

Povidone-Iodine Use in Sinonasal and Oral Cavities: A Review of Safety in the COVID-19 Era

Ear, Nose & Throat Journal
2020, Vol. 99(9) 586–593
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0145561320932318
journals.sagepub.com/home/ear

Samantha Frank, MD¹ , Joseph Capriotti, MD², Seth M. Brown, MD, MBA^{1,3}, and Belachew Tessema, MD^{1,3}

Abstract

Objectives: Approaches to nasal and oral decontamination with povidone-iodine (PVP-I) have been published to reduce nosocomial spread of Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). The safety of PVP-I topically applied to the nasal and oral cavity is addressed by a literature review. The specific efficacy of PVP-I against coronaviruses and its potential efficacy against SARS-CoV-2 is discussed. **Methods:** A review was performed utilizing PubMed and Cochrane Databases. All citations in protocols for nasal and oral PVP-I use regarding COVID-19 were independently reviewed. **Results:** Povidone-iodine has been safely administered for up to 5 months in the nasal cavity and 6 months in the oral cavity. Concentrations less than 2.5% in vitro do not reduce ciliary beat frequency or cause pathological changes in ciliated nasal epithelium, upper respiratory, or mucosal cells. Adverse events with oral use have not been reported in conscious adults or children. Allergy and contact sensitivity is rare. Chronic mucosal use up to 5% has not been shown to result in clinical thyroid disease. PVP-I is rapidly virucidal and inactivates coronaviruses, including SARS-CoV and Middle East Respiratory Syndrome (MERS). **Conclusions:** Povidone-iodine can safely be used in the nose at concentrations up to 1.25% and in the mouth at concentrations up to 2.5% for up to 5 months. Povidone-iodine rapidly inactivates coronaviruses, including SARS and MERS, when applied for as little as 15 seconds. There is optimism that PVP-I can inactivate SARS-CoV-2, but in vitro efficacy has not yet been demonstrated.

Keywords

povidone-iodine, SARS-CoV-2, nasal decontamination, oral decontamination, safety

Introduction

Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2), the virus resulting in the disease COVID-19, is a novel coronavirus in the same family as the SARS and Middle East Respiratory Syndrome (MERS) viruses. The World Health Organization (WHO) declared the spread of COVID-19 a global pandemic on March 11, 2020. This has significantly changed the way that we practice medicine. As otolaryngologists, our workflow has been radically altered.

There have been significant concerns noted regarding infection of health care workers and subsequent nosocomial spread within hospitals. Data from the epidemic in Wuhan by the Chinese Center for Disease Control and Prevention noted that 63% of infected patients in Wuhan were health care workers.¹ A study of hospitalized patients at a tertiary care center in Wuhan noted that 12% of patients and 29% of health care professionals had acquired COVID-19 from nosocomial

spread.² Particular concern has been expressed regarding the safety of otolaryngologists, patients, and staff during routine and endoscopic examination. Reports have demonstrated high viral loads of SARS-CoV-2 in the nasal cavities, nasopharynx, oral cavities, and oropharynx, with the highest viral loads within the nasopharynx.³⁻⁶ In vitro studies have demonstrated that the tissue of the nose and mouth have high expression of ACE2, the main receptor of COVID-19.^{7,8} Nasal goblet and

¹ University of Connecticut School of Medicine, Farmington, USA

² Veloce BioPharma, Fort Lauderdale, FL, USA

³ ProHealth Ear Nose and Throat, Farmington, CT, USA

Received: May 09, 2020; revised: May 13, 2020; accepted: May 15, 2020

Corresponding Author:

Samantha Frank, Division of Otolaryngology, Department of Surgery, UConn Health, 263 Farmington Avenue Farmington, CT 06030, USA.

Email: sfrank@uchc.edu



ciliated cells had the highest expression of ACE2.⁹ Due to high viral load, these areas are sensitive for diagnosis of the virus.¹⁰ The transit of virus via coughing, sneezing, and aerosolizing procedures makes transmission high.¹¹ Aerosols of SARS-CoV-2 have been detected in the air for up to 3 hours.¹² There are concerns that many otolaryngology procedures generate aerosols, which was proven for intranasal high-speed drilling in a cadaveric study.^{13,14}

Transmission reduction by the minimization of aerosolized virus is of key importance. Given that the nasopharynx and oropharynx are principal reservoirs of active SARS-CoV-2 virus, there has been immense desire for an approach to nasal and oral decontamination in the era of COVID-19. Povidone-iodine (PVP-I) has been suggested as a topical solution. PVP-I works by releasing free iodine, which disrupts microbial metabolic pathways, destabilizes structural components of cell membranes, and leads to irreversible damage to pathogens.¹⁵ It is a potent virucidal via inhibition of N1, N2, and N3 neuraminidase as well as inhibition of hemagglutinin. This inhibition blocks viral attachment to cellular receptors and inhibits viral release and spread from infected cells.¹⁶

Protocols have been recommended regarding nasal and oral use of PVP-I in regard to the COVID-19 pandemic, and there has been much discussion regarding the implementation of these practices. A protocol was developed in the United Kingdom recommending 0.3 mL of 0.5% PVP-I solution via each nostril and 9 mL via the oral cavity in conscious COVID-19 patients and persons under investigation (PUIs) prior to undergoing procedures in and around the mouth, as well as in health care workers performing these procedures.¹⁷ In unconscious patients, they recommended applying 2 mL to the mucosal surfaces of the oral cavity. Use was recommended every 2 to 3 hours in health care workers exposed to these patients up to 4 times per day. Another protocol from Pittsburgh recommended 240 mL of 0.4% PVP-I in the nasal cavity via sinus rinse delivery bottle and 10 mL of 0.5% PVP-I oral wash every 2 to 3 hours up to 4 times per day in patients with COVID-19, PUIs, prior to high-risk procedures, and in COVID-19 hotspots.¹⁸ They recommended this procedure in health care workers prior to and after care of COVID patients, PUIs, high-risk procedures in COVID hotspots, and in the setting of inadequate PPE. Parhar et al concurred with the use of PVP-I based preparations to reduce viral loads of coronavirus as there was demonstrated efficacy.¹⁹ An anesthesia guideline for operative room care in the COVID-19 era recommended 2 doses of nasal PVP-I within 1 hour of incision for all OR cases.²⁰ The American Dental Association guidelines for minimizing risk of COVID-19 transmission recommended preoperative use of 0.2% PVP-I mouthwash for all procedures.²¹

To minimize toxicity when using PVP-I as a repeated application, most protocols recommend concentrations of PVP-I between 0.2% and 0.5%. Because nasal and oral viral loads are similar in asymptomatic and symptomatic patients³ and can persist in convalescent seroconverted cases, some of these protocols recommend the use of PVP-I in asymptomatic patients. Unaddressed in any report to date is a discussion of the

interdependence of PVP-I aqueous concentration, chemical stability, reported toxicity, and known biocidal efficacy.

Most commercial PVP-I preparations suitable for sinonasal or oral application are aqueous concentrations of 10% PVP-I or 5% PVP-I intended for presurgical antisepsis. Although additional scrubs, solutions, swab sticks, and other PVP-I containing products are available in the 5% to 10% range, many contain additional salts, sudsing agents, and cosolvents that should be avoided in the nose and mouth. Most are specifically labeled for external use and carry warnings against exposure to eyes, ears, and mucosal surfaces. The chemical stability of PVP-I in aqueous solutions at room temperature declines with dilution, alkalization, and contact with common low-density polymer packaging materials.^{22,23} Naturally acidic aqueous PVP-I solutions reach a critical stability inflection point at about 0.75%.²⁴ Paradoxically, studies have shown that the antibacterial activity of full-strength 10% PVP-I increases with dilution.²⁵ Between 10% and 1%, there is an exponential increase in efficacy which plateaus between 1.0% and 0.1% before decreasing again from 0.1% to 0.001%.

Our objective is to present established uses of PVP-I in the sinonasal and oral cavities and outline the safety profile through the discussion of clinical and in vitro toxicity. In addition, we aim to discuss PVP-I efficacy against coronaviruses and its potential use specifically against SARS-CoV-2 to inform the otolaryngology community regarding its use.

Methods

A review was performed utilizing PubMed and Cochrane Databases. Search terms included “sinonasal povidone-iodine,” “nasal povidone-iodine,” “oral povidone-iodine,” and “povidone-iodine safety.” All citations in published protocols for nasal and oral PVP-I use regarding COVID-19 were independently reviewed. English language studies and studies translated to English were included.

Results

Sinonasal PVP-I Uses and Safety

Nasal decontamination is a routine step to reduce postoperative infectious contamination.²⁶ Efficacy of PVP-I for intranasal antisepsis has been proven. Patients undergoing orthopedic surgery who had tested positive for methicillin-sensitive staphylococcus aureus (MSSA) or methicillin-resistant staphylococcus aureus (MRSA) nasal colonization were treated with 5% PVP-I in both nostrils twice daily for 5 days prior to surgery.²⁷ This completely eradicated MRSA in all patients and reduced rate of MSSA infection by 94%. Another study used 5% PVP-I solution the night before and morning of surgery for hardware implantation and noted a significantly lower rate of surgical site infection (SSI) in the treatment group.²⁸ A randomized controlled trial treated patients with 5% PVP-I 2 hours prior to surgery and noted a significant decrease in the number of patients colonized with MRSA 4 hours after treatment.²⁹

Table 1. Overview of Safety Data for Mucociliary Clearance, Olfaction, Thyroid Function, and Mucosal Appearance for in Vivo Sinonasal Use of PVP-I.

Article	Dilution	Frequency/period of use	Mucociliary clearance	Olfaction	Thyroid function	Mucosal appearance
Panchmatia et al, 2019 ³⁰	0.08%	Every other day for 7 weeks	No significant change in NMC ^a	No significant difference in Sniffin' 16 scores	No significant change in TSH levels	Not evaluated
Mullings et al, 2019 ³¹	0.08%	At least every other day for up to 5 months	No significant change in NMC ^a	Not evaluated	No significant change in TSH levels	Reduction in edema
Gluck et al, 2007 ³²	2.2% and 4.4%	10 time points over 80 days	Improved mucociliary clearance with all sprays	Unchanged detection of 11 odors	Not evaluated	No significant difference in appearance

Abbreviation: PVP-I, povidone-iodine.

^aNasal mucociliary clearance—all based on saccharine test: measure of time patient tastes saccharine after administration to inferior turbinate.

Although safety was not specifically evaluated in these studies, there were no reports of toxicity or adverse events.

The repeated administration of PVP-I to the sinonasal mucosa has been described as a safe and effective treatment for chronic sinus disease (Table 1). Panchmatia et al and Mullings et al reported the use of a 0.08% PVP-I solution for recalcitrant chronic rhinosinusitis (CRS) for up to 7 weeks.^{30,31} Patients showed clinical improvement and decreased bacterial growth. Over the 7 weeks of treatment, there was no detrimental effect on thyroid function or mucociliary clearance. Nasal mucociliary time remained within normal ranges. Thyroid dysfunction was not noted. Panchmatia et al additionally studied olfaction utilizing the Sniffin' 16 smell identification test and did not detect a significant difference after 7 weeks. Safety was evaluated in an in vivo study utilizing 2.2% and 4.4% liposomal dispersions of PVP-I.³² In healthy patients, results did not demonstrate a significant change in mucosal appearance, ciliary activity, or olfactory function based on 11 odors at 10 time points over 80 days.

In vitro safety of nasal PVP-I appears highly concentration dependent with a clear distinction in toxicity that occurs at 2.5% in vitro. A 0.5% PVP-I solution was applied to air liquid interface cultures of human nasal epithelial cells from patients with CRS.³³ PVP-I did not cause pathological effects on paracellular permeability or cilia beat frequency; 10% and 5% PVP-I solutions were applied to human ciliated respiratory cells, which resulted in a drop in ciliary beat frequency³⁴; 5% and 2.5% PVP-I solutions tested in vitro completely inhibited activity of the cilia, whereas there was no inhibitory effect at 1.25%.³⁵

Oral PVP-I Uses and Safety

Diluted concentrations of PVP-I gargle have been shown to be bactericidal.³⁶ Povidone-iodine gargle has been utilized throughout the world for decades. In addition to antiseptics for oral surgical procedures,³⁷ PVP-I gargles have been utilized to prevent respiratory infections in patients with variable

results.³⁸⁻⁴⁰ The Committee for the Japanese Respiratory Society guidelines recommend that inpatients and health care workers gargle with PVP-I 4 times daily to prevent hospital acquired pneumonia.⁴¹

In vitro safety data regarding PVP-I use in the rat oral mucosa demonstrated apoptosis of cells when exposed to a concentration of 1×10^{-2} μ M for 1 day, but did not demonstrate this apoptosis at a concentration of 1×10^{-3} μ M.⁴² Although the concentrations tested were lower than available PVP-I products, they saturated the mucosal cells for 24 hours, as compared to a few minutes, so the cytotoxicity is likely not comparable. In vivo, prolonged use of 1% to 1.25% PVP-I gargle did not cause irritation or damage, and no adverse safety effects were noted in patients for up to 28 months (Table 2).^{36,38,43,44} Povidone-iodine gargle was not shown to stain teeth or cause a change in gustatory function.⁴⁹

There is concern that gargling a PVP-I solution could lead to inadvertent aspiration. When used as oral antiseptics in the operating room, there have been 6 case reports of aspiration pneumonia, in concentrations from 0.25% to 10%. In 2 of these cases, there was overt concern of lack of integrity of the endotracheal tube balloon.^{50,51} One author reports using this solution for antiseptics for over 20 years without any prior complications.⁵² The effect of PVP-I on lung tissue was studied in rats, demonstrating atelectasis, edema, alveolar rupture, and leukocyte infiltration, followed by lung parenchyma loss and pulmonary fibrosis at 1% and 5% concentrations with less severe findings in rats exposed to 0.1% concentrations.⁵³ There were no case reports of aspiration pneumonia in awake patients.

Povidone-Iodine General Safety

Urinary iodine excretion in patients undergoing thyroid surgery with routine application of 10% PVP-I to large surface areas was studied revealing an increase of 7 times the preoperative value compared to patients disinfected with chlorhexidine⁵⁴;

Table 2. Overview of Safety and Tolerance Data for in Vivo Oral Use of PVP-I.

Article	Dilution	Frequency/period of Use	Findings	Adverse findings reported
Shiraishi et al, 2002 ³⁶	0.03%	3 times at one time point	Taste preferred to chlorhexidine gluconate and cetylpyridinium chloride	None
Nagatake et al, 2002 ³⁸	1%	4 times daily for up to 28 months (mean 18.5 months)	No irritation to mucosa	None
Madan et al, 2008 ⁴³	1%	2 times daily for 6 weeks	Incidence and severity of radiation mucositis reduced	None
Rahn et al, 1997 ⁴⁴	1.25%	4 times daily for 9 weeks	Incidence, severity, and duration of radiation induced mucositis reduced	None
Ferguson et al, 1978 ⁴⁵	5%	4 times daily for 2 weeks	No clinical change in thyroid function	None
Ader et al, 1988 ⁴⁶	5%	1 time daily for 6 months	Significant increase in TSH, but all within normal range -No change in T3, T4, or free T4	None
Amin et al, 2004 ⁴⁷	10%	3 times at 2-month intervals	No irritation or damage to mucosa of pediatric patients	None
Reilly et al, 2016 ⁴⁸	10%	1 time use	No irritation or damage to mucosa of pediatric patients	None

Abbreviation: PVP-I, povidone-iodine.

10% PVP-I was used prior to cataract surgery, and urinary iodide excretion at a time point 24 hours after surgery was elevated when the solution was applied to the conjunctiva and periorbital skin.⁵⁵ These studies failed to demonstrate significance for these findings. The recommended daily intake of iodine by the WHO is 0.15 mg.⁵⁶ The majority of iodine is cleared by the kidneys in urine, 35% is excreted in sweat, and a negligible amount is excreted fecally.⁵⁷ When healthy patients were given more than 100 times the recommended intake of iodine daily for 38 days, there were no deleterious effects. The renal iodine clearance has been shown to be stable and not saturatable.⁵⁸

The limited number of in vitro membrane penetration studies has been conducted in experimental models highly dissimilar to typical clinical conditions. In the only quantitative in vitro study to specifically measure iodine flux across a human epithelial membrane, the protocol included an infinite dose regime, saturation of the complete surface area of the experimental membrane, and exposure time of 24 hours.⁵⁹ They concluded that 10% PVP-I applied to human skin demonstrated a maximum “iodine” medium flux of 0.73 $\mu\text{g}/\text{cm}^2$ per hour. However, based on the limitations of the study, this conclusion cannot be utilized as evidence based.

Elevated levels of iodine intake have been associated with autoimmune thyroiditis, goiter, and hypothyroidism.⁶⁰ A study was conducted on healthy patients in areas of Japan with high iodine intake from kelp. Patients had a urinary iodide excretion of 1.5 mg/d in these areas. However, there were no increases in thyroglobulin antibodies or thyroid peroxidase antibodies, and no reported negative health effects⁶¹; 5% PVP-I mouthwash effects on thyroid function were studied in patients 4 times per day for 2 weeks and 6 months daily without effect on thyroid function (Table 2).^{45,46}

There is a single report of possible iodine toxicity after irrigation with 300 mL of 10% PVP-I during a 3 hour functional endoscopic sinus surgery in one patient.⁶² Topical application of 1% PVP-I on denuded skin in rats was shown to compete with I¹²⁵ thyroid uptake.⁶³ Allergy, contact sensitivity, and skin reactions are rare.⁶⁴⁻⁶⁷ Although safety of cutaneous use of PVP-I in pregnant patients has been demonstrated,⁶⁸⁻⁷⁰ the safety of nasal and/or oral use is unclear. Safety regarding oral use of PVP-I gargle in the pediatric population has been demonstrated with single use and intermittent use for 6 months (Table 2).^{47,48}

Virucidal Capabilities and Efficacy Against Coronaviruses

Evaluation against human coronaviruses HCoV 229E, HCoVOC43, SARS, and MERS has demonstrated concentration-dependent virucidal activity in contact times as little as 15 seconds.⁷¹⁻⁷³ The lowest concentration effective against MERS was 1% with reduction of viral activity of more than 99.99%⁷⁴; 0.23% was the lowest effective concentration against SARS-CoV demonstrated in 2 in vitro studies after 15 seconds and 2 minutes of contact.^{73,75} Recent studies have shown up to 82% homology of SARS-CoV-2 with SARS-CoV.⁷⁶ Given the high homology with these viruses proven to be inactivated by PVP-I, there is optimism that PVP-I is effective against novel SARS-CoV-2. However, in vitro inactivation of SARS-CoV-2 by PVP-I has not yet been proven, and studies are needed to determine the factors that will optimize efficacy.

Discussion

The SARS-CoV-2 pandemic has altered the environment in which we practice medicine. Attempts to minimize spread have

mainly concentrated on strict adherence to the use of physical barriers, spatial separation, and personal protective equipment. The nasal cavities, nasopharynx, oral cavity, and oropharynx have high viral loads of SARS-CoV-2. There is a growing interest for decontamination of these areas in patients and health care workers to prevent virus transmission. PVP-I is of primary interest due to its ability to inactivate coronaviruses, the lack of microbial resistance, and the long history of clinical use. Protocols have been published describing regimens for use. We performed a review regarding the use and safety of PVP-I in the nasal and oral cavities to inform protocols based on known in vitro toxicity, clinical safety, in vitro efficacy, and solution chemistry.

PVP-I has been utilized for years in the nasal cavity for preoperative decontamination to prevent SSIs with proven efficacy. Chronic use has been implemented in CRS with efficacy and without effects on thyroid function, mucociliary clearance, or olfaction. Ciliotoxic effects have been demonstrated at concentrations of 2.5% and above, with safety demonstrated at 1.25% and lower.

Oral cavity use of PVP-I has been used acutely for surgical disinfection and chronically to treat plaque and dental caries. Chronic use in patients has not resulted in toxicity, irritation, staining of teeth, or change in taste. There is concern for aspiration of oral PVP-I in unconscious patients leading to aspiration pneumonia, with 6 case reports published in the surgical setting. However, there have been no case reports of aspiration pneumonia following PVP-I use in awake patients. Therefore, it is prudent to take care when instilling PVP-I in unconscious patients.

Chronic mucosal applications of PVP-I in doses up to 5% have been shown to increase urinary excretion of iodine without suggestion of clinical risk or thyroid disease associated with this transient increase in patients with normal renal function when used for up to 6 months. Iodine is primarily metabolized via urinary clearance in a linear, nonsaturable fashion. Povidone-iodine should not be used in patients undergoing radioactive iodine treatment as it was found to compete with thyroid radioactive iodine uptake in rats. Povidone-iodine has been used safely on the skin of pregnant patients but has not been evaluated on nasal or oral mucosa. Chronic oral use of 10% PVP-I intermittently for months has been safely reported in pediatric patients. Allergy and contact sensitivity are rare.

Povidone-iodine is safe in the nose up to 1.25% and mouth up to 5% for up to 5 and 6 months, respectively. Absorption of iodine is poorly described, inconsistently analyzed, and without clear conclusions. Regardless, PVP-I has been demonstrated to be systemically risk free at concentrations up to 5% daily for 5 months. The nose and mouth contain high viral loads of SARS-CoV-2, and aerosolization via these surfaces is of significant concern for virus transmission. Protocols have been put forth regarding PVP-I in the nasal and oral cavities to reduce transmission of SARS-CoV-2. Following our review, based on available data, we recommend nasal mucosal decontamination with 0.5 to 2 mL of 1.25% PVP-I and oral rinse with up to 10 mL at 2.5% as frequently as needed for decontamination

without risk of adverse effects. Povidone-iodine nasal and oral use should be avoided in patients with thyroid disease, pregnant patients, and patients receiving radioactive iodine therapy. If PVP-I is to be used in unconscious patients, care must be taken by using small amounts via direct application to mucosal surfaces to avoid the risk of aspiration.

Povidone-iodine is effective against SARS-CoV and MERS at 0.23% after 15 seconds of exposure in vitro. Based on homology demonstrated between SARS-CoV and SARS-CoV-2, it is likely that PVP-I is effective in safely eradicating SARS-CoV-2 in the nasal cavity, nasopharynx, oral cavity, and oropharynx. However, there are no existing data evaluating the efficacy of PVP-I on SARS-CoV-2. Studies are needed to characterize the utility of PVP-I against this new pathogen.


Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Samantha Frank  <https://orcid.org/0000-0002-5068-1065>

Belachew Tessema  <https://orcid.org/0000-0002-7418-6034>

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323(13):1239-1242.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan China. *JAMA*. 2020;323(11):1061-1069.
3. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020; 382(12):1177-1179.
4. To KK, Tsang OT, Chik-Yan Yip C, et al. Consistent detection of 2019 novel coronavirus in saliva. *Clin Infect Dis*. 2020;361:1319.
5. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. *Nat Med*. 2020; 26(5):676-680.
6. Butowt R, Bilinska K. SARS-CoV-2: olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. *ACS Chem Neurosci*. 2020;11(9):1200-1203.
7. Wu C, Zheng M. Single-cell RNA expression profiling shows that ACE2, the putative receptor of Wuhan 2019-nCoV, has significant expression in the nasal, mouth, lung and colon tissues, and tends to be co-expressed with HLA-DRB1 in the four tissues. *Preprints*. 2020;2020020247.
8. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12(1):8.

9. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26(5):681-687.
10. Beeching NJ, Fletcher TE, Beadsworth MBJ. Covid-19: testing times. *BMJ*. 2020;369:m1403.
11. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9(1):386-389.
12. Van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564-1567.
13. Balakrishnan K, Schechtman S, Hogikyan ND, Teoh AYB, McGrath B, Brenner MJ. COVID-19 pandemic: what every otolaryngologist-head and neck surgeon needs to know for safe airway management. *Otolaryngol Head Neck Surg*. 2020:194599820919751. [Online ahead of print].
14. Workman AD, Welling DB, Carter BS, et al. Endonasal instrumentation and aerosolization risk in the era of COVID-19: simulation, literature review, and proposed mitigation strategies. *Int Forum Allergy Rhinol*. 2020. [Online ahead of print].
15. Rackur H. New aspects of mechanism of action of povidone-iodine. *J Hosp Infect*. 1985;6:13-23.
16. Sriwilaijaroen N, Wilairat P, Hiramatsu H, et al. Mechanisms of the action of povidone-iodine against human and avian influenza A viruses: its effects on hemagglutination and sialidase activities. *Virol J*. 2009;6:124.
17. Kirk-Bayley J, Combes J, Sunkaraneni V, et al. The use of povidone iodine nasal spray and mouthwash during the current COVID-19 pandemic may reduce cross infection and protect healthcare workers. *Papers SSRN.com*. 2020. [Online ahead of print].
18. Mady L, Kubik M, Baddour K, Snyderman CH, Rowan NR. Consideration of povidone-iodine as a public healthy intervention for COVID-19: utilization as “personal protective equipment” for frontline providers exposed in high-risk head and neck and skull base oncology care. *Oral Oncol*. 2020;105:104724.
19. Parhar HS, Tasche K, Brody RM, et al. Topical preparations to reduce SARS-CoV-2 aerosolization in head and neck mucosal surgery. *Head Neck*. 2020. Epub ahead of print.
20. Dexter F, Parra MC, Brown JR, Loftus RW. Perioperative COVID-19 defense: an evidence-based approach for optimization of infection control and operating room management. *Anesth Analg*. 2020.
21. ADA Interim Guidance for Minimizing Risk of COVID-19 Transmission. 2020. https://www.ada.org/~/media/CPS/Files/COVID/ADA_COVID_Int_Guidance_Treat_Pts.pdf
22. Bhagwat D, Iny O, Pedi F. Stabilizing packaged iodophor and minimizing leaching of iodine through packaging. US patent US4996048. 26 February, 1991.
23. Plamondon M. Ophthalmic solution comprising iodine-polyvinylpyrrolidone complex. US patent US4976969. 1990.
24. Capriotti K, Capriotti JA. Topical iodophor preparations: chemistry, microbiology, and clinical utility. *Dermatol Online J*. 2012;18(11):1.
25. Berkelman RL, Holland BW, Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. *J Clin Microbiol*. 1982;15(4):635-639.
26. Perl TM., Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med*. 2002;346(24):1871-1877.
27. Peng HM, Wang LC, Zhai JL, Weng XS, Feng B, Wang W. Effectiveness of preoperative decolonization with nasal povidone iodine in Chinese patients undergoing elective orthopedic surgery: a prospective cross-sectional study. *Braz J Med Biol Res*. 2017;51(2):e6736.
28. Bebeko SP, Green DM, Awad SS. Effect of a preoperative decontamination protocol on surgical site infections in patients undergoing elective orthopedic surgery with hardware implantation. *JAMA Surg*. 2015;150(5):390-395.
29. Rezapoor M, Nicholson T, Mostafavi Tabatabaee R, Chen AF, Maltenfort MG, Parvizi J. Povidone-iodine-based solutions for decolonization of nasal staphylococcus aureus: a randomized, prospective, placebo-controlled study. *J Arthroplasty*. 2017;32(9):2815-2819.
30. Panchmatia R, Payandeh J, Al-Salman R, et al. The efficacy of diluted topical povidoneiodine rinses in the management of recalcitrant chronic rhinosinusitis: a prospective cohort study. *Eur Arch Otorhinolaryngol*. 2019;276(12):3373-3381.
31. Mullings W, Panchmatia R, Samoy K, et al. Topical povidone-iodine as an adjunctive treatment for recalcitrant chronic rhinosinusitis. *Eur J Rhinol Allergy*. 2019;2(2):45-50.
32. Gluck U, Martin U, Bosse B, Reimer K, Mueller S. A clinical study on the tolerability of a liposomal povidone-iodine nasal spray: implications for further development. *ORL J Otorhinolaryngol Relat Spec*. 2007;69(2):92-99.
33. Ramezanpour M, Smith JLP, Psaltis AJ, Wormald PJ, Vreugde S. In vitro safety evaluation of a povidone-iodine solution applied to human nasal epithelial cells. *Int Forum Allergy Rhinol*. 2020. [Online ahead of print].
34. Kim JH, Rimmer J, Mrad N, Ahmadzada S, Harvey RJ. Betadine has a ciliotoxic effect on ciliated human respiratory cells. *J Laryngol Otol*. 2015;129(1):45-50.
35. Reimer K, Wichelhaus TA, Schafer V. Antimicrobial effectiveness of povidone-iodine and consequences for new application areas. *Dermatology*. 2002;204(1):114-120.
36. Shiraishi T, Nakagawa Y. Evaluation of the bactericidal activity of povidone-iodine and commercially available gargle preparations. *Dermatology*. 2002;204(1):37-41.
37. Managutti A, Managutti SA, Patel J, Puthanakar NY. Evaluation of post-surgical bacteremia with use of povidone-iodine and chlorhexidine during mandibular third molar surgery. *J Maxillofac Oral Surg*. 2017;16(4):485-490.
38. Nagatake T, Ahmed K, Oishi K. Prevention of respiratory infections by povidone-iodine gargle. *Dermatology*. 2002;204(1):32-36.
39. Satomura K, Kitamura T, Kawamura T, et al. Prevention of upper respiratory tract infections by gargling: a randomized trial. *Am J Prev Med*. 2005;29(4):302-307.
40. Kitamura T, Satomura K, Kawamura T, et al. Great Cold Investigators-I. Can we prevent influenza-like illnesses by gargling? *Intern Med*. 2007;46(18):1623-1624.

41. Committee for the Japanese Respiratory Society Guidelines in Management of Respiratory. Prevention of hospital-acquired pneumonia (strategies for prevention of hospital-acquired infections). *Respirology*. 2004;9(1):48-50.
42. Sato S, Miyake M, Hazama A, Omori K. Povidone-iodine-induced cell death in cultured human epithelial HeLa cells and rat oral mucosal tissue. *Drug Chem Toxicol*. 2014;37(3):268-275.
43. Madan PD, Sequeira PS, Shenoy K, Shetty J. The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: a randomized control trial. *J Cancer Res Ther*. 2008;4(1):3-8.
44. Rahn R, Adamietz IA, Boettcher HD, Schaefer V, Reimer K, Fleischer W. Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. *Dermatology*. 1997;195(2):57-61.
45. Ferguson MM, Geddes DA, Wray D. The effect of a povidone-iodine mouthwash upon thyroid function and plaque accumulation. *Br Dent J*. 1978;144(1):14-16.
46. Ader AW, Paul TL, Reinhardt W, et al. Effect of mouth rinsing with two polyvinylpyrrolidone-iodine mixtures on iodine absorption and thyroid function. *J Clin Endocrinol Metab*. 1988;66(3):632-635.
47. Amin MS, Harrison RL, Benton TS, Roberts M, Weinstein P. Effect of povidone-iodine on *Streptococcus mutans* in children with extensive dental caries. *Pediatr Dent*. 2004;26(1):5-10.
48. Reilly C, Goettl M, Steinmetz M, Nikrad J, Jones RS. Short-term effects of povidone iodine and sodium fluoride therapy on plaque levels and microbiome diversity. *Oral Dis*. 2016;22(2):155-161.
49. Kovesi G. The use of betadine antiseptic in the treatment of oral surgical, paradontological and oral mucosal diseases [in Hungarian]. *Fogorv Sz*. 1999;92(8):243-250.
50. Hitosugi T, Tsukamoto M, Yokoyama T. Pneumonia due to aspiration of povidone iodine after preoperative disinfection of the oral cavity. *Oral Maxillofac Surg*. 2019;23(4):507-511.
51. Choi WY, Park CW, Cheon JS, Son KM. Aspiration pneumonitis due to povidone-iodine aspiration during a facial bone fracture reduction operation. *J Craniofac Surg*. 2014;25(2):172-174.
52. Chepla KJ, Gosain AK. Interstitial pneumonitis after betadine aspiration. *J Craniofac Surg*. 2012;23(6):1787-1789.
53. Cheong SH, Yang YI, Choi MY, et al. Lung injury induced by the pulmonary instillation of povidone-iodine in rats. *J Anesth*. 2012;26(1):70-79.
54. Tomada C, Kitano H, Uruno T, et al. Transcutaneous iodine absorption in adult patients with thyroid cancer disinfected with povidone-iodine at operation. *Thyroid*. 2005;15(6):600-603.
55. Below H, Behrens-Baumann W, Bernhardt C, Völzke H, Kramer A, Rudolph P. Systemic iodine absorption after preoperative antisepsis using povidone-iodine in cataract surgery—an open controlled study. *Dermatology*. 2006;212(1):41-46.
56. World Health Organization, ICCIDD U. Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness. 1996. https://www.who.int/nutrition/publications/micronutrients/iodine_deficiency/WHO_NUT_96.13/en/
57. Nelson N, Palmes ED. The absorption, excretion, and physiological effect of iodine in normal human subjects. *J Clin Invest*. 1947;26(2):301-310.
58. Verger P, Aurengo A, Geoffroy B, Le Guen B. Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. *Thyroid*. 2001;11(4):353-360.
59. Nesvadbova M, Crosera M, Maina G, Larese Filon F. Povidone iodine skin absorption: an ex-vivo study. *Toxicol Lett*. 2015;235(3):155-160.
60. Foley TP Jr. The relationship between autoimmune thyroid disease and iodine intake: a review. *Endokrynol Pol*. 1992;43(1):53-69.
61. Nagata K, Takasu N, Akamine H, et al. Urinary iodine and thyroid antibodies in Okinawa, Yamagata, Hyogo, and Nagano, Japan: the differences in iodine intake do not affect thyroid antibody positivity. *Endocrine J*. 1998;45(6):797-803.
62. Ramaswamykanive H, Nanavati Z, Mackie J, Linderman R, Lavee O. Cardiovascular collapse following povidone-iodine wash. *Anaesth Intensive Care*. 2011;39(1):127-130.
63. Furudate S, Nishimaki T, Muto T. ¹²⁵I uptake competing with iodine absorption by the thyroid gland following povidone-iodine skin application. *Exp Anim*. 1997;46(3):197-202.
64. Lachapelle JM. A comparison of the irritant and allergenic properties of antiseptics. *Eur J Dermatol*. 2014;24(1):3-9.
65. Gray PEA, Katelaris CH, Lipson D. Recurrent anaphylaxis caused by topical povidoneiodine (Betadine). *J Paediatr Child Health*. 2013;49(6):506-507.
66. Lachapelle JM. Allergic contact dermatitis from povidone-iodine: a re-evaluation study. *Contact Dermatitis*. 2005;52(1):9-10.
67. Reyazulla MA, Gopinath AL, Vaibhav N, Raut RP. An unusual complication of late onset allergic contact dermatitis to povidone iodine in oral & maxillofacial surgery—a report of 2 cases. *Eur Ann Allergy Clin Immunol*. 2014;46(4):157-159.
68. Ngai IM, Van Arsdale A, Govindappagari S, et al. Skin preparation for prevention of surgical site infection after cesarean delivery: a randomized controlled trial. *Obstet Gynecol* 2015;126(6):1251-1257.
69. Valizadeh M, Nazeri P, Fazli F, et al. Application of povidone-iodine at delivery significantly increase maternal urinary iodine but not neonatal thyrotropin in an area with iodine sufficiency. *J Pediatr Endocrinol Metab*. 2017;30(9):967-972.
70. Tahirovic H, Toromanovic A, Grbic S, Bogdanović G, Fatusić Z, Gnat D. Maternal and neonatal urinary iodine excretion and neonatal TSH in relation to use of antiseptic during caesarean section in an iodine sufficient area. *J Pediatr Endocrinol Metab*. 2009;22(12):1145-1149.
71. Kawana R, Kitamura T, Nakagomi O, et al. Inactivation of human viruses by povidoneiodine in comparison with other antiseptics. *Dermatology*. 1997;195(2):29-35.
72. Sizun J, Yu MW, Talbot PJ. Survival of human coronaviruses 229E and OC43 in suspension and after drying on surfaces: a possible source of hospital-acquired infections. *J Hosp Infect*. 2000;46(1):55-60.
73. Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In vitro bactericidal and virucidal efficacy of povidone-iodine gargle/

- mouthwash against respiratory and oral tract pathogens. *Infect Dis Ther.* 2018;7(2):249-259.
74. Eggers M, Eickmann M, Zorn J. Rapid and effective virucidal activity of povidone-iodine products against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA). *Infect Dis Ther.* 2015; 4(4):491-501.
75. Kariwa H, Fujii N, Takashima I. Inactivation of SARS coronavirus by means of povidoneiodine, physical conditions and chemical reagents. *Dermatology.* 2006;212(1):119-123.
76. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. *Microbes Infect.* 2020;22(2):74-79.