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Clinical Commentary Review

Chronic Rhinosinusitis and COVID-19

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Date of Original Release: June 1, 2022. Credit may be obtained for these courses until May 31, 2023.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Concepció Marin, MD, PhD, Thomas Hummel, MD, Zheng Liu, MD, PhD, and Joaquim Mullol, MD, PhD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To identify the main characteristics of chronic rhinosinusitis (CRS) in COVID-19.
2. To understand the role of type 2 inflammation in CRS and COVID-19.
3. To realize the risks of COVID-19 transmission for patients and health professionals during CRS management.
4. To improve efficacy and safety in medical and surgical CRS treatment during the COVID-19 outbreak.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: All authors and reviewers reported no relevant financial relationships.

The COVID-19 pandemic has raised awareness about olfactory dysfunction, although a loss of smell was present in the general population before COVID-19. Chronic rhinosinusitis (CRS) is a common upper airway chronic inflammatory disease that is also one of the most common causes of olfactory dysfunction. It can be classified into different phenotypes (ie, with and without nasal polyps) and endotypes (ie, type 2 and non−type 2 inflammation). However, scientific information regarding CRS within the context of COVID-19 is still scarce. This review focuses on (1) the potential effects of severe acute respiratory syndrome coronavirus 2 infection on CRS symptoms, including a loss of smell, and comorbidities; (2) the pathophysiologic mechanisms involved in the olfactory dysfunction; (3) CRS diagnosis in the context of COVID-19, including telemedicine; (4) the protective hypothesis of CRS in COVID-19; and (5) the efficacy and safety of therapeutic options for CRS within the context of COVID-19. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:1423-32)

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Conflicts of interest: T. Hummel performed research together since 2018 with and/or received funds from Sony, Smell and Taste Lab, Takasago, aspUraclip, Bayer HealthCare, Baia Foods, Primavera, Novartis, Verlag für Chemische Industrie H. Ziolkowsky GmbH, Ismar Healthcare NV-SA, and Frequency Therapeutics. J. Mullol is a member of national or international advisory boards and has received speaker fees or funding for clinical trials and research projects from Allakos, AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe, MSD, Mylan-MEDA Pharma (Viatris), Novartis, Procter & Gamble, Regeneron Pharmaceuticals, Inc, Sanofi-Genzyme, UCB Pharma, and Uriach Group. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 20, 2021; revised manuscript received and accepted for publication March 3, 2022.
Available online March 17, 2022.

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2213-2198

https://doi.org/10.1016/j.jaip.2022.03.003

Abbreviations used
ACE2- Angiotensin converting enzyme 2
CRS- Chronic rhinosinusitis
CRSsNP- Chronic rhinosinusitis without nasal polyps
CRSwNP- Chronic rhinosinusitis with nasal polyps
ENT- Ear, nose, and throat
FFP- Filtering facepiece
HCP- Health care provider
INCS- Intranasal corticosteroids
mRNA- Messenger RNA
NRP1- Neuropilin-1
OB- Olfactory bulb
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
TMPRSS2- Transmembrane serine protease 2

Key words: *Chronic rhinosinusitis; COVID-19; SARS-CoV-2; Olfactory dysfunction; Inflammation endotypes; Angiotensin converting enzyme 2; Corticosteroids; Biologics; Olfactory training; Telemedicine*

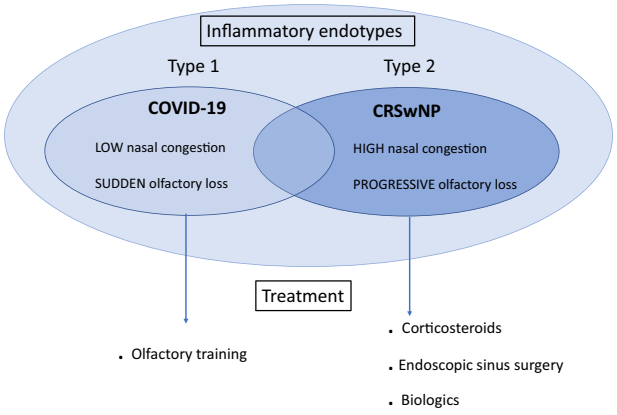

FIGURE 1. Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) who have COVID-19 share type 1 and 2 inflammatory endotypes. This has clear implications for the diagnosis (symptom presentation and evolution) and treatment options.

INTRODUCTION

The COVID-19 pandemic has raised awareness about olfactory and gustatory dysfunction (frequency ranging from 5% to 98%),[1-5] although loss of smell was commonly present in the general population (5% to 20%) even before COVID-19.[6-8] Apart from aging, postinfectious (postviral) rhinosinusitis and chronic rhinosinusitis (CRS) are among the most common causes of olfactory dysfunction.[9] Chronic rhinosinusitis can be divided into different phenotypes (ie, with nasal polyps [CRSwNP] and without nasal polyps [CRSsNP]) and endotypes (ie, type 2 and non−type 2 inflammation).[9] Comorbid conditions are often present in those with more severe disease.[10] However, scientific information regarding CRS within the COVID-19 context remains scarce (Figure 1).

Since March 2020, the COVID-19 outbreak imposed drastic changes in daily ear, nose, and throat (ENT) and allergy clinical practice. During the first phase of the epidemic, the suspension of deferable consultations was necessary. The gradual restoration of daily ENT and allergy activities begun, which must be performed avoiding viral transmission and protecting health care providers (HCPs) from infection.[11]

This review focuses on the potential effects of COVID-19 pandemic on CRS symptoms, including the loss of smell, and comorbidities; the use of telemedicine in CRS diagnosis and management; the possible role of CRS as a protective factor for COVID-19, and the therapeutic options for CRS within the COVID-19 pandemic context.

CHRONIC RHINOSINUSITIS SYMPTOMS AND COVID-19

Chronic rhinosinusitis and olfactory loss

Chronic rhinosinusitis is a disorder with a multifactorial etiology characterized by chronic inflammation of the sinonasal mucosa, affecting 5% to 15% of the general population.[9] The disease is characterized by heterogeneity in the clinical phenotypes and inflammatory profile. Basically, according to the nasal endoscopic findings, CRS is phenotypically classified as CRSsNP and CRSwNP.[9] Chronic rhinosinusitis with nasal polyps accounts for approximately 18% to 20% of CRS and has a greater disease severity and higher levels of morbidity than does CRSsNP.[9,12] The prevalence of CRSwNP is thought to be around 2% to 4% of the general population, in which symptoms (anteroposterior rhinorrhea, nasal congestion or obstruction, loss of smell, and/or facial pain or pressure) persist for greater than 12 weeks.[9]

Based on the degree of eosinophil infiltration in nasal tissue, CRSwNP can be further classified into eosinophilic and noneosinophilic with distinct immunoinflammatory characteristics.[13] Specifically, and mainly in Western countries, eosinophilic CRSwNP has a predominantly type 2 inflammation, whereas noneosinophilic CRSwNP is characterized by non−type 2 inflammation.[9] Type 2 inflammation has high levels of activated T_H2 cell-released cytokines, such asIL-4, IL-5, and IL-13, innate lymphoid cell 2 (ILC2), and infiltrating eosinophils and mast cells, which are more resistant to therapy and exhibit a high rate of recurrence. Non−type 2 is related to T_H1/T_H17 immune response characterized by ILC1/ILC3, T_H cell-released cytokines such as IL-17A, IL-8, and IL-22, IFN-gamma, TNF-α, as well as neutrophilic inflammation (Figure 2).[9,14]

Olfactory dysfunction is present in 56% to 78% of CRS patients.[15,16] It has a progressive and fluctuant course and is strongly associated with the type 2 inflammatory endotype.[17] Patients with eosinophilic CRSwNP report a higher degree of loss of smell,[18] and the degree of smell function is positively correlated with the inflammatory condition of the sinonasal mucosa.[9] Moreover, the frequency and severity of olfactory dysfunction increase when CRSwNP is associated with asthma[19,20] or aspirin- or nonsteroidal anti-inflammatory drug−exacerbated respiratory disease.[21,22]

COVID-19 and olfactory loss

Olfactory dysfunction is an official World Health Organization symptom of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with a frequency of 5% to 85%, depending on the country of study.[1,2,23] Sudden olfactory loss without nasal congestion is among the characteristic early symptoms of COVID-19.[24-27] At the beginning of the SARS-CoV-2 pandemic, the diagnosis of olfactory loss was frequently based on unvalidated questionnaires in many countries,[4] and few studies tested the dysfunction with psychophysical smell tests.[25,28,29] Because many studies found self-ratings of olfactory function to

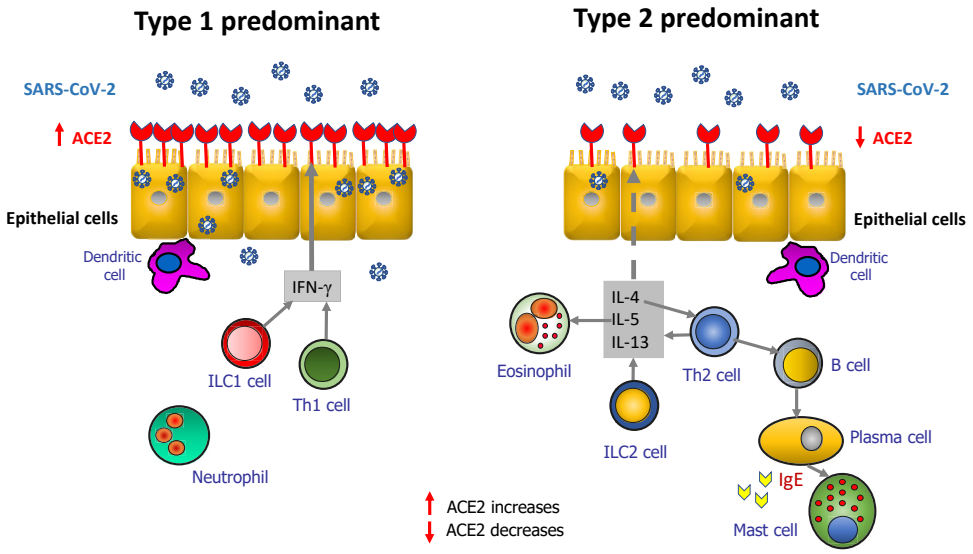

FIGURE 2. Impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (left) in patients without chronic rhinosinusitis with nasal polyps (type 1 predominant) and (right) in those with chronic rhinosinusitis with nasal polyps (type 2 predominant). Type 2 eosinophilic inflammation may decrease angiotensin converting enzyme 2 (ACE2) expression in sinonasal epithelial cells, which potentially represents a protective effect for SARS-CoV-2 infection. *ILC*, innate lymphoid cell.

be unreliable and inaccurate,[4,30,31] short screening tools[27,32] and individual smell tests are needed to assess the related chemosensory dysfunction during the infection as well as to learn about recovery rates after infection. For such testing, numerous alternatives exist that have been shown to be valid and reliable.[33,34] Smell tests also enable tracking of olfactory sensitivity at threshold levels,[35] which appears to be important in addressing more detailed reports of patients with olfactory loss. At the same time, it is important to obtain an in-depth medical history of patients covering the subjective burden of patients with a loss of smell,[36] because olfactory loss can have a significant impact on quality of life leading to social isolation, changes in sexuality and partnership, and depression.[37,38]

In COVID-19, although olfactory loss usually recovers in the first weeks after viral infection, in a significant proportion of patients it may persist for months or even become permanent (long COVID-19).[39] The underlying mechanisms of COVID-19–induced olfactory loss remain controversial and incompletely understood. Several pathophysiologic mechanisms have been proposed for olfactory dysfunction caused by COVID-19,[40,41] including (1) epithelial edema and obstruction of the olfactory cleft; (2) epithelial injury and infection of the sustentacular supporting cells, which are known to express angiotensin converting enzyme 2 (ACE2), an entry receptor for SARS-CoV-2[42,43]; and (3) injury of olfactory sensory cells via neuropilin-1 receptor (NRP1), which can also bind with the spike protein.[44,45]

Although accumulating evidence supports olfactory epithelial injury as a key mechanism,[46] this does not explain all features of loss of smell in COVID-19, such as the duration of loss in some patients, neuroimaging changes, the possible presence of viral particles in the olfactory bulbs (OBs), and the inverse association between COVID-19 severity and the prevalence of olfactory loss.[41] The recent description of a viral entry mediated by NRP1 addresses some of these inconsistencies. Neuropilin-1 receptor is expressed in olfactory neurons and in neuronal progenitor cells.[44] Binding to NRP1 could facilitate direct entry and damage to olfactory neurons, causing loss of smell and the loss of progenitor cells, leading to the delayed recovery of olfactory dysfunction and enabling axonal transport to the OBs.

It has been suggested that all three mechanisms might have a role in SARS-CoV-2–induced olfactory dysfunction.[41] An early olfactory cleft obstruction resulting from olfactory epithelial injury and inflammation mediated by ACE2-related sustentacular cells infection may occur. In addition, in patients with more persistent olfactory loss, a direct injury to olfactory neurons and consequently to the OB, mediated by NRP1 may be present, in which the loss of the progenitor cells is the cause of permanent smell loss.[41] Along this line, the persistence of the inflammatory process in the olfactory mucosa, with consequent damage to the olfactory neurons and alteration of the neurogenesis process, has been associated with persistent olfactory dysfunction in COVID-19.[39]

Relationships between CRS and COVID-19 symptoms

The severity of CRS symptoms and the quality of life of CRS patients involved with COVID-19 was assessed using the Sino-Nasal Outcome Test-22 questionnaire.[47] No differences were found in the four domains (nasal, otologic, sleep and emotional symptoms) of Sino-Nasal Outcome Test-22 in CRS patients with COVID-19 compared with CRS patients without COVID-19.[47] Thus, COVID-19 did not aggravate sinonasal symptoms, including olfactory function, in patients with CRS.

In addition, the severity of symptoms of COVID-19 in patients with CRS was studied,[47] and the results showed that hypoxemia and pulmonary system involvement in patients with CRSwNP were not different from those with CRSsNP. [47]

CHRONIC RHINOSINUSITIS DIAGNOSIS IN THE CONTEXT OF COVID-19

Risk for COVID-19 transmission to HCPs and patients

The COVID-19 pandemic has had a profound impact on the ENT outpatient clinical practice, which is at high risk for

respiratory SARS-CoV-2 transmission because of the close contact between the examiner and the patient's upper respiratory tract.[11,48,49] In addition, ENT specialists are involved in aerosol-generating procedures.[11,50,51] Although ENT nasal endoscopy is not considered an aerosol-generated procedure, it can induce sneezing, coughing, and gagging, resulting in aerosolization.[52,53] Education about how to conduct ENT consultation safely might help to reduce the nosocomial transmission of SARS-CoV-2 and other viral respiratory infections. Before any ENT examination, it is recommended to question all patients about contact with confirmed COVID-19 patients, and about fever, respiratory symptoms, and a recent sudden loss of smell and/or taste.[54]

Several authors have reported the risk for virus transmission during upper airway procedures and have suggested tips and guidelines.[49,55-58] The Centers for Disease Control and Prevention and the World Health Organization recommend that attending health professionals wear full personal protective equipment, including a mask (filtering facepiece [FFP] 2, or preferably FFP3), double gloves, an integral frame eye or full-face shield and gown, hydroalcoholic solution, and closed hospital footwear while performing airway procedures on all patients with active COVID-19.[52,59] Filtering facepiece 2 masks filter approximately 92% of air particles, preventing the inhalation of toxic fluid, dust, and aerosol, whereas FFP3 masks filter 98% of air particles, protecting against toxins of dust and aerosols, as well as bacteria, viruses, and fungal spores.[60] Personal protective equipment creates a barrier to protect ENT specialists, other health care workers, and patients. It is recommended that ENT specialists be fully equipped when examining patients with unknown status.

An association between room ventilation and the transmission or spread of respiratory viral infection has been well-demonstrated. In the COVID-19 era, most guidelines recommend proper ventilation and increased times between patient examinations.[61,62] However, quantification of the minimum ventilation requirements in hospitals and isolation rooms with respect to the airborne spread of infectious disease remains unknown.[63,64]

Regarding ENT examination procedures, it is necessary to consider the following[60]:

1. Nasal endoscopy may be associated with airborne aerosol production irrespective of whether a rigid or flexible scope is used. It requires prolonged close proximity to the patient and carries an unpredictable risk for triggering sneezing.[65] Extreme care should be taken when performing nasal examination with these tools during COVID-19. To prevent a possible COVID-19 infection, a diagnosis analysis by antigen testing immediately before the procedure should be performed. Protection protocols developed for endoscopic procedures include complete personal protective equipment.[66] During nasal endoscopy, the distance between the endoscopist and patient may be maximized using a tower with a camera, screen, and light source, rather than an eyepiece. The use of local anesthetic sprays can be replaced with alternatives such as soaked pledgets, because atomized anesthesia can aerosolize the virus.[67]
2. Acoustic rhinometry, a noninvasive technique for assessing nasal airway obstruction, has a low risk for aerosolization.[68]
3. Anterior rhinomanometry has an indication similar to that of acoustic rhinometry, but with a high risk for aerosolization. This technique is not recommended during the COVID-19 outbreak.
4. Nasal nitric oxide is a colorless, odorless gas present in air exhaled through the mouth or nose and a marker of sinonasal inflammation with a risk for aerosolization.[69] This assessment should be suspended during the current COVID-19 pandemic.[70]
5. Subjective olfactometry is a complementary examination used to assess olfactory dysfunction. Olfactory tests help to study smell identification, discrimination, and threshold, and have a low to high risk for aerosolization, depending on the test applied. Individualized test kits are highly recommended during COVID-19.
6. Nasal sampling (washing, smear, and biopsies) consists of a variety of methods used to evaluate inflammation of the nose and sinuses within nasal mucosa and secretions. These methods may include nasal lavage, cytology, and nasal biopsy. Given the high risk for aerosolization, nonurgent procedures should be avoided in active COVID-19 patients. When necessary, biopsies and smears should be performed with adequate protective measures.

As the COVID-19 pandemic evolves, and with an unpredictable duration, a shift in ENT practice is required to protect patients and health care workers. New systems and protocols will emerge within the field of functional exploration that will replace many of those considered valid to date. Therefore, exploring and implementing strategies to be able to perform ENT procedures safely and effectively is crucial.

Telemedicine in COVID-19

COVID-19 is the first worldwide pandemic in the technology era, and it has encouraged the use of telemedicine. Telemedicine refers to the remote evaluation and treatment of patients using telecommunications technology. Preventive measures challenge HCPs by causing cancelations of in-person outpatient clinic visits in many hospitals, particularly ENT clinics.

Telemedicine has become crucial for providing remote access to rhinology medical care while minimizing patient and HCP exposure to SARS-CoV-2.[71] Other advantages include greater access to specialized care cost-effectively, facilitating timely triage, and broadening geographic practice boundaries. Given the need to incorporate telemedicine into ENT care during COVID-19 pandemics, it is imperative for patients to receive the same quality of care as they did before restrictions.

The applicability and feasibility of telemedicine in rhinology practice were assessed studying outcomes to guide rhinologists on indications for in-office visits during this or future pandemics.[72] The most common diagnosis among follow-up cases was CRSwNP (38.3%), followed by CRSsNP (13%), allergic rhinitis (10%), and deviated nasal septum (16%). Most cases (98.5%) could be managed remotely during the COVID-19 pandemic; only a small percentage of patients (1.5%) required evaluation in the clinic, most in the first visit after surgery. Regarding the satisfaction questionnaire, 83.3% of responses were "agree or strongly agree" when evaluating satisfaction about the telemedicine services received. A total of 67% of respondents expressed trust in telemedicine with a preference to use it again. Most respondents (90.2%) agreed that telemedicine is cost- and time-efficient compared with conventional in-office visits, whereas 85.4% of patients thought it was easy to gain access to specialist care by telemedicine. In contrast, 19% of respondents showed concern about the clinical assessment via telemedicine and thought that their conditions should be evaluated face-to-face in the clinic.[72]

For CRS patients, telemedicine visits enable HCPs to initiate adequate medical treatment, assess response to therapies, and facilitate discussion of surgical options.[71,73] However, a main handicap to incorporating telemedicine visits into clinical practice in CRS patients is the inability to perform a complete physical examination (eg, nasal endoscopy, olfactory test), which is crucial for the diagnosis and management of the disease.[71] A recent study compared CRS patient satisfaction between telemedicine and in-person clinic visits in rhinology practice.[71] No significant differences in patient satisfaction were found between telemedicine and clinical visits, measured by the Patient Satisfaction Questionnaire Short-Form Instrument.

Because sudden-onset anosmia is an early marker for SARS-CoV-2 infection,[74,75] it is necessary to consider that although telemedicine consultations and olfactory self-rating enable the early detection and monitoring of anosmia in COVID-19, it is well-accepted that self-ratings may underestimate olfactory dysfunction.[76]

Although a variety of telemedicine visit types during the COVID-19 pandemic may be adequate in rhinology, in particular regarding CRS management, community medical education is important before implementing telemedicine. In addition, further research is required to investigate the accuracy of diagnostic and treatment strategies and to determine how the lack of an endoscopic or physical examination can change decision-making algorithms.

PROTECTIVE HYPOTHESIS OF CRS IN COVID-19

Chronic rhinosinusitis as potential protective factor for COVID-19 outcomes

Although CRS patients are susceptible to exacerbations to viral infections, CRS has not been reported to be a major comorbidity of COVID-19. It was observed that CRS is not a risk factor for COVID-19; there may even be a protective role against SARS-CoV-2 infection.[47,77-79] Thus, CRS prevalence in hospitalized COVID-19 patients (6.1%) was close to that in the general population in China (8%), and CRS was not associated with severe COVID-19.[79] Moreover, COVID-19 patients with CRS presented a lower risk for hospitalization compared with those without CRS.[79] Similar findings were reported in asthmatic patients, a disorder also associated with type 2 inflammation and a frequent comorbid pathology in CRS patients.[80-83]

Effects of CRS type 2 inflammation endotype on SARS-CoV-2 entry proteins

SARS-CoV-2 uses ACE2 as cellular receptors to enter cells and transmembrane serine protease 2 (TMPRSS2) for SARS-CoV-2 S protein priming.[84,85] Angiotensin converting enzyme 2 expression facilitates viral replication in airway epithelium and susceptibility to infection, whereas TMPRSS2 contributes to cellular entry and promotes the spread of infection.[84,85]

A factor that may underlie variations in COVID-19 clinical outcomes is the extent of airway gene expression of SARS-CoV-2 entry receptors, ACE2, and TMPRSS2.[84] In light of the high expression and broad distribution of TMPRSS2 in human organs, ACE2, rather than TMPRSS2, may be a limiting factor for SARS-CoV-2 infection.[86] Thus, it is considered that factors leading to upregulation of ACE2 expression in host cells are likely to be risk factors for SARS-COV-2 infection.[87]

Evidence has shown that type 1 and 2 inflammation regulates ACE2 expression in the airway epithelium[88] (Figure 2). Interestingly, given the lower risk for COVID-19 among CRS patients, a differential expression of ACE2 has been hypothesized. Along this line, a reduced expression of ACE2 messenger RNA (mRNA) and protein was observed in CRSwNP respiratory airway epithelial cells, including nasal polyps,[86,89-93] and in olfactory mucosa[94] compared with noneosinophilic CRS and control subjects. Similar findings were reported in asthmatic patients.[81,88,95,96] Thus, the protective effect of CRSwNP may be due to reduced viral binding as a result of the downregulated expression of the SARS-CoV-2 receptor, ACE2, on airway epithelium.

In addition, a negative correlation between ACE2 expression and the levels of cytokines associated with type 2 inflammation, including IL-4, IL-5, and IL-13, in airway epithelial cells was shown.[81,97] Moreover, IL-13 stimulation suppresses ACE2 expression in nasal and bronchial epithelial cells cultured with an air—liquid interface method.[81,88,97] All of these data suggest that increased type 2 inflammation reduces ACE2 airway epithelial expression as a potential mechanism by which type 2 inflammation may be responsible for a putative protective effect, and may explain less severe outcome from COVID-19 infection.

Furthermore, increased ACE2 expression was correlated with the expression of type 1 inflammatory cytokines, particularly IFN-gamma in nasal respiratory tissues of noneosinophilic CRSwNP patients,[86] whereas IFN-gamma induces ACE2 expression in primary human upper airway basal cells.[93] All of these findings suggest that noneosinophilic CRSwNP may have increased susceptibility to SARS-CoV-2 infection.[86]

Considering the potential protective effect of the type 2 inflammatory endotype in CRS against SARS-COV-2 infection, the potential antiviral and immunomodulatory functions of eosinophils[98-100] need to be considered because they may represent a complementary mechanism underlying this effect. The ability of eosinophils to attenuate viral replication directly or indirectly may protect against the development of an inflammatory response that underlies the onset of severe COVID-19 disease.[100] Although controversial results were obtained,[101-103] better COVID-19 outcomes were associated with an increase in blood absolute eosinophil counts ($\geq$200 cells/μL) in patients with or without asthma,[101,104] whereas decreased eosinophil levels (eosinopenia) are associated with a poor prognosis in COVID-19 patients.[98,102,104] Moreover, a negative correlation between eosinophil levels and ACE2 expression was described.[105] Thus, an increase in ACE2 gene expression in bronchial epithelial cells was observed in asthmatic patients with low peripheral blood eosinophil counts compared with those with high eosinophil counts.[105]

These findings provide evidence that type 2 inflammation decreases ACE2 expression in the upper and lower respiratory and olfactory epithelium. This is plausible mechanism that may underlie the protective effects of CRSwNP against SARS-CoV-2 infection.

CHRONIC RHINOSINUSITIS TREATMENT EFFICACY AND SAFETY IN THE COVID-19 CONTEXT

Intranasal corticosteroids (INCS), in combination with systemic corticosteroids for severe cases, are recommend by

European[9] and American[106] guidelines for the treatment of CRS. Surgery is used to treat CRS patients who are unresponsive to medical treatment. Emerging type 2 biologics are effective for patients with severe CRSwNP that is poorly controlled by systemic corticosteroids and surgery. These treatments may potentially influence the risk for SARS-Cov-2 infection and COVID-19 development by modulating the host immune response to viral infection, ACE2 expression in airway epithelial cells, and preexisting sinonasal inflammation caused by CRS. On the other hand, the COVID-19 pandemic restricts medical service accessibility and influences treatment decisions for CRS patients, which consequently affects the medical and surgical treatment in CRS patients.

Medical treatment

Corticosteroids. Intranasal corticosteroids constitute appropriate medical treatment for CRS, including CRSwNP.[9] However, the use of corticosteroids to treat COVID-19—related olfactory loss is a matter of debate.[107] *In vitro* studies suggested that INCS treatment may impair antiviral innate immune responses and lead to delayed virus clearance in human airway epithelial cells.[108] SARS-CoV-2 enters cells by binding to ACE2, which may be the limiting factor for viral entry. Jackson et al[81] reported that nasal corticosteroid use at the time of nasal sampling was not associated with alterations in ACE2 mRNA expression in nasal epithelial cells in asthmatic children. Wang et al[109] found that dexamethasone treatment did not change ACE2 mRNA expression in cultured human nasal epithelial cells *in vitro*. In humans, the use of inhaled corticosteroids was not associated with an increased risk for COVID-19—related hospitalization in asthmatic patients after controlling for multiple comorbidities associated with severe COVID-19.[80] Nevertheless, Lee et al[110] reported that CRS patients treated with INCS had a greater risk for SARS-CoV-2 infection and severe COVID-19 outcomes based on a nationwide cohort in South Korea, although the case numbers were small. The influences of INCS on the risk and severity of COVID-19 depend on the interaction between its impact on immune defense against SARS-CoV-2 and the control of CRS symptoms. Therefore, more data are needed to define the impact of INCS on COVID-19 in CRS patients.

Systemic corticosteroids can significantly impair immune system mechanisms to combat viruses. Although there are no data regarding the relationship between systemic corticosteroid use and COVID-19 risk and severity in CRS patients, recent systemic corticosteroid use was associated with an increased risk for mortality owing to COVID-19 in asthmatic patients.[111] According to the European Academy of Allergy and Clinical Immunology position paper on the management of CRS during the COVID-19 pandemic, INCS can be continued in CRS patients, and routine systemic corticosteroids should be avoided.[112,113]

Biologics. Type 2 cytokines can downregulate ACE2 expression in human airway epithelial cells.[91] Uncontrolled and severe CRSwNP is usually characterized by predominant type 2 and eosinophilic inflammation. Angiotensin converting enzyme 2 expression was reduced in eosinophilic nasal polyps.[91] Therefore, it is possible that reversal of type 2 and eosinophilic inflammation by type 2 biologics, such as omalizumab, mepolizumab, benralizumab, and dupilumab, may increase the risk for SARS-CoV-2 infection. Förster-Ruhrmann et al[114] reported the case of a 53-year-old female patient with uncontrolled severe CRSwNP who was treated with dupilumab (anti-IL-4Rα); this patient had an unexpectedly light course of COVID-19 disease. Moreover, in 545 severe asthmatic patients treated with biologics (many of them with CRSwNP) from a Spanish cohort, no increased risk for severe COVID-19 or mortality was found.[115] However, there are no formal studies investigating the influence of type 2 biologics on COVID-19 risk and severity in patients with CRSwNP. Although the European Academy of Allergy and Clinical Immunology position paper on managing CRS during the COVID-19 pandemic recommends that biologics be stopped until patients with COVID-19 symptoms complete recovery,[116] a risk—benefit assessment must be carefully conducted for CRSwNP patients treated with biologics.

Surgery. Otolaryngologists are faced with concerning challenges owing to the significant risk of occupational SARS-CoV-2 infection. Transmission can happen during intraoperative exposure to viral particles carried by droplets or aerosols. Endoscopic sinus surgery is notable for causing aerosolization, putting HCPs at substantial risk.[117] Rescheduling operations should be considered for waiting-list patients, and preoperative screening for COVID-19 is needed during the COVID-19 pandemic. If the possibility of SARS-CoV-2 infection cannot be ruled out, appropriate infection prevention measures should be used during nasal endoscopic examination, diagnostic biopsy, and sinus surgery.

Olfactory training. The loss of smell in COVID-19 patients, characterized as one of the earliest and most common symptoms, has a sudden onset and variability in severity ranging from hyposmia to anosmia.[3] Rates of patients' self-reported subjective smell and taste loss range from 40% to 80%.[118] In most cases, olfactory dysfunction seems to be self-limited, and has been reported to improve in the first 30 days after disease onset.[119,120] Olfactory dysfunction is also a common symptom in CRS patients, particularly in those with CRSwNP. Whether COVID-19 patients with preexisting CRS have a higher risk for loss of smell and a poorer prognosis compared with those without CRS remains unclear.

Olfactory training demonstrates considerable benefit for patients with olfactory dysfunction triggered by upper respiratory viral infection.[121] Although rigorous clinical data are lacking, olfactory training was recommended to COVID-19 patients with persistent smell loss.[122] Recently, based on a small sample size, Le Bon et al[123] reported that the combination of a short course of oral corticosteroids and olfactory training may be more efficient in helping patients with enduring dysosmia recover from olfactory loss due to COVID-19 than olfactory training alone. With regard to the side effects of corticosteroids, the use of oral corticosteroids is best started after polymerase chain reaction results on nasopharyngeal or pharyngeal swab samples become negative. For CRS patients with a sudden loss of smell caused by COVID-19, olfactory training seems to be more important when there is no full spontaneous recovery after 4 to 8 weeks.

COVID-19 vaccination and CRS treatment. Vaccination is considered the most effective strategy to reduce SARS-CoV-2 infections and prevent severe illness after breakthrough infections. Intranasal corticosteroids are unlikely to influence the efficacy of vaccination. However, the effect of vaccination may be reduced by systemic immunosuppressors such as oral

corticosteroids. Rincón-Arévalo et al[124] reported impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. The kidney transplant recipients were receiving a uniform immunosuppressive regimen with mycophenolate mofetil, corticosteroids, and calcineurin inhibitor. Nevertheless, whether the oral corticosteroids treatment will compromise SARS-CoV-2 vaccination efficacy in CRS patients requires further investigations. A previous study demonstrated that the efficacy of tetanus toxoid vaccination was not adversely affected by dupilumab treatment in patients with moderate to severe atopic dermatitis. [125] In contrast, Yao et al[126] reported that patients with allergic rhinitis patients displayed enhanced humoral immune response to SARS-CoV-2—inactivated vaccine compared with healthy controls, which is associated with exaggerated type 2T follicular helper cells responses. Runnstrom et al[127] found that patients with severe asthma or atopic dermatitis who were receiving biologic therapies (benralizumab, mepolizumab, or dupilumab) had lower antibody levels after SARS-CoV-2 mRNA vaccination compared with healthy adults. Therefore, more studies are needed to elucidate the influence of type 2 biologics on SARS-CoV-2 vaccination efficacy, particularly in CRS patients. Currently, a Position Paper of the German Society of Allergology and Clinical Immunology and German Society for Applied Allergology suggests that vaccination in patients receiving systemic therapy with biologics can be performed, but within the interval of two applications of the respective biologics, which is a time lag of at least 1 week after the previous biologic treatment or at least 1 week before the next one is planned.[128]

CONCLUSIONS

Chronic rhinosinusitis and COVID-19 share the impact of an important symptom, the loss of smell, which is progressive in CRS and sudden in COVID-19. As observed in asthma patients, recent data suggests that CRS eosinophilic inflammation could exert a protective effect on SARS-CoV-2 infection, including olfactory dysfunction. However, the mechanisms of action seem to be different in both diseases: olfactory neuroepithelium shedding induced by tissue eosinophilia (type 2 inflammation) in CRS and olfactory neurodegeneration by ACE2/NRP1-mediated SARS-CoV-2 infection (type 1 inflammation) in COVID-19. During COVID-19, CRS diagnosis and examination should be carefully performed to prevent transmission between HCPs and patients, including the use of personal protective equipment, avoiding diagnostic tools that induce airborne aerosol production, or even considering telemedicine. Concerning CRS patients, no data in the literature support discontinuing first-line medications (ie, intranasal or systemic corticosteroids) in COVID-19 patients, although international scientific societies have recommended discontinuing biologics and delaying of endoscopic sinus surgery, but only during the acute phase of COVID-19. Finally, olfactory training was recommended as a unique therapy with efficacy after postviral olfactory dysfunction in COVID-19, whereas prevention and vaccination continue to be the two main efforts to be made across the world to avoid SARS-CoV-2 infections resulting from the different waves and variants of the virus.

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