

Pathogen Reduction Technology: A Novel Possibility for Inactivation of Blood Products Used in Oral and Periodontal Surgeries

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ABSTRACT

Emergency surgical treatment has been challenging and the risk of blood contamination has been high, which is a concern among the medical and dental fraternity. The risk outweighs the benefits in these unprecedented times if proper screening and inactivation of blood products are not performed. Pathogen reduction technologies incorporate various modalities for the inactivation of blood products mainly related to blood transfusion. Oral surgical procedures and periodontal surgeries use platelet-rich fibrin for various regenerative procedures that amplify the prognosis positively. The use of blood products for various treatments could result in contamination, a factor which should be significant attention. The objective of this study was to review the role of pathogen reduction technology in inactivating pathogens in blood products and its use in oral and periodontal surgical procedures. The literature presented in the study is from original studies from a period of 2000 to 2020 which was sourced from Medline, PubMed, and Cochrane central databases. Relevant published papers and in-press papers that provided information were identified and selected. The studies presented have shown data related to implementation of pathogen reduction technologies in relation to the severe acute respiratory syndrome, Middle East respiratory syndrome, and its possible implementation in coronavirus disease-2019 (COVID-19). The paper reviews the various technologies offered and the possibility to eradicate pathogens found in routine blood products, used in oral and periodontal surgical procedures. In all probability, the use of pathogen reduction technology might offer a ray of light to contain the spread among dental treatment procedures

KEYWORDS: COVID-19, implant, oral surgery, periodontal, PRF, PRT

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) was declared a pandemic on March 21, 2020.^[1] The virus caused a global outbreak reaching out to 213 countries, debilitating health systems, and has proven a challenge for medical personnel in containing the virus. The pandemic has established new epicenters in Brazil and recently in India. The infection has escalated drastically, with the number of active cases increasing globally.^[1]

Providing dental health delivery across the globe has been a challenge owing to COVID-19. Dentists have been advised by statutory bodies such as the World Health Organization (WHO) and the Center for disease control (CDC) to be emergency prepared by using personal protective equipment (PPE) and also to perform only elective procedures.^[1,2] Furthermore,

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guidelines issued by CDC and further modified by individual countries depending on various factors have made it mandatory to evaluate all patients by taking a detailed medical, dental history as well as travel and social history. Questionnaires are to be filled by patients to rule out any of the factors that can prove whether a patient is a potential carrier or requires further medical evaluation before instituting dental treatment.^[2]

Furthermore, it was reiterated by governing medical bodies that dental treatment for suspected or laboratory-confirmed COVID-19 patients should be given only if the situation demands it or is definitely an emergency condition.^[3] Infection control measures need to be followed with emphasis on donning and doffing, to be done in an aseptic environment.

Consideration should be given to protection from body fluids mainly blood. The use of blood products, which is routinely used for various dental treatments such as platelet-rich fibrin (PRF) for various oral surgical and periodontal therapy exposes both the patient and dental operator to equal risk. With most COVID-19 cases displaying varied clinical symptoms and some asymptomatic, blood safety while performing dental treatment should be given due importance. The clinical significance of implementing pathogen reduction technologies (PRTs) for dental treatment involving blood products reduces the risk of cross-contamination and infection, which are of paramount importance when delivering evidence-based quality dental care. This narrative aims to detail available pathogen inactivation methods for blood products and its possibility of inactivating coronaviruses.

RATIONALE

Coronaviruses (CoV) are the largest known RNA viruses. Among the known CoV, seven have the ability to cause infections in humans and more importantly respiratory diseases.^[2] The presence of Severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012 has shown similar clinical symptoms as shown by COVID-19, which was isolated from epithelial cells of the human airway.^[2] Using next-generation sequencing (NGS), the virus was classified and identified to be a new member of betacoronaviruses.^[3]

From clinical studies, it is seen that COVID-19 virus infects lymphocytes and has the ability to replicate when blood is drawn from COVID-19 patients, a feature which is similar to the SARS virus. This was seen in plasma where the concentration of COVID-19 did not differ in either the acute or convalescent phase.^[3] This further strengthened the fact that COVID-19 has the

ability to contaminate blood and blood products. The striking feature about SARS-COV-2 with relation to SARS-COV is the presence of negative titer during the screening of blood products, similar to the SARS-COV, although in SARS-COV clinical symptoms shown by patients were severe. In COVID-19 patients, the symptoms were mild.^[4] This becomes more intriguing when CDC has not proposed any guidelines for blood collection as there is no available data for risk of transmission of COVID-19 using blood products.^[5]

OBJECTIVE

The aim of this paper was to evaluate the various PRTs available and to see if this technology can be implemented for oral and periodontal surgical procedures.

MATERIALS AND METHODS

ELIGIBILITY CRITERIA

Articles related to SARS-CoV-2, SARS, MERS, PRT, PRF, periodontal, and oral surgical procedures were investigated. Articles primarily in English language were selected. A Boolean search was implemented to connect a range of keywords. (((((((SARS-COV-2) OR (MERS)) OR (SARS)) AND (PRT)) OR (PRF)) OR (TRANSFUSION)) OR (DISINFECTION)) OR (BLOOD TRANSFUSION)) OR (ORAL SURGERY)) OR (PERIODONTAL PROCEDURES)

INFORMATION SOURCES

The study followed partially the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines as it is a narrative review. Articles were selected from years 2000 to 2020 from databases, PubMed, PubMed Central, and Cochrane. The Pubmed (MEDLINE) search engine was used to collect the most recent and relevant information. The search yielded 15,406 articles, reports, and studies. The studies comprised Randomized trials, clinical trials, and reviews. More studies were also obtained from google scholar. The most relevant studies were selected and reports from statutory institutions such as WHO and CDC were taken into consideration. The selected articles are included in the reference list [Figure 1].

SEARCH CRITERIA

The search for the articles was limited to the keywords used for the study and the articles were localized based on these criteria.

STUDY SELECTION

The studies were filtered and only those that showed possible relation and which had similar steps and guidelines as inactivation procedures for SARS

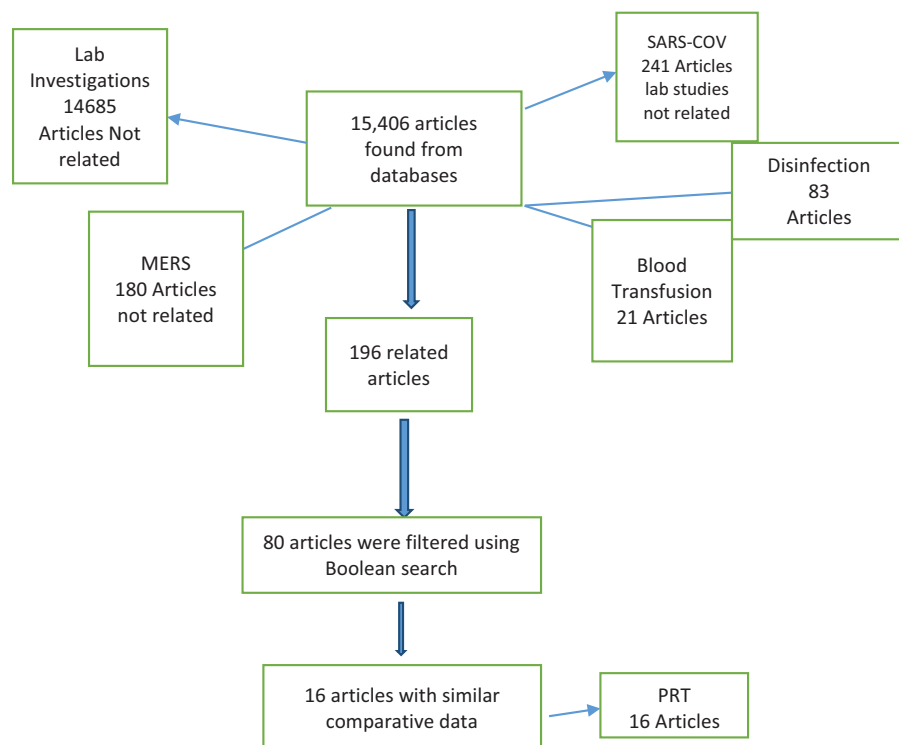


Figure 1: Recruited articles flowchart

and MERS were included. Studies that enumerated inactivation of blood products for other viral and medical conditions were excluded.

DATA COLLECTION PROCESS

The data were extracted from the articles where the emphasis was given to PRT.

DATA ITEMS

A Boolean search incorporating the keywords yielded 15,406 articles. Articles that were pertaining to animal studies, *in vitro* models, lab investigations, and did not signify PRT were excluded from the search. Furthermore, by reviewing the literature with emphasis on use of PRT with relation to COVID-19, SARS, MERS, Disinfection, Blood Transfusion yielded 196 articles. Of the 196 articles, it was further filtered using the keywords PRT OR PRF. A total of 80 articles were found; the literature were reviewed for PRT and of any keywords mentioned such as SARS, MERS, and COVID-19. A total of 16 articles were found which showed data pertaining to inactivation of SARS and MERS [Table 1].

RISK OF BIAS

To standardize selection of studies, relevant literatures pertaining to lab investigations, viral inactivation, and management of viral transmissions were only considered.

DISCUSSION

PERIODONTAL TREATMENT OUTCOME

Periodontists and oral surgeons are susceptible to viral and bacterial infections owing to the risk of invasiveness. The risk is more due to the close contact while treatment is performed and also due to the large amount of aerosols and droplets being generated that are contaminated with the virus.^[1,2] The extended period of time the aerosols and droplets remain has serious implications in increasing the “window of infectivity” among dental personnel. The ability of the COVID-19 virus to remain in inanimate surfaces such as metal, glass, and plastic for extended periods of time also contributes to the transmission.^[6] The longevity of the virus in the environment and the ability to cause secondary infection elsewhere can be attributed to the presence of the virus for about 72 h on plastic and metal tips.^[7] Furthermore, COVID-19 also has the ability to remain viable for up to 6 h in a suspended state.^[7] Periodontal and oral surgical procedures that contribute to this phenomenon are routine prophylaxis, extractions, and dental implants placement procedures that are indicated for appropriate cases. The use of dental implant procedures along with regenerative options such as bone grafts, PRF for oral rehabilitation is advocated depending on the urgency of the treatment. In the present scenario, dentists prefer delayed treatment, owing to COVID-19. Emergency dental treatment is

Table 1: Included viral inactivation studies

Author	Year	Type of virus	Type of study
Wang <i>et al.</i> ^[3]	2004	SARS	Clinical
Yilla <i>et al.</i> ^[4]	2005	SARS	Experimental/clinical
AABB ^[5]	2019	COVID-19	Review
Rabenau <i>et al.</i> ^[11]	2005	SARS	Experimental
Hindawi <i>et al.</i> ^[12]	2018	MERS	Clinical/experimental
Eickmann <i>et al.</i> ^[13]	2020	SARS, NiV, Congo Hemorrhagic fever	Clinical experimental
CDC ^[14]	2020	COVID-19	Review
Chang <i>et al.</i> ^[15]	2020	COVID-19	Review
Darnell <i>et al.</i> ^[16]	2014	MERS	Experimental
Leclercq <i>et al.</i> ^[17]	2014	MERS	Clinical/experimental
Simona <i>et al.</i> ^[18]	2017	General viruses	Experimental
Hashem <i>et al.</i> ^[19]	2019	MERS	Clinical/experimental
Lin <i>et al.</i> ^[20]	2005	General viruses	Clinical/experimental
Eickmann <i>et al.</i> ^[21]	2018	MERS/Ebola	Clinical/experimental
Le Chang <i>et al.</i> ^[22]	2020	COVID-19	Review
CSBT ^[23]	2020	COVID-19	Review

AABB = American Association of Blood Bank, NiV = Nipah Virus, CDC = Center for Disease Control, CSBT = Chinese Society for Blood Transfusion

given importance and elective dental procedures are postponed and the treatment is rated for its overall urgency by seeing clinically if the patient has a definite limitation in dental comfort.^[8] PRF belongs to a group of platelet concentrate that is used routinely in implant surgeries for its excellent regenerative and growth factor signaling properties. The ease of preparation without extensive handling makes it a popular choice among oral surgeons and periodontists to incorporate it routinely during implant surgical procedures.^[9] Furthermore, the ability of PRF to reduce tissue inflammation, promoting vascularization, signaling osteoblastic cell lineage and bone forming as well as improving scaffold topography is reported.^[10] The amount of blood drawn is usually in the range from 8-10cc to get enhanced and viable rich PRF. The ability to offer a cost-effective option without any potential side effects makes it a very popular choice among periodontists and oral surgeons alike.

The presence of varied clinical symptoms of COVID-19 infection is being currently monitored worldwide. As the risk of transmission goes undissipated, the presence of viral RNA in serum or plasma could be detected in a COVID-19 patient within 2 or 3 days post-exposure.^[10] The possibility of infection among COVID-19 patients who are in the incubatory phase is questionable. The neutralizing of the virus to heat and acid-pH was reported in a study.^[11] The coronaviruses tend to be more stable at lower temperature, around 3°C–5°C.^[12]

BLOOD BORNE RISKS AND ADVENT OF PATHOGEN REDUCTION TECHNOLOGY

The concept of PRTs has recently gained momentum with the possibility of completely eradicating the potential risk of transmission of coronaviruses in

blood products and blood derivatives.^[13] Although the technology aimed at inactivating viral contaminants with relation to blood transfusion products, the concept has gained importance and is currently being investigated for its potential benefits with relation to other surgical disciplines where contact with blood or use of blood products is seen. In light of this fact, PRF which is routinely used in dentistry is a blood-derived product where chances of infecting an asymptomatic patient is high. In such cases, the results show positive for COVID-19 in a time frame between 72h to 2 weeks.^[14] There are various modalities of PRT that are used and the applicability of a single PRT treatment for all blood products is not suitable.^[15] In earlier studies involving SARS-CoV and MERS, inactivation of the viruses was performed using heat and solvent/detergent treatment. The plasma would be exposed to a temperature of 60-70°C for a period of 20–30min for reduction of SARS-CoV virus. Correspondingly, exposing the plasma for a period of 50 °C–60°C for 30min would reduce MERS virus.^[16,17] The solvent/detergent treatment mechanism of action is by disruption of lipid membrane. Though it is an effective modality for inactivation, it is effective against SARS-CoV and not applicable for MERS [Table 2].

Use of UV (ultraviolet) light of different wavelengths also offers reduction of SARS-CoV and MERS activity in blood products. Studies indicating use of riboflavin and Amotosalen, which is a DNA, and RNA crosslinked psoralen compound which can inactivate pathogens.^[18,19] Amotosalen interacts with UV-A and interpolates among nucleic acid and causes cross-linking because of UV exposure rendering the virus inactive.

Table 2: Current different methods of pathogen inactivation in blood products by Pathogen reduction technology (PRT)

Methods	Mechanism of action
Heat	Protein denaturation activity
Amotosalen+UV-A light	Interpolates into nucleic acid, influences ribosomal activity and causes cross-linking
Riboflavin+UV-B light	Activates an oxygen dependent electron transport system
Methylene blue+visible light	Inoculates into the nucleic acid and responsible for the formation of free oxygen radicals

UV = ultraviolet

On the contrary, riboflavin combines with UV-B resulting in electron transfer by associating with nucleic acids. The third method of PRT involving UV is UV-C which uses just light and does not use subsidiaries.^[19,20] Further the use of a photodynamic agent, methylene blue which is used as a Laser treatment modality, to decontaminate subgingival pockets using laser, when coupled with visible light results in the formation of radical oxygen species which results in the disruption of virus cell structure [Table 2].^[21,22]

COVID-19 has varied clinical presentations, the ability of the virus to infect when using blood products such as PRF in periodontal procedures is a concern which needs to be looked at with urgency. Clinics, medical establishments and university clinics engaged in performing these procedures especially when lockdown measures are relaxed and statutory bodies approving gradual resumption of elective dental procedures should make it obligatory to take a detailed questionnaire, requesting personal history, travel history, relatives if any who had developed COVID-19, other relevant questions that can sum up an arbitrary conclusion, before embarking on a procedure involving use of blood product of any kind for better treatment prognosis. Although the current literature indicates the use of PRTs to inactivate SARS-CoV and MERS and holds great promise, more studies and tests will be needed to evaluate the role of efficacy of PRT in SARS-CoV2 conditions. One of the proposals is to introduce antibody testing before collecting any blood product and also full screening irrespective of the treatment or procedure to be given such as temperature checks and history taking.^[23-25] Contrary to this and with relation to antibody tests, the CDC has made a statement that currently data are insufficient to determine if an individual has adequate immunity against COVID-19 by detecting the levels of antibodies.^[14] The statement advocated the fact that there could be a cross-reactivity with other coronaviruses, especially in a person who develops common cold where the pathogen belongs to the same family. It further reiterates the fact that IgG and IgM antibodies are normally not seen in early or mild infections and are visible in tests only after a certain period. Further, the choice of testing whether

antigen based or antibody based is at the discretion of the dental operator.

It would be prudent for professional organizations like the CDC, the association of public health laboratories, and Epidemiologists to provide recommendations for dental surgeons performing these dental procedures.

Some of the limitations are that not much literature is present related to PRT. Use of mouthwashes such as chlorhexidine, betadine to control, and reduce viral load in possible laboratory-confirmed cases or carriers of COVID-19 is still being studied and no clear evidence exists.^[25] More tests, research, and guidelines need to be proposed such that dentists can make informed decisions.

CONCLUSION

With the rapid rise of COVID-19 cases globally, great consideration is given for dental treatment delivery with paramount importance for hand hygiene, use of PPE, use of mouth rinses, aerosol spread reduction, and placing high-efficiency particulate air (HEPA) filters within the dental operator. The presence of risk of transmission of COVID-19 through blood products during routine dental procedures is very much a reality.

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CONFLICTS OF INTEREST

There are no conflicts of Interest

AUTHORS CONTRIBUTIONS

Not applicable.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

No clinical study was carried out, hence no patient declaration of consent are needed or appropriate.

PATIENT DECLARATION OF CONSENT

Not applicable.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article.

REFERENCES

- Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on Inanimate surfaces and its inactivation with biocidal agents. *J Hosp Infect* 2020;104:246-51.
- Cleveland JL, Gray SK, Harte JA, Robison VA, Moorman AC, Gooch BF. Transmission of blood-borne pathogens in US dental health care settings: 2016 update. *J Am Dent Assoc* 2016;147:729-38.
- Wang H, Mao Y, Ju L, Zhang J, Liu Z, Zhou X, *et al.* Detection and monitoring of SARS coronavirus in the plasma and peripheral blood lymphocytes of patients with severe acute respiratory syndrome. *Clin Chem* 2004;50:1237-40.
- Yilla M, Harcourt BH, Hickman CJ, McGrew M, Tamin A, Goldsmith CS, *et al.* SARS-coronavirus replication in human peripheral monocytes/macrophages. *Virus Res* 2005;107:93-101.
- American Association of Blood Banks. Update: Impact of 2019 Novel Coronavirus and Blood Safety. Available from: <http://www.aabb.org/advocacy/regulatorygovernment/Documents/Impact-of-2019-Novel-Coronavirus-on-Blood-Donation.pdf>. [Last accessed on 2020-10-7].
- Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: The possible role of dry surface contamination. *J Hosp Infect* 2016;92:235-50.
- van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, *et al.* Aerosol and surface stability of SARS-cov-2 as compared with SARS-cov-1. *N Engl J Med* 2020;382:1564-7.
- Chrcanovic B, Cruz A, Trindade R, Gomez R. Dental implants in patients with oral lichen planus: A systematic review. *Medicina* 2020;56:53.
- Liu R, Yan M, Chen S, Huang W, Wu D, Chen J. Effectiveness of platelet-rich fibrin as an adjunctive material to bone graft in maxillary sinus augmentation: A meta-analysis of randomized controlled trials. *Biomed Res Int* 2019;2019:7267062.
- Ali S, Bakry SA, Abd-Elhakam H. Platelet-rich fibrin in maxillary sinus augmentation: A systematic review. *J Oral Implantol* 2015;41:746-53.
- Rabenau HF, Cinatl J, Morgenstern B, Bauer G, Preiser W, Doerr HW. Stability and inactivation of SARS coronavirus. *Med Microbiol Immunol* 2005;194:1-6.
- Hindawi S, Hashem A, Damanhouri G, El-Kafrawy S, Tolah A, Hassan A, *et al.* Inactivation of Middle East respiratory syndrome-coronavirus in human plasma using amotosalen and ultraviolet A light. *Transfusion* 2018;58:52-9.
- Eickmann M, Gravemann U, Handke W, Tolksdorf F, Reichenberg S, Müller TH, *et al.* Inactivation of three emerging viruses - severe acute respiratory syndrome coronavirus, Crimean-Congo haemorrhagic fever virus and Nipah virus - in platelet concentrates by ultraviolet C light and in plasma by methylene blue plus visible light. *Vox Sang* 2020;115:146-51.
- Centers for Disease Control and Prevention. Association of Public Health Laboratories and Council of State and Territorial Epidemiologists. Public Health Considerations: Serologic Testing for COVID-19. Version 1—May 7, 2020.pdf icon. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html>. [Last accessed on 2020 June 30].
- Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. *Transfusion Medicine Reviews* 2020;34:75-80.
- Darnell ME, Taylor DR. Evaluation of inactivation methods for severe acute respiratory syndrome coronavirus in noncellular blood products. *Transfusion* 2006;46:1770-7.
- Leclercq I, Batéjat C, Burguière AM, Manuguerra JC. Heat inactivation of the middle east respiratory syndrome coronavirus. *Influenza Other Respir Viruses* 2014;8:585-6.
- Simona S, Gobatto S, Infanti L, Reiner M, Bonetti N, Meyer S, *et al.* Amotosalen/ultraviolet A pathogen inactivation technology reduces platelet activatability, induces apoptosis and accelerates clearance. *Haematologica* 2017;102:1650-60.
- Hashem AM, Hassan AM, Tolah AM, Alsaadi MA, Abunada Q, Damanhouri GA, *et al.* Amotosalen and ultraviolet A light efficiently inactivate MERS-coronavirus in human platelet concentrates. *Transfus Med* 2019;29:434-41.
- Lin L, Hanson CV, Alter HJ, Jauvin V, Bernard KA, Murthy KK, *et al.* Inactivation of viruses in platelet concentrates by photochemical treatment with amotosalen and long-wavelength ultraviolet light. *Transfusion* 2005;45:580-90.
- Eickmann M, Gravemann U, Handke W, Tolksdorf F, Reichenberg S, Müller T, *et al.* Inactivation of Ebola virus and Middle East respiratory syndrome coronavirus in platelet concentrates and plasma by ultraviolet C light and methylene blue plus visible light, respectively. *Transfusion* 2018;58:2202-7.
- Le C Yan Y, Wang L. Coronaviruses disease 2019: Coronaviruses and blood safety. *Transfus Med Rev* 2020;34:75-80.
- Chinese Society of Blood Transfusion. Recommendations on Blood Collection and Supply During the Epidemic of Novel Coronavirus Pneumonia in China (1st edition) [Chinese]. Available from: <https://www.csbt.org.cn/plus/view.php?aid=16530>. [Last accessed 2020 June 28].
- Chan W, Yuan S, Kok K, To W, Chu H, Yang J, Yuen Y. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. *Lancet* 2020;395:514-23.
- Patini R. How to face the post-SARS-cov-2 outbreak era in private dental practice: Current evidence for avoiding cross-infections. *J Int Soc Prev Community Dent* 2020;10:237-9.