The role of mucus plugging in severe asthma

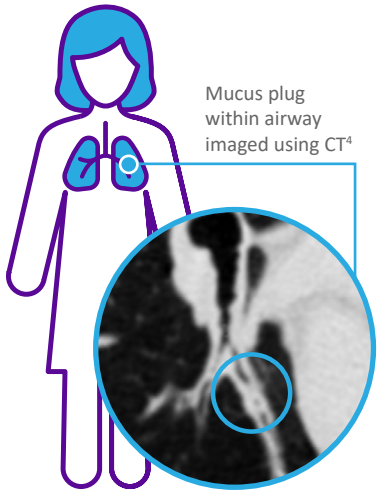
In inflammatory airway diseases, mucus plugging occurs when pathologic mucus accumulates in the airways and obstructs airflow[1]

Mucus plugging is recognized as a contributory factor to airway obstruction and symptoms in persistent asthma[1,2]

- Autopsy studies of fatal asthma demonstrated extensive airway mucus plugging.[1] Lung specimens remained inflated because of air trapping from intraluminal mucus plugging[1]
- Mucus plugs are frequently recovered from the bronchoalveolar lavage fluid of patients experiencing acute asthma exacerbations[1]

Identifying mucus plugs

CT imaging of the lungs is a non-invasive method for quantifying the presence and extent of mucus plugging[1]

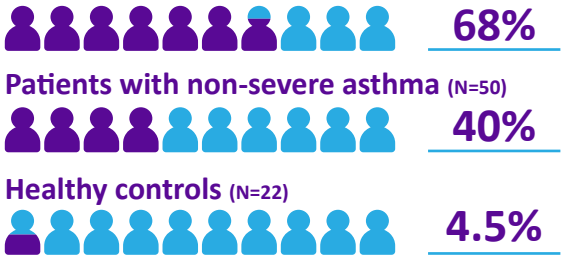


Scoring mucus plugs

Based on the assessment of 20 bronchopulmonary segments, a score of 0–20 is given according to the number of segments with ≥1 mucus plug, for which mucus plugs are defined as complete occlusion of a bronchus[3]

Score	Mucus plug group
0	Zero
0.5–3.5	Low
4–20	High

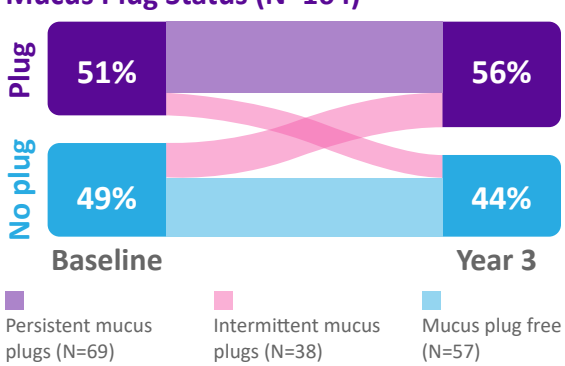
Airway mucus plugs are present in the majority of patients with severe asthma[3,a]



Percentage of patients with ≥1 mucus plug present

Mucus plugs persist over time

In SARP-3, **82%** of patients with mucus plugs at baseline had mucus plugs at year 3[5,b]



IL-5 and IL-13 can stimulate the formation of mucus plugs[1]

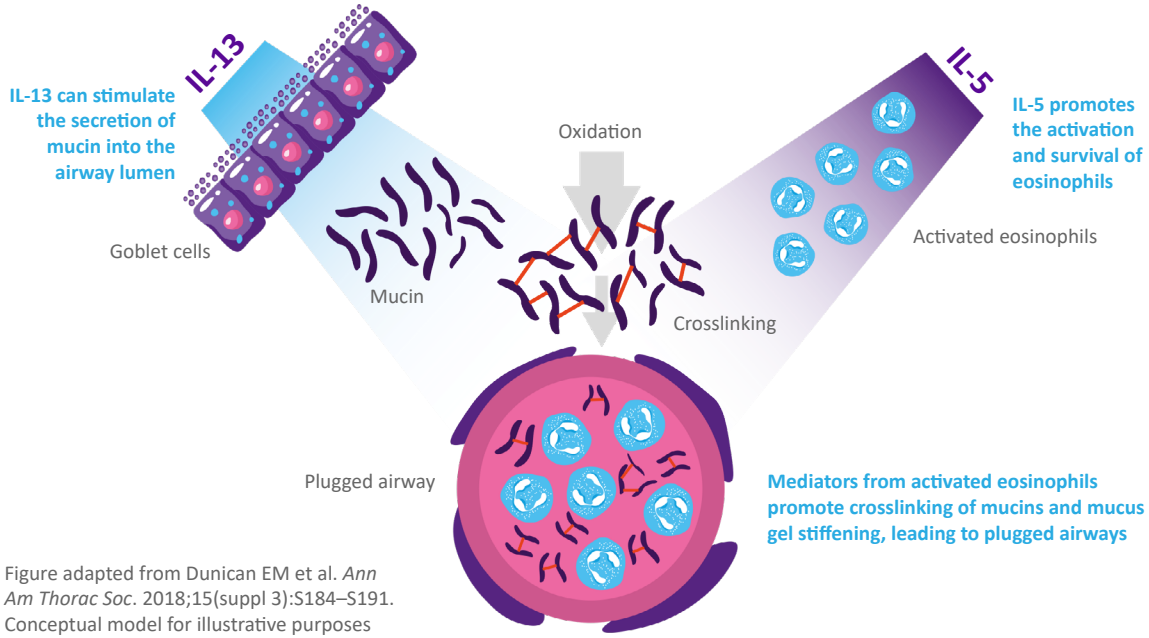


Figure adapted from Dunican EM et al. *Ann Am Thorac Soc*. 2018;15(suppl 3):S184–S191. Conceptual model for illustrative purposes

Mucus plugs are associated with elevated markers of T2 inflammation[3]

Sputum gene expression of IL-13 and IL-5 was significantly increased in patients with a high mucus plug score compared with low and zero subgroups and remained increased following SCS treatment[3,c]

↑ IL-13 mRNA

↑ IL-5 mRNA

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Why is mucus plugging clinically important?

Increased risk of severe airflow limitation

Patients with persistent mucus plugs were **10x** more likely to have severe airflow limitation[5,b,d]

Persistent mucus plugs (N=69)

46%

Mucus plug free (N=57)

4%

Percentage of patients with FEV_1 <60% predicted

Mucus plugs can persist despite conventional therapies, suggesting a need for additional management strategies[5,g]

Increased maintenance corticosteroid use

SCS use was approximately **5x** higher in patients with a high mucus plug score compared with those with a zero mucus plug score[3,a]

Patients using SCS

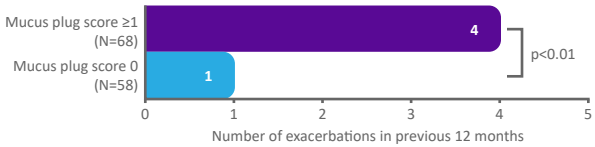
High mucus plug group (N=40) **22.5%**

Zero mucus plug group (N=61) **4.9%**

Increased exacerbations

The number of exacerbations requiring OCS was **4x** higher in patients with mucus plugging than in those without mucus plugging[2,e]

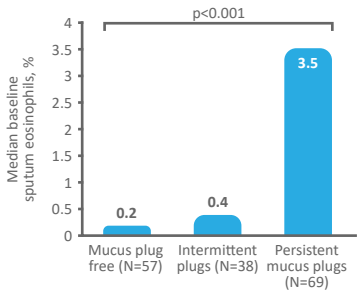
Exacerbations requiring OCS (median)



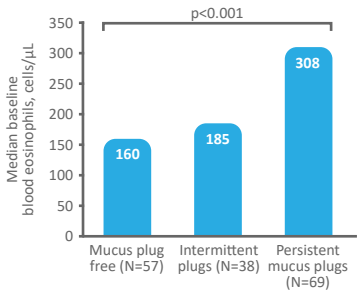
Increased T2 inflammation

Compared with patients without mucus plugs, patients with persistent mucus plugs had higher sputum eosinophils, blood eosinophils, and FeNO[5,b]:

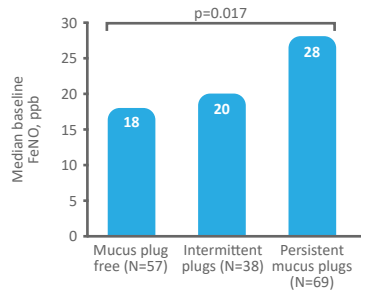
Sputum eosinophils



Blood eosinophils



Fractional exhaled nitric oxide FeNO



Changes in mucus plug score over time are significantly and positively correlated with changes in sputum eosinophils and blood eosinophils[5,b,f]

[a]Study included 146 SARP patients with asthma. Asthma severity was determined using ATS/ERS criteria; [b]Study of 164 patients with asthma and 22 controls enrolled in SARP-3; MDCT lung scans performed at baseline and year 3 to assess mucus plug scores over time; [c]Patients received intramuscular triamcinolone 40mg; [d]Analyzed in relation to changes in lung function measures; p<0.001; [e]Retrospective cohort study of 126 patients with moderate to severe asthma who attended clinic (Jan 2016–Mar 2022); HRCT scanning was performed to analyze relationships between mucus plug scores and clinical features of asthma; number of exacerbations requiring OCS in 12 months prior to HRCT imaging was retrieved from medical records; [f]Annualized rate of change in sputum eosinophils calculated using values from baseline and years 1, 2, and 3; change in blood eosinophils calculated as difference between value at year 3 and baseline; [g]Bronchodilators, inhaled and/or oral steroids, and an intramuscular triamcinolone challenge included in the SARP study design. ATS = American Thoracic Society; CT = computed tomography; ERS = European Respiratory Society; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; HRCT = high-resolution CT; IL = interleukin; MDCT = multidetector CT; OCS = oral corticosteroid(s); ppb = parts per billion; SARP = Severe Asthma Research Program; SCS = systemic corticosteroid; T2 = Type 2. 1. Dunican EM et al. *Ann Am Thorac Soc*. 2018;15 (suppl 3):S184–S191; 2. Chan R et al. *J Allergy Clin Immunol Pract*. 2023;11:195–199.e2; 3. Dunican EM et al. *J Clin Invest*. 2018;128:997–1009; 4. Data on File, REF-176078, AstraZeneca Pharmaceuticals LP; 5. Tang M et al. *Am J Respir Crit Care Med*. 2022;205:1036–1045.

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