Occluding mucous airway plugs in patients with obstructive lung diseases: a new treatable trait?

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Identifying mucous plugs by chest CT should be considered carefully because it is potentially a treatable trait https://bit.ly/4gyJHFW

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Chronic mucous hypersecretion (CMH), often manifested clinically by chronic productive cough (*i.e.* chronic bronchitis), is a well-described feature in several obstructive lung diseases, including asthma, COPD and bronchiectasis. In COPD, it is associated with accelerated loss of lung function [1] and increased frequency of exacerbations [2]. It occurs in 25% of patients with asthma and is associated with a higher frequency of exacerbations and lung function impairment [2]. Finally, it is a common clinical feature in patients with bronchiectasis [3]. Moreover, these conditions can overlap. For instance, bronchiectasis can be detected in computed tomography (CT) scans in about 30% of patients with COPD, and they are associated with chronic bronchial infections, exacerbations, enhanced lung function decline and increased mortality [4]. Importantly, eliminating *Pseudomonas aeruginosa* colonisation reduces disease progression and improves prognosis in COPD [4, 5].

On the other hand, CT of the chest identifies airway mucous plugs occluding subsegmental airways in 25% to 67% of COPD patients, which may persist for up to 5 years in almost three-quarters of them [6]. Importantly, these airway mucous plugs in COPD are associated with all-cause mortality after adjusting for potential confounding factors (including current smoking status, cumulative smoking exposure (pack-years), demographics and body mass index, lung function and airway wall thickness on CT scan, asthma, emphysema, and cardiovascular comorbidities) [6]. The higher the number of lung segments with mucous plugs on CT scans, the higher the mortality [6]. Of note, however, is that the relationship between mucous plugging and CMH or chronic bronchitis is unclear; indeed, chronic bronchitis is absent in 30% of COPD patients with airway mucous plugs [6]. Further, whether these observations can be reproduced in patients with asthma or bronchiectasis needs further investigation. In any case, they are potentially highly clinically relevant. They suggest that airway mucous plugging can be viewed as a novel treatable trait (TT) in patients with chronic airway diseases [2, 7].

TTs are identifiable, clinically relevant, non-mutually exclusive, measurable characteristics of patients with chronic airway diseases. The NOVELTY study has shown that the number (mean±SD) of TTs identifiable in each patient was 4.6±2.6 in those with diagnosed asthma, 5.4±2.6 in those diagnosed with COPD, and 6.4±2.8 in those with both diagnoses [8]. Importantly, TTs often overlap across diagnoses. For instance, chronic bronchitis was present in all these obstructive lung diseases [8]. The TT approach is agnostic to traditional diagnostic labels and proposes searching and treating potential TTs in each patient. Considering the above, we believe that airway mucous plugging is a novel TT in patients with chronic airway diseases.

Then, the question would be: how can we treat it? Airway clearance techniques are essential to controlling and addressing airway mucous plugging, impaired mucociliary clearance and related symptoms in bronchiectasis [9]. In COPD, a systematic review and meta-analysis of randomised controlled trials showed that airway clearance techniques significantly improved sputum clearance and symptom burden and reduced exacerbation frequency by 30% to 50% [10]. Other potential therapeutic alternatives to reduce chronic mucous hypersecretion could consider: 1) altering mucin biosynthesis (MUC5AC secreted by goblet cells and/or MUC5B secreted by submucosal glands) [11]; 2) interfering with mucus structure to achieve the right degree of density and viscosity (*e.g.* by selective EGFR tyrosine kinase inhibitors inhibiting peptides related to myristoylated alanine-rich C kinase substrate (MARCKS)); 3) targeting calcium-activated chloride ion channel 1 (CLCA1). [11, 12]; and/or 4) enhancing mucin clearance by hydrating or mucolytic antioxidant agents like *N*-acetylcysteine (NAC) [13]. To date, NAC is the only option tested in clinical trials. While some older NAC studies failed to prevent exacerbations and deterioration of lung function in "all comers" COPD patients [14], in selected subgroups (*e.g.* patients not receiving inhaled corticosteroids) [14] or in randomised controlled trials with higher doses, NAC reduced exacerbation rates [15]. The efficacy may be even greater if patient selection is more TT-oriented (*i.e.* selecting patients with evidence of mucous plugging on CT). It is interesting to note here, too, that biological treatments in asthma (*e.g.*, tezepelumab, dupilumab) lessened the severity of mucous plugging and that some of these biologics are now available for a selected group of COPD patients with a T2 trait [16].

In conclusion, we propose that identifying mucous plugs by chest CT should be considered carefully in the clinical evaluation of patients with chronic airway diseases because it may be a potential TT (figure 1) [8]. These are exciting times in respiratory medicine because treating chronic respiratory disorders is making significant steps toward personalised treatment.

FIGURE 1 Mechanisms of excess airway mucus in chronic obstructive respiratory disorders: a potentially treatable trait.

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