CPQ Dentistry (2020) 1:5
Literature Review

COVID-19 Infection: What Every Health Care Professional Should Know About It

Marcelo Caliman Sato[1], Gabriel de Toledo Telles Araujo[2], Levy Anderson César Alves[3], Frederico Buhatem Medeiros[4], Lilia Timerman[5], Raquel Garcia D'Aquino Caminha[6] & Paulo Sérgio da Silva Santos[2*]

[1]*Pontifical Catholic University of Campinas, São Paulo, Brazil*

[2]*Department of Surgery, Stomatology, Pathology, and Radiology, Bauru Dental School, University of São Paulo, Bauru, Brazil*

[3]*Municipal University of São Caetano do Sul, Brazil*

[4]*Samaritano Hospital, Brazil*

[5]*Dante Pazzanese Institute of Cardiology, Brazil*

[6]*Department of Surgery, Stomatology, Pathology and Radiology, Faculty of Dentistry of Bauru, University of Sao Paulo, Bauru, SP, Brazil*

[*]**Correspondence to:** Dr. Paulo Sérgio da Silva Santos, Department of Surgery, Stomatology, Pathology, and Radiology, Bauru Dental School, University of São Paulo, Bauru, Brazil.

Copyright

Received: 24 August 2020

Published: 24 September 2020

Keywords: *COVID-19; SARS-CoV-2; Infections*

Abstract

SARS-Cov-2 virus has high infectivity and spreads very quickly throughout the world. The way viruses connect to the host needs to be well understood to establish health care safety preventive measures. Investments in research and adoption of criterious biosafety standards are necessary for

the control of infections caused by viruses. In the absence of medicines and vaccines, all health care providers have readapted local measures protocols to their protection, and to reduce potential virus transmission. These protocols are being readjusted as new studies are being launched, for this paper aims to review COVID-19 publications that have been shed to light throughout this pandemic that have strong scientific evidence about SARS-CoV-2, to help professionals to carefully read, and to be updated in order to establish health care guidelines safely.

Abbreviations (If Used)

SARS-CoV; (Severe acute respiratory syndrome coronavirus);
SARS (Severe Acute Respiratory Syndrome)
MERS-CoV (Middle East respiratory syndrome);
WHO (World Health Organization)
ACE2 (Angiotensin-converting enzyme 2)
COVID-19 (Coronavirus disease -19)
ARA II (angiotensin II receptor)
H1N1 (Influenza A)
TMPRSS2 (Immunoexpression - transmembrane protease)
S (spike), E (envelope), M (membrane), and N (nucleocapsid)
RSV (respiratory syncytial)
PPE (personal protective equipment)
HIV (Human Immunodeficiency Virus)
AIDS (Acquired Immunodeficiency Syndrome)

Introduction

On December 2nd, 2019, in Wuhan (Hubei - China), severe cases of a respiratory syndrome caused by an unknown agent in humans, later called Coronavirus were diagnosed [1]. Although coronaviruses have been known since the 1940s, it was only during the 2000s that the first cases of lethality in humans emerged. In 2002, the first SARS-CoV appeared in Asia, with the lethality of approximately 10% [2]. Two years later, it was reported the appearance of another Coronavirus strain in the Netherlands, called HCoV-NL63 human. Later in 2012, another respiratory coronavirus illness had an outbreak near the Arabian Peninsula. It was identified as the Middle East respiratory syndrome (MERS-CoV), which was transmitted by camels, mainly in the Mediterranean [3].

On March 11, 2020, The World Health Organization (WHO) recognized a new coronavirus pandemic, called COVID-19. According to the WHO, for a pandemic occur, three prerequisites are needed: the appearance of a new virus in worldwide proportion, for which the human population has low or no immunity; the virus can replicate in humans and cause serious illness, and finally the virus must be easily transmitted between humans [4].

Pandemics are not a randomized event and their factors are diverse. Since the 20th century, we have had several "INFLUENZA type" pandemics. The first was H1N1 in 1911 - known as the Spanish flu - which

killed 25% of the world population at the time. The second was H2N2 flu in February 1957 - Asian flu. Later on, H3N3 appeared in Hong Kong, China, in 1968. In 2003, also in Hong Kong, H5N1, called bird flu, was identified, leading to what we know as Severe Acute Respiratory Syndrome (SARS). The 2009 flu, which started in Mexico, was called influenza A (H1N1). Finally, last year, COVID-19, started in the markets of Wuhan, China transmitted by SARS-CoV-2 [5].

This paper aims to perform a scope review of the published studies, up to the moment, about SARS-CoV-2, to aid and to instruct health care providers in their new health professional reality about the disease etiopathogenesis, transmission, pathophysiology, signs and symptoms, and its imaging aspects.

Literature Review

SARS-CoV-2 Definition

The sequence of the SARS-CoV-2 virus was shown to be identical to SARS-CoV-1 by 79.6% [6]. The SARS-CoV virus present in bats is 99% similar to the human virus, hence the hypothesis that humans were contaminated by strains that were genetically modified, due to the consumption of infected animals from the region of Guangdong, China [7].

The virus measures about 50-200 nanometers in diameter and, like other coronaviruses, SARS-CoV-2 has four known structural proteins: S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins [8]. Protein N contains the RNA genome and together with proteins M, E and S create the viral envelope. Protein S is the protein that allows the virus to bind to the cell membrane of a host cell, due to its affinity with the enzyme receptors (ACE2) [9]. For the penetration of SARS-CoV-2, initial priming of protein S, TMPRSS2 (Immunoexpression - transmembrane protease) is essential [10].

SARS-CoV-2 Infection

On January 22, 2020, a group of Chinese scientists and a North American group independently managed to demonstrate that the ACE2 enzyme could be the SARS-CoV-2 receptor. The virus binds to the host cell, fusing its lipid membrane with the cell membrane, and then begins to release its RNA. The cell reads the viral RNA and starts to make proteins that inhibit the immune system and help make new copies of the virus. Each infected cell can produce and release millions of copies of the virus before dying, infecting new cells [11-15].

The enzyme ACE2 is a carboxypeptidase, and is present in several organs, including type II alveolar cells in the lungs, in the heart, gastrointestinal organs, in the kidneys, salivary glands, among others [16-18]. It has been also reported to be abundantly expressed in epithelial cells of the oral mucosa, with greater expression on the tongue, compared to other oral and gingival tissues [19,20].

The positivity rate of COVID-19 in patients' saliva can reach 91.7%, according to To *et al.* 2020 [18], this suggests that COVID-19 can be transmitted through infected saliva [21]. When analyzing the epithelium of smaller salivary gland cells, a high expression of ACE2 was observed. It was higher than that of the lungs (pulmonary mean PTM [transcripts per kilobase of exonmodel per million mapped readings] = 1,010, lower

salivary gland means PTM = 2,013), which suggests that salivary glands may be a potential target for COVID-19. In addition, SARS-CoV RNA can be detected in saliva before lung lesions and other symptoms appear [17,20]. The analysis of the expression of ACE2, in human organs, was carried out on the GTEx portal [21].

Gastrointestinal organs can also be affected since ACE2 is expressed in abundance in glandular cells of the gastric, duodenal and rectal epithelium and in endothelial cells and enterocytes of the small intestine [22]. The virus can also infect heart cells, which are abundant in ACE2, causing heart disease. Respiratory symptoms and prognosis are more severe in patients with cardiovascular disease, which may be associated with greater secretion of ACE2 in these patients compared to healthy people. The density of ACE2 in each tissue may be related to the severity of the disease in that tissue [23].

SARS-CoV-2 also can affect other organs enzymes. The Furin enzyme was detected by immunostaining in the epithelium of the human tongue. It has been implicated in virus infection, viral cleavage of glycoproteins from the envelope and increased infection with host cells. Furin is also highly expressed in lung tissue, possibly providing an increase in infectivity [13,24]. Another enzyme increased in SARS-CoV-2 infection was Troponin. The increase in Troponin can cause an increase in adverse cardiovascular outcomes. Elevation of the enzyme has been demonstrated in patients with heart failure (HF), renal failure, gastrointestinal bleeding, sepsis, respiratory diseases, pulmonary embolism, subarachnoid hemorrhage, stroke and now due to this viral infection. There are three possible causes for this troponin increase: by reflecting a hypercoagulable state, causing microvascular thrombi. It is also possible that elevated Troponin levels are due to coronary microvascular ischemia, mediated by the SARS-CoV-2 binding of the ECA-2 endothelial receptor. Another possibility is due to direct myocarditis through cardio-viral infection [9,25].

SARS-CoV-2 Risk Patients

ACE2 may be increased in patients using angiotensin-converting enzyme inhibitors (ACEI) and type I receptor blockers (BRA). There are 02 types of antihypertensive drugs that inhibit the action of the angiotensin-converting enzyme, ACEI, and those that block the angiotensin II receptor (ARA II). The ACEIs have the suffix "pril" in their name, and the ARA II have "SARTAN" suffix. For example, enalapril, lisinopril, ramipril and candesartan, losartan, valdesartan. These drugs act at the vascular and renal levels, interrupting or inhibiting the signal system, which exists between some molecules that circulate in the blood. They are what generate, the so-called, renin-angiotensin-aldosterone system, which favors the absorption of sodium, water, and increased blood pressure [12].

The ACE2 enzyme is present in the heart muscle and is involved in neutralizing the effects of angiotensin II. Its levels are high in hypertension, congestive heart failure, atherosclerosis, coronary artery disease due to the activation of the angiotensin system. Inhibitors of the renin-angiotensin-aldosterone system can also increase ACE2 levels, so any antihypertensive agent, including BRA, ACEI would possibly worsen the outcome in patients with COVID -19 [26-28].

Theories exist about the difference in severity of Covid-19 cases between children and adults. One of them says about the amount of viral loads, children may have less viral loads, due to the possibility of difference in

expression of ACE2 between adults (+) and children (-). Another theory would have to do with aging. Continuous antigen stimulation and thymic involution lead to a change in the distribution of the subset of T cells from naive T cells to central memory T cells, effector T cells, and memory effector T cells. The third theory is that the simultaneous presence of other viruses in the mucous membranes of the lungs and airways, common in young children, may allow the SARS-CoV-2 virus to compete with other microorganisms, making it difficult for SARS-CoV-2 to multiply. These lines of research are important for the treatment solutions [14].

COVID-19 Pathophysiology

The presentation of the antigen subsequently stimulates the body's humoral system and cellular immunity, mediated by specific viruses, B and T cells. Similar to common acute viral infections, the antibody production. The profile against the SARS-CoV virus has a typical pattern of IgM and IgG production. The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody may last for a long time, which indicates that the IgG antibody may mainly play a protective role [29], and the SARS-specific IgG antibodies are mainly specific for S (protein spike) and specific for N (nucleocapsid)antibodies [30].

SARS is caused by a cytokine storm, uncontrolled systemic inflammation, resulting from the release of large amounts of pro-inflammatory cytokines and chemokines by immune effector cells in SARS-CoV-2 infection. This cytokine storm will trigger a violent attack by immune system to the body, causing multiple organ failure [22].

The injury that SARS-CoV causes in hemoglobin is consistent with that of the malaria plasmodium (iron removal). Free iron is deposited in the lungs and causes "frosted glass" stains [31].

Another characteristic that has been noticed is the coagulation dysfunction (increased D-dimer), and therefore, prophylaxis for deep venous thrombosis may be recommended. Covid-19 patients have presented cyanosis of the extremities, mainly in the toes; when they begin to worsen their clinical condition. Doses of anticoagulant drugs are often used in these cases [32].

In pulmonary area, desaturation occurs because hemoglobin is unable to carry O2. Orotracheal intubation with mechanical ventilation is not effective because the lungs are functioning. Another characteristic of Covid-19 is that the lung injury is more bilateral, being a differential sign for pneumonia that occurs more unilaterally [33].

The Broncho alveolar hemostatic system is used to stop the invasion of the pathogen, forming thrombi in the bloodstream. Pulmonary micro thrombi occur when multiple efforts (including platelets) fail to stop the infection. When the NADIR (cell counting period, widely used in chemotherapy) of platelets increases, there is a significant improvement in the individual's condition. Lung injuries are a secondary effect of the release of iron ions with high oxidative power (+3) [34,35].

SARS-CoV-2 Signs and Symptoms

The most frequently symptoms referred by the patients are: fever, cough, dyspnea, myalgia, fatigue, anosmia, and dysgeusia. They also can present anorexia, sputum, conjunctivitis, sore throat, mental confusion, dizziness, headache, rhinorrhea, chest pain, diarrhea, nausea, vomiting, and hemostasis disorders [36].

SARS-CoV-2 has been revealing certain neuro-tropic and mucus-tropic abilities, which can potentially affect the functioning of the salivary glands, taste / olfactory sensations and integrity of the oral mucosa, interfering in the dynamic oral environment also influencing the balance of the microbiota [17]. Loss of taste (dysgeusia), a well-described symptom, may be due to dysfunction of the enzymes ACE2 and Furin in the tongue, and expression of the salivary gland ACE2 [12]. There are demographic and clinical similarities in patients with COVID-19 reported in a compilation of 43 studies involving 3600 patients. Acute viral infections of the upper respiratory tract that damage the nasal epithelium are the main cause of chronic olfactory dysfunction and it is known that numerous viruses can enter the brain through cellular and peri-cellular transport via the epithelium [34].

Although the exact pathophysiology of anosmia (loss of smell) is not clear, the lesion could probably happen at the level of the neuro epithelium of the olfactory receptor cells in the nasal roof. However, due to the accessibility of the olfactory cleft, many studies have focused on neuro-epithelial changes in patients with post-viral olfactory dysfunction. Several animal studies have explained that different viruses can damage central olfactory pathways and other regions of the brain [37,38].

More recent studies have shown erythematous rash, hives, chickenpox vesicles, with a predilection for the trunk and / or rash with petechiae similar to dengue. There are also reports of acro-ischemia due to the existence of hypercoagulation associated with COVID-19 [25,39].

Oral manifestations were described in a few works by Spanish groups, showing, "ENANTEMA BUCAL" (eruptions on the oral mucosa), mainly in the palate region formed by petechiae; related to viral infection, which acts on the blood system, causing thrombocytopenia [40,41]. Although some case reports showed a potential association between COVID-19 and oral manifestations, the evidences are not strong enough to assure the relationship between both. More studies still need be conducted to clarify the occurrence of these lesions.

SARS-CoV-2 Incubation and Transmissibility

The abbreviation, R0, represents the average number of people likely to be infected by a person transmitting the disease. There are two main forces determining R0: the number of contacts that the infected person has while transmitting the virus, and the speed of spread (the percentage of a given contact's chances of acquiring the disease) [25]. Using a sample of 8866, Yang *et al.* [42] calculated a SARS-CoV-2 R0 of up to 3.77 (95% confidence interval 3.51-4.05). This study demonstrated that the longer the infection period, the greater and longer the reported rate [42].

In a study of 181 confirmed cases of Covid-19, it was shown that the average incubation period was estimated at 5.1 days and 97.5% of those who developed symptoms will do so in approximately 11.5 days of infection. These estimates imply that, under conservative conditions, 101 out of 10,000 cases will develop symptoms after 14 days of monitoring [39,43]. SARS-CoV-2 can remain infectious when inanimate on surfaces for up to 9 days. Surface disinfection with sodium at 0.1% hypochlorite or ethanol between 62 and 71%, rubbing for 1 minute, significantly reduces the risk of transmission on the surfaces. We can expect a similar effect against SARS-CoV-2 [44].

Aerosol droplets can be suspended for up to 3 hours in the environment and on surfaces such as plastic and stainless steel have a half-life of 6.8 hours and 5.6 hours, respectively [45]. Experimentally, aerosols produced containing SARS-CoV-2 remained infectious in tissue culture assays, with only a slight reduction in transmission over an observation period of 3 hours. Aerosols from infected people can therefore, even at considerable distances in enclosed spaces, cause contamination. The possible contribution of aerosol infections to the current pandemic suggests the advisability of using appropriate personal protective equipment [46].

SARS-CoV-2 Differential Imaging Diagnosis

Covid-19 pneumonia imaging findings are nonspecific and resemble other pulmonary infections. They are correlated with the stage of the disease, but mostly presents alveolar changes predominating, such as ground-glass opacities, focal consolidations, and mixed opacities (including reversed halo sign), usually with bilateral and multifocal involvement, peripheral distribution, and predominance in the middle, lower, and posterior lung fields [46].

The differential diagnosis includes all types of respiratory diseases. Viral infections such as influenza, parainfluenza, respiratory syncytial (RSV), adenovirus, human metapneumovirus, can present clinical conditions similar to SARS-CoV-2 infection. It is worth mentioning that the cytokine storm caused by deregulated humoral and cellular mechanisms can worsen conditions in the oropharyngeal area [47].

Clinical Implication in Dental Practice

As in the discovery of HIV (Human Immunodeficiency Virus) , changes are necessary to increase the safety of the patient and health professionals. After the discovery of AIDS (Acquired Immunodeficiency Syndrome), safety standards were changed to prevent contamination. As SARS-CoV-2, it is a virus with high infectious power, through particles suspended in the air or on surfaces, we must take precautions with appropriate personal protective equipment (PPE), according to the recommendations of the competent Entities [48].

In the absence of vaccines or medicines, disinfecting objects and washing hands are essential to stop transmission. This recommendation is strengthened, considering that people touch an average of 23 times an hour, 44% of these occurrences involving the mucous membranes of the mouth and / or nose [49-51].

Dental procedures involve a high risk of contamination by Sars-Cov-2 due to the face-to-face proximity between professional / patient and high exposure to saliva, blood and body fluids from other mucous

membranes such as conjunctival and nasal. Thus, it is essential to standardize fundamental and indispensable care in the routine of the dental office [52-55].

Ideally, elective dental procedures should be postponed and when there is a real need for care, the dental surgeon should perform a previous screening by telephone addressing the criteria of COVID-19. The dental clinic should provide the patient with 70% alcohol gel for hand hygiene and visual alerts with the necessary instructions [54].

In addition to personal protective equipment (PPE) and care that were already part of the routine of care before the pandemic, some measures should be taken into account. Care with the biosafety of the responsibility of the dental surgeon includes: avoiding the use of accessories, use an N95 or PFF2 mask, face shield, disposable lab coat that must be changed at each visit, following a protocol for removing it, in addition to surgical pijamas with exclusive use for attendance [53-55].

In the dental office, surface cleaning and disinfection with sodium at 0.1% hypochlorite or ethanol between 62 and 71% [44] must be carried out, protection with mechanical barriers (eg PVC film) in all places where physical contact with contaminated instruments will occur. and / or patient. In the pre-procedure, the patient must rinse with 0.12% chlorhexidine for 1 minute to reduce viral load in the oral cavity [52]. The production of aerosols during care should be kept to a minimum and, when possible, the dental surgeon should opt for atraumatic treatments and the sensors for radiographs should be covered twice53,55. As previously mentioned in this work, there are asymptomatic patients with COVID-19 and for this reason it is recommended that all patients receive care as if they are contaminated.

A large number of information has been published among COVID-19. According to research carried out at PUBMED, from 1981 to 1990 8,109 papers were published on HIV AIDS, while in 4 months of the Covid-19 pandemic 9178 papers were published. This shows that we are facing a storm of new information every day, proving the necessity of screening papers that have strong scientific evidence from those that are not really substantial in helping the pandemic.

Conclusion

Since the end of the 20th century, viral infections (HIV, influenza, Ebola, Zika virus) have been occurring with increasing frequency and high contagion. The disease caused by SARS-CoV-2 is not a lung disease, but a systemic condition, affecting several organs and highly infectious. Since viruses bind to host cells measured prior to infection, they must be incorporated into the health services' biosafety models.

This brings us back to the principles, that investments in continuing education and research are fundamental to human well-being. So far, in addition to discovering a drug, applied knowledge and planning are still the best treatments to offer. This condition requires the clinical professional to carefully read the scientific literature in order to be updated and to establish health care guidelines safely.

Acknowledgements

None to declare

Conflicts of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Bibliography

1. Wu, F., *et al.* (2020). A new coronavirus associated with human respiratory disease in China. *Nature, 79*(7798), 265-269.

2. Lescure, F. X., *et al.* (2020). Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis., 20*(6), 697-706.

3. Yang, K., *et al.* (2020). Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. *Lancet Oncol., 21*(7), 904-913.

4. Lu, R., *et al.* (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet, 395*(10224), 565-574.

5. Gorbalenya, A. E., *et al.* (2020). The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol., 5,* 536-544.

6. Xu, B., *et al.* (2020). Epidemiological data from the COVID-19 outbreak, real-time case information. *Sci Data, 7*(1), 106.

7. Cyranoski, D. (2020). Did pangolins spread the China coronavirus to people? *Nature.*

8. Chen, N., *et al.* (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet, 395*(10223), 507-513.

9. Wang, K., *et al.* (2020). SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *bioRxiv* (preprint).

10. Hoffman, M., *et al.* (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell, 181*(2), 271-280.e8.

11. Zhou, P., *et al.* (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*(7798), 270-273.

12. Hao X., *et al.* (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J of Oral Sci., 8.*

13. Xu, R., *et al.* (2020). Saliva: potential diagnostic value and transmission of 2019-nCoV. *Int J Oral Sci., 12*(1), 11.

14. Yuki, K., *et al.* (2019). COVID-19 pathophysiology: A review. *Clin Immunol., 20,* 108427.

15. Zhou, M., *et al.* (2020). Coronavirus disease 2019 (COVID-19): a clinical update. *Front Med., 14,* 126-135.

16. El Sahly, H. M. (2020). Genomic Characterization of the 2019 Novel Coronavirus. *The New England Journal of Medicine.*

17. Liu L., *et al.* (2016). Spatiotemporal interplay of severe acute respiratory syndrome coronavirus and respiratory mucosal cells drives viral dissemination in rhesus macaques. *Mucosal Immunol, 9*(4), 1089-1101.

18. To, K. K., *et al.* (2020). Consistent Detection of 2019 Novel Coronavirus in Saliva. *Clin Infect Dis., 71*(15), 841-843.

19. To, K. K., *et al.* (2020). Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis., 20*(5), 565-574.

20. Xu, X., *et al.* (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci Chi Life Sci., 63*(3), 457-460.

21. https://www.gtexportal.org/home/gene/ACE2 # geneExpression22/04/20

22. Xiaowei, L., *et al.* (2020). Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal., 10*(2), 102-108.

23. Liu, P., *et al.* (2019). Viral Metagenomics Revealed Sendai Virus and Coronavirus Infection of Malayan Pangolins (Manis javanica). *Virus, 11*(11), 979.

24. Gupta, A. K., *et al.* (2020). Current perspectives on Coronavirus 2019 (COVID-19) and cardiovascular disease: A white paper by the JAHA editors. *J Am Heart Assoc., 9*(12), e017013.

25. Paolino, G., *et al.* (2020). Diffuse cutaneous manifestation in a new mother with COVID-19 (SARS-Cov-2). *Int J Dermatol, 59*(7).

26. Mishra, A. K., *et al.* (2020). Cardiac drugs and outcome in COVID-19. *QJM: Int J Med., 113*(7), 523-524.

25. Paolino, G., *et al.* (2020). Diffuse cutaneous manifestation in a new mother with COVID-19 (SARS-Cov-2). *Int J Dermatol, 59*(7).

27. Hanff, T. C., *et al.* (2020). Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic Investigations. *Clin Infec Dis., 71*(15), 870-874.

28. Zheng, Y. Y., *et al.* (2020). COVID-19 and the cardiovascular system. *Nat Rev Cardiol., 17*(5), 259-260.

29. Murthy, V., *et al.* (2020). ACEing COVID-19: A Role For Angiotensin Axis Inhibition in SARS-CoV-2 infection? *Circ Res., 126*(12), 1682-1684.

30. Huang, C., *et al.* (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet, 395*(10223), 497-506.

31. Liu, X., *et al.* (2020). Hematological findings in coronavirus disease 2019: indications of progression of disease. *Ann Hematol., 99*(7), 1421-1428.

32. Nicola, M., *et al.* (2020). Evidence Based Management Guideline for the COVID-19 Pandemic - Review article. *Int J Surg., 77,* 206-216.

33. Thachil, J. (2020). What do monitoring platelet counts in COVID-19 teach us? *J Thromb Haemost., 18*(8), 2071-2072.

34. Seiden, A. M., *et al.* (2004). Postviral olfactory loss. *Otolaryngol Clin North Am., 37*(6), 1159-1166.

35. Wu, C., *et al.* (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B., 10*(5), 766-788.

36. Meselson, M., *et al.* (2020). Droplets and Aerosols in the Transmission of SARS-CoV-2. *N Engl J Med., 382*(21), 2063.

37. Doty, R. L. (2008). The olfactory vector hypothesis of neurodegenerative disease: is it viable? *Ann Neurol., 63*(1), 7-15.

38. Mao, L., *et al.* (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol., 77*(6), 1-9.

39. Ehsani, A. H., *et al.* (2020). Pityriasis rosea as a cutaneous manifestation of COVID-19 infection. *J Eur Acad Dermatol Venereol., 34*(9), e436-e437.

40. Casas, C. G., *et al.* (2020). Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol., 183*(1), 71-77.

41. Carreras-Presas, C. M., *et al.* (2020). Oral vesiculobullous lesions associated with SARS-CoV-2 infection. *Oral Dis.,* 2020.

42. Yang, Y., *et al.* (2020). Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. *J med Rxiv.*

43. Lauer, S. A., *et al.* (2020). The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med.,* M20-0504.

44. Kampf, G., *et al.* (2020). Persistence of coronaviruses on inanimate surfaces andtheir inactivation with biocidal agentes. *J Hosp Infect., 104*(3), 246-251.

45. Doremalen, N. V., *et al.* (2020). Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med., 382*(16), 1564-1567.

46. Mehta, P., *et al.* (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet, 395*(10229), 1033-1034.

47. Araujo-Filho, J. A. B., *et al.* (2020). COVID-19 pneumonia: what is the role of imaging in diagnosis? *J. bras. Pneumol., 46*(2).

48. Guidance for Dental Settings.

49. Gould, D. J., *et al.* (2017). Interventions to improve hand hygiene compliance in patient care. *Cochrane Database of Syst Rev.,* (9), CD005186.

50. Kwok, Y. L. A., *et al.* (2015). Face touching: a frequent habit that has implications for hand hygiene. *Am J Infect Control., 43*(2), 112-114.

51. MacIntyre, C. R., *et al.* (2015). Facemasks for the prevention of infection in healthcare and community settings. *BMJ., 350,* h694.

52. Yoon, J. G., *et al.* (2020). Clinical Significance of a High SARS-CoV-2 Viral Load in the Saliva. *J Korean Med Sci., 35*(20), e195.

53. Fini, M. B. (2020). What Dentists Need to Know about COVID-19. *Oral Oncol.,* 105.

54. Ge, Z.Y., *et al.* (2020). Possible aerosol transmission of COVID-19 and special precautions in dentistry. *J. Zhejiang Univ.-Sci. B., 21*(5), 361-368.

55. Peng, X., *et al.* (2020). Transmission routes of 2019-nCoV and controls in dental practice. *Int J Oral Sci., 12*(1), 9.