



Endodontic Treatment During the Evolving Coronavirus Disease 2019 (COVID-19) Pandemic and Its Impact: A Narrative Review

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Submitted: 25 April 2023; Accepted: 19 May 2023; Published: 08 June 2023

ABSTRACT

The Effect of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in large number of cases and also hundreds of thousands of deaths. In spite of all efforts to control the spread of the disease, however the number of infections and deaths still rise, especially in some regions of certain countries. Till current moment, there is no medicine companies have shown up with the proper treatment or protection which can protect dentist from exposing with the virus. In this pandemic situation, the general practitioner and the endodontist should provide only emergency treatments in order to relieve discomfort and dental pain. Thus, it is mandatory to comply the infection control guidelines and patient management steps to produce optimum dental therapy and also prevent nosocomial infection in daily practice. This review provides an insight into the steps taken for infection control and prevention from COVID-19 transmission in endodontic practices, knowledge about the possible route of transmission, pharmacological treatments of dental pain, applying standardized infection control measures, conservative access cavity preparation for RCT, biomechanical precautions, and procedures that should be followed during the SARS-CoV2 pandemic.

Keywords: COVID-19, dental, Endodontic treatment, novel coronavirus disease

INTRODUCTION

Coronavirus disease (COVID-19) has appeared as the largest global pandemic outbreak and has already affected many nations, including Indonesia.⁽¹⁾ Although the disease in certain times shows up as an asymptomatic or symptomatic clinical condition, however the diagnosis is most commonly correlated with fever, dry cough, fatigue and difficulty in breathing. COVID-19 can lead to other serious diseases with severe respiratory symptoms,

including dyspnea and pneumonia, which can even cause death. (1-2)

More than 2 years into the coronavirus pandemic, COVID-19 cases, including hospitalizations and deaths are rising in the many parts of the world and in many countries. Despite widespread of effective vaccines and novel therapeutics, health systems in many regions are still full of largely unvaccinated or medically vulnerable patients. (1-3)

The American Dental Association (ADA) recently introduced guidance to prevent infection of COVID-19 in the times of emergency and non-emergency dental procedures. Infection control procedure in daily practice including the use of Personal Protective Equipment (PPE) and disinfecting the dental care environment as part of the mandatory clinical procedure so as to prevent cross-infection. (2-4)

The result of COVID-19 in dentistry is that clinicians at high risk of exposure to the virus. During the beginning times of the pandemic, many endodontic cases especially emergency patients presented to an emergency dental centre for treatment with particular amount of affected teeth resulting in extraction. Now more than two years from the start of the pandemic, dental primary care services have been reactivated and many protocols introduced for emergency endodontic treatment are still in place even though the introduction of vaccines and easing of public restrictions. (5)

Since the reopening of dental primary care in June 2020 in UK, there has been a great number of patients who are queuing to get their teeth treated and who require endodontic care to control the systemic disease. On account of new variants of disease arising and current easing and reimplementation of regulations in the UK, it is imperative to reduce the risk of transmission when performing dental treatment related to endodontics. (6-7)

Endodontics is the branch of study in scope of dental pulp and tissue medicine including the root canals of a tooth. "Endo" is the Greek word that means "inside", and "odont" is the Greek word that means "tooth". The endodontic procedure or treatment of passage treats the organic tissue the pulp tissue and root canal present within the tooth. A dentist is a specialist who specializes in saving teeth [8]. As dental specialists, we are facing with the big challenge for the dental community and our patients to reduce the exposure and transmission of the virus. Due to the nature of our job, the community is at a high risk of exposing with the virus and transmitting the virus inevitably [8].

Novel Coronavirus Disease (COVID-19) and its evolving variants

In accordance to some studies, severe acute respiratory syndrome coronavirus (SARS-CoV),

this SARS-CoV-2 is zoonotic origin, derived from Chinese horseshoe bats (*Rhinolophus sinicus*) becomes the most likely and pangolins can be an intermediate host [9-11].

Coronaviruses belong to the family of Coronaviridae, of the order of Nidovirales, consisting of single, large, plus-stranded RNA as their genome. At the moment, there are four genera of coronaviruses found i.e: α -CoV, β -CoV, γ -CoV, and δ -CoV. Predominantly coronavirus strain can lead to infectious diseases in human and vertebrates. The α -CoV and β -CoV predominantly infect the respiratory, gastrointestinal, and central nervous system of humans and mammals, meanwhile γ -CoV and δ -CoV predominantly infect the birds [9-11].

In November 2021 the identification of the Omicron variant of SARS-CoV-2 in South Africa and Botswana, classified by the World Health Organization as a Variant of Concern, has again changed the pathway of the pandemic. On the other hand, there is still much to be learned about the epidemiology of Omicron, available data suggest that this variant is significantly more transmissible than the variant of Delta and is capable of significant immune eluding (ie, bypassing the immune system provided by antibodies arising from vaccines or previous SARS-CoV-2 infection). Since its first time identification, Omicron has been found in more than 90 countries and 46 US states. However, as opposed to South Africa and Botswana, where very few cases of COVID-19 were reported when Omicron emerged, there was an ongoing surge due to the Delta variant in the US. (10-11)

During the time of December 20, 2021, in the US, there were about 70000 patients hospitalized and an average of 1300 deaths per day are attributed to COVID-19. Nationwide, in less than 3 weeks, Omicron has become the greater variant, present currently in 73% of the samples for the week ending December 18, 2021. So looking at the experience from some countries like South Africa and Europe and now in the US, Omicron will likely displace Delta as the dominant variant in many parts of the world. (11)

The Feasible Transmission routes of COVID-19 and Its Symptoms Transmission Passage [12]

The three most common transmission pathways of novel coronavirus include: direct route

(through droplets inhalation, cough and sneeze), contact route (through oro-nasal-ocular pathway) and aerosol transmission.

The most common transmission route of COVID-19 including direct transmission route (droplets inhalation transmission, cough and sneeze) and contact transmission route (close contact with nasal, oral fluid and eye mucous membranes). Despite common clinical manifestations found in confirmed patients, COVID-19 infection does not show eye symptoms, the analytical study of conjunctival samples from suspected and confirmed cases of COVID-19 suggests that the transmission of COVID-19 is not limited to the respiratory tract and eye exposure may provide an effective pathway for the virus to enter the body. It has been reported that SARS-CoV-2 remains viable up to 24 hours on cardboard and even up to 72 hours on plastic or stainless steel surfaces [11-12].

Opinions vary as to the degree and extent of the airborne mode of SARS-CoV2 transmission. There is direct and indirect evidence to indicate that aerosols with a particle size of $<5 \mu\text{m}$ can be entrapped in the air and carried over distances of up to 1 m. One recent study has reported the survival of SARS-CoV2 up to 3 hours in aerosol particles, supporting the possibility of airborne transmission [12]. However, another study reported the absence of SARS-CoV2 in air samples collected from an actual clinical environment where symptomatic patients were admitted. Therefore, more studies are required to provide obvious evidence of airborne

transmission of SARSCoV2 in both clinical as well as non-clinical condition (World Health Organization) [12]. Nevertheless, in clinical aspect, as in dental clinics, where large volume of aerosol is produced, air borne infection transmission is likely, and hence dentists and all dental staffs might consider extra airborne and droplet precautions during the pandemic (World Health Organization) [12-13].

Possible Exposure of COVID-19 in Dental Clinics

1. Dental clinic has the largest risk of COVID-19 infection due to the procedures performed. Virus can be exposed and transmitted at dental clinic through inhalation of micro airborne viral particles that can stay suspended in the free air for certain period of time. Direct contact with salivary droplets, oral fluid, blood, and other patient materials present a high risk of contamination. Contact of conjunctiva, oral environment or nasal mucosa with droplets and aerosols generated by dental procedures containing virus particles arise from individual has big chance lead to cross and nosocomial infection. These situations can arise from a short distance by sneezing, coughing and talking to each other without wearing a mask as well as indirect contact with contaminated instruments or environmental surfaces [14-16] (Figure 1).

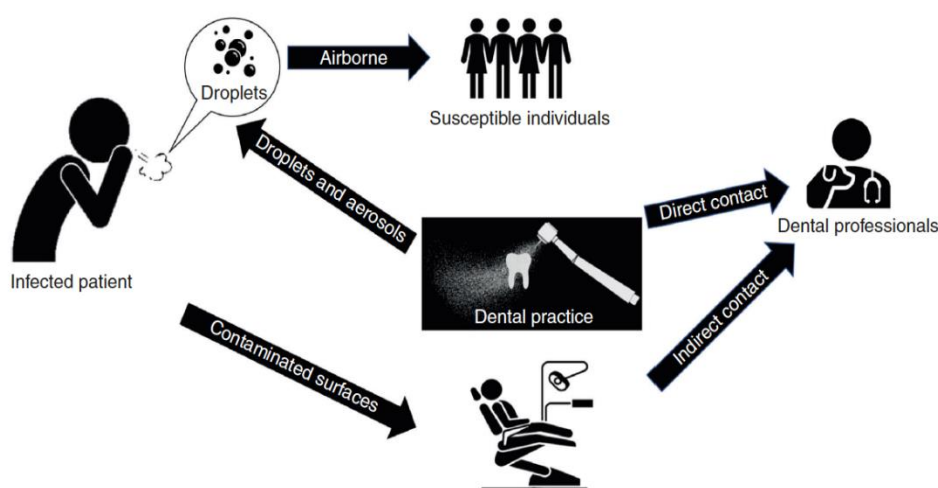


FIGURE 1: Transmission pathway illustration of COVID-19 at dental clinics and hospital during dental procedure [15-16].

2. Aerosol and saliva droplets are the most crucial concerns in dental clinics and hospitals as the source of COVID-19 pathway of transmission. Almost all dental procedures involve the use of high-speed hand piece with water cooling that in turn will result in large volume of small particle aerosols and droplets mixed with patient's oral fluids, saliva and blood during dental treatment procedures. These generated aerosols will remain airborne for a certain period of time before they fall down and come into contact with environmental surfaces or has chance to enter human respiratory tract. COVID-19 has therefore high potential to transmit through salivary droplets and dental procedure generated aerosols from infected man/woman in at clinics and hospitals [17].
3. The viral incubation period for individuals to individuals who get infected with COVID-19 is quite variable but this can be protracted. It has been known that those without symptoms of disease still have high possibility to transmit the virus from one to another. This makes it extremely difficult to identify those individuals that pose a risk. Due to the contagious nature of the disease, while history taking and an examination are carried out for the patient and assess for urgency of dental need, an asymptomatic patient can be as a potent source of infection for others [18].
4. The risk of Nosocomial Infection. Since the health care workers themselves are among the higher risk group for infection, exposure to them and to the health care settings is best avoided or postponed to control community spread. In accordance to case report during the earlier phase of the pandemic, an analysis was done for hospitalized patients with confirmed COVID-19 cases and it demonstrated that 41% out of them were presumed to have been previously infected consisting of 29% healthcare workers and 12% patients [19].

Prevention Measures and Infection Control in Dental Office

Dental clinicians and oral care professionals should have in mind of how COVID-19 spread and gets transmitted, how to identify patients with COVID-19 infection, and what protection equipments are to be utilized during

daily practice, so as to prevent the spread of COVID-19 effectively. Proper and strict infection control steps are therefore mandatory to be followed by dental clinicians as well as oral care professionals, mainly considering the fact that dental/medical generated aerosols and salivary droplets were considered as the main source of COVID-19 infection particularly when dental procedure is being performed [20].

Clinical Examination

Preoperative antiseptic and antimicrobial containing mouth rinse is effective to suppress the count of microorganisms in the oral cavity. Dental procedures that might induce reflux and coughing reflects should be avoided as much as we can or cautiously done if it is really unavoidable. Aerosol-generating dental procedures e.g the use of a three-way syringe and ultrasonic scaler need to be reduced as much as possible because they will cause more chance for the viral particle to spread. Intraoral radiography method is the most frequently performed radiographic technique among all dental imaging types however it easily stimulates saliva production, secretion and coughing. Therefore, extraoral dental radiographic technique such as orthopantomography (OPG) / panoramic radiography and cone beam computed tomography (CBCT) act as good selections during this worldwide outbreak of COVID-19 [20-21].

Hand Sanitization

Fecal-oral transmission pathway was reported for COVID-19, which emphasizes the importance of hand hygiene in daily dental practice. Despite proper hand hygiene protocol is the routine prerequisite for dental practice, hand sanitizing/washing compliance is still relatively low, which constitutes a great challenge to the infection control during this pandemic outbreak of COVID-19 transmission. Reinforcement for proper hand sanitization is of the utmost importance. The dental and oral healthcare professionals should wash their hands properly based on WHO hand washing protocols before starting patient clinical examination, before every regular dental procedures, after treating the patient, after touching the surroundings and equipments without prior disinfection, and also after touching the oral mucosa, oral fluid, tooth,

damaged skin or wound, blood, body fluid, saliva, secretion, and excreta. More cautions must be taken for the dental and oral healthcare professionals to avoid touching their own eyes, nose and mouth [22-23].

Personal Protective Equipment for Dental and Oral Healthcare Professionals

At the moment, there is no standard universal guideline for the protection of dental and oral healthcare professionals from COVID-19 infection at the dental clinics and hospitals. Despite no dental professional has been officially reported to acquire COVID-19 infection from daily dental practice, the previous experience with the SARS-coronavirus has demonstrated large numbers of acquired infection of medical professionals at hospital. Since airborne droplet transmission generated from dental/medical procedure is considered as the main pathway of infection spread, especially in dental clinics and hospitals therefore barrier-protection equipment, including protective eyewear/goggles, protective outwear/suit, medical/surgical masks, hand gloves, surgical head cap/head cover, proper face shields is highly recommended for all dental and oral healthcare providers at dental clinic or hospital during the pandemic outbreak period of COVID-19 [24-25].

Based on the possibility of the transmission of COVID-19 infection, there are three level protection of the dental and oral healthcare professionals are recommended for this specific situation [26-27]. (1) First level protection (standard protection for healthcare personnel at dental clinic or hospital) [26]. This involves wearing disposable surgical cap, surgical mask, surgical suit/clothes, using eye goggles or face shield and latex or nitrile hand gloves [27]. (2) Second level protection (advanced protection for dental and oral healthcare professionals) [26-27]. Wearing disposable surgical cap, surgical mask, protective eye goggles, face shield and working suit with disposable isolation apparel or surgical clothes outside and hand gloves. (3) Third level protection (strengthened protection when it is likely to be in contact with patients of suspected or confirmed COVID-19 infection) [27-28]. Despite patients with COVID-19 infection are not expected to be treated at dental clinic or hospital, in the inevitable event that this case does occur and dental professional cannot avoid close

contact with those patients, special protective outwear is needed [28]. If protective suit is not available, working clothing with extra disposable protective apparel outside must be worn [29-30]. Besides, disposable surgical cap, protective eye goggles, face shield, surgical mask, latex/nitrile hand gloves and shoe cover should be used [29].

Dental High-Speed Handpiece

The high-speed dental handpiece without anti-retraction valves is very likely to expel the debris, oral fluids and saliva during dental procedures [30]. More crucial things are that oral microorganisms including bacteria and virus might further contaminate the air and water tubes present in the dental chair and therefore can potentially cause cross-infection during dental treatment procedure [27-30]. One study has demonstrated that the anti-retraction dental high-speed handpiece can significantly reduce the backflow and spread of oral microorganisms into the tubes of the handpiece and dental chair compared with the dental high-speed handpiece without anti-retraction function [27]. Hence, the use of dental high-speed handpiece without anti-retraction function should be avoided during the pandemic outbreak period of COVID-19. Anti-retraction dental high-speed handpiece with special anti-retractive valves or anti-reflux designs are strongly recommended as an extra preventive method to minimize cross-infection [28-29].

Rubber Dam

Rubber dam is the standard protocol of isolation in dental procedure especially for endodontic treatment as well as restorative procedure. Rubber dam use during dental procedure can significantly reduce the production of saliva and blood generated aerosol especially in cases when dental high-speed handpiece and dental sonic/ultrasonic machine are used [30]. It was reported that the rubber dam use could significantly minimize dental procedure generated small airborne particles in 3 ft diameter of the operational area up to 70% and also prevent the saliva from spreading during dental treatment [30].

Anesthetize and isolate the tooth with a rubber dam before starting endodontic access; ideally, isolation should be performed with the clamp on

the target tooth and the rubber dam should cover the patient's nose throughout the endodontic procedure. The Oraseal or OpalDam should be used sparingly to ensure a moisture tight seal around the tooth (30-31)

When rubber dam is used during dental procedure, high volume suction for aerosol and spatter is suggested be used during the entire procedures along with regular suction. In this case, the implementation of a four handed dentistry with dental assistant becomes very necessary [30]. In certain case, if rubber dam isolation protocol is not possible to be applied, other alternatives such as chemo-mechanical caries removal (using CarisolTM) procedure, atraumatic restorative treatment (ART) procedure, manual/hand scaling procedure (using hand scaler) are recommended for caries removal, restoration and periodontal scaling so as to reduce the generation of aerosol as much as possible [29-30].

Dental Clinic/Hospital Disinfection

Dental/medical institutions should do strict disinfection protocols in both clinic and public area [30]. The clinic area should be sanitized and disinfected following the management of standard surface cleaning and disinfection of medical/dental environment protocols. Public areas around dental clinic and medical/dental appliances must be properly and regularly

disinfected including clinic/hospital floor, door handles, chairs, tables and desks [30]. The elevator/staircase should be disinfected regularly as well. Those who take elevators should wear masks and avoid touching buttons and other objects [29-30].

High Volume Evacuator (HVE)/ Suction and HEPA Filter

Removing airborne contamination from the air of the operating room should use high efficiency HEPA filter, and Ultra Violet chambers in the ventilation system and sanitizing with 1% sodium hypochlorite, or 70 % alcohol based sanitizers preferably [14]. The use of Extra/Intra oral a High-Volume Evacuator (HVE), has been shown to reduce the contamination arising from the operative site by more than 90 percent [30-31]. HVE, an innovative product from unicorn dentmart removes a large volume of air within a short period. An evacuator that pulls a high vacuum but does not remove a large volume of air, such as is used routinely for hospital suction, is not considered an HVE. The usual HVE used in dentistry has a large opening (usually 8 millimeters or greater) and is attached to an evacuation system that will remove a large volume of air (up to 100 cubic feet of air per minute). The small opening of a saliva ejector does not remove a large enough volume of air to be classified as an HVE (Figure 2)

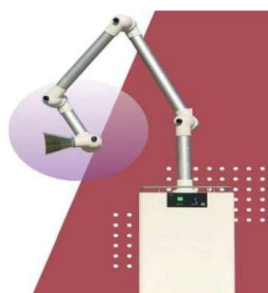


FIGURE 2: High volume suction with HEPA Filter

Emergency Case Plan and Management

Dental emergency cases can be present in our dental clinic and they can exacerbate in a short period of time and those cases therefore need immediate emergency treatment. The use of rubber dam and high-volume suction can contribute to minimize dental procedures generated aerosol[30]. Additionally, medical face

shield and goggles are essential to be used if high-speed or low-speed drilling procedure with water cooling spray is used. Based on clinical experience during this global pandemic, if a tooth presented with symptomatic irreversible pulpitis, access cavity procedure could be done with chemo-mechanical caries removal under rubber dam isolation and a high-volume suction

following local anesthesia and then pulp devitalization procedure can be applied to reduce the emergency pulpal pain [31]. Tooth filling/temporary filling material can be renewed without replacing a devitalizing paste according to the manufacturer's recommendation [32]. If there was a patient who had a spontaneous pulsating dental pain resulted from a crack without visible dental defect or decay resulting in crack tooth syndrome and for this case a high-speed handpiece had to be used for cavity access preparation [32-33]. In this case if the patient wanted to save the tooth, he/she was scheduled as the last patient in the day in order to minimize the risk of nosocomial infection to other patients. After accomplishing the treatment, appropriate environmental cleaning and dental instrument disinfection procedures were to be done properly. In addition, patient with suspected COVID-19 infection should be treated in an isolated well-ventilated room or negatively pressured room [33-36].

The treatment plan of traumatized tooth such as tooth/root fracture, lateral luxation, subluxation, concussion, extrusion, intrusion, infraction, avulsion and alveolar fracture is made based on the case severity, patient's age, the development of the apical tissue and the duration of tooth avulsion. If the particular poor prognosis traumatized tooth needs to be extracted, absorbable suture is chosen. For patient with case of facial soft tissue contusion, proper debridement and suturing should be performed during the procedure [3-4].

It is highly recommended to disinfect and clean the affected trauma site gently and utilize the high-volume saliva ejector/suction to avoid generating small airborne aerosols particles. Life-threatening cases with oral and maxillofacial complication should be admitted to the hospital immediately and chest computer tomography scan (CT-scan) is suggested if available to exclude suspected infection because the real time reverse transcription-polymerase chain reaction (rRT-PCR assay) test takes time and it needs a laboratory with pan-coronavirus or specific COVID-19 detection capacity [22].

Endodontic procedure

Pre-procedural antimicrobial mouth rinses, such as povidone-iodine, cetylpyridinium chloride or chlorhexidine containing mouthwash may turn to

be an advantageous method to suppress the number of microorganisms in procedure generating aerosols and oral fluid drops during dental procedures especially endodontic treatment (37-38).

There are some controversial statements as to whether use a pre-operative mouth rinse before undergoing any endodontic procedures. Latest study identified that cetylpyridinium chloride and povidone-iodine mouthwashes are quite effective in reducing the viral salivary load. Similarly, another study found that povidone-iodine mouthwashes is effective in reducing COVID-19 infection degree. Conversely, one different study demonstrated that the use of hydrogen peroxide and chlorhexidine containing mouthwashes are ineffective in reducing the number of COVID-19 viral load intraorally. Despite the conflicting evidence the current guidance advises the use of pre-operative mouth rinse for at least 30 seconds prior to commencing endodontic treatment, specifically recommended is a 1%–1.5% hydrogen peroxide or 0.2% povidone-iodine rinse for 60 seconds. (39)

Current guidelines recommend single sitting endodontic treatment modality over the multiple visit because it has the advantage to reduce the number of viral exposure. This can be too achieved by performing orifice barrier, coronal seal or indirect restoration under dental dam at the time of root canal filling. (40)

Endodontic treatments can be classified into three categories: (41) emergency procedures requiring immediate treatment care, urgent care procedures which require immediate attention but not as immediate as an endodontic emergency case, elective procedures that can be time lined based on patients'/providers' convenience.

If root canal procedure is indicated the only thing needs to be concerned is during the beginning of treatment such as access cavity preparation because this procedure will lead to aerosol generation. The latter steps do not produce aerosols such as chemomechanical preparation and root canal filling. (41)

Treatment options like pulp capping or pulpotomy can effectively reduce pain as well in case root canal therapy is not indicated or can not be performed in certain oral care center. Proper attention is needed in case selection so as to

minimize possibility of failure, exacerbation of symptoms. (Figure 3) Single sitting RCT is a good treatment option where root canal chemomechanical preparation is utmost essential part in clinical situations especially in the case of symptomatic apical periodontitis or acute/chronic apical abscess. In systematic reviews, Moreira et al (2017) stated that there is no difference between single sitting and multiple sitting root canal treatment (42). In fact, single sitting RCT have lesser post-operative complications and higher efficacy (42)

When using endodontic microscope, then all the barrier/protection covering the equipment should be utilized. Acetate sheets could be used as a protective barrier to protect the binocular of the endodontic microscope. In the case of using a dental loupe and headlight, it can be adapted onto a face shield, as also observed. (43)

Following access cavity preparation step, irrigation with sodium hypochlorite is recommended. For cases of vital pulp, pulpotomy can be useful in terms of reducing treatment time, with high rates of success in pain control. In cases of pulp necrosis or in vital cases where endodontic preparation is necessary, cone beam computed tomography is the good choice because we can avoid, exposing the patient's oral cavity to intraoral radiological procedure. Single file system and one time use of any endodontic file system should be preferred, aiming to minimize working time and avoid the risk of re-sterilization. Selecting a resistant material for

temporary sealing of the tooth and check the occlusion is very important to reduce post operative discomfort. (42-43)

Moreover, it is advisable to give instruction to the patients whenever possible to avoid chewing on the affected tooth for about 24 hours. To manage expectations, inform the patient that the symptoms may take some time to subside. Provide the patient with the pain relieving medication of your choice, if it is necessary. (44)

During the pandemic, extraoral radiographs such as CBCT and OPG were recommended to reduce viral contamination risk, however, diagnostic Intraoral radiographs may now be performed with compliance to universal precautions such as disinfecting film packets and surfaces including control panels and ensuring clean and dirty zones for films and film holders and the use of wrap protection on the intra oral x ray digital sensor. (44)

Following putting of the PPE, immediately use hand hygiene, and staff engaged in environmental cleaning and waste management should wear appropriate PPE. Furthermore, it was recommended to use effective disinfectants against the microorganisms for dental clinic or hospital; dental clinics are particularly important to be regularly cleaned for all touched surfaces. It is very crucial to treat the wastes as infectious clinical waste belong to Category B, according to the local regulations and following policies of the healthcare facility. (44-45)

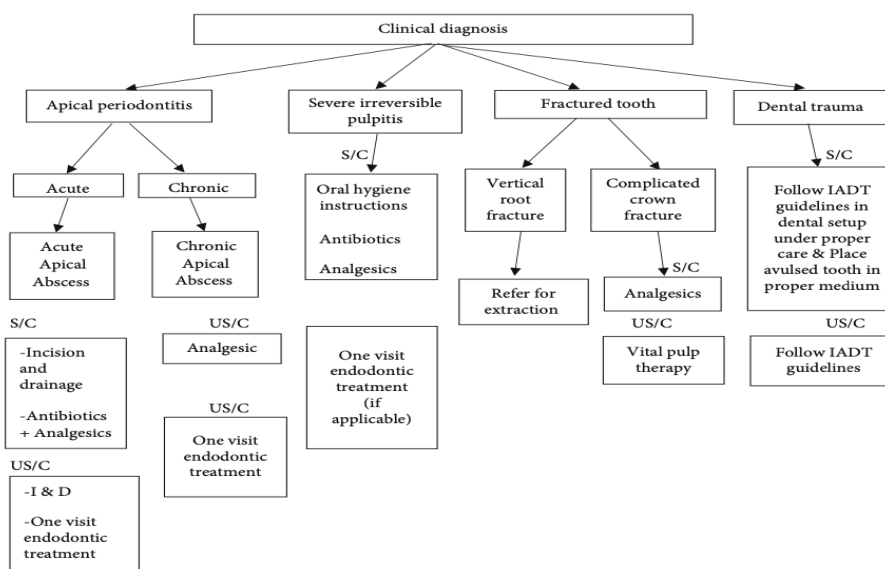


FIGURE 3: Endodontic Clinical Recommendation during Covid-19 pandemic (44)

Pharmacological Management

Managing and controlling the patients symptoms through medication must always be the primary treatment approach both for suspected or confirmed COVID-19 case. (45) A report suggested that the use of ibuprofen caused further worsening of systematic symptoms in four confirmed patients. (45) This thing makes couple of health organizations release statements, including WHO, warning against the administration of ibuprofen for suspected or confirmed COVID-19 patients. In their latest update, WHO has withdrawn their warning regarding the use of ibuprofen because of insufficient evidence. (44-45) Accordingly, clinicians may consider the use of ibuprofen alone or in combination with acetaminophen or dexamethasone to control dental pain for COVID-19 positive patients but it is based on the severity level of symptomatic pain. Clinicians may follow their normal postoperative pain relieving medication protocols and the guidelines for antibiotics prescription. (45-46)

CONCLUSION

The risk of transmission of diseases through dental procedure generating aerosol is an inseparable part of dentistry especially during restorative and endodontic treatment procedure. Those risks can be reduced by using a number of managements, including protection equipments and work-practice infection controls. Emergency patients must be put in utmost priority rather than non-emergency patients. COVID-19 and its variants are the viruses that have a permanent presence and COVID-19 guidelines may therefore always be the gold standard practice for endodontic as well as restorative procedures to ensure safety of patients and dental professionals.

Author Contributions

DD, TA, AP contributed to data acquisition, analysis, and interpretation and drafted the manuscript; DD, TA, AP contributed to conception and design and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

The Conflict of Interest Declarations

Declarations of interest: none

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