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- 11 Personalising exacerbation prediction strategies in chronic obstructive pulmonary disease

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## Personalising exacerbation prediction strategies in chronic obstructive pulmonary disease

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### Abstract

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. One of the most important features of this disease is exacerbations where a patient's respiratory symptoms episodically worsen. Exacerbations accounted for over 140000 hospital admissions in 2012 in the United Kingdom with considerably more exacerbations being treated in primary care. Despite significant research in this area in recent years, treatment of acute exacerbations in the community remains limited to oral glucocorticoids, antibiotics and bronchodilators. One of the issues with unpicking the complexity of exacerbations is trying to find out the exact underlying cause and mechanism that leads to symptoms and lung destruction. Currently symptoms are initially guided by symptoms alone though multiple causes of exacerbations have common presentations. This includes viral and bacterial infections and episodes relating to environmental triggers such as pollen and pollution. There is also evidence that cardiovascular factors can contribute to symptoms of breathlessness that can mimic COPD exacerbations. In this editorial we discuss recent advances in the use of precision medicine to more accurately treat exacerbations of COPD. This includes identification of phenotypes that could help rationalise treatment and more importantly identify novel drug targets. We also consider the future role of precision medicine in preventing exacerbations and identifying COPD patients that are at increased risk of developing them.

**Key Words:** Chronic obstructive pulmonary disease; Exacerbations; Phenotypes; Endotypes; Precision medicine; Clinical

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exacerbations they suffer are complex and heterogenous in nature. They should all be treated on an individual basis with detailed clinical history and initial work up to better understand the impact it is having on their life. Careful consideration of the benefits of treatment should be weighed up against the risks of their side effects to ensure the maximum benefit of treatment. Precision medicine is starting to appear in management of COPD, both for acute exacerbations and their prevention.

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable chronic lung condition that is projected to be the third leading cause of death globally by 2030. It is a diverse disease with a wide variation in symptoms and severity and associated comorbidities including osteoporosis<sup>[1]</sup> and sarcopenia<sup>[2]</sup>. One of the most important features of COPD are episodes of acute worsening of respiratory symptoms, more commonly known as exacerbations. Such episodes often require additional therapy in an attempt to reduce their impact, duration and limit damage to the lungs. COPD exacerbations are associated with increased mortality<sup>[3]</sup>, worse quality of life<sup>[4]</sup> and more rapid lung function decline.

There has been little change to the repertoire of therapies available to acute exacerbation of COPD (AECOPD) in the last 30 years<sup>[5]</sup>. The main stay of treatment remains oral glucocorticoids and inhaled bronchodilators plus antibiotics if a bacterial infection is suspected<sup>[6]</sup>. Treatment of COPD exacerbations in the community is mainly based on symptoms alone. Since the symptoms of COPD exacerbations are the result of numerous possible aetiologies (infection, environmental, psychological, cardiovascular) with little in the way of features that can predict the exact cause, most are treated with a “one size fits all” approach.

COPD patients also suffer with marked variation in day to day symptoms including breathlessness, sputum production, sputum colour, fatigue and levels of stress and anxiety. This presents a challenge for physicians to accurately treat exacerbations. How can a distinction be made between the usual daily variation in symptoms and an emerging exacerbation?

It is clear that more sophisticated and personalised approaches are required to improve accuracy of treating COPD exacerbations and crucially early identification of moderate or severe exacerbations to enable prompt treatment. Precision medicine has been defined as “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations<sup>[7]</sup>”. The ultimate aim of personalised medicine is to improve clinical outcomes for patients whilst avoiding side effects for those who are unlikely to benefit from therapy<sup>[7]</sup>. In the context of treating COPD exacerbations this means diagnosing and treating patients based on factors that separate exacerbations into unique phenotypes. This is likely to include measurement of biological samples (blood, urine or sputum) during the early phase of an exacerbation and potentially by monitoring them at regular intervals to detect when an exacerbation is developing. Such advanced near patient testing is on the horizon with the development of more reliable and cost-effective methods of measuring patient biomarkers in a primary care setting<sup>[8]</sup>.

Precision medicine for COPD exacerbations could also mean identifying those at an increased risk of future exacerbations and tailoring treatment to individuals to reduce the rate and impact of them on the patient. This again is likely to involve cross sectional biomarker measurement or even genetic analysis.

## PERSONALISED APPROACHES TO TREATMENT OF ACUTE EXACERBATIONS

Exacerbations have numerous causes, often with similar presentations, namely breathlessness and sputum production. Similar symptoms do not infer similar underlying pathophysiology. For example, a bacterial exacerbation may respond well to antibiotics but may be worsened by the use of steroids due to immunosuppression. Equally, exacerbations with an allergic or environmental trigger may have little or no response to antibiotics and expose the patient to side effects and potential antibiotic resistance needlessly. It is also difficult to be sure which types of exacerbations lead to lung destruction (if at all). Causes of exacerbations that mimic symptoms of “true” AECOPD, such as those triggered by cardiogenic factors by stress or anxiety, may not be associated with underlying damage to lung tissue or disease progression. Discovery of exacerbation phenotypes; traits that are observed clinically or functionally, or even endotypes; cellular and molecular pathways involved in the pathogenesis of the disease, would enable more personalised treatment of acute episodes<sup>[9]</sup>. This is likely to include use of symptoms, physiological measurements or biomarkers to stratify exacerbations.

The acute phase protein C reactive protein (CRP) is a widely used clinical biomarker of inflammation and infection<sup>[10]</sup> and several studies have looked at its usefulness as a biomarker to select patients who would benefit from antibiotics during COPD exacerbations<sup>[8,11]</sup>. Most studied hospitalised patients and though use of CRP to guide treatment was non-inferior and led to a reduction in antibiotic use it did not lead to any improvement in other outcomes. Only the PACE study<sup>[8]</sup> has carried out a randomized controlled trials (RCT) of COPD patients in a primary care setting and results of other studies may not be generalisable to the majority of COPD exacerbations that are treated in the community.

Procalcitonin has also been touted as a potential biomarker though currently its expense and lack of availability in routine clinical care make it less attractive<sup>[12]</sup>.

As with predicting future risk using eosinophils, acute treatment of exacerbations with oral glucocorticoids in those patients with higher eosinophil counts was found to be non-inferior to standard treatment in hospitalised patients<sup>[13]</sup> and further adds merit to the theory of the eosinophilic exacerbation phenotype.

Despite their promise, use of CRP and procalcitonin to guide antibiotic treatment and eosinophils to guide use of oral glucocorticoids may be seen as a backward step. Instead of pioneering new treatments for exacerbations it is merely rationalising old ones. To truly move forward into the age of precision medicine we must identify specific exacerbation endotypes with the hope of identifying novel drug targets. In order to achieve this, we must deepen our understanding of the pathophysiological process's involved in the early and established stages of the exacerbation period.

An alternative to measuring direct markers of inflammation is to identify biomarkers that represent organ or tissue damage. One well established example is troponin which has revolutionised triage of patients with myocardial infarction<sup>[14]</sup>. It has been proposed that COPD exacerbations should be considered “lung attacks” with each episode furthering damage to the lungs with consequences for future morbidity and mortality<sup>[15]</sup>. Markers of elastin degradation have been proposed as the lung equivalent biomarker of lung tissue destruction since loss of alveolar elastic tissue within the lungs is the main contributor to pulmonary emphysema, a process driven by an imbalance of proteases and anti-proteases<sup>[16]</sup>. This has led to particular interest into elastin degradation products as biomarkers of emphysema progression<sup>[17]</sup> and pulmonary exacerbations of COPD<sup>[18]</sup> though it has proved difficult to validate clinically<sup>[19,20]</sup>. Elastin is also found in blood vessels<sup>[21]</sup> and therefore “non-lung” elastin may introduce additional noise to the data. Furthermore, in advanced pulmonary emphysema the baseline desmosine level may be lower since there is less lung tissue left to be broken down, independent of disease activity<sup>[22]</sup>, making direct comparisons difficult.

An emerging area of study is the role of the lung microbiome and its influence on exacerbations<sup>[23]</sup>. Advances in DNA sequencing in recent years has allowed for sophisticated profiling of the lung microbiome, something that traditional cell culture could not achieve consistently. The interplay between the host immune system and lung microbiota are complex but studies have shown the relative abundance and variety of bacteria within the respiratory tract is dynamic between stable state and exacerbations<sup>[24]</sup>. This may provide new opportunity for identifying biomarkers of exacerbations and crucially new therapies<sup>[25]</sup>.



## PREDICTING FUTURE EXACERBATIONS OF COPD

Assessing individual risk of having pulmonary exacerbations forms a key part in choosing initial and subsequent therapy. Stratifying COPD exacerbation risk continues to be a challenge, particularly when a COPD patient is first diagnosed. Analysis of data from the SPIROMICS cohort in 2017 found marked variation in annual frequency of moderate to severe exacerbations requiring hospitalization<sup>[26]</sup>.

Spirometry is a useful tool to assess COPD severity, and those with a forced expiratory volume in 1 s (FEV<sub>1</sub>) < 50% predicted are at higher risk of suffering with exacerbations. Although GOLD severity level correlates with risk of COPD exacerbations, FEV<sub>1</sub> alone varies too widely to be a reliable predictor. It is, however, useful in conjunction with other patient factors<sup>[3]</sup>. Deteriorating airflow obstruction is associated with increasing prevalence of exacerbations and hospitalisations<sup>[27]</sup>. An important predictor of future exacerbations is a previous history of pulmonary exacerbations<sup>[28]</sup> and should be asked about in all patients with COPD.

In recent years there has been research interest in the role of eosinophils in precision prevention of exacerbations of COPD. A recent systematic review<sup>[29]</sup> examined the results of 11 post-hoc analyses of RCTs ( $n = 25881$ ) and 5 retrospective observational studies ( $n = 109704$ ) of the effect of inhaled corticosteroids (ICS) on COPD exacerbation rates. They found a treatment effect at both a cut off of  $\geq 2\%$  (RR, 0.80, 95%CI, 0.74-0.85) and  $\geq 150$  cells/ $\mu$ L blood eosinophil count (RR, 0.65, 0.52-0.79), though there was no observed effect in 4 of the 5 observational studies. The most recent GOLD guidelines have since incorporated eosinophil count to be considered as a factor for starting an ICS in those with a higher eosinophil count in combination with clinical assessment of exacerbation risk<sup>[6]</sup>. Blood eosinophils are a good example of precision medicine in action today and its use as a biomarker for future exacerbations may mean that patients with a low eosinophil count will avoid unnecessary side effects such as osteoporosis<sup>[30]</sup> who would have ordinarily received an ICS as part of routine care.

There are other factors that may influence a decision to use ICS in patients with COPD. In those with a previous history of asthma or significant bronchodilator reversibility it may be beneficial to add in ICS therapy. Risk of pneumonia should always be thought about too, especially in the elderly, those with a low body mass index and patients with bronchiectasis<sup>[31]</sup>. These may be considered “treatable traits” and may be a flexible alternative to splitting COPD patients into rigid phenotypes<sup>[9]</sup>.

High eosinophils are also an example of a COPD phenotype in which a patient characteristic is associated with a clinically meaningful outcome, namely exacerbations. The underlying mechanism for eosinophilic exacerbations remains poorly understood but clinical trials that target inflammatory pathways that involve eosinophils have show promise<sup>[32,33]</sup>.

Other biomarkers of exacerbation risk have been explored *via* large cohort studies but have been unsuccessful so far. Comparison of SPIROMICS and COPD gene data ( $n = 2146$  patients in total) showed no biomarker candidates that can predict retrospective self-reported exacerbations or prospective exacerbations as defined by health care use<sup>[34]</sup>.

## FUTURE DIRECTIONS

Early changes in the inflammatory profile of an exacerbation may be key to understanding the downstream effects. It is well known that several inflammatory cells have similar end points in activating the immune system<sup>[5]</sup>. If these early changes could be found then it may shed more light on the cause of an exacerbation. This is not easily done in a hospital setting but could be achieved in clinical trials with the use of home biomarker monitoring paired with symptom diaries. This would capture subclinical episodes and daily fluctuations that would otherwise be missed when using the healthcare utilisation criteria for exacerbations. It must be noted that even if a suitable biomarker is found, acceptable and applicable methods would need to be available and cost effective in order to make it clinically useful.

## CONCLUSION

Currently limited therapies are available for the treatment and prevention of COPD exacerbations beyond antibiotics, oral and inhaled steroids and bronchodilators<sup>[35]</sup>. This is in part due to challenges in identifying clinically meaningful endotypes for

COPD and stunted development of targeted therapies. Studies have also often excluded certain subgroups of COPD, such as those with other comorbidities, and subsequent poor identification of COPD endo/phenotypes. There have, however, been promising results from studies in eosinophilic COPD with further phenotypes emerging from more recent studies. In combination with advancements in near patient testing technologies there is hope for more precise treatment of COPD exacerbations in the near future.

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