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Towards Precision Treatment of Chronic Obstructive Pulmonary Disease Exacerbations: The Role of Specialized Proresolving Mediators

Pharmacologic management to prevent acute exacerbations of chronic obstructive pulmonary disease (COPD) has evolved from a one-size-fits-all approach, with a combination of inhaled long-acting β-agonists, long-acting muscarinic antagonists, and inhaled corticosteroids, to inhaled corticosteroid use guided by absolute peripheral eosinophil counts and the addition of precision-based therapies, including roflumilast in individuals with chronic bronchitis or dupilumab in patients with COPD with evidence of type 2 inflammation (1, 2). Although it is well recognized that exacerbation trajectories vary considerably from individual to individual, our approach to management during the acute exacerbation and recovery period remains relatively uniform. Short-acting bronchodilators, systemic corticosteroids, and antibiotics are mainstays of therapy, often with little regard to the viral, bacterial, or environmental etiology of the acute exacerbation when selecting treatment. This untargeted approach to management reflects current limits to COPD exacerbation phenotyping with a paucity of easily measured biomarkers to enrich patient classification.

In a study reported in this issue of the *Journal*, Finney and colleagues (pp. 803–813) evaluated symptoms, lung function, and specialized proresolving mediators (SPMs), lipid mediators derived from dietary essential fatty acids that promote the resolution of both sterile and infectious inflammation, in participants in the London COPD Exacerbation Cohort at exacerbation onset, one week, two weeks, and six weeks during exacerbation recovery (3). Participants with rhinovirus (RV)–triggered COPD exacerbations experienced persistent decreased lung function and respiratory symptoms compared with those with non-virus-triggered acute exacerbations of COPD. Sputum resolvin D1 (RvD1) and RvE1 concentrations increased significantly from baseline at the onset of acute bacterial, but not viral, exacerbations, and sputum concentrations of both RvD1 and RvE1 were higher at the onset of bacterium-triggered exacerbations compared with acute exacerbations caused by viral infection. Notably, lower concentrations of sputum RvD1 during exacerbation recovery at two weeks were associated with persistent respiratory symptoms. Sputum RvD1 was also positively correlated with proinflammatory mediators at one week (CXCL10), two weeks (IL-6 and MPO), and six weeks (CXCL8) after exacerbation onset.

The authors then performed an elegant series of *in vitro* experiments showing that RV-infected bronchial epithelial cells (BECs) isolated from participants with COPD, but not healthy age-matched control BECs, incubated with RvD1 had reduced IL-6 and CXCL8 secretion. Similarly, incubation with RvD1 resulted

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202503-0658ED on March 28, 2025

in a reduced inflammatory cytokine response in *Haemophilus influenzae*–infected BECs from participants with COPD. Finally, expression of *Arachidonate 5-lipoxygenase (ALOX5)*, which encodes 15-lipoxygenase, an enzyme important in the synthesis of D-series resolvins, was reduced in COPD BECs versus healthy control BECs and in BECs infected with RV. These findings suggest that SPMs, including D-series resolvins, represent an emerging and promising therapeutic area for treating patients with acute exacerbations of COPD because of their proresolving properties that not only reduce inflammation but facilitate clearance of bacterial pathogens and apoptotic cells, as shown in mouse coinfection models in which treatment with aspirin-triggered RvD1 reduced the bacterial load in the lungs and the overall severity of pneumonia without compromising immunity to viral infection (4).

An intriguing finding from this study is the failure to increase the synthesis of RvD1 and RvE1 concentrations during the early phase of a viral exacerbation, which contrasts sharply with bacterial exacerbations, in which RvD1 and RvE1 concentrations rapidly rise, peaking at the onset of the exacerbation and declining with recovery. This raises an important question as to why resolvins did not acutely rise during the early phases of a viral exacerbation. The enzymatic machinery needed for synthesizing SPMs may be compromised in the context of a virus-induced COPD exacerbation. *ALOX5* is highly expressed in bronchial airway epithelial cells, and *ALOX5* encodes for 5-lipoxygenase, which is highly expressed in granulocytes and tissue-resident alveolar macrophages. These enzymes metabolize eicosapentaenoic acid or docosahexaenoic acid into intermediate lipid analogs that are crucial for biosynthesis of resolvins. This study provides some evidence to support this hypothesis, as expression of *ALOX15* was reduced in BECs cultured from patients with COPD compared with healthy individuals. More significantly, *ALOX15* expression was rapidly reduced in RV-infected BECs, whereas in *H. influenzae*–infected BECs, *ALOX15* expression increased. It is possible that RV infection actively interferes with *ALOX15* expression to support viral replication. Further work is needed to investigate the mechanisms controlling reduced *ALOX15* expression during RV infections.

A limitation of the present study is that sputum cells were not analyzed in depth, and it remains unknown whether *ALOX5* expression is altered in myeloid cells during viral exacerbations. It is plausible that in bacterial exacerbations, the early influx of *ALOX5*-expressing neutrophils facilitates increased and robust production of D-series resolvins, in contrast to RV infections, in which neutrophil recruitment may be slower and less pronounced. Similarly, the expansion of monocyte-derived macrophage (MDM) subsets in a pathogen-specific manner may dictate the expression of *ALOX5* and 5-lipoxygenase and ultimately the production of newly synthesized SPMs. During influenza infection, a proportion of tissue-resident alveolar macrophages undergo apoptosis and are gradually replaced with MDMs, which are transcriptionally and functionally distinct (5). Using mouse models of acute respiratory distress syndrome and pneumonia (4, 6), emphysema (7, 8), and asthma–COPD overlap (8, 9), tracked dynamic changes in lung myeloid populations reveal increased lung expression of *CCL2*, expansion of blood monocytes, and robust accumulation of lung MDMs proportional to lung injury severity (4, 6–9). Further research is needed to determine whether *ALOX5* expression is altered across distinct lung macrophage clusters that emerge in the diseased setting.

The findings of this study have important implications for improving the treatment of patients with COPD exacerbations in a more precise and targeted manner. The differential regulation of SPM synthesis during bacterial versus viral exacerbations suggests that therapies aimed at restoring or enhancing *ALOX15* expression, particularly during viral infections, may help optimize the production of D-series resolvins and improve patient recovery outcomes. Future studies should focus on identifying patient subsets with impaired SPM synthesis and investigating whether treatment with D-series resolvins or targeting upstream enzymatic pathways can enhance resolution in COPD exacerbations. A more tailored approach that considers the underlying pathogen and individual patient responses could lead to improved strategies for managing COPD exacerbations and reducing disease progression. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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