REVIEW

Sinonasal pathophysiology of SARS-CoV-2 and COVID-19: A systematic review of the current evidence

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Abstract

Objective: The ongoing pandemic of coronavirus disease (2019 coronavirus disease [COVID-19]), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, is highly contagious with high morbidity and mortality. The role of the nasal and paranasal sinus cavities is increasingly recognized for COVID-19 symptomatology and transmission. We therefore conducted a systematic review, synthesizing existing scientific evidence about sinonasal pathophysiology in COVID-19.

Study Design: Systematic review.

Methods: Systematic searches were performed of all indexed studies in PubMed/Medline and Cochrane databases through 28 March 2020 and studies searchable on preprints.com (including ArXiv and Scilit repositories) through 30 March 2020. Data extraction focused on sinonasal pathophysiology in COVID-19.

Results: A total of 19 studies were identified. The sinonasal cavity may be a major site of infection by SARS-CoV-2, where susceptibility genes required for infection are expressed at high levels and may be modulated by environmental and host factors. Viral shedding appears to be highest from the nose, therefore reflecting a major source for transmission. This has been highlighted by multiple reports of health care-associated infection (HAI) during rhinologic procedures, which are now consequently considered to be high risk for SARS-CoV-2 transmission to health care workers. While sinonasal symptomatology, such as rhinorrhea or congestion, appears to be a rarer symptom of COVID-19, anosmia without nasal obstruction is reported as highly specific predictor of COVID-19+ patients.

Conclusion: Sinonasal pathophysiology is increasingly important in our understanding of COVID-19. The sinonasal tract may be an important site of infection while sinonasal viral shedding may be an important transmission mechanism—including HAI. Anosmia without nasal obstruction may be a highly specific indicator of COVID-19.

Level of Evidence: 2a.

1 | INTRODUCTION

The 2019 coronavirus disease (COVID-19) was first identified in December 2019 in Wuhan, China and subsequently found to be caused by a novel coronavirus, now referred to as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1,2] SARS-CoV-2 is highly infectious, with an estimated basic reproduction number in the range of 2 to 3—indicating that on average one infected person will infect 2 to 3 others.[3] To date, SARS-CoV-2 is confirmed to have infected over 1 million individuals worldwide and killed over 50 000. COVID-19 consists of upper and lower respiratory tract components of the SARS-CoV-2 infection.[1,4] Mortality associated with SARS-CoV-2 is due to lower respiratory tract manifestations of the disease, such as severe acute respiratory distress syndrome. This is similar to outbreaks of other coronaviruses including SARS-CoV-1 in 2003 and the middle east respiratory syndrome coronavirus (MERS-CoV) in 2012.[5] However, as the COVID-19 pandemic has spread and our knowledge about it grown, sinonasal pathophysiology has been uniquely brought to the forefront with important roles in infection, transmission, and pathognomonic symptomatology that may identify infected individuals. Given the extreme morbidity that is associated with COVID-19 and the fact that the world's attention is entrained on this disease, many anecdotal reports are disseminated through conventional or social media without the provision of detailed scientific methodology or the performance of a scientific review. Although our understanding of COVID-19 continues to rapidly evolve, there are already clinically informative insights with respect to sinonasal pathophysiology that have been uncovered in the scientific literature. The objective of this systematic review was to synthesize existing scientific evidence on the role of sinonasal pathophysiology in COVID-19.

2 | METHODS

2.1 | Literature search

A computerized search of the PubMed/Medline and Cochrane databases was performed of all indexed studies in those databases up to 28 March 2020 in order to identify all relevant manuscripts. Similarly, given that the majority of knowledge about COVID-19 is still emerging, we also performed a computerized search of scientific manuscript preprints up to 30 March 2020 using the search tool on preprints.com, which queries preprints of scientific manuscripts in not only the preprints.com repository but also the MDPI, ArXiv, and Scilit repositories. The preprints.com search tool therefore allows a broad search of preprints across many repositories.

We included only articles that were in English or Chinese. Combined search terms included: "COVID-19, SARS-CoV-2, coronavirus, nose, nasal mucosa, nasal cavity, respiratory epithelium, sinonasal pathophysiology, sinonasal disease, chronic rhinosinusitis, upper respiratory tract, endoscopic sinus surgery, anosmia, hyposmia, olfactory epithelium, olfactory bulb, otolaryngology." Articles mapping to the exploded medical subject heading "sinonasal pathophysiology and SARS-CoV-2" were combined into one group. Medical subject headings "COVID-19 and otolaryngology" were exploded and the manuscripts were collected into a second group. Medical subject headings "olfaction and coronavirus" were combined into a third group. Medical subject headings "respiratory epithelium and coronavirus" were combined into a fourth group. The four groups were then cross-referenced. Studies were excluded if they did not have full texts or could not be obtained. Adjunctive searches were performed based on the studies that were identified (and their references). Titles and abstracts were then evaluated according to the inclusion/exclusion criteria described hereafter. Two individual reviewers (I. G. and J. C. W.) performed searches independently, blinded to each other's results, with the search results additionally reviewed by the senior author (A. R. S.). Titles and abstracts for all identified studies were reviewed.

2.2 | Inclusion and exclusion criteria

Articles identified by the above search strategy were evaluated to meet these inclusion criteria: (a) studies that included COVID-19 and (b) evaluation of nasal, sinonasal pathophysiology. In the context of the urgency of the pandemic and the rapid accumulation of new information, we also included two studies, one in review and one in press whose data were obtained via professional otolaryngology society communication and/or direct communication.

Articles were excluded if there was no discussion of the upper respiratory tract, and they were only abstracts indexed in a searched database without an associated and accessible full manuscript.

2.3 | Data extraction

Extracted data included study design; epidemiology and population description, including Country in which study/observations were reported; mechanisms of infection in the sinonasal cavity, type of COVID-19 test conducted if applicable; signs and symptoms of COVID-19; COVID-19 risks, and sinonasal anatomy.
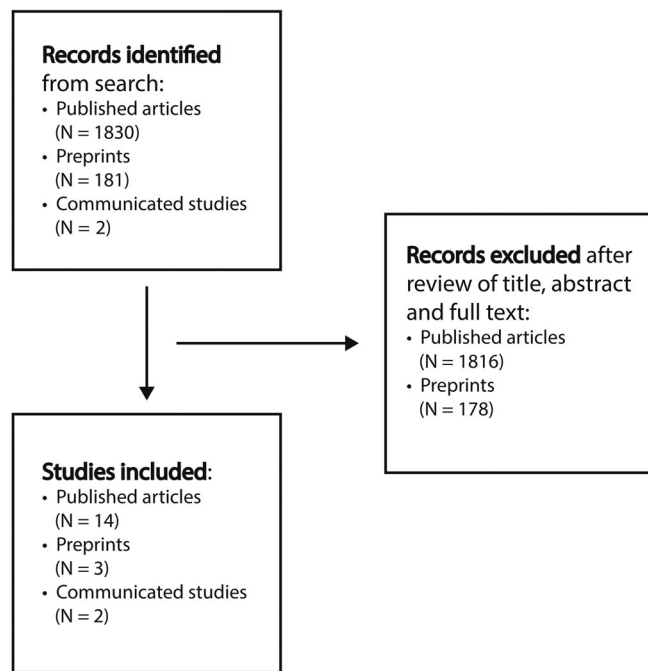
FIGURE 1 Flow diagram for identifying references

3 | RESULTS

Our search identified a total of 2013 studies (1830 published articles, 181 prints, and 2 communicated studies). A total of 1988 studies (1816 published studies, 178 preprints) were excluded as off scope or having unobtainable full text (Figure 1). A total of 19 studies were included (14 published studies,[4,6-18] 3 preprints,[19-21] and 2 communicated studies[22,23]), which described the sinonasal pathophysiology—as it related to infection by SARS-CoV-2, transmission of SARS-CoV-2, and symptoms of COVID-19. Primary literature was sourced and integrated with other available and supporting literature in this review.

4 | DISCUSSION

4.1 | Infection by SARS-CoV-2

Infection by SARS-CoV-2 may occur via inhaled particles as small as aerosol (less than 5 μm in size; capable of staying suspended in the air for long periods of time and easily inhaled into the lungs and distal alveoli) up to droplets (measuring greater than 20 μm in size; quickly pulled to the ground by gravity or, when inhaled, mostly deposited in the nasal cavity),[24] or by direct inoculation of the respiratory epithelium (ie, touching a surface with live virus and then touching one's face). As up to 90% (or more) of inspiration is through the nose,[25] it is reasonable that the sinonasal cavities may be important sites for initial infection by SARS-CoV-2. In fact, SARS-CoV-2 infection via the ocular route is hypothesized to occur via drainage of virus-laden tears into the nasal cavity through the nasolacrimal duct.[19]

Recent work has shown that SARS-CoV-2 utilizes its S1 spike glycoprotein, which resides in the virus' envelope, for attachment to—and infection of—host target cells.[26] Infection by SARS-CoV-2 is likewise dependent on two host proteins for cellular entry and infection.[27] Angiotensin-converting enzyme 2 (ACE2) serves as the cell surface receptor for SAR-CoV-2, which binds to the S1 spike glycoprotein and is required for cellular entry of the virus through endocytosis. A second protein, known as transmembrane protease serine 2 (TMPRSS2), is a protease that resides in the endosomal compartment and is required for priming/cleavage of the S1 spike glycoprotein, which then allows fusion of the viral envelope with the endosomal compartment (with introduction of the viral contents, including genetic material, into the cytoplasm of the host target cell).

ACE2, the host cell surface receptor for SARS-CoV-2, has been shown to be expressed throughout the aerodigestive tract, including the mucosa of the nasal cavity (as well as the mucosa of the oral cavity, and in the epithelium of the lungs and enterocytes of the gastrointestinal tract).[7,28] Recent single-cell RNA sequencing of cells in the aerodigestive tract shows that expression of ACE2 in the nasal cavity is as high as it is in any other site within the aerodigestive tract.[21] Analysis of gene expression data from the Human Cell Atlas Project has further shown that ACE2 is most highly expressed within the ciliated epithelium and goblet cells in the nose.[20] Moreover, single-cell RNA sequencing has shown that ACE2 may be expressed in tissues throughout the body (such as in the heart and kidneys), suggesting direct viral pathogenesis as a potential mechanism for extra-aerodigestive symptoms of COVID-19.[29]

TMPRSS2, which is also required for SARS-CoV-2 infection of host target cells, has also been shown to be expressed in nasal epithelial cells[30] and the upper airway.[7] Expression level of TMPRSS2 in the respiratory epithelium—including the nasal mucosa—may be modulated by external factors such as air pollution or inflammatory airway conditions such as atopy or asthma.[30,31] Such modulation of expression in susceptibility genes for SARS-CoV-2 may, in part, explain geographic and individual-level variation in SARS-CoV-2 infection rates. Although not directly studied with respect to SARS-CoV-2, the inflammatory milieu of the sinonasal mucosa has previously been shown to be associated with higher rates of respiratory virus isolation from the sinonasal cavity,[8] which further suggests that modulation of host susceptibility gene expression in the nasal mucosa could potentially impact SARS-CoV-2 infection rates. However, whether the modulation of SARS-CoV-2 susceptibility gene expression by environmental or host factors translates to a clinically significant impact on susceptibility to SARS-CoV-2 infection is yet unknown and represents an area of future research.

4.2 | Transmission of COVID-19

Different modes of transmission for COVID-19 have been described, and all contribute to the exponential spread of the virus[32] over 196 countries. The major mode of transmission is through the upper respiratory tract,[13] similar to what was observed during the SARS-CoV-1 epidemic.[14] Nasal shedding of live virus is usually quite high

early in the course of COVID-19, precedes lower respiratory tract viral shedding and may even continue after the virus is no longer detected from the lower respiratory tract.[10,18] Zou et al showed higher viral load in nasal swabs when compared to throat swabs obtained from 17 symptomatic patients.[18] They concluded that the viral shedding pattern in patients with SARS-CoV-2 is similar to influenza, and is similar between symptomatic and asymptomatic patients,[18] with suspected prolonged shedding of COVID-19 after recovery.

The important role for transmission of COVID-19 due to sinonasal pathophysiology—and the infectiousness of nasal secretions—is further highlighted by a recent report by Patel et al,[22] who shared the experiences of rhinology colleagues from COVID-19 hot spots around the world, including China, Iran, and Italy. In this report, the risk of health care-associated infection (HAI) posed to health care workers by nasal transmission of SARS-CoV-2 was described during rhinology procedures. One illustrative case described HAI of up to 14 health care workers during a single endoscopic pituitary case procedure in Wuhan, China. The working hypothesis regarding the mechanisms for enhanced HAI during rhinology procedures includes both the higher viral loads in nasal secretions[18] as well as the generation of aerosols by powered rhinologic instrumentation such as the microdebrider or drill.[33] This possibility is also consistent with evidence in the dental literature reporting the generation of 5 μm droplet nuclei, capable of getting through a surgical mask using motorized instrumentation on the oral mucosa.[12,34] At present, rhinology and otolaryngology societies from around the world are recommending that endonasal surgeries be approached as high-risk procedures.[35,36]

4.3 | Sinonasal symptomatology of COVID-19

Cases series of patients with COVID-19 from both China[16,37,38] and Europe[39] have reported a paucity of sinonasal symptomatology. Rhinorrhea has been described as individual cases, for example, being experienced by one child in a cohort of nine children with COVID-19,[17] one adult in a cohort of eleven,[9] or one adult in another cohort of 18 with COVID-19.[4] By contrast, lower respiratory tract and constitutional symptoms, such as fever, cough, fatigue, shortness of breath, and myalgias, are much more commonly reported. However, olfactory dysfunction (hyposmia or anosmia) has recently gained attention as an important symptom in COVID-19.

4.4 | Olfactory dysfunction in COVID-19

The olfactory epithelium resides at the superior aspect of the nasal cavities where olfactory sensory neurons are in direct contact with the environment. The olfactory epithelium comprises approximately 9 cm^2 of the total 150 cm^2 mucosal surface area of the nasal cavities.[40] As the adjacent respiratory epithelium is the primary site of SARS-CoV-2 attachment and infection, it may not be surprising for COVID-19 to impact olfactory function. This is especially true as other coronaviruses, such as the related SARS-CoV-1, have previously been shown to have neurotropic properties with respect to olfactory neurons.[6,11,15]

ACE2, the necessary cell surface host receptor for SARS-CoV-2, has been previously shown to be expressed on neurons and found to play a role in neurodegeneration.[41] The TMPRSS2 gene, also required for SARS-CoV-2 infection, has not been well studied in the nervous system although one study in a rat model has described expression of TMPRSS2 in neurons of the central nervous system.[42] Previous studies in mice have shown that after intranasal inoculation, the SARS-CoV-1 virus is neuroinvasive with infection directly transmitted through olfactory neurons into the central nervous system.[43-45]

Olfactory dysfunction presenting as hyposmia or anosmia is not uncommon as a symptom of active viral upper respiratory tract infections, with up to 30% experiencing some kind of olfactory dysfunction.[40] Described as beginning suddenly in the context of a "common cold," postviral olfactory dysfunction is characteristically described as occurring in a setting with other sinonasal symptoms.[46] In the long term, however, postviral olfactory dysfunction may persist in some as a lasting sequela without other sinonasal symptomatology.[47]

Representing the first systematically collected data on olfactory dysfunction in COVID-19 released for public knowledge, a recent study lead by Pr Dominique Salmon, MD, PhD (Hôtel Dieu, Paris), and Dr Alain Corré, MD (Hôpital Fondation Adolph de Rothschild, Paris) of Parisian COVID-19 patients has revealed several novel insights into the olfactory dysfunction as a symptom of COVID-19 (personal communication shared with permission from Dr Alain Corré; manuscript in review). In a cohort of 55 patients presenting to them with the symptom of anosmia without nasal obstruction within 7 days of the occurrence of this symptom, 94% were found to be COVID-19+ by nasopharyngeal swabbing and reverse transcription polymerase chain reaction (RT-PCR) testing. In a press release given to us dated 28 March 2020,[23] their group writes: "Patients with allergic rhinitis seem more affected. It occurs suddenly 2 to 3 days after the beginning of usually rather mild symptoms related to COVID 19 disease such as headaches, low-grade fever, and diarrhea. In most cases, the signs of cold (such as cough, fever) are absent or have disappeared. The sense of smell usually starts recovering after a few days (5-10 days) and this recovery seems already complete in some patients around day 10 to 15 but unfortunately this trouble of smell persists longer in others." Thus, decreased sense of smell in the absence of nasal obstruction may be a highly predictive marker for COVID-19, which may be particularly helpful in identifying asymptomatic carriers or those with mild symptoms who otherwise would not think that they have the infection. However, it should be noted that while the presence of anosmia without nasal obstruction may be a uniquely described viral phenomenon in COVID-19, it is unknown how many cases of idiopathic anosmia may have occurred in the setting of a viral upper respiratory tract infection that went unnoticed by the affected patient.[46]

5 | CONCLUSION

In COVID-19, there is increasing evidence for the importance of sinonasal pathophysiology. The sinonasal cavity may be an important route for infection and virus shed from the sinonasal cavity may be an important source of transmission. The high viral load in sinonasal

secretions may also reflect an especially high risk for HAI from rhinologic procedures. Although sinonasal symptoms do not appear to be a major component of the clinical presentation of COVID-19, decreased sense of smell may be an underappreciated symptom of COVID-19. Anosmia without nasal obstruction, in particular, appears to be a highly specific indicator of COVID-19.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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