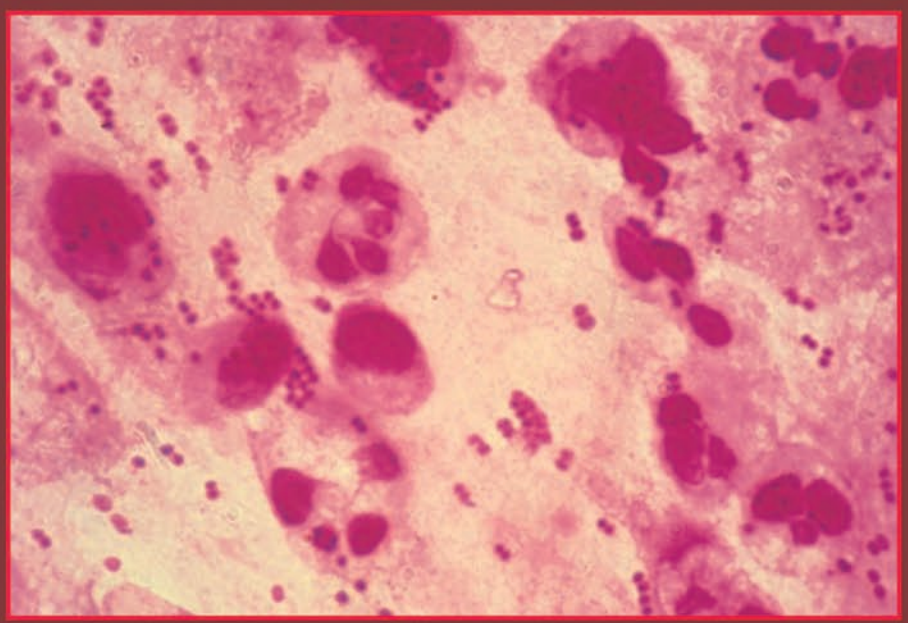
Therapeutic Strategies in ACUTE EXACERBATIONS IN COPD

M. Cazzola · S. Sethi · F. Blasi · A. Anzueto



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ACUTE EXACERBATIONS IN COPD

Edited by

Mario Cazzola, Sanjay Sethi, Francesco Blasi, Antonio Anzueto

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Editors

ANTONIO ANZUETO, MD, Professor of Medicine, Pulmonary/Critical Care; Section Chief at VA Medical Center, South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

FRANCESCO BLASI, MD, Professor of Respiratory Medicine, Dipartimento Toraco-Polmonare e Cardio Vascolare, University of Milan, IRCCS Fondazione Pomare, Milan, Italy

MARIO CAZZOLA, MD, Associate Professor of Respiratory Medicine, Unit of Respiratory Diseases, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome, Italy

SANJAY SETHI, MD, Professor of Medicine, Division Chief, Pulmonary/Critical Care/Sleep Medicine, University at Buffalo, State University of New York; Section Chief, Pulmonary/Critical Care/Sleep Medicine, VA WNY Healthcare System, Buffalo, New York, USA

Contributors

IAN M. ADCOCK, PhD, Professor; Airways Disease Section, National Heart and Lung Institute, Imperial College, London, London, UK

STEFANO ALIBERTI, MD, Research Fellow, Dipartimento Toraco-Polmonare e Cardio Vascolare, University of Milan, IRCCS Fondazione Pomare, Milan, Italy

ALBERT ALONSO, MD, PhD, Researcher, Innovation Projects, Information Systems Directorate, Hospital Clinic-IDIBAPS, Barcelona, Spain

GUY W. AMSDEN, PharmD, FCP, DABCP, Director, Department of Pharmaceutical Care Services, Bassett Healthcare, Cooperstown, New York, USA

ANTONIO ANZUETO, MD, Professor of Medicine, Pulmonary/Critical Care; Section Chief at VA Medical Center, South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Simonetta Baraldo, BSc, PhD, Assistant Professor, Department of Cardiac, Thoracic and Vascular Surgery, Section of Respiratory Diseases, University of Padua, Padua, Italy

Francesco Blasi, MD, Professor of Respiratory Medicine, Dipartimento Toraco-Polmonare e Cardio Vascolare, University of Milan, IRCCS Fondazione Pomare, Milan, Italy

Gaetano Caramori, MD, PhD, Assistant Professor in Respiratory Medicine, Centro di Ricerca su Asma e BPCO, Università di Ferrara, Italy

Mario Cazzola, MD, Associate Professor of Respiratory Medicine, Unit of Respiratory Diseases, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome, Italy

Roberto Cosentini, MD, Consultant, Divisione Medicina d'Urgenza, IRCCS Fondazione Pomare, Milan, Italy

Jeffrey L. Curtis, MD, Professor or Internal Medicine, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Health System; Chief, Pulmonary and Critical Care Medicine Section, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, Michigan, USA

Nicola A. Hanania, MD, MS, Associate Professor of Medicine, Baylor College of Medicine, Pulmonary and Critical Care Section, Houston, Texas, USA

Carme Hernandez, Respiratory Nurse, Coordinator of Integrated Care Programs, Nursing and Medical Directorate, Hospital Clinic-IDIBAPS, Barcelona, Spain

Sonia Khirani, PhD, Doctor in Biomedical Engineering, Pulmonary Division, A.O. Ospedali Riuniti di Bergamo, Bergamo, Italy

Kim Lokar-Oliani, MD, Consultant Pneumologist, Department of Cardiac, Thoracic and Vascular Surgery, Section of Respiratory Diseases, University of Padua, Padua, Italy

Donald A. Mahler, MD, Professor of Medicine, Dartmouth Medical School, Hanover, New Hampshire; Section of Pulmonary and Critical Care Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

Fernando J. Martinez, MD, MS, Professor of Internal Medicine, Medical Director, Pulmonary Diagnostic Services; Co-Medical Director, Lung Transplantation, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan, USA

Marc Miravitlles, MD, Senior Researcher, Fundació Clínic. Institut d'Investigacions, Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain

James A. Murray, DO, Chief, Division of Pulmonary Medicine, Unity Health System, Clinical Instructor of Medicine, University of Rochester, Rochester, New York, USA

Stefano Nava, MD, Chief, Respiratory Intensive Care Unit, Fondazione S. Maugeri, IRCCS Istututo Scientifico Di Pavia, Italy

Paolo Navalesi, MD, Intensive Care Unit, Eastern Piedmont University 'A. Avogadro'; University Hospital 'Maggiore della Carità', Novara, Italy

Alberto Papi, MD, Full Professor in Respiratory Medicine, Centro di Ricerca su Asma e BPCO, Università di Ferrara, Italy

Guido Polese, MD, Pulmologist, Pulmonary Division, A.O. Ospedali Riuniti di Bergamo, Bergamo, Italy

Josep Roca, MD, Chief of Section, Pneumology Department, Hospital Clinic-IDIBAPS, Barcelona; University of Barcelona, Barcelona, Spain

Andrea Rossi, MD, Director, Pulmonary Division, A.O. Ospedali Riuniti di Bergamo, Bergamo, Italy

Marina Saetta, MD, Full Professor, Department of Cardiac, Thoracic and Vascular Surgery, Section of Respiratory Diseases, University of Padua, Padua, Italy

Sanjay Sethi, MD, Professor of Medicine, Division Chief, Pulmonary/Critical Care/Sleep Medicine, University at Buffalo, State University of New York; Section Chief, Pulmonary/Critical Care/Sleep Medicine, VA WNY Healthcare System, Buffalo, New York, USA

Amir Sharafkhaneh, MD, PhD, Associate Professor of Medicine, Baylor College of Medicine, Houston, Texas, USA

Paolo Tarsia, MD, Consultant in Respiratory Diseases, Dipartimento Toraco-Polmonare e Cardio Vascolare, University of Milan, IRCCS Fondazione Pomare, Milan, Italy

Graziella Turato, BSc, PhD, Department of Cardiac, Thoracic and Vascular Surgery, Section of Respiratory Diseases, University of Padua, Padua, Italy

E. F. M. Wouters, MD, PhD, Professor of Respiratory Medicine; Chairman, Department Respiratory Medicine, University Hospital Maastricht, Department of Respiratory Medicine, Maastricht, The Netherlands

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COPD exacerbations: definitions and classifications

G. Caramori, I. M. Adcock, A. Papi

INTRODUCTION

The most recent update of the international NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines defines chronic obstructive pulmonary disease (COPD) with respect to its pulmonary and extrapulmonary (systemic) components, but does not mention exacerbations in the main definition, even though they are the main cause of medical intervention and admission to hospital in these patients [1]. In the same guidelines, an exacerbation of COPD is separately defined as '*an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD*' [1]. The latest GOLD guidelines also provide a classification of the severity of the exacerbations of COPD based on clinical parameters to drive the necessity and the type of antibiotic therapy [1].

Similarly, the latest update of the Canadian Thoracic Society (CTS) recommendations for the management of COPD defines an exacerbation of COPD as '*a sustained worsening of dyspnoea, cough or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications*' [2]. The term 'sustained' implies a change from baseline lasting 48 h or more. In addition, COPD exacerbations are defined as either purulent or non-purulent on the assumption that this is helpful in predicting the need for antibiotic therapy [2]. Again, in a strict analogy to the latest GOLD guidelines, the CTS update also provides a classification of the severity of purulent exacerbations of COPD, recognising both simple and complicated purulent COPD exacerbations, based on the presence of clinical risk factors that either increase the likelihood of treatment failure or are more likely to be associated with more virulent or resistant bacterial pathogens [2].

Although both the GOLD and CTS definitions and classifications of the severity of COPD exacerbations may provide a useful practical tool for clinical studies, they have not been formally validated in clinical trials and are rather cumbersome and difficult to use in clinical practice. Other definitions derived from the literature are also used and are discussed below.

Gaetano Caramori, MD, PhD, Assistant Professor in Respiratory Medicine, Centro di Ricerca su Asma e BPCO, Università di Ferrara, Italy

Ian M. Adcock, PhD, Professor; Airways Disease Section, National Heart and Lung Institute, Imperial College, London, London, UK

Alberto Papi, MD, Full Professor in Respiratory Medicine, Centro di Ricerca su Asma e BPCO, Università di Ferrara, Italy

There are currently no known biomarkers equivalent to the troponin test for myocardial infarction or D-dimer test in pulmonary embolism included in the definition of COPD exacerbation [3].

A standardised definition of an exacerbation of COPD remains an unmet need in respiratory medicine. Indeed, the absence of a standardised definition of COPD exacerbation makes it very difficult to compare the results of the different studies on the pharmacological treatment and prevention of COPD exacerbations.

A prerequisite for a COPD exacerbation is that the patient has known COPD [4]. It may be difficult to distinguish a COPD exacerbation from other diseases presenting with similar clinical features during the first documented episode. This is very important because, for example, a severe asthmatic exacerbation in an old asthmatic patient who smokes may be confused with an exacerbation of COPD if the presence of asthma is unknown to the physician in charge of the patient [5]. Bronchiectasis is also often confused in general practice with COPD [6, 7].

Furthermore, patients with a definite COPD diagnosis may also have comorbidities that need to be considered in the differential diagnosis when looking for other possible causes of an acute deterioration of respiratory symptoms outside of a true COPD exacerbation. The most common of these alternative diagnoses are acute heart failure [8], pneumonia [9], pulmonary thromboembolism [10–13], cardiac arrhythmia (mainly atrial fibrillation) [14], pneumothorax [15, 16] and lung cancer, amongst others. It is worth noticing that COPD patients have an increased risk of developing lung cancer compared with age-matched smokers with normal lung function and similar smoking history [17]. These clinical conditions, even when co-existing (e.g. heart failure), should always be considered in the differential diagnosis of a true COPD exacerbation.

The measurement of the serum level of brain natriuretic peptide (BNP, or its precursor aminoterminus [NT]-proBNP) and troponins may be useful in the differential diagnosis of the cause (cardiogenic vs. pulmonary) of acute dyspnoea in a COPD patient [18–20] although the broad overlap in BNP and NT-proBNP concentrations suggests poor specificity in this patient population [21]. For this reason, clinical judgment must always be part of the evaluation of BNP or NT-proBNP assay results [22].

Interestingly, the presence of COPD does not affect the diagnostic performance of clinical probability estimate (CPE), D-dimer testing, spiral computed tomographic angiography (SCTA), or pulmonary angiography in the diagnosis of pulmonary thromboembolism in these patients [23].

This chapter endeavours to provide an historical overview of the definitions and classifications of COPD exacerbations underlining their strengths and limitations.

FROM THE ANTHONISEN CRITERIA ONWARDS

Since Fletcher first described 'chest episodes' in 1976, interest and research activity in the field of COPD have increased steadily [24]. The best-studied COPD exacerbation definitions were developed for studies of antibiotics for which bacterial exacerbations were required. From such research emerged the classic definition of Anthonisen *et al.* [25]. This description remains the most commonly referenced of all definitions and has formed the basis of many subsequent criteria [26]. There has been much debate in recent years about exactly how a COPD exacerbation should be defined and two contrasting approaches have been proposed.

SYMPTOM-BASED DEFINITIONS OF COPD EXACERBATION

This group contains the most commonly used definition that identifies a COPD exacerbation as '*a sustained worsening of respiratory symptoms that requires a patient to seek medical help*' [27,

28]. A very similar, but more loosely-based, definition was proposed as a consensus definition of an experts' panel: '*a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD*' [29].

An exacerbation of COPD may also be defined as '*a sustained worsening of respiratory symptoms that is acute in onset and usually requires a patient to seek medical help or alter treatment*' [26]. The deterioration must be more severe than the usual daily variation experienced [30].

Another symptom-based definition of COPD exacerbation used in large controlled clinical trials of drugs includes the parameter of duration and indicates COPD exacerbations to be characterised by '*increase in dyspnoea, cough or associated with a change in quality and quantity of sputum that led the patient to seek medical attention and lasts for at least 3 days*' [31, 32]. However, there is no good evidence that 3 days of symptoms are required to define a COPD exacerbation.

Unlike asthma, patients with COPD do not experience sudden increases in symptoms that may disappear spontaneously or with medication in hours or a few days [33]. Moreover, a delay in initiating treatment for an exacerbation may result in a longer duration of the episode [34]. Consequently, no time limit should be required to define an exacerbation of COPD.

Another proposed definition of COPD exacerbation has been '*an increase in respiratory symptoms over baseline that usually requires medical intervention*' [35, 36].

There are a number of advantages and disadvantages to the use of a symptom-based definition. Symptoms are of fundamental importance and are the primary concern of the patient; it is generally a change in symptoms that prompts contact with healthcare professionals. Assessment of patient symptoms and subsequent improvement with therapy is therefore a fundamental consideration for both patient and physician. Interestingly, approximately two-thirds of COPD patients are aware when an exacerbation is imminent and, in most cases, symptoms are consistent from one exacerbation to another [37].

However, identification of a standardised symptom-based definition is likely to be complicated by the highly variable nature of COPD and of its exacerbations. As patient symptoms vary greatly and an absolute level of dyspnoea or sputum volume cannot be described as diagnostic, a subjective assessment of 'worsening' is therefore required. In this case, it is a matter of some debate as to who is best placed to make this judgment – the patient or the doctor? [26]. This is particularly important as a patient's perception of disease can vary with the severity [26].

While some scales for symptom assessment do exist and can be used as a basis for future development, the validity of the scales currently available and their sensitivity have not been established in COPD exacerbations. Thus, validating a new scale would be a significant undertaking. The most common approach to monitoring symptom changes over time requires the use of a paper-based diary card. This approach is increasingly controversial as it is associated with a number of intrinsic disadvantages, the most problematic of which are extremely poor adherence to protocol instructions and data validity issues arising from retrospective record entry [26].

COPD exacerbation rates reported on diary cards for symptom-based studies are higher than for event-based studies because a significant percentage (~50%) of exacerbations will not be reported to the physician or healthcare professional [38–41]. This has been suggested to be due to the fact that patients with COPD may not understand their disease and the importance of seeking treatment. They may also be depressed, or lack mobility. It can also sometimes reflect a patient's self-treatment with pre-prescribed 'emergency' courses of antibiotics and/or glucocorticoids [42].

It also remains unclear whether the COPD exacerbations that are unreported to a physician are clinically relevant [38, 43]. However, it has been observed that patients who report a smaller proportion of their COPD exacerbations tend to have a poorer health-related qual-

ity of life [34]. This difference may be explained by the fact that these patients do not receive treatment and consequently their COPD exacerbations take longer to recover and have a greater impact on the patient's perception of their disease [44].

EVENT-BASED DEFINITIONS OF COPD EXACERBATION

Event-based definitions of COPD exacerbations have been increasingly used in an attempt to circumvent the problems associated with identifying and defining symptoms or groups of symptoms, and simply capture all patients whose condition has changed enough to require an emergency visit, hospitalisation or a change of treatment (generally a requirement for oral glucocorticoids or antibiotics). Classification of exacerbations based on events offers a straightforward approach and is therefore widely used in clinical trials [26, 36, 45–47].

Event-based criteria do, however, require a sequence of decision-making involving both the patient and the doctor. Although this method captures significantly fewer episodes than symptom-based definitions and is likely to select a distinct patient group with more severe COPD exacerbations (see below), in the absence of definitive signs and symptoms on which to base a diagnosis, event-based definitions currently represent the most unambiguous and practical approach to clearly identifying episodes of COPD exacerbation [26]. However, healthcare utilisation definitions of COPD exacerbation are limited by a reliance on factors other than the underlying pathophysiological process. These include access to healthcare and the social and financial situation of the patient [48].

CLASSIFICATION OF SEVERITY OF COPD EXACERBATIONS

The effect of any given therapeutic intervention may be not only to reduce the frequency of COPD exacerbations, but also, and more commonly, to reduce their severity.

No validated scale of severity exists for COPD exacerbations [49]. Some authors have used a composite scale of symptoms to evaluate the resolution of the episode in clinical trials of antibiotics [50] or in observational follow-up studies [51]. However, these scales have not yet been validated in long-term clinical trials of interventions in stable COPD patients. In contrast, most studies have used the intensity of the medical intervention required as a grade of severity, from self-management at home to admission to an intensive care unit (ICU) [49].

The classic definition of Anthonisen *et al.* [25] divided exacerbated COPD patients into three groups according to their symptoms:

- **Type 1** exacerbations were defined by the presence of increased breathlessness, sputum volume and sputum purulence;
- **Type 2** exacerbations were defined by the presence of two of these symptoms; and
- **Type 3** exacerbations were defined by the presence of one of these symptoms in addition to one of the following criteria:
  - an upper respiratory tract infection in the past 5 days
  - fever without other cause
  - increased wheezing or cough
  - an increase in heart rate or respiratory rate by 20% compared with baseline readings [25].

This definition has been widely used in clinical trials of antibiotics for exacerbations of COPD, but it is not a severity scale, more a classification that indicates the likelihood of bacterial infection as a cause of an exacerbation (i.e. a type 1 exacerbation in a 'mild' patient may have a better prognosis that a type 3 exacerbation in a 'severe' patient).

Using this definition:

- Health-status score results were closely related to the exacerbation frequency, with worse health status in patients with frequent COPD exacerbations [34]; and
- Dyspnoea was the most common and important symptom of a COPD exacerbation [40].

The significance of the minor criteria has never been formally studied.

Mild exacerbations of COPD may be defined as increased breathlessness, possibly associated with increased cough and sputum production, which force the patient to seek medical attention outside the hospital [33]. COPD exacerbations may be defined as severe when they are associated with acute or chronic respiratory failure using standard criteria (arterial oxygen tension [PaO_2] <8 kPa [60 mmHg] with or without arterial carbon dioxide tension [$PaCO_2$] >6 kPa [45 mmHg] and hydrogen ion concentration >44 nM [pH <7.35]) based on arterial blood-gas measurement while breathing room air [33, 52]. Severe COPD exacerbations frequently require admission to hospital and/or an ICU [33].

There are no established criteria for assessing severity in less severely ill patients not requiring hospital assessment. In published studies, treatment with oral or parenteral glucocorticoids constituted a more severe COPD exacerbation (severity B) and the others were classified as mild/moderate (severity A) [53].

The most recent American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of COPD provide the following operational classification of severity of COPD exacerbations to help with ranking the clinical relevance of an episode and its outcome [54]:

- **Level I** – treated at home
- **Level II** – requires hospitalisation
- **Level III** – leads to respiratory failure

The major limitation of this classification is that many COPD exacerbations requiring hospitalisation (level II) are associated with respiratory failure (level III). The criteria for hospital admission may also vary from country to country and in different hospitals.

The proposed severity classification of the recent ATS/ERS statement on outcomes for COPD pharmacological trials includes three categories:

- **Mild –** increase in respiratory symptoms controlled by the patient with an increase in the usual medication;
- **Moderate –** exacerbations requiring treatment with systemic glucocorticoids and/or antibiotics; and
- **Severe –** exacerbations requiring hospitalisation or a visit to the emergency department [49].

The methodology surrounding the use of the severity of a COPD exacerbation as a variable has not been standardised [49]. Many large, controlled clinical trials have defined a severe COPD exacerbation as requiring the introduction of a cycle of treatment with oral glucocorticoids and/or antibiotics [36, 46]. The clinical relevance of this approach is at the very least controversial due to the questionable magnitude of the effect of antibiotics and the relatively small effect of systemic glucocorticoid treatment on COPD exacerbations [55, 56].

Most cases of severe COPD exacerbations occur in patients with GOLD stage 3 or 4 COPD [57, 58]. In the long term, COPD patients who experience severe COPD exacerbations have an increased risk of experiencing more severe exacerbations in the future [51, 59].

Interestingly, in a recent meta-analysis of the markers of severity of COPD exacerbations, only the arterial carbon dioxide tension and the breathing rate were statistically different between all levels of exacerbation severity and between out- and inpatient settings. Most

other measures showed weak relationships with either level or setting, or there were insufficient data to permit meta-analysis [60].

There is a complete absence of validated biomarkers that are useful in predicting the degree of severity of a COPD exacerbation [61]. In a recent study, systemic plasma biomarkers were not helpful in predicting COPD exacerbation severity and the acute-phase response at COPD exacerbation was most strongly related to indices of monocyte function [62].

CLINICAL HETEROGENEITY OF THE CAUSE OF COPD EXACERBATIONS

Many studies have shown the heterogeneous nature of the cause of COPD exacerbations, which vary greatly from person to person. There are no available definitions of COPD exacerbations incorporating the cause and it is still unclear whether different causes are associated with different severity of COPD exacerbations. Virus-associated COPD exacerbations treated similarly with antibiotics and glucocorticoids have longer recovery periods than non-viral COPD exacerbations [63], suggesting that exacerbations of different aetiology may behave differently with interventions. Much more research is needed in this area, however.

Most COPD exacerbations are thought to arise as a result of infections, although the type of infection is often unclear [1, 2]. Independently, both bacterial and viral infections have been detected at increased frequencies during COPD exacerbations. The most frequently seen respiratory viruses involved in the aetiology of COPD exacerbations are represented by rhinoviruses, influenza viruses, coronaviruses (but not the severe acute respiratory syndrome [SARS] associated coronavirus) and respiratory syncytial virus (RSV). More rarely, parainfluenza viruses and human metapneumoviruses (HMPV) have also been incriminated [64]. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* are the most common bacteria found in the sputum of patients during a COPD exacerbation [1]. However, atypical bacteria such as *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* and *Mycoplasma pneumoniae* are not isolated from severe COPD exacerbations in the UK and Italy [28].

Until now, only a single study has comprehensively investigated both bacteria and viruses during the same severe COPD exacerbations. Viral and/or bacterial infection was detected in 78% of COPD exacerbations, viruses in 48.4% (6.2% when stable) and bacteria in 54.7% (37.5% when stable). Infectious exacerbations (29.7% bacterial, 23.4% viral, 25% viral/bacterial co-infection) had longer hospitalisations and greater impairment of several measures of lung function than non-infectious exacerbations. Importantly, exacerbations with co-infection had more marked lung function impairment and longer hospitalisations [28]. However, the relationships between viral and bacterial infections, especially when combined together, and whether viral infections can lead to bacteriological exacerbation (possibly of previously colonising bacteria) remain unanswered questions that deserve a properly designed longitudinal study to further investigate them [64].

The purulence and colour of the sputum during COPD exacerbations has been proposed in the past as a marker of bacterial infection and this is still considered a reason for starting antibiotic treatment in the most recent GOLD and CTS guidelines [1, 2]. However, COPD exacerbations associated with purulent sputum production have been associated with a large bacterial load in some, but not all, studies [28, 65, 66].

In a small proportion of cases of severe COPD exacerbation, however, there is no evidence of infection, and environmental triggers, such as air pollutants or changes in airway temperature, are thought to be the initiating factors [67].

Another major characteristic of COPD exacerbations is their seasonal variation. This consideration is of primary importance when analysing the clinical relevance of pharmacological trials investigating the effect of drugs in preventing COPD exacerbation frequency during a period of time shorter than 12 months [39, 68].

To date, no sputum or plasma biomarker has been found with good sensitivity and specificity that can identify the cause of a COPD exacerbation [3, 61]. However, two large controlled clinical trials have shown that many COPD exacerbations of variable severity and different sputum purulence may be managed without antibiotic therapy, simply using the level of serum pro-calcitonin as a marker of the presence of bacterial infection [69, 70]. If this is further validated in ongoing studies, this novel biomarker of bacterial infection may soon help to guide decisions regarding the need for antibiotic therapy during a COPD exacerbation.

THE NEED FOR A STANDARDISED DEFINITION OF COPD EXACERBATION IN CONTROLLED CLINICAL TRIALS

Many symptom- and event-based definitions of COPD exacerbation have been adopted in controlled clinical trials of new and old drugs used for the treatment and prevention of COPD exacerbation (recently reviewed in [26]). These have arisen from the need to establish criteria by which to select patients for inclusion and the absence of a clear and widely accepted definition of COPD exacerbation. Controlled clinical trials of old and new drugs conducted today still use a wide variety of definitions by which treatment success is judged, with increasing focus on event-based definition of COPD exacerbations [36, 46, 55, 56, 71–73]. There is, however, no evidence of improving consistency and many publications still feature inadequate descriptions of the definition of COPD exacerbations. The lack of a consistent definition of COPD exacerbation makes comparison of study findings and treatment effect virtually impossible [26].

The choice of definition of COPD exacerbations can significantly affect study outcomes, with varying criteria likely to result in different levels of demonstrated treatment success [26]. Usually, the looser the definition of a COPD exacerbation, the more likely it is that the drug being tested will show some clinical efficacy. For example, the prevention of COPD-related hospital admissions has been demonstrated only using salmeterol, formoterol and tiotropium but not with inhaled glucocorticoids, whereas a prevention of symptoms of COPD exacerbations has been demonstrated with all of the previous pharmacological classes [46, 74, 75].

The methodology concerning the recording of exacerbation frequency as a variable has not been standardised, but it has been used in several clinical trials of inhaled glucocorticoids and/or bronchodilators in COPD [49].

The statistical methodology used to calculate the annual ratio of COPD exacerbations in a given cohort and to compare the different ratios between treatment arms in clinical trials must be described in detail, because large and significant differences have been reported when using different approaches [76].

In observational studies of COPD patients, a skewed distribution of this variable has been found with a large number of patients having 0–2 exacerbations per year and small number of patients having ≥10 exacerbations per year [39, 51, 77]. The mean number of COPD exacerbations is generally related to the severity of the baseline disease and the definition used, and in observational studies ranges between 1 and 2.5 episodes per year, but it is highly variable and as many as 40% of COPD patients may not have any exacerbations at all [2, 39, 51, 77]. However, if unreported COPD exacerbations are included, severe patients (GOLD III) have a mean of 3.43 exacerbations per year and GOLD II have a mean of 2.68 exacerbations per year [49, 51]. In the short term (i.e. weeks or months), this variable does not appear to be reproducible due to the small number of episodes per year; the chance of a repeat episode in weeks or months is small. However, in the long term, COPD patients with frequent exacerbations in the past have a larger probability of suffering frequent COPD exacerbations in the future [49, 51, 78]. This suggests that short-term studies

may show a positive effect of a drug on COPD exacerbation rate that is not seen with longer-term studies.

SUMMARY

A decade on from our previous review of this topic our conclusions are unfortunately very similar [33]. The definition of exacerbation of COPD still relies on clinical empiricism with little scientific support. As often happens when reviewing the literature on a clinical topic, one finds more questions than answers. Exacerbations of COPD are certainly clear events in the minds of practising physicians. However, when one tries to provide simple concepts such as definition and classification of severity, it becomes clear how little we know [33]. Efforts to assess the efficacy of new therapies in the treatment and prevention of COPD exacerbations have been hampered by the lack of a widely agreed and consistently used definition. This conclusion should reinforce the necessity for greater investment in research on COPD exacerbations in order to promote a better understanding of and clinical approach to this sometimes dramatic event in the natural history of the disease.

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