

Oral Manifestations in COVID 19 Patients

—

María Magdalena Patiño Suárez

Alejandro Meza Castillejos

Ángel Gutiérrez Zavala
guzava@hotmail.com

SCHOOL OF DENTAL SCIENCES AND PUBLIC HEALTH.
UNIVERSIDAD DE CIENCIAS Y ARTES DE CHIAPAS. TUXTLA GUTIÉRREZ,
CHIAPAS, MÉXICO



To quote this article:

Patiño Suárez, M. M. ., Meza Castillejos, A. ., & Gutiérrez Zavala, Ángel. (2022). Manifestaciones orales en pacientes con COVID 19. *Espacio I+D, Innovación más Desarrollo*, 11(29). <https://doi.org/10.31644/IMASD.29.2022.a09>

— Abstract—

The 2019-nCoV is officially called SARS-CoV-2. It causes a disease which is called COVID 19. This is considered a pandemic by the World Health Organization (WHO). The infection produces a severe acute respiratory syndrome characterized by fever, respiratory and gastrointestinal symptoms, and systemic manifestations. In this context, clinical manifestations have been reported in patients with positive SARS-CoV-2, which have been improving the knowledge about the characteristics of the clinical picture, however, one of the scarcely documented aspects is the semiology at the level of the oral cavity. New evidence shows the relevance of the oral cavity as a reservoir of the virus, so it plays a fundamental role in the diagnosis, evolution, and epidemiological transmission of COVID 19 infection patterns. This document aims to review and analyze the available evidence about oral manifestations in the context of SARS-CoV-2 infection.

Keywords:

Oral manifestations; COVID 19; SARS-CoV-2 .

The oral cavity is a site of manifestation of different systemic conditions, as it can be considered the gateway to the environment's viruses and bacteria, therefore, it is one of the first interfaces between the outside and the body (Farook, *et al.*, 2020). It has been suggested that the oral cavity is a perfect habitat for invasion by the severe acute respiratory syndrome (SARS-CoV-2) due to the special affinity that the virus has for cells with receptors for the angiotensin-converting enzyme 2 (ACE2), (Xu, *et al.* 2020; Herrera, *et al.* 2020). The organs that are at risk and vulnerable to SARS-CoV-2 by coronavirus 2 infection are the lung, heart, esophagus, kidney, bladder, and ileum, and localized specific cell types, i.e., type II alveolar cells (AT2), stratified epithelial cells, myocardial cells, proximal renal tubule cells, epithelial cells of the ileum and esophagus, bladder urothelial cells, T cells, and epithelial cells of the oral mucosa, gingiva, tongue, salivary glands, and tonsils; these cell types are vulnerable to COVID 19 infection and can become virus host cells and cause an inflammatory response in related organs and tissues, such as the mucosa of the tongue and salivary glands (Wang, *et al.*, 2020; Zou, *et al.*, 2020; Gaitan, *et al.*, 2019).

There are reports of some cases of COVID 19 that report oral manifestations that include acute and chronic sialoadenitis, anosmia, ageusia, non-specific oral ulcerations and/or vesiculobullous in the oral mucosa and the palate, changes in the characteristics of mucous membranes, desquamative gingivitis, changes in the production and quality of saliva, stomatitis, pigmentation, lichenoid reaction, petechiae and co-infections such as candidiasis, among others (Amorim, *et al.*, 2020 and 2021; Cebeci & Çaşkurlu, 2019; Carreras, *et al.*, 2020; Herrera, *et al.*, 2020; Cardoso, *et al.*, 2020). On the other hand, although there are many studies in the literature on clinical signs in patients with positive SARS-CoV-2 (Wu, *et al.*, 2020; Struyf, *et al.*, 2020; Gralinski & Menachery, 2020; Gutiérrez & Zambrano, 2020; Nemeth, *et al.*, 2020), most of them have not verified the oral health status of patients, so the interrelationship of the oral cavity with SARS-CoV-2 is little known. Because this strain of the virus has a wide range of clinical expressions, at the same time, it becomes debatable because it must be established whether oral manifestations are the result of direct viral infection, whether they are the product of the patient's systemic compromise or whether they present as negative reactions or even possible opportunistic infections to the treatments received to treat COVID 19, so the objective of this article is to carry out an updated review of the literature, clinical case reports, and letters to the editor about the oral manifestations in the context of the SARS-CoV-2 infection.

BACKGROUND

Three new coronaviruses have emerged as new human lethal zoonotic pathogens over the past 17 years: the SARS coronavirus (SARS-CoV) that emerged in China between 2002 and 2003, the Middle East respiratory syndrome coronavirus (MERS-CoV) that emerged in Saudi Arabia in 2012, and recently SARS-CoV-2 (Hui, *et al.*, 2020).

In December 2019, Chinese health authorities first reported dozens of pneumonia infections in the city of Wuhan (Hubei province) without a recognized etiology (Zhou, *et al.*, 2020). The first patients reported with pneumonia in Wuhan had a history of visits or association with a local market where wild animals are sold. The causative agent was identified as a novel coronavirus (2019-nCoV) that is believed to have originated in the Huanan sea products market (Wang, *et al.*, 2020). Due to its marked similarity in terms of clinical symptoms and biological nature with the SARS-causing agent, the new coronavirus was named SARS-CoV-2 (Lu, *et al.*, 2020; Chen, *et al.*, 2020).

After rapid virus isolation, phylogenetic analyses showed that SARS-CoV-2 is closely related to two bat-origin SARS coronaviruses, bat-SL-COVZC45 and bat-SL-COVGXC21, but is distant from human SARS-CoV (79% sequence homology) and MERS-CoV (50%), (Mousavizadeh & Ghasemi, 2020). Epidemiological investigations showed that different animals (bats, pangolins, snakes) could have been intermediate hosts that facilitated the spread of SARS-CoV-2 as a human *Betacoronavirus* other than bats to the human population (Abduljalil & Abduljalil, 2020). Currently, there is genetic and experimental evidence that documents a process of natural selection (zoonotic origin) of the outbreak, between wild species and humans. The COVID 19 outbreak originated in bats and was transferred to humans through an intermediate host, the pangolin. A single animal-to-human transmission initiated the COVID 19 outbreak, followed by sustained human-to-human transmission (Chan, *et al.*, 2020). Structural and biochemical studies show that SARS-CoV-2 has been optimally adapted to recognize the human protein ACE2, which functions as a receptor to bind to the membrane of human cells. The virus protein responsible for this binding has been found to have a six amino acid domain, which is responsible for the recognition of ACE (angiotensin-converting enzyme) with high affinity, but this domain has also been found to have high affinity for ACE in ferrets, cats, and other species. These observations are strong evidence that SARS-CoV-2 is not the product of laboratory manipulation, but originates in other species (Andersen, *et al.*, 2020; Torres, 2020).

CLINICAL PRESENTATION

The clinical picture, in patients with COVID 19, can manifest through very different symptoms; from being asymptomatic, or presenting a mild disease, with fever, myalgia or fatigue, dry cough, and, in some cases, difficulty breathing, as the main symptoms (Herrera, *et al.*, 2020); some may experience muscle discomfort and pain, nasal congestion, nasal discharge, sore throat, vomiting, diarrhea, and skin manifestations (Huang, *et al.*, 2020). However, almost 14% have signs and symptoms of severe illness, requiring hospitalization and oxygen support, and 5% need to be admitted to intensive care units. Severe cases generally include impairment of the function of different organs such as acute kidney lesion, cardiac lesion, liver dysfunction, and severe complications such as SARS, sepsis, and septic shock (Herrera, *et al.*, 2020; Wang, *et al.*, 2020; Chan, *et al.*, 2020; Huang, *et al.*, 2020; Wu, *et al.*, 2020; Chen, *et al.*, 2020).

The entire population is susceptible to becoming infected with COVID 19, the most affected population is concentrated in adulthood (average age of the first 41 cases: 49 years CI 95% 41.0 - 58.0) and males (Huang, *et al.*, 2020; Sifuentes & Palacios, 2020). Elders and patients with comorbidities such as diabetes, asthma, hypertension, coronary heart disease, aging, and obesity are at increased risk of developing severe pneumonia and complications associated with COVID 19 (Herrera, *et al.*, 2020; Wu, *et al.*, 2020; Struyf, *et al.*, 2020; Gutierrez & Zambrano, 2020). No evidence of vertical transmission of intrauterine infection has been observed in pregnant women (Sifuentes & Palacios, 2020).

2019-nCoV

Novel coronaviruses appear to emerge periodically in humans, mainly due to the high prevalence and wide distribution of coronaviruses, the great genetic diversity, the frequent recombination of their genomes, and the increase in human-animal interface activities (Zhu, *et al.*, 2019). SARS-CoV-2 is a virus belonging to the kingdom of Riboviria, order Nidovirales, suborder Cornidovirineae, family Coronaviridae, genus Betacoronavirus and to the SARS-related coronavirus species. It is a pleomorphic spherical virus that contains a single-stranded RNA strand that is positively associated with a nucleoprotein protected by a protein matrix capsid; on its surface, it has a spike-shaped glycoprotein that serves as a binding receptor (Gorbalenya, *et al.*, 2020; Villanueva & Escalante, 2020). The viral genome encodes four major structural proteins: spine protein (S or Spike protein), nucleocapsid protein (N), membrane protein (M), and envelope protein (E). The S protein

facilitates entry into the host cell, so it is very important to determine the virulence of SARS-CoV-2 (Gaitan, *et al.*, 2019).

The oral route and inoculation are given by drops of saliva and aerosols produced by an infected patient and the host's inhale. The virus, once located on the stratified squamous epithelium of the tongue and the glandular epithelium, searches for the ACE2 receptors using the spike-shaped surface glycoprotein acting as a key. For the virus to complete entry after the initial process the spike glycoprotein must be activated by a protease called TMPRSS2 (Mousavizadeh & Ghasemi, 2020). Once within the host cell, the genome is transcribed and then translated, replication and transcription are carried out on the cytoplasmic membranes and involve coordinated processes of continuous and discontinuous RNA synthesis, which are mediated by viral replication (Villanueva & Escalante, 2020; Chen, *et al.*, 2020).

Two of the places with the greatest number of ACE2 receptors are the glands and the stratified squamous epithelium of the tongue's mucosa which confers them to be a reservoir of the virus that allows adequate replication and increase of its viral load; therefore, it is potentially infectious in the chewing, swallowing, speaking, breathing, and other functions of the upper airway (Mousavizadeh & Ghasemi, 2020; Villanueva & Escalante, 2020; Chen, *et al.*, 2020).

ORAL MANIFESTATIONS

An online cross-sectional survey included 1480 patients with flu-like symptoms, and in 59 of 102 patients who tested positive for COVID 19, 40 (68%) reported loss of smell, and 42 (71%) reported loss or changes in taste. Unfortunately, no medical and/or oral comorbidities were reported in this study (Yan, *et al.*, 2020). On the other hand, a European multicenter epidemiological study, where the prevalence of olfactory and gustatory dysfunctions was analyzed as clinical presentation in a cohort of 417 laboratory-confirmed cases of COVID 19 with mild to a moderate presentation of the disease, found that 88.8% of the patients had taste disorders. Several patients also presented with various comorbidities, the most common of which included allergic rhinitis, asthma, hypertension, and hypothyroidism, but the percentage of patients with these conditions was low (Lechien, *et al.*, 2020). In a meta-analysis of 9 studies from Europe, North America, China, and the Middle East, the presence of taste dysfunction (n = 1390) was reported in 43.93% (IC_{95%} 20.46% to 68.95%) of COVID 19 patients (Tong, *et al.*, 2020).

In this same context, in a systematic review (Amorim *et al.*, 2021), where 40 studies published in any language (33 cross-sectional and 7 case reports) from 19 countries were included, 10228 patients with COVID 19 were

analyzed. Reverse transcriptase-polymerase chain reaction for viral RNA detection and serological assays for IgG / IgM antibody detection was the most commonly used methods for COVID 19 confirmation in these studies. Taste impairment was found to be the most common oral manifestation, with a prevalence of 45% (CI_{95%}, 34% to 55%). When each disorder was assessed separately, the prevalence of dysgeusia was 38% (CI_{95%}, 22% to 56%), 35% for hypogeusia (CI_{95%}, 21% to 51%; I₂ = 97%), and 24% for ageusia (CI_{95%}, 15% to 35%). Other studies also detail that taste alteration was the most reported oral manifestation and therefore described during COVID 19 with a prevalence range between 5.6% (Mao, *et al.*, (2020) and 92.64% (Bénézit, *et al.*, 2020). An investigation carried out in Milan, Italy, found that of 59 patients with SARS-COV-2, 34% had ageusia (Gutiérrez & Zambrano, 2020). Other authors reported that in 11% of cases patients mentioned taste alteration as the first symptom of COVID 19 infection, (Hjelmesæth & Skaare, 2020), while other reports even described taste alteration as the single or onset symptom in mild disease or as an initial symptom of patients who ultimately present with more severe respiratory failure due to atypical pneumonia (Jang, *et al.*, 2021; Biadsee, *et al.*, 2020). Another result indicates that mouth dryness and amblygeusia, manifested in a relatively high proportion in 108 patients with COVID 19 (47.2% and 46.3%, respectively); and 11.1% of the patients presented dryness and inflammation of the mouth (Chen, *et al.*, 2020).

Recently, xerostomia or dry mouth syndrome has been linked to COVID 19, as it has been found mainly among COVID 19 patients. In a case series study of 128 outpatient patients who were quarantined, 72 patients (28 men, 44 women) had xerostomia, and a strong association was found between the burning mouth and taste changes ($p = 0.002$, $p = 0.009$, respectively), (Biadsee, *et al.*, 2020).

Regarding lesions of the oral mucosa, in a review of case reports (Amorim *et al.*, 2021), they are described as presenting various clinical aspects, such as ulcers, blisters, macules, and plaques, varying in quantity, color, size, and location (table 1). The tongue, palate, lips, gingiva, and oral mucosa were affected. In mild cases, lesions of the oral mucosa developed before or at the same time as the initial respiratory symptoms; however, in those requiring medication and hospitalization, lesions developed approximately 7 to 24 days after the onset of symptoms.

Another study observed that in 666 patients with COVID 19, who had mild to moderate pneumonia, 40.65% (304) had one or more mucocutaneous manifestations. Oral cavity findings occurred in 78 cases (25.7%), including transient lingual papillitis (11.5%), glossitis with lateral indentations (6.6%), and aphthous stomatitis (6.9%), glossitis with irregular depapillation (3.9%) and mucositis (3.9%). The burning sensation was

reported in 5.3% of patients, and taste disturbances (dysgeusia) were commonly associated (Capocasale, *et al.*, 2021).

In another narrative review of cases (Jimenez, *et al.*, 2020), three different oral manifestations were found: taste alteration, oral blisters and ulcers, and oral lesions associated with Kawasaki-like diseases (erythema, lip bleeding, "strawberry tongue"). From the literature analysis, oral manifestations associated with other dermatological alterations were also reported; such is the case of three women positive for COVID 19, between 58 and 77 years old, with palatal spots and petechiae associated with an erythema multiforme-like rash. This manifestation was found to occur on average 19.5 days after infection. In addition, one case of herpetic stomatitis was recorded in 100 intubated patients (Rivera, *et al.*, 2020).

One of the topics of interest during the COVID 19 outbreak is the possible association between Kawasaki disease (KD) and coronavirus infection. KD may show changes in the lips and oral cavity, including erythema, dryness, fissures, peeling, cracking, bleeding from the lips, and "strawberry tongue". When KD is presented in association with COVID 19, its clinical manifestations are worse compared to the clinical characteristics reported in the literature; therefore, in these cases, it was reported as a disease similar to Kawasaki (Verdoni, *et al.*, 2020). An observational study showed that, during the COVID 19 outbreak, KD had a monthly incidence at least 30 times higher than the monthly incidence of the previous five years in the district of Bergamo. The study reported ten pediatric patients affected by this condition, five of them presented the classic form and five the incomplete form. 80% of classically diagnosed patients had alterations of the lips or oral cavity, or both and one of them had posterior cervical lymphadenopathies. Non-exudative conjunctivitis associated with changes in the lips and oral mucosa was highlighted in one of the patients affected by the incomplete form of Kawasaki (Verdoni, *et al.*, 2020). In addition, a case report from the United States described a 5-year-old patient diagnosed with incomplete Kawasaki associated with fever (up to 39.4°C for 8 days), dry, chapped, and erythematous lips, non-exudative conjunctivitis, and lymphadenopathy without rash (Rivera, *et al.*, 2020).

In the analysis of another review (Iranmanesh, *et al.*, 2021), oral manifestations included ulcer, erosion, blister, gallbladder, pustule, fissured or depapilated tongue, macula, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most commonly affected places in descending order were: the tongue (38%), labial mucosa (26%), palate (22%), gum (8%), buccal mucosa (5%), oropharynx (84%), and tonsils (1%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiformis lesions, candidiasis, vasculitis, Kawasaki-like, erythema multiforme-like, mucositis, pharmacological rash,

necrotizing periodontal disease, bullous angina, angular cheilitis, atypical, Sweet's syndrome, and Melkerson-Rosenthal syndrome.

Oral lesions were symptomatic in 68% of cases and were almost the same in both sexes (49% female and 51% male). The latency time between the onset of systemic symptoms and oral lesions was from four days before to twelve weeks after the onset of systemic symptoms. In three cases, oral lesions preceded systemic symptoms, and in four cases oral and systemic symptoms appeared simultaneously. The oral lesions healed between three and 28 days after onset. Older and more severe COVID 19 patients had more extensive and severe oral lesions (Iranmanesh, *et al.*, 2021). The description of the lesions was as follows: **a) aphthous lesions**, appeared as multiple superficial ulcers with erythematous and pseudomembranous halos of yellowish-white color in the mucous membranes both keratinized and non-keratinized. In one patient, oral lesions appeared simultaneously with systemic symptoms. Aphthous lesions without necrosis were observed in younger patients with a mild infection, while aphthous lesions with necrosis and hemorrhagic crusts were more frequently observed in older patients with immunosuppression and severe infection. Regression of oral lesions was associated in parallel with improvement of systemic disease (Iranmanesh, *et al.*, 2021; Brandáo, *et al.*, 2021); **b) ulcerative or erosive lesions**, appeared as painful lesions with irregular edges on the tongue, hard palate, and labial mucosa, after a latency time of four to seven days and in one case, the lesions appeared three days before the onset of systemic symptoms and recovered after five to 21 days (Iranmanesh, *et al.*, 2021; Chaux-Bodard, *et al.*, 2020; Soares, *et al.*, 2020; Indu, 2020); **c) herpetiform lesions**, presented as multiple painful, unilateral, round yellowish-gray ulcers with an erythematous border on the keratinized and non-keratinized mucous membranes. Manifestations of these lesions preceded, coincided with, or followed systemic symptoms. In one case, the geographic tongue appeared after recovery from herpetiform lesions (Carreras, *et al.*, 2020; Iranmanesh, *et al.*, 2021; dos Santos, *et al.*, 2020; Aghazadeh, *et al.*, 2020; Kämmerer, *et al.*, 2020). White and red plaques or patches on the back of the tongue, gum, and palate of patients with confirmed or suspected COVID 19 were reported (Iranmanesh, *et al.*, 2021; Dos Santos, *et al.*, 2020; Díaz, *et al.*, 2020; Corchuelo & Ulloa, 2020); **d) erythema multiforme-like lesions** appeared as blisters, scaly gingivitis, erythematous macules, erosions, and painful cheilitis with hemorrhagic crust in patients with target skin lesions on the extremities. Lesions appeared between seven and 24 days after the onset of systemic symptoms and recovered after two to four weeks; (Carreras, *et al.*, 2020; Rivera, *et al.*, 2020; Iranmanesh, *et al.*, 2021; Labé, *et al.*, 2020). **e) lesions similar to angina bullosa**, asymptomatic violet erythematous blisters without spontaneous bleeding on the tongue and

hard palate occurred in two confirmed cases of COVID 19 (Iranmanesh, *et al.*, 2021; Cruz, *et al.*, 2020); **f) necrotizing periodontal disease (EPN)**: A 35-year-old woman with suspected COVID 19 is reported to have a fever, submandibular lymphadenopathy, severe halitosis, and oral lesions which included a painful, erythematous and generalized edematous gum with necrosis of the interpapillary areas and bleeding. The suggested diagnosis was necrotizing gingivitis from bacterial co-infections (especially *Prevotella intermedia*) along with COVID 19 (Patel & Woolley, 2021). In this regard, metagenomic analyses of people infected with SARS coronavirus 2-CoV-2 frequently detect abnormally high bacterial readings of *Prevotella Intermedia* in addition to common pathogenic genera involved in the onset and progression of oral diseases such as *streptococci*, *Fusobacterium*, *Treponema*, and *Veillonella*. *Prevotella intermedia* is considered one of the main etiological bacterial species of several acute periodontal lesions that, together with the species of *Fusobacterium* and *Treponema*, constitute a large proportion of the microbiota present in EPN lesions. EPNS are more prevalent in patients with HIV. Similarly in mechanical terms, SARS-CoV-2 infection may predispose individuals to EPN through bacterial co-infection spread by *Prevotella intermedia* (Chakraborty, 2020). In one study, which aimed to investigate the presence of SARS-CoV-2 in periodontal tissue by performing post-mortem biopsy in seven fatal cases of COVID 19, the seven autopsies studied with positive laboratory tests for COVID 19 included 57.14% of patients with an average age of 47.4 (range eight to 74). In five cases, periodontal tissue was positive for SARS-CoV-2 (RT-PCR). Histopathological analyses showed morphological alterations in the keratinocytes of the binding epithelium, vacuolization of the cytoplasm and nucleus, and nuclear pleomorphism. The findings of this study show that periodontal tissue appears to be a target of SARS-CoV-2 and may long contribute to the presence of the virus in saliva samples, noting that the periodontal tissue response can be different in individuals with COVID 19 who are asymptomatic or have only mild symptoms. These findings may indicate a new approach to understanding the pattern of COVID 19 contamination (Fernandes, *et al.*, (2020); **g) vesicles and pustules**, A report of a 9-year-old girl who developed fever, weakness, abdominal pain, and diarrhea was found to coincide with an oral and acral erythematous papillate rash. Oral lesions included vesicular eruptions and erosions on the tongue and buccal mucosa. The PCR test for COVID 19 was positive. The lesions healed after one week (Aghazadeh, *et al.*, 2020). There was also another report about a 51-year-old man who developed fever, fatigue, dry cough, dysgeusia, anosmia, and a COVID 19-positive serology. After ten days, generalized erythema appeared on the hard palate and oropharynx with petechiae and pustules on the edge of the soft palate. The suggested diagnosis was COVID 19 enanthema and the lesions healed within

a few days (Díaz, *et al.*, 2020); **h) petechiae**, in some studies, was reported in the lower lip, palate, and mucosa of the oropharynx. The latency time for petechiae patients was shorter compared to patients with petechiae and macular lesions (Cebeci & Çaşkurlu, 2019; Rivera, *et al.*, 2020; Corchuelo & Ulloa, 2020; Jimenez, *et al.* (2020), **i) nonspecific lesions (mucositis)**, several studies reported purplish macules, plaques, papules and erythematous plaques on the tongue, mucosa of the lips, hard palate and oropharynx (Cebeci & Çaşkurlu, 2019; Rivera, *et al.*, 2020; Soares, *et al.*, 2020; Cruz, *et al.*, 2020; Patel & Woolley, 2021; Malih, *et al.*, (2020; Tomo, *et al.*, 2020); and **j) post-inflammatory pigmentation**, a report of pigmentation in the adhered and interpupillary gum in a 40-year-old woman (Corchuelo & Ulloa, 2020).

CONCLUSIONS

Current research shows that coronavirus damage to respiratory organs and other organs could be related to the distribution of ACE2 receptors in the human system. It has been proven that the oral cavity is the perfect entry portal for SARS-CoV-2 infection due to the special affinity of the virus with the ACE2 receptors present in the cells of the oral mucosa, tongue, and salivary glands. Once the disease is established, the virus would have the ability to alter the balance of the oral microbiota and immunosuppress the patient, allowing the possible appearance of opportunistic infections. This, combined with drug therapy and salivary gland disorders, the etiology of which is not yet entirely clear, would contribute to the development of sensory disorders and adverse oral health-related outcomes.

Taste disturbance is considered one of the most frequent oral manifestations directly related to SARS-CoV-2 infection, with varying degrees ranging from ageusia, dysgeusia, and hypogeusia. Taste disturbances may be one of the first signs of COVID 19 and maybe the only symptom of COVID 19 in asymptomatic and mild forms of the disease although they have also been considered as a side effect of COVID 19 treatment.

Apart from the alteration of taste, several cases of oral manifestations were detected that most likely present as co-infections and secondary manifestations with multiple clinical aspects due to treatments for COVID 19 or related to a weakened systemic condition of patients and not as a type of condition caused by SARS-CoV-2. There is no scientific evidence in the literature to certify what oral symptoms SARS-CoV-2 may cause. In fact, from the analysis of the literature consulted, it is difficult to notice that the clinical conditions manifested by patients are due to SARS-CoV-2. Lack of oral hygiene, opportunistic infections, stress, underlying diseases (diabetes mellitus, immunosuppression, among others), trauma (secondary to intubation), vascular involvement, and hyperinflammatory response secondary

to COVID 19 could be the most important predisposing factors for the development of oral lesions in COVID 19 patients.

Finally, it is important to have a team specialized in dentistry within hospitals to understand and evaluate oral signs and symptoms in patients diagnosed with SARS-CoV-2 infection to be able to show if oral manifestations are part of the semiology of the infection of this new coronavirus.

REFERENCES

- Abduljalil**, J.M., Abduljalil, B.M. (2020). Epidemiology, genome, and clinical features of the pandemic SARS-COV-2: a recent view. *New Microbes and New Infections*, 35:1-8.
- Aghazadeh**, N., Homayouni, M., Sartori-Valinotti, J.C. (2020). Oral vesicles and acral erythema: report of a cutaneous manifestation of COVID-19. *Int J Dermatol* ,59(9):1153-1154.
- Amorim** Dos Santos, J., Normando, A., Carvalho da Silva, R. L., De Paula, R. M., Cembranel, A. C., Santos-Silva, A. R., & Guerra, E. (2020). Oral mucosal lesions in a COVID-19 patient: New signs or secondary manifestations?. *Int J of infectious diseases*, 97, 326–328.
- Amorim** Dos Santos, J., Normando, A., Carvalho da Silva, R.L., Acevedo, A.C., De Luca Canto, G., Sugaya, N., Santos-Silva, A.R., Guerra E. (2021). Oral Manifestations in Patients with COVID-19: A Living Systematic Review. *J Dental Res*, 100(2): 141–154.
- Andersen**, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., Garry, R.F. (2020). The proximal origin of SARS-COV-2. *Nat Med*,1-3.
- Bénézit**, F., Le Turnier, P., Declerck, C., Paillé, C., Revest, M., Dubée, V., RAN COVID Study Group. (2020). Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *The Lancet Infectious Diseases*, S1473-3099(20), 30297–30298.
- Biadsee**, A., Biadsee, A., Kassem, F., Dagan, O., Masarwa, S., Ormianer, Z. (2020). Olfactory and Oral Manifestations of COVID-19: Sex-Related Symptoms—A Potential Pathway to Early Diagnosis *Otolaryngol Head Neck Surg*, 163(4): 722–728.
- Brandão**, T.B., Gueiros, L.A., Melo, T.S., et al. (2021). Oral lesions in patients with SARS-COV-2 infection: could the oral cavity be a target organ? *Oral Surg Oral Med Oral Pathol Oral Radiol*, 131(2):e45-e51.
- Capocasale**, G., Nocini, R., Faccioni, P., Donadello, D., Bertossi, D., Albanese, M., & Zotti, F. (2021). How to deal with coronavirus disease 2019: A comprehensive narrative review about oral involvement of the disease. *Clin Experimental Dental Res*, 7(1), 101–108.
- Cardoso**, F.T., Lima, M.J., Cavlcante, C.M., Buzzati, P.L., Perez, O.S. (2020). COVID-19 e a Cavidade Bucal: Interações, Manifestações Clínicas e Prevenção. *ULAKES J Med* 1 (EE) 98-105.
- Carreras**, P.M., -Presas, C., Amaro Sánchez, J., López-Sánchez, A. F., Jané-Salas, E., Somacarrera Pérez, M. L. (2020). Oral vesiculobullous lesions associated with SARS-COV-2 infection. *Oral diseases*, 27(53):710-712.
- Cebeci**, K.F., Çaşkurlu, H. (2019). Mucosal involvement in a COVID-19-positive patient: A case report. *Dermatol Ther.*, 4(6):E272-7.

- Chakraborty, S.** (2020). Metagenome of SARS-COV2 patients. OSF Preprints. <https://osf.io/jegwq/>
- Chaux- Bodard, A.G., Deneuve, S., Desoutter, A.** (2020). Oral manifestation of COVID-19 as an inaugural symptom? *J Oral Med Oral Surg.*, 2020;26(2):18.
- Chan, J.F., Yuan, S., Kok, K.H., To, K.K., Chu, H., Yang, J., Xing, F., Liu, J., Yip, C.C., Poon, R.W., Tsoi, H.W., Lo, S.K., Chan, K.H., Poon, V.K., Chan, W.M., Ip, J.D., Cai, J.P., Cheng, V.C., Chen, H., Hui, C.K., Yuen, K.Y.** (2020). A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.*, 15; 395(10223):514-523.
- Chen, L., Zhao, J., Peng, J., Li, X., Deng, X., Geng, Z., et al.** (2020). Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Cell Prolif., 53(12): e12923.
- Chen, X., Tian, J., Li, G.,** (2020). Initiation of a new infection control system for the COVID-19 outbreak. *Lancet Infect Dis.*, 20(4):397-398.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., et al.** (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*, 395: 507-13.
- Corchuelo, J., Ulloa, F.C.** (2020). Oral manifestations in a patient with a history of asymptomatic COVID-19. *Case Report Int J Infect Dis.*,100:154-157.
- Cruz, T.R.O., Peraza, L.A.J., Guimaraes, D.M., Matos, V.L.H.** (2020). Oral mucosal lesions in patients with SARS-COV-2 infection. Report of four cases. Are they a true sign of COVID-19 disease? *Spec Care Dentist.*, 40(6):555-60.
- Dos Santos, J.A., Normando, A.G., da Silva, R.L., et al.** (2020). Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? *Int J Infect Dis.*, 9.
- Díaz, R.M., Jimenez, R. A., Villarroel M.** (2020). Oral manifestations associated with COVID-19. *Oral Dis. Advance online publication.* <https://doi.org/10.1111/odi.13555>.
- Falcón, G.B., Falcón, P.G.** (2021). Repercusiones en la Cavidad Oral Causadas por la Infección con COVID-19. *Int. J. Odontostomat.*,15(1):23-26.
- Farook, F. F., Mohamed Nuzaim, M. N., Taha Ababneh, K., Alshammari, A., & Alkadi, L.** (2020). COVID-19 Pandemic: Oral Health Challenges and Recommendations. *European J Dent.*, 14(S 01), S165–S170.
- Fernandes M.B., Dolhnikoff, M., et al.,** (2020). Periodontal tissues are targets for SARS-COV-2: a post-mortem study. *J Oral Microbiol.*, 13(1):1848135.
- Gaitán, L., Leyva, E., Cruz, R., Carmona, D., Ruiz, Rodríguez, M., Arenas, A.** (2019). COVID-19 y el cirujano dentista. *Rev Odont Mex.*, 23(4):207-2015.

- Gorbalenya, A.E., Baker, S.C., Baric, R.S., Groot, R.J., Drosten, C., Gulyaeva, A.A., et al.** (2020). Severe acute respiratory syndrome-related coronavirus: The species and its viruses –a statement of the Coronavirus Study Group. *bioRxiv*. 2020. *Nature Microbiology*, 5(3):536-544.
- Gralinski, L.E., Menachery, V.D.** (2020). Return of the Coronavirus: 2019-nCoV. *Viruses* 12 (2): 135. <https://doi.org/10.3390/v12020135>.
- Gutiérrez, F., Zambrano, R.** (2020). Implicaciones bucales por COVID-19. Revisión de tema. *Odontol. Sanmarquina*, 23(4): 419-424.
- Herrera, D., Serrano J., Roldán S., Sanz M.** (2020). Is the oral cavity relevant in SARS-COV-2 pandemic? *Clin Oral Invest.*, 24:2925-2930.
- Hjeltnes, J., Skaare, D.** (2020). Loss of smell or taste as the only symptom of COVID-19. *J Norwegian Med Associat.*, 140(7).
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al.** (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395:497-506.
- Hui, D. S., Azhar, E. I., Memish, Z. A., Zumla, A.** (2020). Human Coronavirus Infections—Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and SARS-COV-2. *Reference Module in Biomedical Sciences*, B978-0-12-801238-3.11634-4. <https://doi.org/10.1016/B978-0-12-801238-3.11634-4>.
- Indu, S.** (2020). Multiple oral ulcerations—an initial manifestation of COVID-19 infection: a personal experience. *J Oral Maxillofac Pathol.*, 24 (2):227.
- Iranmanesh, B., Khalili, M., Amiri, R., Zartab, H., & Aflatoonian, M.** (2021). Oral manifestations of COVID-19 disease: A review article. *Dermatol Therapy*, 34(1), e14578.
- Jang, Y., Son, H. J., Lee, S., Lee, E. J., Kim, T. H., Park, S. Y.** (2020). Olfactory and taste disorder: The first and only sign in a patient with SARS-COV-2 pneumonia. *Infect Control and Hospital Epidemiol.*, 41,1103.
- Jimenez, C.J., Ortega, Q.D., de Perosanz, L.D., et al.** (2020). Enanthem in patients with COVID-19 and skin rash. *JAMA Dermatol.* 2020;156(10):1134-6.
- Jimenez, C. J., Ortega, Q. D., Carretero, B. I., Suarez, V. A., Saceda, C. D., Moreno, G.C., Fernandez, N D.** (2020). Erythema multiforme-like eruption in patients with COVID-19 infection: Clinical and histological findings. *Clin Experimental Dermatol.*, 45, 892–895.
- Kämmerer, T., Walch, J., Flaig, M., French, L.E.** (2020). COVID-19 associated herpetic gingivostomatitis. *Clin Exp Dermatol.*, 46(1):174-176.
- Labé, P., Ly, A., Sin, C., et al.** (2020). Erythema multiforme and Kawasaki disease associated with COVID-19 infection in children. *J Eur Acad Dermatol Venereol.*, 34(10):e539-e541.
- Lechien, J.R., Chiesa-Estomba, C.M., De Siati, D.R., et al.** (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate

- forms of coronavirus diseases (COVID-19): a multi-center European study. *Eur Arch Otorhinolaryngol.*, 277(8), 2251–2261.
- Lu, H., Stratton, C.W., Tang, Y.W.** (2020). Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol.*, 92(4):401-402.
- Malih, N., Hajinasrollah, G., Zare, M., Taheri, M.** (2020). Unexpected presentation of COVID-19 in a 38-year-old male patient: a case report. *Case Rep Dermatol.* 2020;12(2):124-131.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q. Hu, B.** (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology*, 77, 683–690.
- Mousavizadeh, L., Ghasemi, S.** (2020). Genotype and phenotype of COVID-19: Their roles in pathogenesis. *J. Microbiol. Immunol. Infect*, 54(2):159-163.
- Nemeth, M., Matus, C., Carrasco, R.** (2020). Manifestaciones Orales de la Infección por COVID-19. *Int J Odontostomat.*, 14(4): 555-560.
- Nuno, G.A., Carrillo, M.P., Magaletsky, M.K., Ríos, C.M., et al.** (2021). Prevalence of mucocutaneous manifestations in 666 patients with COVID-19 in a field hospital in Spain: oral and palmoplantar findings. *British J Dermatol.*, 184(1): 184–185.
- Patel, J., Woolley, J.** (2021). Necrotizing periodontal disease: oral manifestation of COVID-19. *Oral Dis.*, 27 Suppl 3:768-769.
- Rivera, F.E.I., Santos, R., Simpson, S., Garg, P.** (2020). Incomplete Kawasaki disease in a child with COVID-19. *Indian Pediatrics*, 57, 680–681.
- Sifuentes, R.E., Palacios, R.D.** (2020). COVID-19: The outbreak caused by a new coronavirus. *Bol Med Hosp Infant Mex.*, 77(2), 47-53.
- Soares, C.D., de Carvalho, R.A., de Carvalho, K.A., de Carvalho, M.G., de Almeida, O.P.** (2020). Letter to editor: oral lesions in a patient with Covid-19. *Med Oral Patol Oral Cir Bucal.*, 25(4):e563.
- Struyf, T., Deeks, J.J., Dinnes, J., Takwoingi, Y., Davenport, C., Leeftang, M.M.G., Spijker, R., Hooft, L., Emperador, D., Dittich, S., Domen, J., Horn, S.R., Van den Bruel, A.** (2020). Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database of Systematic Reviews Issue 7.* doi: 10.1002/14651858.CD013665. Accessed 12 March 2021.
- Tomo, S., Miyahara, G.I., Simonato, L.E.** (2020). Oral mucositis in a SARS-cov2-infected patient: secondary or truly associated condition? *Oral Dis.*, Letter to the editor. <https://doi.org/10.1111/odi.13570>.
- Tong JY, Wong A, Zhu D, et al.** (2020). The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg.*, 163:3-11.

- Torres, L.J.** (2020). ¿Cuál es el origen del SARS-COV2? *Rev Med Inst Mex Seguro Soc.*, 58(1):1-2.
- Verdoni, L., Mazza, A., Gervasoni, A., Martelli, L., Ruggeri, M., Ciuffreda, M., D'Antiga, L.** (2020). An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-COV-2 epidemic: An observational cohort study. *Lancet*, 395, 1771–1778.
- Villanueva, S.F., Escalante, M.L.** (2020). SARS-COV-2 modelo de inoculación en la cavidad oral. *Revisión de la literatura. Int. J. Odontostomat.* 14(4):495-500, 2020.
- Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., et al.** (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.*, doi: 10.1001/jama.2020.1585.
- Wang, C., Wu, H., Ding, X., Ji, H., Jiao, P., Song, H., Li, S, Dua, H.** (2020). Does infection of 2019 novel coronavirus cause acute and/or chronic sialadenitis? *Med Hypotheses.*, 140:109789.
- Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., Zhou, F., Jiang, J., Bai, C., Zheng, J., Song, Y.** (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.*, 180 (7), 934–943.
- Wu, Y.C., Chen, C.S., Chan, Y.J.** (2020). The outbreak of COVID-19: an overview. *J Chin Med Assoc.*, 83(03):217–220.
- Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., Li, T., Chen, Q.** (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci.*, 12(1):8.
- Yan, C.H., Faraji, F., Prajapati, D.P., et al.** (2020). Association of chemosensory dysfunction and Covid-19 in patients presenting with Influenza-like symptoms. *Int Forum Allergy Rhinol.*, 10(7):806-813.
- Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., et al.** (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 579(7798):270–273.
- Zhu, N., Zhang, D., Wang, W., et al.** (2019). A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.*, 382:727-733.
- Zou, X., Chen, K., Zou, J., Han, P., Hao, J., Han, Z.** (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection.