Persistent Airway Plugs: A Call for Clinical Recognition and Novel Therapies

Much has been written about mucus accumulation and plugging of the airway lumen as pathologic features of asthma. Sir William Osler (1849–1919) made early clinical descriptions of "gelatinous mucus expectoration by asthmatics" that were subsequently recognized in pathological specimens by Huber and Koessler (1), Dunnill (2), and many others. Despite this, the role of intraluminal mucus in the clinical presentation of asthma, and its contribution to airflow obstruction, have not been extensively studied. Further, very little attention has been made by most international guidelines to recognize or treat mucus impaction of the airways in asthma, nor is it considered in daily clinical practice. This has likely been in part owing to our inability to directly measure airway mucus plugging *in vivo*, with most of our knowledge gained from postmortem pathology.

In 2018, Dunican and colleagues were the first to describe the radiographic "mucus score" as the summation of bronchopulmonary segments with one or more mucus plugs visualized on computed tomography (CT) lung scans (3). Since this initial report, the recognition of CT as a noninvasive means to quantify the burden of mucus plugging *in vivo* has garnered significant clinical interest. Although the term "mucus plug" has generally been accepted to describe the CT observation of complete occlusion of the airway lumen (3–8), it is important to recognize nuances of the mucus score. First, the composition of CT-visible intraluminal plugs has not been directly characterized and may contain not only mucus but also inflammatory cells, plasma exudate, extracellular traps, and Charcot–Leyden crystals. Second, peripheral airways are beyond the spatial resolution limit of CT, and therefore, the score is representative of mucus plugs in the larger proximal airways. Third, partial occlusions of the airway lumen are not scored. Finally, the score for each bronchopulmonary segment is binary (0 or 1), with no weight given to the proximal location of plugging (segmental vs. subsegmental), plug size, or the number of airways involved within an individual bronchopulmonary segment. Regardless of these uncertainties and potential limitations, cross-sectional cohort studies from the United States (85 of 146 [58%]) (3), United Kingdom (69 of 116 [60%]) (8), and Canada (18 of 27 [66%]) (6) conclusively agree that mucus plugging assessed by the CT mucus score is surprisingly common in severe asthma. With that preface, in this issue of the *Journal*, Tang and colleagues (pp. 1036–1045) take advantage of baseline and Year 3 chest CT scans acquired from the SARP-3 (Severe Asthma Research Program-3) study to provide new information regarding the temporal behavior of airway mucus plugs and their relationship with changes in lung function (9).

Mucus plugs observed on CT were discovered to be a persistent asthma phenotype. This is supported by the observation that 82% of people with asthma with airway mucus plugs reported on their baseline CT also had mucus plugs on their follow-up scan acquired 3 years later. A less compelling but similar observation was made at the level of the bronchopulmonary segment, where 65% of segments with mucus plugs at baseline were reported to have mucus plugs at follow-up. Without additional time points, it is unknown if the plugs truly persisted in the same location throughout the duration of the study or if they resolved and reoccurred. Regardless, the segmental agreement across two time points implicates the local airway environment in the formation of mucus plugs and perhaps a vicious feedback mechanism.

The urgent need to reduce the burden of airway mucus is underscored by the observation that mucus is an important and perhaps dominant contributor to airflow obstruction, asthma severity, and control. Temporal changes in the mucus plug score were associated with changes in airflow obstruction measured by FEV_1% predicted, FVC% predicted, and FEV_1/FVC. These global structure–function associations reported by Tang and colleagues are supported by elegant magnetic resonance imaging studies that visualize the functional consequence of an individual mucus plug on distal airflow obstruction (5, 6). Taken together, there is now compelling evidence supporting a causal role for mucus plugs as a major mechanism of airflow obstruction in asthma.

While there was no net change in the mucus score between baseline and Year 3, decreases in blood and sputum eosinophil counts were associated with decreases in the mucus score. Additionally, asthmatics with persistent mucus plugging had elevated biomarkers of T2 inflammation, including sputum eosinophils and fractional exhaled nitric oxide. This raises the question, "if therapy had been adjusted to normalize sputum eosinophil counts, would the conclusion that mucus plugs are persistent in existence and location hold true?" It seems likely that if steroid doses were adjusted to normalize eosinophils, mucus plugs would concomitantly decrease or resolve. Our own data support this notion as two-thirds of people with severe asthma with $<3\%$ sputum eosinophils were mucus free (6). Furthermore, the expression of MUC5A is decreased when treatment is adjusted to normalize sputum eosinophils (10). However, it is important to recognize that of the SARP-3 subjects with asthma with persistent mucus plugging, 74% were prescribed high-dose inhaled corticosteroids, and 23% were oral corticosteroid dependent. This suggests that mucus plugs are resistant, at least in part, to maintenance corticosteroid therapies. Unfortunately, very few SARP-3 subjects with asthma were receiving monoclonal antibody therapies targeting IL-5 signaling (21 of 164 [13%]); therefore, the study was not powered to comment on the ability of IL-5 blockage to resolve mucus that might be associated with eosinophils. No participants were prescribed dupilumab, which targets the IL-4

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receptor-α that blocks both IL-4 and IL-13 signaling and is of particular interest given what we now know about the signaling mechanism of mucus production (11).

In conclusion, intraluminal mucus or plugs are an important feature of asthma pathophysiology. Tang and colleagues advance this understanding by establishing plugs as a stable asthma phenotype and contributor to airflow obstruction (9), collectively framing intraluminal plugs as a therapeutic target. We share the authors' enthusiasm and call for novel interventions to eliminate intraluminal plugs but also question if old tricks, including the normalization of sputum eosinophils, expectorants, mucoregulators, or mucolytics, may be effective strategies for most people with asthma. The impaction of mucus might also be determined by the anatomy of the airways. Although old mucolytic therapies and expectorants may be partially effective to dislodge impacted mucus, they may not prevent the formation of new mucus. New therapies such as anti-IL4R monoclonal antibodies, directly targeting MUC5 (by aerosolized or other routes), or targeting consequences of mucin crosslinking facilitated by the interaction of thiocyanate and peroxidase (12) might be more effective. It would appear that mucus clearance might be just as important, if not more important, than luminal eosinophil clearing in some patients with severe asthma, and even in milder asthma for symptoms such as cough. The CT mucus score will likely be leveraged as an outcome measure or for participant selection in forthcoming intervention studies. Although CT is a promising tool to assess intraluminal mucus, its limitations must be recognized, and there is a need for optimization, automation, validation, and standardization before integration into daily clinical practice. ■

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Getting to the How and Why: Are Individuals with Chronic Obstructive Pulmonary Disease More Susceptible to the Health Effects of Air Pollution Exposure?

It's practically public health dogma: individuals with chronic obstructive pulmonary disease (COPD) are at increased risk of adverse health effects related to pollution exposure. This assertion is based on a large number of epidemiologic studies demonstrating that short-term exposure to pollutants is a trigger for acute COPD exacerbations, as determined by increased respiratory symptoms, medication usage, urgent care visits, and hospitalizations (1, 2). Long-term pollution exposure has also been linked with increased COPD incidence, severity, and progression (3–6). According to one analysis in the Global Burden of Diseases study, ambient air pollution is the second most common cause of death and disability owing to COPD (7).

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