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.

Correspondence

COVID-19: Start with the nose

To the Editor:

We read with interest the data from Jackson et al[1] that revealed lower angiotensin-converting enzyme 2 (ACE2) expression in nasal brushings from children with allergic sensitization, along with a progressive decline in ACE2 expression in relation to increasing IgE sensitization in those with asthma. Moreover, in nasal brushings from adults with allergic rhinitis, ACE2 expression was lower after exposure to cat allergen.

This may be clinically relevant because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the respiratory epithelium via an endocytic process mediated by ACE2, especially because the nose is usually the first portal of entry for viral infection. The nasopharynx is a common site for SARS-CoV-2 testing. Nasal secretions are swept by rapid nasociliary clearance into the oropharynx and thereby aspirated into the lower respiratory tract, where SARS-CoV-2 causes severe hypoxic pneumonia followed by an associated systemic cytokine–induced autoimmune hyperinflammatory response and coagulopathy.[2]

Pointedly coronavirus disease-2019 (COVID-19) often presents initially with impaired smell due to involvement of the olfactory nerve endings in the nose. ACE2 expression is highest in the nose, with decreasing levels throughout the respiratory tract, which is mirrored by a gradient of SARS-CoV-2 infection along the airway epithelium.[3] The nasal expression of ACE2 also appears to be age dependent, with lower levels in children compared with adults.[4] Whether or not this might explain the higher prevalence and worse outcomes of COVID-19 in older people remains uncertain.

We believe these observations may be clinically relevant when considering strategies to modify early SARS-CoV-2 infection. One possibility is to suppress replication of SARS-CoV-2 in the nose with topical delivery of antivirals, which would achieve a high local concentration. In a study of experimental coronavirus cold in healthy volunteers, the use of prophylactic treatment with intranasal IFN-α-2b resulted in shortened duration and attenuated severity of symptoms.[5]

Another putative therapeutic strategy might be to use intranasal corticosteroids on a prophylactic basis. The premise is that inhaled corticosteroids are associated with dose-dependent down-regulation of expression of both ACE2 and transmembrane protease, serine 2 in induced sputum from patients with asthma.[6] Whether the same might occur with intranasal corticosteroids warrants further investigation. Furthermore, there is evidence of a corticosteroid-specific effect with ciclesonide and mometasone, but not fluticasone beclomethasone or budesonide, in terms of suppressing *in vitro* replication of SARS2-CoV-2.[7]

For patients with unified allergic airways disease, this reinforces the importance of adhering to both inhaled and intranasal corticosteroid therapy, which will achieve optimal upper and lower airway disease control and may also afford protection against viral triggers including SARS-CoV-2.

We also believe there is also a need to assess whether prophylactic use of intranasal corticosteroid might modify disease progression of COVID-19 in susceptible older individuals with comorbidities, including those in care homes.

Brian Lipworth, MD
Rory Chan, MBChB
Chris RuiWen Kuo, MBChB

From the Scottish Centre for Respiratory Research, Ninewells Hopsital and Medical School, University of Dundee, Dundee, United Kingdom. E-mail: b.j.lipworth@dundee.ac.uk.

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Reply

To the Editor:

Lipworth et al[1] raise interesting and important concepts related to the central role that the nose plays in susceptibility to respiratory viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The nasal epithelium is the initial target for SARS-CoV-2 infections, and Hou et al[2] recently demonstrated greater angiotensin-converting enzyme 2 expression and an associated enhanced susceptibility to SARS-CoV-2 infection in upper versus lower airway cells. Furthermore, a progression of infection from the upper to lower airway has been clearly demonstrated for other respiratory viruses. For example, inoculation studies with rhinovirus have shown that there is often a delay of 2 to 4 days from upper to lower airway rhinovirus infection.[3] Collectively, these data suggest that targeting the upper airway with prophylactic strategies to prevent infection and/or therapeutic approaches in early infection to avoid progression to the lower airway hold significant promise in impacting coronavirus disease-2019 (COVID-19) susceptibility and disease outcomes.

Lipworth et al suggest that intranasal corticosteroids should be tested for their ability to prevent severe COVID-19. Although intriguing in concept, data to date have been mixed on the impact of

corticosteroids on COVID-19 outcomes. This is highlighted by preliminary findings in a recent study demonstrating the efficacy of dexamethasone in reducing mortality in critically ill patients with COVID-19, but showing no benefit in those not requiring respiratory support.[4] Furthermore, our study[5] demonstrated a "dose-response," with greater degrees of respiratory allergy being associated with larger reductions in angiotensin-converting enzyme 2 gene expression in the nasal epithelium, and the impact of suppressing type 2 inflammation in these individuals is not currently known. Thus, we agree that strategies targeting the upper airway for the prevention and/or treatment of COVID-19 are of significant interest. Studies with nasal/inhaled corticosteroids as postexposure prophylaxis for very early stages of the disease (prehospitalization) may be worth considering. Furthermore, various additional approaches are available for consideration, including topical therapy with intranasal antivirals, immune stimulants, and/or vaccines.

Daniel J. Jackson, MD[a]
William W. Busse, MD[a]
Alkis Togias, MD[b]
James E. Gern, MD[a]
Mathew C. Altman, MD[c,d]

From [a]the University of Wisconsin School of Medicine and Public Health, Madison, Wis; [b]The National Institute of Allergy and Infectious Diseases, Bethesda, Md; and [c]the Department of Medicine, University of Washington, and [d]Benaroya Research Institute, Systems Immunology Division, Seattle, Wash. E-mail: djj@medicine.wisc.edu.

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Corrigenda

With regard to the article in the July 2020 issue entitled "COVID-19: Unanswered questions on immune response and pathogenesis" (J Allergy Clin Immunol 2020;146:18-22), it has been brought to the Editors' attention that the affiliation for the second author, Giorgio Walter Canonica, MD, was incorrect as printed. The correct affiliation for Dr Canonica should be listed as: Personalized Medicine, Asthma & Allergy - Humanitas Clinical and Research Center IRCCS, Rozzano (MI), Italy. The authors regret the error.

With regard to the article in the February 2020 entitled "Intrathymic delivery a new route for adenoviral-associated vector gene therapy" (J Allergy Clin Immunol 2020;145:499-501), it has been brought to the Editors' attention that the authors' names were incorrect as printed. The names were shown as Gregori Silvia, PhD, and Aiuti Alessandro, MD, PhD. The first and last names of both authors were inadvertently reversed and should be Silvia Gregori, PhD, and Alessandro Aiuti, MD, PhD. The authors regret the error.