

COVID 19 and Oral Manifestation: Current State and Perspective

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ABSTRACT

Background: The clinical manifestations produced by SARS-CoV-2 are well described in the literature. However, information about oral manifestations is limited. The oral cavity is a perfect habitat for SARS-CoV-2 invasion due to the special affinity that the virus has for cells with the receptors for the converted angiotensin enzyme (ACE2), present in the respiratory tract, oral mucosal, tongue and salivary glands, thus being able to affect the functioning of the salivary glands, sensations of taste, smell and integrity of the oral mucosa. The novel coronavirus has the ability to alter the balance of the oral microbiota, which added to a depressed immune system would allow opportunistic infection colonization. The objective of this article is to review and analyse the available evidence in relation to oral manifestations at the mucosa, salivary glands, and olfactory and gustatory alterations in the context of SARS-CoV-2 infection.

Keywords: COVID 19, Oral cavity, Saliva, salivary gland, Ulcers, Mucosal Lesions, Periodontitis, Mouthwash.

INTRODUCTION

COVID-19 is a disease caused by a novel coronavirus named SARS CoV-2 that causes damage to the lungs and other vital organs. Most COVID-19 patients present mild symptoms; however, a few could develop severe illness having pulmonary pneumonia and edema, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndromes, or even die. Of all infected, only a small percentage reach into critical illness state, considering the presence of any comorbidity or condition, which can be diabetes, hypertension, obesity, asthma, pregnancy, lung diseases, liver diseases, oral dysbiosis, aging, and gender.

After the first reports of COVID-19 cases in Wuhan (China) it became evident that due to the high contagiousity of COVID-19 transmitted by virus-laden droplets and/or even airborne viral particles in aerosols, dentists and head and neck health care providers have one of the highest risks of SARS-CoV-2 exposure, infection and dissemination. In

order to eliminate superspreading events originating from SARS-CoV-2 positive healthcare personnel, the World Health Organization has recommended to limit medical treatment involving the throat and oral cavity to medical emergencies. The outbreak of novel communicable diseases urges epidemiologic and clinical researchers to establish highly sensitive case definitions to track all true-positive cases; therefore, there is emerging evidence on the oral lesions that may be indicative of the coronavirus disease (COVID-19).

COVID 19 AND ORAL CAVITY

Early COVID-19 research has identified the upper respiratory tract (nose, naso and oropharynx) as the primary site of SARS-CoV-2 entry and replication. Nasal and olfactory epithelial cells seem to be of crucial importance for SARS-CoV-2 invasion and dissemination³.

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When compared with other oral tissues, cells of the salivary glands, tongue and tonsils carry the most RNA linked to proteins that the coronavirus needs to infect cells. Namely, these include the ACE2 receptor, which the virus plugs into, and an enzyme called TMPRSS, which allows the virus to fuse its membrane with that of the host cell and slip inside^{2,3}. Furthermore, periodontal pockets and crevices as well as the gingival sulcus are suspected to provide favourable conditions for virus replication and maintenance.

There are theories that synergistic effects of high expression of virus receptors and the lytic activity of periodontal bacteria might promote early and prolonged SARS-CoV-2 colonization of the oral cavity. These ideas might be corroborated by literature stating that saliva samples have been tested positive for SARS-CoV-2 RNA before clinical symptoms appear and remain highly positive for an extended period of time even after symptom relief. These findings could imply that the oral cavity is the key area for SARS-CoV-2 transmission⁹. There is evidence that the virus accumulates at the oral mucosae in the first 10 days of infection and at a subsequent time it will accumulate in the lungs.

In some cases, oral sulcular epithelial cells and their underlying connective tissue were free of detectable SARS-CoV-2 RNA despite a positive throat swab in a clinically symptom-free COVID-19 patient. This also proves that the transmission of various viruses, can be inhibited by antiviral agents secreted into or produced within the oral cavity¹².

The true shedding duration of potentially infectious SARS-CoV-2 particles from the upper respiratory tract and the oral cavity by acutely or formerly infected patients remains unknown and seems to be variable¹³.

Many reports of concomitant oral mucosal lesions during active COVID-19 infection have created alertness about the tentative increased susceptibility of oral tissue cells to SARS-CoV-2. These findings have sparked the discussion whether medical procedures involving the oral cavity can be resumed safely at all during the pandemic period.

SALIVARY GLANDS AND SALIVA

Dry mouth was shown to be manifested in a relatively high proportion of COVID-19 patients. A

recent communication has drawn attention to hyposalivation as responsible for exposing patients to a higher risk of getting coronavirus disease.

"If the saliva production is somehow compromised, one could speculate that one could develop taste changes or loss of taste," because saliva carries molecules to taste receptors on the tongue,

Another study drives home one important point: Asymptomatic people can carry plenty of viral particles in their saliva. In two asymptomatic people included in the study, the virus was found in their saliva 14 days after their first positive test, even though they had already tested negative for the virus in their nose and throat at that point^{14,15}. The expression of SARS-CoV-2 has been detected in the oral epithelium and in cough out and swabs of human saliva. These studies point to the importance of saliva for diagnostic strategies.

PERIODONTITIS AND CLINICAL EVOLUTION OF COVID-19

Periodontitis is considered a chronic multifactorial inflammatory disease due to presence of dental plaque. This condition causes periodontal pathogens and their products, including inflammatory mediators such as IL-6, could enter the bloodstream, and chronic periodontitis has been found to be a risk factor for diabetes mellitus, and still being studied for cardiovascular disease, respiratory disease, rheumatoid arthritis and others. The systemic inflammatory burden of periodontitis is well-documented also thanks to the evidence of high sensitivity C-reactive protein¹⁰.

The association of Periodontal Disease with smoking and COPD could be helpful to identify risk groups to develop severe COVID-19, since COPD increased importantly the risk of this affection¹⁰.

Patients with severe COVID-19 illness has reported the emergence of genera *Prevotella*, *Fusobacterium*, *Veillonella*, which are associated with periodontal disease. Alterations in oral microbial communities can affect the microenvironment with increases in pathogens and over-stimulation of the immune system¹¹.

Future studies on the periodontal status of patients with COVID-19, including from mild to severe forms, could allow the opportune identification of

people in risk of severe illness, and generation of relevant recommendations.

COVID 19 AND MOUTH RINSES

The use of preprocedural mouthrinses has been proposed to reduce the viral load in saliva and oropharyngeal tissues, thus decreasing viral load in dental aerosol. Although some mouthrinses demonstrates an antiviral effect, there is limited evidence about the clinical efficacy of any mouthrinse in the reduction of SARS-CoV-2 in the dental aerosol.

A recent meta-analysis showed that mouthrinses with essential oils, chlorhexidine (CHX) and cetylpyridinium chloride significantly reduced the number of bacteria on the dental aerosol by 64.8%¹³. The clinical study that analyzed effects of CHX mouthwash on SARS-CoV-2 viral load showed that the viral load in saliva decreased transiently for 2 hours after using 15 mL of 0.12% CHX mouthrinse⁸.

A recent randomized controlled trial has evaluated the efficacy of PVP-I, CHX, CPC and water mouthrinses in reducing salivary SARS-CoV-2 viral load in 16 COVID-19 positive patients. Saliva samples were collected from all patients at baseline and 5 min, 3 hours and 6 hours after mouthrinse and subjected to RT-PCR analysis¹³. CPC and PVP-I formulated commercial mouthrinses reduced SARS-CoV-2 viral load. The effect was sustained after 6 hours of follow-up. A highly varied efficacy of CHX mouthwash on SARS-CoV-2 in saliva was observed⁸.

Table 1: Oral manifestations in COVID 19 cases – Reported until now.

Oral manifestations in COVID 19 cases – Reported until now
• Aphthous-like + necrosis • Haemorrhagic ulcerations with necrotic area • Herpetic infection • Erythema multiforme • Desquamative gingivitis • Oral candidiasis • Vascular disorder • Angina bullosa hemorrhagica-like lesion • Nonspecific mucositis

ORAL LESIONS

Given a small number of reported studies, taste alterations are the most prevalent reported oral manifestation. The global prevalence of taste disorders in patients with COVID-19 is 45%.

After infection of the oral keratinocytes/glandular tissues, there is an increase in the permeability of the cell walls to foreign pathogens and viral replication in the cells lining the oral mucosa, leading to ulcers and necrosis.

Oral lesions and skin rashes are an "important" manifestation of COVID-19, according to evidence published in the *British Journal of Dermatology*. A study conducted in Spain of 666 COVID-19 patients with mild to moderate pneumonia being treated during the pandemic's peak in Madrid found that 26 per cent had some form of oral manifestation¹⁸.

Skin problems on the hands and feet were particularly common (40 per cent), as well as findings inside the mouth (26 per cent). The most common issue found in the mouth was transient lingual papillitis, also known as lie bumps, characterised by the appearance of small red or white bumps on the tongue¹⁸. The oral mucosae lesions were referred to as viral enanthemas⁶.

Chaux-Bodard et al and Martín Carreras-Presas et al reported ulcerative and vesiculobullous lesions in the oral cavity in patients confirmed and suspicious of new coronavirus disease³.

Chaux-Bodard et al described the first oral association with COVID-19. The reported oral ulcer was preceded by macular erythema and pain (probably associated with vasculitis) in an adult female patient, who also developed a skin lesion³.

Martín Carreras-Presas et al reported different types of oral mucosal lesion (ulcer, vesicle, bulla, and desquamative gingivitis) that would be clinically similar as in other viral mucocutaneous infections, including herpes simplex, herpes zoster, or immunologic disorders⁴. The oral lesions were self-limiting and the resolution was seen between 3 and 10 days after examination with symptomatic treatment.

Related to the pathogenesis of oral manifestations of COVID-19, there have been some theories of

vascular and thrombotic effect in the oral mucosa, and these mechanisms are based on histological examination of vascular ectasia and perivascular lymphocytic infiltrate with eosinophilia in biopsies of COVID-19 patients, who also have had dermatologic affection.

The high prevalence of COVID-19 associated mucocutaneous manifestations in this study differs from previous ones, possibly because it included manifestations not previously described, particularly lesions inside the mouth.

The oral health of COVID-19 patients can be affected by the infection, there is still doubt whether these manifestations could be a typical pattern resulting from the direct viral infection. Perhaps oral lesions may result from systemic deterioration, considering the possibility of opportunistic infections and also adverse reactions to treatments⁹.

Most COVID-19 acute infection, along with associated therapeutic measures, could potentially contribute to adverse outcomes concerning oral health, likely leading to various opportunistic fungal infections, recurrent oral herpes simplex virus (HSV-1) infection, unspecific oral ulcerations, fixed drug eruptions, dysgeusia, xerostomia linked to decreased salivary flow, ulcerations and gingivitis as a result of the impaired immune system and/or susceptible oral mucosa¹⁶.

The oral mucosal lesions were described in only in a few case reports, presented diverse theories and conclusions on whether this type of condition is directly caused by SARS-CoV-2 or represents secondary manifestations. Nonetheless, the manifestations showed minor clinical symptoms, such as ulcers, blisters, macules, and plaques, varying in quantity, color appearance, and localization¹⁷. A divergent mucosal lesion pattern related to a single virus is uncommon (Galván Casas et al. 2020). Cox et al. (2020), thus accentuating the importance of coinfection investigation in severe respiratory diseases⁹.

The patients presented oral mucosal injury during the hospitalization period, supporting the hypothesis of coinfections, immunity impairment, or adverse reactions from medications to COVID-19 treatment¹.

Thus, the importance of the clinical dental examination of patients with infectious diseases in the ICU should be emphasized. The multiple clinical aspects suggest coinfections, immunity impairment, and adverse reactions rather than a genuine oral mucosa infection primarily caused by SARS-CoV-2.

CONCLUSION

To conclude, dentists may have a life-saving role in intervening with the pandemic severity among children by early detection of the mucosal symptoms. The epidemiologic significance of the oral manifestations remains unclear, thus necessitating larger observational studies to reveal the prevalence and the onset of these symptoms while maintaining the methodological quality by following the guidelines. Awareness of such oral manifestation is important because the lesions may precede the typical respiratory symptoms by several days, and worsening of the oral lesions may precede a more serious clinical scenario.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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