Review Article

Coronavirus disease: Dental review

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Abstract

COVID-19 was declared a pandemic outbreak by the World Health Organization, creating a significant impact on health care system. Realizing the high risk associated with this disease and its high rate of transmission, dentists were instructed by health authorities, to stop providing treatment which includes aerosols and droplets and only except emergency complaints. This was mainly for protection of dental healthcare personnel, their families, contacts, and their patients from the transmission of virus. Hence, this review focuses on the life cycle of COVID-19, its clinical symptoms and several issues concerned directly to dental practice in terms of prevention, treatment, and orofacial clinical manifestations.

Keywords: Coronavirus disease-2019, dental aspect, SARS-CoV-2

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INTRODUCTION

Coronaviruses (CoVs) belong to the *Coronaviridae* family in the *Nidovirales* order. The novel coronavirus, named SARS-CoV-2 (colloquially known as 2019-nCoV, human coronavirus-2019 [HCoV-2019]), was discovered in December 2019 in Wuhan, Hubei province of China and was sequenced and isolated by January 2020. Coronavirus disease-2019 (COVID-19) is the disease caused by virus named SARS-CoV-2.[1-3] SARS-CoV-2 is an enveloped, positive-sense single-strand RNA genome containing virus which can infect humans.[3-5] These viruses belong to the coronavirus family as they have spherical virions with core-shell and surface projections resembling a solar corona. SARS-CoV and MERS-CoV are two well-known members of this family which have caused severe human life loss in recent pasts.[5] SARS-CoV was responsible for severe acute respiratory syndrome, a major outbreak in 2002–2003, whereas MERS-CoV causes the middle east respiratory syndrome, a disease which was pandemic in 2012–2013.[4,5]

These viruses spread from human-to-human through air or droplets.[1] Nucleotide sequence homology of SARS-CoV-2 with SARS-CoV and MERS-CoV is 77.5% and 50%, respectively.[3] Dental professionals are particularly at risk due to the nature of their clinical work due to constant exposure to saliva, droplets, blood and aerosols. Therefore, inhalation of infected droplets/aerosols and direct contact with contaminated instruments or surfaces puts both dental practitioners and patients at stake. During a pandemic, there will be times when dentists will have no choice but to treat patients presenting with emergency procedures, such as pain, bleeding and sepsis. Therefore, guidelines and standard operating procedures, which encompass

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their clinical work, workspace as well as the principles guiding their practices, must be well formulated and strictly followed to protect themselves, dental staff and the patients they serve. Thus, utilizing proper and effective disinfection control measures within dental settings cannot be overemphasized. In addition, the dental personnel must wear personal protective equipment (PPE) to prevent being infected by symptomatic and asymptomatic patients.

Here, we will explain the structure, mode of infection and spared of SARS-CoV-2 virus, the clinical features, preventive measures and management of COVID-19 disease as well as potential way to control the disease.

GENOME, PROTEINS AND STRUCTURE OF SARS-COV-2

SARS-CoV-2 genome is around 30 kb long and polycistronic.[3] This single-strand RNA genome code for multiple nonstructural proteins, structural proteins, and lineage-specific accessory proteins.[6] The CoVs family is a class of enveloped positive-sense, single-stranded RNA viruses that are genotypically and serologically divided into four subfamilies of α, β, γ and δ-CoVs among which α-and β-CoVs are responsible for human infections, causing respiratory, hepatic, enteric and neurologic diseases.[5] SARS-CoV-2 as a β-CoV is evolved into two major types of *L* and *S*. [Figure 1] It has been suggested that the *S* type depicts a more aggressive behavior and quicker spread whereas the *L* type is considered to have a relatively milder nature.

These genes code for the following proteins Table 1.[7-9]

INFECTION AND SPREAD OF SARS-COV-2

The life cycle of SARS-CoV-2 can be explained with the following points:

Infection

Using the spike proteins (S) virus binds to specific cell membrane proteins named angiotensin-converting enzyme 2 (ACE2)[3,10] or glucose-regulated protein 78.[11]

ACE2 is an important enzyme of renin-angiotensin system[12] which regulates blood pressure, blood volume, etc., ACE2 expresses on almost all the tissue but the highest expression was found on endothelium cells,[13] heart, tongue, pneumocytes and enterocytes cells of respiratory system.[13-15] After S–ACE2 interaction, E protein and M protein interact with cell membrane, and the whole structure (virus with ACE2 receptor) is endocytosis. Due to E and M protein fusion with cell membrane, the RNA genome is released into the host cells.[16]

Replication and reformation of viral particles

Once inside the host cell, the first ORF (ORF1ab) is translated and forms polypeptide (pp1a and 1ab) which is cleaved by viral proteinase into viral replicase. These replicase form several subgenomic mRNA and make negative full-length viral mRNA too. Now, these viral mRNA produces several copies and start translation of accessory and structure protein (S, E, M and N). These proteins are transported along with viral genome into ER (endoplasmic reticulum) and Golgi complex. The proper formation of viral particles takes place at ER-Golgi intermediate complex (ERGIC). Once formed, these particles are transported from the host cells and bud off into the matrix.[16]

Table 1: Genes and their function and similarities with the genome of SARS-CoV, CoV2 and MERS-CoV2

Gene	Coded protein	Function	Similarity of SARS-CoV (%)
ORF-1ab	A polypeptide which gets processed into Nsp1-5, Nsp9, and Nsp12-15	Replication, transcription, and protease activity	67-98
S	Spike	Host cell-binding form first on infection	75
E	Envelope	Envelop surrounding the viral shell control assembly, release, and infectivity of virus	89
N	Nucleocapsid	Binds and package the RNA genome also hides virus from the host immune system	96
M	Membrane	Glycoprotein present beneath spikes which shapes mature viral particles and binds the inner layer of the host cell membrane during infection	90
Orf3	AP3	Viral replication and pathogenesis	74
Orf4	AP4	IFN antagonism, NF-kB antagonism	NA
ORF5	AP5	IFN antagonism, NF-kB antagonism	NA
ORF6	P6	Accelerate viral infection, IFN and NF-kB antagonism	
ORF7a	7a	Induction of apoptosis in host cells, inhibition of host protein synthesis, cell cycle arrest, enhances pro-inflammatory signals, and MAPK pathway	90
ORF7b	7b	Unknown	NA
ORF8	8a, 8b	Unknown	58
ORF9	9	Unknown	NA

IFN: Interferons, SARS-CoV: Severe acute respiratory syndrome coronavirus, Nsp: Nonstructural proteins, NA: Not applicable

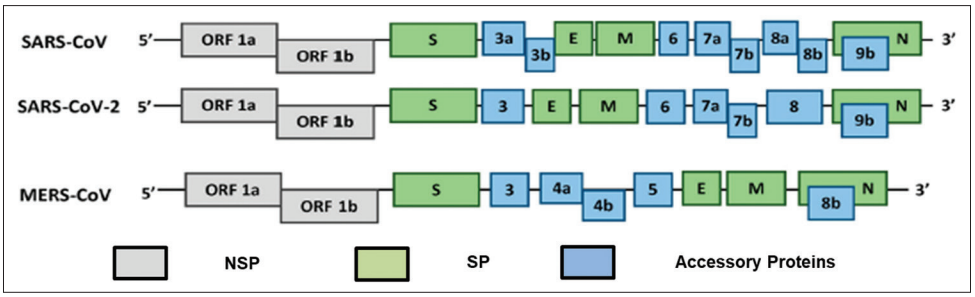

Figure 1: Schematic presentation of genes in the genome of SARS-CoV, CoV-2, and MERS-CoV2 (Adopted from Fung *et al*. emerging microbes and infection, Vol.9, 558-570, 2020)

Spread of virus

The virus can multiple times infect the host cells and can travel and infect other tissues as renal, cerebral neurons, immune cells and intestinal mucosa cells as ACE2 receptors express on these cells too. Normally, patients die due to acute respiratory distress syndrome (ARDS). Patient with heart, lung or kidney-related diseases are more susceptible to COVID-19.[16,17]

CLINICAL MANIFESTATIONS

The signs and symptoms of COVID-19 may appear 2–14 days after exposure. This time after exposure and before having symptoms is called the incubation period. The incubation period for COVID-19 is generally within 14 days following exposure, with most cases occurring approximately 4–5 days after exposure. The common signs and symptoms can include fever, cough and tiredness, myalgias and headache. Early symptoms of COVID-19 may include a loss of taste or smell. Pneumonia is the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea and bilateral infiltrates on chest imaging.

- Cough in 50%
- Fever (subjective or >100.4°F/38°C) in 43%
- Myalgia in 36%
- Headache in 34%
- Dyspnea in 29%
- Sore throat in 20%
- Diarrhea in 19%
- Nausea/vomiting in 12%
- Loss of smell or taste, abdominal pain, and rhinorrhea in fewer than 10% each.[7-9]

RECENT COMPLICATIONS OF CORONAVIRUS DISEASE-2019

Mucormycosis or black fungus

Our immune system is usually more than a match for the fungi, but an "unholy trinity" of diabetes, COVID-19 and steroid treatment can weaken a person's immunity to such an extent that these microorganisms can gain a foothold. Diabetes not only increases a person's risk of severe COVID-19 but also provides conditions in which fungal infections can thrive. To make matters worse, both COVID-19 and the steroid dexamethasone, which intensive care doctors use to treat it, suppress immunity. Thus, ensuing infection, known as mucormycosis or zygomycosis, spreads rapidly from the nose and sinuses to the face, jaw, eyes and brain. On May 26, 2021, there were 11,717confirmed cases of mucormycosis in India, which has more people living with diabetes than any other country in the world except China.[11]

Even before the pandemic, the prevalence of mucormycosis may have been 70 times higher in India than the overall figure for the rest of the world. The fungus blocks blood flow, which kills infected tissue, and it is this dead or necrotic, tissue that causes the characteristic black discoloration of people's skin, rather than the fungus itself. From a mycological point of view, the term "black fungus" (or "black yeasts") is restricted to fungi called dematiaceous, which have melanin in their cell walls. Mucormycosis is caused by saprophytic fungi such as *Rhizopus*, *Mucor*, *Cunninghamella*, *Rhizomucor, Apophysomyces* or *Lichtheimia*.[10-12]

Fatality rate

Without immediate treatment with antifungal medication and a surgery to remove necrotic tissue, mucormycosis is often fatal. Before the pandemic, the Centers for Disease Control and Prevention (CDC) reported an overall mortality rate of 54%. A 2021 systematic review of all COVID-19-related cases published in the scientific literature found 101 cases: 82 of them in India and 19 from the rest of the world. Among these cases, 31% were fatal. Dr. Awadhesh Kumar Singh and his coauthors report that around 60% of all the cases occurred during an active SARS-CoV-2 infection and that 40% occurred after recovery. In total, 80% of the patients had diabetes, and 76% had been treated with corticosteroids.

Myths about transmission

Mucormycosis can be transmitted from person to person, fungi growing in water, oxygen cylinders and humidifiers. Face masks harbor black fungus. Another popular theory is that the black mold sometimes seen on onions in refrigerators is Mucorales fungus and, therefore, a potential source of infection. As we have seen, the species in question are not black. In fact, the black mold found on onions and garlic is usually the fungus *Aspergillus niger*. All this information is not true.

Possible routes of transmission

Published evidence points to several potential sources of the infection in hospitals, but it does not mention oxygen tanks, humidifiers or face masks. Two studies published in 2014 and 2016, respectively, implicate hospital linens from poorly managed laundries as a source. A 2009 review of research into hospital outbreaks identifies ventilation systems, wooden tongue depressors, adhesive bandages and ostomy bags as other possible sources of infection.

Clinical signs and symptoms

Six well-recognized clinical forms of mucormycosis are the pulmonary, cutaneous, gastrointestinal, rhinocerebral, central nervous system and disseminated. Oral mucormycosis occurs usually in paranasal sinuses or nasal areas. Serious involvement of paranasal sinuses leads to palatal necrosis and/or ulceration. Symptoms include fever, cough, chest pain, shortness of breath, one-sided facial swelling, headache, nasal or sinus congestion, black lesions on nasal bridge or upper inside of the mouth that quickly become more severe.[10,11]

Management

Almost all patients require surgical debridement of infected tissue, antifungal drugs (mainly amphotericin B) and good control (treatment) of underlying medical problems such as diabetes.[12]

OTHER COMPLICATIONS

Respiratory failure

ARDS is the major complication in patients with severe disease and can manifest shortly after the onset of dyspnea.

Cardiac and cardiovascular complications

Other complications have included arrhythmias, myocardial injury, heart failure and shock.[7]

Thromboembolic complications

Venous thromboembolism, including extensive deep-vein thrombosis and pulmonary embolism, is common in severely ill patients with COVID-19, particularly among patients in the intensive care unit, ranged from 10% to 40%.

Neurologic complications

In one-third of cases, encephalopathy is a common complication of COVID-19, particularly among critically ill patients. Stroke, movement disorders, motor and sensory deficits, ataxia and seizures occur less frequently.

Inflammatory complications

Some patients with severe COVID-19 have laboratory evidence of an exuberant inflammatory response, with persistent fevers, elevated inflammatory markers (e.g., D-dimer and ferritin) and elevated pro-inflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses.[7,8]

Laboratory findings

The common laboratory findings among hospitalized patients with COVID-19 include are leukopenia (25%), lymphopenia (25%), elevated aminotransaminase levels (37%), elevated lactate dehydrogenase levels, elevated inflammatory markers (e.g., ferritin, C-reactive protein and erythrocyte sedimentation rate) and abnormalities in coagulation tests.[9]

PROTECTIVE MEASURES AND INFECTION CONTROL IN THE DENTAL SETTING

Screening of patients

The use of infrared thermal scanner and pulse oximeter, questions including any recent travel history to any areas with a high incidence of COVID-19, any exposures to a person with suspected/known COVID-19 infection, and the presence of any symptoms of the disease.

Type of waiting room

Patients should be placed in a well-ventilated room with minimum of 6 feet distance between one another with surgical face mask and hand sanitizer. All instructing the patients to cover their nose and mouth with a tissue or their elbows when sneezing or coughing followed by immediate disposing of the tissue and hand disinfection.

Preprocedural steps

Hand washing in COVID-19 prevention plays a crucial role when coming into contact with patients, surfaces and equipment and touching nose, mouth and eyes with contaminated hands. Soap and alcohol-based hand rub are equally effective cleansers. Recommendations also include special preprocedural oral mouthwashes mainly povidone-iodine for all dental disciplines, use of rubber dam to isolate the working area in aerosol-generating clinics, use of disposable mirrors, high-volume ejectors and avoidance of procedures where high-speed equipment creating aerosols are required.

Personal protective equipment

Standard PPE for patients with suspected or confirmed COVID-19 and dentists includes the use of a gown, gloves, a respirator or medical mask, eye and face protection. Although surgical masks protect mucous membranes of the nose and mouth for droplet spatter, they do not ensure full protection against inhalation of airborne transmission agents as declared by the CDC and prevention.

Disinfecting dental room

High-efficacy particulate arrestor should be used during aerosol-generating procedures. With six air changes per hour, a time gap of 46 min is required between patients for 99.9% removal of airborne contaminants by efficacy. Surface disinfectants containing 62%–71% ethanol, 0.5% hydrogen peroxide and 0.1% (0.1 g/L) sodium hypochlorite within 1 min should be used.

CONCLUSION

Overall, it is commendable that many dentists have risen to the challenge in the fight against COVID-19. While the currently available evidence has not demonstrated a clear and direct relationship between dental treatment and COVID-19, there is clearly the potential for transmission. This could result due to contaminated dental fluids, saliva or aerosol spread during close human-to-human contact during dental treatment or by contact with contaminated instruments or surfaces. Therefore, following the protective protocols in the COVID-19 crisis is of utmost importance in a dental setting.

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Conflicts of interest

There are no conflicts of interest.

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