

# The impact of coronavirus infectious disease 19 (COVID-19) on oral health

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## Abstract

Health services across the world face an unprecedented situation as a result of a global COVID-19 outbreak. Urgent joined research efforts regarding the SARS-CoV-2 rapid tests, accurate diagnosis, especially early recognition, and effective treatment of life-threatening complications would be highly desirable for humanity and medical workforce all over the world that try to combat a current global pandemic threat. Due to indirect complex effect, intensified COVID-19 therapies and multi-drug treatment, it is believed that some oral conditions could be aggravated by COVID-19 disease, particularly those with autoimmune aetiology, linked to compromised immune system or long-term pharmacotherapy.

## KEYWORDS

COVID-19, immunopathology, oral health, oral medicine, SARS-CoV-2 coronavirus, therapy

## 1 | ANTI-IMMUNE GIFTED CORONAVIRUS?

Recently emerged human-to-human transmission of COVID-19, a novel lethal strain (Chan et al., 2020) of coronavirus, caused a global pandemic burden, affecting hundreds of thousands of individuals, having life-threatening outcomes, not only in medically compromised persons but also in perfectly healthy young individuals with immunocompetent system. Apparently, this specific coronavirus must possess special abilities to spread and compromise the immune mechanisms in humans. Unfortunately, there are limited evidence-based data available, as, which is understandable clinicians and scientists must focus on life-saving aspects (Prompetchara, Ketloy, & Palaga, 2020). At the same time, the question arises, whether this strain possesses unique abilities to penetrate via oropharyngeal epithelial barriers and, which is even more intriguing, why infection of SARS-CoV-2 triggers such abnormal “cytokine storm” and immune dysregulation? For unknown reasons, SARS-CoV-2 does not seem to be effectively defeated by human first-line protective mechanisms, neither biomolecular nor cellular, as number of death cases in middle aged, healthy persons were reported,

regardless their immune status (Mehta et al., 2020). Penetrability through natural barriers, shielding from first-line defence mechanisms, and other undiscovered modes, biological and cellular actions made the virus resilient to standard defences which appear not to respond efficiently to inflammatory invasion and cytokine storm (Guo et al., 2020; Shi et al., 2020). Undoubtedly, this coronavirus strain, recently named as “hit and run” virus, alters the immune system, causing distinct changes in response reactions that can turn against the host, leading to autoimmune damage, particularly of connective tissue of lungs.

Although it not confirmed, hypothetically, there might be a link between the epithelial expression/localization of ACE2 protein in oral and nasal mucosa, nasopharynx as ACE2 protein found to be the functional receptor for SARS coronavirus (Hamming et al., 2004). Lymphocytopenia, overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells were reported in COVID-19 cases (Xu et al., 2020). For unexplained reason these features reduce the likelihood of effective humoral/cellular immune response and expose perfectly healthy individuals and make them prone to extremely serious complications, primarily associated with lower respiratory tract.

There is conflicting information regarding the efficacy of different groups anti-inflammatory medications for treatment of symptomatic COVID-19 cases. Amid all this confusion, corticosteroids therapy, which is usually effective to modulate immune reaction for a vast majority of severe inflammatory conditions, with associated “cytokines cascade/storm,” seems to be inefficient in COVID-19 positive cases, or even contraindicated (Mehta et al., 2020). Similarly, leukotrienes modifiers, such as leukotriene receptor antagonists (montelukast, zafirlukast) and leukotriene biosynthesis inhibitors do not appear to be applicable in the treatment of COVID-19 cases, despite of the fact that they reverse the early effects of inflammatory response. On the contrary, other groups of powerful may have a positive impact on treatment outcomes in case of COVID-19. For instance, interestingly, leukotriene B4 (LTB4), which activates neutrophils induces defence actions, has the potential to efficiently kill human coronavirus, respiratory syncytial virus, and influenza B virus (Widegren et al., 2011). Nevertheless, another group of novel anti-inflammatories, so-called numb-associated kinase family, including adaptor-associated protein kinase 1 (AAK1), such as baricitinib and ruxolitinib, were also identified and approved that could inhibit SARS-CoV-2 viral infection of cells via clathrin-mediated endocytosis (Stebbing et al., 2020). Enzyme AAK1 plays an important role in regulating the process of endocytosis, a way how viruses enter human host cells via intercellular compartment.

Due to indirect complex effect, intensified therapeutic methods, multi-drug treatment, it is believed that some pathological oral conditions could be aggravated by SARS-CoV-2, particularly those with the aetiology of compromised immune/defence mechanisms, or linked to long-term pharmacotherapies. Therefore, strategies to boost immune responses (via various routes) at this stage or pandemic are essential. It seems to reasonable to predict that we should expect increase of cases with oropharyngeal symptoms/conditions, and it is certain that more reliable scientific data will appear in the nearest future, including information relevant to oral medicine/oral pathology in the light of COVID-19 infection, allowing us to understand SARS-CoV-2 pathogenesis and its impact on head and neck pathologies.

## 2 | PHARMACOTHERAPY, INTENSIVE COVID-19 HOSPITAL TREATMENT AND ORAL HEALTH

Medications used routinely and experimentally in the treatment of COVID-19 patients cause side effects, however their benefits outweigh the disadvantages. As a consequence of intense pharmacotherapy, some of patients even after full recovery from COVID-10 may suffer from dental/oral problem associated with soft tissues, saliva production, neurological-based oral sensations, etc. As specific pharmacological treatment for COVID-19 is still undefined, the World Health Organization recently commenced SOLIDARITY trial to validate various medications for potential treatment of severe COVID-19 complications. They comprise remdesivir,

chloroquine/hydroxychloroquine, combined lopinavir and ritonavir, and interferon- $\beta$  (Mahase, 2020; Sayburn, 2020). Currently, joined research efforts concentrate on developing and implementing new drugs, primarily anti-inflammatories, immune-modulatory and/or monoclonal antibodies, to control the immune response associated with some of the most severe cases of the COVID-19, rather than attacking the virus directly. Although, no therapeutics have yet been proven effective for the therapy of symptomatic SARS-CoV-2 infection.

The experimental anti-viral treatment using lopinavir and ritonavir, combinations of protease inhibitors typically employed in HIV cases, can provide a way to reduce the viral load, the severity, adverse clinical outcomes, and potentially reduce death rates in patients with SARS (Chu et al., 2004). These anti-viral drugs may be responsible for side effects (<2%) affecting oral cavity among the other parts of gastrointestinal track, such as stomatitis, mouth ulcers and dry mouth (Pubchem database, 2020). It has been reported that interferon alfa/beta, well known for their anti-viral activity, reduce the severity of COVID-19 disease, potentially improving survival rate (Mahase, 2020). It decreases symptoms of severe respiratory illness, such as COVID-19 related pneumonia and can support improvements in lung function. Interferon's more common side effects related to oral medicine are well reported and comprise dry mouth, which can result in frequent cases of oral thrush.

Meanwhile, it comes as no surprise that a broad spectrum of antibiotics, that are effective against wide strains of Gram-positive and Gram-negative bacteria, such as meropenem or moxifloxacin, used also in severely ill COVID-19 patients (Xu et al., 2020) with multiple-organ disfunctions, undoubtedly have significant effects on the subtle balance of microorganisms, leading to further health impairments (Jensen et al., 2015). At present, when facing the reality of lack of data about the relationship between SARS-CoV-2 and oral diseases, it could be easy to imagine that a vast proportion of COVID-19 symptomatic and intensely treated patients must develop some sort of oral problems and pathological. If the patient survives, especially during recovery phase, it is likely that will need an adjunct antifungal and/or antimicrobial treatment, supported by cytoprotective topical measures.

Additionally, as systemic and topical steroids are deemed not to be suitable in COVID-19 infection (Mehta et al., 2020), some of immune-related long-term oral medicine conditions (pemphigus, lichen planus, pemphigoid) may potentially exacerbate in SARS-CoV-2-positive patients who were advised to discontinue such therapy (Yuen, Ye, Fung, Chan, & Jin, 2020). On the contrary, in theory, as some patients with oral conditions and other co-existing comorbidities are already on specific anti-inflammatory medications (Sjogren's syndrome) due to eg. rheumatoid arthritis, they might benefit from these drugs, protecting them against severe COVID-19 complications. It is worth noting that chloroquine, a drug under clinical trials and investigation with the aim to be used in severe COVID-19 cases, is sometimes prescribed in active rheumatoid arthritis, as well as systemic and discoid lupus erythematosus, medical conditions that cause manifestations in oral cavity (Gao, Tian, & Yang, 2020).

Accordingly, tocilizumab (atlizumab), an immunosuppressive humanised monoclonal antibody which targets the IL-6 receptor, that so far has been mainly used in the therapy of autoimmune diseases, such as rheumatoid arthritis, cytokine release syndrome and systemic juvenile idiopathic arthritis, was recently also approved to be employed in the treatment of severe COVID-19 cases associated with lung damage as a result of high levels of IL-6 (Dong, Hu, & Gao, 2020).

As a direct result of life-saving therapies, including external ventilation and blood oxygenation, in severely ill hospitalized patients, oral health had been found to deteriorate, especially in case of those staying in intensive care units. A lack of mouth care as treatment priority is given to advanced medical care, intubation, tracheostomy, external ventilation, as well as mouth breathing, hyposalivation can lead to rapid oral health deterioration and subsequent complications, affecting also the lower respiratory track, similar to aspiration pneumonia (Wu et al., 2020). Disturbances of oral microbiota balance are a result of systemic therapies and intraoral environment alteration may lead to further problems. Hence, it would be prudent for professional associations (European Association of Oral Medicine, European Society of Anaesthesiology) to provide urgently the recommendations for persons who are or have been “aggressively” treated for COVID-19, supporting medical and dental professionals with their care provision.

Nevertheless, the overall impact of COVID-19 on oral health seems to be multi-directional, immune-related and most probably indirect, acting through various routes, reflecting the pathological nature of coronavirus respiratory track invasion via mucous membranes. The effect of complex pharmacotherapy should not be underestimated when assessing patient's oral health following intense hospitalization, and it can be even more profound as new experimental drugs recommended for COVID-19 disease will inevitably emerge in the nearest future. As reported, SARS-CoV-2 revealing its certain neurotropic and mucotropic abilities may potentially affect the functioning of salivary glands, taste/smell sensations and oral mucosa integrity, interfering with dynamic oral environment also by exerting influence on microbiota balance (Lovato, de Filippis, & Marioni, 2020; Sabino-Silva, Jardim, & Siqueira, 2020). Severe COVID-19 acute infection, along with associated therapeutic measures, could potentially contribute to negative outcomes with regard to oral health, likely leading to various opportunistic fungal infections, xerostomia linked to decreased salivary flow, ulcerations and gingivitis as a result of impaired immune system and/or susceptible oral mucosa. It is worth noting that cytokine storm caused by dysregulated humoral and cellular mechanisms can aggravate existing autoimmune conditions within the oropharyngeal area. Persons recovering from COVID-19 need additional postacute care to recuperate from primary and concomitant infection, with a recommendation of close monitoring of their oral health, particularly during transition from hospital to other care settings and homes. The reinforcement of existing oral medicine facilities should also allow to continue the provision of secondary care for patients with existing

oral diseases, regardless their COVID-19 negative/positive status, whose follow-up treatment was postponed due to emergency measures introduced.

#### AUTHOR CONTRIBUTIONS

**Arkadiusz Dzedzic:** Conceptualization, validation, writing - original draft, writing - review. **Robert Wojtyczka:** Validation, writing - review.

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**How to cite this article:** Dziedzic A, Wojtyczka R. The impact of coronavirus infectious disease 19 (COVID-19) on oral health. *Oral Dis*. 2021;27(Suppl. 3):703–706. <https://doi.org/10.1111/odi.13359>