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Management of Various Covid-19 Patients and Its Periodontal Considerations

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ABSTRACT
The recent coronavirus disease 2019 (COVID-19) outbreak, triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents an unprecedented global challenge for healthcare systems.The clinical course of the disease and its deadly complications required urgent development of novel therapeutic agents to both prevent and treat COVID-19. Various vaccines and drug therapies have been discovered,ongoing research and clinical trials are being conducted to investigate the efficacy of repurposed drugs for treating COVID-19. In this review, the drugs that have been suggested to treat COVID-19 are discussed. These include anti-viral agents, immunomodulatory agents, and adjunctive agents, among other miscellaneous agents. The mechanisms of action and different pharmacological properties are explored, focusing on the evidence-based safety and efficacy of each agent.Secondly, Coronavirus disease (COVID-19) and Periodontitis share common characteristics, such as an exaggerated inflammatory response.So we have discussed the association between both and written about oral manifestations and complications of COVID-19 and how essential it is to maintain periodontal health and good oral hygiene to prevent and manage COVID-19 and its complications.

Key Words: COVID-19, Periodontitis, SARS-CoV-2, Coronavirus, Oral health, Oral Hygiene.

I. INTRODUCTION

Coronaviruses are a large group of viruses that cause illness in both humans and animals. Novel coronavirus disease (COVID-19) was initially found in Wuhan city of China in December 2019. WHO declared this outbreak a "Public Health Emergency of International Concern" (PHEIC) on 30th January 2020 and subsequently declared it a pandemic on 11th March 2020. The causative virus (SARS-CoV-2) is an enveloped RNA virus related to the Severe Acute Respiratory Syndrome (SARS) virus. The incubation period ranges 2-14 days, and the infection starts two days before the onset of symptoms. Several variants have been identified which are designated as variants of concern (VOC) and variants of interest (VOI).

Currently designated Variants of Concern (VOC): Alpha, Beta, Gamma, Delta.

Currently designated Variants of Interest(VOI): Eta, Iota, Kappa, Lambda, mu.

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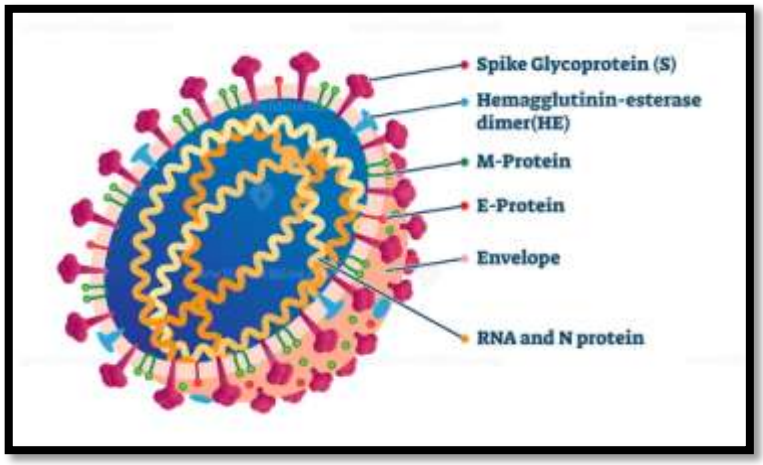

Figure 1 : CORONA VIRUS STRUCTURE

THERAPEUTIC MANAGEMENT OF COVID – 19 PATIENTS

Patients with COVID-19 have been divided into Mild, Moderate, and Severe depending on the Clinical Severity. They predominantly have a respiratory tract infection which progresses to Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, multi-organ failure, including acute kidneyand cardiac injury.

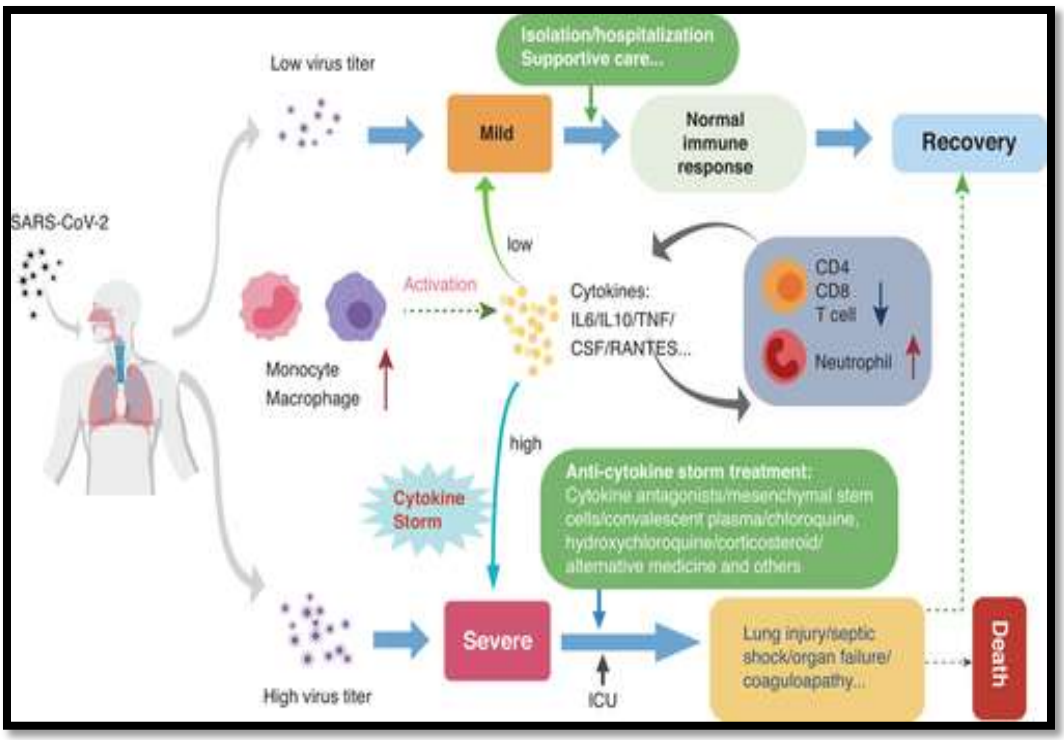

Figure 2: Cytokine Storm And Leukocyte Changes In Mild Versus Severe SARS- CoV- 2 Infection

1. MILD CASES :

- Patients with uncomplicated upper respiratory tract infection.
- May have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache.
- Without evidence of breathlessness or Hypoxia (normal saturation).
- Managed at Covid Care Centre or home (subject to fulfillment of conditions stipulated in guidelines).

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Management:

- The patient is followed up daily for temperature, vitals, and Oxygen saturation (SpO2).
- Symptomatic treatment such as antipyretic (Paracetamol) for fever and pain.
- Adequate nutrition and appropriate rehydration.
- Anti-SARS CoV-2 monoclonal antibody products are recommended –
  - Casirivimab plus imdevimab or
  - Sotrovimab
- Tab Hydroxychloroquine (HCQ) or Remdesivir may be appropriate for high-risk patients (such as age> 60; Hypertension, diabetes, chronic lung/kidney/ liver disease, Cerebrovascular disease, and obesity) under strict medical supervision.

2. MODERATE CASES:

- Pneumonia with no signs of severe disease.
- Dyspnea and or Hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute.

Management:

- Tab. Hydroxychloroquine (400mg) BD on 1st day followed by 200mg 1 BD for four days. (after ECG Assessment).
- Use one of the following options:
  - Remdesivir(e.g., for patients requiring minimal supplemental oxygen)
  - Dexamethasone plus remdesivir (e.g., for patients who require increasing amounts of supplemental oxygen)
  - Dexamethasone (when combination therapy with Remdesivir cannot be used or is not available)
- Anticoagulation: Prophylactic dose of UFH or LMWH (e.g., enoxaparin 40 mg per day SC) for anticoagulation.
- In case of secondary bacterial infection, antibiotic therapy should be considered.

3. SEVERE CASES :

- Pneumonia
- Respiratory rate >30 breaths/min or severe respiratory distress or SpO2 <90% on room air.
- Sepsis
- Septic Shock

Management :

a) Early Supportive therapy – Supplemental Oxygen therapy and use of one of the following:

- **Remdesivir**(e.g., for patients requiring minimal supplemental oxygen)
- **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of supplemental oxygen)
- **Dexamethasone** (when combination therapy with Remdesivir cannot be used or is not available)

b) In case of severe **Hypoxemic respiratory failure** when a patient is failing standard oxygen therapy - Deliver oxygen through a High-Flow Device or Noninvasive Ventilation. Also, use one of the following options:

- Dexamethasone (add baricitinib or tocilizumab in case of increased oxygen need and systemic inflammation)
- Dexamethasone plus Remdesivir (Also add baricitinib or tocilizumab in case of increased oxygen need and systemic inflammation)

c) In patients with **refractory hypoxemia** despite lung protective ventilation-

- Consider Invasive mechanicalventilation or Extracorporeal membrane oxygenation and Dexamethasone.
- Invasive mechanical ventilation or Extracorporeal membrane oxygenation and Dexamethasone plus tocilizumab for patients within 24 hours of admission to the ICU.

ANTI VIRAL DRUGS AND COVID -19

1. **Remdesivir**

- Remdesivir is approved by the Food and Drug Administration (FDA) to treat COVID-19patients (aged ≥12 years and weighing ≥40 kg).
- It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription.[1]
- It causes gastrointestinal symptoms (e.g., nausea), elevates transaminase and prothrombin time values (without changing the international normalized ratio), and leads to hypersensitivity reactions.[2]
- It should not be continued in patients whose ALT levels increase to > 10 times the upper limit of normal.[2]
- It is also not recommended for patients with eGFR < 30 ml/min.[2]
- Coadministration of Chloroquine/Hydroxychloroquine and Remdesivir is not recommended as chloroquine/hydroxychloroquine may reduce the anti-viral activity of Remdesivir.[2]

2. **Lopinavir/Ritonavir** is not recommended for the treatment of COVID-19 patients.[3]

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ANTIMALARIAL DRUGS

- Both **Chloroquine and Hydroxychloroquine** inhibit the fusion of the SARS-COV-2 virus with the host cell membrane by increasing the endosomal PH and inhibiting glycosylation of cellular angiotensin-converting enzyme 2 (ACE2) receptor.[4]
- Cardiac side effects include QTc prolongation, Torsades de Pointes, ventricular arrhythmia, anddeath.[5]
- So these are not recommended by Food and Drug Administration for the treatment of Covid-19.[3]

ANTIPARASITIC DRUGS

1. Ivermectin

- **Ivermectin** acts by inhibiting the host's alpha/beta-1 nuclear transport proteins and preventing the attachment of the virus to the host's cell membrane.[6,7]
- Adverse effects may include dizziness, pruritis, nausea, or diarrhea.
- A very high plasma concentration is required for Ivermectin to have an anti-viral effect. Doses may go 100-fold higher than those approved for use in humans.[8,9]
- So the use of Ivermectin for the treatment of COVID-19 is currently underway or in development.

2.Nitazoxanideis not recommended for the treatment of COVID-19.

Anti-SARS-CoV-2 Monoclonal Antibodies

- After ten days of disease onset, individuals with COVID-19 produce neutralizing antibodies against S(spike) and N(nucleocapsid) proteins of SARS-COV-2.[10]
- Bamlanivimab, Casirivimab, Etesevimab, and Sotrovimab are the neutralizing antibodies for the treatment of COVID-19.
- Gamma and Beta Variants Of Concern have reduced susceptibility towards Bamlanivimab and Etesevimab. So the Panel recommends against its use.[11]

Thus any one of the following is used to treat non-hospitalized patients with mild to moderate COVID – 19 outpatients who are at high risk of clinical progression, and its use for hospitalized patients is not recommended :

- Casirivimab plus imdevimab; or
- Sotrovimab 500 mg intravenous (IV) infusion
- When using casirivimab plus imdevimab, the Panel recommends:
- Casirivimab 600 mg plus imdevimab 600 mg IV infusion

If IV infusions are not feasible or would cause a delay in treatment, casirivimab 600 mg plus imdevimab 600 mg administered by four subcutaneous (SQ) injections (2.5 mL per injection) can be used as an alternative

CONVALESCENT PLASMA

- The plasma of patients who have recovered from COVID-19 may contain antibodies to SARS-CoV-2that suppress the virus and modify the inflammatory response.[12]
- Adverse Effects include transfusion-transmitted infections like HIV, hepatitis B, hepatitis C, allergic reactions, anaphylactic reactions, circulatory overload, hemolytic reactions, hypothermia, metaboliccomplications, and post-transfusion purpura.[13,14,15]
- The Panel recommends **against** convalescent plasma for Nonhospitalized patients and Hospitalized patients with COVID-19 who do not have Impaired Immunity.
- For Hospitalized patients with impaired immunodeficiencies, studies suggest the benefit of COVID – 19 convalescent plasma.

IMMUNOGLOBULINS : SARS- CoV-2 Specific

- SARS-CoV-2 immunoglobulins (concentrated antibody preparations) can be manufactured from pooled plasma collected from individuals who have recovered from COVID-19, potentially suppressing the virus and modifying the inflammatory response.[3]
- The Panel has insufficient evidence to recommend either for or against the use of SARS-CoV-2 immunoglobulins to treat COVID-19.[3]

MESENCHYMAL STEM CELLS

- Mesenchymal stem cells have been hypothesized to reduce acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2.[16]
- These are multipotent adult stem cells present in most human tissues, including the umbilical cord, which has self-renewal properties and differentiates into multiple tissue types like osteoblasts, chondroblasts, adipocytes, hepatocytes, etc.[17,18]
- The COVID-19 treatment panel recommends against its use for the treatment of COVID-19.

IMMUNOMODULATORS

1. COLCHICINE

- It is an anti-inflammatory drug used to treat various conditions like gout, recurrent pericarditis, and familial Mediterranean fever.[19]

- It works by reducing of chemotaxis of neutrophils, inhibiting inflammasome signaling, and decreasing the production of cytokines such as interleukin – 1 beta.[20]
- All these mechanisms may mitigate or prevent inflammation-associated manifestations of COVID-19.
- The Panel recommends against the use of Colchicine for hospitalized patients with COVID-19 and has insufficient data for its use for the treatment of non-hospitalized patients with COVID-19.

2. FLUVOXAMINE

- Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) found to reduce the production of inflammatory cytokines and the expression of inflammatory genes.[3]
- Side effects include nausea, diarrhea, indigestion, insomnia, and sweating. It may enhance the anticoagulant effects of antiplatelets, anticoagulants and increase the serotonergic effects of other SSRIs.[21]
- The COVID-19 Treatment Guidelines panel has insufficient data to recommend either for or against the use of Fluvoxamine to treat COVID-19.

3. GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR INHIBITORS

- GM-CSF is a myelopoietic growth factor, and proinflammatory cytokine secreted by macrophages, T-cells, mast cells, etc., regulates macrophage number and function.[22,23]
- Side effects include bacterial infection, acute kidney injury, and elevated liver transaminases.[24]
- The Panel has insufficient data to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.[3]

4. INTERLEUKIN – 1 INHIBITORS

- Anakinra is a recombinant human IL-1 receptor antagonist used to treat COVID-19 because of endogenous IL-1 level elevation.[3]
- Its prolonged use causes increased rates of infection.[25]
- The Panel has insufficient data to recommend for or against the use of interleukin – 1 inhibitors, such as anakinra, for the treatment of COVID-19.[3]

5. INTERLEUKIN – 6 INHIBITORS

- IL-6 are proinflammatory cytokines produced from bronchial epithelial cells associated with systemic inflammation and hypoxic respiratory failure in COVID-19 patients.[26]
- There are two classes of IL-6 inhibitors :

1. Anti-IL-6 receptor monoclonal antibodies, e.g., sarilumab, tocilizumab.
2. Anti-IL-6 monoclonal antibodies, e.g., siltuximab.[3]

- Side Effects include elevated liver enzyme, the risk of severe infections (like tuberculosis, bacterial or fungal infections), and bowel perforations.
- The Panel recommends using tocilizumab (single IV dose of 8mg/kg actual body weight up to 800mg) in combination with dexamethasone (6mg daily for up to 10 days) in certain hospitalized patients exhibit rapid respiratory decompensation.
- There is insufficient data for or against the use of sarilumab for hospitalized patients with COVID-19.[3]
- The Panel recommends against the use of anti - IL-6 monoclonal antibody therapy, i.e. siltuximab, for treatment of COVID-19.[3]

6. INTERFERONS (Alpha, Beta)

- Interferons are a family of cytokines suggested for the treatment of COVID-19 because of its anti-viral properties.[3]
- Interferon beta is better tolerated than Interferon-alpha. Interferon-alpha causes flu–like symptoms, nausea, fatigue,weight loss,hematological toxicities, elevated transaminases, and psychiatric problems.[27,28]
- So, the COVID-19 Treatment Panel recommends against the use of interferons for the treatment of patients with severe or critical COVID-19.[3]

CORTICOSTEROIDS

- Corticosteroids are drugs that have potent anti-inflammatory effects and might mitigate or prevent deleterious systemic inflammatory conditions in patients with severe COVID-19, which can further lead to lung injury and multisystem organ dysfunction.[29]
- Adverse Effects include hyperglycemia, secondary infections, psychiatric effects, and avascular necrosis. Prolonged use may increase the risk of reactivation of latent infections, e.g., hepatitis B virus, herpes virus infections, strongyloidiasis, and tuberculosis.[30]

KINASE INHIBITORS: Baricitinib and other Janus Kinase Inhibitors, and Bruton's Tyrosine Kinase Inhibitors

- The kinase inhibitors are those classes of drugs that produce immunosuppression that potentially reduces inflammation.[31]

- They interfere with signal transducer and activator of transcription protein's phosphorylation, thus affecting vital cell functions like signaling, growth, and survival.[3]
- Baricitinib has anti-viral activity by interfering with viral endocytosis, potentially preventing entry into and infection of susceptible cells.[3]
- Adverse effects include respiratory and urinary tract infections, reactivation of Herpes, myelosuppression, and transaminase elevations.
- The Panel recommends against the use of JAK inhibitors other than baricitinib for the treatment of COVID – 19.[3]

ANTITHROMBOTIC THERAPY

- A number of incidences of venous thromboembolism (VTE) in patients with COVID-19 have been reported.[3]
- In non-hospitalized patients with COVID-19, there is no evidence in support of measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen).[3]
- In hospitalized patients with COVID-19, coagulation parameters are commonly measured, but there is no evidence using this data as a guide to making the treatment decisions. To them, prophylactic dose anticoagulation should be prescribed except for conditions like severe thrombocytopenia and haemorrhage where it is contraindicated. Low molecular weight heparin or unfractionated heparin is preferred over oral anticoagulation.[3]
- Patients with COVID-19 diagnosis should continue with their anticoagulant or antiplatelet therapies for underlying conditions.
- In patients with COVID-19, VTE prophylaxis after hospital discharge is not recommended.

SUPPLEMENTS

1. VITAMIN C

- Vitamin C (ascorbic acid) is a water-soluble vitamin, an antioxidant, free radical scavenger, has anti-inflammatory properties, influences cellular Immunity and vascular integrity, and serves as a cofactor in the generation of catecholamines.
- It is required in oxidative stress and COVID-19 patients. It is used for alleviating inflammation and vascular injury.[32]
- There is insufficient data for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in both critically and non-critically ill patients.[3]

2. VITAMIN D

- Vitamin D is critical for bone and mineral metabolism and can modulate innate and adaptive immune responses.[33]
- There is insufficient data for Vitamin D to be recommended for COVID-19 treatment.

3. ZINC

- Zinc impairs replication in a number of RNA viruses. It has been shown to enhance cytotoxicity and induce apoptosis.[34]
- The recommended dietary allowance for elemental Zinc is 11mg daily for men and 8mg for nonpregnant women.[35]
- Long term supplementation can cause copper deficiency leading to hematologic defects (i.e., anemia, leukopenia) and neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity)3
- There is insufficient data to recommend the use of Zinc for the treatment of COVID-19, and the Panel recommends against using it above the recommended dietary allowance for the prevention of COVID-19.3[3]

ASSOCIATION BETWEEN PERIODONTITIS AND COVID-19

- Periodontitis is a chronic, multifactorial, inflammatory disease associated with plaque biofilms and characterized by the progressive destruction of the tooth-supporting structures.
- Periodontitis increases the systemic inflammatory burden, as the inflamed periodontal tissues release host-derived proinflammatory cytokines and tissue destruction mediators into the circulatory system, which can activate an acute-phase response in the liver and can amplify systemic inflammation.
- The inflammatory reaction in periodontitis results in increased inflammatory mediators, such as tumor necrosis factor-α, interferon-γ, prostaglandin E2, interleukin (IL)-1β, IL-4, IL-6, IL-10,ferritin, and C-reactive protein.
- Periodontopathic bacteria are involved in the pathogenesis of respiratory diseases, such as pneumonia and chronic obstructive pulmonary disease (COPD), as well as systemic diseases, including diabetes and cardiovascular disease.
- Periodontopathic bacteria were detected in the bronchoalveolar lavage fluid of patients with COVID-19. There are similarities between the cytokine storm in severe COVID-19 infections and the cytokine expression profile in Periodontitis, suggesting a possible link between Periodontitis and COVID-19 and its associated complications.
- The increased expression level of angiotensin-converting enzyme 2 (ACE2) in the oral cavity, promoted by periodontopathic bacteria, may increase the SARS-CoV-2 infection rate.An elevated IL-6 level is associated with

excess inflammation, contributing to increased mortality in patients with COVID-19.

- Periodontal diseases can increase the inflammatory response in patients, which might exacerbate the systemic symptoms and clinical course of COVID-19.[36]

ORAL MANIFESTATIONS AND COMPLICATIONS

1) **Gustatory and Olfactory Changes**: Hypogeusia, dysgeusia and ageusia is seen.[37]
2) **Oral mucosal lesions**: Ulcers, erosions, blisters, plaque-like lesions, reactivation of herpes simplex virus 1(HSV1), and geographical tongue are observed.[37]
3) **Ulcers ad erosions**: Herpetiform ulcers or multiple apthoid ulcers with a diffuse erythematous base. This multiple apthoid ulcers, later on, merge to form large ulcers with yellowish fibrin covering them, resembling erythema multiform- like disease.[37]
4) **Vesicobullous lesions**: Such as blisters, petechiae, erythematous lesions, and erythema multiform- like lesions.Tongue and palate (soft and hard) are the most common reported location of these lesions. Erythema multiform- like lesions are the most commonly reported lesions accompanied by skin target lesions.[37]
5) **Plaques (white or red)**: Candidal plaque- like lesions are also observed in association with Covid- 19. Both red and white plaques are observed. They are located on the dorsum of the tongue and palate.[37]
6) **Reactivation of Herpes Simplex 1(HSV 1)**is also observed.[37]
7) **Angina bullosa**: These blood-filled blisters are observed on the soft palate, tongue, and cheek. They are brown-black single or multiple lesions and may appear after initiation of therapies for Covid- 19.[37]
8) **Gingival changes**: Gingival changes such as generalized erythematous and edematous gingivae, Gingivo- periodontal bleeding, necrotic interdental papillae, desquamative gingivitis, and aggravation of Periodontal disease are reported in the literature.[37]
9) **Dry mouth**is also reported.[37]
10) **Other manifestations**: Symptoms such as halitosis, tongue, and masticatory muscle pain and swelling, geographical tongue, hyperplasia of papilla associated with taste changes, and macroglossia are also reported.[37]
11) **MUCORMYCOSIS:** Mucormycosis can occur among COVID-19 patients, especially with poor glycaemic control, widespread and injudicious use of corticosteroids and broad-spectrum antibiotics, and invasive ventilation. Owing to high mortality, a high index of suspicion is required to ensure timely diagnosis and appropriate treatment in high-risk populations.[38]

II. CONCLUSION

The COVID-19 pandemic is still severe, and the spectrum of medical therapies to treat coronavirus disease 2019 (COVID-19) is growing and evolving rapidly, including both drugs approved by U.S. Food and Drug Administration (FDA) and drugs made available under FDA emergency use authorization (EUA).This article has discussed various therapeutic measures of COVID-19, drug interactions, side effects, and oral manifestations of COVID-19 treatment drugs. This will help dental professionals to focus on detailed intraoral examination before initiating any dental treatment on Covid- 19 suspected or confirmed patients. Clinicians and patients who wish to consider their use, or the use of any other available investigational therapies, should review the COVID – 19 Treatment Guidelines.Also, we have discussed association of oral bacteria, periodontopathogens, and, in general, a periodontal disease with this novel virus. Periodontal health has been known to be reflective of systemic health, and further studies are needed to check PDL disease activity concerning the CORONA virus. The oral cavity has been one of the most significant points of entry of the novel coronavirus. Considering the presence of SARS-CoV-2 RNA in the nasopharyngeal swab sampling as a gold standard, there is no definitive evidence of the recovery of SARS- CoV-2 from saliva and GCF, so much so that these will form the basis of testing methodology.[39]

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