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**How should we treat COPD exacerbations in the future?
By Endophenotyping, Of Course!**

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Chronic obstructive pulmonary disease (COPD) affects over 400 million worldwide and is responsible for three million deaths every year.^{1,2} The incidence of COPD is projected to increase in years to come.^{1,2} Most of the COPD deaths occur during acute exacerbations. Even among survivors, exacerbations negatively impact their quality of life, accelerate declines in lung function, and impose significant personal and economic costs. Chronic therapies in COPD aim to reduce the risk of exacerbation, but even with the best of current treatment options, many patients continue to suffer from recurrent exacerbations.³ In the last few decades, the treatment of acute COPD exacerbations has generally relied on a one-size-fits-all approach with antibiotics and systemic corticosteroids.⁴ However, we argue that this empiric approach is outdated given our improved understanding of exacerbation endophenotypes in COPD and the development of precise therapies for airway diseases.⁵ Here, we discuss how integration of biomarkers helps to classify exacerbation endophenotypes and guide therapies in the future.

In clinical practice, diagnosing a respiratory exacerbation as a distinct event from day-to-day symptom variation can be challenging due to the lack of a validated and precise definition.⁴ In 1987, Anthonisen and others first described an exacerbation as the symptoms of increased dyspnea, sputum production, and sputum purulence.⁶ This definition was based on subjective description and lacked specificity. In 2022, the Lancet Commission on COPD defined respiratory exacerbation as an increase in symptoms driven by pathophysiological activity.³ Thus, diagnosing an exacerbation should include an objective demonstration of a significant decline in airflow limitation, an increase in ventilation heterogeneity, an augmentation of airway or systemic inflammation, or evidence of acute bacterial or viral infection, in the absence of an alternative diagnosis.³ This should prompt clinicians to collect lung function, imaging, and/or laboratory data to support a diagnosis of COPD exacerbation rather than relying on history and physical examination alone and prescribing empiric therapy.

Acute COPD exacerbations result from biologically distinct endophenotypes of airway inflammation.⁷⁻⁹ In a study by Bafadhel et al.,⁷ among 182 acute COPD exacerbations (from 86 COPD patients), 55% were deemed to be caused by a bacterial infection; whereas 29% of the events were triggered by a viral infection. Regardless of the microbial trigger, approximately 30% of the exacerbations were characterized by a predominance of eosinophilic or type 2 inflammation, while the remainder showed mostly neutrophilic inflammation.⁷ Identifying the endophenotype helps to guide treatment of current and future exacerbations because the exacerbation endophenotype tends to be consistent longitudinally.⁸ Bacterial and eosinophil-driven exacerbations also tend to be more recurrent in nature compared to viral exacerbations.⁸

Importantly, exacerbation endophenotypes are indistinguishable based on clinical features alone. This calls for the need to integrate biomarkers in the algorithm of exacerbation management. Biomarkers are measurable indicators that reveal the underlying pathobiological mechanisms.¹⁰ Broadly speaking, the utility of biomarkers is in differentiating between an infectious and non-infectious respiratory exacerbation. To identify a bacterial infection-associated exacerbation, serum biomarkers such as C-reactive protein (CRP) and procalcitonin have moderate evidence from heterogeneous studies that support its value in predicting the presence of bacterial pathogens in the sputum of patients with exacerbations.¹¹ Other sputum biomarkers, such as interleukin (IL)-1 β , have been investigated. Using a cut-off 125 pg/ml, sputum IL-1 β had a sensitivity of 90% and a specificity of 80% (area under receiver operating characteristic curve, AUROC = 0.89 (95% CI, 0.83–0.95)).⁷ To identify a viral infection-associated exacerbation, serum CXCL10 with a cut-off of 56 pg/ml provided a sensitivity of 75% and specificity of 65% (AUROC = 0.76 (95% CI, 0.67–0.86)).⁷ The clinical relevance of using biomarkers to identify a bacterial infection-associated exacerbation is to select patients who may benefit from antibiotic treatment alone.

Blood eosinophil counts are the most studied biomarker and may indicate the presence of type 2 airway inflammation in acute exacerbations. The presence of airway eosinophilia helps to guide the use of oral corticosteroids.¹² The role of blood eosinophil counts in representing airway eosinophilia and guiding therapies during acute COPD exacerbations is more controversial. In one study, a blood eosinophil cut-off of 2% had a sensitivity of 90% and specificity of 60% for identifying type 2 airway inflammation (AUROC = 0.85 (95% CI, 0.78–0.93)).⁷ In a recent multicentre, randomised, double-blind study by Ramakrishnan et al., a blood eosinophil-guided oral prednisolone therapy was non-inferior for the primary endpoint of treatment failure relative to standard care in the treatment of acute COPD exacerbations.¹³ Furthermore, in approximately 33% of the patients in the eosinophil-guided arm of the study, systemic corticosteroid therapy was fully avoided because their blood eosinophil counts were below 2% at the time of enrolment.¹³ In contrast, 100% of patients in the standard care arm received 14 days of systemic corticosteroids.¹³ By using blood eosinophil counts to guide therapy, the overall systemic corticosteroid exposure was reduced by half compared with the standard approach of treating all patients with steroids during exacerbations. Findings of this study and those of other previous randomized trials show that the blood eosinophil count identifies patients who are likely to benefit with systemic corticosteroid treatment from those who probably would not, and this practice can help reduce the exposure and toxicity of empiric corticosteroid therapy.^{13,14}

The detection of eosinophilic exacerbations is a promising and exciting area of research because of the development in biologic therapies that precisely inhibit type 2 airway inflammation. In a recent phase-2 trial called ABRA (Acute exacerbations treated with BenRALizumab), the long-lasting eosinophil-depleting effects of benralizumab, an interleukin-5-receptor antibody, were explored in the setting of acute eosinophilic respiratory exacerbations for patients with asthma (56% of patients), COPD (32% of patients) or asthma-COPD overlap (12% of patients).¹⁵ Benralizumab targets the alpha subunit of the IL-5 receptor to induce antibody-dependent cell-mediated cytotoxicity and to deplete circulating eosinophils with sustained effects over 12 weeks. In ABRA, compared to patients who were treated with systemic prednisolone (30mg daily for 5 days) alone, patients who received one 100mg subcutaneous dose of benralizumab (either alone or with prednisolone) in an urgent care setting experienced fewer respiratory symptoms at 28 days and an astonishing 74% relative risk reduction (and a 28% absolute risk reduction) in treatment failure (defined as a composite of death, hospitalization, or need for re-treatment) at 90 days of follow-up.¹⁵ The results were similar across all disease subtypes: asthma (56% relative risk reduction), COPD (57% relative risk reduction), and asthma-COPD overlap (31% relative risk reduction).¹⁵ If these findings can be generalized into the clinics, the number needed to treat with benralizumab would be only 4 to prevent 1 treatment failure event.¹⁵ The findings of ABRA need to be validated with larger, more robust studies. Nevertheless, this study marks a paradigm shift from a non-discriminatory approach to a more refined, biomarker-guided approach in managing patients with COPD exacerbation.⁵ In contrast to the success in targeting eosinophilic inflammation, biologics targeting non-eosinophilic or neutrophilic inflammation have largely been disappointing and remain an area of research need. **Figure 1** summarizes the conceptual approach to how COPD exacerbations should be treated in the future. The key message is that we must move away from the current one-size-fits-all diagnosis and management approach. We emphasize the importance of defining inflammatory endophenotypes because COPD exacerbations are heterogeneous. We argue for the integration of appropriate biomarkers to guide treatment decisions. There is a pressing need to investigate accessible and robust biomarkers that can translate into clinical practice. With the growing incidence of COPD, appropriate treatment of acute exacerbations continues to be an important priority among chronic respiratory diseases.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

No

3. Does your study include a clinical trial?:

No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

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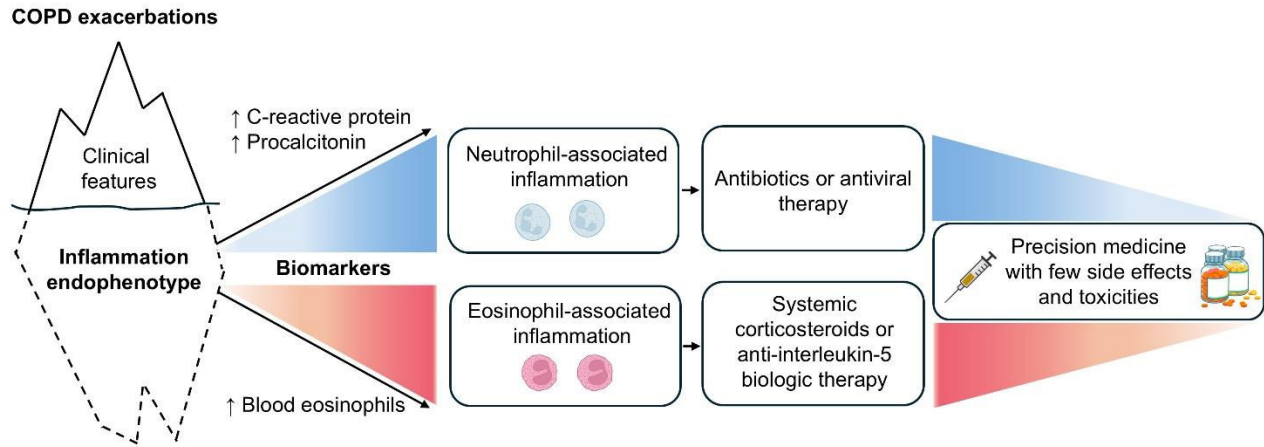
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Figure Legend

Our proposed conceptual approach to management of COPD exacerbations in the future. Biomarkers are used to differentiate airway inflammation endophenotypes. High blood eosinophil counts (often defined as $\geq 2\%$ or ≥ 300 cells/ μl) indicate eosinophil-associated inflammation. The absence of high blood eosinophil counts, along with other supportive biomarkers such as elevated C-reactive protein and elevated procalcitonin, indicates neutrophil (or infection)-associated inflammation. Inflammation endophenotyping helps to guide appropriate management in acute COPD exacerbations to achieve precision medicine with few side effects and toxicities.



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