

# Perspective: COVID-19, implications of nasal diseases and consequences for their management



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**Key words:** SARS-CoV-2, COVID-19, chronic rhinosinusitis, allergy, corticosteroids, biologics

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has caused a global health emergency. With increasing numbers of infected people and deaths worldwide reported daily since the beginning of the year, we have to urgently focus on a new pandemic caused by the SARS-CoV-2, a betacoronavirus related to SARS-CoV. We have to urgently learn more about this virus, its ways of transmission to spread infection so fast all over the world, the pathomechanisms involved in human infection and intracellular entry, the consecutive spreading within the body, and finally the factors that determine the difference between a mild or even asymptomatic infection in one and a deadly disease in another patient.<sup>1</sup> Obviously, the age and health condition of the infected person including hypertension, diabetes, and cardiovascular disease play an important role in the clinical course of a coronavirus disease. Urgently, we need to find adequate treatments, and there might be more than adequate masks and social distancing on the one hand and vaccination on the other hand. SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), is highly contagious.

It is of utmost importance to understand how the virus succeeds in infecting an individual person and entering first an outer surface cell and starts replicating, because this might offer therapeutic approaches in the near future. The major entrance door to the patient obviously is the nose and nasopharynx. In a study of infected patients, SARS-CoV-2 viral load was detected

higher in the nose than in the throat.<sup>2</sup> Also, we have painfully learned from the fact that many health care professionals, specifically also ear-nose-and-throat (ENT) specialists, died from COVID-19.<sup>3</sup> Surgery in the nose of an infected patient has been shown to not only put the surgeon at risk, but everyone in the operation room, specifically when drills and endoscopes are used and aerosols are formed during the surgery. Furthermore, it was quite apparent early on that one of the early symptoms of COVID-19 is a loss of smell and consecutively of taste, clearly differentiating the SARS-CoV-2 infection from a normal common cold or a flu. Although most reports are still anecdotal, anosmia/hyposmia was reported in up to 60% of the patients, even among those without typical symptoms such as cough, fever, or dyspnea (<https://www.entuk.org/categories/covid-19>). This led to the statements by the American and British ENT societies, proposing a particular attention to recent-onset olfactory dysfunction as an early possible sign of COVID-19. It has been confirmed later that olfactory epithelial support cells and stem cells express both of these genes discussed below, as do cells in the nasal respiratory epithelium.<sup>4</sup>

What do we know about upper airway conditions such as chronic rhinosinusitis (CRS) with or without polyps, or allergic rhinitis; would these diseases increase the risk of infection? These are diseases affecting 10% to 30% of the population in the United States and Europe, and most often type 2 immune reactions associated with an anyway weak immune defense and reduced IFN production upon infection. We have learned, also from the related coronavirus SARS-CoV, causing SARS outbreak in 2003, that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) exposed at the airway surface and uses it as receptor (Fig 1).<sup>5</sup> To invade the cell, there is need for another player, the transmembrane protease TMPRSS2, a serine protease expressed in airway epithelial cells, mucosal glands, and inflammatory cells such as macrophages, that activates the viral S protein and enables human airway cell entry.<sup>6</sup> How is this receptor and the protease regulated in the nasal cavity, and how does that change with age, sex, or disease status,<sup>1</sup> and would that possibly explain some of the questions posed above?

Of 110 patients hospitalized for SARS-CoV-2 infection from Wuhan and Zhuhai hospitals, only 1 patient reported CRS, 2 allergic rhinitis, and 1 chronic pharyngitis as preexisting diseases (Li Jian, personal communication, 2020). During infection, only 2 patients reported pharyngeal dryness and pain, and 1 nasal obstruction as symptoms, whereas 5 reported loss of smell, in accordance with recent reports.<sup>1,4</sup> Differences in interviewing the patients may account for different prevalences of loss of smell. In the data sets from healthy individuals generated by the Human Cell Atlas consortium, when assessing

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Disclosure of potential conflict of interest: C. Bachert acted as speaker and member of advisory boards for Sanofi-Aventis, Novartis, Glaxo, Astra-Zeneca, Stallergenes, ALK, and Mylan. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 3, 2020; revised April 13, 2020; accepted for publication April 24, 2020.

Available online May 1, 2020.

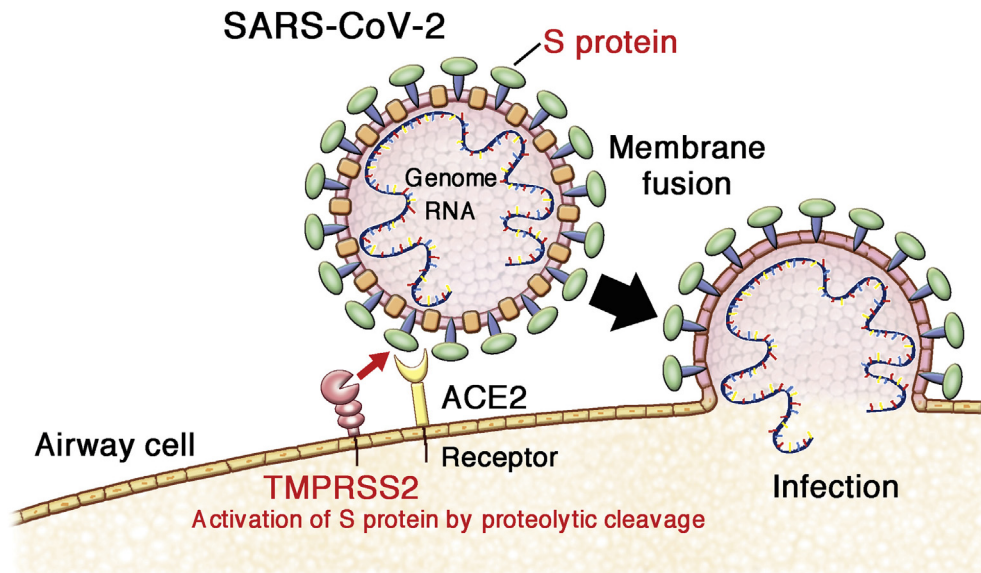
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J Allergy Clin Immunol 2020;146:67-9.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2020.04.030>



**FIG 1.** SARS-CoV-2 binds to ACE2 expressed on human airway cells; the activation of the serine protease TMPRSS2 activates the spike protein to allow virus-cell fusion and cell entry. Regulation of ACE2 in upper airway disease and by corticosteroid treatment is largely unknown, but may offer a chance for intervention.

the RNA expression of the coronavirus receptor (ACE2) as well as the viral S protein priming protease TMPRSS2, nasal epithelial cells displayed the highest ACE2 PCR measurements of all cells analyzed.<sup>7,8</sup> However, it needs to be mentioned that the protein expression was not demonstrated. Furthermore, the corona virus receptor ACE2 may be an IFN-stimulated gene.<sup>8</sup> This could imply that any viral infection could facilitate SARS-CoV-2 infection by releasing IFNs and upregulating ACE2. However, type 2 immune conditions such as CRS without nasal polyps (CRSwNP) with a pronounced type 2 immune reaction and a deficit in IFNs might rather downregulate ACE2 expression. In fact, we observed a reduced expression of ACE2 in nasal polyp disease versus control tissue based on RT-PCR in 20 nasal samples (O. Krysko, N. Zhang, and C. Bachert, unpublished data, 2020). In a rat model of allergic asthma, the expression of ACE2 in lungs was decreased compared with negative control.<sup>9</sup> In summary, these findings might suggest that type 2 inflammatory condition in the airways could have a protective effect against COVID-19 infection or its severity. However, further studies are warranted to clarify causal relationships.

Meanwhile, it also needs to be clarified whether ACE2 expression in the nasal tissues was influenced by intranasal corticosteroid (INCS) treatment often used in these patients. This leads us to the question whether treatment in patients with allergic rhinitis, normally INCS, or in severe patients with CRSwNP, nowadays including biologics to suppress type 2 immune reactions, should be continued in case of a SARS-CoV-2 infection.

The Global INitiative for Asthma statement (<https://ginasthma.org/recommendations-for-inhaled-asthma-controller-medications/>) advised that patients with asthma should not stop their prescribed inhaled corticosteroid controller medication (or prescribed oral corticosteroids), because stopping inhaled corticosteroid may lead to the potentially dangerous worsening of asthma, and avoiding oral corticosteroids during severe asthma attacks may have serious consequences. The administration of oral corticosteroids for COVID-19 lung injury is not advised by the

World Health Organization ([https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected)); however, the World Health Organization does not discourage the use of corticosteroids when indicated independently from COVID-19. Referring to the Global Initiative for Asthma statement, the Allergic Rhinitis and its Impact on Asthma-European Academy of Allergy and Clinical Immunology statement authored by Bousquet et al<sup>10</sup> based on a Delphi process advised to continue INCS treatment for allergic rhinitis, because there is no current evidence that INCS would increase infectivity or symptoms of SARS-CoV-2 infection. However, discontinuation of corticosteroid therapy could induce more coughing or more sneezing because of the loss of control of inflammation, and therefore may increase the risk of infection of so far healthy subjects. Sneezing may spread the virus over several meters, distancing of 2 m clearly is not enough, and face masks are advised in this situation.

SARS-CoV-2 may also infect patients with severe asthma and CRSwNP, who might be under treatment with a type 2 biologic drug such as dupilumab, omalizumab, or mepolizumab. Again, no data are available for any on the type 2 biologics today, but balancing the risk of losing disease control and the lack of evidence or expectation of increased infectivity or mortality, there already are recommendations to continue the treatment with biologics and even start new treatments (eg, from the German Allergy Society [<https://dgaki.de/>]). In fact, in a situation in which surgery of the sinuses is not advised to prevent infection of the operation theater staff, a biologic may in fact offer a possibility to severe patients with nasal polyps. We (Ulrike Förster, Charité Berlin) actually just report on a patient on dupilumab for recurrent severe CRSwNP, who developed a SARS-CoV-2 infection without any additional difficulties. The smell, which was restored after dupilumab, disappeared as the only symptom under the CoV infection, but returned fast thereafter. No other symptoms or changes have been observed.

The emergence of COVID-19 will bring a major change to our practice. However, we begin to recognize that diseases of the upper airways or their management by corticosteroids and biologics do not seem to increase the risk of infection nor the risk for severe COVID-19. A narrow follow-up certainly is advised. Because health care workers at ENT departments are prone to the viral exposure, a consensus is needed very urgently on protective measures for the professionals.

In research perspective, because the airway passage of nose and nasopharynx is the main entry for respiratory viruses including the SARS-CoV 2, the expression and its regulation of the ACE2 receptor and the TMPRSS2 protease are key topics for research and targets for interventions. However, given the potential of new respiratory viral outbreaks in the future, further attention should be given to how to modulate protective roles of upper airway mucosa against different viral infections.

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