

# Immunocompromised patients and coronavirus disease 2019: a review and recommendations for dental health care

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**Abstract:** In less than four months, an unprecedented pandemic changed the world scenario, closing institutions and commerce, paralyzing sports championships, blocking frontiers, and putting almost all populations in a house quarantine regimen. Immunocompromised patients are within the high-risk group to severe outcomes from COVID-19. However, there is no clear evidence of the association between impaired immune host status and complications from SARS-CoV-2 infection so far. The virus is transmitted by inhalation or direct contact with infected secretions, and therefore the dental office is a highly susceptible environment for such transmission. Here, we review the literature and discuss immunological COVID-19 related issues. We also make suggestions for immunocompromised patients' support in this new emerging context of clinical dental practice. Until comprehensive findings are published, individuals with impaired immunity should be considered as high-risk. Cross infection control procedures for the clinical care of immunocompromised patients should follow the same guidelines that are being proposed for immunocompetent ones. However, during the active outbreak, people under immunosuppressive conditions should not receive elective procedures, even if they do not have symptoms or exposure history to COVID-19, and in case of emergence, care must be done in a separate airborne room. In the pos-pandemic phase, the dental care general recommendations should be the same for all subjects. Changes in the current guidelines have been proposed to SARS-CoV-2 infection control in order to provide the best and safe dental practice. However, they still need to be validated by future studies.

**Keywords:** Coronavirus Infections; COVID-19; Immunosuppression; Dental Care; Dentistry.

## Introduction

On 12 December 2019, a patient was hospitalized with severe pneumonia of unknown etiology, in Wuhan, Hubei province, China. Clusters of similar cases were spreading within the province, and, in early January 2020, the unidentified pneumonia was discovered to be caused by a novel viral subtype of the *Coronaviridae* family, designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1,2,3</sup> By the end of January 2020, WHO



declared SARS-CoV-2 infection as a Public Health Emergency of International Concern and a few days after, officially named the disease as “coronavirus disease 2019” (COVID-19). The pandemic state was declared on the 12<sup>th</sup> of March 2020, and, since then, the outbreak exponentially advanced worldwide.

Although mild respiratory tract infection characterizes most COVID-19 cases with cold symptoms, it is a serious global situation.<sup>4</sup> Severe outcomes usually occur in older male patients with secondary comorbidities.<sup>5</sup> Hypertension, chronic respiratory system diseases, diabetes and cardiopathies were highlighted as potential risk factors to severe outcomes from COVID-19.<sup>5</sup> These findings are supported by the current epidemiological evidence that recently added obesity into the high-risk group.<sup>6</sup> Serum analysis showed higher plasma levels of pro-inflammatory cytokines in severely ill patients.<sup>7</sup> Since chronic diseases may lead to low immune function, a strong correlation between the host immune status and COVID-19 prognosis is highlighted.<sup>7</sup> Therefore, immunosuppressed patients were added within higher risk group for severe illness from COVID-19.

The current pandemic is a unique and unprecedented situation that represents the biggest public health challenge on the 21<sup>st</sup> century. Several guidelines have been proposed for safe dental health care practice and pandemic spread control.<sup>8,9,10</sup> However, there are no specific measures directed to immunocompromised patient management. These patients are frequently affected by a wide range of oral diseases requiring prompt care, which in turn, increases their increased exposition to high-risk environments. Therefore, we aimed to review the literature and to discuss immunological COVID-19 related issues. We also make suggestions for immunocompromised patients’ support in this new emergent context of clinical dental practice.

## Discussion

### Coronaviruses, virology and SARS-CoV-2 pathophysiology

Coronaviruses (CoVs) are a family of enveloped, nonsegmented positive-sense single-strand RNA viruses that have an expansive coding capacity

and are divided into four subfamilies:  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ -CoVs.<sup>11</sup> Until the 50s, these species were identified in vertebrate animals only.<sup>11</sup> Human infections are caused by  $\alpha$  and  $\beta$  CoVs and emerged as cases of the common cold in the mid-1960s.<sup>12</sup> The COVID-19 pandemic is the third CoVs outbreak since the turn of the millennium.<sup>11</sup> Severe acute respiratory syndrome coronavirus (SARS-CoV) was the etiological agent of the first epidemic that started in November 2002 in China and ended in July 2003, accounting for 8,422 confirmed cases and 774 deaths in 26 countries.<sup>13</sup> The second one emerged in June 2012 in Saudi Arabia and was caused by a novel CoV subtype named as Middle East respiratory syndrome coronavirus (MERS-CoV).<sup>14</sup> The MERS-CoV epidemic remains ongoing, and until December 2019 2,499 cases and 858 deaths were reported in 27 countries.<sup>11</sup> The current pandemic has started in China, however, the European and American continents are the most severely affected.

Just like SARS and MERS, SARS-CoV-2 is a member of the  $\beta$ -CoV family.<sup>3</sup> This pathogen was included within *SARSr-CoV* species because it shares 87% of genomic sequences and 94% of similarities among conserved protein domains with SARS-CoV.<sup>2</sup> The SARS-CoV-2 also shares 96% of overall genome sequence identity with the BaTCoV RaTG13, a bat coronavirus.<sup>2</sup> Phylogenetic analysis showed that RaTG13 is the closest relative of SARS-CoV-2 and they form a distinct lineage from others SARS-CoVs, which supports the evidence that COVID-19 emerged from bats.<sup>1,2</sup>

SARS-CoV-2 has the same physical structure as other CoVs. Its genomic RNA and phosphorylated nucleocapsid protein (N) are buried inside a phospholipid bilayer covered by three types of proteins: spike glycoprotein trimmer (S), membrane protein (M) and envelope protein (E).<sup>15</sup> The S proteins are responsible for the attachment of CoVs to host cells, playing a crucial role in its virulence.<sup>2</sup> SARS-CoV-2 S proteins are longer and molecularly divergent to all previously described CoVs, and it exhibits several molecular alterations in the N-terminal domain and the receptor-binding motif compared with the sequence of SARS-CoV.<sup>2</sup>

Human angiotensin-converting enzyme 2 (ACE2) is a type I membrane protein that provides a direct

binding site for the S proteins, being essential for viruses to enter cells.<sup>2</sup> SARS-CoV-2 binds to ACE2 with approximately 10 to 20-fold higher affinity than SARS-CoV, which may explain the easier human to human transmission when compared to SARS-CoV.<sup>16</sup> During the invasion of the cells, the S protein is cleaved into two subunits (S1 and S2). The receptor-binding domain (RBD) is on S1 subunit and directly binds to ACE2, while S2 subunit is cut by transmembrane proteases and merges with the cell membrane, releasing the viral genome into the cytosol.<sup>17</sup> A dimeric ACE2 can accommodate two S protein trimmers, simultaneously, which may facilitate the invagination of the cell membrane and endocytosis of the viral particle.<sup>17</sup>

Because of the increased expression of ACE2, some organs such as the salivary glands, lung, heart, esophagus, kidney, bladder, and ileum have a higher potential risk of SARS-CoV-2 infection.<sup>18</sup> The severe lung alveolar damage of some cases is linked to the accentuated ACE2 expression by type II alveolar cells (AT2), which also express many other genes favoring the viral infection.<sup>19</sup> The ACE2 expression was also detected in male reproductive cells and the nervous system,<sup>20,21</sup> which explain some neurological manifestations presented by COVID-19 patients.<sup>21</sup> Therefore, testis and brain were added within the group of SARS-CoV-2 infection vulnerable organs.

Inflammation is the hallmark of SARS-CoV-2 infection. Severely ill patients had higher plasma levels of IL-2R, IL-6, IL-10, IL-17 and TNF- $\alpha$  than less severe patients.<sup>7,22</sup> Even asymptomatic individuals showed classic findings related to the inflammatory response of the lung cells on chest CT images.<sup>7,23</sup> The causes of the exuberant inflammation is unknown so far, and different possible mechanisms were postulated based on the previous knowledge about SARS-CoV infection.<sup>24</sup>

After contagion via respiratory droplets, direct contact and/or fecal-oral route, the viruses enter human cells mainly through the ACE2-binding described above, infecting epithelial, endothelial and immune system cells.<sup>24</sup> Fu and colleagues,<sup>24</sup> proposed a separation of the possible inflammatory responses during SARS-CoV-2 infection into primary and secondary responses. In the primary inflammatory response, the active viral replication may drive ACE2

downregulation and shedding, and activates host viral response with increased cytokine production, apoptosis and/or pyroptosis,<sup>24</sup> which is a form of programmed cell death due inflammation that was previously associated with SARS-CoV infection.<sup>25</sup> The secondary inflammatory response is characterized by the appearance of neutralizing antibodies (NAb) that can trigger the monocytic/macrophagic response through FcR binding, leading to severe lung injury. The antibody-dependent enhancement (ADE) mechanism, a viral cellular uptake of virus-antibody complexes, may also occur in this phase, mainly in immunocompromised patients.<sup>24</sup> These patients have an early suboptimal antibody activity and cannot completely clear the virus, leading to persistent viral replication, inflammation, and increased fatality risk.<sup>24</sup> However, the role of the immunological suppressed status on COVID-19 severity remains controversial so far.

### COVID-19 and immunocompromised patients

As discussed above, the biological response to SARS-CoV-2 infection requires the activation of the innate and acquired immunity.<sup>15</sup> In a postmortem study, the overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8+T cells, were related with the severe lung immune injury.<sup>26</sup> Lymphopenia is a common finding in COVID-19 affected patients, extensively associated with severe complications and death,<sup>7</sup> and could be caused by lung sequestration of hyperactivated T cells.<sup>27</sup> Since overactivated immune responses may be the main driver for organ damage, the anti-inflammatory effects of immunosuppression may be protective, mitigating the “cytokine storm” related to COVID-19 poor outcomes.<sup>27</sup>

Some studies have reported an overall asymptomatic or mild COVID-19 course in immunocompromised patients, such as children under anticancer therapy,<sup>28</sup> immunosuppressive chronic drugs users,<sup>29</sup> transplant recipients,<sup>30</sup> and poorly controlled HIV or AIDS patients.<sup>31</sup> In these reports, the few severely affected individuals recovered and low fatality rates were registered. Also, immunosuppression was not found to be a risk factor either for SARS nor MERS.<sup>32</sup>

On the other hand, in a case-control study, immunocompromised children were predisposed to infection of the lower respiratory tract from SARS-CoV<sup>33</sup> and a nationwide analysis showed that infected patients with cancer had poorer prognosis.<sup>34</sup> Recently, the chronic use of corticosteroids previous to SARS-CoV-2 contamination was associated with critical illness outcomes, including a high risk of death.<sup>7</sup> Moreover, the recovery of a liver transplant recipient severely affected by COVID-19 has been only achieved after the temporary withdrawal of immunosuppression and normalization of immunity.<sup>35</sup>

These contradictory observations show that the knowledge about the relationship between COVID-19 and host immunological status is limited. Further studies are required to elucidate the immune responses and inflammation features from SARS-CoV-2 infection.<sup>7,15</sup> According to the Centers for Disease Control and Prevention (CDC) guidelines, immunocompromised patients remain under the high-risk group for severe illness progression. These individuals should be carefully followed-up until large case-control cohorts, which provide more solid results, are published.

### **Changes and challenges in dental practice: general recommendations for immunocompromised patient management and dental health care team safety**

Almost all dental care procedures generate aerosols, which represent the most important clinical concern within the pandemic situation. The viral aerosol spreading was confirmed by SARS-CoV-2 detection in air samples up to four meters away from general COVID-19 wards,<sup>36</sup> and the virus can survive on surfaces exposed to infected saliva droplets for at least nine days.<sup>8,9</sup> On optimal experimental conditions, SARS-CoV-2 also showed great viability on stainless steel and plastic,<sup>37</sup> the major constituents of the dental instruments and equipment. Additionally, oral cavity tissues express ACE2, especially salivary glands<sup>38</sup> and epithelial cells of the tongue.<sup>39</sup> Hence, beyond being a source of infected aerosol spread, oral mucosa is highly susceptible to SARS-CoV-2 infection. These facts place dental practitioners and patients in one of the most vulnerable positions in COVID-19 context.<sup>9</sup>

The immunocompromised status is directly linked to a wide range of oral pathologic conditions. Transplant receivers are at high risk of having oral bacterial, fungal and viral infections, oral mucosa lesions, as well as neoplastic diseases.<sup>40</sup> Oral candidoses has already been associated with a poorly controlled immunological status of HIV-infected individuals<sup>41</sup> and patients under anticancer therapy.<sup>42</sup> Those under head and neck cancer radiotherapy are broadly susceptible to severe oral health issues, including mucositis, dental radiation cavities, among others.<sup>42</sup>

There are two main concerns regarding patients that suffer from autoimmune and inflammatory conditions such as inflammatory bowel diseases, autoimmune bullous diseases, lupus erythematosus, Sjögren syndrome and Behcet disease. First, the long-term immunomodulating approaches employed on the treatment of these diseases may inhibit antiviral immunity and predispose to worse course of COVID-19.<sup>43</sup> Additionally, a potential exacerbation of the autoimmune-related oral lesions may occur if the patients are advised to discontinue such therapy during the pandemic.<sup>44</sup>

Several guidelines have been proposed to SARS-CoV-2 infection control to provide safe dental practice.<sup>8,9,10,45</sup> To date, during the pandemic outbreak, an initial tele screening has to be made to assess the presence of COVID-19 symptoms and evaluate the previous exposure to risky situations such as recent travel and human-to-human contact history.<sup>45</sup>

During the outbreak, elective procedures should be avoided for at least two weeks if the individual has symptoms or known exposure history and should not be performed for SARS-CoV-2 positive subjects.<sup>45</sup> Urgent care such as acute pain relieve or mild swelling must be treated remotely with medicine prescription and close follow-up by telephone or video conference.<sup>45</sup> Emergency care, such as swellings compromising the airways, should be performed in a negative pressure or airborne isolation rooms, following the above-mentioned infection control procedures.<sup>45</sup> Radiographic evaluations on dental emergencies could be done through sectional dental panoramic radiography or intraoral radiography with adequate personal protective equipment (PPE) use by dentists and radiography staff.<sup>46</sup> Elective and urgent procedures should be avoided in immunocompromised

patients, even if they are asymptomatic. In the case of emergency, care must be done in an airborne isolated room, following the recommendations for clinical procedures described below.

For immunocompetent patients with no symptoms or exposure history, the dental treatment can be performed under specific conditions.<sup>45</sup> An extensive hand hygiene protocol employing 60% to 85% hydroalcoholic solution, use of all PPE, and, if possible, the 4-handle technique should be used.<sup>9,10</sup> The equipment should be covered with disposable physical barriers and anti-refraction valves installed on handpieces.<sup>9,10</sup> Aerosol generating can be mitigated avoiding the use of ultrasound, bicarbonate jet, 3-way syringe, and with the use of rubber dams and high-volume saliva ejectors.<sup>8</sup> Preprocedural mount rinses with 1% hydrogen peroxide or 0.2% povidone are indicated to reduce potential SARS-CoV-2 carriage.<sup>9</sup> The clinical environment should be disinfected before and after dental care, with 70% isopropyl alcohol or 0.1% sodium hypochlorite.<sup>10</sup> The garbage must be discharged into double-layer yellow color medical waste package bags with “gooseneck” ligation.<sup>9</sup>

It is worth noting that the current guidelines are useful along with the acute phase of pandemic, and some changes are needed for daily dental practice after the control of the situation. The same guidelines for immunocompetent subjects are recommended for immunocompromised patients after the pandemic phase. The previous assessment of COVID-19 risk and the measurement of body temperature using a contact-free thermometer should still be performed. Suspected patients should be cared for in an isolated room, or the definition of a particular scheduling day must be adopted. Elective care should not be performed in SARS-CoV-2 positive individuals. These patients should be managed following the acute pandemic phase guidelines.<sup>45,46</sup>

Patients with no symptoms or known exposure history could be taken care on collective clinical

places. However, since asymptomatic or mild course characterizes most of COVID-19 cases, some cautions must be taken. Dental and waiting room chairs should be distributed in at least four and one meter of distance each, respectively. The consultations flow must be reduced, and thirty minutes after the end of care should be designated for the disinfection of the room. 70% ethanol, masks, and disposable shoe covers must be available for the auxiliary staff and patients. The protective measures regarding dental procedures must still be followed.<sup>8,9,10,45,46</sup>

## Conclusion

Elderly, males, hypertensive, patients with diabetes, and individuals with chronic respiratory and cardiovascular diseases, constitute the most well-characterized high-risk group for severe manifestations from COVID-19. To date, the disease outcomes regarding the immunosuppressed patients are unclear. The assessment of symptoms and laboratory findings in a greater sample size of immunologically impaired individuals will help to elucidate the mechanisms by which SARS-CoV-2 induces exacerbated inflammatory responses. These studies will help define the real risk of complications and death under immunosuppressive conditions.

The efforts made worldwide to minimize the risk of COVID-19 spreading during dental care procedures provided clear and usable guides for best dental practices.<sup>8-10,45,46</sup> However, the effectiveness of the acute phase and post-pandemic infection control measures should be verified on prospective epidemiological and comparative multicenter studies. Here, we discussed the COVID-19 outcomes in individuals with an immunocompromised health state, and elective procedures, after the end of the pandemic, should follow specific cross-infection control recommendations.

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