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Blood Eosinophil–directed Management of Airway Disease
The Past, Present, and Future

I suspect that history will judge the introduction in the early 1990s of a noninvasive method to assess airway inflammation using induced sputum as the most important advance in the assessment of airway disease in the last 50 years (1–3). The use of this technique in the clinic established that the pattern of airway dysfunction, the severity of impaired function, demographic characteristics (including diagnostic label), and severity of symptoms or lung function impairment provide a very limited insight into the nature and severity of lower airway inflammation (4–6). It also become clear that identification of type 2–high eosinophilic airway inflammation is important because it is associated with an increased risk of exacerbations of asthma (7–9) and chronic obstructive pulmonary disease (COPD) (10) and a better response to corticosteroids (9–11) and biologic agents targeting type 2 cytokines (12–16). Thus, an approach to risk stratification and the introduction and titration of treatment that relies on symptoms and recognition of different patterns of airflow limitation is flawed. There is now strong evidence that this is the case; proof-of-concept studies have shown consistently that biomarker-directed use of corticosteroid results in better outcomes (10, 17) and targeting biomarker-identified type 2 inflammation was key to the recognition of the efficacy of biologics targeting type 2 cytokines (12, 14, 15).

Progress in rolling out this thinking into everyday clinical practice has been slow, probably reflecting the technical challenge of performing induced-sputum inflammatory-cell counting outside specialist centers. Horn and colleagues suggested 45 years ago that the blood eosinophil count, a more clinically accessible biomarker, was useful for regulating corticosteroid doses and predicting asthma attacks (18). Two observations 10 years ago put the blood eosinophil count back in the spotlight. First, Bafadhel and colleagues showed that the blood eosinophil count was the standout biomarker of an exacerbation of COPD associated with a raised sputum eosinophil count and a positive response to prednisolone (19, 20). Second, the blood eosinophil count emerged as the best predictor of response to the anti–IL-5 monoclonal antibody Mepolizumab in the DREAM (Dose Ranging Efficacy And Safety with Mepolizumab in Severe Asthma) study (13). In both studies, a count less than 0.15×10^9/L (near the upper end of the normal range in a nonatopic healthy population) (21) identified patients who did not respond to treatment (22).

The evaluation of the blood eosinophil count as a prognostic and predictive biomarker has since proceeded at pace, driven by a very receptive pharmaceutical industry that saw an opportunity to increase the therapeutic index of inhaled corticosteroid (ICS) treatment and clarify the role of dual bronchodilator therapy. Their willingness to devote considerable resources to this area and produce clinical practice–changing research outputs over a short period has been impressive. In this issue of the *Journal*, Singh and coauthors (pp. 660–671), all leading players in this area, provide an excellent review of the many *post hoc* and prespecified analyses of phase 3 studies of ICS/long-acting β_2-agonist combination treatment in patients with moderate and severe COPD (23). These studies have firmly established the blood eosinophil count as a prognostic biomarker and a predictor of response to ICS. The Global Initiative for Chronic Obstructive Lung Disease guidelines have changed to reflect these new findings, and now, for the first time in COPD, treatment with ICS is targeted at a measured biological process rather than at

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potentially unrelated symptoms and airway dysfunction (24). This radical change has been difficult for some to digest, and questions on the validity, accuracy, and diagnostic value of the blood eosinophil count continue to be asked. These issues are dealt with effectively and systematically by Singh and colleagues (23). They remind us that the additional information provided by a biomarker is greater if the context of the test is known, if the result is clearly abnormal (or normal), and if the finding is persistent. This is not rocket science, and I believe that biomarker-directed management of airway disease is eminently suitable for nonspecialist primary care clinicians. This group has, after all, delivered a remarkable 70% reduction in cardiovascular disease mortality over the last 10 years in adult men in the United Kingdom, primarily by delivering high-quality biomarker-directed primary and secondary risk-reduction treatments.

So where might we be heading with biomarker-directed management of airway disease? I see progress in three main areas. First, there is growing evidence that blood eosinophil–directed use of oral corticosteroids to treat acute exacerbations of COPD is an effective and safe way to limit exposure to a potentially toxic treatment (20, 25). This approach needs to be evaluated in larger definitive studies involving different healthcare settings and different patient groups. Second, biomarker-directed risk stratification and reduction should be extended beyond COPD and severe asthma clinics. There is now evidence from large intervention studies in mild, moderate, and severe asthma that the blood eosinophil count is independently associated with up to a fivefold increased risk for severe exacerbations as well as a greater response to ICS and biological agents (8, 9, 14, 26). Most studies have shown that another easy to measure biomarker, exhaled nitric oxide, adds prognostic and predictive information to blood eosinophil–based stratification (8, 26). It seems obvious that this information would help clinicians and patients make good decisions about the need for long-term preventative treatment. Why, then, do guideline groups continue to make weak and equivocal recommendations on the question of whether type 2 biomarkers should be used to predict outcomes and guide asthma treatment (27, 28)? It is becoming crucial that this stance is reconsidered, particularly because any concerns about the safety of not treating biomarker-low patients with regular ICS disappear completely if as-needed ICS/rapid-onset β_2-agonist becomes the standard of care for milder asthma (29).

A third area requiring more work is whether we should move from secondary to primary prevention of problems associated with biomarker-identified type 2 airway inflammation. Might early use of ICS or a biologic in patients with raised biomarkers of type 2 airway inflammation but mild or no symptoms improve longer-term outcomes? This is a possibility, as a raised blood eosinophil count has been associated with increased rate of decline in FEV_1 in a community population independent of the presence of symptoms or an asthma label (30). In addition, there is existing evidence from *post hoc* analysis of intervention studies that ICS prevents decline in FEV_1 in patients with COPD and a blood eosinophil count greater than 0.15×10^9/L (31) and that the anti–IL-4 receptor-α biologic dupilumab prevents decline in FEV_1 over 12 months (14). Prospective studies are needed to answer this important question definitively. ■

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Do Plasticizers within the Indoor Environment Increase Airway Allergen Responsiveness?

There is an increasing appreciation that a wholistic consideration of the impact of air pollutants on health requires us to understand the continuum of exposures an individual may experience across the indoor and outdoor environment. This extends beyond the infiltration of ambient pollution into the home, school, or workplace to a consideration of exposures to the complex and highly heterogeneous chemical cocktail within indoor air. Although the literature on the adverse health impacts of ambient air pollution is extensive and mature, as highlighted by a joint European Respiratory Society/American Thoracic Society policy statement (1), work on indoor sources is less evolved (2). Although the population spends most of its time within the indoor environment, traveling from home to work and back again, a fraction that has increased as modern lifestyles have become more sedentary, the study of indoor air pollution has remained largely focused on a few common indoor pollutants: common allergens such as house dust mites and mold, carbon monoxide, second-hand tobacco smoke, radon, asbestos, and nitrogen dioxide. But the indoor environment is also a source of volatile and nonvolatile chemical species derived from modern synthetic building materials, furnishings, and household chemical products. The importance of these indoor sources has increased as our homes have become more airtight and energy efficient, such that now the indoor concentrations of volatile organic compounds are often significantly elevated compared with outdoor air (3). In addition, indoor air is also enriched with respirable microplastic fibers and particles that have the potential to deliver chemical additives to the lung (4).

In the paper by Maestre-Batlle and colleagues (pp. 672–680) in this issue of the *Journal* (5), the authors drill down onto the potential acute impacts of one common indoor air pollutant, dibutyl phthalate (DBP), on allergic airway responses. Phthalates (classified as plasticizers) are typically solvents found in plastic-based products that have aroused concern historically as endocrine-disrupting chemicals, but there is observational data also linking indoor concentrations, often in household dust, with increased risk of asthma, allergy, and wheeze (6).

The interaction between air pollutants and allergy has been shown by many studies (7, 8), with causative links proposed by epigenetic and other mechanisms (9), although these assertions have been questioned (10). Controlled human-exposure studies have also shown the potential of diesel exhaust and nitrogen dioxide to potentiate airway responses to allergen challenge (11–14). The findings have indicated that pollutants may affect the magnitude of the allergic response but also the threshold of allergen challenge demanded to induce a bronchoconstrictive response. In this issue, a team from the University of British Columbia, Vancouver, extend this consideration to DBP, investigating

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