International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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Open Access Full Text Article REVIEW

COPD Exacerbation Syndrome: The Spanish Perspective on an Old Dilemma

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Abstract: The definition of exacerbation of COPD as a syndrome, as proposed by the Spanish COPD guidelines (GesEPOC) 2021 update, and the consequences that this implies, have direct implications on patient care. This review analyzes this novel vision of the COPD exacerbation syndrome, its rationale, and its clinical implications, as opposed to the traditional symptoms-based or event-based definitions. An exacerbation conceived as a syndrome provides us with an umbrella term to include a set of diverse alterations, which, either in isolation or more frequently in combination, are clinically expressed in a similar way in patients with COPD. In patients with COPD, this occurs as a consequence of worsening expiratory airflow limitation or the underlying inflammatory process, producing a worsening in symptoms with respect to the baseline situation. This definition therefore assumes a worsening in at least one of the two key physiopathological markers, lung function and inflammation. The main features of this new physiopathological proposal include a syndromic approach with narrower differential diagnosis, the use of several biomarkers, treatable traits to better guide treatment, and a new severity classification. Further research is needed to examine the role of eosinophils in this context, but currently, the early results are promising. The evaluation of severity is key in the multidimensional characterization of exacerbation and the GesEPOC 2021 proposes new approaches and also recommends the use of multidisciplinary scores for severity categorization in patients. Finally, another innovation in the GesEPOC 2021 refers to the recurrence of exacerbations, which has implications for disease prognosis or long-term clinical impact which need to be elucidated in further studies.

Keywords: COPD, exacerbations, syndrome, guideline

Introduction

Our understanding of chronic obstructive pulmonary disease (COPD) has advanced apace in recent decades, and the options for a more comprehensive and personalized approach to the disease have led to a paradigm shift that is continually changing.[1] Beyond the recent innovations in pharmacological treatments,[2,3] various aspects of non-pharmacological treatments, including exercise programs,[4] vaccinations, surgical techniques,[5] home therapies[6] or the technologies of information and communication,[7] have allowed us to provide patients with more satisfactory, multidimensional care.[8] Consequently, the recommendations on the management of the disease have been recently updated with these new recommendations in the light of the available evidence.[9,10]

Recently, the Spanish National Guideline for COPD management (GesEPOC) released the latest 2021 version, in 4 different documents covering the treatment of stable COPD, exacerbations, comorbidities and palliative care, and non-pharmacological interventions.[10–13] Altogether, these documents reflect the current challenges in the management of the disease and the possible solutions provided by the group of Spanish experts following evidence-based medical principles. In particular, many proposals are considerably innovative, including the risk stratification of patients, clinical phenotyping for selection of treatment, the concept of disease control in the escalation of treatment, the selection of treatable traits for advanced, complex patients, a new paradigm for the identification and classification of exacerbations, the organization of different comorbidities, the evidence for palliative care and the implementation of non-pharmacological approaches.

Received: 15 October 2022
Accepted: 30 November 2022
Published: 29 December 2022

One of the key aspects which may be seen as innovative for the scientific community is the GesEPOC 2021's approach to the concept, categorization, and management of exacerbations. The definition of exacerbation as a syndrome, and the consequences that this involves, have direct implications on the patient that are worth explaining in more detail. In the following lines, we intend to explain this new vision of COPD exacerbation, its rationale, and its clinical implications, in order to help the clinician to identify, manage and prevent these adverse events in real clinical practice.

Current Approaches to a Definition

Within the clinical expression of COPD, its chronic and often progressive clinical course is frequently altered by an acute worsening of the symptoms, usually accompanied by an increase in inflammatory mediators and a functional worsening known as exacerbations. Although clinicians are usually clear about what an exacerbation is, the operational definitions given so far have not yet received unanimous agreement from the scientific community.[14–16] The importance of clearly identifying an exacerbation lies not only in its short- and long-term clinical impact: an exacerbation is also in many cases the initial reason why a patient turns to the health services, which allows the case to be diagnosed.[17] Consequently, in recent years, different definitions of exacerbation have been proposed (Table 1). These definitions are not entirely compatible, contain subtle nuances and have been subject to considerable controversy.

Symptoms-Based Vs Event-Based Definitions

According to the 2022 Global Obstructive Lung Disease Initiative (GOLD) document, a COPD exacerbation is defined as an acute worsening of respiratory symptoms that requires additional treatment.[18] This definition, mainly based on symptoms and the therapy used to relieve them, is extremely simple and non-specific, but has remained unchanged over the last quarter of a century. In a position paper published in 1995, the American Thoracic Society recognized that an exacerbation was difficult to define, and its pathogenesis was very poorly understood.[19] At that time, the document already highlighted the need for a standardized definition that would be universally accepted and useful for clinicians, researchers, and other health providers. Five years later, responding to that challenge, a group of experts defined an exacerbation as a sustained worsening of the clinical condition of the patient with COPD, going beyond the variations of symptoms, and which is acute in its onset and necessitates a change in the habitual medication.[20] Since that initial proposal, more than two decades have passed and our knowledge of COPD has substantially improved. It is now understood as a complex and heterogeneous syndrome that requires an increasingly personalized approach.[21] Nevertheless, the concept, diagnosis and management of acute exacerbations have seen relatively few changes.

Despite being simple and easy to adopt, the GOLD proposal for a symptom-based definition of exacerbation has several limitations. First, it is highly non-specific, which can lead to it being confused with other diseases it must be differentiated from, such as pneumonia, heart failure, acute ischemic heart disease, arrhythmias, pulmonary embolism, or anxiety, which are some of the other concomitant diseases that may produce similar clinical expression. Of note, differential diagnosis is not easy and frequent overlapping occurs. For example, about one of five patients admitted to hospital with a diagnosis of exacerbation show biomarkers of ventricular dysfunction or ischemic damage.[22,23] Pulmonary embolism has been detected in 16% of exacerbations of unknown etiology[24] and up to 27% of patients

Table 1 Definitions of Exacerbation According to Different Recommendation Documents

Document	Definition
GOLD 2022[74]	Acute worsening of respiratory symptoms that results in additional therapy.
GesEPOC 2021[11]	Episode of clinical instability that occurs in a patient with COPD as a result of the aggravation of the expiratory limitation to airflow or the underlying inflammatory process and is characterized by an acute worsening of respiratory symptoms with respect to the baseline situation of the individual.
Rome 2021[40]	In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over#14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the airways.

have shown infiltrates on computed tomography, which are not detected by a chest X-ray.[25] Computed tomography is not a routine examination, so many of these infiltrates (in many cases, caused by pneumonia) could be misdiagnosed as COPD exacerbations. Second, the underlying biological or physiopathology mechanism is not taken into account in the GOLD definition, even though inflammation (pulmonary or systemic) and functional changes, such as a worsening of expiratory airflow limitation, air trapping and hyperinflation, seem to be key symptoms.[26] Third, it does not recognize the heterogeneity and complexity of the exacerbation, although some different phenotypes or endotypes have been described.[27,28] Fourth, although the GOLD definition includes the need for "additional treatment", some patients suffer from worsening of respiratory symptoms at home without contact with their doctors, or using different medications.[29] Despite this, many clinical trials define exacerbations and their severity based on the treatment used (event-based definition).[30,31] Finally, the treatment has not changed in decades, probably because this non-specific definition has led to inconsistent research. Bronchodilators, systemic steroids, or antibiotics are prescribed to nearly all patients, regardless of their interindividual differences.

On the other hand, certain initiatives such as the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) have attempted to standardize the method of studying these events through the development of electronic diaries (again, using a symptoms-based definition).[32,33] These types of instruments have been specially developed for use in clinical research, and their transfer to clinical practice entails certain difficulties. Using these diaries, it has been possible to evaluate the clinical course of an exacerbation, observing that about half of the patients have an abrupt onset in a few hours, while the other half show a more insidious onset over a period of a few days or weeks.[33] Some intrinsic concepts of exacerbations have also been qualified with this methodology, by differentiating the intensity of symptoms, the duration, and the frequency of the events. Among these, the frequency of exacerbations is the one that has received the most attention. On average, COPD patients experience 1–4 exacerbations per year. However, their distribution is highly variable. While some people do not experience these episodes at all, others experience them repeatedly (termed in the GesEPOC as the exacerbator phenotype).[34] In addition, many of these episodes occur in clusters,[35] raising the question of whether each one constitutes a new exacerbation or they are simply incomplete resolutions of one single episode, which adds to the confusion.

All in all, using symptoms-based definitions or event-based definitions, scientific progress over the last few decades has been heterogeneous and inconsistent, and has led to unsuccessful clinical outcomes. Today, despite using treatment recommended by current guidelines, there is still a high proportion of patients showing recurrent exacerbations,[36] therapeutic failures are observed in one of four patients, the readmission rate at 30 days is 20%, and in-hospital mortality is about 5%, increasing to 11% at 3 months.[37–41] Therefore, we urgently need a new strategy for COPD exacerbations, which should start by redefining the existing definition.

The Rome Definition

To overcome the limitations related to this symptoms-based definition, an international group of experts has recently published a new consensus proposal, the so-called Rome definition.[40] According to this initiative, an exacerbation in a patient with COPD is defined as

> an event characterized by dyspnea and/or cough and sputum that has worsened within the last 14 days, which can be accompanied by tachypnea and/or tachycardia, and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other airway insults.

The main novelties of this proposal are: (1) a time limit (less than 14 days) has been established; (2) the underlying pathophysiological process has been included, considering tachypnea and tachycardia as important clinical biomarkers; and (3) the main triggering factors are also indicated. The time limit is of interest, since, according to some studies, the time from onset of worsening respiratory symptoms to full exacerbation expression ranged from 0–5 days in 90% of patients, with an overall range of 0–14 days.[33]

In our opinion, the Rome proposal represents an important step forward in the challenging task of establishing a more precise definition for exacerbation. However, there are still several unresolved issues. First and probably foremost, this is not an operational definition: in other words, it does not establish specific criteria for diagnosis, with the exception of the

time limit. The authors have shown that an exacerbation "may be" accompanied by tachypnea and/or tachycardia, as differential pathophysiological elements. However, both clinical signs can appear in many other acute respiratory and non-respiratory diseases, and are therefore non-specific. There are no precise thresholds to distinguish the exacerbation through respiratory or heart rates. The panelists also proposed cutoff points to assess severity classification, but not for the definition itself. Second, the Rome proposal also noted that exacerbations are "often associated" with increased local and systemic inflammation.[40] However, some studies have described 'pauci-inflammatory' exacerbations in a non-negligible proportion of patients ranging between 14–40%.[27,28] This scenario leaves us with uncertainties about whether these non-inflammatory episodes fall outside the Rome definition. Finally, the definition includes precipitating factors as airway infection, pollution or "other insults", the latter being a very open, non-specific term.

Like the GOLD definition, the Rome proposal does not recognize overlapping with other concomitant diseases which also worsen respiratory symptoms. These other diseases are not considered as exacerbations, and a broad differential diagnosis has been proposed.[11] Nonetheless, the panelists acknowledge that on many occasions these other diseases can coincide with the exacerbation and influence the evolution of each one (38).

The Rationale Behind the COPD Exacerbation Syndrome

Probably one of the most relevant conceptual changes in exacerbations is the new definition in the GesEPOC 2021,[11] which uses the term COPD exacerbation syndrome (CES). The Spanish guideline defines the CES as an "episode of clinical instability that occurs in a patient with COPD as a consequence of worsening expiratory airflow limitation or the underlying inflammatory process and is characterized by an acute worsening of respiratory symptoms with respect to the patient's baseline situation". The GesEPOC recognizes that, from the pathophysiological point of view, an exacerbation is a complex, heterogeneous event that includes a set of diverse alterations, which either in isolation or more frequently in combination, are clinically expressed in a similar way in patients with COPD. Additionally, although not included in the definition, the GesEPOC concept also proposes we consider potential treatable traits in each patient in order to better guide their treatment. Altogether, the new physiopathological proposal, a syndromic approach with a narrower differential diagnosis, and the use of several biomarkers, treatable traits and a new severity classification are some of the major innovations proposed by the GesEPOC 2021.[11]

Physiopathology

As in the Rome proposal, the underlying physiopathology of exacerbation is also included in the GesEPOC definition, although two key elements are highlighted here: (1) the increase in inflammation (airway or systemic) and/or (2) the worsening of expiratory flow limitation.[11] This detail has important consequences for the diagnosis, since to confirm the presence of a CES, one or two key pathophysiological mechanisms must first be documented, as some patients may suffer an exacerbation without a clear increase in inflammation.[27,28] In these cases, the worsening of symptoms may be justified by changes in lung mechanics, including the narrowing of the airway, air trapping or hyperinflation.[26,41] On other occasions, increased inflammation can be observed without a worsening in expiratory airflow limitation. For this reason, the GesEPOC definition requires that at least one of these two key mechanisms occur. In our opinion, this conceptual change will make it possible to better define what is or what is not an exacerbation, thus increasing the specificity of the diagnosis.

Although inflammation and airflow limitation are key, the new definition does not exclude the co-participation of other pathogenic mechanisms under a syndromic concept. Systemic inflammation has been associated with muscular, nutritional, or cardiovascular manifestations that may also be present in these patients, which condition the final clinical expression.[42] Dynamic hyperinflation has also been associated with cardiovascular repercussions. In summary, Figure 1 shows the main pathophysiological mechanisms involved. However, we must bear in mind that, although it is conceptually attractive to have this dual inflammatory and functional vision, in some care settings it may not always be possible to have access the necessary on-site diagnostic tests in order to confirm a greater or lesser degree of involvement of each of these components. This confirms the importance of the differential diagnosis and the evaluation of overlapping comorbidities in this clinical scenario. In addition, thanks to the new syndromic approach, the differential diagnosis is

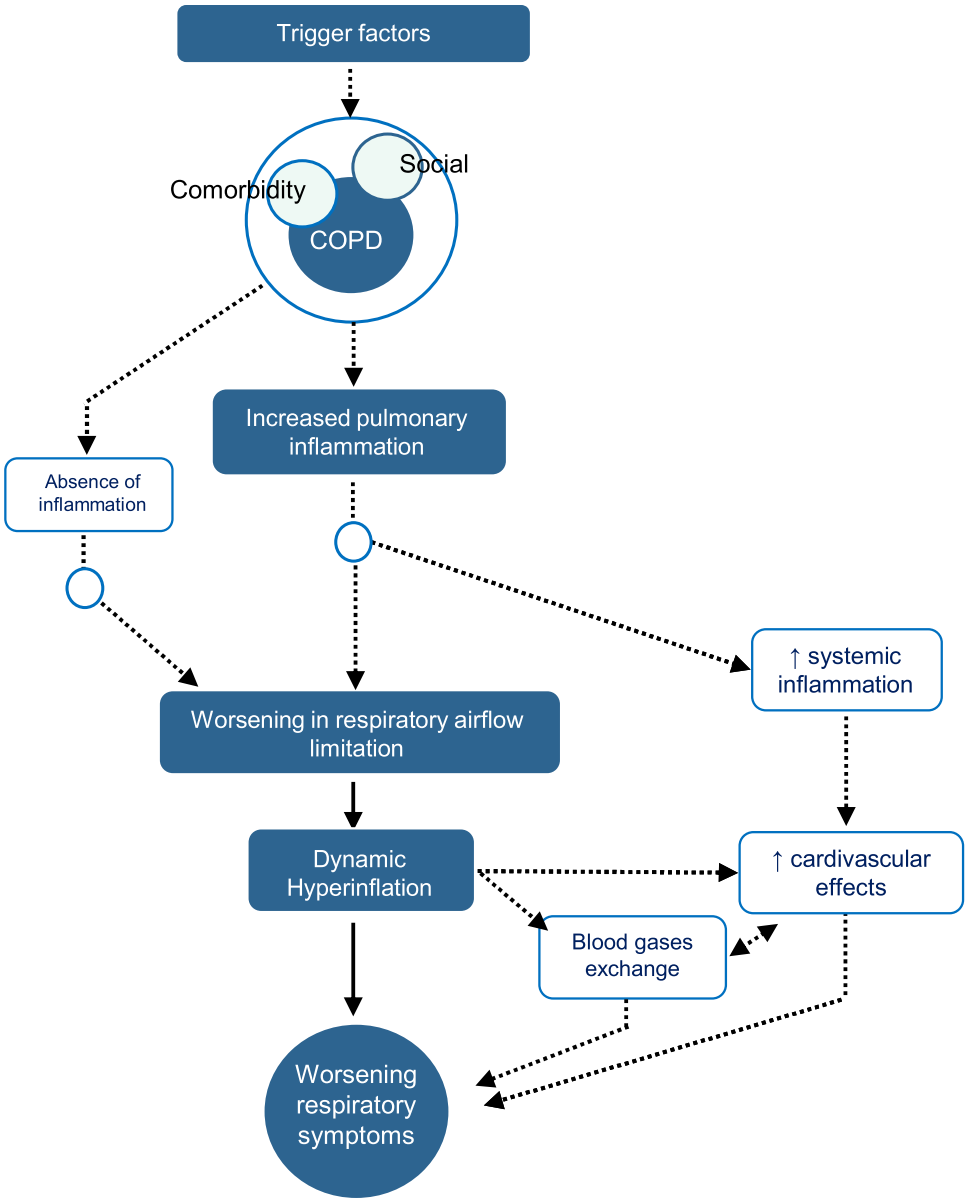

Figure 1 Pathophysiology of COPD exacerbation syndrome. Reproduced with permission from Soler-Cataluna JJ, Pinera P, Trigueros JA, et al. Spanish COPD guidelines (GesEPOC) 2021 update diagnosis and treatment of COPD exacerbation syndrome. Arch Bronconeumol. 2022;58(2):159–170.[11] Copyright © 2021 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

substantially reduced, and the overlapping disorders included under the umbrella of CES have increased. In the absence of both inflammation and expiratory flow limitation, other alternative diagnoses should be evaluated.

Consequences of the New Concept

An approach such as that proposed by the GesEPOC, which implies a conceptual and paradigmatic change in the approach to exacerbations, entails a series of consequences that can directly influence the management of these acute processes. Several other concomitant diseases (pneumonia, heart failure, pulmonary embolism, etc.), which have been considered 'alternative diagnoses' in both the GOLD and Rome definitions, can now be included under the umbrella of CES, which is more inclusive than previous category and allows for overlaps between concurrent diseases. One direct consequence of this huge umbrella term is that pneumonia is now considered within CES. Approximately 20% of patients with exacerbation present parenchymal infiltrates on chest X-rays[43,44] and slightly over a third of severe cases also present them on computed tomography, despite them not being visible on simple chest x-ray.[25] Traditionally, these

infiltrates, labeled as pneumonia, have been considered a comorbidity in COPD. However, there is a fine line between COPD exacerbation and pneumonia. The symptoms are practically identical, and the underlying mechanisms are similar, so from a syndromic point of view, both situations fall under CES. In addition, the lung microbiome between COPD patients with or without pulmonary infiltrate does not differ, the triggering factors are similar and so is the treatment.[45,46] However, the main difference is the fact that, in the presence of pneumonia, the inflammation is greater and the prognosis worse,[44,47] which suggests that we may possibly be facing different expressions of the same pathological process. For this reason, pneumonia, classified in previous editions of the GesEPOC as a comorbidity,[48] is currently considered a type of CES. Another consequence of this concept is the better identification and characterization of exacerbations, by including symptoms, lung function and inflammation, the three main pillars of this acute process.

A few years ago, it was proposed that the evaluation of exacerbations should necessarily involve a multidimensional evaluation in which various complementary aspects are taken into consideration. One all these proposals was to evaluate exacerbations on at least two axes,[49] with one axis showing the nature (type) of these exacerbations. Today, we know that not all exacerbations are the same, neither endotypically nor phenotypically. It is therefore necessary to identify features that differentiate some exacerbations from others and that make their management different, which have come to be known as treatable traits. On the other axis, the intensity of the exacerbation, measured as its clinical severity, continues to be a mainstay in the management of these acute processes and a challenge for the clinician. Consequently, severity and treatable features are two crucial aspects that are contemplated in the GesEPOC 2021 proposal.

Treatable Traits

The new GesEPOC 2021 proposal also recognizes the heterogeneity and complexity of exacerbations, not only in their pathophysiological mechanisms, but also in their biology (endotypes) or final clinical expression (phenotypes). This opens up the possibility of using different treatments for different patients, ie, providing personalized medical treatment. The GesEPOC proposes identifying different treatable traits, defined as the clinical, physiological, or biological characteristics present in each individual patient, which can be identified by diagnostic tests or biomarkers, each of which has a specific treatment.[8,11,50] Studies have identified different treatable traits that can be grouped into different categories (Table 2).

Among the treatable features listed in Table 2, eosinophils probably deserve a comment. In recent years, the relationship between peripheral blood eosinophil and stable COPD has been strengthened by several observational studies and post-hoc analyses of clinical trials.[51] Leaving aside the debate about its role in stable COPD,[52–56] these findings have led to two complementary debates. Firstly, whether peripheral blood eosinophil could be a marker for the choice of treatment during exacerbation. According to the systematic review performed by the GesEPOC 2021, the use of oral corticosteroids is recommended in patients with severe or very severe CES and their use is suggested for moderate CES. The efficacy of systemic steroids is greater in patients with eosinophil counts $\geq$ 300 cells/μL.[11] Accordingly, eosinophils are associated with readmissions after medium-term exacerbation.[57] The second debate deals with the relationship between peripheral blood eosinophils during the stable state of the disease and during exacerbations. Some studies have found a relationship between eosinophils in stable and exacerbated COPD.[27,58] However, the debate is even more interesting since even if we assume that stable eosinophilic COPD is prone to having eosinophilic exacerbations, an eosinophilic COPD could also suffer a bacterial infection, therefore leading to a neutrophilic type of exacerbation. There are therefore a number of biological mechanisms that need to be unraveled to deepen our understanding of the different relationships of COPD blood eosinophils in its stable state and during exacerbations.

Evaluation of Severity

Once the diagnosis of CES has been established, it is crucial to describe the severity of the episode, which in most cases is the result of the interaction between the underlying disease and the intensity of the acute episode. Traditionally, this assessment of severity has been based on use of the resources or treatment received by the patient: mild, if no specific additional treatment is prescribed; moderate, if oral steroids and/or antibiotics are used; or severe, if the patient is hospitalized.[18] However, this approach does not help the attending physician to determine the best treatment and

Table 2 Treatable Trait Domains to Consider in a Patient with COPD Exacerbation Syndrome

Treatable Traits	Biomarkers	Treatments
Endotypes		
Bacterial infection	Dark sputum CRP (≥20 mg/L) Neutrophils to Lymphocyte ratio	Antibiotic
Th2 inflammation	Blood eosinophils	Systemic corticosteroids
Ventricular dysfunction	NT-pro-BNP	Diuretics Beta-blockers ARA-II ACE inhibitors
Ischemic heart disease	Troponin	Antiaggregant Beta-blockers
Lung function		
Worsening of airflow limitation	FEV_1 PEF	Bronchodilators
Acute hypoxemic respiratory failure	PaO2 < 60 mmHg	Oxygen therapy
Acute hypercapnic respiratory failure	PaCO2 > 45 mmHg	Avoid sedative drugs / Ventilatory support
Respiratory acidosis	pH<7.35	Ventilatory support
Imagen by radiography or CT		
Pneumonia Pulmonary embolism	Infection D-dimer levels CT-angiography	Antibiotics Anticoagulants
Pulmonary hypertension	Pulmonary / aortic arteries ratio	Consider oxygen
Behavioral, Educational, and social		
Smoking	CO-oximetry Questionnaires	Nicotine replacement therapy, varenicline, bupropion Behavioral treatment
Anxiety-Depression	Questionnaires	Anxiolytics, antidepressants Behavioral treatment
Low therapeutic adherence	Adherence questionnaires	Educational programs
Poor inhaling technique	Critical errors check	Educational and training programs
Social and family support	Questionnaires	Social support programs

Abbreviations: CRP, C-reactive protein; CT, computed tomography; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; ARA-II, angiotensin receptor antagonist type II; ACE, Angiotensin converting enzyme inhibitor; EKG, electrocardiogram; PEF, peak expiratory flow; TAI, test of adherence to inhalers, FEV_1, Forced expiratory volume in one second.

prognosis at the point-of-care. The GesEPOC proposes a new approach which considers baseline status (low or high risk stratification) and several clinical or biological biomarkers (Table 3).

For severe exacerbations, various prognostic indices have emerged for the evaluation of exacerbations in recent years. The availability of predictive risk scales can be of great interest for stratifying patients and designing care circuits of different intensity and/or complexity.[59] Although the GesEPOC 2021 suggests the use of the DECAF index to complete severity assessment in severe exacerbations,[60] there are many others currently validated that show an excellent

Table 3 Severity Classification of COPD Exacerbation, According to GesEPOC Proposal (11)

Severity	GesEPOC Proposal Criteria for Judging Severity
Mild (All criteria must be met)	• Low-risk stratification according to baseline status* and all the following: o Dyspnea ≤ 2 (mMRC) o RR < 24 breaths/min o Resting SaO2 ≥ 95% breathing ambient air o Normal level of consciousness
Moderate (Any of the criteria must be met)	• High-risk stratification according to baseline status* and all the following: o Dyspnea ≤ 2 (mMRC) o Normal level of consciousness • Low or high-risk stratification and any of the following: o RR, 24–30 breaths/min o Resting SaO2, 90–95% breathing ambient air
Severe (Any of the criteria must be met, regardless of baseline risk level)	• Dyspnea ≥3 (mMRC) • Somnolence • RR, >30 breaths/min • Resting SaO2<90% or PaO2<60 mmHg, breathing ambient air
Very severe (Any of the criteria must be met, regardless of baseline risk level)	• Stupor / coma • pH<7.35 orPaCO2≥60 mmHg

Notes: *Baseline risk stratification according to GesEPOC (11), Low risk, Dyspnea, 0 −1 (mMRC), FEV_1>50%, 0–1 exacerbation in the last year and no hospitalizations in the last year (all criteria must be met); High risk, Dyspnea≥2 (mMRC) or FEV_1<50% or Two or more moderate exacerbations in the last year or at least 1 hospitalization in the last year.
Abbreviation: mMRC, modified Medical Research Council Dyspnea scale.

relationship with the prognosis of exacerbation and are easy to apply in emergency departments, such as BAP-65,[61] DeCOPD[62] or the index by Roche et al,[63] among others.[64,65]

In GesEPOC we aimed to propose a more simple and clinically applicable way of identifying severe cases of COPD exacerbation, beyond the simple verification of acute respiratory failure, but, at the same time, using a limited number of variables that make its application viable in real clinical practice. These different degrees of severity clearly identify different locations from which to deal with these clinical situations. On the other hand, the type of treatment should be more related to the type of exacerbation (Figure 1) than to its severity. Although we have indications of the different impact of the different therapeutic measures in the different types of exacerbations, clinical trials will really be needed to more precisely define the impact of these options in the treatment of exacerbations.

Recurrence of Exacerbations

During the clinical presentation of COPD, it is common to find patients whose exacerbations accumulate in clusters. In this context, it has been noted that the appearance of one exacerbation leads to future exacerbations, which increase in frequency and time proximity.[66] For this reason, the GesEPOC 2021 differentiates conceptually between therapeutic failure (a worsening of the symptoms that occurs during an exacerbation and that requires a change in therapeutic strategy), relapse (a new worsening of the symptoms after treatment has ended and less than 4 weeks after the previous episode) and recurrence (when symptoms reappear during the year following an exacerbation). The pathophysiological mechanism behind this perpetuating inflammatory influx,[67] the response to different treatment options[68] and their implications on disease prognosis or clinical impact in the long-term[38,69] are yet to be fully elucidated and will become one of the key objectives for research in COPD in the coming years.

Conclusions

Despite the advances made in recent decades, the concept of what is an exacerbation continues to be an ongoing source of debate. The GesEPOC 2021 has sought to provide an updated assessment based on the methodology of evidence-

based medicine, bringing to the table an innovative proposal that forces us to think outside the box and accept a definition and a conceptual and practical approach which is closer to the patient and the variability of the disease. Strategies such as the concept of control[41,70,71] or the stratified assessment of these clinical situations will improve clinical decision-making even in complex scenarios. On the other hand, the incorporation of information and communication technologies[72] applied to respiratory medicine will also help us to achieve a more personalized management of the disease.[73]

Acknowledgments

The authors would like to thank Simon Armour of the British Academy for his work on improving the English text.

Funding

There is no funding to report.

Disclosure

JJSC has received research grants from GlaxoSmithKline, speaker fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, FAES, Menarini and Novartis, and consulting fees from Bial, Chiesi, GlaxoSmithKline and Novartis JLLC has received honoraria during the last 3 years for lecturing, scientific advice, participation in clinical studies or writing for publications from (alphabetical order): AstraZeneca, Bial, Boehringer, Chiesi, CSL Behring, Faes, Ferrer, Gebro, Grifols, GSK, Megalabs, Menarini, Novartis, Rovi. The authors report no other conflicts of interest in this work.

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