Urine: A Lens for Asthma Pathogenesis and Treatment?

In this issue of the *Journal*, Kolmert and colleagues (pp. 37–53) in the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Diseases Outcomes) Study Group report urinary eicosanoid levels from healthy control subjects, subjects with mild–moderate asthma, and subjects with severe asthma (SA) (1). The rationale for this study is that there is a lack of predictive biomarkers for which patients with asthma may be stratified based on the pathobiological mechanisms that lead to disease severity, and such biomarkers may be able to be used to improve treatment selection. As the authors note, the amount of eicosanoids in each urine collection represent the integration of the systemic load of these mediators since the last urination, therefore providing an ongoing assessment of their production. Before we discuss the results of their study, it is important to understand the context in which eicosanoids are currently understood to have a role in asthma pathogenesis.

Leukotrienes and prostaglandins are lipids produced from arachidonic acid metabolism that have pleiotropic biologic functions in the lung. For specialists in pulmonary medicine and allergy/immunology, these mediators have a particular importance in that they regulate many aspects of asthma pathophysiology (2). For instance, the cysteinyl leukotrienes (cysLTs), measured in the U-BIOPRED study, can be synthesized as a result of allergen-induced, IgE-mediated reactions by mast cells and basophils (3). Eosinophils are also important producers of cysLTs (4). The cysLTs consist of LTC_4, LTD_4, and LTE_4, which are sequentially produced, as shown in Figure 1. The half-lives of LTC_4 and LTD_4 are very short, making it challenging to measure them in biologic fluids; however, LTE_4, the end product of cysLT metabolism, is stable and can be measured in the urine (5), thus providing an opportunity to quantify cysLT production as performed by Kolmert and colleagues. The cysLTs cause bronchoconstriction and induce airway epithelial cell mucin expression, both cardinal features of allergic asthma (6, 7).

Although cysLTs are products of arachidonic acid metabolism through the 5-LO (5-lipoxygenase) pathway, arachidonic acid may also be metabolized through the COX (cyclooxygenase) pathway to produce the prostaglandins, also shown in Figure 1. PGD_2 is the major prostaglandin produced by IgE-mediated mast cell activation, whereas basophils, eosinophils, and macrophages are inflammatory cells in the airway that can also synthesize PGD_2 (8, 9). PGD_2 promotes allergic inflammation in multiple ways by signaling through the receptor DP2, which is also known as CRTH2. DP2 is expressed on eosinophils, basophils, CD4 T-helper cell type 2 (Th2) cells, and group 2 innate lymphoid cells (ILC2) (10, 11). DP2 signaling in eosinophils augments their release from bone marrow, increases their respiratory burst, stimulates the chemotactic response to other chemokines such as eotaxin, and primes them for degranulation (12). PGD_2 signaling through DP2 stimulated human peripheral blood ILC2 to secrete large amounts of IL-13 to the same level produced in response to IL-25 and IL-33, whereas the addition of IL-25 and IL-33 to PGD_2 synergistically increased IL-13 expression by ILC2 (13), and PGD_2 increased ILC2 expression of the IL-33 and IL-25 receptor subunits, ST2 and IL-17RA, respectively (10). Importantly, there seem to be synergistic effects of PGD_2 and cysLTs in promoting allergic inflammatory responses. For instance, LTE_4 enhanced the activation of ILC2 and type 2 cytokine production by PGD_2 (14). Therefore, understanding the possible contribution of cysLTs and PGD_2 to asthma, and in particular SA, would provide insight into disease pathogenesis.

In their study, Kolmert and colleagues stratified the results of the subjects with SA into groups that are in the highest or lowest 25th percentile for urinary eicosanoids. Those subjects with SA who were in the highest 25th percentile of urinary LTE_4 and PGD_2 metabolites had significantly lower lung function yet had increased levels of exhaled nitric oxide and blood and sputum eosinophils, in addition to other markers of type 2 inflammation, such as periostin. The authors interpret these results as justifiably suggesting that there is increased mast cell activation in SA. The authors also report that males had higher levels of the urinary PGE_2 metabolite than females. This is important because, as the authors point out, there is strong data that PGE_2 signaling through receptors that activate cyclic AMP downregulates allergic inflammation and bronchoconstriction (15, 16), thus suggesting a potential mechanism as to why adult females have a greater incidence of asthma as well as more severe disease.

The authors further stratified subjects into those that were treated with oral corticosteroids and found, somewhat surprisingly, there was no difference in the majority of the eicosanoid measurements based on usage of this medication. Interestingly, when patients were stratified based on omalizumab treatment, the authors found that, in contrast to the oral corticosteroid data, omalizumab use significantly decreased the urinary levels of LTE_4 as well as metabolites of PGD_2 and thromboxane. Based on these results, the authors suggest that urinary eicosanoid levels possibly could be used as a predictive biomarker of response to biologics such as omalizumab. However, there is no information that the subjects treated with omalizumab had a response to this medication; therefore, in this instance, we have no idea as to whether the change in the urinary eicosanoids signaled successful treatment to this biologic.

The merits of this manuscript include the enormous amount of data, particularly in the supplemental data section, that will be of use

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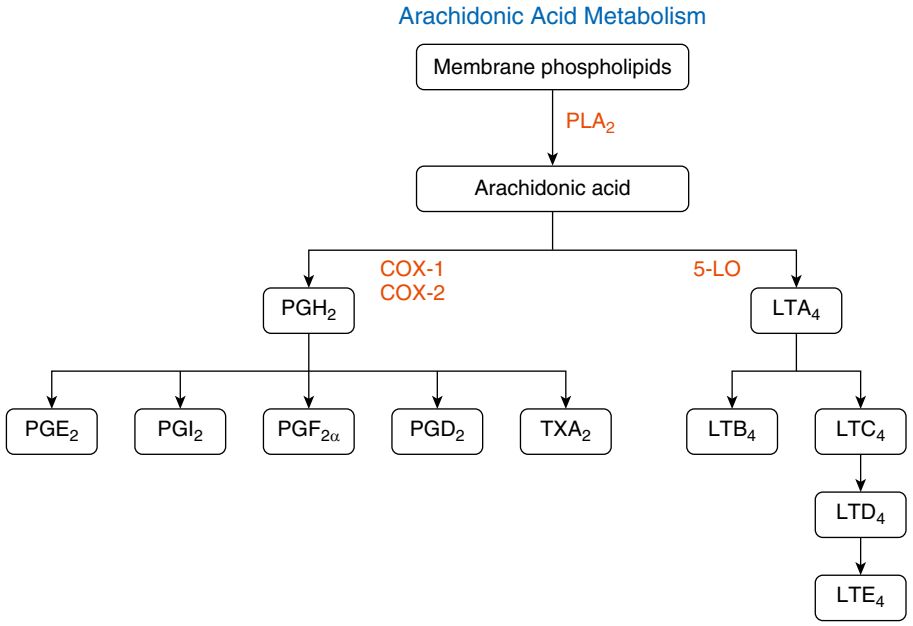

Figure 1. Metabolism of arachidonic acid in the production of leukotrienes and prostaglandins. 5-LO = 5-lipoxygenase; COX = cyclooxygenase; LT = leukotriene; PG = prostaglandin; PLA_2 = phospholipase A_2; TXA_2 = thromboxane A_2.

to other investigators at the intersection of the eicosanoid and asthma fields. Other major strengths of this project include the internal validation of the original results with a follow-up study of adults with SA 12–18 months after the original study. The authors went even a step further by performing an investigation of adolescents who had asthma, the results of which provided external validation of the data found in the adults with asthma. The data certainly provides evidence for both a role for eicosanoids as determinants of asthma severity and the possibility that urinary eicosanoids could be used to stratify asthma by pathobiology as an adjunct to clinical severity. The authors propose that urinary eicosanoids could be used to phenotype patients before treatment with biologics to predict response to these expensive drugs. The next step would be to measure urinary eicosanoids before entry into trials of biologic agents to determine if these could be predictors of success or failures, followed by prospective trials to confirm that urinary eicosanoids are indeed true biomarkers of response to therapy. Though there are many strengths of this project, there are some shortcomings. For instance, PGI_2 metabolites were not examined because they were lost. PGI_2 is a negative regulator of CD4 and ILC2 type 2 cytokine production, inhibits dendritic cells from inducing Th2 immune responses, and promotes immune tolerance in the airway (2). It would have been interesting to see if there was an inverse correlation of the stable urinary PGI_2 metabolite with asthma severity, suggesting that PGI_2 may be protective. Furthermore, lipids that have antiinflammatory effects and that promote resolution of inflammation, such as lipoxins, protectins, resolvins, and maresins, were not measured, and such data would have provided insight into the importance of these mediators in asthma pathogenesis (17). However, despite these limitations, the work by the U-BIOPRED study group is an important addition to the asthma field, and future clinical trials will be important in defining how this data can be used to direct precision treatments. ■

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R. Stokes Peebles, Jr., M.D.
Department of Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

ORCID ID: 0000-0002-1429-7875 (R.S.P.).

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Estimating the Case Fatality Risk of COVID-19 among Mechanically Ventilated Patients

The current coronavirus disease (COVID-19) pandemic has exerted significant strain on the delivery of critical care worldwide (1, 2). Published reports describing the characteristics and outcomes of critically ill patients with COVID-19 have shown they have similar features to patients with non–COVID-19–related acute respiratory distress syndrome (3, 4). The reported all-cause in-hospital mortality for those patients with COVID-19 requiring intensive care and invasive mechanical ventilation is very high but also varies across countries and regions (5–7). More precise estimation of the case fatality risk in patients with severe COVID-19 would help to provide a better understanding of the overall burden of the pandemic and to identify the subgroups who are at greatest risk of dying (8).

The case fatality risk of an infection is represented by the proportion of patients who die among all infected cases in a population over a period of time (9). The estimation of case fatality risks during an ongoing pandemic—especially during periods marked by exponential increases in number of cases—is not without challenges (9, 10). Major pitfalls include overestimating the case fatality risk if less severe (or asymptomatic) cases are not identified or included in the denominator or underestimating the risk if follow up is too short, leading patients who are still alive but who ultimately die to be missed in the numerator (9, 11).

In this issue of the *Journal*, Lim and colleagues (pp. 54–66) present a rigorous and comprehensive systematic review and meta-analysis of 69 studies involving 57,420 adult patients with severe COVID-19 (12). Their main objective was to estimate the overall global case fatality risk among the sickest subgroup of infected patients—those receiving invasive mechanical ventilation. The review included patients from 23 countries, and these tended to be mostly from North America, Europe, or Asia. The authors used appropriate methods to pool estimates in the presence of high heterogeneity, and their results were robust to a variety of sensitivity analyses and under a diverse set of assumptions (13). The overall case fatality risk for these ventilated patients was approximately 45%, or about one death for every two patients. The case fatality risk ranged from 0 to 100% across all studies, owing to significant variability across included reports, including clinical, methodological, and statistical heterogeneity. The latter was most notably associated with the quality of individual studies and those arising from so-called early epicenter locations. This case fatality risk consistently increased with older age, reaching 84% overall among patients older than 80 years.

These findings have important clinical and epidemiological implications. First, the estimated case fatality risk among patients receiving mechanical ventilation is high and similar to that of other patients with severe acute respiratory distress syndrome (14). This information may, in turn, aid in ongoing pandemic planning, resource allocation, and the estimation of both the health-related and socioeconomic impact of COVID-19 (8). It should help inform the design of future studies of critically ill patients with COVID-19 by providing a more precise estimate of mortality risk. Furthermore, it may also help to motivate the development of strategies to reduce the occurrence of COVID-19–related critical illness or the need for invasive mechanical ventilation (15). Finally, the very high case fatality risk among older patients highlights the importance of preventing further outbreaks among this extremely vulnerable group (16).

The results reported by Lim and colleagues showcase useful methods for estimating risk across multiple studies during an evolving pandemic and also their inherent limitations. First, the authors did not provide an estimate of the overall case fatality risk but rather only the risk for a highly selected group of critically ill patients who received invasive mechanical ventilation. This approach helped to avoid the major challenge of identifying all asymptomatic or mildly symptomatic patients for inclusion in the denominator, but it also limits generalizability to a broader spectrum of critically ill patients or to the entire population. This approach also assumes that the

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