From the pages of AllergyWatch (R)

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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For this issue of "From the Pages of AllergyWatch," I have selected 2 articles related to coronavirus disease 2019 (COVID-19) and asthma. The first review by Dr Lee from the November-December AllergyWatch postulates that the angiotensin-converting enzyme 2 (ACE2) receptors may be protective in our patients with allergic asthma and reduce the risk for hospitalization with COVID-19. The next article, reviewed by Dr Mahr from the September-October AllergyWatch, warns about stepping down controllers in pediatric patients with asthma during the pandemic. The last article, reviewed by Dr Chipps, evaluated the role of exhaled nitric oxide (eNO) as a guide to inhaled corticosteroid (ICS) stepdown decisions for our patients with asthma.

Stanley M. Fineman, MD
Allergy Watch Editor in Chief

Allergic Asthma Linked to a Lower Risk of Coronavirus Disease 2019 Hospitalization

In addition to other chronic airway diseases, asthma has been considered a likely risk factor for severe COVID-19. Surprisingly, initial studies from the People's Republic of China did not find more severe illness in patients with asthma or respiratory allergy. One explanation could be that allergic disease is associated with lower expression of the severe acute respiratory syndrome coronavirus 2 receptor ACE2. Airway cell expression of ACE2 was studied in 3 cohorts of carefully phenotyped children and adults with asthma or allergic disease. In 318 children from the Urban Environment and Childhood Asthma cohort, allergic sensitization was inversely related to ACE2 expression in the nasal epithelium, independent of asthma status. Among children with asthma, moderate and high allergic sensitization were linked to progressively greater reductions in ACE2 expression, compared with no or minimal sensitization. Higher ACE2 was also associated with lower levels of type 2 biomarkers, including a number of positive specific immunoglobulin E results and total immunoglobulin E. In a study of 24 adults with allergic rhinitis, experimental cat allergen challenges—nasal challenge and in an environmental exposure chamber—were followed by reductions in ACE2 expression. In a cohort of 23 adults with mild asthma not receiving asthma controller therapy, allergen bronchoprovocation to dust mite, ragweed, or cat was associated with reduced ACE2 expression in the lower airway epithelium. The findings suggest that respiratory allergy and allergen challenge are associated with reduced ACE2 expression. ACE2 expression is lowest in patients with asthma and high levels of allergic sensitization but is not affected by nonatopic asthma. The investigators concluded that "the modulation of ACE2 expression by type 2 inflammatory processes suggests the need to comprehensively evaluate the role of type 2 immune regulation in COVID-19 pathogenesis."

Comments from Gerald B. Lee, MD: Many of our patients with asthma have been concerned about severe COVID-19 illness but given that asthma has heterogeneous endotypes, individual risks may vary. The ACE2 receptor is important for severe acute respiratory syndrome coronavirus 2 infection. This study of nasal or lower airway epithelial samples found that ACE2 expression is decreased in atopic patients, suggesting a potential mechanism by which atopy may protect against severe COVID-19 infection. Other articles in the same issue of *The Journal of Allergy and*

Disclosures: Dr Fineman reports serving as a clinical investigator for Aimmune Therapeutics, Biocryst Pharmaceuticlas, Inc, DBV Technologies, and Regeneron; and as a speaker/teacher for Takeda Pharmaceutical Company Limited. Dr Mahr reports serving as a speaker/teacher for AstraZeneca, GlaxoSmithKline, Kaleo, Inc, Optinose US, Inc, Regeneron, and Sanofi; and served as a consultant of Kaleo, Inc, Regeneron, and Sanofi. Dr Chipps served on the advisory board and as a consultant or a speaker/teacher for Circassia, Genentech, Inc, Novartis, Regeneron, Sanofi, and Teva Pharmaceutical Industries Ltd. Dr Lee has no conflicts of interest to report.
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Clinical Immunology include a United Kingdom study, which found that COVID-19 hospitalizations were increased only in patients with nonallergic asthma, especially those with chronic obstructive pulmonary disease. A US study found that asthma or inhaled steroid use was not associated with COVID-19 hospitalization, despite a higher prevalence of comorbidities such as diabetes.

Jackson DJ, Busse WW, Bacharier LB. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol*. 2020;146(1):203-206.e3.

Managing Pediatric Asthma During Coronavirus Disease 2019

About 7 million US children have asthma, and they experience higher morbidity than adults with asthma. As of Summer 2020, the United States is the epicenter of the global COVID-19 pandemic. Current knowledge of the impact of COVID-19 on the management of pediatric asthma is reviewed and discussed. Symptoms of COVID-19 may be similar to those of asthma, including dry cough and shortness of breath. The presence of fever may help to differentiate COVID-19 or other viral infections from asthma exacerbations. Moderate to severe asthma is considered a risk factor for COVID-19 morbidity and mortality. In March 2020, more than a quarter of young adults (aged 18-49 years) hospitalized for COVID-19 had a history of asthma. Although the risk of COVID-19 morbidity in children with asthma continues to be unclear, good asthma control is essential. Guidelines recommend that children with asthma remain on their current medications to prevent exacerbations during the pandemic. Unless there is some clear benefit, stepping down controller medications is not recommended. Treatment with biologic agents should be continued; children using nebulized relievers should be switched to a metered-dose or dry-powder inhaler. Oral corticosteroids are not recommended for the treatment of COVID-19 but are appropriate as part of aggressive therapy for asthma exacerbations. There are few data to guide the treatment of children with asthma exacerbations known or suspected to be associated with COVID-19. Ongoing challenges to the management of pediatric asthma include shortages of medications, particularly albuterol. Children with poorly controlled asthma should be prioritized for virtual visits; having a home peak flow meter may help in diagnosing acute exacerbations. The social determinants of health may affect the risks of COVID-19 in children with asthma. Loss of daily structure because of school closures might lead to breakdowns in adherence to controller medications in some families.

Comments from Todd Mahr, MD: Since the onset of coronavirus, it has been noted that children tend to have milder symptoms than adults. This review stresses the attention needed for our pediatric patients with asthma, given that viral respiratory illnesses, in general, are a common trigger for asthma exacerbations. Often, asthma controller therapy may be stepped down or even trialed off for the warmer months before being restarted during the viral season. Given the current pandemic status, it would be prudent to consider this a “viral season” for the foreseeable future.

Abrams EM, Szefler SJ. Managing asthma during coronavirus disease-2019: an example of other chronic conditions in children and adolescents. *J Pediatr*. 2020;222:221-226.

Exhaled Nitric Oxide Can Support Stepdown Decisions

Patients with asthma with high eNO are at increased risk of exacerbations. It is unclear whether eNO, as a measure of interleukin-13–driven, corticosteroid-responsive airway inflammation is a useful guide to making reductions in ICS dose. This issue was addressed in a meta-analysis of patient-level data from studies that measured eNO before stepping down ICS. A systematic review identified 8 observational studies or randomized controlled trials in which adult patients (12 years or older) with asthma receiving low- or moderate-dose ICS underwent eNO measurement before ICS dose reduction. Data on 384 participants from 7 studies were included in a mixed-effects multilevel meta-analysis for the primary outcome of exacerbations within 12 weeks after ICS stepdown. Patients in 4 studies underwent a 50% reduction of ICS dose, whereas ICS treatment was withdrawn in 3 studies. In about half of patients, eNO was 20 parts per billion (ppb) or less. The rate of acute exacerbations within 12 weeks of stepdown was 11.2%. On meta-analysis, patients with a baseline eNO of 50 ppb or higher had about a threefold increase in exacerbation risk. The adjusted odds ratio of 3.08 translated into an estimated exacerbation risk cutoff of 15%. If ICS were stepped down at an estimated exacerbation risk of less than 15%, only 10.4% of patients would continue on the same ICS dose. By comparison, stepping down at an estimated exacerbation risk of less than 10% would result in 36.7% of patients staying on the same dose. With either strategy, a large majority of patients would avoid exacerbations (91.4% and 90.4%, respectively). Available evidence supports the use of eNO as a guide to ICS stepdown decisions in patients with mild to moderate asthma. Reducing ICS dose when eNO is less than 50 ppb may reduce ICS exposure without increasing exacerbation risk. Larger, prospective studies are needed to validate this strategy.

Comments from Bradley E. Chipps, MD: The use of eNO as a stepdown strategy in mild to moderate asthma is receiving more attention. In patients who have a type 2–high signal in their airways, eNO of greater than 50 ppb has been found to be a cutoff above, which stepdown therapy should not be attempted. These data can be used to help payers understand the need to cover eNO as an adjunct to the management of patients with significant reactive airway disease.

Wang K, Verbakel JY, Oke J, et al. Using fractional exhaled nitric oxide to guide stepdown treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis. *Eur Respir J*. 2020;55(5):1902150.