COPD frequent exacerbators: time for the recycle bin?

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The definition of frequent exacerbators has changed with time. The use of previous history to identify frequent exacerbators is far from robust and has implications for the instigation of therapy based on the current GOLD algorithm. https://bit.ly/33TfGxg

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Introduction

COPD is a highly prevalent chronic disease with increased mortality and morbidity. The chronic symptoms result in impaired quality of life interspersed with episodes of acute worsening (exacerbations), which increase patient stress, and the likelihood of hospital admissions and death. These episodes are not only dangerous but also worsen background quality of life, increase the general healthcare burden and lead to disease progression [1, 2]. Therefore, they represent a key target in patient management and have become a primary clinical outcome measure in pharmaceutical drug registration.

The study of the causes and management of these episodes has led to an ever increasing literature in order to understand their nature, although therapeutic manipulations dominate with multiple large cohort trials and studies using variations of usual background inhaled therapies. The management, however, remains largely empirical, based on statistical generalisations.

In 1987 only 13 papers were published on exacerbations of COPD but included the classical "Anthonisen" paper describing the three major symptoms of such episodes, namely an increase in dyspnoea, new or increased sputum volume and new or increased sputum purulence [3]. This study confirmed that although many episodes resolved spontaneously, antibiotics were beneficial particularly if all three symptoms were present, which includes the purulence being consistent with a neutrophilic response to a heavy bacterial load [4, 5]. A change in 1–3 of these largely subjective symptoms remains central to diagnosing an exacerbation used in most of the literature to date.

In 2000 147 papers were published, introducing a clearer definition of exacerbation [6] that included the concept that it requires an increase in usual therapy or the addition of further therapeutic agents. Again this definition remains a cornerstone of the current diagnosis and retrospective identification of episodes, even though the treatments may not be specifically for exacerbations of COPD. Furthermore, clinical episodes of the acute change in the Anthonisen triad of symptoms may not receive extra treatment (the so called "unreported episodes") and yet still have an impact on health status [7]. This issue remains largely unaddressed, although data suggests failure to change therapy reflects a subjective feeling of "wellness" or its rapid improvement [8].

In 2019 1163 papers were published on the topic, but despite the plethora of observational, scientific and interventional studies, have we really moved forward in this era of personalised medicine?

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Frequent exacerbators

Many patients with COPD rarely have exacerbations, although the likelihood increases with disease severity and certain subtypes of COPD, including those with established cough and sputum production, those colonised with bacteria and those with concomitant bronchiectatic change.

Some of the "episodes" may have nothing to do with COPD itself, but reflect other comorbidities especially cardiovascular disease and ambient pollution. In addition, viral and bacterial colonisation are common even in the stable state and although identified in exacerbations, may not be the driving aetiology. Increased inflammation in the lung is only a feature of some episodes and usually those associated with a likely bacterial or viral aetiology, especially when it changes.

However, increased and partially reversible airflow obstruction is also a feature even in primary care [9], which drives the acute therapeutic management and most of the current "preventative" strategies.

To dissect these issues and determine whether they can be prevented requires large cohorts of patients studied over prolonged periods. This can be partially offset by studying patient cohorts enriched for those who are likely to have recurrent episodes during the period of study.

This "frequent exacerbator" phenotype (defined initially as three or more episodes in a year) was first described by Seemungal *et al.* [1], who also noted the impact of such episodes on health status, and Donaldson *et al.* [2], who noted the contribution to physiological progression (albeit on average <10 mL decline in forced expiratory volume in 1 s (FEV_1) per year). However, with improvements in patient management such recorded episodes have become less likely [10] and a "frequent exacerbator" has more recently been defined as having two or more episodes each year. In the classical paper by Hurst *et al.* [11] using the ECLIPSE cohort, the best predictor of the "frequent exacerbator" was the preceding history. However from personal experience and that of clinical trials enriched for such patients, the reality is that those recruited have an average exacerbation frequency between 1 and 1.5 per year. Nevertheless, interventions with two or three inhaled therapies produce statistical reductions in the average rate of up to 30%. This in turn leads to generalisations that influence starting or follow-up therapy for long term management as stated in the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) algorithms [12] and many guidelines whereby "frequent exacerbators" are prescribed dual or triple inhaled therapy. This strategy depends on identifying such patients by word of mouth or, at best, previous medical records.

Time to rethink

Exacerbations are sporadic events with multiple causations and even the number of episodes from medical records fails to note the "unreported episodes" by definition.

The study reported by Sadatsafavi *et al.* [13] in the current issue of the *European Respiratory Journal* recognises this frequent exacerbator conundrum and analysed "reported" episodes in two major cohorts noting divergent data concerning the prevalence of "frequent exacerbators", one of which (SPIROMICS) found such individuals to be rare [14], whereas the other (ECLIPSE), that lead to the Hurst *et al.* [11] paper of identification from previous history, found them to be more prevalent. This was probably related to the former cohort having a significant proportion of patients with less severe COPD and who were hence less likely to exacerbate. However, although the stability of exacerbation phenotype was statistically likely in both cohorts, past history as a predictor of future episodes was at best marginally better than tossing a coin. The implications of this theoretical and observational analysis may not influence the statistical outcome of large clinical trials but means a rethink of how our personalised algorithms of patient management should be designed. Unless of course, we remain happy to manage COPD as if each is the average patient with the average likelihood of exacerbations using the average therapeutic strategy: surely a retrograde step in individual patient management and a move towards triple therapy for all, which clearly has a financial impact, and a one course fits all management plan. In a synchronous publication the same group published the outcome of a new tool (ACCEPT) which takes into account multiple other factors from the placebo arms of several large interventional studies [15]. This tool, using relatively easily obtainable features, including the previous number of episodes, in addition to age, sex, smoking status, FEV_1, St George's Respiratory Questionnaire score, body mass index and medications. This tool proved better (at least statistically) than history alone in predicting future episodes, although the receiver operating characteristic (ROC) curves look less convincing. However, the ROC curves for severe (hospital admission) episodes do show a clearer advantage using the composite dataset advocated in ACCEPT.

The alternative is to bin the term "frequent exacerbator" and move towards the "recurrent exacerbator" based on accurate monitoring of episodes and defining their nature. This requires a change of approach with a proactive format and based (as with GOLD [12]) on a newly diagnosed patient, be that at hospital admission or first medical visit achieving a diagnosis.

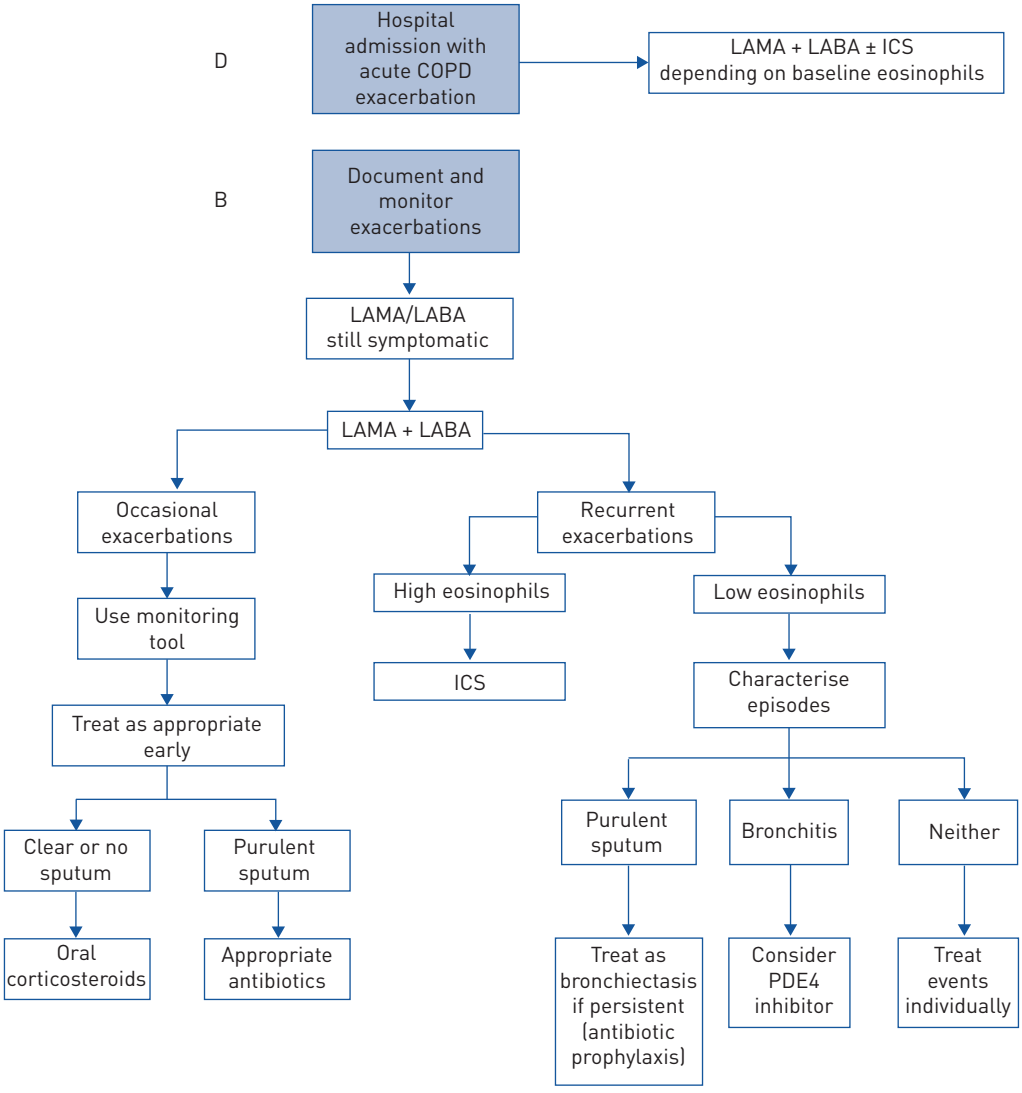

FIGURE 1 Implications for the Global Initiative for Chronic Obstructive Lung Disease (GOLD). For new patients with a high symptom load, GOLD places them in box B or D, depending on the exacerbation history. One hospital admission still places the patient in box D and the current algorithm still applies. However, if the patient has a history of two or more exacerbations the current publication [13] suggests this cannot be assumed to be a long term pattern. Therefore, it seems logical to put such new patients into box B and start therapy with a long-acting β-agonist (LABA) or long-acting muscarinic antagonist (LAMA) and review progress, changing or adding the alternative depending on symptom response. The use of a monitoring tool to document and characterise exacerbations and provide relevant rescue packs seems reasonable for sporadic events. For those with multiple recurrent events, the addition of inhaled corticosteroids (ICS) may be indicated if the eosinophil count is high [16], but alternative strategies would be indicated for those with low eosinophil counts depending on the documented features of the COPD patient and the characterisation of the episodes.

The former clearly represents a severe event and such patients would still be classified as GOLD group D, as indicated in figure 1, and should be managed along the current algorithm with dual bronchodilator therapy, with or without inhaled corticosteroids (ICS) depending on baseline eosinophil count [16]. However, a different strategy might be more applicable, based on the current weakness of previous history to tip the patient from box B to box D as intimated by the current paper by Sadatsafavi *et al.* [13]. Here the approach may be based on the stable state driving symptoms alone, and hence starting in box B, with introduction of a long-acting bronchodilator and a lack of improvement or continuing disabling dyspnoea at follow-up leading to a change or addition of a second agent, respectively.

Continued management should therefore include symptom monitoring and, in particular, documentation of features of exacerbations utilising the Anthonisen criteria together with documented requests for intervention. Its appropriateness will provide a clear understanding of whether the episodes likely represent a bacterial origin (documented purulent sputum episodes) or are on the background of a

documented baseline eosinophilia. Either can be managed on an as-required basis to start with, or if recurrent (three or more per year?) on the basis of an appropriate long term antibiotic or anti-inflammatory strategy (as applied in bronchiectatic guidance) or with the introduction of ICS based on the background eosinophil count [16].

Is it too late to start again?

The answer is likely to be yes for established patients already on a multidrug treatment strategy. However, adapting a more cautious and staged approach for newly diagnosed patients may well be the opportunity to adjust our therapeutic approach. Current therapy (even triple) does not prevent all exacerbations, so it is not just an anti-inflammatory or bronchodilatory strategy we need. Although part of the impact of such a strategy may be to reduce the symptomatology of some episodes, moving them into the "non-reported" category rather than modifying their pathophysiological nature. For instance, although purulent exacerbations are inflammatory and proteinase rich, increasing tissue damage, if they represent the only Anthonisen symptom they are rarely treated [17], which might just be the time to do so and protect lung structure. So our strategy should be to treat both the symptoms of the episode and its nature.

The time has come to review all the lessons of the past 30 years and treat patients as individuals rather than applying statistical generalisations with average outcomes of saving 30% of an exacerbation per patient per year. It is up to us!

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