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A Potential Benefit of Hypochlorous Acid - Facial Sanitisation

Authors:

Avis Aman Nowbuth, MBCHB (UNZA), BSc HB (UNZA); BSafe^{HOCl}, Research and Development, Lead Medical Researcher, Johannesburg, South Africa; nowbuthaman@gmail.com; +27783516465

Avis Aman Nowbuth is a qualified doctor with a keen interest in improving public health and public health education. He is currently awaiting board exams in order to practice. During this period, he has dedicated his time towards research in order to improve the public health of South Africa.

Josh Barrie Armstrong, MBCHB (UNZA), BSc HB (UNZA); BSafe^{HOCl}, Research and Development, Medical Researcher, Johannesburg, South Africa; josharmstrong149@gmail.com; +447754259388

Josh Barrie Armstrong is a qualified doctor, currently in his internship phase in The United Kingdom. He has a focus on the improvement of health practices of the general population, with an aim of providing accurate and unbiased information internationally.

Thomas Eugene Cloete; BSc, BSc (Hons), MSc, DSc, Professor of Microbiology, Department of Microbiology, Stellenbosch University, Stellenbosch, South Africa; eugenecloete@sun.ac.za; +27829210217

Professor Thomas Eugene Cloete is a world-renowned microbiologist, and is currently the Deputy Vice Chancellor Research, Innovation and Postgraduate studies at Stellenbosch University. With multiple publications under his name, he is focused on tackling misconceptions and demonstrating efficacy of antimicrobial agents.

Pieter Fourie; BSc Eng. (Electrical), MBChB, PhD (Medical Physiology), MMed (Paediatrics), Pr. Eng, Innovation4Life, Cape Town, South Africa; pieter@stix.co.za; +27825511845

Professor Pieter Fourie has decades of experience as a practicing physician in South Africa. In addition to being a renowned paediatrician, he is also the head of Innovation4Life and Gears4Life – non-profit organisations with aims towards improving access to education of STEM courses.

These authors contributed equally to this work

ABSTRACT

Sanitisation has become a major component of everyday life, with emphasis on the hands and surfaces. The face remains unsanitised due to the lack of an acceptable sanitiser. The use of masks has been mandated to reduce the spread of the pathogens by covering the face, however, there remain issues with the use of personal protective equipment. The face remains a harbour for upper respiratory tract infections, with constant deposition of microbes. By reducing microbial load, the risk of both infection and severity are reduced. HOCl has proven antimicrobial and anti-inflammatory activity, including efficacy against SARS-CoV-2. A facial sanitiser, alongside hand sanitisers and masks, improves protection against SARS-CoV-2. The advantages of regular sanitising of the face and mask include reduced level of microbial contamination, risk of biofilm formation, and respiratory tract and skin infections. HOCl was reviewed as a face and mask sanitiser, concluding that it was an ideal product.

METHODS

The majority of bibliographic sources were obtained from reputable scientific journals. Relevant articles were selected which demonstrate clear presentation of data obtained and without bias. Other bibliographic sources included reputable medical textbooks, as well as confidential or private reports from labs testing HOCl. A single website source is included, as this website is run by a reputable American healthcare company, and information on this site is regarded as accurate.

The search strategy has been based around using HOCl as a key word from databases, as well as the alternative names for HOCl – electrochemically activated water, anolyte, electrolysed water, slightly acidic electrolysed water (SAEW).

Keywords: HOCl; hypochlorous; antimicrobial; anti-inflammatory; SARS-CoV-2; infections; sanitisation

1.0. Introduction

The face, namely through the oral and nasal mucosa and the conjunctiva, is a major point of entry and point of infection for many pathogens involved in human diseases and serves as a harbour for the growth of microorganisms. This is particularly true for SARS-CoV-2, among other significant infections (e.g., *S. pyogenes*, *S. aureus*, *M. tuberculosis*) involving the respiratory tract. The pathogenic contamination of the face is by both airborne pathogens and surface borne pathogens, and via unsanitised hands. On average, individuals who are well-educated on infection control involuntarily touch their faces 23 times per hour where 44% of the face touches involved mucosal areas, with the remainder 56% being non-mucosal surfaces[1]. With the ongoing Covid-19 pandemic, regular hand and surface sanitisation and regular hand washing has been emphasised in order to reduce cross contamination and risk of infection. While this is beneficial, involuntary face touching, especially around the mucosal regions, alongside the presence of airborne pathogens, increases the risk of infection. Consequently, the use of disposable or reusable face masks has been made mandatory. Although it is true that the use of a face mask is beneficial in reduction of the risk of infection, there remains certain issues with use of the face mask – the main issues being improper usage of face masks, prolonged usage of disposable face masks, and infrequent and inadequate washing of reusable masks. It should also be considered that poor handling of masks and frequent removal and reapplication of the same masks further increases the surface area of the face mask which is contaminated.
As face masks only cover the nose and mouth, there remains an exposure risk of the eyes and conjunctiva. This poses a risk of contact and entry for pathogens even whilst wearing a mask. In addition to this, upon removal of face masks and other personal protective equipment (PPE), there is still the risk of contamination of skin surfaces[2]. Errors in doffing (removal) procedures of PPE was studied by Okamato et. al., (2019) whereby 125 participant healthcare workers (HCW) were enrolled. The findings demonstrated that 39.2% made multiple doffing

errors and 36% were found to be contaminated with multidrug resistant organisms[3]. Lim et. al. (2015) performed a study in Samsung Medical Center in South Korea, whereby they identified a 20.6% error rate of donning of respirators or hoods. Contamination on the doffing process identified a 48.3% rate of contamination of the head, 6.9% contamination rate of the face, and 72.4% rate of contamination of the neck[4].

Even though it is clear that the primary focal point of many infections is the face and facial mucosal surfaces, there is a need for disinfection products that can be used to sanitize the face and to rid the face and mucosal surfaces of pathogens. A facial sanitiser would be a great tool to add to the current arsenal against the Covid-19 pandemic, as well as against other respiratory tract infections. HOCl is a secondary reactive oxygen species produced by neutrophils, macrophages, and masts cells. Physiologically HOCl can be said to be present in all tissue systems, including the skin[5].

HOCl has proven to be a highly effective disinfectant, demonstrating rapid activity against a wide spectrum of microbes, including drug resistant bacteria and bacterial spores, fungi, viruses, prions, and amyloid seeds[6,7].

In this review, the mechanism of action of HOCl will be briefly discussed alongside the safety of use of HOCl on sensitive areas such as the face. The potential benefits of using HOCl to reduce the number of pathogens will be discussed, and other potential benefits which may be associated with the use of HOCl will be identified.

2.0. The Antimicrobial Mechanism of Action and Safety of HOCl

2.1. Mechanism of Action

Hypochlorous acid is a secondary reactive oxygen species (ROS). It is a naturally occurring molecule present in the human body, produced during the respiratory burst of phagocytosis. The composition of the molecule is HOCl – the molecule itself being the secondary reactive oxygen species. The molecule then dissociates into free radicals – H^+ and OCl^-. Hypochlorite (OCl^-) is a potent free radical (oxidant) which rapidly causes damage to bacterial cell walls and cell contents[8]. The following summarises the antimicrobial action of HOCl:[9]

1. Hypochlorite (OCl^-) react with membrane lipids and cell walls of pathogens resulting in:
    a. Peroxidation of polyunsaturated fatty acids and destruction of cross-linkages in cell walls
    b. A chain reaction of peroxidation of membrane lipids and decreased membrane fluidity
2. Cellular dysfunction occurs due to inhibition of enzymes required for glycolysis, thus, pathogens, specifically bacteria, are unable to metabolise glucose to produce ATP resulting in:
    a. An increase in the presence of free radicals, resulting in a change in intracellular redox potential further inhibiting glycolysis
    b. The complete disruption of essential cellular functions and depletion of adenosine triphosphate (ATP)
3. Additionally, there is activation of enzymes resulting in cellular lysis. Human cells make use of a group of defence mechanisms collectively known as the Antioxidant Defence System (ADS)[10]. Microbial cells, however, do not have this defence mechanism and for this reason HOCl is effective against microbes.

HOCl demonstrates efficacy against a wide range of microorganisms. Efficacy has been demonstrated against *pseudomonas aeruginosa* and *escherichia coli*[11,12], poultry derived

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salmonella spp.[13], *staphylococcus spp.*[12], *enterococcus faecalis*[14], among other bacteria as mentioned later in this review. Sporicidal activity has also been demonstrated[15]. Virucidal activity is also well noted, with efficacy against resistant organisms such as *norovirus spp.*[16].

2.2. Safety

The potential for HOCl to damage mammalian cells appears to be present. However, inherent mechanisms in human cells are in place in order to prevent cellular damage. The physiological protective mechanism is based on the antioxidant defence mechanism. As HOCl is a ROS (oxidant), the antioxidant defence mechanism of human cells protects against the oxidative stress caused by HOCl. This specific quality is what renders HOCl safe for use in humans while making it toxic to microbes. SkinSafe, developed by Mayo Clinic, designates HOCl as hypoallergenic, irritant free, eyelid and lip safe, safe for teens and safe for babies[17].

Antioxidants are molecules which slow down or prevent oxidation of other molecules. The mechanism of action of antioxidants are as follows:[18]

1. Removal of radical intermediate species
2. Blocking secondary production of toxic metabolites and inflammatory mediators
3. Converting free radicals into less toxic compounds
4. Blocking chain propagation of secondary radicals
5. Repairing molecular injury
6. Enhancing the endogenous antioxidant system function of exogenous antioxidants
7. Inhibiting other oxidation reactions by being oxidised themselves

As such, there are two classes of antioxidants – enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants include superoxide dismutases, catalases, glutathione system, thioredoxin system. Non-enzymatic antioxidants include ascorbic acid (vitamin C), glutathione and thiocyanate, tocopherols and tocotrienols (Vitamin E), beta-carotene (Carotenoids – provitamin A).

The Antioxidant Defence System (ADS) is what protects the body from oxidative damage. The presence of the ADS alone makes HOCl safe for use in humans and other species that make use of this kind of system.

2.3. The Skin Microbiome

The skin is the human body's largest organ and is colonised by a plethora of microorganisms. This colonisation is highly dependent on topographical location, host, and environmental factors[19]. The skin is the body's primary defence mechanism against microbial infection, acting as a physical barrier. The skin on the face is particularly susceptible to colonisation by foreign microbes, due to frequent face touching and deposits of airborne microbes (droplets) on the skin and mucosa of the face. Many common skin disorders are postulated (although having not been scientifically proven in most cases) to have an underlying microbial cause because clinical improvement is seen with the use of antimicrobial treatments. However, there are certain skin disorders, such as acne vulgaris, with definitive causative microorganisms (e.g., *Cutibacterium acnes* (formally *Propionibacterium acnes*) and *Staphylococcus epidermidis*)[20].

The presence of *Staphylococcus aureus* on the skin and scalp in itself is a cause of many infections, such as boils, folliculitis, impetigo, and cellulitis. Additionally, *S. aureus* is highly prevalent in cases of atopic dermatitis (eczema)[21]. *S. aureus*, in addition with group A

streptococcus (*S. pyogenes*), and other microorganisms, can cause a severe polymicrobial infection – necrotising fasciitis. As such, microorganisms on the face may pose a threat of a range of skin infections ranging from minor easy to treat infections to severe life-threatening infections[22].
The variety of bacteria which form the microbiome of the face may create biofilms. This begins with microorganisms forming a microcolony and surface colonisation. Biofilms provide advantages to microorganisms including: protection from host defences, differential gene expression, and increased resistance to antimicrobials Epithelial biofilms are implicated in a number of dermatological conditions, such as chronic wounds, atopic dermatitis, candidiasis, and acne vulgaris. These biofilms pose a challenge, as there are limitations for their detection, and their resistance to conventional antimicrobial therapy due to persistence and their chronic nature[23, 24].

2.4. The Face as a Harbour for Respiratory Infections

The entry points to the nose, mouth and eyes are key regions which predispose infections of the upper respiratory tract. Microorganisms proliferate on the surface of the skin, and constant touching of the face, nose, mouth, and eyes results in an increase in presence of the number and variety of microorganisms present. The major causative agents for upper respiratory tract infections (URTIs) are viral in nature, although not limited to viruses alone[25].

Microorganims involved in the pathogenesis of upper respiratory tract infections include *rhinovirus, respiratory syncytial virus (RSV), parainflenza virus, coronavirus, influenza viruses, adenovirus, enterovirus, S. aureus, S. pneumoniae, H. influenzae, P. aeruginosa, M. catarrhalis, E. coli, K. pneumoniae, N. gonorrhoeae*, among other pathogens.

SARS-CoV-2 is a major pathogen of interest in recent times which causes upper respiratory tract infections. Wim Van Damme et. al.(2021) discuss the relationship of inoculum dose and disease severity of SARS-CoV-2 due to three possible factors:

1. At an individual level: “viral dose in inoculum is related to severity of disease (dose-dependent relationship)”
2. At a cluster level: “Severity of disease is related to transmission potential” leading to clusters of mild cases and clusters of severe cases.
3. At a community level: “In certain contexts, chains of severe cases can build up through intensive transmission with high inoculum to severe local outbreaks, which can result in large-scale intensive epidemics, while this is less likely in other contexts”

This theory plays out in practice on three levels:[26]

1. Individual level: A person infected with a small dose viral inoculum will on average develop milder disease than a person infected with a high viral inoculum and vice versa. This is independent of other well known risk factors for severity of disease, mainly old age, and comorbidities, such as diabetes.
2. Cluster level: A person with asymptomatic infection or mild disease, will on average spread lower dose of the virus, and is less likely to transmit disease; and when the person transmits, the newly infected person is more likely to have a mild disease compared to a person infected by a severely ill person, who spreads on average higher doses of the virus. This causes clusters and chains of milder cases or more severe cases.

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3. Community level: In certain contexts, such as dense urban centres with a moderate climate, during the season that people live mostly indoors, the potential for intensive transmission and explosive outbreaks is higher than in rural areas, or in regions with a hot and humid climate where people live mostly outdoors. Hence, a cascade of intensive transmission is more likely in certain contexts than others.

This model is based on other pathogens which show dose-dependent severity, such as:

- Influenza virus
- Coronavirus (seen with MERS and HCoV-229E)
- Human immunodeficiency virus (HIV)
- Measles
- *Mycobacterium tuberculosis* (TB)
- *Streptococcus pneumoniae*

It is of note that the inoculum dose-dependent hypothesis needs further investigation in order to be well established, and medical experts need to pay close attention to these factors[26].

3.0. Dermatological Benefits of Hypochlorous Acid

As the use of alcohol-based sanitisers has increased drastically since the onset of the Covid-19 pandemic, resulting in an increase in the incidence of contact dermatitis and allergic contact dermatitis associated with the use of alcohol-based sanitisers[27]. The incidence of allergic contact dermatitis increased with use of other non-alcohol-based hand sanitisers (such as chlorhexidine and quaternary ammonium compounds). Another concern with the use of alcohol-based sanitisers is the depletion of the lipid barrier with repeated exposure, resulting in increased risk of destruction or changes of the skin flora and colonisation of pathogens[28].

Additionally, the use of personal protective equipment (PPE) has shown an increase in dermatological conditions such as allergic dermatitis, irritant dermatitis, friction blisters, contact urticaria, acne, and infections[29].

HOCl is a possible solution to the aforementioned conditions, while possessing other benefits associated with dermatological applications. In a mouse model, anti-inflammatory properties were demonstrated on sensitised mice, whereby HOCl demonstrated effective reduction in an inflammatory response quantified by reduced secretion of inflammatory cytokines. Associated with this was a reduction in itch and scratching behaviour[30].

The antimicrobial and anti-inflammatory (immunomodulatory) properties of HOCl correlate with a clinical improvement in a variety of cutaneous disorders – including atopic dermatitis, seborrheic dermatitis, diabetic ulcers, pruritis, and acne vulgaris. Other clinical benefits are demonstrated with the promotion of wound healing and reduction or prevention of scar formation[31].

4.0. Potential Benefit of HOCl on the Face and Skin

Due to the high efficacy of HOCl and the inherent safety profile, it offers very good potential for use for face as well as nasal and oral sanitisation. HOCl acts as secondary reactive oxygen species when produced endogenously and this is the way it carries out its mechanism of action. Due to its own endogenous nature, HOCl possesses an inherently good safety profile as demonstrated in numerous international studies[32-35].

Testing of antimicrobial efficacy of HOCl has been sponsored by Aquaox LLC, Loxahatchee, Florida, on multiple pathogens following the USP <51> testing protocol[36]. Relevant pathogens tested include *Candida albicans*, *S. aureus*, and *S. epidermidis* demonstrated a reduction of >99.9999% with 15 seconds of contact. *P. aeruginosa* showed a reduction of >99.9999% with 60 seconds of contact and MRSA had a reduction of >99.999% with 60 seconds of contact. The 2009 Pandemic strain of H1N1 had a >99.963% reduction with 5 minutes of contact, and *M. bovis* demonstrated a >99.99% reduction with 10 minutes of contact. From the above results it is clear that Hypochlorous Acid (HOCl) will offer an additional defence mechanism to prevent microbial infection.

Due to the wide antimicrobial efficacy, and the lack of toxicity, HOCl has been described as having potential pharmaceutical applications in the control of soft tissue infections[37].

5.0. Discussion and Conclusion

The published literature indicates that HOCl is highly efficacious against a wide range of microorganisms. This, alongside knowledge of the mechanism of action provides insight into the antimicrobial properties which may bypass the potential of microbial resistance against HOCl. The range of microorganisms killed by HOCl are all significant microbes which cause dermatological or respiratory tract infections. As such, it can be deduced that use of HOCl as a facial and face mask sanitiser would decrease incidence of the skin conditions mentioned. The safety of HOCl to mammalian cells has been demonstrated even the most sensitive cells. As HOCl with a concentration of 200 ppm (0.2%) and 210 ppm (0.21%) has been proven safe using Vero cells, it can be concluded that HOCl is a safe to use as a facial sanitiser[35]. In addition to the benefits of preventing upper respiratory tract infections, HOCl has further benefits with the potential to treat a range of dermatological disorders, such as acne vulgaris, seborrheic dermatitis, and atopic dermatitis. Furthermore, a range of cutaneous conditions associated with the use of PPE and alcohol-based sanitisers can see a benefit from the use of HOCl. As such, the combined benefits of HOCl use further potentiates the use of the compound as a facial sanitiser. HOCl has a proven efficacy against biofilms, and as such, the presence of epithelial biofilms would be eradicated, alongside conditions associated with them[38,39]. Use of a facial sanitiser, in addition to the arsenal of hand sanitiser and masks, further improves protection against and prevention of the spread of SARS-CoV-2. The inoculum dose-dependent relationship with severity of infection postulation brings to consideration that any reduction of SARS-CoV-2 numbers on the face and mucosal surfaces will be beneficial with reduction of both risk of infection and severity of ongoing infection. The potential administration forms of HOCl for the purpose of a facial sanitisation could be by the use of a spray due to ease of application, as well as the ability to use the spray for sanitisation of masks and hands as well. Alternative methods of sanitisation could be by use of a gel formulation. This method would result in increased dermatological benefits, however, ease of use and sanitisation of masks would not be possible with this method. Thus, there are great benefits with the use of HOCl as a facial sanitiser, and this provides the another arm of tackling URTIs and COVID-19.

6.0. Data Availability

All article and book references are available online and can easily be found using their respective DOI references. Reference 35 (Kabamba & Malatji, 2020) is available on request. Reference 36 is unavailable to readers as it contains confidential information.

7.0. Conflicts of Interest

Dr. Avis Aman Nowbuth is an employee of BSafe^{HOCl}, whereby he researches possible uses, benefits, and safety aspects of hypochlorous acid. His affiliation does not influence the quality and integrity of the data in this review article. Dr. Josh Barrie Armstrong was contracted to assist and review the integrity of the data by BSafe^{HOCl}, in order to verify the data was unbiased and accurate.

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10.0. References

1. Kwok, YLE, Gralton, J; McLaws, M-L. Face touching: a frequent habit that has implications for hand hygiene. Am. J. Infect. Control. 2015;43(2):112–114. https://doi.org/10.1016/j.ajic.2014.10.015
2. Erukunuakpor, K, Mumma, J, Kraft, C. Self-Contamination and Failure Modes During PPE Doffing: A Comparison of Two Powered Air-Purifying Respirator Hoods, Infect Control Hosp Epidemiol. 2020;41(S1): S384-S385. https://doi.org/10.1017/ice.2020.1019
3. Okamoto, K, Rhee, Y, Schoeny, M, et. al. Impact of doffing errors on healthcare worker self-contamination when caring for patients on contact precautions. Infect. Control Hosp. Epidemiol. 2019;40(5):559–565. https://doi.org/10.1017/ice.2019.33
4. Lim, SM, Cha, WC, Chae, MK, et. al. Contamination during doffing of personal protective equipment by healthcare providers. Clin Exp Emerg Med. 2015;30;2(3):162–167. https://doi.org/10.15441/ceem.15.019
5. Degrossoli, A, Muller, A, Xie, K, et. al. Neutrophil-generated HOCl leads to non-specific thiol oxidation in phagocytized bacteria. eLife. 2018;6;7:e32288. https://doi.org/10.7554/eLife.32288
6. Eryılmaz, M, Palabıyık, IM. Hypochlorous Acid - Analytical Methods and Antimicrobial Activity. Trop. J. Pharm. Res. 2013;12(1):123–126. https://doi.org/10.4314/tjpr.v12i1.20
7. Hughson, AG, Race, B, Kraus, A, et. al. Inactivation of Prions and Amyloid Seeds with Hypochlorous Acid. PLoS Pathog. 2016; 12(9): e1005914. https://doi.org/10.1371/journal.ppat.1005914
8. Block, MS, Rowan, BG, Hypochlorous Acid: A Review. J Oral Maxillofac Surg. 2020;78(9):1461-1466. https://doi.org/10.1016/j.joms.2020.06.029
9. Dobyns, E. L.; Stenmark, K. R. Kendig's Disorders of the Respiratory Tract in Children, 7th ed.; Elsevier: Philidelphia, USA, 2006; pp. 224–242.
10. Birben, E, Sahiner, UM, Sackesen, C, et. al. Oxidative Stress and Antioxidant Defense. World Allergy Organ. J. 2012;5(1):9-19. https://doi.org/10.1097/WOX.0b013e3182439613
11. Cloete, TE, Thantsha, MS, Maluleke, MR, Kirkpatrick, R. The antimicrobial mechanism of electrochemically activated water against Pseudomonas aeruginosa and Escherichia coli as determined by SDS-PAGE analysis. J Appl Microbiol. 2006; 107: 379-384. https://doi.org/10.1111/j.1365-2672.2009.04233.x

 doi:10.20944/preprints202107.0129.v2

12. Jacobs, J. NOSA Testing Final Report. 248 Jean Avenue, Lyttleton, Centurion, South Africa: NOSA Testing, 2020; 1-2.
13. Wilsmann, DE, Carvalho, D, Chitolina, GZ, et. al. Electrochemically-Activated Water Presents Bactericidal Effect Against Salmonella Heidelberg Isolated from Poultry Origin. Foodborne Pathog. Dis. 2020; 17:3, 228-233. https://doi.org/10.1089/fpd.2019.2682
14. Gulabivala, K, Stock, C. J. R., Lewsey J.D., et al. Effectiveness of electrochemically activated water as an irrigant in an infected tooth model. Int Endod J. 2004; 37: 624-631. https://doi.org/10.1111/j.1365-2591.2004.00867.x
15. Bradley, CR, Fraise, AP, Babb, JR. Report on the efficacy of Anolyte in hospitals. Hospital Infection Research Laboratory: City Hospital NHS Trust, 1996; 1-6.
16. Park, GW, Boston, DM, Kase, JA, et. al. Evaluation of liquid- and fog-based application of Sterilox hypochlorous acid solution for surface inactivation of human norovirus. Appl Environ Microbiol. 2007;73(14):4463-4468. https://doi.org/10.1128/AEM.02839-06.
17. SkinSafe. Hypochlorous Acid. Mayo Clinic. https://www.skinsafeproducts.com/ingredients/hypochlorous-acid (accessed on 10 May 2021).
18. Kabel, AM, Free Radicals and Antioxidants: Role of Enzymes and Nutrition. J. Nutr. Health. 2014;2(3) 35–38. https://doi.org/10.12691/jnh-2-3-2
19. Grice, EA, Segre, JA, The Skin Microbiome. Nat. Rev. 2011;9(4) 244–253. https://doi.org/10.1038/nrmicro2537
20. Bek-Thomsen, M, Lomholt, HB, Kilian, M. Acne is Not Associated with Yet-Uncultured Bacteria. J. Clin. Microbiol. 2008;46(10):3355–3360 https://doi.org/10.1128/JCM.00799-08
21. Tong, SYC, Davis, JS, Eichenberger, E, et. al. Staphylococcus aureus Infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management. Clin. Microbiol. Rev. 2015;28(3):603–661. https://doi.org/10.1128/CMR.00134-14
22. Yamamoto; LG. Treatment of Skin and Soft Tissue Infections. Pediatr. Emerg. Care. 2017;33(1):49–55. https://doi.org/10.1097/PEC.0000000000001001
23. Vaishnavi, KV, Safar, L, Devi, K. Biofilm in Dermatology J. Skin Sex. Transmitted Dis. 2019;1(1):3-7. https://doi.org/10.25259/JSSTD_14_2019
24. Brandwein, M, Steinberg, D, Meshner, S. Microbial biofilms and the human skin microbiome. Npj. 2016;2(3). https://doi.org/10.1038/s41522-016-0004-z
25. Dasaraju, P V; Liu, C. Medical Microbiology, 4th ed.; University of Texas Medical Branch at Galveston: Galveston, USA, 1996. Chapter 93.
26. Van Damme, W, Dahake, R, Van de Pas, R, et. al. COVID-19: Does the infectious inoculum dose-response relationship contribute to understanding heterogeneity in disease severity and transmission dynamics? Med. Hypotheses 2021;146:110431. https://doi.org/10.1016/j.mehy.2020.110431
27. Alves, S; Arendse, A; Kannenberg, S, COVID-19 collateral damage: Alcohol rub dermatitis as an emerging problem. S. Afr. Med. J. 2020;110(12):1148 https://doi.org/10.7196/SAMJ.2020.v110i12.15354
28. Jing, JLJ, Yi,TP, Bose, RJC, et. al. Hand Sanitizers: A Review on Formulation Aspects, Adverse Effects, and Regulations. Int. J. Environ. Res. Public Health 2020;17(9):3326. https://doi.org/ 10.3390/ijerph17093326
29. Sanghvi, AR. COVID-19: An overview for dermatologists. Int. J. Dermatol. 2020;59(12)1437–1449. https://doi.org/10.1111/ijd.15257
30. Fukuyama, T, Martel, BC, Linder, LE, et. al. Hypochlorous acid is antipruritic and anti-inflammatory in a mouse model of atopic dermatitis. Clin. Exp. Allergy 2018;48(1):78–88. https://doi.org/10.1111/cea.13045

31. Del Rosso, JQ, Bhatia, N. Status Report on Topical Hypochlorous Acid: Clinical Relevance of Specific Formulations, Potential Modes of Action, and Study Outcomes. J Clin Aesthet Dermatol. 2018;11(11):36–39.
32. Kubota, A, Goda, T, Tsuru, T, et. al. Efficacy and safety of strong acid electrolyzed water for peritoneal lavage to prevent surgical site infection in patients with perforated appendicitis. Surg. Today. 2015;45(7):867–879. https://doi.org/10.1007/s00595-014-1050-x
33. Burian, EA. Sabah, L, Kirketerp-Møller, K, et. al. The Safety and Antimicrobial Properties of Stabilized Hypochlorous Acid in Acetic Acid Buffer for the Treatment of Acute Woulds - A Human Pilot Study and In Vitro Data Int. J. Low. Extrem. Wounds. 2021;15347346211015656. https://doi.org/10.1177/15347346211015656
34. Dissemond, J. Wound cleansing: benefits of hypochlorous acid. J. Wound Care. 2020;1(29)(Sup10a):S4–S8. https://doi.org/10.12968/jowc.2020.29.Sup10a.S4.
35. Kabamba, A, Malatji, KB. Measuring the Inhibitory Activity of BSafe HOCl Samples 3 and 5 Against SARS-CoV-2 using in vitro Cell Based Assay. Pretoria, South Africa: CSIR Biosciences, 2020; 1-18.
36. Aquaox LLC, HOCl GLP Efficacy Data, Loxahatchee, Florida, USA: Aquaox LLC, 1
37. Wang, L, Bassiri, M, Najafi, R, et. al. Hypochlorous Acid as a Potential Wound Care Agent. J. Burns and Wounds (now ePlasty). 2007; 6e5
38. Chen, C-J, Chen, C-C, Ding, S-J. Effectiveness of Hypochlorous Acid to Reduce the Biofilms on Titanium Alloy Surfaces in Vitro. Int. J. Mol. Sci. 2016; 17(7):1161. https://doi.org/10.3390/ijms17071161
39. Marais, JT, Brozel, VS. Electro-chemically activated water in dental unit water line. BDJ. 1999; 187:154-158. https://doi.org/10.1038/sj.bdj.4800228
40. Nowbuth, AA, Armstrong, JB, Cloete, TE, et. al. A Potential Benefit of Hypochlorous Acid - Facial Sanitisation. Preprints. 2021. https://doi.org/10.20944/preprints202107.0129.v2