EDITORIALS

Type 2 or Non–Type 2 Asthma Exacerbations? That Is the Question

Although we have made considerable progress in understanding the risk factors associated with asthma exacerbations and to a certain extent have developed effective therapeutic strategies to prevent them, they continue to be a leading cause of morbidity resulting in excess healthcare use and increased healthcare expenditures (1). Moreover, there have been limited scientific advancements regarding therapeutic strategies for the treatment of asthma exacerbations over the past decade. Unlike the use of newer biological therapies that rely on determining the underlying inflammatory endotype (2), a similar decision algorithm to treat acute exacerbations is lacking. Understanding how different inflammatory asthma phenotypes exacerbate is critical to the development of new therapeutic strategies for asthma exacerbations and to limit exposure to harmful or ineffective therapies.

In a study published in this issue of the *Journal*, McDowell and colleagues (pp. 545–553) used data from the Refractory Asthma Stratification Program to better understand the association between asthma exacerbation rates and the underlying inflammatory asthma phenotype (T2 biomarker–low [$T2^{LOW}$] vs. $T2^{HIGH}$) (3). This was a 48-week, multicenter study of adult participants meeting Global Initiative for Asthma asthma severity steps 4 and 5 criteria, who were randomized either to a treatment algorithm led by composite type 2 biomarkers (fractional exhaled nitric oxide [$F_{E_{NO}}$], blood eosinophils, and serum periostin) or to a symptom/risk-based algorithm to optimize the maintenance dose of corticosteroids. To enrich for a $T2^{LOW}$ population within the cohort, participants were enrolled only if they had an $F_{E_{NO}} < 45$ ppb at the screening visit. The inflammatory phenotype was determined at the baseline visit and at the time of each exacerbation and was defined as being either $T2^{LOW}$ if the $F_{E_{NO}}$ was ≤ 20 ppb and peripheral blood eosinophils were $\leq 0.15 \times 10^9$/L or $T2^{HIGH}$ if these values were above this cutoff. Exacerbations were protocol defined as "severe asthma symptoms worsening outside of a patient's normal daily variation." The study population, which included 301 participants, was mostly middle aged; predominantly female; and, on average, obese. There were 390 exacerbation events during follow-up with 60.8% (183 of 301) experiencing one or more exacerbations. Compared with those without exacerbations, those who did have exacerbations had a higher body mass index, were more likely to be female, and more likely to have received oral corticosteroids (OCSs) in the past. Interestingly, >70% of participants were $T2^{HIGH}$ at baseline, in spite of the fact that the study design attempted to enrich for a $T2^{LOW}$ population. Those in the $T2^{HIGH}$ group had worse airway obstruction and, as expected, a greater preponderance of T2 biomarkers and nasal polyps. In contrast, the $T2^{LOW}$ participants were more likely to have a prior ICU or hospital admission for asthma. Nearly half of this population was receiving maintenance OCSs (vs. only one-third of the $T2^{HIGH}$ participants), which could have reduced the eosinophil blood counts and bias toward a more severe group.

Longitudinally, exacerbations in both groups equally impacted lung function and asthma control; although T2 biomarkers increased in the $T2^{HIGH}$ group, no incremental increases were observed in the $T2^{LOW}$ group, despite similar physiological impairments. Only 33% of patients produced sputum for analysis, limiting the interpretation of these findings. As expected, the $T2^{HIGH}$ subgroup had higher baseline sputum eosinophils, which increased during exacerbations. Remarkably, all the sputum samples in the $T2^{LOW}$ group had a quantitative PCR finding above threshold for a virus or bacterium that occurred in the absence of concomitant sputum neutrophilia or elevations in C-reactive protein. Some evidence of augmented T2 inflammation was evident during exacerbations in two-thirds of patients classified as being $T2^{LOW}$ at baseline, which could be partly explained by OCS reductions during follow-up. Importantly, the inflammatory phenotype at baseline or during the initial exacerbation was not predictive of having the same profile at subsequent exacerbations ($\kappa = 0.19$).

There are several important findings in this large observational study of asthma exacerbations. First, patients with $T2^{LOW}$ asthma are a heterogeneous phenotype representing a combination of underlying true non-T2 biological pathways and additional pharmacologically suppressed T2 inflammation because of prior OCS use. This group of patients exhibit similar pulmonary physiological impairments and loss of asthma control as compared with those with higher T2 inflammation. Second, all of the non-T2 exacerbations that were sampled were associated with either bacterial or viral infections. Although the small number of microbiological samples limits interpretation of these findings and precludes a valid comparison across inflammatory phenotypes, it does raise the question whether infections play a preferential role in asthma exacerbations with a low T2 inflammatory profile or when the use of systemic OCSs in some patients augments subsequent risk of infection, ultimately increasing the odds of exacerbating. Viral and bacterial pathogens are known to play a role in asthma exacerbations in children and adults, and a higher serologic prevalence of atypical bacterial infections has been documented in patients with asthma with higher inhaled steroid doses and lower T2 biomarkers. However, whether the risk of infection-induced exacerbations is greater in those with a low T2 inflammatory phenotype requires further confirmation (4, 5). Third, the $T2^{LOW}$ group was a longitudinally unstable phenotype not adequately predicting subsequent events, which could be partly explained by changes in OCS exposure over time. This pattern of lack of phenotypic stability over time is more consistent with previous studies in the pediatric population (6). In adults, phenotypic inflammatory stability has been more variable, depending on how phenotypes are defined, the type of biomarkers used, and the characteristics of the study population (7–9).

Although the study by McDowell and colleagues is a welcome effort to understand the nature of asthma exacerbations through the T2/non-T2 phenotypic lens, it unfortunately falls short in providing robust data to draw solid conclusions because of several limitations. The limited number of clinically assessed exacerbations introduces potential biases that limit the external validity of the study. Furthermore, the small number of sputum samples analyzed limits the ability to draw meaningful conclusions with regard to the role of the microbiome in exacerbation phenotype. Finally, the concurrent use of OCSs is an important confounder of the study, limiting the ability to fully elucidate the biological basis of the exacerbation phenotype. Although some of these limitations, as pointed out by the authors, are the result of conducting large multicenter asthma exacerbation studies, they do limit the generalizability of their findings.

As outlined by the Lancet Commission on asthma, it is critical to deconstruct airway disease into component parts before planning treatment, with a focus on traits that are identifiable and treatable (10). It is clear that this recommendation should also be applied to the evaluation and treatment of asthma exacerbations. McDowell and colleagues get us closer to this goal but with still lingering important questions, including how much of what we see in patients with exacerbations is truly underlying low T2 biology versus OCS-suppressed T2 inflammation. Additional investigation of asthma exacerbations that incorporates additional biological mechanisms, including a broader interrogation of the microbiome, would be beneficial to further understand the complex pathobiology of exacerbations. ∎

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Is It Time to Abandon the Postbronchodilator Requirement in Defining Chronic Obstructive Pulmonary Disease?

Definitions used in clinical medicine are, by nature, dogmatic and somewhat arbitrary. They do, however, serve a useful purpose in helping to determine who may be more likely to benefit from an intervention.

A particular problem with definitions relates to thresholds. Values of any measurement close to a threshold may be within the measurement error for that value, yet one slightly above the threshold is considered "normal" and one slightly below the threshold is considered "abnormal".

Using spirometry to measure lung function and determine the presence of obstruction presents some of the challenges of these definitions and thresholds. The Global Initiative on Chronic Obstructive Lung Disease (GOLD) recommends classifying