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Oral implications related to COVID-19: What Can we expect in Times of Pandemic?

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ABSTRACT:
Objective: to report the drugs most used in the treatment of COVID-19 and their possible adverse effects on the oral cavity so that the dental surgeon is aware of their role in the treatment of secondary manifestations of COVID-19 and is prepared to handle and treat the cured patient of COVID-19 who presents such manifestations.
Materials and methods: through a survey of the pubmed and scielo database, we conducted a search for papers that included current approaches on COVID-19, its tropism by the salivary glands and epithelium of the oral mucosa, as well as its handling and oral manifestations of drugs used to treat COVID-19.
Results: the drugs used to treat COVID-19 include drugs known to manage other diseases, such as antivirals, corticosteroids, antiparasitic, antibiotics, among which the oral manifestations induced by their use are well founded in the literature.
Conclusion: given the above, it is concluded that the dental surgeon needs to be prepared to handle the cured patient of COVID-19 because they used medications that can induce oral injuries

Keywords: coronavirus infection, salivary glands, oral mucosa, medicines, intensive care unit

I. INTRODUCTION

In December 2019, in the city of Wuhan, Hubei province, China, 27 cases of pneumonia whose etiology was unknown were identified, among the clinical symptoms, common among patients, were dry cough, dyspnea, fever and bilateral pulmonary infiltrates [1]. In the investigation of a possible etiology, it was observed that the same patients were linked to a wholesale market of seafood in the city of Wuhan, which sold fish, birds, snakes and bats. From throat smear of these contaminated patients the causative agent was identified and named SARS-CoV-2 [2].
What is known about the pathogen is that it is a simple ribbon RNA virus, of the family *coronaviridae*, belonging to the genus β-Coronavirus (subgenus *sarbecovirus*, subfamily *Orthocoronavirinae*) [3]. Previous reports refer to Middle East Respiratory Syndrome caused by MERS-CoV and Severe Acute Respiratory Syndrome caused by SARS-CoV. Currently, SARS-CoV-2, the causative agent of the coronavirus, has been compared with SARS and both have an amino acid sequence and share the same receptor, the angiotensin-2 converting enzyme (ECA2). What is known is that SARS-CoV-2 is the virus responsible for COVID-19, an infection in the lower respiratory tract with the potential to cause fatal complications [4].
The natural host of the virus can be the *Rhinolophus affinis* bat, however, transmission can occur directly from infected people, by inhalation of droplets from sneezing and coughing or by contact with oral, ocular and nasal

mucous membranes. Due to the spreading power of the virus, there has been a rapid and widespread growth in the number of cases worldwide thus, the World Health Organization (WHO) has declared a global outbreak [3].
Since then, the WHO and several bodies have issued reports on the Prevention of COVID-19, such as hand hygiene, use of PPE and facial masks, social isolation, among others. However, even with implemented strategies of measures, the cases increase dramatically, which makes the situation worrying, since there is no specific antiviral for the treatment of COVID-19 and an efficient vaccine is still being studied. Thus, much has been discussed about the therapy addressed and, until then, are nonspecific, including antivirals, corticosteroids, antimalarials, antibiotics, among others. Severe patients require hospitalization in intensive care units (ICU), and often, long periods of mechanical ventilation, overloading health systems around the world [2,4].
Odontology has been inserted in this scenario due to the high infectivity of the disease by droplets of saliva and, since it is known that infected patients can be asymptomatic and transmission vectors. In the dental office, the spread of the virus by aerosols generated during the care within a closed area is a potential transmission mechanism, either at a short distance, directly from the patient to the professional, or at a long distance, when the salivary particle with viral load reaches surfaces [5,6].

Objectives

Highlighting the importance of alerting dental surgeons to the possible oral manifestations caused by the disease as well as oral changes related to the treatments used so that they can act assisting in early diagnosis and, especially, in the management of therapeutic consequences. Therefore, the objective of this study is to conduct a review of the current literature seeking to highlight the oral manifestations of COVID-19 and oral alterations secondary to the treatments employed in order to enable the dental surgeon to recognize and treat these complications.

LITERATURE REVIEW

1. Oral manifestations related to COVID-19

1.1 Possible manifestations of the patient with COVID-19

Skin and oral manifestations in patients infected with SARS-CoV-2 have been described. One study reports erythema multiforme lesions with varying patterns on the skin and oral cavity. In all patients evaluated, the lesions began with the pattern of erythematous papules that evolved into erythematoviolaceous spots with central pseudo-vesicle, on the upper trunk, back, face and limbs. On intraoral examination three patients showed palatine macules and petechiae. All patients had progressive remission of lesions with the use of systemic corticosteroids [7].
With the hypothesis that oral manifestations may occur in patients with COVID-19, a case was reported of a infected patient who, on the 8th day presented ulcerated oral lesion on the back of the tongue, with painful inflammation in the lingual papillae for about 24 hours, followed by erythematous macula with evolution to irregular and asymptomatic ulcer with remission after 10 days. An erythematous and painful lesion has also been reported on the toe [8].
It is believed that the virus can induce vascular inflammation which would explain erythematous eruptions and inflammation, however, the authors state greater need for studies on oral lesions in patients with COVID-19 [7,8].

1.2 Dysgeusia and anosmia

In human physiological mechanisms considered “normal”, taste is a function mainly of the taste buds present in the lingual papillae and smell contributes essentially to taste perception [9]. In patients diagnosed with COVID-19 there is a prevalence of anosmia, that is, olfactory dysfunction, as well as dysgeusia, which concerns the taste alteration, and by the influence of these stimuli they may represent an early symptom that suggests infection by SARS-CoV-2, however, there are few studies investigating dysgeusia and anosmia when compared to other symptoms of the disease [10].

The pathophysiological mechanisms related to olfactory and palate dysfunctions due to COVID-19 infection are not yet fully clarified. SARS-CoV-2 is part of a viral family that may be associated with anosmia and dysgeusia. The expression of the ECA2 receptor in the various human tissues can be a critical factor for the emergence of symptoms [11].

1.3 Tropism by the epithelium

Knowledge about the host cell receptor of SARS-CoV-2 is relevant for both prevention and treatment. The literature and research show the affinity of the virus with the ECA2 receptor, which is distributed by the human body and can be a potential indicator of the routes of the virus, when an organ expresses high amount of ECA2, it considers the risk of the development of the disease. Based on these assumptions, recent studies have indicated high ECA2 expressions in the oral mucosa. The expression of ECA2 receptors was much higher in the tongue when compared to other locations of the oral cavity, according to data from this study and as a conclusion of it, the oral cavity is susceptible to infection by the virus causing COVID-19 [6].

The ECA2 receptor has high expressiveness in the oral cavity and salivary glands, but mainly in the tongue. Furin is in high quantity in the tongue, this enzyme collaborates with viral cleavage and improves infection of host cells, i.e., high rates of furin in the tongue associated with ECA2 receptors found in this oral anatomical locality suggest a high risk of infection by SARS-CoV-2 [12].

1.4 Tropism by the salivary glands

Recent literature has drawn attention to the role of salivary glands in the epidemic process of COVID-19 infections. There are three different hypotheses to explain the presence of the virus associated with the salivary fluid: the SARS-CoV-2 present in the respiratory tract enters the oral cavity, along with the droplets of the liquid to be exchanged between the organs, the other possibility is that SARS-CoV-2 enters the oral cavity through the crevicular fluid, and, ultimately, the infection of the salivary glands would lead to the release of viral particles by means of a salivary duct, since epithelial cells of the glands may also be affected by a SARS-CoV-2 [5].

The affinity of the virus by ECA2 receptors, present mainly in the respiratory tract and in the epithelial cells of the salivary glands, makes them the target of SARS-CoV-2, asserting the presence of the virus at high rates in the salivary fluid [13].

Oral pathologies associated with COVID-19 should be considered when it comes to the affinity of the virus by ECA2 receptors expressed in salivary glands, such as sialadenitis. This pathology is an inflammation in the salivary glands of infectious or non-infectious etiology, and the infectious can be caused by viruses, and leads to the obliteration of the salivary duct [14]. There are assumptions that SARS-CoV-2 induces sialadenitis by connecting with ECA2 receptors present in the salivary glands, and the connection would lead to cell lysis and trigger symptoms such as discomfort, inflammation and pain in the gland region [5].

In addition, considering the protective function of saliva, hyposalivation could be associated with severe respiratory infections, because, with the decrease in salivary flow installed, the mechanisms that prevent infections by saliva would be deficient, and with this, there would be disturbance of the oral mucosa and airways, culminating in better adhesion of viral microorganisms, therefore, given this hypothesis, patients with hyposalivation are more prone to the development of COVID-19 [13].

II. Oral implications secondary to COVID-19

Due to the exacerbated spread of COVID-19, without the pre-existence of vaccine or treatment, the drugs used to treat the disease were initially prescribed based on medical experience and therefore several clinical trials are being conducted to verify the safety and efficacy of the drugs. According to the National Health Commission of China, it is recommended to use antivirals such as: lopinavir/ ritonavir, ribavirin, chloroquine phosphate and arbidol [15]. The mechanism of action of these antiviral therapies, as well as their possible oral implications secondary to the drug are described in Table 1.

Table 1: Mechanism of action of antiviral therapies, as well as their possible oral implications secondary to the drug.

Drug	Mechanism of action	Oral implications
Remdesivir	It is incorporated into the virus at its source, preventing its synthesis [15].	The use of ritonavir, as well as other antivirals, can generate oral complications such as perioral paresthesia, parotid lipomatosis, xerostomia, taste disorder, facial edema [21].
Favipiravir and ribavirin	Further studies are needed to relate its effects to the SARS-COV2 virus [15].	
Lopinavir and ritonavir	They are protease inhibitors targeted at the main COVID-19 protein (3C and 3CL pro) [15].	
Chloroquine	Inhibitor of endocytic pathways through an elevation of endosomal pH and may interfere with terminal glycosylation of ECA2, a potential blocker of peak ganglioside interaction that occurs in the first stage of the viral replication cycle [17].	The most common oral manifestation associated with the use of chloroquine is hyperpigmentation of the hard palate [31,32,33].
Azithromycin	It is a weak base that by accumulating in intracellular vesicles increases pH and can block endocytosis and viral genetic spread, limiting the replication of the virus [19].	Oral adverse effects related to the use of azithromycin include: paresthesia, discoloration of the tongue, candidiasis, Steven Johnson syndrome, erythema multiforme and epidermal necrosis (medicine package leaflet).
Corticosteroids	They act by suppressing the excessive inflammatory response, however they should be used with caution [15].	Drug-induced pseudomembranous candidiasis [26].
Ivermectin	Ivermectin binds to the Impa/β1 heterodimer causing its destabilization and preventing its binding with viral proteins [20].	The prominent oral reactions of this drug include: skin rashes, face edema, reactions in the glands, painful unequal lymph nodes [34].
Intubation of the patient in the Intensive Care Unit (ICU)		The patient in the ICU is more prone to oral manifestations mainly those resulting from decreased salivary flow and poor oral hygiene, such as halitosis, traumatic ulcers, tongue coating and candidiasis [37].

With the unregulated response of cytokines the infected patient with SARS-CoV-2 enters a hyper inflammatory condition.There are reports that patients in ICU have more cytokines in plasma than patients outside the ICU, suggesting that cytokines in greater quantity are related to greater severity of the disease, therefore, inhibiting the inflammatory response may be a treatment for COVID-19, being applied the use of corticosteroids in this therapy. In this line, studies are conducted to verify the efficacy and action of tocilizumab, a specific antibody to the IL-6 receptor whose mechanism of action is specified in Table 1 [15].

In an attempt to suppress pulmonary inflammation in MERS and SARS corticosteroids were proposed because they have immunomodulatory responses, however, evidences indicate that in spite of having no benefits in their use, this adjuvant therapy is common in the care of patients with COVID-19. Glucocorticoids can be used in patients at high risk of disease progression in short and low dose, because in patients with mild conditions the immune system itself is able to produce a beneficial response to the virus, therefore, these drugs should be used at the beginning of excessive inflammatory reactions [16].

In the search for adequate therapy, chloroquine, known antimalarial drug, began to be used due to promising results in pneumonia associated with COVID-19, its mechanism of antiviral action is still an open question considering that the researchers conclude that this drug is able to act in several stages of the replication cycle of SARS-CoV-2 [17]. Chloroquine can act by increasing the intra-vesicular pH generating the Prevention of

endosomal trafficking, compromising protein synthesis, these changes inhibit early viral replication, this drug also influences the terminal glycosylation of expression of the eca2 receptor, preventing the Binding of SARS-CoV-2 in its receptor and the spread of the virus in the host cell [18].

Studies report data from a research conducted in France whose objective was to evaluate the association of hydroxychloroquine and azithromycin, the results found demonstrated a lower mortality rate compared to previously reported cases, however, due to the lack of control group it is still necessary more studies about this association [16]. The mechanism of action of azithromycin as antiviral potential is described in Table 1 [19].

Considered a parasitic action drug, ivermectin can act as antiviral and has been used in the therapy of COVID-19 and has already been proven, through in vivo studies its potential. This drug has already been used as antiviral therapy against viruses of other systemic pathologies, presenting good results. The mechanism of action of ivermectin against SARS-CoV - 2 is described in Table 1 [20].

The drugs used to treat systemic diseases can show manifestations in the oral cavity, from inflammatory lesions, nonspecific ulceration, salivary flow dysfunction, hyperpigmentation, among others. Therefore, it is essential that the dental surgeon knows these manifestations and knows how to manage them.

2.1 Oral manifestations related to the use of antivirals

The use of ritonavir, an antiviral, was associated with oral complications such as perioral paresthesia, parotid lipomatosis, xerostomia, taste disorder and facial edema [21].

Paresthesia can occur after injury to innervations. Several treatments are proposed for the recovery of the injured nervous tissue, such as: vitamin B and C, anti-inflammatory drugs, physiotherapy, electrical stimulation and acupuncture.Among them, there is no therapy that promotes the full recovery of the injured tissue. The low-power LASER is being proposed for the management of oral paresthesias, increasing the functional activity of the injured nerve, helping in the recovery of sensitivity [22].

The use of medications has been associated with salivary dysfunctions, such as xerostomia, hyposalivation and consequently taste disorders, interfering in the social behavior of the patient, in this study, a direct-acting antiviral was associated with hypogeusia, that is, abnormally reduced taste [23]. The treatment of salivary dysfunctions is challenging, since it can be unsatisfactory, it should be indicated the increase in water consumption, as well as the prescription of artificial saliva and inputs that stimulate salivary flow such as sugar-free bullets [14]. The low-power LASER is again an effective therapeutic possibility in salivary gland disorders such as xerostomia and hyposalivation [24].

2.2 Oral manifestations related to the use of corticosteroids

The use of corticosteroids may be a predisposing factor for oral manifestations, such as induced oral candidiasis, because corticosteroids influence the immunity and ecology of the oral microbiota, the data have already reported that oral candidiasis could be induced with the use of corticosteroids and broad-spectrum antibiotics, causing both erythema and pseudomembranes in the most diverse anatomical locations of the oral mucosa [21].

Candida albicans is a fungus present in the normal microbiota of the mouth that under ideal conditions, such as the use of corticosteroids, develops oral candidiasis pathology, which can lead to changes in taste and local discomfort [25]. The use of inhaled corticosteroids with daily doses and frequency of inhalations was associated with the occurrence of oral candidiasis, a dose-dependence relation between the rate of candidiasis and the number of prescriptions received was identified in this study, it was also reported higher occurrence of candidiasis in users of metered dose inhaler [26].

For the treatment of oral candidiasis, antifungal agents are proposed, systemic ones such as triazois, fluconazole and conazole can be used for topical intolerants, and topical antifungal agents including nystatin, miconazole, clotrimazole and amphotericin B are used as therapy against *Candida albicans*. Nystatin is still considered the gold standard in the treatment of this fungal infection due to its effectiveness, low cost and reduced side effects [27]. However, when considering the possible side effects that some antifungal agents present, new therapeutic alternatives for the treatment of oral candidiasis have been explored. In a systematic review and meta-analysis, probiotics were an alternative to treatment of candidiasis because they inhibited the colonization of *Candida* in the oral mucosa and reduced the clinical signs of fungal infection, however, more evidence is needed to confirm the efficacy when compared to conventional treatments [28].

2.3 Oral manifestations related to the use of azithromycin

Azithromycin is a well tolerated drug with a low incidence of side effects. Among the adverse effects cited, to the exclusion of systemic effects, the ones that stand out are: paresthesia, tongue discoloration, candidiasis, Stevens Johnson syndrome, erythema multiforme, epidermal necrosis[BULA, Azithromycin].

Steven Johnson syndrome is a severe adverse reaction and high mortality in the skin and mucous membranes, the initial treatment is the removal of the inducing agent, glucocorticoids and cyclosporine are the most promising in the treatment of the syndrome, while glucocorticoids still need further studies on its effectiveness, cyclosporine is an adequate therapy in the management of patients [29].

Steven Johnson's syndrome differs from erythema multiforme, although both have mucosal erosions, the first is characterized by erythematous purpuric macules, localized in the trunk or generalized with displacement of the epidermis, while erythema multiforme has elevated or atypical acral skin lesions. Erythema multiforme can be acute and its treatment aims to reduce the duration of injuries or prevent complications and sequelae, it can be chronic with treatment aimed at avoiding new outbreaks and reducing its severity. Among the proposed drugs include anti-herpetics such as acyclovir, corticosteroids, antibiotics and immunosuppressants [30].

2.4 Oral manifestations related to the use of Hydroxychloroquine

There are reports in the literature of multifocal hyperpigmentation in the oral mucosa, induced by the use of chloroquine and hydroxychloroquine. Due to the prolonged administration of these drugs that results in the stimulated production of melanin or the deposition of metabolic products of the drugs in the tissues, adverse reactions such as these depend on the pharmacodynamics and pharmacokinetics of the drug, however, several drugs are able to generate this oral manifestation [31]. Two authors associated drug-related lichenoid eruptions with chloroquine, corroborating with previous studies [14, 21].

Due to the affinity of chloroquine for cells containing melanin and retina, this drug can induce pigmentations in the skin, nail and sclera, affecting the patient's vision. Pigmentation in varying sizes in the oral mucosa is an adverse effect due to the use of chloroquine, however, it is reversible [32]. Patient management is based on dose adjustment, with its decrease or discontinuation of treatment, lesions tend to regress [33].

2.5 Oral manifestations related to the use of Ivermectin

To determine the safety of ivermectin in the treatment of parasitic diseases, results related to its adverse effects were evaluated. These reactions include: pain, fever, itching, rashes, lymphadenopathy, swelling and reactions in the glands. Glandular reactions include pain and swelling being reported as moderate intensity, and among the anatomical sites the face has been reported [34].

2.6 Oral manifestations related to long periods of hospitalization

The admission of the patient to the ICU will depend on the severity of the disease and the capacity of care, however, with the advance and the exacerbated number of patients with COVID-19 these units should be prepared for the high rate of patients and qualified professionals for intensive treatment [35]. The Swiss Society of Intensive Care Medicine recommends that patients whose need is oxygen therapy and vital signs monitoring be admitted to an intermediate care unit or a high dependence unit with oxygen administration by cannula or nasal tube and high flow oxygen therapy, whereas patients with increased organic dysfunction, such as respiratory failure, should be transferred to the ICU, preferably for care in a special area for COVID-19. At least 15 to 20% of patients need specialized ventilatory support from the second week of symptoms and many of the patients need to go to the ICU [36].

The patient in the ICU is more exposed to infections and susceptible to dryness of the oral mucosa due to decreased salivary flow, mainly associated with inability to nutrition, hydration and breathing, therefore, the importance of hospital dentistry within the ICU is extremely important, related to the fact that oral manifestations may occur due to the condition that the patient needs to undergo. Since the patient in the ICU is more prone to biofilm accumulation due to poor sanitation and decreased salivary concentration, the bacteria present in the oral microbiota can interact with pulmonary pathogens through aspiration and result in nosocomial pneumonia, responsible for significant morbidity and mortality rates in patients [37].

During intubation of patients in the ICU, fungal microorganisms and gram-negative bacteria increase in the oral cavity, consequently oral changes are manifested, confirming the need of the dental surgeon in the oral hygiene

of patients. The most common manifestations associated with intubated patients relate to decreased salivary flow that leads to dysphagia, i.e. difficulty swallowing and favors halitosis, traumatic ulcers, tongue coating and candidiasis [38].

In order to aim at the multiprofessional treatment of patients in the ICU, the integration of the dentist surgeon in the treatment of the patient is fundamental, since he is the most qualified professional to provide adequate oral hygiene for hospitalized patients, however, dental practice in ICUs is still scarce [37].

CONCLUSION

Far beyond the high incidence of infectivity during dental care and the increased biosafety care before, during and after care, it is necessary that the dental surgeon be prepared for the management of patients during and after COVID-19, in the management of oral health as a whole, relating oral manifestations as the disease manifested and as the consequence of the medications used in the patient cured of SARS-CoV-2 infection.

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