbations, sputum production increases and is purulent, dark yellow or dirty green with a touch of grey. It is very

important to ask a patient about sputum color or analyze a sample. If sputum is purulent, antibiotic therapy may be indicated. It is very important to perform bacteriological examination of a sputum sample if an exacerbation is suspected. Chronic bronchitis, a COPD phenotype, is characterized by chronic cough and sputum production. Patients categorized under this phenotype are more often COPD frequent exacerbators. Identifying phenotypic traits can further guide the therapeutic strategy in patients.

Why is chronic fatigue associated with COPD?

About half of COPD patients do not have typical respiratory symptoms like chronic cough and/or expectoration and often are not aware of their chronic pulmonary disease. In such patients, chronic fatigue may be an important indicator/sign of the disease. Fatigue is almost three times more common in patients with COPD than in a healthy population [27-29]. If a person has chronic fatigue, is older than 45 years, is a smoker and if there is absence of other chronic or infective diseases (i.e. tuberculosis, liver cirrhosis, chronic heart failure), a COPD diagnosis should be considered in parallel with other possible disease etiologies of chronic fatigue.

Why do anxiety/depression stand out in COPD?

COPD is associated with multiple comorbidities; almost two-thirds of the COPD patients have at least one or two other chronic diseases [30]. Approximately 40% of COPD patients suffer from severe depressive symptoms or clinical depression [31]. Recent data from 52,095 patients showed that depression and alcohol abuse were significantly associated with subsequent diagnosis of COPD [32]. The symptoms of COPD and depression may overlap, thus it is challenging to diagnose depression in COPD [31]. If a patient has anxiety/depression, is older than 45 years and is a smoker, a COPD diagnosis should be considered in parallel with the other chronic diseases that contribute to mental state.

Why is low BMI on the checklist for COPD screening?

Body mass index (BMI) is an important factor in COPD diagnosis, especially in patients who do not have respiratory symptoms. Loss in body weight can be the first sign of the disease in such patients [33]. It is considered that 15 - 20% of patients with COPD have pulmonary cachexia [34]. If a patient has cachexia, is older than 45 years, is a smoker and shows no presence of other chronic or infective diseases (i.e. tuberculosis, liver cirrhosis, chronic heart failure, depression), a COPD diagnosis should be considered in parallel with other possible etiologies of low BMI.

COPD diagnosis

Timely and accurate diagnosis of COPD is crucial for effective treatment of the disease. A clinical diagnosis of COPD should be considered in the presence of the aforementioned screening indicators specified in table 1. COPD diagnosis involves chest radiography (x-ray) and spirometry. Chest radiography should generally be performed during the initial evaluation of COPD to identify comorbidities, complications and alternative diagnoses. Chest radiography alone may not be very useful for the diagnosis of COPD, as other lung diseases (i.e. lung cancer, tuberculosis, and interstitial lung diseases) may also be prominent in radiology images. If no visible lung disease explaining the patient's complain is evident in the chest x-ray, and/or a COPD is suspected, the patient should be referred for spirometry. Spirometry should be conducted in all patients suspected of having COPD. It is the most common lung function test and is used to measure the amount (volume) and/or speed (flow) of air that is inhaled and exhaled from the lungs.

Semiologic signs of COPD are extremely useful for diagnosis of COPD, but also for easily monitoring patients. Typical semiologic signs of COPD include: an ongoing cough or a cough that produces a lot of mucus; this is often called "smoker's cough"; shortness of breath, especially with physical activity; wheezing or a whistling or squeaky sound when you breathe and chest tightness.

COPD assessment

The key goals of COPD assessment include determining the level of airflow limitation, impact on quality of life and risk of future exacerbations, hospitalization and mortality. The following aspects of the disease should be considered for COPD assessments: degree of spirometric abnormality, symptoms, exacerbation history and future risk and comorbidities. Spirometric evaluation is used to measure airway obstruction. A post bronchodilator FEV1/FVC (forced vital capacity) < 0.7 confirms the presence of persistent airflow limitation. If a bronchodilator reversibility test is negative, it rules out asthma. The Modified Medical Research Council (mMRC) scale (dyspnea score) and COPD Assessment Test (CAT) are recommended for comprehensive evaluation of COPD symptoms [2,35,36]. The mMRC scale assesses the impact of breathlessness based on a score of 0 to 4 (Table 2) [35]. The CAT is an 8-item unidimensional measure of health status

impairment [36]. Each question of the CAT questionnaire is scored on a scale of 0 to 5 (0 - without symptoms, 5 - significant symptoms). The questions are related to cough, production of sputum, chest tightness, degree of breathless when walking up a hill or one flight of stairs, confidence in leaving home unaccompanied, sleep quality (in terms of lung condition) and lack of energy [36]. Exacerbation frequency and severity increases with worsening of airflow obstruction. Exacerbation history is the best predictor of future risk of exacerbations. The number of exacerbations and hospitalizations due to exacerbations within the last year should be assessed. GPs should register hospitalizations, and particularly exacerbations regularly in their clinical patient records. Exacerbation information is commonly missing, and its impact remains unknown in the majority of cases. This aspect should be briefly implemented in the text. Comorbidities should be routinely assessed and treated appropriately to reduce the risk of hospitalization and mortality. Both questionnaires are very simple and easy to use and should be regularly given to COPD patients with all levels of severity.

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

(A)

Example: I am very happy	1 2 3 4 5	I am very sad
I never cough	1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	1 2 3 4 5	I have no energy at all

(B)

Table 2: *(A) Modified Medical Research Council (mMRC) dyspnea scale and (B) COPD Assessment Test (CAT) GOLD 2017 [2].*

The GOLD combined evaluation method provides a subjective and objective evaluation of the key components of COPD [2]. It takes into account the patients' symptoms and the exacerbation history for planning diagnostic and treatment approaches for COPD. In the GOLD combined evaluation method, the patients are classified into four groups; A, B, C and D (Table 3). Firstly, assess the patients for symptoms and categorize into boxes on the left side (less symptoms and less breathlessness [CAT total score < 10 and mMRC grade 0 - 1], Group A and C) or boxes on the right side (more symptoms and more breathlessness [CAT total score > 10 and/or mMRC grade ≥ 2]; Group B and D). Furthermore, determine if the patient belongs to the lower or to the upper boxes. This is completed by evaluating the number of exacerbations and hospitalizations for COPD exacerbation in the last year. Patients that experience ≥ 2 exacerbations with or without hospitalization in the previous year are at high risk of COPD (e.g. a patient with an FEV_1 of 30% with 3 exacerbations in the previous year and CAT score of 12 is classified as GOLD D; a patient with a FEV1 of 30% with 0 exacerbations in the previous year and CAT score of 12 is classified as GOLD B). The combined assessment takes into account the limitations of FEV1 in predicting COPD prognosis and highlights the importance of patient symptoms and exacerbation risk in making therapeutic decisions for individualized patient care. Treatment recommendations are based on factors triggering patient symptoms at any given point in time. The combined evaluation method cannot

precisely assess the risk of mortality at an individual level. Multidimensional assessment tools such as BODE (Body-Mass Index, Obstruction, Dyspnea, Exercise), ADO (Age, Dyspnea, Obstruction) and DOSE (Dyspnea, Obstruction, Smoking, Exacerbation) are useful in this situation. These scores are not equivalent and are characterized by different predicting values. These are composite scores which also consider the exercise test results and smoking status in addition to the lung function parameters of airway obstruction. However, these tools do not assess the comorbidities associated with COPD [37].

Drug	Inhaler (mcg)	Oral	Adverse reactions
Beta2-agonist			
Short acting			Sinus tachycardia, heart rhythm disturbances (rarely, in susceptible patients), tremor (elderly patients), hypokalemia (especially in combination whit thiazide diuretics)
Fenoterol	100-200 (MDI)	2.5mg (pill), 0.05% (syrup)	
Levalbuterol	45-90 (MDI)		
Salbutamol	90, 100, 200 (MDI & DPI)	2, 4, 5 mg (pill), 8 mg (extended release tablet) 0.02%/0.4 mg (syrup)	
Terbutaline	500 (DPI)	2.5, 5 mg (pill)	
Long acting			
Arformoterol			
Formoterol	4.5-12 (MDI & DPI)		
Indacaterol	75-300 (DPI)		
Olodaterol	2.5, 5 (SMI)		
Salmeterol	25-50 (MDI & DPI)		
Anticholinergic			
Short acting			Dry mouth, prostatic symptoms, metallic taste, glaucoma attack (when administering solutions through facemasks)
Ipratropium bromide	20, 40 (MDI)		
Oxitropium bromide	100 (MDI)		
Long acting			
Aclidinium bromide	400 (DPI), 400 (MDI)		
Glycopyrronium bromide	15.6 & 50 (DPI)	1 mg (solution)	
Tiotropium	18 (DPI), 2.5 & 5 (SMI)		
Umeclidinium	62.5 (DPI)		
Combination short acting beta2-agonist plus anticholinergic in one device			
Fenoterol/Ipratropium	50/20 (SMI)		
Salbutomol/Ipratropium	100/20 (SMI), 75/15 (MDI)		
Combination long acting beta2-agonist plus anticholinergic in one device			
Formoterol/Aclidinium	12/400 (DPI)		
Formoterol/Glycopyrronium	9.6/18 (MDI)		
Indacaterol/Glycopyrronium	27.5/15.6 & 110/50 (DPI)		
Olodaterol/Tiotropium	5/5 (SMI)		
Vilanterol/Umeclidinium	25/62.5 (DPI)		

Metylxanthines			
Aminophylline		105 mg/ml (solution)	Atrial and ventricular arrhythmias, grand mal convulsions, headache, Insomnia, nausea - depending on the serum concentration
Theophylline		100-600 mg (pill)	
Combination long acting beta2-agonist plus inhaled corticosteroids in one device			
Formoterol/Beclomethasone	6/100 (MDI)		Inhaled corticosteroids: Oral candidiasis, hoarseness, increased risk of pneumonia
Formoterol/budesonide	4.5/160 (MDI), 4.5/80 (MDI), 9/320 (DPI, 9/160 (DPI)		
Formoterol/mometasone	10/200, 10/400 (MDI)		
Salmeterol/fluticasone	50/100, 50/250, 5/500 (DPI), 21/45, 21/115, 21/230 (MDI)		
Vilanterol/fluticasone furoate	25/100 (DPI)		
Phosphodiesterase-4 inhibitors			
Roflumilast		500 mcg (pill)	Nausea, loss of appetite, abdominal pain, diarrhea, headache, Sleep disturbances, loss of body weight

Table 3: *COPD pharmacological treatment options GOLD 2017 [2].*

MDI: Metered-Dose Inhalers; DPI: Dry-Powder Inhalers; SMI: Soft-Mist Inhalers.

Note: *Only choose the product available in your country.*

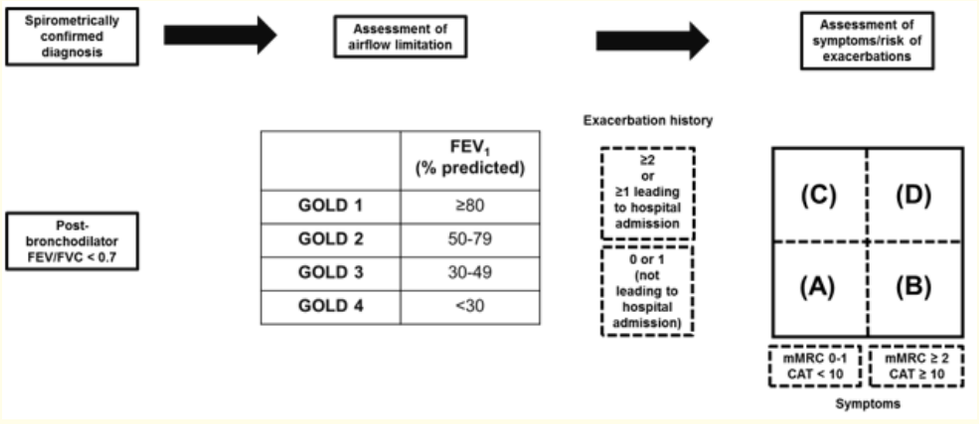

Figure 1: *Combined COPD assessment GOLD 2017 [2].*

CAT: COPD Assessment Test; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: Modified Medical Research Council.

COPD treatment

The treatment of stable COPD involves both pharmacological and non-pharmacological treatment. A pharmacological treatment algorithm based on the GOLD strategy is shown in figure 2. Pharmacological treatment options are outlined in table 3. The management strategy for stable COPD should be predominantly based on the individualized assessment of symptoms and future risk of exacerbations. Pharmacological treatment algorithms involve subsequent escalation and/or de-escalation of treatment according to symptoms and exacerbation risk.

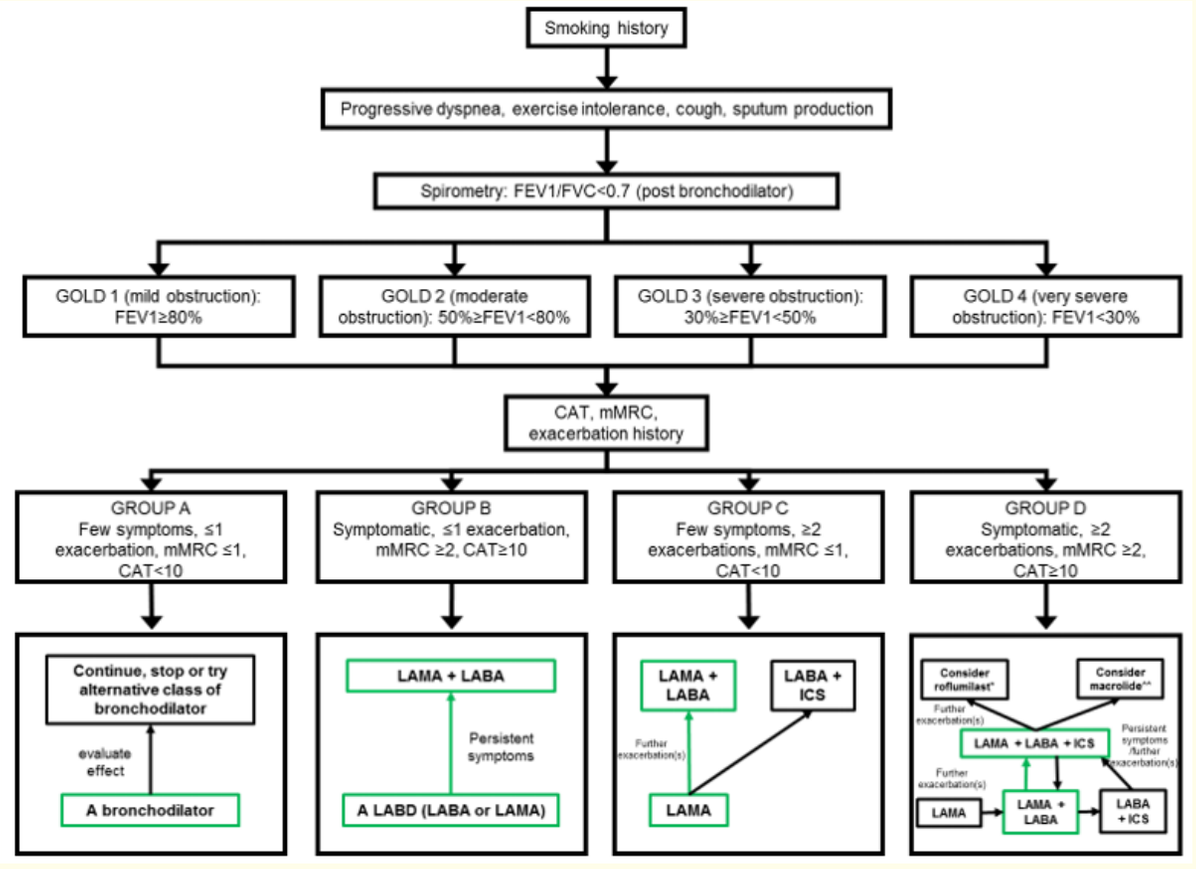

Figure 2: *COPD treatment options GOLD 2017 [2].*

Preferred treatment

**Considered in patients with an FEV1 < 50% predicted and chronic bronchitis.*

***In former smokers.*

CAT: COPD Assessment Test; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; GOLD: Global Initiative for Chronic Obstructive Lung, Disease; LABA: Long-Acting Beta2 Agonist; LAMA: Long-Acting Muscarinic Antagonist; ICS: Inhaled Corticosteroids; mMRC: Modified Medical Research Council.

Group A: Recommended treatment is either a short- or long-acting bronchodilator. Bronchodilator treatment should be continued if symptom reduction is seen. If symptoms continue, the current bronchodilator should be discontinued and/or an alternative class of bronchodilator tried [2].

Group B: Recommended treatment is a long-acting bronchodilator in patients with less severe symptoms. Patients with persistent symptoms may be escalated to long-acting dual bronchodilation. Patients with severe breathlessness may be started on long-acting dual bronchodilation [2].

Group C: Recommended first-line treatment is a long-acting muscarinic antagonist. In patients with persistent exacerbations the preferred treatment is long-acting dual bronchodilation. An alternative escalated treatment is long-acting beta-2 agonist/inhaled corticosteroids combination. Triple therapy is not recommended due to associated risks with inhaled corticosteroids [2].

Group D: Recommended initial treatment is long-acting dual bronchodilation. Treatment should be escalated to triple therapy in patients who experience further exacerbations despite treatment with long-acting dual bronchodilation or long-acting beta-2 agonist/inhaled corticosteroids combination. If further exacerbations persist despite treatment with triple therapy, the addition of a macrolide or roflumilast is suggested. The withdrawal of inhaled corticosteroids is also recommended if exacerbations persist on triple therapy [2].

Non-pharmacological treatment includes smoking cessation, physical activity, pulmonary rehabilitation and vaccinations. Smoking cessation is the most important component of non-pharmacological treatment [38] and is the only non-pharmacological method which along with long term oxygen therapy has proven to prolong the life of the patient. Long-term oxygen therapy (> 15 hours/day) requires a prescription by a specialist. The criteria for prescription in stable patients are [2]: partial pressure of oxygen in arterial blood (PaO_2) of ≤ 55 mmHg or arterial oxygen saturation (SaO_2) of ≤ 88%, with or without hypercapnia, or a PaO_2 between 55 - 60 mmHg, or SaO_2 of 88% if there is pulmonary hypertension, cardiac failure (peripheral edema) or polycythemia (hematocrit > 55%). Reevaluation of arterial blood gas or oxygen saturation should be repeated between 60 to 90 days of treatment to determine if therapy is still indicated.

There is insufficient evidence to make general recommendations for use of noninvasive ventilation at home. This method improves survival in some specific cases but does not improve quality of life. Initiation and control must be performed by a specialist. Physical activity is recommended for all patients with COPD [2]. COPD patients benefit from rehabilitation and regular physical activity, improving exercise tolerance and decreasing dyspnea and fatigue symptoms. Those with significant dyspnea (mMRC ≥ 2) seem to benefit the most. Upon completion of a rehabilitation program, it is advisable that patients continue performing exercises at home [2]. Pneumococcal vaccination is indicated in patients older than 65 years or in young patients with significant comorbidities [2]. Influenza vaccination once a year is also recommended.

Indications for hospital admission

Indications for hospital admission include: marked increase in intensity of symptoms (e.g. tachypnea), severe underlying COPD, severe hypoxemia (e.g. respiratory failure), onset of new physical signs (e.g. peripheral edema, central cyanosis), failure of an exacerbation to respond to initial medical management, presence of serious comorbidities (e.g. heart failure, cardiac arrhythmias, metabolic/endocrine disorders, obstructive sleep apnea), frequent exacerbations, old age and insufficient home support [2].

COPD monitoring

COPD being a progressive disease, regular follow-up to monitor disease status over time is important. Routine monitoring and reassessment can help delay disease progression and minimize the impact of exacerbations. General monitoring should include spirometry, questionnaires (i.e. mMRC, CAT), symptoms assessment, smoking status, treatment efficacy, exacerbations and comorbidities. Spirometry monitoring is recommended at diagnosis and annually. Questionnaires (i.e. mMRC, CAT) should be performed regularly. Symptoms such as cough, sputum production, breathlessness, fatigue, activity limitation, and sleep disturbances should be assessed at every visit. Furthermore, smoking status, treatment efficacy (i.e. compliance, accuracy of medication administration, adverse effects), exacerbation rate and comorbidities should be determined at each visit.

Management of COPD exacerbations

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy [2]. Frequent COPD exacerbations result in faster annual decline of FEV_1, worsening of the disease [39,40], deterioration of health related quality of life [39] and increased mortality rate [41]. Patients who are frequent exacerbators (at least 2 within 12 months) are particularly susceptible to additional exacerbations with worse health status and faster disease progression than those who have infrequent exacerbations [42]. Hence, rapid diagnosis and effective treatment of COPD exacerbation is critical. From a clinical standpoint, it is important to determine the cause of an exacerbation as it influences the choice of treatment. COPD exacerbations can be triggered by several infectious (i.e. bacterial, viral) and non-infectious (i.e. environmental, lifestyle) causes. The most common causes appear to be respiratory tract infections (viral and bacterial) and infections of the tracheobronchial tree [43]. The most common bacterial pathogens in COPD exacerbation are [44] *Hemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Mycoplasma pneumoniae* and *Pseudomonas aeruginosa* [31]. *Pseudomonas aeruginosa* is an important bacterial pathogen present in severe and very severe COPD patients. Bronchiectasis is commonly caused by lung infections and significantly increases mortality risk in COPD patients [23]. However, the cause of approximately one-third of severe

exacerbations of COPD is not identified. Factors that increase risk of severe COPD exacerbations are: altered mental status, repeated exacerbations in the previous 12 months, BMI ≤ 20 kg/m^2, pronounced increase in symptoms or change in vital signs, medical comorbidities (i.e. cardiac ischemia, congestive heart failure, pneumonia, diabetes mellitus, renal or hepatic failure), poor physical activity levels, poor social support, severe baseline COPD (FEV_1 < 50% of predicted) and poor compliance to treatment [45].

The diagnosis of COPD exacerbation is based on the clinical presentation or aggravation of at least two out of the three hallmark respiratory symptoms: dyspnea, cough and sputum production. In addition to the major respiratory symptoms of COPD exacerbation, other extra-pulmonary symptoms may occur (Table 4). Assessment of COPD exacerbation using medical history, clinical signs and laboratory tests is shown in table 5. Spirometry is not recommended during an exacerbation as the measurements are usually not accurate due to increased dyspnea and cough. A sputum culture test is a classic approach in identifying potentially pathogenic bacteria that may trigger exacerbations, however, the relationship between presence of pathogenic organisms and an etiologic diagnosis of acute exacerbation of COPD has been questioned [44,46]. In addition, for outpatients, sputum culture testing has technical limitations and therefore is not routinely recommended. Sputum culture test may be recommended in the following circumstances: lack of response of an infectious exacerbation to the initial antibiotic treatment, patients recently hospitalized due to severe COPD exacerbation (increased risk of pseudomonas aeruginosa infection), previous isolation of pseudomonas aeruginosa during COPD exacerbation and exacerbations in patients with increased risk of antibiotic resistance due to recent (up to 3 months) antibiotic or/and oral steroids therapy, frequent COPD exacerbations within the last year [28] or very severe airway obstruction (FEV_1 < 30% of predicted) [42,47].

Body System	Symptoms
Pulmonary (New presentation of or aggravation of preexisting)	• Dyspnea • Cough • Change in volume and/or color of sputum • Tachypnea • Wheezing
Cardiac	• Chest tightness • Tachycardia
Psychiatric	• Confusion • Depression • Insomnia • Sleepiness
Systemic	• Decreased exercise tolerance • Malaise • Fatigue • Fever

Table 4: *Symptoms of COPD exacerbation.*

Assessment Type	Assessment Characteristics
Medical History	• Severity of COPD before exacerbation • Duration of worsening of respiratory symptoms or new symptoms • Number of previous exacerbations including hospitalizations • Comorbidities • Current treatment • Previous use of mechanical ventilation

Clinical Signs	• Breathing frequency • Dyspnea severity (e.g. mMRC) • Cough intensity • Sputum production (volume and hue) • Use of accessory inspiratory muscles • Paradoxical chest wall movements • Presence and intensity of central cyanosis • Presence and severity of peripheral edema • Hemodynamic instability • Deteriorated mental status

Laboratory Tests	• Pulse oximetry to assess arterial oxygen saturation (SaO_2)
	  • SaO_2 < 92% when breathing room air may indicate acute or acute-on-chronic respiratory failure and necessity of supplemental oxygen therapy
	  • Arterial blood gas measurements is recommended when SaO_2 drops <92% to confirm/exclude respiratory failure
	• Chest radiograph (x-ray)
	  • Useful to exclude alternative diagnoses/sources of dyspnea (e.g., pneumonia, pulmonary edema, pneumothorax, lung tumor)
	• Electrocardiogram (ECG)
	  • Useful to exclude coexisting cardiac problems (arrhythmias, ischemia)
	• Whole blood count
	  • Identify leukocytosis, polycythemia or anemia
	• Biochemical tests
	  • Identify electrolyte disturbances, renal failure, hypo- or hyperglycemia, CRP, D-dimer, NT pro-BNP

Table 5: Assessment of COPD exacerbation.

mMRC: Modified Medical Research Council (MMRC) Dyspnea Scale; CRP: C-Reactive Protein; D-dimer: Fibrin Degradation Fragment test for blood clot; NT pro-BNP: N-terminal pro b-type natriuretic peptide test to detect, diagnose, and evaluate the severity of heart failure.

The important treatment goals for COPD exacerbation are to reduce the severity and frequency of exacerbations and the future risk of exacerbations. The pharmacological drugs that generally are prescribed for exacerbations include bronchodilators, corticosteroids, and antibiotics. The choice of drugs and treatment strategy largely depend on the severity of exacerbations and/or severity of the underlying disease. Short-acting inhaled beta2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of acute COPD exacerbation. Increased doses and/or frequency of short-acting bronchodilators should be used, if necessary. A short-acting beta2-agonist (e.g. salbutamol) can be combined with an anticholinergic (e.g. ipratropium), if necessary. Nebulizers should be used for delivery of short-acting bronchodilators in sicker and/or older patients. Systemic corticosteroids can not only shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2), but also reduce the risk of early relapse, treatment failure, and length of hospital stay. The optimal duration of corticosteroid therapy for acute COPD exacerbation is yet not established. An oral daily dose of prednisone ranging from 30 mg for 14 days to 40 mg for 5 days may be recommended [48]. The short course (up to 8 days) of steroid therapy may be terminated abruptly. There is no need to reduce progressively the dosage of oral steroids during the treatment period. If any adverse response to oral steroids is observed or if the exacerbations become frequent, the patient should be referred to a specialist. Inhaled corticosteroids have no role in the management of an acute exacerbation of COPD. Antibiotics should be administered if there is an increase in dyspnea, sputum volume and sputum purulence, suggesting an infectious cause. Treatment should be continued

for 5 - 10 days. The choice of antibiotics should be guided by local flora and sensitivity pattern [2,49]. Nevertheless the use of antibiotics in COPD exacerbations remains controversial. Antibiotics used for empirical treatment of bacterial COPD exacerbations include: amoxicillin or amoxicillin/clavulanate, second- or third-generation cephalosporins, macrolides and fluoroquinolones. Antibiotic recommendation should be adopted according to current chemoresistance of pathogens in every country [2].

Classification of COPD exacerbations is based on the intensity of the medical intervention required to control the patient's symptoms. Mild exacerbations can be controlled with an increase in dosage of regular medications. Moderate exacerbations require treatment with systemic corticosteroids and/or antibiotics. Severe exacerbations require hospitalization or emergency department evaluation. Very severe exacerbations are classified based on purulent sputum, increased volume of sputum and increased dyspnea [46].

COPD and comorbidities

Almost one third of COPD patients have one additional disease condition, and 39% have two or more additional chronic conditions [50]. A recent study found that 78.6% of COPD patients reported to have at least one comorbidity, while 68.8% patients had at least 2 and 47.9% had at least 3 comorbidities [51]. The presence of comorbidities in COPD is associated with increased risk for hospitalization. In addition to respiratory complaints, the incidence of hospitalizations for non-respiratory causes, including cardio-vascular, gastrointestinal and musculoskeletal diseases, is significantly higher in patients with COPD [52]. Comorbid conditions also contribute to the social and economic burden of COPD [53]. Hence, there is an increasing need for early diagnosis and treatment, not only of COPD, but also of concomitant diseases. Cardiovascular disease is often diagnosed in COPD patients. Heart failure has been recorded in 20% of COPD patients [54]. More than 40% of COPD hospitalizations are linked to a cardiovascular cause [55]. Osteoporosis has been diagnosed in 36-70% of COPD patients [56]. Patients with COPD are at increased risk of osteoporosis and fractures when compared to patients without COPD [57]. Anxiety and depression are present in up to 40% of COPD patients as compared to 15% in the general non-COPD adult population [58]. Depression in COPD patients leads to reduction in quality of life, greater impairment of physical and mental function and decreased adherence to therapeutic intervention [59]. The prevalence of COPD among lung cancer patients ranges between 40 - 70% [60] and is associated with poorer prognosis [61]. The incidence of lung cancer is much higher in a cohort of COPD patients than in the general population [61]. Diabetes is associated with an increased risk of pulmonary infections, exacerbations and worsened COPD outcomes [62]. Women with COPD have 1.8 times increased risk of developing type 2 diabetes compared to non-diabetic women without COPD [63]. Identifying comorbidities in COPD is integral to accurate diagnosis and disease management. Simplicity of treatment is important to minimize polypharmacy where COPD is part of a multimorbidity care plan. Checklist for comorbidities and tools for identifying comorbidities are presented in table 6.

COPD Comorbidities	Methods for Identifying comorbidities
Is there evidence for? • Cardiovascular diseases: • Ischemic heart disease • Heart failure • Atrial fibrillation • Hypertension • Osteoporosis • Anxiety and depression • Lung cancer • Metabolic syndrome and diabetes • Gastroesophageal reflux disease • Respiratory infections • Bronchiectasis • Impaired cognitive function	Selective patient history, family history and physical examination. The following can be done according to patient risk: • Echocardiography • Echocardiography plus Holter • Blood pressure monitoring, 24 hours blood pressure monitoring • Bone density measurement • Mini Mental State • Psychological and or Psychiatric evaluation • Chest radiograph, chest CT plus intravenous contrast (high-resolution CT) • pH test and or proton pump inhibitor therapeutic trial

Table 5: *Checklist for COPD comorbidities.*

BMI: Body Mass Index; CT: Computerized Tomography; pH: Power of Hydrogen.

Conclusion

There are several guidelines that offer strategies for diagnosis and treatment of COPD. Most of them are complex and not well implemented. We present a simplified, practical and easy-to-use document together with checklists which can be easily applied in everyday medical practice to help better understand and implement current COPD guidelines. This document serves as a simplified and easy-to-use guidance tool that can help further discipline and standardize the approach for patient care in COPD to benefit both physician and patient.

Acknowledgements

The authors thank Clarice Field PhD and Ananya Chikramane PhD of Novartis for providing medical writing support which was funded by Novartis AG, Basel, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Contributions

GI, SPG, FM, VC and PS participated in writing the paper and approved the final manuscript.

Competing Interests

All the authors declare to have no conflict of interest in regard with this paper.

Funding

Writing support was funded by Novartis Pharma. None of the authors received any compensation related to the development of this manuscript.

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