Gaining Insights into Asthma-related COVID-19 Risk

Viral infection is a major risk factor for exacerbations in patients with all asthma phenotypes, and risk for viral exacerbation seems to be enhanced among those with type 2 inflammation (1). Early reports from case cohorts during the coronavirus disease (COVID-19) pandemic suggested that asthma, in addition to other lung diseases such as chronic obstructive pulmonary disease, could be a risk factor for COVID-19 infection and severe disease (2). However, some disease characteristics of asthma seemed to moderate the risk. For example, the presence of type 2 inflammation and use of corticosteroids were shown to have potential protective effects through the reduction of cellular receptors of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus (3, 4). In contrast, patients with severe asthma, such as those who require systemic corticosteroids or multiple medications, may be at increased risk of morbidity and mortality because of this infection (5). A major challenge to the interpretation of the remarkable epidemiologic and translational research thus far lies in limitations related to study design. Those limitations include lack of longitudinal data prior to and subsequent to the diagnosis, limited asthma phenotype data, and restriction to individuals already diagnosed with disease or hospitalized with disease.

In this issue of the *Journal*, Bloom and colleagues (pp. 36–45) took what may be the most comprehensive and highly integrated approach yet published to attempt to define the risk of SARS-CoV-2 infection among patients with asthma across multiple phenotypes as well as the severity of the COVID-19 disease among those phenotypes (6). To achieve this goal, the authors used a large, validated healthcare database of primary care electronic medical records in combination with hospitalization records, socioeconomic data, mortality data, and public health surveillance records, some of which are primarily for COVID-19 disease surveillance. The authors identified a cohort with a diagnosis of asthma, a comparison cohort of allergic rhinitis to represent the presence of atopy or type 2 inflammation without lung disease, and a nonasthma, nonallergic rhinitis matched group. Asthma was characterized by medication use in the previous year, exacerbations, and presence of type 2 inflammation, indicated as a history of atopy and blood eosinophil measurement. Statistical models were adjusted for sex, age, ethnicity, socioeconomic indicators, and comorbid diseases. COVID-19 outcomes were assessed from February 1, 2020, through June 26, 2020, and therefore assessed the first wave of the pandemic, during which testing was not universally available. Therefore, diagnosis codes included both "suspected" and "confirmed" cases, as only 9.4% of suspected COVID-19 cases were confirmed because of the lack of testing availability.

The authors found that patients with a diagnosis of asthma were more likely than control subjects to consult their primary care physician for evaluation of COVID-19–related concerns and to receive a diagnosis, but despite a diagnosis of "suspected" disease, confirmed disease was mostly in older individuals. Many providers across both primary care and respiratory subspecialties were acutely aware of the heightened state of concern over asthma-related risk for COVID-19, particularly early in the pandemic. The allergic rhinitis group was also more likely to receive a diagnosis but was not at increased risk for hospitalization. This discrepancy may be identifying the increased risk of severe disease related to asthma itself. However, this also likely captures the challenge in making a diagnosis of infection versus other allergic and inflammatory types of rhinitis in the absence of objective testing because of the many overlapping and nonspecific symptoms across these disorders.

Rates of admission to the hospital for treatment of COVID-19 were increased among patients with asthma over those in the general population. However, this increase was of the same magnitude as the historic increase in influenza- and pneumonia-related hospitalizations among those with asthma.

When assessing phenotypic characteristics, the authors found that patients with more severe asthma, described as more frequent exacerbations and more medication use, were more likely to have ICU admission or death. Interestingly, the hazard ratios do not clearly reflect a consistent dose-dependent effect of inhaled steroids, which is most pronounced in those with intermittent and, even more so, regular use of inhaled corticosteroid plus add-on therapy. These findings suggest that there may be a threshold of asthma severity, or a phenotype indicated by the use of add-on therapy, for which this risk is most substantial. Neither atopy or eosinophil count significantly influenced the risk of diagnosis, hospitalization, or mortality in this dataset.

Importantly, comorbidities and other confounding factors (male sex, socioeconomic deprivation) were included in the models of overall risk. It is noteworthy to recognize that even in a cohort of patients with asthma and allergic rhinitis, these known comorbidities, including obesity, vascular disease, diabetes, renal failure, dementia, and cancer, were again proven to influence the adverse outcomes associated with COVID-19. Indeed, the hazard ratio of asthma severity markers for hospital admission and death was similar to hazard ratios for markers of lower socioeconomic status and the chronic disease comorbidities.

This study shows findings consistent with other studies, wherein more severe asthma is associated with adverse COVID-19 outcomes and disease severity. One major limitation, which is admittedly a limitation of most epidemiologic work, is that disease control and asthma severity is inferred from medication use and exacerbation history as captured by the electronic medical record. Lung function, exhaled nitric oxide levels, symptom severity, albuterol use, and

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smoking history would lend more depth of understanding about these patients and their disease and could be utilized in more granular phenotyping toward COVID-19 risk. In contrast to some previously published work, in this study, markers of type 2 inflammation were not protective against COVID-19. It is possible that a more objective definition of atopy, including levels of specific or total IgE with the relevant associated diagnoses, would clarify this finding. A full understanding of these relationships would require translational work, such as experiments using nasal epithelial or sputum samples among individuals before and after infection, stratified by disease and treatment, but such a study is unlikely to be completed. However, there are cohorts with COVID-19 that have been evaluated longitudinally and will likely provide more detailed clinical and immunologic data that should lend clarity to the role of asthma and atopy in SARS-CoV-2 infection (7). ■

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From Mass to Flow: Emerging Sepsis Diagnostics Based on Flow Cytometry Analysis of Neutrophils

Sepsis mortality decreases dramatically with timely initiation of standardized clinical management protocols (1), including source control, adequate antibiotic therapy (2), and aggressive hemodynamic resuscitation (3). Despite best practice recommendations by international critical care societies for the implementation of sepsis screening tools in health systems (4), the ability to diagnose sepsis early and accurately remains a major challenge for emergency and critical care clinicians (5). Current diagnostic criteria primarily reflecting sepsis-related organ dysfunctions rather than pathobiological mechanisms lack specificity, often leading to under- (6) or overdiagnosis (7). New translational research approaches to study the pathogenesis of sepsis in humans are needed to identify immunologic, metabolic, and microbial dysfunctions specific to sepsis and to provide the biological elements of accurate diagnostic tools.

In this issue of the *Journal*, Meghraoui-Kheddar and colleagues (pp. 46–59) used a high-dimensional mass cytometry approach for an in-depth and single-cell immune profile comparing patients with sepsis with those with sterile inflammation (8). Using a state-of-the-art unsupervised analysis to capture the cellular diversity of the neutrophil compartment, the authors identified and prospectively validated a neutrophil immunological signature that accurately differentiates patients with sepsis from control subjects. The results provide the foundation for the development of a sepsis-specific diagnostic test that will enhance the precision of managing critically ill patients.

High-dimensional mass cytometry and other single-cell technologies have revolutionized our ability to study complex immunologic states at the bedside and identify clinically relevant biological markers of human diseases (9, 10). In the context of sepsis, the study by Meghraoui-Kheddar and colleagues is the first to harness the cellular complexity of the neutrophil compartment to identify novel and diagnostically relevant biology. Using a 42-parameter mass cytometry immunoassay, the authors quantified the phenotype and abundance of circulating immune cell subsets in whole blood samples from 17 patients with sepsis and 12 control subjects with noninfectious inflammation (i.e., patients recovering from cardiac surgery) on Day 1 and Day 7 after hospital admission in addition to analysis of 11 samples

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