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Research Article

Intranasal therapy and COVID-19: A comprehensive literature review

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is highly virulent and can be transmitted via respiratory droplets and close contact. Recent studies suggest that although viral load could be a poor predictor of disease, the concentration of the virus in the respiratory tract may be linked to contagiousness when coupled with significant co-variables factors such as nasal discharge and cough, hence impacting transmission. This review aims to explore the effectiveness of using agents with antiviral properties administered intranasally as a novel strategy for decreasing the viral activity in the nasal pathway, preventing disease transmission which might impact the disease severity and possibly limit the complications. Medications were evaluated for their antiviral properties against SARS-CoV-2 and other viruses. Various compounds with virucidal activities are highlighted in this review including xylitol and grapefruit seed extract, povidone-iodine, intranasal corticosteroids, hydrogen peroxide, chlorpheniramine, hypertonic and saline. The safety and effectiveness of these potential agents when used via intranasal routes in humans, and the clinical implications of using intranasal therapy in medical practice are discussed.

Keywords: Intranasal Therapy, Xylitol, Grapefruit Seed Extract, Povidone-Iodine, Chlorpheniramine, SARS-CoV-2, COVID-19

Introduction

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China was brought to international notice, declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. SARS-CoV-2 is a highly virulent and transmissible virus that spreads primarily through respiratory droplets and close contact [2]. The SARS-CoV-2 binds to host cells surface Angiotensin Converting Enzyme II (ACE II) using a Spike (S1) protein (Figure 1A and 1B), subsequently gaining entry into host cells and infecting neighboring cells. A second protein, transmembrane protease series 2 (TMPRSS2), plays a pivotal role in priming/cleavage of the S1 protein to allow fusion of the viral envelope to endosome to further allow entry into the host cell and release viral genetic material to infect host cells [3]. Immunohistochemistry studies have shown significant ACE2 and TMPRSS2 gene expression in nasal and bronchial epithelium [4]. As the SARS-CoV-2 viral entry is through the nose or the mouth using the ACE2 receptors, it is critical to our understanding of the virus pathway to the respiratory system [5]. The World Health Organization (WHO) established nasal and oropharyngeal swab tests to be used for screening of COVID-19. Interestingly, approximately 30% of swabs from clinically symptomatic patients may test negative (false negative), and therefore current tests are considered screening tests, and not the diagnostic test. It is also important to note that the viral load in nasal and oral cavity may still be low, and therefore contributing to false negative test results [6].

The transmission of the virus in asymptomatic patients is similar to that in symptomatic patients, indicating that the earlier could transmit the infection [2,7]. The infected patients are at risk of a wide array of symptoms such as complications of respiratory, cardiac, neurological, and gastrointestinal systems, posing a higher risk to immunocompromised and organ failure patients [1,2,7,8]. Hence, early recognition of an infected person as well as blocking the transmission route might be essential strategies for managing COVID-19 spread and severity. The COVID-19 cycle of infection, symptomatology and antibody development is demonstrated in Figure 2.

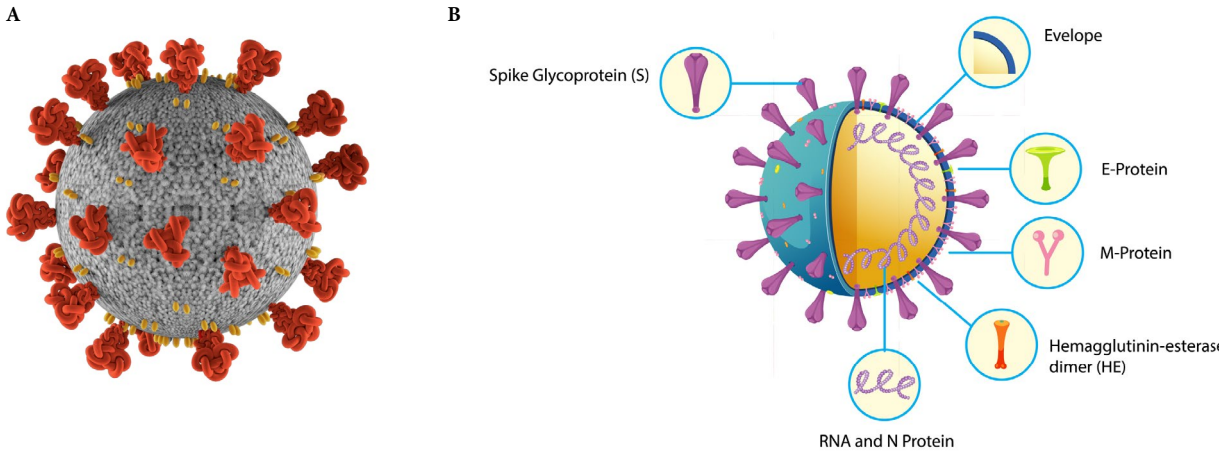
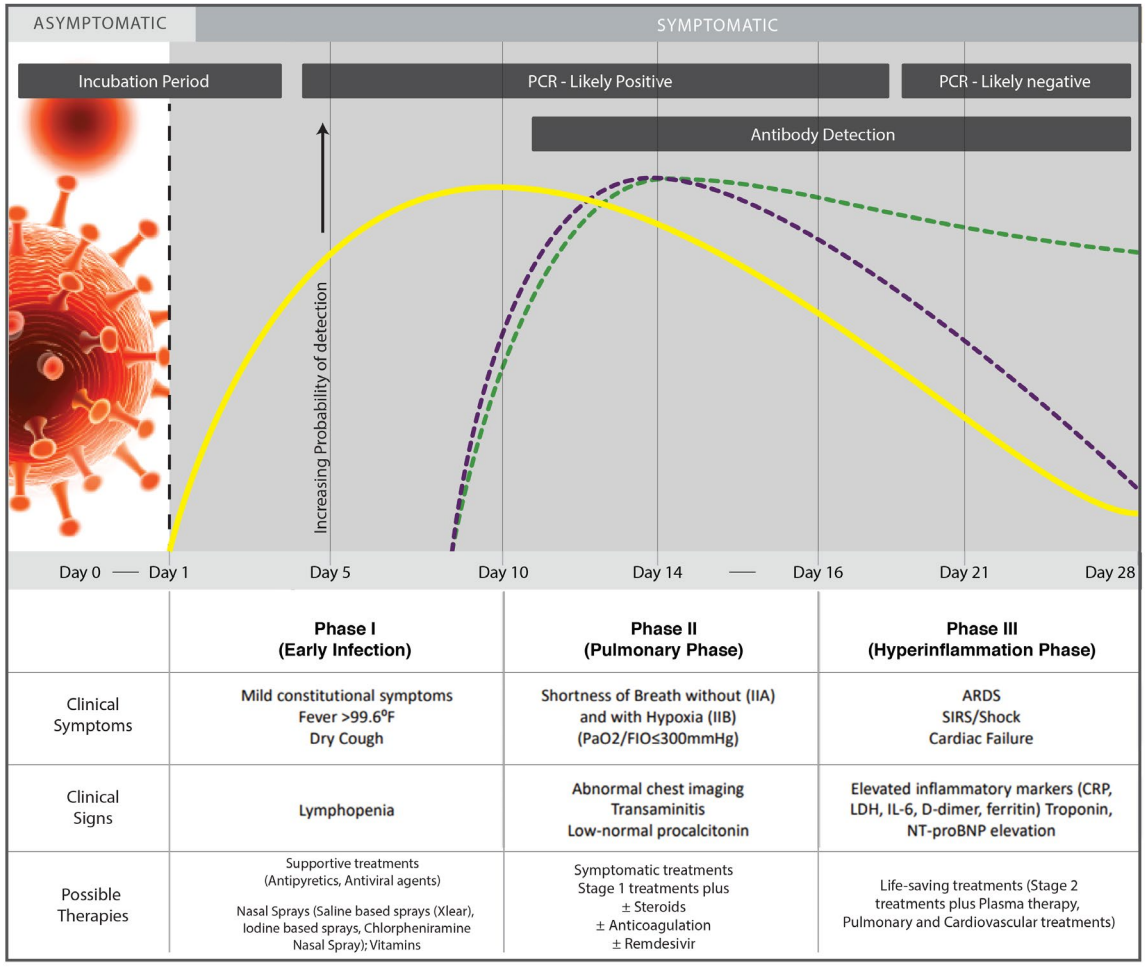


Figure 1A and 1B: Images representing SARS-CoV-2.



	Phase I (Early Infection)	Phase II (Pulmonary Phase)	Phase III (Hyperinflammation Phase)
Clinical Symptoms	Mild constitutional symptoms Fever >99.6°F Dry Cough	Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FIO≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
Possible Therapies	Supportive treatments (Antipyretics, Antiviral agents) Nasal Sprays (Saline based sprays (Xlear), Iodine based sprays, Chlorpheniramine Nasal Spray); Vitamins	Symptomatic treatments Stage 1 treatments plus ± Steroids ± Anticoagulation ± Remdesivir	Life-saving treatments (Stage 2 treatments plus Plasma therapy, Pulmonary and Cardiovascular treatments)

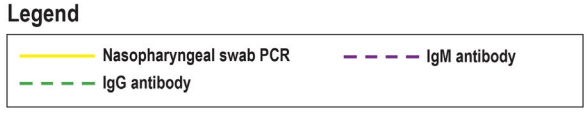


Figure 2: Visual representation of COVID-19 cycle of infection, symptomatology and antibody development.

Recent studies suggested that the viral load can be a poor predictor of disease outcome. However, the viral concentration in the respiratory tract may be indirectly associated with contagiousness when coupled with significant co-variables like nasal discharge and cough impacting transmission [7,9]. Practical strategies, such as social distancing, self-isolation, quarantine, travel restrictions, and group gatherings, have been recently implemented to prevent the spread of COVID-19 [10]. Nevertheless, inadequate personal protective equipment (PPE) and complexity in achieving social distancing in hospital settings has put healthcare workers at higher risk [11]. Limited strategies are currently accessible in modifying the viral content in infected patients' respiratory tracts, justifying the need for novel therapeutic interventions targeting the principal route of infection.

We propose that intranasal administration of virucidal and antiviral therapies may be a novel strategy to provide an added clinical benefit by decreasing the viral activity in the nasal pathway, thus preventing disease transmission, managing the disease severity and limiting complications. This manuscript aims to determine the optimal management of known antiviral agents used via the intranasal route and summarize their effectiveness against SARS-CoV-2.

Antiviral Agents with Intranasal Use Potential

Xylitol & Grapefruit seed extract

Xylitol, a naturally occurring sugar alcohol [12-17] commonly used as a low-calorie sweetener for sugar-free confectionery, demonstrates antiviral properties when administered both orally [18] and intranasally [19]. In a study conducted by Xu and colleagues, they demonstrated that dietary xylitol showed antiviral activity against the human respiratory syncytial virus (hRSV) in mice. Mice were given xylitol orally for 14 days before the virus challenge and three days post-challenge. The results indicated a reduction of lung virus titers found with mice receiving xylitol orally, which inhibited and decreased the infection severity. It was also found that fewer CD3+ and CD3+ CD8+ lymphocytes were activated in the mice receiving dietary xylitol, which indicated a reduced inflammation-associated response to the hRSV infection [18].

Bansal et al. conducted an *in vitro* study to test the antiviral action of iota-carrageenan and xylitol against SARS-CoV-2. They found that iota-carrageenan in concentrations as low as 6 μg/mL and xylitol at a concentration of 5% m/V has shown to inhibit SARS-CoV-2 infection in Vero cell cultures. These concentrations can be easily incorporated in intranasal sprays already available over the counter [19] supporting our notion of the potential use of xylitol as a prophylactic regimen for antibacterial and antiviral pathogens such as SARS-CoV-2. With xylitol's excellent safety profile [13] and unique activity to reduce viral loads, it may be a possible alternative to those who are against using synthetically derived products.

Grapefruit seed extract (GSE) is well known to inhibit bacteria growth such as *Pseudomonas aeruginosa*, Escherichia coli, *Staphylococcus spp*. and *Enterococcus spp*. [20]. Recently, antiviral properties of GSE were also evaluated *in vitro* with several viruses such as the avian influenza virus (AIV), Newcastle disease virus (NDV), infectious bursal disease virus (IBDV). GSE was then diluted (×100, ×500 and ×1,000 with redistilled water) and incubated with the pathogens. Diluted GSE was sprayed in the air and was collected at a distance of 1 cm and 30 cm to assess efficacy against viruses and bacteria. The results showed activity against gram negative bacteria used in this study, indicating Noteworthy, GSE also showed antiviral effect in enveloped viruses such as the AIV and NVD but resistance with non-enveloped viruses (IBDV). GSE is highly acidic, therefore sensitive to enveloped viruses and bacteria, but resistant to non-enveloped viruses like IBDV [21]. Therefore, intranasal GSE may prove to be a potent antiviral for the enveloped SARS-CoV-2.

Another study showed the effects of GSE for the first time in human enteric virus surrogates such as feline calicivirus (FCV-F9), murine norovirus (MNV-1), bacteriophage MS2 and hepatitis A virus (HAV) strain HM175 [22]. The viruses were individually mixed with GSE at different concentrations and then incubated at room temperature of 37°C, then evaluated with plaque assays. The titers showed a significant reduction in all four viruses when evaluated at different GSE dosages and concentrations. The study showed that GSE has some activity with FCV-F9, MNV-1 and HAV adsorption that may be through host cell receptor blocking or viral binding inhibition. Given its safety profile [23] and antiviral components, the usage of GSE may benefit further research for utilization against viral diseases such as the enveloped SARS-CoV-2.

Moreover, in a recently published article by Go et al., three mild-moderate COVID-19 positive patients were administered xylitol plus GSE in the form of a nasal spray. Remarkable results including a reduction of clinical course and noted improvement of symptoms as early as day 4. Furthermore, on day 7, patients tested negative on repeat RT-PCR nasopharyngeal swab instead of the average 14-day period of negativization of COVID-19. By using xylitol plus GSE in the form of an intranasal spray (Xlear nasal spray), as an adjunct to the ongoing treatment, the time to negativization was reduced by 50%. This suggests that intranasal xylitol plus GSE nasal spray, when used as an adjunct therapy to ongoing treatments for COVID-19, has a potential to show positive outcomes in these patients [24].

Povidone-Iodine (PVP-I)

Povidone-Iodine, also known as Betadine, Iodine, Disphex, Povadyne or Ultradine, is a water-soluble iodophor solution that was developed in the 1950s and has been used for infection prevention and control since then [25-27]. It contains a complex of iodine and polyvinylpyrrolidone (PVP) and is a broad-spectrum antimicrobial. Polyvinylpyrrolidone complex (PVP-I) contains free iodine which is slowly liberated. The free iodine causes the iodination of lipids and oxidation of cytoplasmic and membrane compounds which kills the eukaryotic or prokaryotic cells [1]. PVP-I is widely used as a surgical skin prep agent and a mouthwash [10]. PVP-I with concentration of 1.25% and below can safely be used intranasally [28]. It has been shown that SARS-CoV-2 can be inactivated by PVP-I with concentrations as low as 0.5% in a contact time of as low as 15 seconds [28].

In 2006, Kariwa et al. demonstrated that PVP-I products can reduce the SARS-CoV virus infectivity from 1.17×10^6 TCID50/ml to below the detectable level when treated for two minutes [29]. In a study published by Eggers et al., it was demonstrated that PVP-I 7% gargle/mouthwash at a concentration of 0.23% PVP-I showed rapid bactericidal activity against *Klebsiella pneumoniae* and *Streptococcus pneumoniae* and antiviral activity against SARS-CoV, MERS-CoV, influenza virus A (H1N1) and rotavirus after 15 seconds of exposure [30].

Considering the proven efficacy of PVP-I against the oral and respiratory pathogens, gargling/mouthwash, Povidone-Iodine might be an effective method of prevention of the spread of pathogens which spread via airborne/droplet route. Since SARS-CoV-2 (causative agent of COVID-19) has a similar route of transmission and share some common characteristics with SARS-CoV [31,32], there is certainty that the SARS-CoV-2 can be inactivated by Povidone-Iodine, although there is need for in vitro studies to prove the efficacy of the same.

Currently, an open label, interventional study of 300 participants for studying the prophylactic role of intranasal Povidone-Iodine in front-line health-care workers and inpatients is being conducted at the University of Kentucky. This study is estimated to be completed by May 2021 [33].

Intranasal corticosteroids

Intranasal corticosteroids are first-line therapy for allergic rhinitis. They have been well known for their safety and effectiveness for allergic rhinitis [34]. Apart from allergic rhinitis, intranasal corticosteroids have also been used for adenoidal hypertrophy and adenotonsillar hypertrophy, decreasing surgery rates for the former [35]. In the US, various glucocorticosteroids are available in the intranasal form. Some examples include beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, flunisolide, mometasone furoate and triamcinolone acetonate. The side effects are limited, occurring in about 5-10% of patients and include dryness, burning, stinging of the nasal mucosa, sneezing, headache and nasal bleeding. The rate of systemic bioavailability of intranasal corticosteroids is less than 1% [36,37].

The ARIA-EAACI (The Allergic Rhinitis and its Impact on Asthma initiative-The European Academy of Allergy & Clinical Immunology) published as a statement regarding the use of intranasal corticosteroids for the COVID-19 patients with allergic rhinitis. They recommended these patients keep using intranasal corticosteroids. The statement mentioned that if the patients stop using intranasal corticosteroids, the sneezing could worsen, which could lead to the spread of the virus, which explains the recommendation of maintenance of the use of local intranasal corticosteroids in these patients [38].

Based on the studies mentioned above, intranasal corticosteroids used in COPD, and asthma patients with overlapping COVID-19 is yet to be answered. Several clinical trials are ongoing in the United States, Canada, South Korea and Sweden to assess ciclesonide as a potential therapeutic option for COVID-19.

Surfactants/ Shampoos

Surfactants are the most versatile and widely used products in the chemical industry. In pharmaceutical formulations, these are used primarily as excipients. Surfactants have the property of adsorbing, the lower surface tension of liquids, increase the solubility of substances and, to an extent, alter the interface of the system [39,40]. Promod K et al., hypothesized the use of surfactant-based prophylaxis against the SARS-CoV-2 peplomers and treatment of COVID-19. It was proposed that any virus entering the mouth, nose and eyes could be inactivated using a surfactant-based gargle and subsequently entrapped by surfactant micelles through inactivation [41]. Surfactant-based gargle or spray will be an invaluable prophylaxis treatment against viruses that utilize the oropharyngeal route. Additional studies are warranted to explore this possibility.

The diluted surfactant therapy showed *in vitro* antimicrobial inhibition against bacterial biofilm formation in patients with rhino-pathologies [40]. Pulmonary surfactants palmitoyl-oleoyl-phosphatidylglycerol (POPG) and phosphatidylinositol (PI) are found to antagonize Influenza A(H1N1) pdm09 virus (pH1N1) infection effectively and have a significant reduction of lung inflammation and viral burden in mice [42].

Recently, the emergence of new biosurfactants that have been studied accelerated the advances in biosurfactants' application. They have an essential role in the physiological roles in increasing bioavailability of hydrophobic molecules, possess antimicrobial activity, and form complexes with heavy metals. They are further used as antimicrobial agents and improve the degradation of chemical contaminants [43]. Although surfactant nasal-based irrigation may be associated with moderate congestion and olfactory acuity reduction, it appears to be reversible after discontinuation, hence generally safe for use [44]. The use of surfactant-based nasal spray as treatment and prophylaxis may be beneficial given its relatively safe profile.

Hydrogen peroxide (H_2O_2)

SARS-CoV, MERS-CoV, and influenza virus can stay on surfaces for extended periods, sometimes up to months [45]. The transmission of coronavirus from surfaces has been hypothesized to persist in inanimate surfaces. Use of 0.1% Sodium Hypochlorite or 62-71% ethanol significantly reduces coronavirus infectivity on surfaces within 1 min exposure time [46]. An in vitro study of the efficacy of H_2O_2 vapor, a vapor-phase disinfection method, has shown that it was virucidal for structurally distinct viruses in inanimate surfaces, suggesting that it can be considered for the disinfection of the virus-contaminated surfaces [47]. Moreover, H_2O_2 is commonly used by otolaryngologists because it is relatively safe for gargling or spraying intranasally [48]. Caruso et al., considering the higher sensitivity of the mucosa of the nasal cavity to H_2O_2, proposed a regimen of H_2O_2 gargling and H_2O_2 nasal washes via nebulizer, 3 times per day and 2 times a day, respectively [48]. In another article, Caruso et al. proposed spraying 2 puffs of 1.5% H_2O_2 nasal spray (0.28 ml) as initial testing dose into each nostril twice daily in combination with gargle and mouth washing with 3% H_2O_2 solution twice daily for one minute [49]. Although an in vitro study has shown the efficacy of H_2O_2 against COVID-19 on inanimate surfaces [47], theoretically intranasal use of H_2O_2 against SARS-CoV-2 could have potential. However, additional larger randomized trials are needed to further validate the above-mentioned proposals, to determine its efficacy and to obtain a detailed safety profile for human use against COVID-19.

Chlorpheniramine (CPM)

CPM is a safe and effective antihistamine with potent antiviral activity against various strains of Influenza A/B, thus suggesting that CPM has broad antiviral activity. CPM is a safe and effective antihistamine with drowsiness as the main side effect. However, evidence suggests that intranasal delivery shows high efficacy with no side effects. An animal study of intranasally delivered CPM has shown that it does cross into the brain circulation [50]. The systemic bioavailability and safety of a nasal spray solution developed to deliver doses of 1.12 and 2.24 mg CPM intranasally (0.4% nasal

spray) and have found no adverse events [51]. Intranasal delivery of CPM significantly inhibits histamine-induced symptoms [52].

Ferrer G et al. conducted a study to test the virucidal activity of chlorpheniramine maleate using viral stock of SARS-CoV-2, USA-WA1/2020 strain in Vero 76 infected cells. The end-point titer 50% cell concentration inhibitor doses (CCID50) values were calculated with the Reed-Muench (1948) equation. Three independent replicates of each sample were tested, and the average and standard deviation were calculated. As a result, after 25 minutes of contact time, the nasal spray reduced the virus's levels from 4.2 to 1.7 log10 CCID50 per 0.1 mL, a statistically significant reduction of 2.5 log10 CCID50. This study demonstrates that CPM, which has strong virucidal effect against SARS-CoV-2, can be administered intranasally [53].

Acid buffered/ Hypertonic saline

Human rhinoviruses (HRVs) are quite sensitive to low pH. Low pH inhibits as well as reduces the replication of influenza virus. The surface pH of the human nasopharynx could be transiently lowered to pH ~4.0 by topical administration of citrate/phosphate (CP) buffers. Many serotypes of HRV were exquisitely sensitive to pH <6.0 *in vitro*. combined low pH and a chelating agent is able to reduce the amount of viral shedding during the acute cold but did not reduce common cold symptoms. An in vivo study done by Gern JE et al., showed that the administration of a low CP buffer was able to reduce viral shedding by 1 log unit. These findings provide the rationale for conducting a double-blinded, placebo-controlled, clinical trial to determine whether low-pH buffers will further decrease viral replication rate [54].

Tano L et al. conducted a study involving 69 subjects of otherwise healthy adults, ascertaining whether a daily nasal spray with saline could prevent symptoms of common colds. They found out that during the spray period the number of days with nasal secretion and/or blocked nose (mean 6.4 days) was significantly (p=0.027) lower than that during the observation period (mean 11 days). Participants also had a mean of 0.7 episodes of upper respiratory tract infection during the spray period, compared with 1.0 episodes during the observation period (p=0.05). They were able to conclude that the use of a daily nasal spray with saline can prevent nasal symptoms of common colds in a population of healthy adults [55]. The usage of isotonic saline (0.9% sodium chloride) and hypertonic saline (concentration greater than 0.9% sodium chloride) are most often used in commercially prepared nasal irrigation. Although in theory, the hypertonic solution has increased osmotic pressure and should demonstrate higher efficacy in reducing mucosal edema and eliminating airborne allergens and chemical mediators. The optimal saline irrigation concentration remains equivocal [56].

Furthermore, post hoc secondary analysis of data from a randomized controlled trial showed that the usage of hypertonic saline nasal irrigation and gargling effectively reduced the duration of coronavirus upper respiratory tract infection (URTI) by an average of two-and-a-half days, hence it may be used as a potentially safe intervention from SARS-CoV-2 [57].

Clinical Implications for Practice

Intranasal antiviral therapies may yield possible beneficial outcomes. Their application needs to be extensively studied, majorly targeting the efficacy and safety of the treatments. The recent studies by Hou et al. and Jacot et al., demonstrated that the descending order of ACE-2 receptors expression in the upper respiratory tract to lower respiratory tract, correlated to an increased degree of SARS-CoV-2 infection in the upper respiratory tract compared to distal pulmonary epithelial cultures [58,59]. Thus, the treatments focusing on decreasing the viral load, such as intranasal antiviral therapies may have a broad range of clinical implications in practice.

The authors of this review collectively consider that these agents' provisional application might have the following uses:

- Expedite recovery of mild-moderate COVID-19 patients.
- Reduce transmission of COVID-19 infection from person to person.
- Help decrease the rate of hospitalization.
- Prevention of healthcare workers contracting the viral infection via procedural exposure and perioperative exposure
- Decrease of symptom progression and severity.
- Use as post-exposure prophylaxis agents.
- Decrease intranasal symptoms.
- Open a pathway to reformulating existing treatments.
- Provide appropriate time to develop vaccines.
- Utilizing available over the counter (OTC) nasal sprays namely Xlear® Nasal Spray.

Health care workers are at increased risk of acquiring COVID-19 due to varied factors [11]. In one multinational prospective cohort study, the healthcare worker's risk of acquiring COVID-19 during the intubation of an infected patient is noted as 10.17% [60]. While clinical settings are at increased possibility of disease transmission, placing healthcare workers and other patients at risk, Intranasal antiviral therapy may help in widespread restriction of disease spread and improvement in intranasal symptoms. Nasal cavity and nasopharynx shelters for a notable amount of SARS-CoV-2, in both asymptomatic and symptomatic carriers of the virus and the IAT's use, may help decrease the viral load, thus minimizing the symptom severity and progression [58,59]. Various potential agents exist for the intranasal delivery of antiviral drugs. However, the clinical efficacy of an agent is better achieved by efficient mechanism against target, appropriate route of delivery, supplying proper media, enhancing the effect by increasing the mucosal efficiency [60,61]. The potential application of the intranasal antiviral agents in the clinical practice are summarized in Figure 3.

Conclusion

The world is going through unprecedented times facing a pandemic. Due to the limited understanding of the SARS-CoV-2, the available treatment options are minimal. Innovative treatment options and prophylaxis are being utilized despite limited literature to find the appropriate treatment against COVID-19. This manuscript proposes that intranasal administration of virucidal and antiviral therapies may be a novel strategy to provide an added clinical benefit to COVID-19 treatment. Based on the literature review, it is encouraging to note that studies reviewed note that using nasal spray with antiviral properties has promising efficiency and safety in the treatment and prophylaxis against SARS-CoV-2. GSE

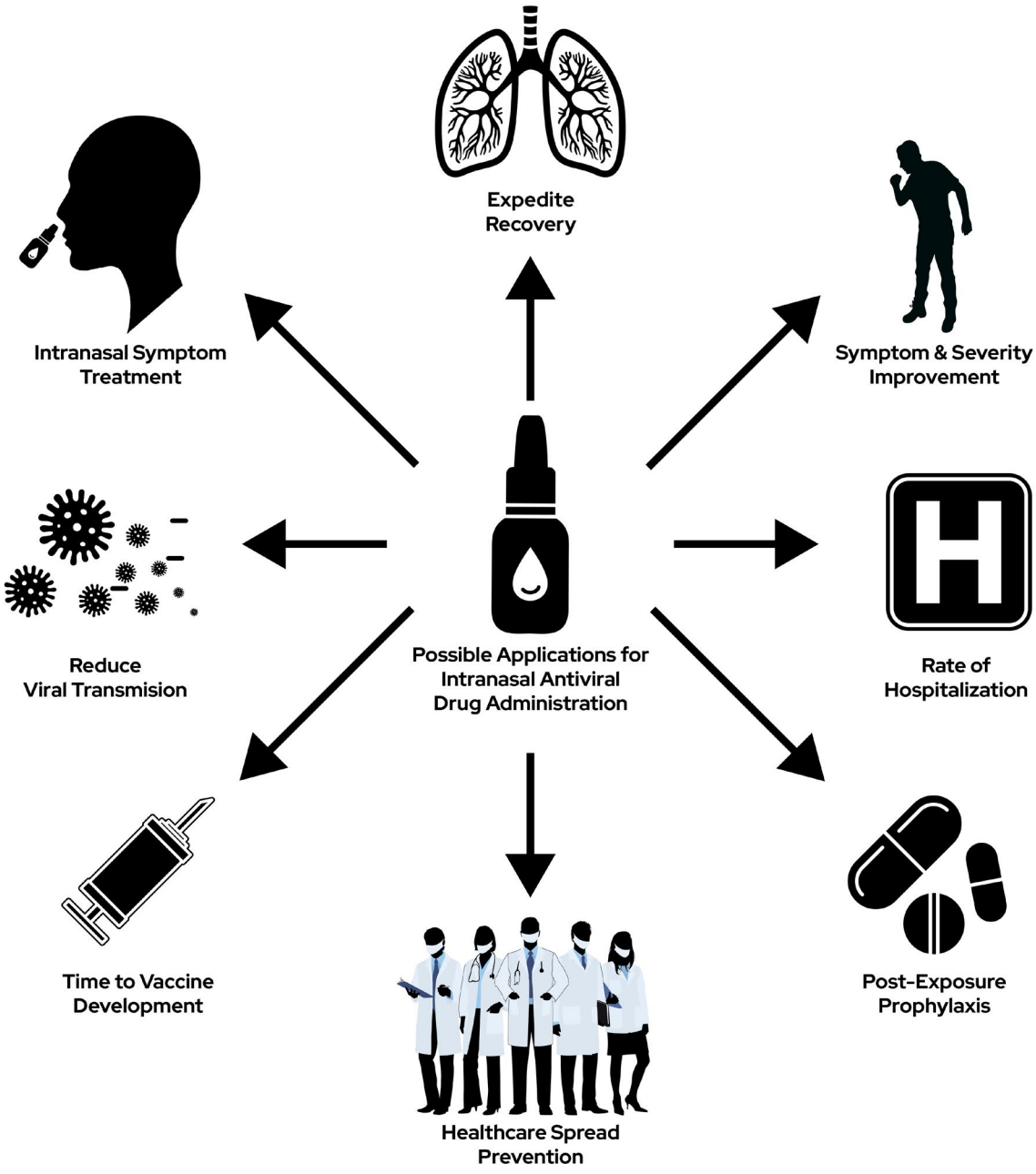


Figure 3: Summary of the potential applications of the intranasal agents in the clinical practice against COVID-19.

is highly acidic and sensitive to enveloped viruses and bacteria. PVP-1 contains iodine, which kills the SARS-CoV-2 through iodination of lipids and oxidation of cytoplasmic membrane compounds. Use of intranasal glucocorticoids in allergy patients is recommended to reduce sneezing, which could lead to spread of the viruses like SARS-CoV-2. Surfactant based gargle and spray can entrap viruses entering through the mouth, nose, and eyes and therefore, may play a vital role in prophylaxis against SARS-CoV-2. Low pH of acid buffered/hypertonic saline can reduce the amount of viral shedding during the acute viral shedding symptoms. The mechanism of action for CPM and H_2O_2 is not known, however they both have shown in-vivo and in vitro antiviral properties against SARS-CoV-2, respectively. Many of the ongoing approved and utilized therapeutics for COVID-19 are reserved for patients in the inpatient setting. All therapeutics reviewed in this review can be used in the outpatient setting, and therefore could potentially provide more outpatient-based interventions for COVID-19 infection. We propose that intranasal administration of antiviral and virucidal therapies decrease the viral

activity in the nasal pathway, thus preventing disease transmission, expedite recovery of mild-moderate COVID-19 patients, decrease severity of symptoms, reduce hospitalizations and mortality. Further clinical research is needed as application of these agents may not only be limited to the current COVID-19 pandemic, but also for future epidemics and pandemics.

Authors' Contributions

C.C.G., K.P., M.R.S., G.F., conceived the paper; C.C.G., K.P., M.R.S., J.K.G., A.B.M. reviewed, analyzed the available literature, and wrote the manuscript. The manuscript was reviewed by G.F. and M.A.S. All authors participated in writing and drafting the manuscript. All authors read and approved the final manuscript.

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