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REVIEW

Identification and assessment of COPD exacerbations

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Abstract Chronic Obstructive Pulmonary Disease (COPD) exacerbations play a central role in the disease natural history of the disease, affecting its overall severity, decreasing pulmonary function, worsening underlying co-morbidities, impairing quality of life (QoL) and leading to severe morbidity and mortality. Therefore, identification and correct assessment of COPD exacerbations is paramount, given it will strongly influence therapy success. For the identification of exacerbations, several questionnaires exist, with varying degrees of complexity. However, most questionnaires remain of limited clinical utility, and symptom scales seem to be more useful in clinical practice. In the assessment of exacerbations, the type and degree of severity should be ascertained in order to define the management setting and optimize treatment options. Still, a consensual and universal classification system to assess the severity and type of an exacerbation is lacking, and there are no established criteria for less severely ill patients not requiring hospital assessment. This might lead to under-reporting of minor to moderate exacerbations, which has an impact on patients' health status.

There is a clear unmet need to develop clinically useful questionnaires and a comprehensive system to evaluate the severity of exacerbations that can be used in all settings, from primary health care to general hospitals.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) exacerbations play a central role in the natural history of the disease, affecting its overall severity, decreasing pulmonary function, worsening underlying co-morbidities, impairing quality of life (QoL) and leading to severe morbidity and mortality.[1,2] Indeed, progression of COPD is highly determined by the frequency and severity of exacerbations, deriving short and long-term clinical consequences and potentially more aggressive patterns of disease.[1]

Exacerbations vary greatly in terms of severity at clinical presentation, etiological factors and response to treatment, reflecting the heterogeneity of the disease.

The definition of COPD exacerbation has evolved over time, from more specific to broader definitions, based on symptoms or event-based, according to treatment needed or to health care resources used.[3] Lack of expert consensus may be responsible for this shift toward generic definitions. The large clinical and physiopathological heterogeneity of COPD exacerbations between patients, and within the same patient, leads to the absence of an evidence-based or generally agreed definition.[3]

As such, a widely accepted definition is indeed of paramount importance, as it would determine the rate of reported exacerbations, facilitating a more precise clinical and research approach to the issue.

Definition of exacerbation

Despite growing evidence supporting the importance of COPD exacerbations in disease burden and the implications on its natural history, many remain unreported and untreated by health care professionals.[3,4] It is known that unreported exacerbations have an impact on the health status of patients, although they are usually shorter in duration and with lower severity.[2] The early recognition of exacerbations allows for early therapy, leading to faster recovery, better QoL and reduced risk of hospitalization.[5]

The choice of a definition for exacerbation determines the rate of the observed events, permitting better treatment. There are numerous definitions of COPD exacerbations, of which we will only mention a few: (a) a worsening of at least one key symptom (dyspnea, sputum amount, sputum color) for at least 2 consecutive days[6]; (b) a sudden symptomatic worsening that is beyond daily variability[7]; (c) an unscheduled or emergency visit due to worsening of COPD or a course of oral steroids[8]; (d) the use of antibiotics, steroids, or both or hospital admission related to worsening respiratory symptoms[9]; (e) a sustained acute/subacute worsening of the severity or frequency of symptoms such as dyspnea, cough or sputum production, with increased QoL impairment, lasting at least 3 days, which prompts the patient to seek medical attention or leads to a change in medication.[1]

Generally, most definitions include one of the following criteria: need to use health care resources; the use of additional therapy (antibiotics or corticosteroids); deterioration of two major symptoms or one major symptom and two minor symptoms (Anthonisen criteria; major symptoms: dyspnea, sputum volume, sputum purulence; minor symptoms: cough, wheezing, sore throat, coryzal symptoms)[10]; deterioration of one major symptom; change in two or more symptoms; or a combination of the previous criteria.[11] Centralizing the definition in the occurrence of major symptoms has the risk of not identifying exacerbations with need of hospitalization, as well as the total number of exacerbations. On the other hand, including minor symptoms will increase the number of patients treated, and decrease the number of patients with need of in-hospital treatment.[11]

Less usually, definitions are event-based, taking into account the necessity to search health care resources. However, these definitions tend to fail to capture all exacerbations, underestimating true rates by 50%, as patients do not always seek medical attention.[6] Moreover, they depend on the organization of each specific health system and resources.

Currently, the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 defines an exacerbation as an acute worsening of respiratory symptoms that results in additional therapy.[2]

The authors acknowledge the difficulty in establishing a consensual definition of COPD exacerbation and favor the definition provided by GOLD 2017[2] after excluding worsening of comorbidities. It has the advantage of increasing the number of exacerbations detected, allowing for early treatment even if at the expense of over-diagnosis.

Types of exacerbations

COPD is a highly heterogeneous disease, during both stable and acute states, with an extensive range of clinical presentations, and prevention of exacerbations is usually based on the phenotype of stable disease.

Different COPD exacerbations phenotypes have been identified, with specific inflammatory profiles and biomarkers, and there is some evidence that these profiles show diverse clinical patterns in terms of prognosis and response to treatment. Therefore, identifying these phenotypes and developing a phenotype-specific treatment approach and prevention strategies has the potential to improve outcomes.

Etiologically, exacerbations of COPD can be precipitated by several factors. The most common causes appear to be respiratory tract infections, either viral-predominant, bacteria-predominant, eosinophil-predominant or mixed.[2,3,7,12–16] Exacerbations may also be pauci-inflammatory,[16] or mediated by a decrease in mean ambient temperatures,[17] air pollution and comorbidities.[2,7] Poor compliance to maintenance therapy has also been shown to lead to exacerbations.[2,18,19] However, in one-third of severe COPD exacerbations the cause cannot be identified.[2,7]

Some authors report that approximately 70% of exacerbations may have viral origin,[7] whilst others report that bacterial infections account for more than 50% of the acute episodes.[14,15] Bacterial infection is usually mediated by *Haemophilus influenza, Moraxella catarrhalis, Streptococcus pneumonia, Staphylococcus aureus* and *Pseudomonas*

aeruginosa.[16] The occurrence of mixed viral–bacterial infections has also been confirmed in several studies.[7,12–14]

At least 50% of patients have bacteria in their lower airways during COPD exacerbations, but a significant proportion of these patients also have bacteria colonizing the respiratory tract in the stable phase of the disease.[20] There is some indication that the bacterial burden increases during some exacerbations and that the acquisition of new bacterial strains is associated with exacerbation episodes.[2] The probability of attributing an exacerbation to a bacterial infection is established by the Anthonisen criteria, and is associated with the following: increase in the degree of dyspnea, increase in sputum production and increase in sputum purulence.[7] Bacteria-associated exacerbations can also be identified by biomarkers such as sputum IL-1β (sensitivity of 90% and a specificity of 80%) and serum C-reactive protein (CRP) (sensitivity of 60% and a specificity of 70%).[16] As for viral predominant exacerbations, the same authors describe CXCL10 as the best biomarker, with a sensitivity of 75% and a specificity of 65%.[16]

There is also a subset of patients in whom an eosinophilic airway inflammation predominates, which is associated with higher all-cause mortality.[16] These patients manifest increased eosinophilic peripheral and sputum counts, and may represent the subgroup amenable to systemic corticosteroids-based treatment.[16]

Less frequently, patients reveal a pauci-inflammatory pattern, with limited changes in the inflammatory profile, as well as low sputum mediator concentrations related to bacterial, viral or eosinophilic etiologies.[16]

Comorbidities can act as etiological factors, triggering exacerbations but also mimicking them.[7] These conditions include pneumonia, pulmonary embolism, congestive heart failure, cardiac arrhythmia, pneumothorax, and pleural effusion, need to be considered, and treated if present.[2,19]

A diagnosis of certainty or probability must be made, a differential diagnosis must be performed and an etiologic diagnosis must be established.[7] Etiology can be partially determined from the diary card and this emphasizes the importance of careful monitoring of patients to detect exacerbations.[3]

Identification of exacerbations

The early identification of exacerbations is of utmost importance since these events have a great impact on patients' morbidity, mortality and quality of life.[2,6,7,21] Less than one third of exacerbations are estimated to be reported, with the number of symptoms at onset being the most important predictor of reporting an exacerbation,[6] meaning if more symptoms are present it is more likely that the patient reports an exacerbation. Therefore, a specific questionnaire that captures the onset of an exacerbation is necessary.

Questionnaires can be self-administered, based on self-perception, symptoms and quality of life records, and can detect significant clinical changes.[22–26] Scales that are symptom-based seem to be better suited to support clinical decisions.[27–29]

Several questionnaires exist for the assessment of both symptoms and quality of life in COPD patients, namely the modified Medical Research Council (mMRC), the Clinical COPD Questionnaire (CCQ), the COPD Assessment Test (CAT), and the health-related quality of life St. George's Respiratory Questionnaire (SGRQ).[2,6]

Questionnaires such as the mMRC, CCQ and CAT may be helpful in the evaluation of exacerbations.[1] Although a specific CAT score increase, suggesting the presence of an exacerbation, has not been validated,[7] two studies have shown that this questionnaire is sensitive to the change in health status associated with COPD exacerbations,[30,31] and that changes in CAT correlate well with changes in SGRQ.[31] CAT can indeed be used to predict COPD exacerbations, health status deterioration, depression and mortality.[27] Another study proposes that, in primary care, a shortened and more specific version of the CCQ could be used to screen for exacerbations by measuring dyspnea, coughing and phlegm[32] production. CCQ was found to be a promising low burden method to detect unreported exacerbations, in a multicenter prospective study.[24] Daily symptom diaries (eDiary) have also been used both in clinical practice and in the research setting to identify and predict symptoms worsening. In the FLAME and SPARK studies exacerbations have been captured using this tool.[33,34] One study using smartphone-based collection of COPD symptom diaries enabled near-complete identification of exacerbations at inception.[35] Regarding the EXAcerbations of Chronic pulmonary disease Tool (EXACT), it has been found that exacerbations fully met the criteria for an EXACT event, in a patient-report outcome diary, however this is more useful for research than for clinical practice.[23]

It is recognized that further research is needed to identify new features associated with symptoms and physiological signals that may enable the early detection of deteriorations in COPD.[21] As most questionnaires remain of limited clinical utility, the panel recommends using symptom scales as they seem to be more valuable.

Severity and referral

The degree of exacerbation severity should be ascertained in order to define the management setting.[7] However, a consensual and universal severity classification system for an exacerbation is still lacking[1] and there are no established criteria for the assessment of severity in less severely ill patients, not requiring hospital care.[3]

The American Thoracic Society/European Respiratory Society severity scale can be used in the assessment of exacerbations: level I (mild) patient is treated at home; level II (moderate) patient requires hospitalization; and level III (severe) exacerbation leads to respiratory failure, one of the indications for intensive care.[36] Other severity scales exist, e.g., in mild exacerbations the patient is treated at home, in moderate exacerbations the patient is medicated with systemic corticosteroids, antibiotics or both, and severe exacerbations require hospital admission or emergency treatment.[34] Yawn et al. propose an algorithm for the management of exacerbations of different severities.[36]

The GOLD 2017 recommendations classify exacerbations as mild – treated with short acting bronchodilators only, SABDs, moderate – treated with SABDs plus antibiotics and/or oral corticosteroids, severe – patient requires hospitalization or visits the emergency room; these exacerbations

may also be associated with acute respiratory failure – and very severe if they require admission to an Intensive Care Unit (ICU).[2] In 2013, Trigueros Carrero proposed a more complex classification, grading exacerbations in mild, moderate, severe and very severe, based on past medical history, history of present illness, clinical examination features and severity of stable COPD.[7] The panel considers that despite being an interesting classification, comprising a larger complexity of characteristics, it has limited prognostic value and has not been validated for clinical use.

Potential indications for hospitalization assessment focus on acute respiratory failure, severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion and drowsiness, failure to respond to initial medical treatment, presence of serious comorbidities and insufficient home support.[2] The NHS protocol for management of COPD exacerbations in primary care also recommends referral to a Hospital in severe exacerbations as patients need to be assessed by a specialist in adequate settings.[37] One study proposes that CAT provides a reliable score, with scores increasing at the time of exacerbation and reflecting its severity.[38]

For patients who are hospitalized, the GOLD 2017 guidelines propose to differentiate those with and without respiratory failure, and, among the former, between those who have and do not have a life-threatening disease.[2] It is a simple classification, however of limited operational utility, and it is the panel's opinion that it does not help in clinical decision making.

The panel recommends that a useful classification should include features of the baseline disease characteristics as well as characteristics of clinical worsening.

Management

Acute phase

The optimal management should take into account not only the severity but also the type of exacerbation, in order to select the appropriate treatment and to improve outcomes. A standardized color chart is available to differentiate between bacterial and non-bacterial exacerbations by sputum color, which separates exacerbations that can be safely managed without an antibiotic from those requiring an antibiotic.[3,7,12] This color chart has a 94.4% sensitivity and a 77.0% specificity.[39] Sputum color can be reproducibly classified by trained technicians using this standardized color chart.

An exacerbation associated with purulent sputum production will be associated with a large bacterial load, and should be responsive to appropriate antibiotic treatment, while an exacerbation associated with a common cold or with upper respiratory tract symptoms is likely to be viral in origin.[3,7,12] Exacerbations associated with viral infections are related to more airway inflammation than non-viral ones, and thus, it would be expected that these exacerbations may be more responsive to therapy with anti-inflammatory agents.[3] CRP levels have been reported to be higher in bacterial infections, and may therefore be a useful biomarker for the management of exacerbations in patients with severe disease.[14] Procalcitonin has been extensively evaluated as a biomarker for bacterial acute exacerbations of COPD and it has been shown that it can be safely used to reduce inappropriate antibiotics in acute exacerbations of COPD.[40] A high level of eosinophils is a biomarker of exacerbations that respond better to corticosteroid therapy.[16]

Determining exacerbation frequency is important for treatment success with empirical antibiotic selection,[41] since different bacterial etiology has been observed depending on the number of annual episodes.[13,41]

Management of acute exacerbations should be based on their severity.

Prevention of future exacerbations

Strategies for the prevention of exacerbations include non-pharmacological and pharmacological approaches. Smoking cessation, influenza and pneumococcal vaccination, early pulmonary rehabilitation, and encouragement of patients to maintain physical activity are proven strategies. Regarding pharmacological treatment, LABA + LAMA are the preferred option for symptomatic patients with ICS, macrolides or phosphodiesterase inhibitors reserved for specific patient sub-populations.[2,4,36]

A change of $\leq$4 points in the CAT score at discharge compared to that obtained at hospital admission due to a severe exacerbation predicts therapeutic failure, namely a new exacerbation, hospital re-admission or death in the subsequent three months.[42] CAT seems to be a simple tool to assist in the identification of patients at increased risk of further exacerbations.[22] Viral exacerbations do not seem to be associated with a higher rate of successive exacerbations or mortality during the following year.[43]

Conclusions

The identification and correct assessment of COPD exacerbations is vital, given that it will strongly influence therapy success and impact on patients' morbidity, mortality and quality of life. Currently, there is a lack of clinically useful questionnaires and a widespread classification system to assess severity of exacerbations that can be used in all settings, which might not only lead to under-reporting of less severe exacerbations but may also hamper their proper management.

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Conflicts of interest

The authors declare collaborating and receiving fees from Novartis and other pharmaceutical companies other than Novartis either through participation in advisory board or

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