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Novel concepts in the pharmacotherapy of chronic obstructive pulmonary disease

Nowe koncepcje dotyczące farmakoterapii przewlekłej obturacyjnej choroby płuc

Abstract

Chronic obstructive pulmonary disease (COPD) is highly prevalent and will continue to be an increasing cause of morbidity and mortality worldwide. COPD is now viewed under a new paradigm as preventable and treatable. In addition, it has become accepted that COPD is not solely a pulmonary disease but also one with important measurable systemic consequences. It follows, that patients diagnosed with COPD have to be comprehensively evaluated to determine the extent of disease so that therapy can be adequately individualized. We now know that smoking cessation, oxygen for hypoxemic patients, lung reduction surgery for selected patients with emphysema, and non-invasive ventilation during severe exacerbations have an impact on mortality. The completion of well planned pharmacological trials have shown the importance of patient centered outcomes and the possible impact on mortality and rate of decline of lung function. This monograph presents an update on the pharmacological therapy of COPD. The future for patients with COPD is bright as primary and secondary prevention of smoking becomes more effective and air quality improves. In addition, current research will unravel the pathogenesis, clinical and phenotypic manifestations of COPD thus providing exciting therapeutic targets. Ultimately, the advent of newer and more effective therapies will lead to a decline in the contribution of this disease to poor world health.

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Chronic Obstructive Pulmonary Disease (COPD) is defined as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences [1, 2]. This definition changes the paradigm that characterized older ones [3, 4] in two important aspects. First, it presents a positive attitude towards the disease, and secondly, it highlights a salient feature of COPD, its frequent expression of systemic manifestations [5]. This monograph summarizes the recent advances in the pharmacological management of this disease, provides the evidence that patients with COPD respond to treatment, and that the treatment is effective in multiple outcomes of importance to patients.

COPD is highly prevalent, under-diagnosed, under-treated and under-perceived. It is also a multi-component disease. The airflow obstruction of COPD, as expressed by the forced expiratory volume in one second (FEV_1) is by definition only partially reversible [1, 2]. In a paradoxical way, this defining physiology has been used as the outcome to determine the effectiveness of interventions. It is no surprise that the lack of large response in FEV_1 to different therapies [6–15] has resulted in an undeserved nihilism. There is increasing evidence that independent of the degree of airflow obstruction, lung volumes are important in the genesis of the symptoms and limitations of patients with more advanced disease. A series of elegant studies have demonstrated that dyspnea perceived during

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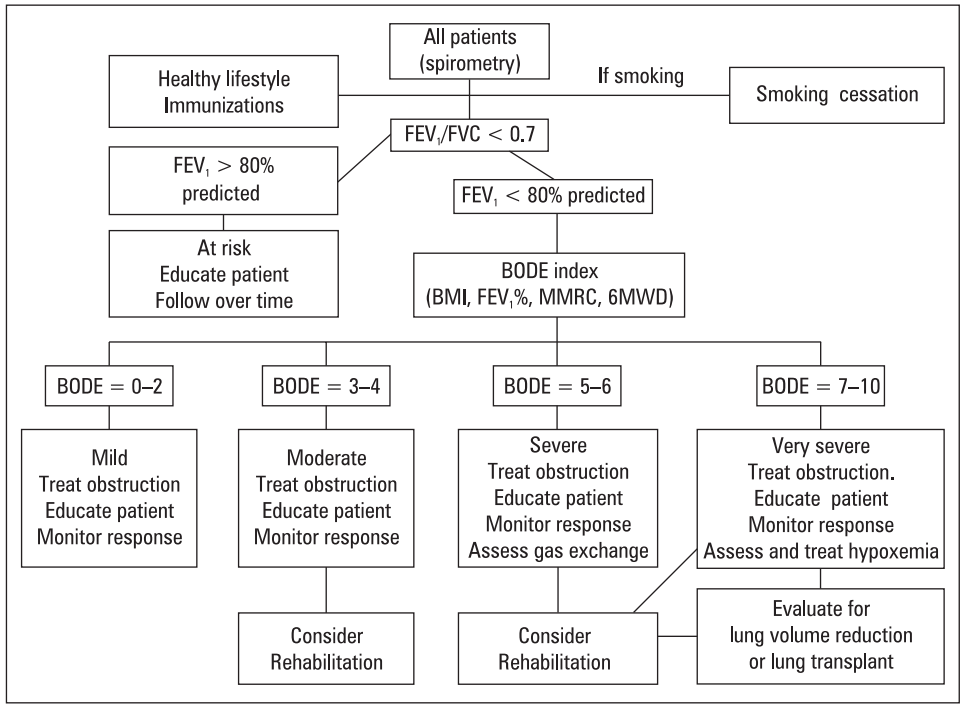


Figure 1. Schematic algorithm to approach patients with chronic obstructive pulmonary disease (COPD). The evaluation of the multiple domains using simple validated tools can better help stage the global severity of the disease. FVC — forced vital capacity, FEV_1 — forced expiratory volume in one second, BMI — body mass index, MMRC — modified medical research council dyspnea scale, 6MWD — six minute walk distance

exercise, including walking, more closely relates to the development of dynamic hyperinflation than to changes in FEV_1 [16–20]. Further, the improvement in exercise brought about by several therapies including bronchodilators, oxygen, lung reduction surgery and even rehabilitation is more closely related to delaying dynamic hyperinflations than by improving the degree of airflow obstruction [16–19, 21]. Casanova et al showed that hyperinflation, expressed as the ratio of inspiratory capacity to total lung capacity (IC/TLC) predicted survival better than the FEV_1 [22]. The importance of lung volume as determinant of outcomes provides us not only with new insights into pathogenesis, but also opens the door for new imaginative ways to alter lung volumes and perhaps impact on disease progression.

It is now accepted that COPD may be associated with important systemic expressions in patients with more advanced disease [1, 5, 23]. Perhaps as a consequence of a persistent systemic inflammatory state or due to other yet unproven mechanisms such as imbalanced oxidative stress or abnormal immunological response the fact is that many patients with COPD may have decreased free fat mass, impaired systemic muscle function, anemia, osteoporosis, depression, pulmonary hypertension and cor-pulmonale, all of which are important determinants of outcome. Indeed, dyspnea measured with a simple tool such as the modified medical research scale (MMRC) [24], the body mass index (BMI) obtained by dividing the weight in kg by the height in meters squared (kg/m^2) [25, 26] and the timed walked distance in 6 minutes or 6MWD [27, 28] are all better predictors of mortality than the FEV_1. The incorporation of these variables into the multidimensional BODE index (body mass index [B], airflow obstruction [O], dyspnea [D], exercise capacity [E]) predicts survival even better [5]. The index is also responsive to exacerbations [29] and more importantly act as a surrogate marker of future outcome after interventions [30] may better help clinicians determine the comprehensive severity of disease (fig. 1).

COPD, a treatable disease

Once diagnosed, the patient should be encouraged to actively participate in disease management. This concept of *collaborative management* may improve self-reliance and esteem. All patients should be encouraged to lead a healthful lifestyle and exercise regularly. Preventive care is extremely important at this time and all patients should receive immunizations including pneumococcal vaccine and yearly influenza vaccinations [1, 3].

As smoking is the major cause of COPD, smoking cessation is the most important component of

therapy for patients who still smoke [1, 3]. Because second hand smoking is known to damage lung function, limitation of exposure to involuntary smoke, particularly in children, should be encouraged. The factors that cause patients to smoke include: the addictive potential of nicotine, conditional responses to stimuli surrounding smoking, psychosocial problems such as depression, poor education and low income, and forceful advertising campaigns. As the causes that drive the patient to smoke are multi-factorial, smoking cessation programs should also involve multiple interventions. The clinician should always participate in the treatment of smoking addiction because a physician's advice and intervention and use of the appropriate medications including nicotine patch, gum or inhalers, bupropion and verenicline help determine successful results [31–34]. The significant burden of COPD in patients exposed to the fumes of biomass fuel consumption in certain areas of the world should improve by changing to more efficient and less polluting sources of energy.

Pharmacological therapy of airflow obstruction

Many patients with COPD require pharmacological therapy. This should be organized according to the severity of symptoms (dyspnea and functional capacity), the degree of lung dysfunction, and the tolerance of the patient to specific drugs [1, 3]. A stepwise approach similar in concept to that developed for systemic hypertension may be helpful since medications alleviate symptoms, improve exercise tolerance and quality of life and may decrease mortality. Tables 1 and 2 provide a summary of the evidence supporting the effect of individual and combined pharmacological agents on outcomes of importance to patients with COPD.

Bronchodilators

Several important concepts guide the use of bronchodilators. In some patients the changes in the FEV_1 may be small and the symptomatic benefit may be due to other mechanisms such as a decrease in lung hyperinflation [35, 36]. Some older COPD patients cannot effectively activate metered dose inhalers (MDI), and we should work with the patient to achieve mastery of the MDI. If this is not possible, use of a spacer or nebulizers to facilitate inhalation of the medication will help achieve the desired results. The advent of once or twice daily nebulized bronchodilators such as formoterol offers an interesting alternative to the MDI in those patients unable to activate them effectively. Mucosal deposition in the mouth can result in local side effects (i.e. thrush with inhaled steroids) or general absorption and its consequences (i.e. tremor after beta-agonists). Finally, the inhaled route is preferred over the oral administration [1, 3] and long-acting bronchodilators are more effective than short acting ones [1, 2].

The currently available bronchodilators include:

Beta-agonists. These drugs increase cyclic adenosine monophosphate (AMP) within many cells and promote airway smooth muscle relaxation. Other non-bronchodilator effects have been observed but their significance is uncertain. In patients with mild intermittent symptoms it is reasonable to initiate drug therapy with an MDI of a short acting beta agonist as needed for relief of symptoms [1, 2]. In patients with persistent symptoms, it is indicated to use long acting beta-agonists [1, 2, 37–40], at a dose of 1 or 2 puffs twice daily. They prevent nocturnal bronchospasm, increase exercise endurance and improve quality of life. The safety profile of Salmeterol in the *TOwards a Revolution in COPD Health* (TORCH) trial [41] is reassuring to clinicians who frequently prescribe selective long acting beta-agonists to their patients with COPD. The advent of longer acting agents and preparations that can be provided via nebulizers will increase our choices and perhaps help increase compliance.

Anticholinergics. These drugs act by blocking muscarinic receptors that are known to be effective in COPD. The appropriate dosage of the short acting ipratropium bromide is 2–4 puffs three or four times a day, but some patients require and tolerate larger doses [1, 3]. The therapeutic effect is a consequence of a decrease in exercise induced dynamic hyperinflation [18]. The long acting tiotropium is very effective in inducing prolonged bronchodilation [7, 10] and decreasing hyperinflation [35] in patients with COPD. In addition it improves dyspnea, decreases exacerbations [42] and improves health related quality of life when compared to placebo and even to ipratropium bromide [43]. The results of the *Understanding Potential Long Term Impacts on Function with Tiotropium* (UPLIFT) trial [44], evaluating the potential role of tiotropium as a disease modifying agent has been completed [45]. In that large trial of close to 6000 patients followed over 4 years, lung function was significantly better at all points of the trial when compared with placebo, however, the rate of decline of FEV_1 was not different between the two groups. Although this could be taken as an indication that tiotropium failed to change the course of the disease, the fact is that over 90% of the patients in the control group were on respiratory medications

Table 1. Effect of individual pharmacological agents on important outcomes of patients with chronic obstructive pulmonary disease. A Yes supports an improvement in the outcome whereas a No defines no improvement in the outcome (modified from ref. [1])

	FEV_1	Lung volume	Dyspnea	QoL	AE	Exercise endurance	Disease modifier by FEV_1	Mortality
Albuterol	Yes (A)	Yes (B)	Yes (B)	NA	NA	Yes (B)	NA	NA
Ipratropium bromide	Yes (A)	Yes (B)	Yes (B)	No (B)	Yes (B)	Yes (B)	No	NA
Long acting beta-agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	Yes	No
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes	No	Yes
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	Yes	No
Theophylline	Some (A)	Yes (B)	Yes (A)	Yes (B)	NA	Yes (A)	NA	NA

Level of evidence: A — more than one randomized trial; B — limited randomized trials; NA — not available

Table 2. Effect of some combined pharmacological agents on important outcomes of patients with chronic obstructive pulmonary disease. A Yes supports an improvement in the outcome whereas a No defines no improvement in the outcome (modified from ref. [1])

	FEV_1	Lung volume	Dyspnea	QoL	AE	Exercise endurance	Disease modifier by FEV_1	Mortality
Salmeterol + Theophylline	Yes (B)	NA	Yes (B)	Yes (B)	NA	NA	NA	NA
Formoterol + Tiotropium	Yes (A)	NA	Yes (B)	Yes (B)	NA	NA	NA	NA
Salmeterol + Fluticasone	Yes (A)	Yes (B)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	Yes	Yes
Formoterol + Budesonide	Yes (A)	NA	Yes (A)	Yes (A)	Yes (A)	NA	NA	NA
Tiotropium + Salmeterol + Fluticasone	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	NA	NA

Level of evidence: A — more than one randomized trial; B — limited randomized trials; NA — not available

and 60% of them were on long-acting beta-agonist (LABA) or inhaled corticosteroids. Thus, the trial was not a placebo controlled trial but rather a "usual care" comparison. Interestingly, the rate of decline of FEV_1 was 39 ml/year for tiotropium and 42 ml/year for the control, values that were lower than those recorded in the TORCH study. Further, when compared to older studies, the rate of decline in UPLIFT showed the lowest values ever recorded. This suggests that it is going to be very difficult to further decrease FEV_1 with treatment as we may be approaching the ceiling of decline in patients with COPD who have stopped smoking. In addition to the benefits in lung function, the UPLIFT trial results indicated a decrease in time to first exacerbation, a sustained improvement in health related quality of life and a significant impact on mortality at 4 years. All of these findings taken together support the use of tiotropium as a first line agent for patients with persistent symptoms.

Phosphodiesterase inhibitors. Theophylline is a non-specific phosphodiesterase inhibitor that increases intra-cellular cyclic AMP within airway smooth muscle. The bronchodilator effects are best

seen at high doses where there is also a higher risk of toxicity. Its potential for toxicity has led to a decline in its popularity. Theophylline is of particular value for less compliant or less capable patients who cannot use aerosol therapy optimally. The previously recommended therapeutic serum levels of 15 to 20 mgs/dl are too close to the toxic range and are frequently associated with side effects. Therefore, a lower target range of 8 to 13 mgs/dl is safer and still therapeutic [1, 3]. The combination of two or more bronchodilators (theophylline, albuterol and ipratropium) has some rationale as they seem to have additive effects and can result in maximum benefit in stable COPD [2, 46]. A possible action of theophylline on the expression of genes central to inflammation in COPD [47] deserves further investigation.

The specific phosphodiesterase E4 inhibitors cilomilast and roflumilast may have an anti-inflammatory and bronchodilator effect but less gastrointestinal irritation and this could prove extremely useful if these theoretical benefits are clinically confirmed. Data from the first 6 months studies show modest bronchodilation effects and some benefits on quality of life [48, 49].

Non-steroidal anti-inflammatory therapy

In contrast to their value in asthma, non-steroidal anti-inflammatory drugs have not been documented to have a significant role in the treatment of patients with stable COPD [1, 2]. Cromolyn and nedocromil could possibly be helpful if the patient has associated respiratory tract allergy. One study using monoclonal antibody against interleukin-8 [50] and another using an antibody against tumor necrosis factor alpha [51] failed to detect any response. However, patients were selected according to the degree of airflow obstruction and not based on the presence or increased level of the specific targeted molecules. The groups of leucotriene inhibitors that have proven useful in asthma have not been adequately tested in COPD so that final conclusions about their potential use can't be drawn at this time.

Corticosteroids. Glucocorticoids act at multiple points within the inflammatory cascade although their effects in COPD appear more modest compared with bronchial asthma. In outpatients, exacerbations necessitate a course of systemic corticosteroids as we will discuss later in the monograph but it is important to wean patients quickly since the older COPD population is susceptible to complications such as skin damage, cataract development, diabetes, osteoporosis and secondary infection. These risks do not accompany standard doses of inhaled corticosteroid aerosols, which may cause thrush but pose a negligible risk for other outcomes such as development of cataract and osteoporosis. Several large multi center trials evaluated the role of inhaled corticosteroids in preventing or slowing the progressive course of symptomatic COPD [12, 13, 52–54]. The results of these earlier studies showed minimal if any benefits in the rate of decline of lung function. On the other hand, in the one study where it was evaluated, inhaled fluticasone decreased the rate of loss of health related quality of life and frequency of exacerbations [12]. Recent retrospective analyses of large databases suggesting a possible effect of inhaled corticosteroids on improving survival [55, 56] were not confirmed in the TORCH trial in which the combination of inhaled corticosteroids and long acting beta agonists was superior to inhaled corticosteroids alone with regard to all outcomes evaluated, including survival [41]. This coupled with the more frequent development of pneumonia (described as an adverse event but not precisely diagnosed with chest roentgenogram, sputum cultures or laboratory confirmation) in the patients receiving inhaled corticosteroids (ICS) suggests that in patients with COPD, ICS should not be prescribed alone but rather in combination with a long-acting beta-agonist.

Combination therapy

Most studies that have explored the value of combination therapy have shown significant improvements over single agents alone and it may be time to think of it as first line therapy. Inititally, the inhaled combination of ipratroprium and albuterol proved effective in the management of COPD [15]. More recently, the combination of tiotropium once daily and formoterol twice daily was better than either agent alone [43]. In that study the administration of once daily tiotropium and once daily formoterol was very effective suggesting that once a day dosing of combinations may offer a viable option to the more complex twice a day therapy [43]. In another trial, the combination of theophylline and salmeterol were significantly more effective than either agent alone in lung function and health status [11].

The TORCH study showed the benefits of the salmeterol/fluticasone combination on survival, FEV_1, exacerbation rate and quality of life compared with placebo and either of the single components [41] confirming earlier studies evaluating the combination of beta-agonists and corticosteroids [57–59]. A recent analysis of the spirometric re-

cords obtained during the TORCH trial provided very important evidence that the disease can be modified. In that trial, all of the medications (salmeterol, fluticasone and the combination of both) significantly slowed the rate of decline of the FEV_1 compared with placebo [60]. However, at all time points, the lung function was significantly better in the groups receiving the combination than either agent alone. This raises the question of whether triple therapy could not be better than double therapy at least in some patients. A recent trial comprising over 400 patients with symptomatic COPD compared the effectiveness of therapy using tiotropium in all patients combined with placebo in group 1, with salmeterol in group 2 and with the combination of salmeterol and fluticasone in the third group [61]. Although the primary outcome, the exacerbation rate, was similar among the groups, the number of hospitalizations, health related quality of life and lung function was significantly better in the group receiving tiotropium plus salmeterol and fluticasone compared with tioropium plus placebo and tiotropium plus salmeterol. Once symptoms become persistent, therapy should begin with long acting antimuscarinic agent such as tiotropium or long acting beta-agonists twice daily. Once a patient reaches an FEV_1 lower than 60% predicted, and continues to be symptomatic, the evidence from the TORCH trial supports the addition of the combination of ICS and LABA. Continuation of tiotropium is reasonable, given its effectiveness and safety record. I believe that all of the trials support the concept that intense and aggressive therapy does modify the course of the disease including rate of decline of FEV_1 as was shown in the TORCH study and even mortality as was shown both in the TORCH and the UPLIFT trials.

Mucokinetic agents

These drugs aim to decrease sputum viscosity and adhesiveness in order to facilitate expectoration. The only controlled study in the Unite States suggesting a value for these drugs in the chronic management of bronchitis was a multi center evaluation of organic iodide [62]. This study demonstrated symptomatic benefits. Oral acetylcysteine is favored in Europe for its anti-oxidant effects. A large trial failed to document any substantial benefit [63] but patients were not selected by the presence or absence of increased oxidative stress but rather upon the degree of airflow limitation. Genetically-engineered ribonuclease seems to be useful in cystic fibrosis, but is of no value in COPD [1, 2].

Antibiotics

In patients with evidence of respiratory tract infection, such as fever, leukocytosis and a change in the chest radiograph, antibiotics have proven effective [64–68]. If recurrent infections occur, particularly in winter, continuous or intermittent prolonged courses of antibiotics may be useful [68]. The major bacteria to be considered are Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis, although patients with more severe airflow limitation appear to have a higher prevalence of gram negative bacteria such as pseudomona aureginosa. The antibiotic choice will depend on local experience, supported by sputum culture and sensitivities if the patient is moderately ill or needs to be admitted to hospital [1, 2].

Alpha 1-antitrypsin

Although supplemental weekly or monthly administration of this enzyme may be indicated in non-smoking, younger patients with genetically determined enzyme deficiency and emphysema, in practice such therapy is difficult to initiate because of its cost and need of long-term weekly or monthly intravenous administration. Alpha-1 antitrypsin is relatively safe [1, 3, 69, 70]. Although not entirely clear, the best candidates for replacement therapy would be patients with mild to moderate COPD in whom progression of the disease can be stalled.

Vaccination

Ideally, infections of the respiratory tract should be prevented in patients with COPD by using effective vaccines. Thus routine prophylaxis with pneumococcal and influenza vaccines is recommended [12, 71, 72].

Exacerbations

An exacerbation is an event in the natural course of the COPD characterized by a change in the patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management [1, 3, 73, 74]. Care must be taken to rule out heart failure, myocardial infarction, arrhythmias and pulmonary embolism, all of which may present with clinical signs and symptoms similar to exacerbation of COPD. An algorithm describing a rational approach to exacerbations is summarized in figure 2.

The pharmacological therapy of exacerbations is initiated with the same therapeutic agents available for the chronic management of COPD [1, 3]. The most important agents include anticholinergic and beta-agonists aerosols by nebulization.

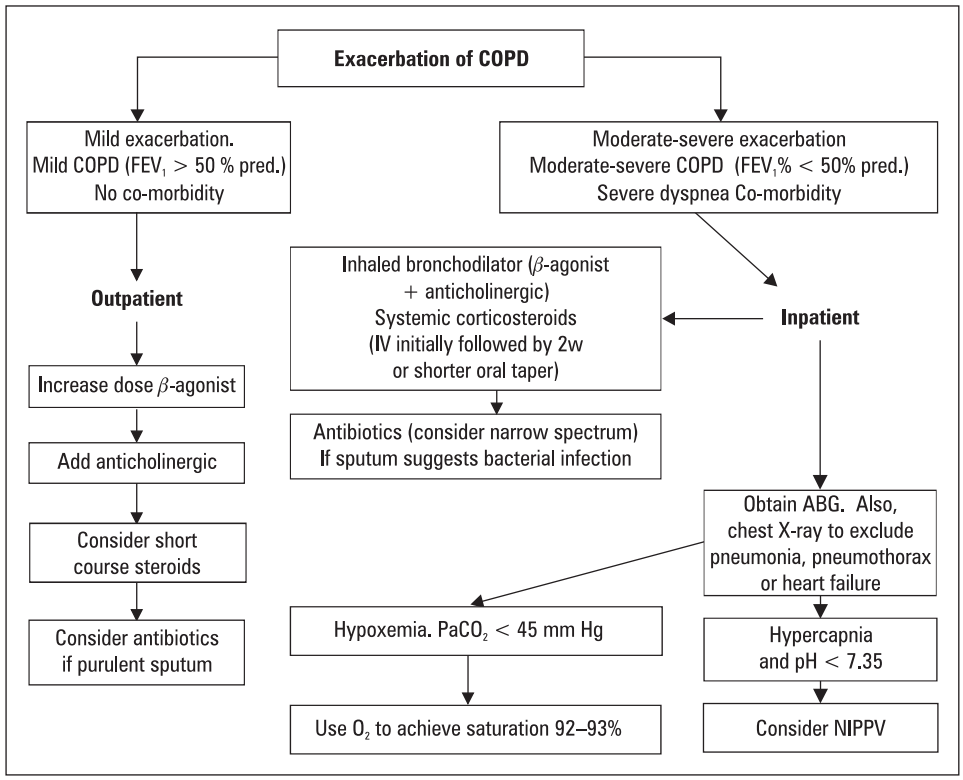


Figure 2. Algorithm describing the approach to patients with COPD who develop exacerbations characterized by increased dyspnea, cough, change in the color or volume of sputum

Several trials [75–77] have proven the usefulness of systemic corticosteroids. It is important to avoid prolonged (over 2 weeks) or high dose therapy since older patients are susceptible to severe complications such as psychosis, fluid retention and a vascular necrosis of bones. Antibiotics have been helpful in purulent exacerbations of COPD [78]. The antibiotics used in severe exacerbation have to be guided by knowledge of the prevalent pathogens in that area [1, 2]. Exacerbations are to be prevented and treated aggressively because they have a prolonged and intense effect on health related quality of life and can result in accelerated loss of lung function [29, 79–81]. Besides pharmacological therapy, some patients may need temporary administration of supplemental oxygen [1, 2]. Ventilatory support should be considered if patients have persistent hypoxemia and/or hypercapnia with low pH (< 7.35) despite maximal medical therapy [1]. Several randomized trials have shown that non-invasive positive pressure ventilation (NIPPV) is beneficial in selected patients with respiratory failure, decreasing the need for invasive mechanical ventilation and its complications, and possibly, improving survival. Certain conditions would make patients less likely to respond to NIPPV. These conditions include respiratory arrest, medical instability (shock, cardiac ischemia), inability to protect the airway, excessive secretions, agitation or uncooperativeness, cranio-facial trauma, or deformity. Despite the usefulness of NIPPV in acute on chronic respiratory failure, its use in stable patients with COPD remains debatable and is not routinely recommended [82, 83].

Conclusions

Over the years, our knowledge about COPD and the capacity to treat it has increased significantly. We now know that COPD is not just a disease affecting the lungs [84] but that it has important systemic consequences [85]. Smoking cessation campaigns have resulted in a decrease in smoking prevalence in the United States. Similar efforts in the rest of the world should have the same impact. The widespread application of long term oxygen therapy for hypoxemic patients has resulted in increased survival. During this time, we have expanded our pharmacological armamentarium to effectively improve lung function and alter its rate of decline, exercise capacity, dyspnea, quality of life and even survival. With all these options a nihilistic attitude toward the patient with COPD is not justified. The evidence supports a positive and aggressive attitude.

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