SARS-CoV-2 and Oral Health

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in Wuhan, China, was first reported to the China Ministry of Health and the World Health Organization (WHO), on 31 December 2019. These initial cases were linked to an animal wet market. The SARS-CoV-2 and its virulent variants cause coronavirus disease 2019 (COVID-19), which is highly contagious and spreads rapidly. The WHO declared it a global emergency on 30 January 2020, and a global pandemic on 11 March 2020. The SARS-CoV-2 genome was identified to be 70–80% identical to the severe acute respiratory syndrome coronavirus (SARS-CoV) and several bat coronaviruses. The similarity between these coronaviruses suggests that the bat may be the natural host and potential reservoir for SARS-CoV-2, which may have been inadvertently transmitted to humans. SARS-CoV-2 transmits readily via droplet transmission; other modes of transmission may include aerosol and oral-fecal routes. It can also be transmitted via contact with infected surfaces and oral fluids. This puts dentists and healthcare professionals at risk of COVID-19 infections, and highlights dental and medical offices as a main risk setting for cross infection of patients and healthcare professionals. Mask, face shields, handwashing, and personal protective equipment (PPE) are currently used in dental and medical facilities for COVID-19 prevention consistent with CDC guidelines.

COVID-19 oral hygiene periodontitis bacteria SARS-CoV-2 mouthwash vaccines

1. Pathogenesis and Cellular Mechanism of Action

SARS-CoV-2 comprises a single stranded RNA with cell-surface spike glycoproteins, which facilitate adherence and penetration of host cells[1]. The main cellular receptor for the SARS-CoV-2 spike glycoprotein is the angiotensin-converting enzyme 2, found in the lungs, kidneys, myocardial cells, salivary glands, and tongue.

The clinical presentation of SARS-CoV-2 infections are often asymptomatic or have mild to moderate symptoms; 5% or less develop multi-organ failure or acute respiratory distress syndrome. An epidemiologic study reported 17% of COVID-19 patients are asymptomatic, and that asymptomatic patient transmission of COVID-19 is statistically similar to the symptomatic patient [2]. The disease can progress in 3 main stages. Stage 1 involves the activation of innate immunity. Stage 2 involves the activation of adaptive immunity. Stage 3 involves the cytokine release syndrome or the “cytokine storm” [3]. The cytokine storm is an exaggerated cytokine release by a hyper-responsive host [4][5]. It is characterized by hyper-coagulability, dysfunction of multiple organs, acute lung injury, and shock [3]. The enhanced vascular permeability facilitates effector cells infiltration, and intensifies pro-

inflammatory cytokine release. This cytokine release can induce excessive monocyte proliferation and lymphocyte apoptosis, resulting in potential immunodeficiency states [6].

Pro-inflammatory cytokines such as IFN-γ, IFN-γ-induced protein 10, IL-1, IL-6, IL-12, and monocyte chemoattractant protein were reported in earlier studies of SARS-CoV-2 infected patients [7]. Recent studies reported that elevated serum levels of IL-6 were positively associated with disease severity [8][9][10][11][12] and mortality in older patients and patients with comorbidities [13]. Dysregulation of immune functions and overproduction of early response pro-inflammatory cytokines can lead to multi-organ failure, especially of the heart and kidneys [14][15][16]. The IL-6 levels in non-survivors are higher than in SARS-CoV-2 survivors [5].

Periodontal inflammation, among other chronic inflammatory diseases and conditions, may influence COVID-19 susceptibility and pathogenesis. Three different clinical responses in the periodontium to bacterial burden may shed light on COVID clinical responses to SARS-CoV-2 virus challenges. These host inflammatory clinical responses to oral bacteria were designated as “high”, “low”, and “slow” [17]. The high clinical response group to similar bacterial concentrations resulted in high IL-1β levels in inflamed tissues. Applying this model to COVID-19 infected individuals, the varying levels of inflammatory response may be a plausible explanation for non-vaccinated individuals being at varying levels of risk for pulmonary “cytokine storms”, resulting in outcomes from hospitalizations to possible death [17].

2. Systemic Ramifications

Clinical symptoms of SARS-CoV-2 appear approximately 5.2 days following infection [18]. Symptoms reported were fever, fatigue, myalgia, diarrhea, dry cough, sore throat [19][20], and loss of taste [21]. During the initial days after SARS-CoV-2 infection, COVID patients primarily appear asymptomatic; the virus colonizes the oral, nasal, and pharyngeal mucosa, and is highly infectious [22].

Risk factors of SARS-CoV-2 were highlighted by Zhou et al. in a retrospective cohort study of COVID-19 patients [23]. Some of the risk factors cited were advanced age, male gender, hypertension, diabetes, heart disease, and obesity [23][24][25]. Complications of severe SARS-CoV-2 infection were blood clots, sepsis, septic shock, pneumonia, and acute respiratory distress syndrome (ARDS) [26]. In severely infected patients in China, 41.8% developed ARDS. Of these patients with ARDS, respiratory failure resulted in 52.4% mortality [27]. In infected patients in Italy, 96.5% of reported complications were ARDS, followed by 29.2% acute renal failure [28]. Thus, these post-viral complications, especially ARDS, were likely the cause of death rather than the initial viral infection. Most respiratory viral infections increase the patient’s vulnerability to respiratory bacterial superinfections and inflammatory lung damage [29].

Antibody response to SARS-CoV-2 viral antigen, nucleoprotein, and spike protein peaks 14–21 days after symptom onset [30]. In the oral cavity, immunoglobulin A (IgA) dominates early mucosal immune response [31]. Individuals who have who have been exposed to the SARS-CoV-2 virus appear to have high levels of neutralizing secretory antibodies.

3. Targets for SARS-CoV-2 Entry in the Oral Cavity

SARS-CoV-2 infectivity depends on its ability to penetrate the cell. SARS-CoV-2 uses the angiotensin-converting enzymes 2 (ACE2) receptor for cellular entry [32]. The ACE2 receptors were present in oral mucosa tissues including the floor of the mouth, tongue, buccal mucosa, and gingiva [33]. The oral ACE2-positive cells reside mainly in the taste organs [33]. Loss of taste has been commonly reported [21][34], with 91% of patients experiencing this before hospitalization due to COVID-19 [33].

In the early stage of COVID-19 infection, SARS-CoV-2 has been consistently detected in whole saliva [35]. ACE2-positive salivary glands are also targets for SARS-CoV-2, and may affect salivary gland function [36]. In Wuhan, 46% of COVID-19 infected patients reported a dry mouth [21]. The ACE2 receptors in the salivary glands is higher than the lungs, and is a suggested reservoir for SARS-CoV-2 in asymptomatic patients [37].

The ACE2 receptors are also present in fibroblasts in the periodontium [38], and elevated protease levels due to chronic periodontitis can increase risk for viral entry [39]. While the pulmonary system remains the primary modality for infectivity by SAR-CoV-2, it is plausible that selected components of the oral cavity may be a contributing factor.

In addition, the S protein of the SARS-CoV-2 needs to be cleaved by transmembrane protease serine 2 (TMPRSS2) or furin to enable fusion to the host cell [40][41][42]. Besides TMPRSS2, furin, or ACE2 in the oral cavity [23][43], pathogenic bacteria found in the oral cavity can also cleave the S protein of the SARS-CoV-2 [44].

4. Effects of Oral Health on COVID-19

Oral health affects overall health and well-being [45]. Since the oral cavity is one of the interfaces that connects to the exterior of the body, the ability of SARS-CoV-2 to utilize this interface for entry will determine its infectivity [33][37]. The health of the oral cavity and its structures may contribute to increased or decreased risk of COVID-19 [33][37]. A healthy oral cavity consists of a symbiotic balance of gram-positive bacteria. Poor oral hygiene and periodontitis can tip this balance towards dysbiotic biofilms that promote cytokine release. This elevated level of cytokines may have proinflammatory systemic effects, and may have a role in propagating pulmonary infections [46]. In addition, the interbacterial exchange of pathogenic bacteria from the oral cavity to the lung may contribute directly to lung infections [47]. Poor oral hygiene and the aspiration of periodontal pathogens can aggravate COVID-19 [44]. Aspirated bacteria may cause inflammation of the lower respiratory tract and exacerbate COVID-19. In patients with severe COVID-19, half were reported to die of secondary bacterial infections rather than from the virus [23]. This bacterial superinfection can supersede the original COVID-19 infection. Patients with severe COVID-19 present with higher neutrophils compared to lymphocytes. Higher neutrophil counts have been indicative of bacterial infections rather than viral infections [48].

In the medically compromised and the elderly, the increased risk of bacterial aspiration due to a poor swallowing reflex [49] may increase the severity of COVID-19 [50][51]. Periodontal bacteria are not indigenous of the lower respiratory bacterial flora, but have been isolated in patients with COVID-19 [52]. Poor oral hygiene increases

periodontal pathogens, which can raise expression of ACE2, increase pro-inflammatory cytokines, and degrade the S-protein. *F. nucleatum* can upregulate ACE2 transcription, and induce IL-8 and IL-6 production in alveolar epithelial cells [53]. The degradation of the S protein by microbial proteases may increase SARS-CoV-2 penetration and infectivity [41][42]. Moreover, the lack of proper oral care in COVID-19 patients on long-term hospitalization may increase the risk of aspirated pathogenic oral bacteria and inflammation in the lower respiratory tract. Thus, the increased prevalence of pathogenic bacteria associated with poor oral hygiene may contribute to the progression of COVID-19 via upregulation of ACE2 and proinflammatory cytokines [44].

Chronic inflammation from periodontitis may also increase the risk of more severe COVID-19 outcomes. In a survey from 2009–2014 of adults older than 30 years, 42% had periodontitis [54]. Periodontal disease and associated co-morbidities, including chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and cardiovascular and cerebrovascular disease, can worsen the COVID-19 prognosis [55]. According to the CDC, diabetes and cardiovascular disease are the most prevalent underlying comorbidities among those hospitalized due to COVID-19 [56].

COVID-19 patients with periodontal disease have a higher mortality risk than patients without periodontitis [57]. The immune cellular release of cytokines including IL-1 and TNF in periodontitis may contribute and exacerbate the recognized “cytokine storms “associated with COVID-19 infections.

Thus, oral hygiene plays a significant role; non-optimal brushing may result in increased levels of gingival inflammation and higher cytokine levels. Higher cytokine levels may increase COVID risk. It is reasonable to assume that the management and control of periodontitis-induced destructive cytokines may reduce or minimize the risk of SAR-CoV-2 infections.

5. Current Preventive Strategies in the Oral Cavity

Oral antiseptics used as pre-procedural rinses, to reduce the risk of cross-infection and the amount of bacteria in aerosols, have been shown to be effective. A meta-analysis evaluating the effectiveness of pre-procedural mouth rinses reported a reduction in the number of aerosolized microbes during dental treatment [58]. Other studies evaluated oral antiseptics indirectly by reporting on in vitro antiviral activity [59]. Oral antiseptics can reduce viral load and disease transmission, by disrupting the viral lipid envelope [59]. Selected oral antiseptics used to prevent viral cross-contamination include 1% povidone-iodine [60], 0.05–0.10% cetylpyridinium chloride [61], 0.12% chlorhexidine [62], 1% hydrogen peroxide [63], beta-cyclodextrin with citrox [64], and essential oil mouth rinses (e.g., eucalyptol, thymol, menthol, methyl salicylate) [65]. A combination of two mouth rinses, 1% hydrogen peroxide, and 0.2–0.3% chlorhexidine can also be advantageous in utilizing two active ingredients in sequence for dual mechanism of action [66]. These antiseptic rinses can decrease salivary viral load and reduce the risk of SARS-CoV-2 dissemination [67].

A recent randomized control clinical trial explored the efficacy of antimicrobial mouth rinses when rinsed for 60 s in reducing viral load in asymptomatic SAR-CoV-2 patients [68]. It is likely that pre-symptomatic and post-

asymptomatic patients form a minor but significant portion of patients seeking dental therapies. This randomized triple blinded study evaluated chlorhexidine (0.12%), povidone iodine (0.5%), and hydrogen peroxide (1%), with sterile saline as a control. The PCR viral load was measured 15- and 45-min post-rinsing. All four mouth rinses, including the saline control, decreased viral load from 61% to 89% at 15 min post-rinsing, and 70% to 97% at 45 min. SARS-CoV-2 viral copies were measured using real time reverse transcriptase quantitative PCR. Antimicrobial rinses may be a productive means to reduce salivary viral risk in a dental practice utilizing antimicrobial pre-rinsing.

The major limitation is that primarily SARS-CoV-2 viral loads were evaluated, in exclusion of other respiratory viruses and oral bacteria. A dental practice must also take into consideration preventing the overwhelming bacterial load of the oral cavity in aerosol sprays emanating from dental and hygiene procedures. This may suggest that povidone iodine, hydrogen peroxide, and chlorohexidine may be the optimal antiviral and antibacterial rinse. However, another research also suggests that cetypyridinium chloride, povidone iodine, and chlorohexidine exhibits optimal anti-SARS-CoV-2 activity [63]. Perhaps substantivity and long-term bioactivity of antimicrobial mouth rinses must also be taken into consideration for the dental practice.

Thus, gargling antimicrobial mouthwashes or the use of antimicrobial nasal sprays in suspected or confirmed COVID-19 patients may inhibit transmission of infection and protect healthcare providers [69]; however, more completed data from these ongoing studies are required.

Optimal oral hygiene and treatment of periodontal disease can reduce ACE2 expression, inflammatory cytokines, and aspiration pneumonia [70]. Thus, maintaining periodontal health may reduce host susceptibility to COVID-19, and may prevent COVID-19 aggravation in infected patients [44]. Periodontal disease therapy also improves systemic diseases such as COPD and diabetes [71][72]. Ideal dental health may reduce mortality and morbidity due to pneumonia and influenza, respectively [73][74]. Meticulous oral hygiene may reduce ACE2 expression and decreased inflammatory cytokine release. Thus, preventing aspiration pneumonia and COPD by the management of oral hygiene may lower host susceptibility to COVID-19. In addition, for SARS-CoV-2 infected patients, maintenance of good oral conditions may lead to prevention of COVID-19 aggravation. Thus, periodontal disease therapy and maintaining good oral hygiene are crucial for overall health.

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