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Article type : EAACI Position Paper

Management of patients with chronic rhinosinusitis during the COVID-19 pandemic – An EAACI Position Paper

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14629](https://doi.org/10.1111/ALL.14629)

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Summary

Background: CRS is regarded as a chronic airway disease. According to WHO recommendations, it may be a risk factor for COVID-19 patients. In most CRSwNP cases, the inflammatory changes affecting the nasal and paranasal mucous membranes are type-2 (T2) inflammation endotypes.

Methods: The current knowledge on COVID-19 and on treatment options for CRS was analyzed by a literature search in Medline, Pubmed, international guidelines, the Cochrane Library and the Internet.

Results: Based on international literature, on current recommendations by WHO and other international organizations as well as on previous experience, a panel of experts from EAACI and ARIA provided recommendations for the treatment of CRS during the COVID-19 pandemic.

Conclusion: Intranasal corticosteroids remain the standard treatment for CRS in patients with SARS-CoV-2 infection. Surgical treatments should be reduced to a minimum and surgery preserved for patients with local complications and for those with no other treatment options. Systemic corticosteroids should be avoided. Treatment with biologics can be continued with careful monitoring in non-infected patients and should be temporarily interrupted during the course of the COVID-19 infection.

Key Words:

Chronic Rhinosinusitis; COVID-19; SARS CoV-2; nasal Polyps; CRSwNP; Biologics; intranasal Corticosteroids, Dupilumab

Introduction

COVID-19 is caused by a new virus strain - SARS-CoV-2 - from the coronavirus family that has not previously been identified in humans. Coronaviruses are zoonotic, i.e. they can be transmitted between animals and humans. Common signs of SARS-CoV-2 infection include fever, cough, muscle aches, shortness of breath and difficulties in breathing. Anosmia and dysgeusia have also been reported recently as important symptoms [1]. In South Korea, where testing for COVID-19 has been extensive, 30% of the patients tested positive have had anosmia as their major presenting symptom in otherwise mild cases [2]. Other signs of viral airway infection may include nasal symptoms and sore throat. In more severe cases, COVID-19 can cause pneumonia, acute respiratory distress syndrome, kidney or myocardial failure, leading to death in approximately 1-8% of the affected population [3, 4]. High virus load can be found in the nose and pharynx, making the upper airways an important target for preventing transmission [5].

On March 11, 2020, the World Health Organization officially declared COVID-19 a pandemic [4]. Since its outbreak in December 2019, the number of people infected has continued to increase and it has affected all regions worldwide.

The latest epidemiological data and guidelines on infection control and management can be found on the WHO [4] and Center for Disease Control and Prevention (CDC) [6] websites.

In the published scientific literature on COVID-19, chronic respiratory diseases, diabetes, arterial hypertension, obesity, coronary artery disease and primary or secondary immunodeficiency are listed as risk factors for severe/critical illness, hospitalization and lethal outcome [3, 7-9].

Interestingly, allergic rhinitis (AR), atopic dermatitis, and controlled asthma were not reported in a retrospective chart review of 140 hospitalized, infected and symptomatic patients in Wuhan [8]. In the same study, it was reported that chronic rhinosinusitis (CRS) has not even been asked for, probably due to the fact that there were no spontaneous reports from patients. These observations suggest that allergic and upper airway diseases - or their treatment including intranasal corticosteroids (INCS) - do not increase the risk for infections. ACE2 expression was decreased in patients with atopic inflammatory upper airway disease [10]. This expression was not influenced by INCS use [10].

Chronic rhinosinusitis (CRS)

CRS is a chronic respiratory disease that is defined as a persistent inflammation of the mucous membranes of the nose and paranasal sinuses leading to at least 2 of the following symptoms: nasal obstruction and/or rhinorrhea with either facial pressure and/or smell problems [11-14].

Recently, a number of reports have indicated that a sudden isolated onset of anosmia (ISOA) may be present in COVID-19 patients who are otherwise asymptomatic. This should be considered especially in the differential diagnosis for loss of smell in CRS and as a marker symptom in screening for SARS CoV-2 infection in general [1, 15].

In epidemiological studies, approximately 5-12% of the general population worldwide and 3-6% of the patients in clinical trials are affected by CRS. This causes considerable costs for health systems and economies [11-14, 16, 17]. Diagnosis is determined by the presence of typical symptoms with additional endoscopic and / or radiological evidence of inflammatory changes of the sinus mucosa [14, 17, 18]. CRS is traditionally classified by the presence of nasal polyps (NP) into a phenotype either with NP (CRSwNP) or without NP (CRSsNP) [19, 20]. From a mechanistic point of view, CRS can be divided into type-2 (T2) and non-T2 immune-inflammatory response.

CRS is typically associated with epithelial damage and tissue destruction [21] that can promote viral infections [12]. Asthma often coexists with CRS and it is known that deterioration in the control of CRS can promote asthma exacerbations [11].

As CRS is a chronic inflammatory disease [22], it can be treated with INCS sprays, systemic glucocorticosteroids (sGCS) or, specifically for CRSwNP, T2 endotype-driven [22, 23] anti-inflammatory therapies [24, 25], depending on the severity of disease.

The latter is considered the corner-stone of precision-based medicine in the case of CRSwNP [26]. This is more and more often regarded as the preferred treatment option, specifically for patients with severe disease, in whom classical treatment options such as sGCS or surgery are insufficient or have too many side effects [26-29].

Comorbidities of CRSwNP

CRSwNP patients form a very heterogeneous patient group with a great variability in disease factors such as age of disease onset and disease severity. They can present with different comorbidities such as allergies, NSAID-exacerbated respiratory disease (N-ERD), but also autoimmune diseases such as EGPA (eosinophilic granulomatosis) polyangiitis [30-33]. It has been shown that 30-70% of CRSwNP patients suffer from comorbid asthma [23, 32, 34, 35]. Also, the severity of asthma is associated with the presence of CRSwNP [36, 37], with only 10-30% of mild asthma patients presenting with CRSwNP, compared to 70-90 % of patients with severe and especially late-onset asthma [36, 37]. Both diseases have similar pathophysiological and immunological mechanisms with T2 inflammation being the most common endotype [23, 38-40]. This inflammatory type is characterized by an eosinophilic infiltration associated with the presence of typical T2 cytokines such as interleukin (IL)-4, IL-5, and / or IL-13 as well as circulating but especially local IgE [23, 41].

Treatment of CRSwNP

The treatment of both CRSwNP and asthma is based on anti-inflammatory therapies with topical GCS administration. For CRSwNP, daily administration of INCS is the baseline therapeutic golden standard [17, 42-46]. A Cochrane Review demonstrated a consistent but moderate improvement in subjective symptoms, especially nasal breathing, rhinorrhea, olfactory disorders, headache and facial pain [47], but also a reduction in the size of nasal polyps and a decrease in the recurrence rate of polyps after sinus surgery with INCS treatment [48, 49].

If this treatment is insufficient in obtaining disease control, short-term courses of oral GCS (usually over a maximum of 2-3 weeks) are often prescribed for severe cases of CRSwNP [50, 51]. Systemic GCS can be used alone or in addition to INCS therapy and, when combined, have a greater effect size [52, 53]. With long-term use, however, undesirable effects of systemic GCS are relatively common [29]. Some of these side effects might even occur at cumulative dosages as low as 1 g prednisolone-equivalent [54].

The increased risk of contracting viral infections by sGCS may be assumed specifically relevant for SARS-CoV-2 infection, resulting in COVID-19 disease. However, there are no controlled studies currently available on this aspect and whether sGCS have a promoting effect on SARS-CoV-2-

infection remains a matter of debate. Corticosteroid therapy in patients suffering from Middle East Respiratory Syndrome (MERS) , another SARS- like disease induced by Coronaviruses, induced a delayed viral RNA clearance [55]. But hospitalized COVID-19 patients receiving oxygen and dexamethasone in the second week of illness showed lower 28-day mortality [57].

Alternatively, long-term antibiotics and / or an adaptive Aspirin desensitization/deactivation are treatment options for certain selected patients [50, 51, 58-60].

Recently, various biologics have been developed that intervene in different pathways of the immunological pathophysiology of multiple inflammatory diseases. With regards to CRSwNP, the IL-4 / IL-13 monoclonal antibody Dupilumab (Dupixent®) was the first biologic therapy to receive regulatory approval in the EU and the US. Dupilumab binds to the alpha subunit of the IL-4 receptor, which inhibits the IL-4 / IL-13 signaling pathways and thus the T2 type inflammation [61, 62]. It has been approved in Europe as an add-on therapy to INCS for the treatment of adults with severe CRSwNP that cannot be adequately controlled with sGCS and/or surgical intervention. Recently published consensus documents propose different criteria for implementing Dupilumab in the treatment of CRSwNP patients [19, 63]. These include:

- Previous sinus surgery
- Evidence of type 2 inflammation (biomarkers)
- Use of systemic GCS in the past 2 years (≥ 2 short courses/year OR a long-term course for >3 months with low dose sGCS)
- Significantly reduced quality of life
- Significant loss of smell
- Co-morbid asthma

Biologics are indicated in patients with bilateral nasal polyps who had undergone sinus surgery in the past and meet 3 of the above mentioned criteria [63].

We agree with these recommendations and state that if therapeutic drug alternatives have already been used unsuccessfully - or are not available due to unacceptable risk for the patient- then dupilumab should be considered in CRSwNP.

When these criteria are not met, surgery is the treatment of choice to achieve disease control in CRSwNP [64-66]. However, surgery may have to be postponed in the current pandemic to save medical resources and to protect medical staff and patients from aerosolized virus particles (Recommendations of the ERS; <https://www.europeanrhinologicsociety.org>).

CRS treatment and COVID-19

According to current WHO guidelines, patients at risk, or with diagnosed COVID-19, should continue to be treated for all other diseases, if the treatment does not interfere with COVID-19 or vice versa [4]. CRS is no exception for this general rule and INCS is the standard therapy of choice [67]. With regards to the possible increased infection risk, control of inflammation to avoid systemic GCS is paramount for avoiding exacerbation in the airways. In the case of no other options, patients should quarantine during the course of sGCS and for 1 extra week afterwards.

Also, the reduction of the inflammatory reaction of the nasal mucosa by INCS may shorten the duration and decrease the severity of symptoms in viral upper respiratory tract infections. Although current evidence does not support the use of INCS for symptomatic relief of the common cold [68], INCS are effective in reducing the total symptom score in adults suffering from acute post-viral rhinosinusitis [20, 69, 70].

In view of the disease mechanisms, it can be assumed that INCS reduce the virally induced inflammatory reaction within the nasal mucosa and that this may decrease the severity of symptoms in the upper respiratory tract [71].

In the current COVID-19 pandemic, some opinions have been published stating that "cortisone preparations" increase the risk of developing COVID-19 or may cause a more severe course of the disease. This has massively unsettled numerous patients with AR, CRS and asthma [72]. In line with a current statement by ARIA and EAACI on AR treatment [67], we feel obliged to put forward the following for the treatment of CRS:

- INCS are the therapeutic standard for CRS, and modern INCS are effective in treating symptoms and inflammatory changes, thus avoiding mucosal damage.

- there is no evidence that the use of INCS in the approved doses and indications (see product information and/or package leaflet) leads to an increased risk of SARS-CoV-2 infection or trigger a more severe course of COVID-19.
- adults and children with CRS should consistently and regularly take their INCS in the individually prescribed dose and not change or stop without consulting their doctor.
- there is a risk that CRS will deteriorate due to discontinuation of INCS. Such worsening can promote droplet infection in other people due to increased secretion and sneezing in CRS patients infected with SARS-CoV-2. In addition, worsening of CRS might require systemic GCS which may have a negative effect on the immune defense against SARS-CoV-2. Ultimately, worsening of CRS can trigger exacerbations of asthma, which the WHO also regards as a risk factor for severe courses of COVID-19 disease.
- as discussed above, systemic GCS should be used with caution in CRS in the current COVID-19 pandemic and should be reserved for patients with severe symptoms and in the absence of a therapeutic alternative. Such an indication could exist for severe CRSwNP patients if surgical treatment is not possible in the current pandemic situation. These patients should quarantine during the course of sGCS and for 1 extra week afterwards, to minimize the risk of infection.

Treatment of asthma in CRS patients

To date, there is little information available on SARS-CoV-2 infection in asthma patients. In general, infection, and particularly viral infection, is a common precipitant of asthma exacerbations [73]. Coronaviruses are known to aggravate asthma attacks or exacerbations [74, 75] during infection. Bacterial infections and colonization have also been associated with exacerbation and recurrent wheeze, an effect that may be independent or a cofactor with viruses [74, 75]. In addition, certain individuals are known to have a genetic predisposition towards viral-induced wheezing and the consequent development of asthma [74, 75].

In agreement with asthma specialists worldwide, we recommend that adults and children suffering from CRS with concomitant asthma should neither change nor stop an adequate and individually adjusted anti-asthmatic inhalation therapy (especially inhaled corticosteroids

therapy) during the current COVID-19 pandemic (e.g. [76]). The risk that their asthma will deteriorate severely, requiring otherwise unnecessary doctor visits or hospital stays (increasing possible contact with COVID-19 patients), is far more threatening for the asthma patient than a possible undocumented increased risk of infection with SARS-Cov-2, caused by topical GCS. Moreover, hospitals that are currently committed and even forced to focus on the treatment of COVID-19 cases may have difficulties in treating asthma exacerbations.

Successful GCS inhalation therapy in patients with asthma should therefore be continued, especially during the current COVID-19 pandemic.

Based on current available evidence, it is even recommended that asthma patients who previously took their baseline therapy with inhaled corticosteroids (ICS) on an irregular basis (alone or in a fixed combination with a long-lasting, bronchodilator, LABA) should switch to the regular application of their ICS. In the case of persistent uncontrolled asthma symptoms, they should contact their physician to adjust the therapy accordingly.

In severe COVID-19 disease, special caution should be given to biologics dampening blood eosinophils, as resolving eosinopenia indicates recovery of COVID-19 disease [77].

Eosinopenia was reported in association with severe cases of COVID-19 without clear data on pathomechanisms, while an elevated eosinophil count was associated with a better prognosis [3]. However, no causal or functional relationship has been demonstrated so far and this finding may be an epiphenomenon [78].

A permanent discontinuation of biologics may lead to a worsening of the underlying disease, which in turn could have a negative impact on the course of COVID-19. Virus-related asthma exacerbations occur less frequently or are less severe under biologic therapy [76]. In the absence of biologic therapy, especially in severe asthma, patients would have to be switched to therapy with sGCS, which can compromise their immune defense against SARS-CoV-2 [76]. However, since it takes between several weeks and 3 months for the therapeutic effects of many biologics to disappear, it would seem that there is no major impact on CRS control when withholding biologics during the acute phase of COVID-19.

Therapy with biologics for CRSwNP

Monoclonal antibodies (biologics) are used successfully to treat severe forms of various chronic diseases. These include asthma, atopic dermatitis, CRSwNP and chronic spontaneous urticaria. Specifically, omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab are authorized for at least one of these indications. The immunopathology of chronic rhinosinusitis with the overview of biologics and their targets is shown in Figure 1. While the immunological processes modified by the mentioned biologics probably do not play a central role in the defense against viruses, the use of these drugs must be clearly based on the instructions for use of each individual monoclonal biologic. The treating physician should determine the treatment for each patient based on an individual benefit / risk assessment.

In severe COVID-19, sepsis may occur. Eosinopenia is well known as a feature of sepsis [79, 80], and may be a consequence, not a cause. Anti-IL-5 strategies such as Mepolizumab reduce eosinophils by approximately 50%, but do not abolish tissue and blood eosinophils [81]. Benralizumab may have a more profound effect [82], but no observations in relation to COVID-19 are available for this drug either. In severe asthma studies, Mepolizumab and Benralizumab reduce exacerbations, mostly induced by viruses, by approximately 50% [83, 84].

Regarding Dupilumab, the only authorized biologic for the treatment of CRSwNP, over 8,000 patients have received this drug during the clinical development program for various indications (e.g. atopic dermatitis, bronchial asthma, CRSwNP) [85]. Various respiratory infections, including respiratory viral rhinovirus infections, have been identified during the clinical trial programs and these events are not listed as adverse drug reactions in the European public assessment report EPAR and Summary of Product Characteristics (SPC) [86].

On the other hand, virus-triggered exacerbations can be reduced, and this is associated with a restored production of IFN- α . The possible risk of COVID-19 does not therefore constitute a contraindication to continuing or starting therapy with Dupilumab for CRSwNP. Adequate symptom and inflammation control is independent of the current pandemic situation.

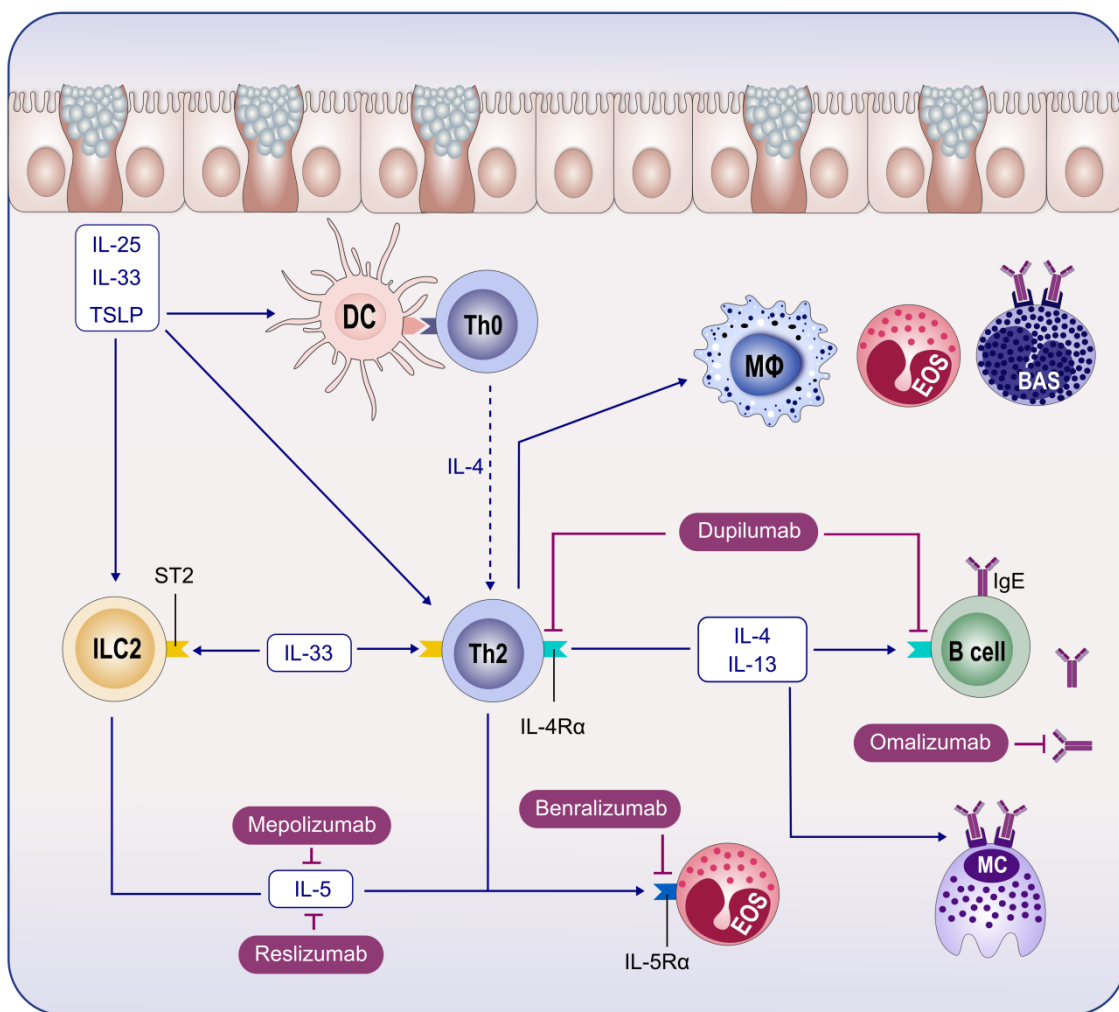


Figure 1_Klimek et al.

For the use of biologics in CRS under the conditions of the current COVID-19 pandemic, we recommend the following:

- **Patients on biologic therapy who have not tested positive or exhibited signs/symptoms of COVID-19:** there is insufficient evidence to recommend the discontinuation of biologics. Physicians should continue to weigh the risks vs. benefits of the use of biologic medication on a case-by-case basis. The discussion, at the level of the individual patient, should include the patient's age and multimorbidities, including serious chronic medical conditions such as cardiovascular disease, diabetes, severe hypertension, liver disease, kidney disease, respiratory system compromise, cancer or tobacco use, among others.

- **Patients on biologic therapy who have tested positive for COVID-19:** We recommend physicians to discontinue or postpone the biologic therapy until the patient recovers from COVID-19.
- **Patients being considered for biologic therapy initiation:** We suggest physicians assess the risks vs. benefits in low-risk patients before initiating biologics therapy on a case-by-case basis. In a high-risk population (e.g. individuals 60 years and older, or patients with recognized multimorbidities such as cardiovascular disease, diabetes, severe hypertension, liver disease, kidney disease, respiratory system compromise, cancer or tobacco use, among others), we suggest that physicians consider deferring the initiation of biologic therapy if the risk/benefit assessment does not favor biologic treatment [87, 88]. It should be considered that the commencement with biologic therapy is likely to reduce the need for sGCS. Continuation of sGCS is likely to increase the risks associated with SARS-Cov-2 infection mitigated by a biologic. Furthermore, the COVID-19 pandemic may span many months and possibly years.

The recommendations for the use of biologics in CRSwNP during the COVID-19 pandemic are summarized in Table 1.

Recommendations for the use of biologics in CRSwNP during the COVID-19 pandemic
Patients on biologic therapy not tested positive nor exhibited signs/symptoms of COVID-19: There is insufficient evidence to recommend discontinuation of biologics. Physicians should consider the risk vs. benefits on a case-by-case basis.
Patients on biologic therapy tested positive for COVID-19: Physicians are recommended to discontinue or postpone the biologic therapy until the patient recovers from COVID-19.
Patients being considered for biologic therapy initiation: Physicians should assess the risk vs. benefits in low-risk patients on a case-by-case basis. In a high-risk population, the physicians should consider deferring initiation of biologic therapy if the risk/benefit assessment is not favouring biological treatment.

Table 1: Recommendations for the use of biologics in CRSwNP during the COVID-19 pandemic

How do ENT surgeons deal with CRS / CRSwNP patients in practice?

In accordance with ERS recommendations [89], diagnostic procedures for rhinology patients such as nasal endoscopy should be avoided when possible. When nasal endoscopy is unavoidable, appropriate protection including FFPW/FFP2 masks, full eye protection and full body protective clothing should be used. Also, when applying local anesthesia with or without decongestants, atomized forms should be avoided and actuated pump sprays or soaked pledgets should be used. It is generally recommended that ongoing successful therapies in CRS, asthma or both should continue and that patients should have a medication supply, sufficient for a 14-day quarantine, if necessary.

Elective endoscopic sinus surgery should be avoided and only performed in the case of suspected malignancy or local complications of disease. If elective surgery is necessary, patients should be tested for SARS-CoV-2 infection, when and where available, and should be shown to be negative before proceeding. In the case of emergency surgery or unavailability of testing, the patient should be considered as SARS-CoV-2-positive. When endoscopic surgery is performed, the surgeon should wear specific PPE, preferably a PAPRs (Powered, Air Purifying Respirators) and patients should be advised to practice hand hygiene and social distancing prior to surgery. In a recent study, the application of standard cold instrumentation or microdebridors did not generate detectable aerosols. On the contrary, high-speed drills produced significant aerosol contamination [90]. The number of health care professionals in the OR needs to be kept to a minimum and adequate PPE should be worn during surgery [89].

Training staff members before patient management is essential for staff and patient safety. We should be aware that asymptomatic SARS-CoV-2 infected patients can also transmit this infection [91]. The median incubation time between infection and first symptoms of disease is 7 days (range between 2-14) [92].

General recommendation / preventive measures for CRS patients

The COVID-19 pandemic necessitates considerable restrictions in social life, especially to protect particularly vulnerable patient groups and to maintain a functioning health system.

Viral airway infections like COVID-19 are most frequently transmitted by direct contact with coughed or sneezed droplets from an infected individual. Hand-to-hand contact, inhaling particles from the air from an infected person or touching an infected surface are less common mechanisms of transmission. General recommendations for patients include washing hands with soap and water, avoiding people with flu-like symptoms, therapeutic adherence to control upper airway disease and asthma. CRS patients (as all other patients) with suspected or confirmed diagnosis of COVID-19 that seek medical advice should wear a face mask and be examined in a private room with the door closed, ideally in an isolation room equipped with technical measures to protect against airborne infectious agents [93].

The transmission of SARS-CoV-2 takes place primarily through droplet spread. The amount of viral particles is higher in the nose of infected patients compared to the throat [94]. Hence, ENTs and especially rhinologists are potentially exposed to a high reservoir of viral load since they are dealing with pathology in the upper respiratory tract [95]. Therefore, if an airway-involving procedure in a SARS-CoV-2-positive patient cannot be avoided, it is of utmost importance to supply healthcare staff with the necessary PPE to avoid viral transmission.

In accordance with the European Centre for Disease Prevention and Control (ECDC) and WHO, we recommend preventive measures in the current pandemic situation, such as:

The recommended preventive measures during the COVID-19 pandemic are summarized in Table 2.

Recommended preventive measures during the COVID-19 pandemic in accordance with the European Centre for Disease Prevention and Control (ECDC) and WHO
Maintain a distance of 1.5 – 2 m between people
Promote compliance with general hygiene measures, such as regular hand disinfection/hand washing for at least 30 s and avoid touching mucous membranes with your hands
Minimize social contacts
Limit personal patient contacts to what is absolutely necessary
Wear personal protective clothing
Encourage regular surface disinfection, especially door handles, etc.

Table 2: Recommended preventive measures during the COVID-19 pandemic

Discussion

In view of the ongoing and emerging COVID-19 pandemic, the safety and well-being of our patients, personnel, and colleagues globally are of primary importance. EAACI and ARIA are closely monitoring the situation and recommend aligning any diagnostic and treatment operations with guidance from the World Health Organization (WHO) and Centers for Disease Control (CDC). These should be conducted in accordance with all applicable national, regional and local government and public health authority requirements.

Even if firm data are currently lacking, patients with CRS suffering from a chronic airway inflammation can be regarded as having a higher risk for contracting a SARS-CoV-2 infection or having a more severe disease course. Therefore, it is recommended that CRS patients with or without polyps and/or concomitant asthma continue their baseline therapy. This will most likely maintain disease control and the consequent reduction of sneezing may even reduce eventual spreading of SARS-Cov-2. Systemic GCS should however be avoided in CRS patients. For those with concomitant asthma, interruption/diminution should be considered after reassessment of the risk/benefit ratio.

Treatment with biologics should be continued in patients non-infected with SARS-CoV-2, with careful (tele)monitoring, unless there are arguments against this treatment. Safety and efficacy of the mentioned biologics in COVID-19 patients, have so far only been presented in case reports [96-98]. Here only mild cases were observed without any negative influence of the biologics to COVID-19 severity. The EAACI-ARIA expert panel recommends a temporary discontinuation of the treatment with biologics in COVID-19 patients until viral clearance.

To be noted that CRS patients - and especially those with comorbid asthma - may confound symptoms (cough, shortness of breath, nasal and pharyngeal symptoms) with those of COVID-19, especially in the early stages. Reduction of doctor and hospital visits is imperative and may be

achieved by adequate treatment of chronic airway problems. Main priority should be given to ensure safety and ongoing access to medical care, which means compliance with the implemented local public health rules and COVID-19 guidelines. Patients with a suspected or definite SARS-CoV-2 infection should follow the local treatment and quarantine guidance. Patients should be informed about possible interactions between medical therapy and COVID-19 disease. Patients may be unable to attend clinic visits, have examinations and/or receive prescriptions. Clinic staff should keep in contact with the patient, preferably through telephone calls or video/skype conferences, to maintain awareness of their status in the case of symptom exacerbations. Dispensing of medication and especially INCS for the entire foreseen period is a way of enabling patient self-treatment.

Physicians dealing with CRS patients need to take special care of PPE when examining and treating them due to the increased viral transmission risk upon exposure to the upper airway. Nasal endoscopy in any SARS-CoV-2-positive or suspected case should be postponed until a negative test result is achieved or until recovery. Elective sinus surgery as well as other invasive procedures for any patient should only be carried out after negative SARS-CoV-2 testing.

EAACI has a prevailing requirement to protect the safety and welfare of our patients, doctors and staff and is working diligently to ensure that we respond to new recommendations as quickly as possible. The EAACI statements on the treatment of CRS during the COVID-19 pandemic are summarized in Table 3.

Conclusion

Following the WHO recommendations, we conclude that CRS patients with suspected or diagnosed SARS-CoV-2 infection should continue to be treated according to current guidelines, with the exception of biologics which should be temporarily interrupted until viral clearance. Currently, adequate anti-inflammatory control of the upper and lower respiratory tract using topical steroids in patients with chronic airway diseases is, according to the current state of medical knowledge, a protection against exacerbations caused by viruses. Patients who interrupt their therapy regimen, and thus experience poorer disease control, are presumably more

susceptible to severe courses of viral infections. Non-infected CRS patients should continue their background treatment, including biologics, under careful monitoring, to maintain disease control.

It should be pointed out that currently there are no reliable data on the course of COVID-19 in patients with CRS in general and especially with CRSwNP and comorbid asthma. Therefore, as healthcare professionals, scientists and Academia, we are required to observe our patients, to provide optimal advice and treatment based on the current state of medical knowledge, to inform them accordingly when new knowledge is available and to adapt the therapies.

EAACI statements on the treatment of CRS during the COVID-19 pandemic
INCS are the therapeutic standard for CRS. Modern INCS are effective in treating symptoms and inflammatory changes, thus avoiding mucosal damage.
There is no evidence that the use of INCS in the approved doses and indications (see product information and/or package leaflet) leads to an increased risk of SARS-CoV-2 infection or induces a more severe course of COVID-19 disease.
Adults and children with CRS should consistently and regularly take their INCS at the individually prescribed dose and should not modify or stop the treatment without consulting their physician.
There is a risk of CRS deterioration due to discontinuation of INCS, which can trigger a droplet infection in other people resulting from increased secretion and sneezing. In addition, worsening of CRS might require systemic GCS which comprise immune defence. Worsening of CRS can trigger exacerbation of asthma, which is regarded by WHO as a risk factor for severe COVID-19 disease.
Systemic GCS should be used with caution in CRS in the current COVID-19 pandemic and only in patients with severe symptoms and absence of a therapeutic alternative. This should be reserved for severe CRSwNP patients if surgery is not possible during the current pandemic. These patients should keep quarantine during the course of sGCS and 1 additional week afterwards to minimize the risk of infection.

Table 3: EAACI statements on the treatment of CRS during the COVID-19 pandemic

Figure legend

Figure 1. Immunopathology of chronic rhinosinusitis with the overview of biologics and their targets.

Several factors, including allergens, bacteria and viruses, can stimulate nasal epithelial cells to induce the production of epithelial-derived cytokines such as TSLP, IL-33 and IL-25, which activate group 2 innate lymphoid cells (ILC2s). TSLP stimulates dendritic cells (DCs) to induce the

differentiation of naïve T cells to T helper (Th)2 cells, which, together with ILC2s, orchestrate inflammation through the production of type 2 cytokines: IL-4 induces IgE production, IL-5 promotes eosinophil recruitment and survival, and IL-13 initiates and amplifies inflammation.

Several biologics that target specifically relevant cytokines or effector cells have demonstrated therapeutic potential for the treatment of chronic rhinosinusitis. Dupilumab (anti-IL-4R α , covering both IL-4 and IL-13 pathways) decreases IgE production, Th2 differentiation and eosinophil recruitment and cause a class-switch in the B-cells to produce IgE. Mepolizumab and reslizumab (anti-IL-5) induce apoptosis and decrease the recruitment of eosinophils. Benralizumab (anti-IL-5R α) depletes tissue eosinophils by enhanced antibody-dependent cell-mediated cytotoxicity. Omalizumab (anti-IgE) captures circulating IgE, reduces expression of high-affinity IgE receptors and decreases mast cell mediator release.

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Table 1

Recommendations for the use of biologics in CRSwNP during the COVID-19 pandemic
Patients on biologic therapy not tested positive nor exhibited signs/symptoms of COVID-19: There is insufficient evidence to recommend discontinuation of biologics. Physicians should consider the risk vs. benefits on a case-by-case basis.
Patients on biologic therapy tested positive for COVID-19: Physicians are recommended to discontinue or postpone the biologic therapy until the patient recovers from COVID-19.
Patients being considered for biologic therapy initiation: Physicians should assess the risk vs. benefits in low-risk patients on a case-by-case basis. In a high-risk population, the physicians should consider deferring initiation of biologic therapy if the risk/benefit assessment is not favouring biological treatment.

Table 2

Recommended preventive measures during the COVID-19 pandemic in accordance with the European Centre for Disease Prevention and Control (ECDC) and WHO
Maintain a distance of 1.5 – 2 m between people
Promote compliance with general hygiene measures, such as regular hand disinfection/hand washing for at least 30 s and avoid touching mucous membranes with your hands
Minimize social contacts
Limit personal patient contacts to what is absolutely necessary
Wear personal protective clothing
Encourage regular surface disinfection, especially door handles, etc.

Table 3

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INCS are the therapeutic standard for CRS. Modern INCS are effective in treating symptoms and inflammatory changes, thus avoiding mucosal damage.
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Systemic GCS should be used with caution in CRS in the current COVID-19 pandemic and only in patients with severe symptoms and absence of a therapeutic alternative. This should be reserved for severe CRSwNP patients if surgery is not possible during the current pandemic. These patients should keep quarantine during the course of sGCS and 1 additional week afterwards to minimize the risk of infection.

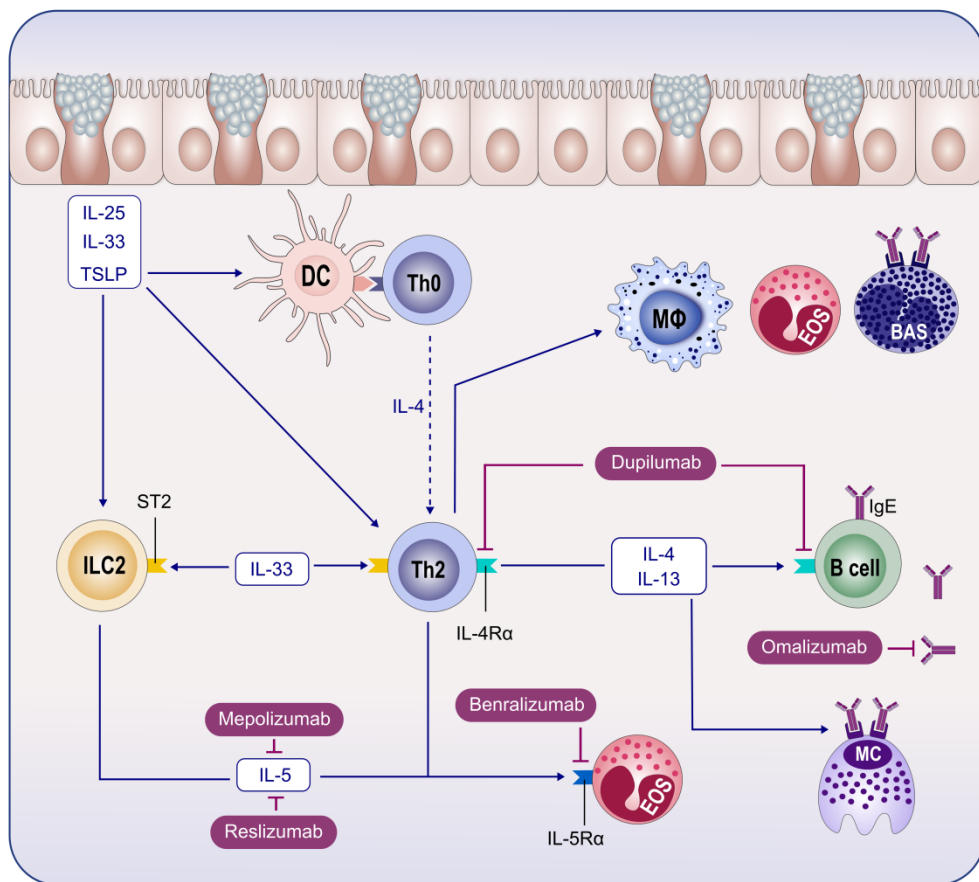


Figure 1_Klimek et al.

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