

## Hydrogen Peroxide and Viruses

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Significant evidence exists for the antiviral activity of hydrogen peroxide toward coronaviruses. The US Environmental Protection Agency regulates disinfectants, and 0.5% hydrogen peroxide and other products are registered as a disinfectant for human coronaviruses (EPA List N). Inactivation of SARS-CoV-2 on surfaces can occur with a variety of biocidal agents, including hydrogen peroxide (Kampf et al.). The FDA allows use of vaporized hydrogen peroxide for sterilizing respirators for reuse under the Emergency Use Authorization Act.

Hydrogen peroxide kills SARS-CoV-2 on surfaces. It likely disrupts the viral envelope by interacting with the spike protein or disrupting the envelope and attacking the viral RNA, either of which would prevent the virus from replicating. In the presence of iron ( $\text{Fe}^{2+}$ ) or copper ( $\text{Cu}^{2+}$ ), the hydroxyl radical is generated (Floyd, Zs-Nagy), which can form 8-oxoguanosine in the viral mRNA. The formation of 8-oxoguanosine leads to incomplete translation of the viral genome (Dai; Sims et al.). RNA is more reactive with reactive oxygen species than DNA (Hofer et al.).

Exposure to SARS-CoV-2 can occur via aerosolization (Bourouiba; Anfinrud et al., Lu et al., Santarpia et al., Meselson). SARS-CoV-2 can be detected in saliva and sputum (Wang et al.; Han et al.; To et al.; Sabino-Silva et al.). Salivary glands have ACE-2 receptors to which the SARS (SARS CoV-1) virus can attach and enter the cells (Liu et al.). It is reasonable to assume that SARS-CoV-2 will also infect the salivary gland cells that have ACE-2 receptors, in addition to cells with the ACE-2 receptor within the respiratory tract (Liu). To decrease the risk of viral transmission, the American Dental Association (ADA) recommends rinsing the mouth with 1.5% hydrogen peroxide prior to conducting procedures in a dental office (ADA COVID-19 Center).

Dental team exposure can occur from a variety of processes, including direct transmission of viral particles in saliva, by inhalation of droplets, and indirect transmission through contact with procedure tools or surfaces in the examining room (Peng et al.). The likelihood of developing COVID-19 symptoms and transmitting SARS-CoV-2 to additional patients would be reduced by preprocedural treatment with hydrogen peroxide. Although it has not been tested in clinical trials against SARS-CoV-2, hydrogen peroxide is recommended as a pre-procedural rinse (Peng et al.).

Hydrogen peroxide has a long history of use in dentistry and is considered safe for daily use at concentrations up to 3% (Marshall et al. 1995). Patients rinsing with hydrogen peroxide should not swallow the rinse; however, if they accidentally do swallow peroxide in a concentration of 3% or less, it poses very little risk (21 CFR Part 356. [Docket No. 81N-033P]; Mahoney, et al.).

When used as a topical agent in the oral cavity, concerns have been raised regarding free oxygen radicals. Any peroxide product will initiate the production of free radicals, but this is not necessarily harmful. Peroxide is generally present in the human mouth. Active inflammatory cells, like pulmonary alveolar macrophages, release peroxide in the lungs and it is carried into the mouth in exhaled breath (Teng et al.; Olin et al.). In the oral cavity, the enzyme catalase breaks down hydrogen peroxide into oxygen and water very quickly. Salivary peroxidase and glutathione provide additional protective properties. Some products, like Perio Gel<sup>®</sup>, are also formulated with free radical trapping agents.

Humans make hydrogen peroxide in the liver (Chance et al.) and it is used by white blood cell for phagocytosis. In the body, phagocytic cells release active oxygen species and use reactive oxygen species internally to destroy phagocytized pathogens, including bacteria and viruses, as a normal part of the host defense system against pathogens. In treatment for oral health, the oxidizing elements of peroxide help debride bacterial cell walls. (Schaudinn et al.; Dunlap et al.) The oxygenating effects are multiple but the most important for long-term gingival health is the modification of the microenvironment of the periodontal pocket or sulcus so that healthy bacteria repopulate at the expense of pathogens. This is possible when hydrogen peroxide gel is administered with a Perio Tray® (Schaudinn et al.; Keller and Cochrane; Putt et al., 2012-2014). Against viral agents, the oxidizing properties of hydrogen peroxide are the most important against viral agents.

Although the FDA has not approved any hydrogen peroxide product for treatment or prevention of SARS-CoV-2, the preceding information provides compelling evidence for use of hydrogen peroxide in patients who present for treatment in a dental office to protect dentists, hygienists, and dental assistants from exposure to persons who may be infected with SARS-CoV-2 but are asymptomatic. Hydrogen peroxide is more stable in the oral cavity when delivered as a gel in a tray, rather than rinsing as a liquid or delivery without a tray (Marshall MV unpublished observations), including brushing with a gel (Marshall et al. 2001).

In summary, hydrogen peroxide can inhibit virus replication through a number of different mechanisms – altering the viral envelope, which can decrease binding of a virus to cells leading to reduced infectivity, alteration of nucleic acids, leading to reduced protein synthesis, and alteration of viral and intracellular proteins, leading to enzyme inactivation. On surfaces, levels of hydrogen peroxide as low as 0.5% are effective in decontamination. In the presence of iron ( $\text{Fe}^{2+}$ ) or copper ( $\text{Cu}^{2+}$ ), hydrogen peroxide can form the hydroxyl radical, which greatly increases potency as a decontaminant. Following the recommendation of the ADA to rinse with 1.5% hydrogen peroxide prior to procedures, use of a delivery tray to apply hydrogen peroxide gel will enable extended release of hydrogen peroxide, which should provide a more effective pretreatment to avoid exposure to dental office personnel to SARS-CoV-2.

\* Milton Marshall received a PhD from the University of Texas Health Science Center at Houston. His PhD dissertation was, “The mengovirus replicative form RNA: Properties and possible role in inhibition of host protein synthesis”. Mengovirus is in the family of picornaviruses in a subgroup called enteroviruses that includes poliovirus, and it has the same type of genetic material as SARS-CoV-2, a positive strand of RNA that acts like a messenger RNA, which produces an enzyme that replicates the viral RNA in a duplex (double-stranded) form; these RNAs are further replicated and proteins are translated from the positive strand. SARS-CoV-2 is an enveloped virus that contains elements of the host cell in its envelope, along with the spike protein that attaches to acetylcholinesterase-2 (ACE-2) receptors to gain entry into susceptible cells. Mengovirus and other picornaviruses have a capsid rather than an envelope. Both viruses must gain entry into a cell for replication to occur.

Milton Marshall has also worked on hydrogen peroxide-containing or -generating products to ensure their safety, presenting safety data on hydrogen peroxide to the FDA (Final Monograph for Over-the-Counter Drug Products for the Reduction or Prevention of Dental Plaque and Gingivitis, Docket No. 81 N-033P). He was also involved in establishing safety testing recommendations for peroxide-containing or -generating products that were developed by the ADA (ADA Council on Dental Therapeutics, Guidelines for the Acceptance of Peroxide-Containing Oral Hygiene Products. JADA 125(8): 1140-1142, 1994).

## References

21 CFR Part 356 [Docket No. 81N-033P] Oral Health Care Drug Products for Over-the-Counter Human Use; Antigingivitis/Antiplaque Drug Products; Establishment of a Monograph; Mahoney C, et al.

American Dental Association. [COVID-19 Center](#).

Anfinrud P et al., Could SARS-CoV-2 be transmitted via speech droplets? medRxiv, in press, 2020.

Bourouiba L. Turbulent Gas Clouds and Respiratory Pathogen Emissions Potential Implications for Reducing Transmission of COVID-19. JAMA published online 3/26/20.

Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization to Decontaminate Millions of N95 Respirators 4/12/2020.

Chance B, et al., Hydroperoxide metabolism in mammalian organs. [Physiol Rev.](#) 59(3):527-605, 1979.

Costerton W, et al., The application of biofilm science to the study and control of chronic bacterial infections. *J. Clin. Invest.* 112:1466–1477, 2003.

Dai, D-P, et al., Transcriptional mutagenesis mediated by 8-oxoG induces translational errors in mammalian cells. *Proc Natl Acad Sci USA*, 115 (16): 4218-4222, 2018.

Dunlap T, Keller D, Marshall M, Costerton J, Schaudinn C, Sindelar B, and Cotton J. Subgingival Delivery of Oral Debriding Agents: A Proof of Concept. *The Journal of Clinical Dentistry*. 2011 Nov;XXII(5):149-158.

[EPA List N](#): Products with Emerging Viral Pathogens AND Human Coronavirus claims for use against SARS-CoV-2.

Floyd RA, Zs.-Nagy I. Formation of long-lived hydroxyl free radical adducts of proline and hydroxyproline in a Fenton reaction. *Biochimica et Biophysica Acta (BBA) - Protein Structure and Molecular Enzymology*, 790(1): 94-97, 1984.

Han H et al., SARS-CoV-2 RNA more readily detected in induced sputum than in throat swabs of convalescent COVID-19 patients. *Lancet*, published online 3/18/2020.

Hofer T, Badouard C, Bajak E, Ravanat JL, Mattsson A, Cotgreave IA. Hydrogen peroxide causes greater oxidation in cellular RNA than in DNA. *Biol Chem*, 386(4):333-337, 2005.

Kampf G, et al., Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Inf*, 104:246-251, 2020.

Keller DC and Cochrane B. Composition of Microorganisms in Periodontal Pockets. *JOHD* 2019:2(2):123-36.

Liu L, et al., Epithelial cells lining salivary gland ducts are early target cells of severe acute respiratory syndrome coronavirus infection in the upper respiratory tracts of Rhesus Macaques. *J Virol* 80(8):4025-4030.

Lu Y, et al., Aerodynamic characteristics and RNA concentrations of SARS-CoV-2 aerosol in Wuhan hospitals during COVID-19 outbreak. *bioRxiv*, in press, 2020.

Mahony C, et al., An exposure-based risk assessment approach to confirm the safety of hydrogen peroxide for use in home tooth bleaching. *Regulatory Toxicol Pharmacol*, 44:75-82, 2006.

Marshall MV, et al., Hydrogen peroxide decomposition in the oral cavity. *Am J Dent*, 14:39-45, 2001.

Marshall MV, Cancro LP, Fischman SL. Hydrogen Peroxide: A Review of Its Use in Dentistry. *J Periodontol*. 1995 Sept;66(9):786-96.

Meselson, M. Droplets and Aerosols in the Transmission of SARS-CoV-2. *NEJM* in press.

Olin AC. Et al., Factors influencing level of hydrogen peroxide in exhaled breath condensate. *Microchem J* 82(10):17-21, 2006.

Peng X et al., Transmission routes of 2019-nCoV and controls in dental practice. *Int J Oral Sci*, 12:9, published online March 3, 2020.

Putt M, Mallatt M, Messmann L, and Proskin H. A 6-month clinical investigation of custom tray application of peroxide gel with or without doxycycline as adjuncts to scaling and root planning for treatment of periodontitis. *American Journal of Dentistry*. 2014;27:273-284.

Putt M and Proskin H. Custom Tray Application of Peroxide Gel as an Adjunct to Scaling and Root Planing in the Treatment of Periodontitis: Results of a Randomized, Controlled Trial after 6 Months. *The Journal of Clinical Dentistry*. 2013;24:100-107.

Putt M and Proskin H. Custom Tray Application of Peroxide Gel as an Adjunct to Scaling and Root Planing in the Treatment of Periodontitis: A Randomized, Controlled Three-Month Clinical Trial. *The Journal of Clinical Dentistry*. 2012;23(2):48-56.

Sabino-Silva R, et al., Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis. *Clin Oral Invest* 24:1619-1621, 2020.

Santarpia JL, et al., Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center. *medRxiv*, in press, 2020.

Schaudinn C, Gorur A, Keller D, Sedghizadeh P, Costerton W. Periodontitis An archetypical biofilm disease. *JADA* 2009;140(8):978-86.

Sims, CL, et al., An active role for the ribosome in determining the fate of oxidized mRNA. *Cell Rep* 9(4):156-1264, 2014.

Teng Y, et al. Hydrogen peroxide in exhaled breath condensate in patients with asthma: a promising biomarker? *Chest*. 2011 Jul;140(1):108-116.

To KK-W, et al., Consistent detection of 2019 novel coronavirus in saliva. *Clin Inf Dis* published online, 2/12/2020.

Wang W, et al., Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* published online 3/11/2020.