13

Chronic Obstructive Pulmonary Disease in Primary Care – From Diagnosis to Therapy

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1. Introduction

The Global Strategy for the Diagnosis, Management and Prevention of COPD guidelines (GOLD, 2010) and the UK National Institute of Clinical Excellence guidelines (NICE, 2010) recommend an early diagnosis of Chronic Obstructive Pulmonary Disease (COPD) in any patient over the age of 35 who has chronic cough (present intermittently or every day throughout the day), chronic sputum production, shortness of breath (dyspnoea), frequent winter 'bronchitis' or wheeze and/or a history of exposure to disease risk factors.

COPD is a progressive, but preventable and treatable disease, characterised by airflow limitation, that is not fully reversible and an abnormal inflammatory response of the lungs to noxious particles or gases; COPD is associated with significant extrapulmonary effects and comorbidities that may affect the severity (GOLD, 2010). COPD is a complex disease, a combination of emphysema and chronic bronchitis, although only one of these may be present in some people.

- Emphysema is characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis.
- Chronic bronchitis is characterized by chronic cough or mucous production for at least 3 months in at least 2 successive years when other causes of chronic cough have been excluded (GOLD, 2010).

The typical symptoms are cough, with large amounts of mucus, wheezing, shortness of breath, chest tightness. Cigarette smoking is the leading cause of COPD. It is estimated that over 50% of smokers will develop during the life a chronic respiratory disease (Mannino & Buist, 2007). Other than tobacco smoking, risk factors for development of COPD are being

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increasingly recognised (Soriano et al, 2009) and include environmental factors such as occupational exposure to dust and fumes in developed and developing countries (Blanc et al, 2009; Soriano et al, 2009) and indoor biomass fuel burning in many developing countries. Other environmental risk factors that seem unimportant for development of COPD, but that might worsen disease include outdoor pollutants and passive smoke exposure. Therefore, adequate monitoring air pollution, accompanied by appropriate strategies for cessation of cigarette smoking, are of primary importance for the care of these patients. COPD mainly affects middle-aged and older people.

The prevalence of COPD in the general population is estimated to be about 1% across all ages, rising to 8-10% or higher in individuals aged 40 years or older (Soriano et al, 2009). Actually is the fourth leading cause of death in the U.S. and is projected to be the third leading cause of death for both males and females by the year 2020. The true prevalence of this disease within the same population can vary depending on the tool used to identify COPD, such as self-reported respiratory symptoms, medical diagnosis, or lung function. The correct diagnosis and staging of the disease, based on spirometric functional assessment of the patient, are prerequisites for the implementation of rational and therapeutic measures with proven effectiveness. The prevention of complications, including through appropriate interventions vaccine, along with rehabilitation programs, is critical to positively influencing the patient's medical history (GOLD, 2010).

2. Diagnosis of COPD: From evidence to practice

In view of the increasing prevalence of the disease around the world, it is tried to create and spread worldwide guidelines and programs for the dissemination of current knowledge in order to better diagnosis and management of the disease by all health organizations (CTS, 2008; GOLD, 2010; NICE, 2010; Qaseem et al, 2011). Despite the efforts of implementation of existing guidelines COPD remains an underdiagnosed disease and it is poorly treated when diagnosed. In population studies, findings show that underdiagnosis of COPD is high and independent of overall prevalence (Buist et al, 2007; Soriano et al, 2009). Up to 80% of COPD cases remain undiagnosed until the disease is advanced and substantial end-organ damage is present (Buist et al, 2007; GOLD, 2010; Price et al, 2010). Furthermore, respiratory disease misdiagnosis is common: up to 25% of patients older than 40 years who are labelled as having asthma actually have COPD. Conversely, many patients in primary care are labelled as having COPD when they have asthma (Jones et al, 2008). It is estimated that there are twice as many patients with impaired lung function (indicative of early stage COPD) than patients with diagnosed COPD (Price et al, 2010). The symptoms of COPD may be similar to those of other respiratory conditions (Table 1) and an accurate differential diagnosis may be performed in general practice (GOLD, 2010).

2.1 Symptoms and questionnaires

The underestimation of symptoms by the patients is an important problem: despite experiencing such symptoms as dyspnoea, chronic cough, or sputum production for months or years, patients fail to recognize or report them, believing such symptoms to be a normal consequence of smoking, aging or deconditioning (Price et al, 2010; Yawn et al, 2009).

Diagnosis	Suggestive features	Recommended investigations to confirm diagnosis
COPD	Onset in midlife; symptoms slowly progressive; long history of exposure to noxious particles, typically tobacco smoking or air pollution; dyspnoea during exercise; airflow limitation that is not fully reversible	Spirometry confirms presence of airflow limitation that is not fully reversible
Asthma	Onset early in life (often childhood); variation in symptoms from day to day; symptoms at night or in early morning; other atopic conditions present (eg, allergy, rhinitis, eczema); family history of asthma	Spirometry confirms presence of largely reversible airflow limitation
Chronic heart failure	Fine basilar crackles on auscultation	CXR shows dilated heart, pulmonary edema; spirometry confirms restrictive rather than obstructive lung disease
Bronchiectasis	Large volume of purulent sputum; commonly associated with bacterial infection; coarse crackles/clubbing on auscultation	CXR or CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset at all ages; high local prevalence of tuberculosis	CXR shows lung infiltrate; microbiological confirmation
Obliterative bronchiolitis	Onset at younger age in nonsmokers; may have history of rheumatoid arthritis or fume exposure	CT on expiration shows hypodense areas
Diffuse pan-bronchiolitis	Most patients are men and nonsmokers; almost all have chronic sinusitis	CXR and HRCT show diffuse small centrilobular nodular opacities and hyperinflation
Carcinoma of the bronchus	Symptoms may include dyspnea, hemoptysis, coughing wheezing, pain in chest or abdomen, cachexia, fatigue and loss of appetite; history of exposure to carcinogens (such as those in tobacco smoke), ionizing radiation, or viral infection	CXR; CT; bronchoscopy

COPD = chronic obstructive pulmonary disease; CXR = Chest radiography;
CT = computed tomography; HRCT = high-resolution CT.

Table 1. Differential Diagnosis of COPD (adapted from GOLD, 2010).

A significant number of patients perceived incorrectly the severity of their disease, based on the modified Medical Research Council (MRC) dyspnoea scale (Table 2): 35.8% of subjects

with the most severe breathlessness scale and 60.3% of subjects with the next most severe scale considered their condition to be mild or moderate (Rodin & Cote, 2008).

Patient questionnaires are an effective and economic instrument for discriminating between subjects with and without COPD (Barnes & Fromer, 2011; Price et al, 2011). Questions include items on age, body mass index (BMI), smoking intensity, cough, phlegm, dyspnoea on exertion and wheeze, as well as prior diagnosis consistent with asthma or COPD (Table 3) (Price et al, 2011). Examples of disease-specific instruments include the MRC dyspnoea scale (Table 2), the Clinical COPD Questionnaire (CCQ), and the COPD Assessment Test (CAT) (Jones et al, 2011).

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Table 2. The MRC Breathlessness Scale (from Bestall et al, 1999)

2.2 Spirometry

The diagnosis of COPD has to be confirmed by spirometry (GOLD, 2010; NICE, 2010; Qaseem et al, 2011), but in real life, only 30–50% of new cases are confirmed by this method (Barnes & Fromer, 2011; Bolton et al, 2005; Joo et al, 2008). Inadequate use of spirometry affects not only primary care but also specialised management: analysis of medical records of patients admitted to academic tertiary-care hospitals showed that only 31% of those diagnosed with COPD had spirometry, by contrast with individuals with congestive heart failure, of whom 78% had echocardiography, the golden standard examination (Soriano et al, 2009). On the contrary spirometry should not be used to screen for airflow obstruction in asymptomatic individuals (GOLD, 2010; NICE, 2010; Qaseem et al, 2011).

Spirometry is a reliable, simple, non-invasive, safe, and non-expensive procedure for the detection of airflow obstruction. Spirometry can be performed in primary care to assess lung function in terms of maximal volume of air forcibly exhaled from the point of maximal inspiration [Forced Vital Capacity (FVC)] and the volume of air exhaled during the first second of this manoeuvre [Forced Expiratory Volume in 1 s (FEV1)]. It is suggested that a postbronchodilator FEV1 < 80% of predicted, together with a FEV1/FVC ratio of < 0,7, is indicative of airflow limitation that is not fully reversible (GOLD, 2010; NICE, 2010; Qaseem et al, 2011.)

A basal spirometry, without bronchodilator, has been shown to lead to overdiagnosis of COPD by 11% in primary care (Jones et al, 2008) and by 27% in screening studies (Johannessen et al, 2005). The impairment of FEV1 in COPD is partially related to symptoms and disease severity. For this reason the main COPD guidelines define FEV1 thresholds for

classifying stages of disease severity (table 4). The classifications are not all the same because the correlation between FEV1 values and clinical manifestations of COPD are not well defined. In 2012 the new GOLD guidelines will propose a new COPD severity classification, which will be based not only on spirometric evaluation but also on symptoms intensity and exacerbations frequency. However, after a medical diagnosis of COPD, guidelines (GOLD, 2010) recommend that patients should undergo a spirometry follow-up every 6 months or yearly. The assessment of sequential spirometry values in COPD is important because the Lung Health Study showed significant differences between individuals who continued to smoke (they lost 63 mL of their FEV1 per year) versus non-smokers (-30 mL of FEV1 per year) (Anthonisen et al, 2002b).

	Response choices	Points*
What is your age?	40-49 years	0
	50-59 years	5
	60-69 years	9
How many pack years of cigarettes have you smoked?	0-14 pack years	0
	15-24 pack years	3
	25-49 pack years	7
	50 + pack years	9
Have you coughed more in the last few years?	yes	0
	no	1
During the past 3 years, have you had any breathing problems that have kept you off work, indoors, at home or in bed?	Yes	0
	no	3
Have you ever been admitted to hospital with breathing problems?	yes	6
	no	0
Have you been short of breath more often in the past few years?	yes	1
	no	0
On average, how much phlegm (sputum) do you cough up most days?	None or less than 1 tablespoon (15 ml)	0
	or more per day	4
If you get a cold, does it usually go to your chest?	yes	4
	no	0
Are you taking any treatment to help your breathing?	yes	5
	no	0

***Scoring system:** Add up the total number of points based on the patient's response. 18 or fewer points suggests a diagnosis of asthma; 19 or more points suggests a diagnosis of COPD

Table 3. Differential diagnosis questionnaire to determine between COPD and asthma (adapted from Price et al, 2011)

The International Primary Care Respiratory Group (IPCRG) currently recommends a case identification spirometry in all patients over 35 years who present with respiratory symptoms and risk factors, such as prior or current smoking history (Decramer et al, 2011; Levy et al, 2006; NICE 2010). Spirometry undertaken at the primary-care level aims to

exclude individuals with normal lung function and to identify those who need a complete investigation for COPD (Figure 1).

Stage	CTS 2008	NICE 2010	GOLD 2010	ACCP, ACP, ATS, ERS (Quaseem, 2011)
I - Mild	>= 80	>= 80	>= 80	> 80
II - Moderate	79,9-50	79,9-50	79,9-50	80-60 (> 50)
III - Severe	49,9-30	49,9-30	49,9-30	< 60
IV - Very severe	<30	<30	<30	

Table 4. FEV1 thresholds (% of theorical values) for classification of COPD

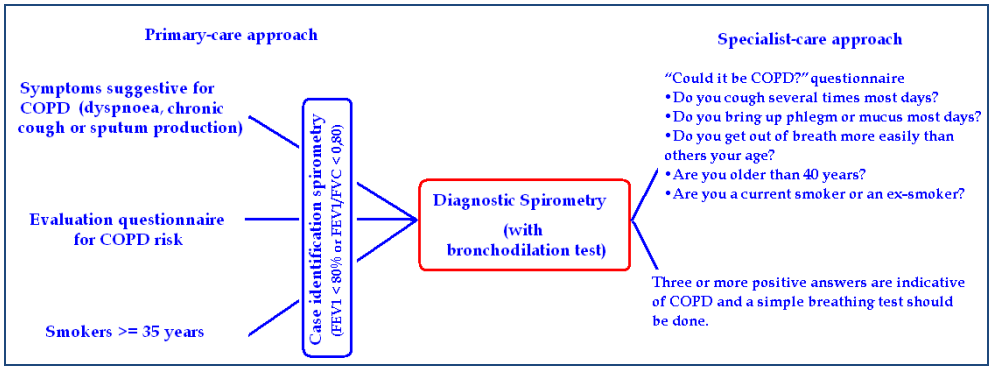

Fig. 1. Screening strategies for COPD (modified from Soriano et al, 2009)

However, spirometry is not commonly performed in primary care practice for many reasons, including limited access, lack of training, cost and time constraints (Barnes & Fromer, 2011; Perez et al, 2011). Spirometric results need a clinical interpretation, with a minimum time commitment of 2–10 min. Interpretation of one value should be assessed in conjunction with many others and by review of the shape of the best curves (ie, flow-volume loops and timing) (Soriano et al, 2009). An English survey find that most of the general practices in UK have a spirometer (82.4%) and use it (85.6%), but confidence in use and interpretation of results varied widely: 58.1% are confident in use but only 33.8% are confident in values interpretation (Bolton et al, 2005). A Swiss survey evaluated that spirometries in general practice are of acceptable quality with reproducible data in 60% of measurements (Leuppi et al, 2010). On the contrary a Dutch study (Schermer et al, 2003) assessed that the proportion of non-reproducible tests was 16% for laboratory tests and 18% for general practice tests in the first year, and 18% for both in the second year of evaluation, confirming that validity and quality of spirometric tests in general practice were as satisfactory as the procedure performed in the same group of COPD patients in a pulmonary function laboratory.

Adherence to the guidelines on the use of spirometry for diagnosis and follow-up is quite different in countries and often not comparable. A recent study (Chavez & Shokar, 2009) has estimated that only 50% of patients diagnosed with COPD performed a functional testing to

confirm the presence of bronchial obstruction and only 40%, once diagnosed, received appropriate treatment. The adherence to GOLD guidelines by primary care providers have been recently evaluated (Perez et al, 2011): the study showed that less of 60% of general practitioner (GPs) complied with at least 5 to 7 key recommendations of the GLs used for evaluation. Cazzola, using an italian database in general practice, observed that a COPD population, registered in a period of 10 years, had a prevalence of chest radiograph in 67.7% while in the same period only the 31.9% of the patients had a spirometry (Cazzola et al, 2009). An important barrier to adherence is constituted by the lack of familiarity with specific recommendations due to the inadequate training in the management of COPD. In addition, medical students complain of inadequate training in the interpretation of spirometric tests (Perez et al, 2011; Soriano et al, 2009).

2.3 Radiology

There are no specific features of COPD on a plain chest radiograph. The features which are usually described are those of lung overinflation, vascular changes and bullae. However, even in patients with very appreciable disability, chest radiography results may be normal (Simon et al, 1973). The accuracy of diagnosing emphysema by plain chest radiography increases with the severity of the disease and it has been reported as being 50–80% accurate in patients with moderate-to-severe disease (Remy-Jardin et al, 1993). Modern imaging techniques, particularly with the advent of CT and, more recently, high resolution CT (HRCT), have provided a more sensitive means of diagnosing macroscopic emphysema during life (Gevenois & Yernault, 1995; Klein et al, 1992).

3. Treatments for stable COPD

The pharmacological treatment of COPD is based on the severity of the disease, defined by functional impairment and frequency of exacerbations (CTS, 2008; NICE, 2010; GOLD, 2010;

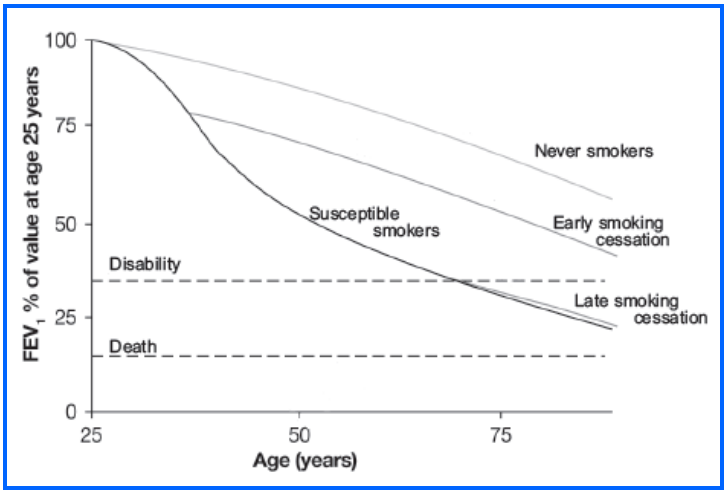

Fig. 2. Effects of smoking and smoking cessation on decline in lung function among adults with COPD (modified from Jones & Østrem, 2011).

Qaseem et al, 2011). It is currently under definition an algorithm that takes into account the intensity of symptoms, assessed with different scales (MRC and CAT). Smoking cessation is the first therapeutic measure, and perhaps most important in changing the natural history of disease. As it has been well demonstrated (Anthonisen et al, 2002a; Fletcher & Peto, 1977; Jones & Østrem, 2011) smoking cessation significantly improves survival, including the reduction of the pulmonary function decay. The relationship between long-term cigarette smoking, decline in lung function (FEV1 reduction) and life expectancy was demonstrated by Fletcher & Peto in 1977, but recently Jones & Østrem (2011) have redrawn the curves (Figure 2) to take into account data from recent studies.

3.1 Treatment strategies with inhaled drugs and COPD severity

The therapeutic approach to stable COPD is progressive, in steps, in relation to the 4 levels of severity defined by all guidelines (GLs) (CTS 2008; NICE, 2010; GOLD, 2010; Qaseem et al, 2011). As an example, the treatment schedule proposed by GOLD GLs (2010) is reported in figure 3.

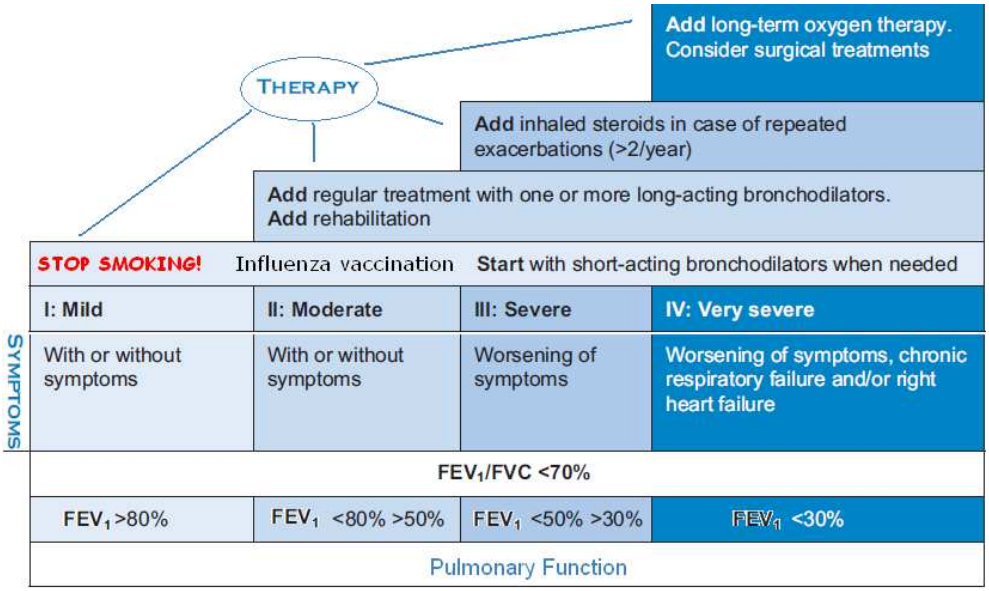

Fig. 3. COPD treatment strategies proposed by GOLD GLs (2010 – modified)

- **Stage 1 (mild COPD):** Initially, the drug treatments are based on the use to need of short-acting bronchodilators (in particular beta2-agonists with short duration of action - SABA). Some GLs (NICE, 2010; GOLD, 2010) suggest starting to use a long-acting bronchodilator (LABA or tiotropium) if symptoms (including cough and dyspnoea) are not well controlled with SABA.
- **Stage 2 (moderate COPD):** All recent GLs (CTS, 2008; NICE, 2010; GOLD, 2010; Qaseem et al, 2011) agree in recommending the use of a long-acting bronchodilator alone (LABA

or tiotropium) as first choice. If the symptoms persist or in the presence of frequent exacerbations (2 or more in the previous year) it is recommended to combine LABA and tiotropium and sometimes even an inhaled corticosteroid (ICS).

- **Stage 3 (severe COPD):** All recent GLs (CTS, 2008; NICE, 2010; GOLD, 2010; Qaseem et al, 2011) agree in recommending the use, as first choice, of a long-acting bronchodilator alone (LABA or tiotropium) and, in case of ineffectiveness, of associating LABA and tiotropium. The introduction of an ICS, usually associated with a LABA in a fixed combination, should be reserved for patients who have frequent exacerbations (at least 2 or more in the previous year).
- **Stage 4 (very severe COPD):** Treatment strategy is the same as Stage 3, although the introduction of an ICS, or the simultaneous use of LABA + ICS + tiotropium (Triple association) is from an early diagnostic findings (Karner & Cates 2011).

3.2 Efficacy of Inhaled treatments for COPD

In recent years the inhalation therapy of COPD has been shown to be effective in reducing symptoms, the frequency and severity of exacerbations, improve health status and exercise tolerance (NICE, 2010; GOLD, 2010; Spencer et al, 2011). In severe cases the only fixed combination of LABA and ICS, given twice a day and for several years, has also been shown to reduce mortality compared to placebo (Baker et al, 2009; Kliber et al, 2010; Nannini et al, 2007a; Wilt et al, 2007). However, the benefit is very modest, so that combination therapy (LABA + ICS, with or without tiotropium) does not appear to significantly improve clinically important outcomes (such as mortality, hospitalizations, severe exacerbations) than treatment with single products (Baker et al, 2009; Kliber et al, 2010; Nannini et al, 2007b; Puhan et al, 2009; Rodrigo et al, 2009; Welsh et al, 2010; Wilt et al, 2007). The association between LABA and tiotropium does not demonstrate advantages when compared with tiotropium alone (Wang et al, 2011).

The choice of the drug to start with, and any subsequent associations has to be customized, since the relationship between the severity of symptoms and the severity of airflow obstruction is influenced by other factors, such as the frequency and severity of exacerbations, presence of one or more complications, respiratory failure, comorbidities (cardiovascular disease, sleep disorders, etc.) and general health.

Fundamental to the effectiveness of prescribed treatments is that the patient has been properly teached on how to use various devices inhalers (Al-Showair et al, 2007; Dolovich et al, 2011). Patients with COPD may have problems in coordination and find it difficult to use a metered-dose inhaler (MDI) or, in cases of severe emphysema, fail to produce the inspiratory depression (Peak Inspiratory Flow - PIF) required to inhale the powder of a device DPI (Dry Powder Inhaler). The inhaler technique should be checked at each visit (see Table 5).

Many drugs are available for nebulising to be used in patients who have very low inspiratory flow (PIF), i.e. for severe hyperinflation. However, there are few randomized studies on their benefits compared to many other devices, and the use of nebulizers often depends on personal preferences, the availability and price. The nebulizer treatment should be continued only if patients report a clear benefit on symptoms.

Metered dose inhalers (MDI)	Dry powder inhalers (DPI)
	Load the dispenser
Exhale away from device	Exhale away from device
Put mouthpiece in your mouth	Put mouthpiece in your mouth
Take a slow, deep breath at the same time you press down on the medication canister.	Take a deep breath and breath in quickly.
Continue inhaling slowly for 4-5 seconds	Hold your breath for 10 second or as long as possible.
	Do not exhale through the mouthpiece to avoid wetting the chamber.
At the end of inhalation always rinse the mouth.	

Table 5. Patient information for optimal use of inhaled devices
(adapted from Dolovich et al, 2011)

3.3 Safety of Inhaled treatments for COPD

β2-agonists. The β2-adrenergic receptors stimulation can give sinus tachycardia at rest and induce changes in heart rate in patients highly susceptible. A recent review of the literature has also ruled out that prolonged treatment with LABAs increase the risk of cardiovascular death (Rodrigo et al, 2008). In older patients treated with high doses of β2-agonists can occur over a tremor that creates problems, regardless of the administration route, thus limiting the tolerated dose. Other metabolic effects, subject to tachyphylaxis, are hypokalaemia, especially when the beta2-agonist therapy is associated with a thiazide diuretic (Lipworth et al, 1990), and the increase of oxygen consumption at rest (Uren et al, 1993).

Anticholinergics. Inhaled anticholinergic drugs are poorly absorbed, which limits the occurrence of important systemic adverse effects (AEs), that are atropine-like (Tashkin, 2010). The most common AE is dry mouth. Some patients using ipratropium report a bitter and metallic taste. It has rarely been reported prostate (dysuria, urinary retention) and ocular (worsening of acute glaucoma) disorders. A slight increase in cardiovascular events compared with placebo, was observed in COPD patients regularly treated with ipratropium (Anthonisen et al, 2002b; Michele et al, 2010) or tiotropium used with Respimat MDI device, (a death in every 124 patients treated per year) (Singh et al, 2011).

Inhaled corticosteroids. Inhaled steroids in COPD are used almost exclusively associated with LABAs and at doses lower than those used in the treatment of asthma in adults. There are adverse events (AEs) both local and systemic:

- **Topic AEs** (oral candidiasis, dysphonia and pharyngitis): affect 8-10% of patients and the frequency increases by increasing the administered dose (Rachelefsky et al, 2007). Typically there is a lower incidence of AEs using DPI formulations compared to MDI formulations. The risk of such AEs can be reduced by rinsing the mouth after inhalation.
- **Systemic AEs**: the most important are the increased frequency of pneumonia and fractures. An increased frequency of pneumonia and severe pneumonia (respectively +2.7% and +2.1%), without increasing total mortality, has been documented with ICS treatment, alone or in combination with LABAs (Singh et al, 2009). The risk of pneumonia increases especially in patients with more severe COPD (FEV1 <40%). A

modest increase (+0.3%) in the risk of bone fractures related to the dose of ICS has been recently documented in a systematic review of 16 randomized controlled trials with 17,513 patients affected with moderate to severe COPD (Loke et al, 2011). In prolonged treatments with high doses of ICS were also reported cases of adrenal cortical insufficiency, cataracts, glaucoma and dermal dystrophy (thinning skin, easy bruising). (Tashkin et al, 2004).

3.4 Oral treatments for COPD

Methylxanthines (theophylline). The most commonly used methylxanthine is theophylline, whose clearance decreases with age. Low-dose theophylline reduces exacerbations, but do not improve post-bronchodilator lung function (Zhou et al, 2006). The evidence supporting the use of theophylline in stable COPD, limited because of its side effects, is insufficient. The toxicity of theophylline is dose-dependent, the therapeutic index is low and most of the benefits appear only with the administration of doses close to those toxic (Ram, 2006b). The AEs include the development of atrial and ventricular arrhythmias (which can be fatal), grand mal seizures (which may occur regardless of a previous history of epilepsy). Other AEs include headache, insomnia, nausea and epigastralgia, which can also occur within the therapeutic range of theophylline. Methylxanthines also have significant interactions with commonly used medications, such as digitalis, warfarin, etc..

Phosphodiesterase-4 inhibitors (roflumilast). The main activity of the inhibitors of phosphodiesterase-4 (PDE4 inhibitors) is to reduce inflammation by inhibiting intracellular cyclic AMP degradation (Rabe, 2011). The use of roflumilast is not worldwide approved. This drug is administered orally once a day, without direct bronchodilator activity, although it has been shown to improve FEV1 in patients treated with tiotropium or salmeterol (Calverley et al, 2009; Fabbri et al, 2009). In patients with severe to very severe COPD and a history of exacerbations, the roflumilast is able to reduce moderate and severe exacerbations (Calverley et al 2009; Rabe, 2011). There is a lack of evidence for comparing roflumilast vs or added to inhaled corticosteroids. The PDE4 inhibitors cause more AEs than inhaled medications for COPD (Calverley et al, 2009; Fabbri et al, 2009; Rabe, 2011). The most frequent AEs are nausea, decreased appetite, abdominal pain, diarrhoea, headache and sleep disorders; these AEs seem to occur early during treatment, are reversible and reduced over time during continued treatment. Since in registrative clinical trials was seen a decline in average weight of 2 kg in patients treated with roflumilast, the drug is not recommended in patients underweight. Roflumilast should be used with caution in patients with depression, too. The roflumilast and theophylline should not be administered concurrently.

3.5 Oxygen therapy

The long-term oxygen therapy (LTOT) is usually administered in patients with stable COPD who have:

- PaO_2 equal to or less than 7.3 kPa (55 mmHg) or SaO_2 equal to or less than 88%, with or without hypercapnia or
- PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 > 88%, if there is pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit > 55%).

LTOT has been shown to increase survival in patients with chronic respiratory failure and severe hypoxemia at rest only if practiced over 15 hours a day (Stoller et al, 2010).

Oxygen therapy can be administered in three ways (ATS, 1995; Celli & McNee, 2004):

- Long-term continuous therapy,
- during physical exertion and
- to relieve acute dyspnoea.

The main goal of oxygen therapy is to increase the baseline PaO_2 to a minimum of 8.0 kPa (60 mmHg) at sea level and at rest, and / or produce an O_2 saturation of at least 90%. Oxygen is usually released through face masks, with adequate flow concentrations, ranging from 24 to 35%. The facemask get an accurate titration of oxygen; however, many patients prefer the oxygen released by nasal cannula. The release of oxygen by this route requires additional monitoring of blood gases to ensure a satisfactory oxygenation, and may require individual titration. Additional oxygen at home is usually the most expensive part of the therapy of patients with COPD (Petty & O'Donohue, 1994). The oxygen concentrators can be cheaper than the systems of delivery of liquid or gaseous oxygen (Heaney et al, 1999).

3.6 Non-pharmacologic treatments for stable COPD

Vaccinations. The annual flu vaccination has been shown to reduce both hospitalizations and mortality in patients with COPD (Nichol et al, 1999a; Poole et al, 2006). Pneumococcal vaccination has been shown to produce important benefits, such as the reduction of hospitalizations and total mortality, particularly in patients with severe COPD (Nichol et al, 1999b).

Pulmonary Rehabilitation The main goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life and increased physical and emotional participation in everyday activities (Nici et al, 2006; Ries et al, 2007).

The minimum length of an effective rehabilitation period is 6 weeks, but better results are obtained with activities even longer. However, no effective program has been developed so far to maintain the effects over time (Ries et al, 2007). Although the benefits have not been studied, it is reasonable to suggest to COPD patients, who can not follow a structured rehabilitation program, to exercise on their own (such as walking for 20 minutes a day). In any case, patients with more severe dyspnea (stage MRC 4 - see table 2) may not have the benefit of rehabilitation (Wedzicha et al, 1998)

The components of pulmonary rehabilitation programs are:

- **Physical training.** The exercise tolerance can be assessed with various tests, the simplest of which is the 6-minute walking test, measuring the distance traveled. The duration of physical training generally ranges from 4 to 10 weeks, resulting in greater effects for longer than the shorter lengths (Lacasse et al, 1996). The patient should be encouraged to move until it has been completed a walking period of 20 minutes. In patients severely disabled, the use of a simple walker with wheels improves walking distance and decreases the sensation of dyspnoea. The addition of upper limb exercises or other aerobic training is effective in improving the muscular strenght, but does not improve the quality of life or exercise tolerance (Bernard et al, 1999).

- **Smoking cessation.** Smoking cessation has the greatest impact on the natural history of COPD (figure 2). The evaluation of smoking cessation in a multicenter, long-term study (Anthonisen et al, 1994) indicates that, if effective resources and time are devoted to smoking cessation, can be maintained long-term quit rate of 25%.
- **Nutritional counselling.** Nutritional status is an important part of certain symptoms, disability and prognosis of COPD. Both overweight and underweight can be a problem (Nici et al, 2006). Approximately 25% of patients with COPD shows a reduction in body mass index, especially against the lean mass, which turns out to be an independent risk factor for mortality (Schols et al, 1998). The current evidence suggests that the nutritional supplement alone may not be sufficient if a strategy is not associated with exercise. In patients with COPD, nutritional supplements (eg creatine) do not substantially increase the training effect of a multidisciplinary pulmonary rehabilitation program (Deacon et al, 2008). Anabolic steroids in COPD patients with weight loss increase body weight and lean body mass, but have little or no effect on exercise ability (Weisberg et al, 2002).
- **Education.** Most pulmonary rehabilitation program includes an educational component, but the specific contributions of education to the improvements obtained after pulmonary rehabilitation are still not clear. Patient education alone does not improve exercise performance or lung function, but may play a role in improving the skills, the ability to cope with the disease and health status (Celli, 1995).

Table 6 summarizes the benefits of pulmonary rehabilitation in descending order with respect to the robustness of available evidences (from A to C grading system).

*Grading**	
A	Improves the ability to exercise
A	Reduces the intensity of the perceived sense of breathlessness
A	Improves the quality of life related to health
A	Reduces the number and days of hospitalisation
A	Reduces anxiety and depression associated with COPD
B	Strength and endurance training of the upper limbs improves the function of the arms.
B	The benefits extend beyond the immediate period of training
B	Improves survival
B	Increases the effect of long-acting bronchodilators
B	Improves recovery after hospitalisation for an exacerbation
C	Training of respiratory muscles is useful, especially when combined with physical training
C	Psychosocial intervention is helpful

*The grading system express the robustness of scientific evidence: an A recommendation is sustained by a strong scientific proofs, while a D evidence is mainly based on expert-opinion. Grade B and C express intermediate levels of evidence.

Table 6. Benefits of pulmonary rehabilitation in patient with COPD
(modified from GOLD GLs, 2010)

4. COPD and comorbidity

COPD often coexists with other diseases that have a significant impact on prognosis (Barnes & Celli, 2009; Mannino et al, 2008; Soriano et al, 2005; Sin et al, 2006). Some of these more often coexist and may be correlated, both for shared risk factors that impact on the mutual development (Fabbri et al, 2008), although the risk of comorbidity may also be the result of consequences of COPD, for example, reduced physical activity.

Cardiovascular disease is probably the main comorbidity in COPD (Fabbri et al, 2008; Soriano et al, 2005). Heart Failure (HF) is common in COPD: about 30% of patients with stable COPD have some degree of HF (Rutten et al, 2005). Worsening of HF is a significant differential diagnosis to an acute exacerbation of COPD. About 30% of patients in a cardiologic clinic is diagnosed with COPD (Hawkins et al, 2009) which will often be the cause of hospitalization for acute HF, with significant implications on prognosis (Iversen et al, 2010). In the treatment of HF with concomitant COPD is preferable to use a β-selective blocker (β-1 selective) compared to a non-selective β-blocker (Jabbour et al, 2010). Patients with COPD also have an increased incidence of Atrial Fibrillation (AF) (Buch et al, 2003). There are no reliable data on the use of drugs in COPD patients with AF and these patients were often excluded from clinical trials. In cardiac patients, however, it seems reasonable to avoid particularly high doses of β-agonists.

Other diseases commonly associated with COPD are osteoporosis (often under-diagnosed and at risk of deterioration with the use of systemic corticosteroids) and depression (associated with poor prognosis, but can favorably affected by exercise rehabilitation - Knubben et al, 2007). Lung cancer is often observed in patients with COPD and was found to be the most frequent cause of death in patients with mild COPD (Anthonisen et al, 2002a).

5. Management of acute exacerbations of COPD (AECOPD)

An authoritative definition of acute exacerbation of COPD (AECOPD) is the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement one: "an exacerbation of COPD is an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum beyond day-to-day reliability sufficient to warrant a change in management" (Celli & McNee, 2004).

On average, COPD patients have one to four AECOPD per year, of various intensity/severity (Hagedorn, 1992). Patients who have frequent exacerbations (more than 3 per year) have a more rapid decline in lung function than patients who relapsed less frequently (-40 mL FEV1/year vs. -32 mL FEV1/year) (Donaldson et al, 2002). The economic burden of this common condition is extremely high, taking into consideration that during an AECOPD there is an intensification of treatment and often the need for hospitalisation, or even use of the intensive care unit (ICU). Hospital mortality for AECOPD is about 10% per year (Siafakas & Wedzicha, 2006) and the long-term outcome is rather poor: 3 years after hospitalization mortality from all causes rises up to 49% (Gunen et al, 2005; Wouters, 2003).

5.1 Diagnosis of AECOPD

The diagnosis of COPD exacerbation is clinical and does not depend on the results of ad hoc surveys, however, such investigations may help to define an optimal strategy of treatment.

The presence of greenish phlegm is a good indicator of high bacterial load and the potential success of antibiotic therapy; patients with light-colored phlegm do not derive additional benefit from antibiotic treatment (Stockley et al, 2000). Pulse oximetry may be useful in assessing the severity of an exacerbation and to identify patients who may benefit from oxygen (Bach et al, 2001). Chest radiographs are useful in the differential diagnosis, distinguishing pneumonia, congestive heart failure, pneumothorax, pleural effusion , etc. (Emerman & Cydulka 1993; Sherman et al, 1989; Tsai et al, 1993). During an exacerbation, lung function changes are usually limited , then spirometry takes little diagnostic significance (Bach et al, 2001).

5.2 Causes of AECOPD

For adequate management of the patient it is of paramount importance to identify the causes of AECOPD (Celli & McNee, 2004; GOLD, 2010) (Figure 4); however, in approximately one-third of the cases, this is not feasible. In more than half of the episodes, the cause of an exacerbation is a viral infection. Bronchoscopic studies have shown that at least 50% of patients have bacteria in high concentrations in their lower airways during exacerbations of COPD (Pela et al, 1998), but a significant proportion of these patients have bacteria in their lower airways in the stable phase of the disease, too (Sethi & Murphy, 2008). Conditions that may mimic the symptoms of an COPD exacerbation in a patient with COPD include pneumonia, congestive heart failure and/or arrhythmias, pulmonary embolism, pneumothorax, pleural effusion, metabolic diseases, inappropriate use of drugs (hypnotics) or end-stage disease (Siafakas & Wedzicha, 2006).

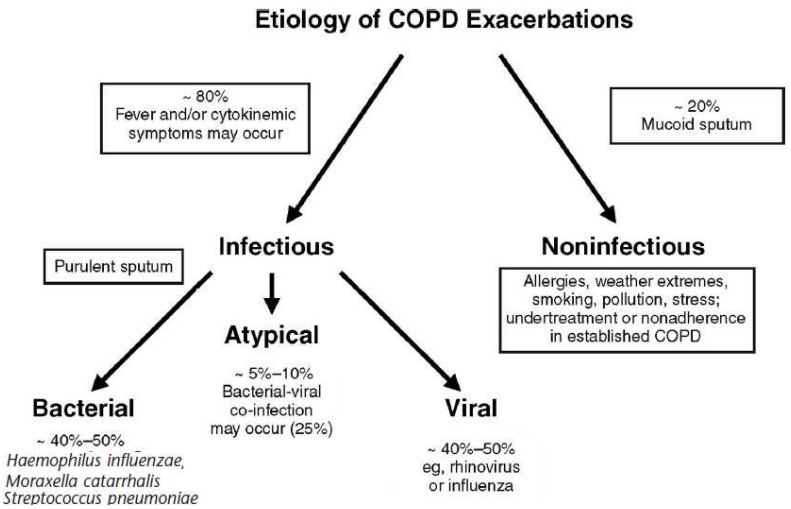

Fig. 4. **Etiology of AECOPD** (modified from Anzueto, 2010)

5.3 Home management of AECOPD

Proper decision about the management of an AECOPD requires information on the previous condition of the patient in the stable state and a precise assessment of the severity of the

present episode (Celli & McNee, 2004; GOLD 2010). In table 7 the factors to consider to decide whether to manage an AECOPD at home or in hospital are reported (NICE, 2010).

	Treat at home?	Treat in hospital?
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes)	No	Yes
$SaO_2 < 90\%$	No	Yes

Table 7. Patient's factors to consider when deciding where to manage an AECOPD (modified from NICE, 2010)

A review shows that, when the patient does not require intensive hospital care and can be adequately cared at home, the home management of exacerbations is effective as the hospital management (mortality and hospital readmissions are similar) (Ram et al, 2004) and is most appreciated by patients and carers. The objectives of outpatient or home management are (Hurst & Wedzicha, 2004; Ram et al, 2004):

- educate patients and families on the signs of deterioration and the actions to be taken (with written instructions);
- increase maximum airflow;
- remove excess bronchial secretions;
- treat infection, if present;
- improve respiratory muscle strength and, thus, facilitate cough;
- avoid or monitor adverse events of treatment.

A decisional algorithm to facilitate decisions in treating at home a mild to moderate AECOPD exacerbation is reported in figure 5 (modified from Siafakas & Wedzicha, 2006**).**

Education: it was shown that education can reduce utilisation of health services and result in better survival rates after an AECOPD (Nici et al, 2006; Tougaard et al, 1992). Educational intervention (better with written instructions) should underline the following features:

- The patient, but just as importantly the family, should be instructed on the signs and symptoms that indicate a worsening of the patient's condition and the actions that should be taken, e.g. contact a physician or go to the hospital.

- Self-clearance of sputum by frequent coughing and/or by performing forced expiratory manoeuvres from middle lung volume. An effective cough consists of a slow, deep inspiration, a few seconds of breath holding followed by a cascade of two to three voluntary cough efforts.
- If the patient is on LTOT, advise him/her not to change the dose by him/herselve;
- Adequate training in usage of treatment to ensure maximum compliance to prescribed treatment.
- Usual nutrition may need to be modified (i.e. small and frequent meals with low carbohydrate content) and fluid intake increased.
- Advise the patient or his/hers family to avoid sedatives and hypnotics, as well as cough mixtures that contain such agents.

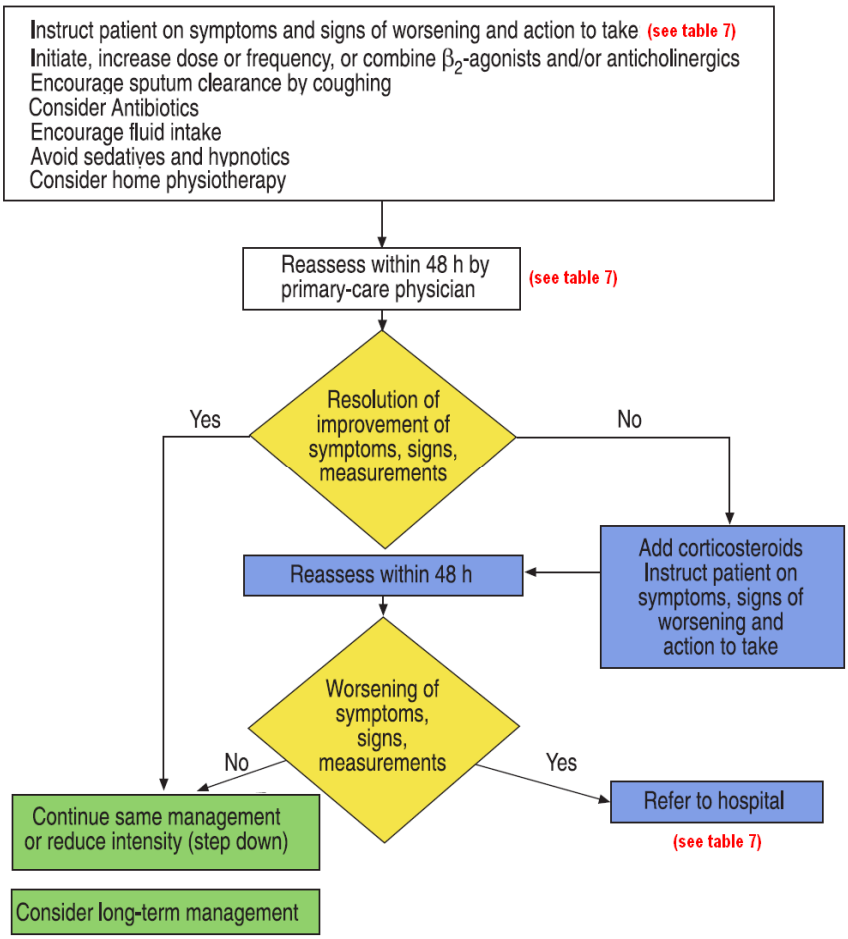

Fig. 5. Algorithm for the home management of an AECOPD
(Modified from Siafakas & Wedzicha, 2006)

Bronchodilators (short acting and long acting): increasing doses of beta 2 agonists "short acting" (isoprenaline, salbutamol, terbutaline) may effectively counteract the increased dyspnoea; standard pressurized inhalers (MDI) and nebulizers are equally effective dose inhalers to administer bronchodilators; doses to be administered and the patients' conditions may influence the choice of method of administration (see table 5). There is no evidence on the effectiveness of LABAs in the treatment of exacerbations. The use of ipratropium or tiotropium (alone or in combination) does not appear justified in the first instance (McCrory & Brown, 2003).

Inhaled and Oral Corticosteroids: Initiating or increasing the dose of inhaled corticosteroids (ICS) is the first step-up when steroid treatment is required. If a spacer is used and an adequate dose is given, this mode of administration (inhaled) is efficient in most cases. However, oral corticosteroids may be needed in more severe cases, often with beneficial results (Thompson et al, 1996; Siafakas & Wedzicha, 2006). A daily dose of 30–40 mg of prednisolone for 10–14 days may be required. Systemic corticosteroids shorten the length of hospital stay, improve lung function (FEV_1) and arterial hypoxemia (PaO_2) (Davies et al, 1999, Maltais et al, 2002; Thompson et al, 1996); they also reduce the risk of early recurrence and treatment failure (Aaron et al, 2003; Davies et al, 1999).

Antibiotics: although only half of AECOPD are due to infections, and a large part of these are viral (Wedzicha, 2004), it is common practice to administer a course of antibiotics for 7–14 days. A systematic review of the few placebo-controlled studies available has shown that antibiotics reduce the risk of short-term mortality by 77%, by 53% of the treatment failure and sputum purulence by 44%. This review supports antibiotics for patients with moderate or severe AECOPD, with increased cough and sputum purulence (Quon et al, 2008; Ram et al, 2006a). The benefits of antibiotics are still more pronounced in patients with more severe exacerbations (Bach et al, 2001).

The local bacterial resistance should be taken into account when empirical treatment is given (Celli & McNee, 2004). Broad-spectrum antibiotics, such as amoxicillin, with or without clavulanic acid, tetracyclines, erythomycin or oral cephalosporin are recommended (Siafakas et al, 2005). In particular conditions (patients with frequent episodes of exacerbation, recent antibiotic treatments or hospitalizations, stays at facilities for the elderly) is likely the selection of multiresistant (bacterial strains especially Pseudomonas or Staphylococcus aureus). In these cases, when the targeted therapy is not possible, you should choose between fluoroquinolones or cephalosporins (Woodhead al, 2005).

Mucolytic agents: recent guidelines conclude that: "there is no evidence to support prescription of mucolytics in acute exacerbation". However, these agents can be beneficial in a few cases with copious and tenacious sputum (Celli & McNee, 2004; GOLD, 2010).

Oxygen therapy: Initiation of oxygen therapy at home during an exacerbation of COPD may lead to serious complications and should be avoided. If the patient is on long-term oxygen therapy (LTOT), a thorough inspection of the apparatus and dosage of oxygen administered is recommended (see paragraph 3.5). In addition, a clinical evaluation of adequate oxygenation is required. However, when the evaluation is in doubt, the assessment should take place in the hospital with emogasanalysis. (Siafakas & Wedzicha, 2006; NICE 2010).

5.4 Hospital discharge and follow-up

The following features were found to be predictive of re-hospitalization (Bahadori & Fitzgerald, 2007): a previous hospitalization, use of oral corticosteroids or long-term oxygen, the poor quality of life associated with reduced physical activity. Regular home visits by a community nurse may permit earlier discharge of patients hospitalized for AECOPD without increasing re-hospitalizations (Celli & McNee, 2004; Hermiz et al, 2002; Hughes et al, 2000; Siafakas et al, 2005). However, the exact criteria for this approach remain uncertain and vary depending on the scope rated health (Hermiz et al, 2002). The use of a written action plan increased therapeutic interventions appropriate for an acute exacerbation, an effect that does not diminish, however, the use of health resources (Wood-Baker et al, 2006). For patients who are hypoxemic during the AECOPD, blood gases and / or pulse oximetry should be reevaluated before hospital discharge and if the patient remains hypoxemic, it may be necessary to add an additional long-term oxygen therapy.

5.5 Prevention of AECOPD

Smoking cessation, anti-flu and anti-pneumococcal vaccines, knowledge of current treatment, including inhaler technique, the constant treatment with inhaled bronchodilators in long duration of action, with or without inhaled corticosteroids, significantly reduces the number of exacerbation and hospitalization (Calverley et al, 2007; Nannini et al, 2007a; Nannini et al, 2007b; Tashkin et al, 2008). Early outpatient pulmonary rehabilitation after hospitalization is safe (see paragraph 3.6) and leads to significant clinical improvements in terms of exercise capacity and health status at 3 months (Man et al, 2004). If the patient has a significant persisting disability should be evaluated in social welfare issues, identifying the main caregivers with whom agree the treatment plan.

6. Conclusions

COPD is a chronic disease whose prevalence is increasing, and the diagnosis and management is primarily the task of general practitioners. Screening for COPD is not recommended in asymptomatic smokers, but running an office spirometry in heavy smokers older than 35 years and with symptoms can be an initial framework for early detection of COPD and provide effective interventions to reduce mortality. Smoking cessation has been shown to improve the prognosis of patients with COPD, especially if applied early. Treatments with combined inhaled LABA and ICS have also been shown to reduce mortality in patients with more severe COPD, while the use of long-acting bronchodilators (LABAs or/and tiotropium) reduces only the number of exacerbations and hospitalizations. Pulmonary rehabilitation is a key to improving treatment outcomes (important for patients with COPD), but is rarely used, especially in home management of COPD. Able to prevent or control the AECOPD at home is a very important goal of the GP, for which it is necessary to apply the recommendations of the best guidelines and obtain the cooperation of patients and their families.

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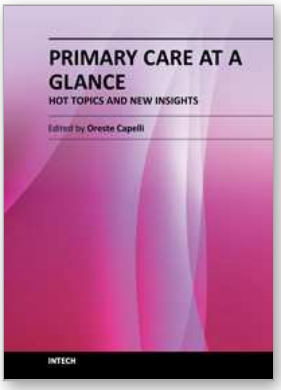

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"Both among scientists and clinical practitioners, some find it easier to rely upon trivial explanations, while others never stop looking for answers". With these surprising words, Augusto Murri, an Italian master in clinical medicine, reminds us that medical practice should be a continuous journey towards knowledge and the quality of care. The book brings together contributions by over 50 authors from many countries, all around the world, from Europe to Africa, from Asia to Australia, from North to South America. Different cultures are presented together, from those with advanced technologies to those of intangible spirituality, but they are all connected by five professional attributes, that in the 1978 the Institute of Medicine (IOM)1 stated as essentials of practicing good Primary Care: accessibility, comprehensiveness, coordination, continuity and accountability. The content of the book is organized according to these 5 attributes, to give the reader an international overview of hot topics and new insights in Primary Care, all around the world.

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