AER-01:
Mucus Plugs in COPD and Asthma: A Clinical Overview for Healthcare Providers

Mucus Plugs: A Long-Standing Challenge in Lung Disease

Chronic obstructive pulmonary disease (COPD) and asthma affect millions worldwide, causing shortness of breath, persistent cough and frequent hospitalizations. Beyond inflammation, airway remodeling, and bronchoconstriction, mucus plugs – accumulation of thick mucus in airway lumen – are increasingly recognized as a major driver of disease pathophysiology, morbidity, and mortality.[1]

Lung CT imaging studies in COPD and asthma demonstrated that 50-60% of GOLD-3 and GOLD-4 COPD patients and 67% of asthma patients with FEV_1<60%[2] have high mucus plug burden.[2,3] Patients with high mucus plug burden report worse quality of life, more frequent exacerbations, and increased all-cause mortality than patients with no or low mucus plug burden.[4–6]

Why Lung Imaging Matters

Symptoms such as chronic cough or sputum production do not reliably identify patients with high mucus plug burden.[2] High resolution CT scans (HRCT) and image-based scoring provides the most sensitive and specific method to assess and quantify airway mucus plugs.[2]

This scoring system has been successfully applied both in observational and interventional clinical trials, allowing physicians to learn about the relationship between mucus plugs and clinical outcomes and to develop strategies to treat plugging.[7,8]

Pathogenesis of Mucus Plug Formation

Airway inflammation drives changes in mucus composition and structure. Goblet cell hyperplasia and submucosal gland enlargement increase mucus production, while inflammatory mediators alter mucin biochemistry. At the molecular level, oxidative stress causes excessive disulfide cross-linking between mucin polymers, creating a highly elastic gel that resists clearance by ciliary transport or coughing and blocks airflow.[9] Breaking these abnormal cross-links pharmacologically represents a rational approach to restoring mucus clearance and improving airway function.

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[1] Diaz, A. A. Beyond Bronchodilation and Airway Inflammation: Mucus Plugs as a Therapeutic Target in COPD. Chest,167 34–36 (2025).
[2] Dunican, E. M. et al. Mucus plugs and emphysema in the pathophysiology of airflow obstruction and hypoxemia in smokers. Am J Respir Crit Care Med 203, 957–968 (2021).
[3] Dunican, E. M. et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest 128, 997–1009 (2018).
[4] Diaz, A. A. et al. Airway-Occluding Mucus Plugs and Mortality in Patients with Chronic Obstructive Pulmonary Disease. JAMA 329, 1832–1839 (2023).
[5] Wan, E. et al. Airway Mucus Plugs on Chest Computed Tomography Are Associated with Exacerbations in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 211, 814–822 (2025).
[6] Chan, R., Duraikannu, C. & Lipworth, B. Clinical Associations of Mucus Plugging in Moderate to Severe Asthma. J Allergy Clin Immunol Pract 11, 195-199.e2 (2023).
[7] Castro, M. et al. Effect of dupilumab on exhaled nitric oxide, mucus plugs, and functional respiratory imaging in patients with type 2 asthma (VESTIGE): a randomised, double-blind, placebo-controlled, phase 4 trial. Lancet Respir Med 13, 208–220 (2025).
[8] Nordenmark, L. H. et al. Tezepelumab and Mucus Plugs in Patients with Moderate-to-Severe Asthma. NEJM Evidence 2 (2023).
[9] Yuan, S. et al. Oxidation increases mucin polymer cross-links to stiffen airway mucus gels. Sci Transl Med 7, 276ra27 (2015).

Limitations of Existing Therapies

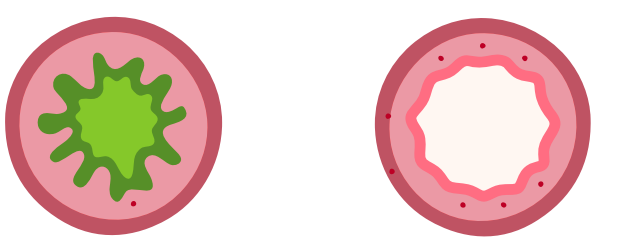
Older mucolytics like Mucomyst (inhaled acetylcysteine) and Pulmozyme (recombinant human DNAse) are used to thin mucus in conditions like cystic fibrosis but are not designed or not approved to treat the specific pathobiology of COPD or asthma. Limitations of these therapies include:

- Mucomyst® (acetylcysteine): Mucomyst has limited use in obstructive lung diseases due to low potency, strong odor and risk of bronchospasm (poor patient tolerability).[10]
- Pulmozyme® (dornase alfa): Pulmozyme is effective in cystic fibrosis, where sputum contains abundant DNA. In COPD or asthmatic sputum, mucins, not DNA, are the most abundant component (lack of target).[11]

Biologic agents such as dupilumab (Dupixent®) and tezepelumab (Tezpire®) reduce the upstream inflammation that contributes to mucus plug formation. However, their effects on mucus plugging are incomplete, with persistent plugs still observed in treated patients.[2,7,8] Additionally, these agents have limited utilization in patients with COPD.

AER-01: First-in-class Mucolytic with Potential to Improve Lung Function

AER-01 is a mucolytic agent that was specifically designed to dissolve mucus plugs when administered by inhalation (to the site of action). AER-01 directly cleaves the disulfide cross-links responsible for forming mucus plugs, thereby improving clearance and restoring airflow. In patient-derived sputum samples, AER-01 rapidly reduces viscoelasticity and liquifies pathologic mucus. In an animal model of mucus plugging, AER-01 clears the plugs, reduces inflammation, and improves survival.[12]



Plugged airway | Open airway

> **"AER-01 is unique because it acts directly on the mucus and should be additive or synergistic with the existing treatments for COPD and asthma. When mucus plugs are cleared, other inhaled therapeutics can more effectively reach diseased airways, thereby improving symptoms and overall lung function."**
>
> — William Thelin, PhD
> SVP, Drug Development
> Aer Therapeutics

[10] Acetylcysteine Solution: Prescribing Information.
[11] Pulmozyme (dornase alfa) Inhalation Solution: Prescribing Information.
[12] Addante, A. et al. A novel thiol-saccharide mucolytic for the treatment of muco-obstructive lung diseases. Eur Respir J 61:2202022 (2023).

Clinical Trials with AER-01:

Aer Therapeutics evaluated the safety and tolerability of AER-01 in a Phase 1 study in healthy volunteers, where AER-01 demon-strated a strong safety profile across a wide range of doses and dosing duration. These results enabled Aer to advance AER-01 into Phase 2 clinical studies in patients with lung disease.

Aer Therapeutics is currently conducting a Phase 2a study (NCT06731959) to evaluate the efficacy, safety, and tolerability of AER-01 in patients with moderate-to-severe COPD.

- **Design: Randomized, double-blind, placebo controlled**
- **Population: Moderate-to-severe COPD**
- **Intervention: Once daily inhalation (nebulizer) for 28 days**
- **Endpoints: Changes in lung function (FEV_1), mucus plug burden, and patient-reported outcomes (COPD questionnaires)**
- **Sites: Australia, New Zealand, and United Kingdom**

Key Takeaways for Physicians

1. Mucus plugs are prevalent in moderate-to-severe COPD and asthma. The presence of mucus plugs is associated with decreased lung function and increased morbidity and mortality.
2. Current therapies manage inflammation and airway tone but cannot clear existing plugs.
3. AER-01 directly liquefies plugs, works rapidly, and complements standard therapies.
4. Phase 2a trial (NCT06731959) is focused on moderate-to-severe COPD patients and is using CT imaging, lung function tests, and patient-reported outcomes to assess efficacy.
5. Patient selection and trial design maximize the ability to detect meaningful improvements.

> **"Our Phase 2a trial is designed with a precision medicine approach: by integrating CT imaging, we can confirm mucus plug burden at baseline and directly measure how AER-01 impacts it and ensure that we are testing the drug in the patients most likely to benefit."**

— Irina Gitlin, PhD
Vice President, Research and Development
Aer Therapeutics

Next Steps

Physicians interested in learning more or referring patients to clinical trials can contact Aer Therapeutics at ***clinical@aertherapeutics.com.***