

Advances in the Management Of COPD Exacerbation

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Abstract

Introduction: Chronic Obstructive Pulmonary Disease exacerbations are considered to be clinically relevant events as regards prognostic and therapeutic applications. However, significant heterogeneity of clinical manifestations and condition prognosis still exist among patients who have acute exacerbations of Chronic Obstructive Pulmonary Disease.

Aim of Work: In this review of published literature, the subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease will be categorized according to causes, the inflammatory biomarkers, clinical presentations, other comorbidities, the rates of developing acute exacerbations of Chronic Obstructive Pulmonary Disease, and other bases.

Methodology: We did a systematic search for recent advances in the management of COPD using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). Most of relevant studies were retrieved and discussed. We only included full articles. The terms used in the search were: Chronic Obstructive Pulmonary Disease, COPD, acute exacerbation, subtypes, management, treatment, prognosis, recent advances.

Conclusions: Acute exacerbation of Chronic Obstructive Pulmonary Disease is a heterogeneous medical condition. Investigations of the different subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease have led to the definition of different subtypes of patients with prognostic and therapeutic importance. Because the variations in the subtypes of each disease is better understood, physicians will be presented with opportunities to develop from a "one size fits all" approach to more individualized approaches, with the main goal of improving care and decreasing, delay in patient improvement and possible complications from unneeded treatments.

Keywords: COPD; Acute Exacerbation; Phenotype; Treatment; Prognosis; Recent Advances

Introduction

Chronic Obstructive Pulmonary Disease exacerbations are considered to be clinically relevant events as regards prognostic and therapeutic applications. However, significant heterogeneity of clinical manifestations and condition prognosis still exist among patients

who have acute exacerbations of Chronic Obstructive Pulmonary Disease. nowadays, several subtypes have been generally applied to describe the characteristics among patients with acute exacerbations of Chronic Obstructive Pulmonary Disease. This has been found to be important and beneficial for the therapy and prediction of clinical outcomes of the condition.

In this review of published literature, the subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease will be categorized according to causes, the inflammatory biomarkers, clinical presentations, other comorbidities, the rates of developing acute exacerbations of Chronic Obstructive Pulmonary Disease, and other bases. This review will focus on advancements in categorization of subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease.

Methodology

We did a systematic search for recent advances in the management of acute exacerbations of Chronic Obstructive Pulmonary Disease using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine(<https://scholar.google.com>). Most of the relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Chronic Obstructive Pulmonary Disease, COPD, acute exacerbation, subtypes, management, treatment, prognosis, recent advances.

Acute exacerbations of Chronic Obstructive Pulmonary Disease is an acute condition that is characterized by a significant rapid worsening of the patient's respiratory clinical situation that is worse than normal day-to-day respiratory alterations and can result in significant changes in administered pharmacological agents [1]. Initially, this definition can look clear. On the other hand, it has multiple caveats and unknowns that can potentially differ based on each patient's clinical manifestations, pathophysiological heterogeneity, and treatment required. Chronic Obstructive Pulmonary Disease subtype is generally known as "a single or multiple diseases attributes that describe the presence of discrepancies between individuals who have Chronic Obstructive Pulmonary Disease as they relate to clinically relevant outcomes". thus, the subtypes must be able to be used to categorize patients into groups with a prognostic importance that allows choosing the best management options in order to get the best clinical outcomes [2]. Taking this into consideration, we can proceed with a more individualized management plan that is made based on the severity of clinical presentation, airflow's obstruction and that is conditioned by the clinical subtype.

Recent findings of published studies suggested that acute exacerbations of Chronic Obstructive Pulmonary Disease can be considered as heterogeneous events and that this heterogeneity may have clinically significant prognostic and therapeutic effects [3]. In a viewpoint that was published in the prestigious journal *The Lancet Respiratory Medicine* [4], the authors suggested a two-axis categorization of acute exacerbations of Chronic Obstructive Pulmonary Disease by considering the pathophysiological and clinical discrepancies of acute exacerbations of Chronic Obstructive Pulmonary Disease. They grouped patients into four categories (E1-E4), each of which may need a different management protocol and have a different short-term risk, and thus the requirement for a different care setting. However, subtype in acute exacerbations of Chronic Obstructive Pulmonary Disease is still in a stage of exploration.

Etiology phenotypes

It is considered to be generally well-known that acute exacerbations of Chronic Obstructive Pulmonary Disease commonly stimulated by the presence of underlying infections with bacteria (homophiles influenza, streptococcus pneumonia, etc.) or viruses (parainfluenza, influenza, etc.) or by other non-infectious environmental (like pollution, temperature, allergens, diet and others) or internal (immune dysregulation) factors. The cause of almost thirty percent of exacerbations of Chronic Obstructive Pulmonary Disease could not be accurately detected [5]. Patients who have detectable respiratory infections have been demonstrated to show a more marked influence on their lungs' functions and longer duration of hospital admissions when compared to patients who have exacerbations of another non-infectious cause [6]. With thorough studies of microorganisms, some studies concluded that there are multiple discrepancies in the clinical presentation, management, and outcomes between cases associated with bacterial infections and cases associated with viral

infections. Symptoms like sore throat, dyspnea, cough, and chills are generally more common in viral infections than they are in bacterial infections. Viral exacerbations are usually linked to higher Interleukin-6 concentrations, lower concentrations of C-Reactive Protein, and longer duration of hospitalization (with an average of nine days) [7].

On the other hand, as for the use of antiviral treatment in management, the current therapies for the virus-induced Chronic Obstructive Pulmonary Disease exacerbations are often not very beneficial [7]. The guidelines for the lower respiratory tract infections management that was published in the year 2011 by the European Respiratory Society pointed out that patients who have acute exacerbations of Chronic Obstructive Pulmonary Disease often were not advised to receive empiric antiviral drugs. whereas, if in the flu season, or at high risk of getting the flu, patients who demonstrate classical influenza clinical manifestations (including hyperthermia, muscle aches, fatigue, and respiratory infection manifestations), if onset is within two days, must receive antiviral drugs as early as possible in their management plan [8].

In cases with bacterial Chronic Obstructive Pulmonary Disease exacerbations, purulent sputum is usual clinical manifestation, as is neutrophil inflammation in both airways and blood. Concentrations of C-Reactive Protein and Procalcitonin (PCT) would generally be higher than those in cases with non-bacterial Chronic Obstructive Pulmonary Disease exacerbations. Several guidelines suggested that acute exacerbations of Chronic Obstructive Pulmonary Disease with the presence of purulence of sputum are considered to be the most important clinical manifestations, which calls for the use of antibiotics [9].

To summarize, understanding the characteristics of several causes of Chronic Obstructive Pulmonary Disease might lead to significant therapeutic implications and give evidence for local surveillance of acute exacerbations of Chronic Obstructive Pulmonary Disease pathogens and ideal choice of antimicrobials agents. This might give physicians some indications to prevent the abuse of antibiotics and antiviral to a significant extent.

Inflammatory phenotypes

Patients with acute exacerbations of Chronic Obstructive Pulmonary Disease also show heterogeneous inflammation. Currently, the diagnosis of acute exacerbations of Chronic Obstructive Pulmonary Disease is generally based on the presence of clinical manifestations. There is a significant lack of quantitative markers. Inflammatory indicators as a kind of quantitative marker are widely used in detecting acute exacerbations of Chronic Obstructive Pulmonary Disease and evaluating outcomes. Systemic inflammatory indicators usually include C-Reactive Protein, PCT, serum amyloid A, surfactant protein D (SP-D), fibrinogen, inflammation cell chemotactic factor, and other markers. All the markers mentioned here will show increased concentrations in patients with acute exacerbations of Chronic Obstructive Pulmonary Disease and show decreased concentrations in recovery phases. As a consequence of these investigations using bioindicators, acute exacerbations of Chronic Obstructive Pulmonary Disease patients were categorized into different subtypes [10,11].

C-Reactive Protein is considered to be one of the most important bioindicators in patients who have acute exacerbations of Chronic Obstructive Pulmonary Disease. A previously published small study demonstrated that a cutoff value of 19.65 mg/L has a sensitivity of seventy-eight percent and a specificity of eighty-four percent to detect a bacterial related acute exacerbations of Chronic Obstructive Pulmonary Disease. In patients who have acute exacerbations of Chronic Obstructive Pulmonary Disease with mucoid sputum, elevated concentrations of C-Reactive Protein [11]. On the other hand, a previous study that was recently published concluded that both PCT and C-Reactive Protein could not distinguish between the presence of bacterial or viral infections in patients with acute exacerbations of Chronic Obstructive Pulmonary Disease requiring emergency department visits [12]. Another study concluded that C-Reactive Protein of 100 mg/mL was correlated with about a fourfold higher possibility of developing complications [13].

PCT is also considered to be an important indicator in patients with acute exacerbations of Chronic Obstructive Pulmonary Disease. PCT levels of 0.5 ng/mL and more are considered to be independently correlated with the presence of bacterial isolation in cases of severe acute exacerbations of Chronic Obstructive Pulmonary Disease. additionally, in patients who needed intubation and/or mechanical

ventilation, PCT concentrations have been found to be independently linked to higher risk for mortality in the intensive care unit [11]. Despite this, a post hoc analysis of a previous trial that did not succeed in showing a beneficial effect of antibiotic drugs in acute exacerbations of Chronic Obstructive Pulmonary Disease proposed that patients who have low PCT levels during acute exacerbations of Chronic Obstructive Pulmonary Disease could also benefit from the use antibiotic therapy [14].

Some other bioindicators, including fibrinogen, troponin T(TNT), Vascular endothelial growth factor (VEGF), 4-hydroxynonenal (4-HNE), Platelet Factor 4 (PF4), β -thromboglobulin, and copeptin, might also reflect to the severity of acute exacerbations of Chronic Obstructive Pulmonary Disease and could be used as predictive prognostic markers. Despite this, there is no valid cut point to enable these indicators to distinguish between patients with different subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease. In the period of acute exacerbations of Chronic Obstructive Pulmonary Disease, the airway inflammation is usually more than that in stable Chronic Obstructive Pulmonary Disease. The most generally used indicators for the presence of inflammation in the airways are fractional exhaled Nitric Oxide (FeNO) and induced sputum analysis. nowadays, FeNO is considered to be the most indicator that has promising results [15]. In fact, previous studies have concluded that patients who have high concentrations of FeNO will show a better response to corticosteroids and better improvement in FEV1 [15]. The cause of these outcomes might be explained by the fact that the FeNO concentrations are associated with the eosinophils levels, that is a relatively good predictor for the response to corticosteroids [16]. In their published study, Antus., *et al.* demonstrated that the ideal cutoff value for FeNO as an indicator for the presence of a significant increase in FEV1 was 26.8 ppb (with a sensitivity of seventy-four percent and a specificity of seventy-five percent) [17].

Additionally, patients could generally be divided into different subtypes based on the type of inflammatory cells present in induced sputum analysis. These inflammatory subtypes are clinically important because of the presence of possible differences in the response to different therapies. Gao., *et al.* detected and defined the following four subtypes: eosinophilic predominant, neutrophilic predominant, pauci-granulocytic predominant, and mixed granulocytic predominant, induced sputum analysis has been shown to have beneficial effect on the management and outcomes of patients with acute exacerbations of Chronic Obstructive Pulmonary Disease [18].

Clinical manifestation of phenotypes

As we mentioned previously, acute exacerbations of Chronic Obstructive Pulmonary Disease is considered as a heterogeneous disease and this heterogeneity could also be reflected in the clinical manifestations. During exacerbations, the most important clinical symptoms are feeling of more dyspnea, more cough, wheezing, increased sputum production, and purulent sputum. currently, the known criteria that are used to categorize acute exacerbations of Chronic Obstructive Pulmonary Disease based on clinical manifestations are the Anthonisen criteria where the authors classified acute exacerbations of Chronic Obstructive Pulmonary Disease into three categories: Type 1 acute exacerbations of Chronic Obstructive Pulmonary Disease that involve the presence of increased dyspnea, sputum volume, and sputum purulence. Type 2 acute exacerbations of Chronic Obstructive Pulmonary Disease that involve any two of the type 1 manifestations, and Type 3 acute exacerbations of Chronic Obstructive Pulmonary Disease that just involve one of those manifestations but present with cough, wheeze, or manifestations that indicate the presence of an upper respiratory tract infection [19].

In Type 1 acute exacerbations of Chronic Obstructive Pulmonary Disease, patients showed better response to the antibiotics and the C-Reactive Protein concentrations in Type 1 were higher than in the other two subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease. It advised that antibiotic therapy is used as early as possible in Type 1 acute exacerbations of Chronic Obstructive Pulmonary Disease [20]. Moreover, before an episode of acute exacerbation of Chronic Obstructive Pulmonary Disease, the prodromes can be relatively varying among different patients. Aaron., *et al.* categorized acute exacerbations of Chronic Obstructive Pulmonary Disease into two distinct groups, such as acute and chronic onsets, according to worsening respiratory manifestations from diary cards [21]. Patients who had rapid onset of acute exacerbations of Chronic Obstructive Pulmonary Disease showed higher mean daily clinical manifestations scores, higher peak clinical manifestations scores, earlier peak clinical manifestations, and shorter median recovery times. More importantly, these prodromes are essential for differentiating the triggers of acute exacerbations of Chronic Obstructive Pulmonary Disease. For example, dyspnea, common colds, sore throat, and cough elevate significantly during a prodromal phase, demonstrating

that the triggers are more likely to be viral. Colds are also linked to longer and more severe acute exacerbations of Chronic Obstructive Pulmonary Disease, and there is no debate that a Chronic Obstructive Pulmonary Disease patient who gets a cold must be considered for early treatment [22]. It is generally well known that the severity clinical manifestations of acute exacerbations of Chronic Obstructive Pulmonary Disease are evaluated not only by assessing lungs functions, but also with CAT, mMRC questionnaires, and CCQ that also have great benefits in evaluating the condition severity and estimating the severity of exacerbations [23].

Frequent exacerbations phenotypes

The frequency of acute exacerbations of Chronic Obstructive Pulmonary Disease generally varies among different patients. currently, a “frequent exacerbator” subtype has been introduced and evaluated in several clinical studies. The pathology underlying the frequent exacerbations subtype includes the presence of increased airway and systemic inflammation, dynamic lungs hyperinflation, alterations in the lower airway bacterial colonization, relatively higher susceptibility to getting viral infection, and higher risks from other comorbid extra pulmonary diseases. On the other hand, as for the criteria of frequent exacerbators, there is no standard definition currently. Most clinical research distinguished frequent exacerbators as those who have a higher rate of exacerbations than the median of the study population each year, those who need the administration of oral antibiotic drugs or oral glucocorticoid treatment, or those needing to be hospitalized at least twice a year as a result of acute exacerbations of Chronic Obstructive Pulmonary Disease [24].

In the ECLIPSE study of susceptibility to develop acute exacerbations of Chronic Obstructive Pulmonary Disease, about twenty percent of patients with GOLD stage II disease and as many as forty-seven percent of those with stage IV condition were categorized as usual exacerbators (which is defined as two or more exacerbations every year). A previous study has demonstrated that patients with multiple exacerbations and those with rare exacerbations tended to be in the same category of exacerbation frequency for the full three years of the study, although some patients might have shifted from one group to other [24]. This stability may propose that the rate of exacerbations is associated with the susceptibilities of COPD patients. A recent review has demonstrated the potential causes of the frequency of acute exacerbations of Chronic Obstructive Pulmonary Disease. It demonstrated that patients with high levels of inflammation, with increased susceptibility to viral infection and bacterial colonization, rapid FEV1 decline, poor health status, and more comorbidities have a higher risk of acute exacerbations of Chronic Obstructive Pulmonary Disease [25]. In addition, several other studies also showed some important factors that are associated with the frequency of acute exacerbations of Chronic Obstructive Pulmonary Disease. Patients who have a history of frequent acute exacerbations of Chronic Obstructive Pulmonary Disease show a higher increase in both the systemic inflammation and the inflammation of airways [26], faster reduction of lungs functions, poorer quality of life [27] and increased rates of mortality [28], compared to other patients who have less frequent acute exacerbations of Chronic Obstructive Pulmonary Disease.

On the other hand, the categorization of the frequent exacerbations subtype is usually dependent on clinical records with or without patient recall, and the history of acute exacerbations of Chronic Obstructive Pulmonary Disease is given by the patients themselves. It is thus essential to ask about the history of acute exacerbations of Chronic Obstructive Pulmonary Disease during the clinical interview in order to detect patients who might need further management. The management advised in GOLD is also not the same for frequent exacerbators, such as long-term inhalation of corticosteroids.

Adopting anti-inflammatory drugs and anti-infection drugs in frequent exacerbators might be non-therapeutic. In the summary of the GesEPOC [29], patients who are frequent exacerbators are more subdivided into the following two subgroups: those who have emphysema predominant or those who have with chronic bronchitis predominant. The management for the two types also differs. For the emphysema predominant subtype, the basic management is the use of long-acting bronchodilators and in some cases with inhaled corticosteroids. The bronchitis-predominant exacerbator subtype patients, they might be managed with bronchodilators and inhaled corticosteroids, and in contrast to exacerbators with emphysema, they respond to treatment with Roflumilast. Some specific cases with frequent exacerbations might respond to long-term treatment with macrolides [30] and when inhaled corticosteroids cannot be used, mucolytics might be beneficial in decreasing the rates of exacerbations [31].

However, another study demonstrated that whatever the reducing degree of lungs functions, it is advised that patients with frequent acute exacerbations of Chronic Obstructive Pulmonary Disease use inhaled corticosteroids combined with the use of bronchial relaxation drugs could significantly decrease the rate of acute exacerbations of Chronic Obstructive Pulmonary Disease and significantly improve the quality of life [32]. The use of inhaled corticosteroids is still a controversial topic that requires large-scale, randomized, controlled trials in order to evaluate its potential benefits. In summary, the frequent exacerbation subtype as a special subtype is of great importance and physicians must develop a professional management for subset of patients, that could be used for health economic purposes [33].

Conclusions

Acute exacerbation of Chronic Obstructive Pulmonary Disease is a heterogeneous medical condition. Investigations of the different subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease have led to the definition of different subtypes of patients with prognostic and therapeutic importance. Because the variations in the subtypes of each disease is better understood, physicians will be presented with opportunities to develop from a "one size fits all" approach to more individualized approaches, with the main goal of improving care, management, outcomes and decreasing, delay in patient improvement and possible complications from unneeded treatments. On the other hand, research into acute exacerbations of Chronic Obstructive Pulmonary Disease phenotypes is still in its infancy, and with a detailed study of the subtypes of acute exacerbations of Chronic Obstructive Pulmonary Disease, it is possible that a new subtype allowing individualized treatment and estimation of prognosis will be found. This means that there is an urgent need for well-designed clinical studies focused on acute exacerbations of Chronic Obstructive Pulmonary Disease subtypes.

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