Intranasal Antiviral Drug Delivery and Coronavirus Disease (COVID-19): A State-of-the-Art Review

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ABSTRACT (WHITE JOURNAL FORMAT)

Objective: To provide a state-of-the-art review of intranasal antiviral drug delivery and to discuss current applications, adverse reactions, and future considerations in the management of Coronavirus Disease (COVID-19).

Data sources: PubMed, Embase, and www.clinicaltrials.gov search engines.

Review Methods: A structured search of the current literature was performed of dates up to and including April 2020. Search terms related to topics of antiviral agents and intranasal applications were queried. A series of video conferences was convened of experts in otolaryngology, infectious diseases, public health, pharmacology, and virology to review the literature and discuss relevant findings.

Conclusions: Intranasal drug delivery for antiviral agents have been studied for many years. Several agents have broad-spectrum antiviral activity, but they still require human safety and efficacy trials prior to implementation. Intranasal drug delivery has potential relevance for future clinical trials in the settings of disease spread prevention and treatment of SARS-CoV-2 and other viral diseases.

Implications for Practice: Intranasal drug delivery represents an important area of research for COVID-19 and other viral diseases. The consideration of any potential adverse reactions is paramount.

INTRODUCTION

The rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the immunologically naïve human population has led to a global pandemic. SARS-CoV-2 is spread primarily through airborne droplet and contact transmission with contaminated fomites. While SARS-CoV-2 particles may persist on surfaces for several days, as enveloped viruses, they are sensitive to desiccation and mild detergent disinfection.[1] Small population studies indicate that between 6 and 88% of SARS-CoV-2 infections do not result in overt disease.[2-4] The impact of asymptomatic or subclinical individuals to public health is clear, with up to 44% of infected individuals having contracted the virus from asymptomatic persons.[5] Individuals who display clinical symptoms of SARS-CoV-2 infection, or coronavirus disease (COVID-19), exhibit a range of symptom severity, with high case fatality rates in the elderly, immunocompromised patients, or those with comorbid diabetes, cardiac, pulmonary, and immunocompromised conditions.[6]

The nasal cavity and nasopharynx contain some of the highest viral loads in the body, and viral loads are similar in symptomatic and asymptomatic individuals. Accordingly, these "silent spreaders" may unknowingly contribute to the exponential growth of disease as nasal secretions contain spreadable virus, and contagiousness appears to be highest before or shortly after symptom onset.

Current strategies to mitigate the pandemic have focused on public health initiatives, such as social distancing, community hygiene awareness, testing and tracing, and travel restrictions. Intranasal delivery of antiviral drugs or agents may provide an additional option for preventing disease transmission, treating the nasal disease, and providing perioperative

antisepsis. This article summarizes our findings for the potential role of studying topical intranasal delivery of drug and agents known to have antiviral properties in SARS-CoV-2.

METHODS

A search of PubMed, Embase, and clinicaltrials.gov was conducted to identify relevant peer-reviewed English articles related to intranasal application of drugs and agents with antiviral properties. A multidisciplinary team of specialists in the areas of otolaryngology, infectious diseases, public health, pharmacy, and virology was assembled to review and summarize the literature. A series of video conferences were held to interpret the findings and discuss potential applications of intranasal application of antiviral agents in the setting of the COVID-19 pandemic. The panel discussed several topics relevant for consideration in intranasal antiviral drug therapy (Figure 1). Agents were assessed for evidence of antiviral activity, either in SARS-CoV-2 and other viruses, and efficacy or potential feasibility in human intranasal use. Potential intranasal adverse reactions were evaluated—specifically—mucosal or skin irritation, smell and taste disturbance, headaches, allergic reactions, nasal bleeding, fungal infection or colonization, and rhinosinusitis. Additional items of discussion included adequacy of mechanisms of target or viral cell infiltration, routes of delivery, medium suspension, additives to enhance mucosal or cellular absorption of the agents, and the reliability of compounding these substances.

DISCUSSION

Viral Structure and Mechanism

Coronaviruses, such as SARS-CoV-2, are enveloped positive-sense RNA viruses with a genome length of approximately 30k nucleotides encoding 16 nonstructural proteins, and at least

4 main structural proteins, although the absolute number varies amongst the members of Coronavirinae (Figure 2).[7] Coronaviruses, such as SARS-CoV-2, are enveloped positive-sense RNA viruses with a genome length of approximately 30k nucleotides encoding 16 nonstructural proteins, and at least 4 main structural proteins, although the absolute number varies amongst the members of Coronavirinae.[7] Architecturally, coronavirus particles are spherical with an average diameter of 125 nanometers, from which the projection of the Spike glycoproteins create a crown-like appearance responsible for the name of the genus. In addition to the Spike glycoproteins, coronavirus particles consist of the E and M integral membrane proteins, a host-derived lipid envelope, and the helical viral nucleocapsid consisting of the N protein and the viral genomic RNA.

As summarized in Figure 3, the coronavirus cellular viral life cycle begins with the attachment of the viral particle to the host cell via the viral Spike glycoprotein.[8] SARS-CoV-2 utilizes the human Angiotension-Converting Enzyme 2 (hACE2) protein as its primary receptor for viral entry.[9] The coronavirus cellular viral life cycle begins with the attachment of the viral particle to the host cell via the viral Spike glycoprotein. The cellular receptor involved in viral entry varies amongst the members of Coronavirinae; however, the SARS-CoV-2 virus, in addition to the original SARS virus (SARS-CoV-1) and the endemic human coronavirus HCoV-NL63, utilize the human Angiotensin-Converting Enzyme 2 (hACE2) protein as its primary receptor. The entry of the virus into the host cytoplasm requires a series of two proteolytic cleavage events of the Spike glycoprotein to reveal the fusion peptide which mediates the fusion of the viral and cellular lipid bilayers. The delivery of the viral RNA into the cytoplasm results in the expression of the viral replicase complex, which consists of 16 nonstructural proteins encoded by the genomic RNA. Within the viral replication compartment, viral RNA synthesis

produces a nested set of mRNA transcripts produced via a complex discontinuous RNA synthesis mechanism, which produces complementary negative sense RNA templates. The nested mRNAs produce the remainder of the viral structural proteins, and progeny viral genomes are produced by way of continuous viral RNA synthesis. The formation of new viral nucleocapsids occurs in the cytoplasm of the infected cells, and mature viral particles are budded into the Endoplasmic Reticulum-Golgi Intermediate Complex (ERGIC) via an interaction between the ERGIC membrane associated M protein and the N protein of the nucleocapsid. The mature viral particles are trafficked to the cell membrane in smooth walled vesicles and released to the extracellular space.

To date, seven CoVs capable of infecting humans have been identified and account for 5% to 10% of acute respiratory infections. Most endemic CoVs cause self-limiting upper respiratory infections; however, SARS-CoV, SARS-CoV-2, and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) have notably high mortality rates.[7] Transmission of SARS-CoV-2 appears to occur primarily through respiratory droplets[6], with secondary surface contact transmission and aerosol transmission possible. The incubation time is typically 3 to 7 days with up to 2 weeks between time of infection and symptoms. This long asymptomatic phase is thought to contribute to the large basic reproduction number (R0) of 2.5 to 3.[10] Viral shedding has been detected in multiple anatomic sites, including the nasal cavities, nasopharynx, sputum, oropharynx, bronchial fluid, and stool.[11] However, the nasopharynx had a much higher detection rate than the oropharynx.[12]

Agents with Antiviral Capability

While no drug has been developed to specifically treat the SARS-CoV-2 virus, a few agents have been found to inactivate SARS-CoV-2 on surfaces, including ultraviolet radiation, heat, ether, ethanol, and isopropanol.[6] Other agents have been studied with other viruses. Table 1 shows a summary of the antiviral agents discussed.

Alcohol and Isopropanol

The World Health Organization (WHO) hand hygiene in healthcare guidelines contain two alcohol-based formulations, including ethanol and isopropanol.[13] These compounds are fast-acting, inexpensive, and broad-spectrum, previously showing the ability to inactivate both SARS-CoV[14] and MERS-CoV.[15] WHO recommends the use of at least 60% ethanol or 70% isopropanol in hand sanitizer formulations.[16] Although, there is evidence that both alcohols inactivate the SARS-CoV-2 down to a concentration of 30%.[17]

Intranasal application of alcohol formulations has been studied in a placebo-controlled RCT of 387 healthcare workers.[18] Health care workers colonized with nasal *S. aureus* were swabbed intranasally three times a day with 70% ethanol combined with natural oil emollients and the preservative benzalkonium chloride or placebo. Antiseptic use reduced *S. aureus* colony forming units by a median of 99% (P<0.001) compared with placebo. The participants reported no adverse effects during the study.

Povidone-Iodine

Povidone-iodine (PI) has rapid bactericidal and virucidal activity, including against SARS-CoV and MERS-CoV.[19] It is widely available in the clinical settings and has been utilized as a skin disinfectant as well as an oral wash or gargle rinse. 3M developed and evaluated an intranasal formulation (PI solution 5% w/w [0.5% available iodine] USP) application to the

anterior nares. A blinded expert grader assessment of the level of intranasal skin erythema and edema in 30 patients demonstrated no significant irritation by the Draize scale. Formulations of 5-10% PI have been evaluated intranasally with regards to potential side effects and results have shown no gross injury though ciliotoxicity has been demonstrated *in vitro* at these concentrations.[20] A randomized control trial (RCT) of nasal application of 10% PI, 5% PI, or placebo preoperatively for arthroscopic surgeries for methicillin-resistant staphylococcus aureus (MRSA) prophylaxis found equal rates of nasal irritation.[21] However, another study of 5% and 10% PI applied to ciliated human respiratory epithelial cells showed ciliotoxicity.[22] Lower concentration formulations (0.5% povidone-iodine [Nasodine]) applied *in vitro* to air-liquid interface cultures of primary human nasal epithelial cells was found to lack cytotoxicity or ciliotoxic effect.[23] Calls for the consideration of PI application intranasally or orally has been advocated as a preventative for patients and healthcare workers involved in head and neck oncologic care at risk of COVID-19 exposure.[24,25] A search of clinicaltrials.gov reveals that a few initiated protocols evaluating intranasal or intraoral formulations of PI for SARS-CoV-2.[26-29]

Carrageenan

Carrageenan is a polysaccharide food additive extracted from red seaweed extract widely used as a thickening agent for food. *In vitro* and animal studies demonstrate that carrageenan shows antiviral properties to human rhinovirus and influenza A and prevents viral attachment to host cells without systemic absorption or nasal mucosal penetration. Four placebo-controlled RCTs have been performed evaluated iota-carrageenan nasal spray in the treatment of respiratory viral infections (including rhinovirus, enteroviruses, and influenza) with variable reduction in symptoms and viral loads versus placebo saline spray. [30,31] Formulations of nasal sprays

containing carrageenan are available over the counter, but the FDA currently has only approved this agent as a food additive permitted for human consumption.

Acid-Buffered Saline

Acidic pH is frequently used for virus inactivation. Acidic solutions are commonly used in the pharmaceutical industry to inactivate viruses in the isolation of viral proteins and also for cleaning and prevention of infection.[32,33] Acid-buffered saline has been investigated as a topical therapy for various upper respiratory viruses, showing inactivation of influenza A, decreased symptoms and viral shedding of influenza A, reduced viral shedding of human rhinovirus with the use of solutions and nasal gels, and reduced symptom severity and duration of illness in the common cold.[32,34] Unfortunately, SARS-CoV-2 has been shown to be highly stable in a wide range of pH environments, limiting the viability of acidic therapies as options against this virus.[1]

Hypertonic Saline

Hypertonic saline may reduce symptoms of various upper respiratory viruses, as well as potentially reduce viral shedding and promote inactivation.[35,36] Ramalingam et al. demonstrated via *in vitro* studies that increasing the availability of NaCl may facilitate the innate immune response in non-myeloid cells via an increase in intracellular hypochlorous acid levels.[36] Ramalingam et al. found in an RCT of hypertonic saline irrigation and gargling for the common cold that the use of hypertonic saline reduced symptom severity, length of illness, intrahousehold transmission, and viral shedding.[35] Meta-analyses have shown good tolerability with some reports of nasal irritation, headache, and epistaxis.[37]

Hydrogen peroxide

Hydrogen peroxide (H_2O_2) has long been known to cause viral inactivation and H_2O_2 0.5% efficiently deactivates SARS-CoV-2 on surfaces. [38,39] While H_2O_2 is commonly used for surface, surgical, and oral disinfection[38], there are currently no human clinical trials demonstrating the safety or efficacy of intranasal application of H_2O_2.

Probiotics

The use of ingested oral probiotics has have been evaluated in the current COVID-19 pandemic, but the evidence of its use are from small case series and correspondences, and experts concluded that even if oral probiotics were useful, they were unlikely to have a direct effect on the severe acute respiratory syndrome that most patients with COVID-19 present with acutely.[40] However, there is evidence that both the nasal and gastrointestinal microbiome are important factors in the innate immune system and, particularly, in the defense against respiratory viral pathogens. Nasal microbiota clusters were found associated with host inflammatory response, viral load, and symptom severity in rhinovirus.[41] The *Corynebacterium*-rich cluster of patients had overall reduced symptoms during rhinovirus infection despite the addition of oral probiotics not changing the host microbiome (nasal and gastrointestinal) significantly. *Corynebacterium* was also found to be protective against Respiratory Syncytial Virus (RSV) infection in an *in vivo* mouse model.[42] Also, in a mouse model, Zelaya et al. found that *Lactobacillus* introduced nasally helped prevent influenza pulmonary damage and inflammation.[43] While the effects of orally administered probiotics on a variety of viruses has been studied, we found no studies directly investigating the introduction of intranasal probiotics for the treatment of human upper respiratory virus infections. Further studies on both nasal and

oral administration of probiotics are warranted for COVID-19 and other upper respiratory viral infections.

Surfactants/Shampoo

Surfactants and, in particular, baby shampoo have been studied most extensively in chronic rhinosinusitis. Most studies have evaluated potential bactericidal and anti-biofilm effects.[44] We found no studies that evaluated evaluating surfactant application to the nasal cavity and its ability to prevent or diminish viral infection. However, intrinsic pulmonary surfactant has been found to be an important part of our innate immune system, and its use has recently been shown to help prevent several respiratory viruses such as H1N1 and influenza.[45-47] The pulmonary surfactant phospholipids are thought to prevent viral infections by inhibiting viral binding to epithelial cells. The use of surfactants to achieve the same results in the upper aerodigestive tract is intriguing but has not been studied. One proposed trial aims to investigate the effect of saline irrigations and baby shampoo/saline irrigations on COVID-19 patients.[48] Most surfactants have been reported to have good tolerability, but it is worthy to note that surfactant additive in nasal saline rinses has been associated with nasal congestion and temporary smell loss in normal volunteers.[49]

Ultraviolet Radiation

Based on the physiologic effects, UV radiation can be divided into: UVC (100–280 nm), UVB (280– 320 nm) and UVA (320–400). The majority of evidence of the biological effect of UV light has come from the field of dermatology, where various forms of phototherapy have been applied for decades.[50]

Intranasal phototherapy has been explored for the treatment of other rhinologic conditions, primarily based on its immunomodulating effect on inflammatory processes. Two RCTs demonstrated that combined low dose UVB, low dose UVA, and visible light are effective in reducing symptoms scores of moderate to severe ragweed-induced allergic rhinitis uncontrolled by anti-allergic drugs.[51,52] However, a similar treatment protocols does not appear to have efficacy for treatment effective for of chronic rhinosinusitis.[53]

The carcinogenic risk of rhinophototherapy on the nasal mucosa appears to be limited at the exposure levels used in the studies above. Nasal epithelial cells are capable of repairing UV-induced DNA damage in allergic rhinitis patients receiving intranasal phototherapy.[54] Significant DNA damage was observed immediately after completing two weeks treatment of which reduced at the day-10 assessment and but was equivalent to the control group at 2-month follow-up. Parallel experiments demonstrated similar repair kinetics in human skin *in vitro* and animal models.[55] Animal studies with UV-A and UV-B irradiation demonstrate no histopathological changes[56], and no induction of apoptosis at lower doses.[57] Other animal studies have demonstrated similar reduction in histopathological changes with phototherapy compared to nasal corticosteroid treatment without increasing apoptosis of mucosal cells.[58]

UV-C is strongly absorbed by the nucleic acids of a microorganism and, therefore, is the most lethal range of wavelengths for microorganisms. UV-C sterilization has been proposed as an effective method for simultaneous disinfection of both the water source and saline irrigation bottle[59], and has been used in combination to reduce titers of SARS-CoV-2 to non-detectable levels in human blood transfusion products.[60]

Multiple clinical studies dating back to the 1940s[61] demonstrated that UV exposure of the wound during surgery resulted in markedly decreased SSI rates. However, conventional UV-C light sources, typically emitting at 254 nm, are a human health hazard, causing skin cancer and cataracts.[62,63] In contrast, far-UVC light in the range of 207–222 nm has the same bactericidal potential of 254-nm light, but without the damaging effects to mammalian cells and tissues. Due to its short range in biological materials, far-UVC light does not penetrate the outer layer of the skin or the outer surface of the eyes but can efficiently inactivate the nucleic acids and proliferative capacity of surface microbes. [64,65]

While intranasal UV-A and UV-B light is safe, phototherapy at this wavelength has limited antimicrobial activity. UVC light is an effective method for sterilization, but the intranasal safety profile for UV-C phototherapy has not been studied.

Oxymetazoline and Xylometazoline

Oxymetazoline and xylometazoline are commonly using over-the-counter nasal decongestants. Adverse effects include local irritation and rhinitis medicamentosa in which overuse causes paradoxical nasal obstruction. Small studies have shown transient decreased viral load in rhinovirus utilizing topical oxymetazoline nasal spray.[66] These agents have not been studied in other viruses or SARS-CoV-2. Given that it has been shown to reduce rhinovirus viral load, caution may be advisable with is use prior to nasal swab viral testing.

Interferon

Interferons are complex cytokines intricately involved in innate cellular immunity and are named for their ability to interfere with viral replication. Interferons increase expression of major histocompatibility complex (MHC) molecules. Increased MHC I expression up-regulates viral

presentation to cytotoxic T cells. Stimulation of MHC II expression potentiates helper T cell response and subsequent release of cytokines that increase activity of other immune cells.[67]

Viral cellular invasion activated type 1 interferons, which secrete fibroblasts and monocytes with interferon-specific receptors. Subsequently, this activates the classical Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. The downstream result is an expression of proteins that inhibit viral replication.[67] The role of interferon in SARS-CoV-2 is intriguing but duplicitous. The SARS-CoV-2 virus enters the cell following binding of a spike protein domain with the ACE2 receptor, which is upregulated by interferons and has previously been suggested to help lung cells tolerate damage. However, in the case of SARS-CoV-2, the up-regulation of ACE2 may actually exacerbate the disease. It is unclear if SARS-CoV-2 is utilizing the important role of interferon in our innate clinical immunity or if the beneficial effects of interferon outweigh the increased cellular entry it allows.[68]

Interferons have been previously investigated for use against SARS-CoV. An in-vitro study of cell lines from patients infected with SARS-CoV showed that interferon alpha, beta, and gamma all inhibited SARS-CoV replication; however, interferon beta was five to ten times more effective and showed both prophylactic protection as well as antiviral potential after infection. [69] Others suggest that type 3 interferons—specifically interferon lambda—could be a better therapeutic option in respiratory infections. Sun, et al. showed that interferon lambda was superior to type 1 interferons due to their specificity in the respiratory tract, thereby decreasing systemic side effects specifically an inflammatory response that is sometimes characterized by type 1 interferons.[70]

Aerosolized interferon treatment has been shown to be effective in viral-mediated respiratory disease. Type 1 interferons have been shown to induce undesirable systemic side effects, such as fatigue, headache, pyrexia, myalgia, rigors, and psychiatric symptoms. However, topical formulations of recombinant human interferon alpha-2b have been shown to have no significant side systemic side effects.[71] This formulation was used as a topical nasal spray in a placebo-controlled trial in children with hand, foot, and mouth disease. The children treated with the topical nasal interferon alpha-2b had a shorter duration of fever, oral ulcers, skin rash, and decreased appetite when compared to the placebo group. [71] A new formulation of type 1 interferon – interferon beta-1a – was used in a double blind, placebo-controlled trial of asthma patients in attempts to decrease viral respiratory infections and thus asthma exacerbations (NCT 01126177). The proprietary interferon beta-1a formulation is the only aqueous preparation and is pH balanced to the respiratory mucosa making it an ideal therapeutic for inhalation. Although this study failed to meet its primary end point of better asthma control, it did show good evidence of enhanced innate immunity with increased production of antiviral genes in induced sputum [72].

Topical interferon is an intriguing target for SARS-CoV-2 therapy. Preliminary results of its use as a prophylactic for healthcare workers in Hubei, China shows no infections in the 2944 healthcare workers using the medication as a nasal drop.[73] While well conducted, prospective trials are certainly needed in peer reviewed literature, this therapy offers immense promise as a well-tolerated, easy to deliver topical prophylactic against SARS-CoV-2 infection.

Enhancing Mucosal Absorption Efficiency

The advantages in nasal mucosa as a drug delivery medium include increased absorption rate, possible increased bioavailability through avoidance of hepatic first pass metabolism, and a less acidic pH environment. However, challenges include a poor retention time on membrane,

narrow absorption value, degradation via mucolytic enzymes, and a continuous mucociliary movement leading to washout.[74]

Chitosan

Chitosan is a cationic polysaccharide widely studied for its mucoadhesive enhancing properties in medication delivery. Chitosan can contain a wide array of chemically altered functional groups to enhance mucoadhesive properties and permeation effects via opening of epithelial tight junctions, and several studies have demonstrated superiority in chitosan bound medications compared to unbound forms. Currently, chitosan has FDA-approved uses as a wound healing agent. However, limited study has been conducted on nasal chitosan-based antiviral medications. Given chitosan's flexibility and study as a strong mucoadhesive with generally low toxicity, more research is needed into possible nasal chitosan-based antiviral medications.[75]

Liposomes

Lipophilic/liposomal formulations have aided drug delivery across lipid bilayer cell membranes. Many FDA-approved medications such as doxorubicin, amphotericin B and others have liposomal drug formulations. Several in vitro and in vivo animal studies have found liposomal formulations to improve drug bioavailability across the mucosal membrane barrier. [80]. However, despite the significant quantity of research around both chitosan and liposomal nasal nanoparticle formulations, there remains no FDA approved products of chitosan and liposomal based nasal drug delivery systems and further research in humans is needed to support clinical safety and efficacy.[76]

Poloxamers

Poloxamers are a class of hydrogels, which are water-soluble and nonionic copolymers with amphiphilic and surface-active properties. Increasing temperature of their aqueous solutions creates a sol-to-gel transition above a critical gelation temperature. Hydrogels are used to facilitate localized, sustained release of a drug, thereby lower drug dosage, limiting administration frequency, and avoiding adverse effects. Poloxamers are FDA-approved as non-toxic solubilizer, emulsifier, stabilizer, and can be administered through oral, parenteral, and topical routes.[77]

Route and Medium of Drug Delivery

Solution Sprays

Intranasal drug delivery has been used for allergic rhinitis, chronic rhinosinusitis, opioid overdose, and topical anesthesia/decongestion for many years and has been widely studied in the literature.[78] Factors that make this delivery option favorable are the relative ease of use in a home environment and good patient tolerance. The risk of inducing viral shedding is unknown, as these sprays are aerosolized and could elicit sneeze or coughing. Most sprays generate an aerosol that deposits in the anterior nasal cavity, with mucociliary clearance further carrying medications deeper into the nasal cavity. Newer exhalation delivery nasal sprays have been shown to distribute further within the nasal cavity (Figure 4).[79] Nasal nebulizers have also been employed in the treatment of chronic rhinosinusitis and nasal polyposis; however, distribution of medication is not significantly different than that of the exhalation delivery systems and has higher associated equipment cost. The mucous layer within the nose renews within 20 minutes and is discarded into the nasopharynx, thus the speed at which the medication dissolves within the mucous layer and penetrates mucosa is critical for drug efficacy. Computational fluid

dynamics could be utilized to determine appropriate particle size, spray velocity, and dosing to help guide effective therapies.

Saline Rinses

Like solution sprays, intranasal saline rinses are widely available, utilized with and without the addition of medications, and generally well-tolerated. Further investigation on the risk of viral shedding are needed. Advantages suggested over sprays include the removal of the mucous barrier with the rinse action, in order to provide maximum interface between the drug and the mucosa itself.[80] However, formulations of medications must be water-soluble in order to administer in this method.

Gel

Intranasal nanogels have been utilized for drug delivery in Alzheimer's disease, migraines, depression, and schizophrenia.[81] This medium can be utlizied for both hydrophilic and hydrophobic drugs, distinguishing it from the above mentioned intranasal sprays and rinses that typically require a suspension. Additionally, the increased viscosity of the gel formulation may increase the residence time of the drug on the nasal mucosa, therefore increasing drug absorption through the mucosa.[82] Increasing the viscosity may, in turn, interfere with normal ciliary beating and cause untoward negative side effects. Challenges include maintaining stable formulations with consistent dosing while preserving an adequate shelf-life and designing an efficient delivery system to administer the gel within the nasal cavity. Wang et al also propose a hybrid of technologies via an in-situ gel-forming system, where a solution instilled intranasally undergoes phase transition to a viscoelastic gel have been formulated to offer. Advantages of this system include increased retention in the nasal cavity and increased permeability through the mucous membranes.

Foam/Packing

Intranasal foam and dissolvable packing have been utilized for many years by Otolaryngologists for treatment of epistaxis, chronic rhinosinusitis, and treatment of post-surgical sinus cavities. Applications for drug delivery for psychiatric conditions, such as bipolar disorder and schizophrenia, have also been studied. Examples of intranasal foams include chitosan, carboxymethylcellulose, hyaluronic acid, and synthetic polyurethane foam. Nanoparticles used as reservoirs for hydrophobic drugs can be compounded within these foams to provide increased mucoadhesive properties and enhanced absorption of medications. This method would likely be more challenging for patients to self-administer, as most Otolaryngologists employ its use by direct administration by a medical professional rather than by patients themselves. Additionally, these foams are traditionally applied under at least topical anesthesia, and may be less tolerated by eliciting more sneezing and irritation than sprays/rinses.

Dry powders

Most intranasal sprays on the market are liquid suspensions; however, recreational drugs have been used in powder form for many years. More recently, dry mist nasal sprays have been introduced, which dissolves the medication in hydrofloruoalkane (HFA) propellant. Non-aqueous propellants such as propylene glycol, isopropyl alcohol, and PEG400 are known to cause local irritation with chronic use, thus careful attention to the choice of propellant and possible adverse reactions must be considered. Other challenges for utilization of powders includes ability to distribute within the nasal cavity, controlling the particle size, protecting viability of powder during storage from humidification, and maximizing absorption by the mucous membranes.[79]

Ointment

Nasal ointments have been in use for control of folliculitis within the nasal vestibule as well as for prevention of epistaxis; however, more recently interest has increased in drug delivery via nasal ointments, such as for allergic rhinitis.[83] Via intranasal swabs, these ointments are easily applied by patients to the anterior nasal vestibule, with mucociliary clearance carrying medications further within the nasal cavity. The higher viscosity ointments again result in lower tendency to spread and may increase retention time within the nasal cavity, and the lipophilic properties of the ointment may enhance absorption by the nasal mucosa. Disadvantages of ointments, specifically long-chain mineral hydrocarbons, include risk of paraffin granulomas and case reports of lipoid pneumonia from long-term nocturnal intranasal application.[83]

IMPLICATIONS FOR PRACTICE

Topical intranasal antiviral drug delivery has several potential applications, but further studies are necessary. Efficacy in many settings is currently unknown, and considerations for any potential adverse effects, including loss of taste and smell, epistaxis, and mucosal irritation, are important.

The panel discussed the following settings in which studies of topical intranasal delivery of antiviral medications could be considered (Figure 5):

- Perioperative prevention for healthcare workers and patients
- Prevention of the well person from contracting the virus
- Prevention of the infected person or presymptomatic carriers from spreading the virus
- Systemic drug delivery
- Treatment of intranasal viral disease
- Reduction in progression of viral disease

Perioperative application as an antiseptic is the most mentioned use of intranasal (as well intraoral) antiviral agents. Several articles have described considerations of usage of povidone-iodine during oral and head and neck surgery, as well as in-office application for prevention of viral spread during minor endoscopic procedures, such as diagnostic nasal endoscopy and flexible fiberoptic nasolaryngoscopy.[24,25] While clinical settings are the ideal initial areas for investigation, studies of community populations could be considered for the widespread prevention of spread and as potential therapeutic options for nasal symptomatology.

The nasal cavities and nasopharynx harbor a significant amount of SARS-CoV-2, even in asymptomatic or presymptomatic carriers of the virus. Several possible candidates exist for intranasal delivery of virucidal drugs and agents; however, clinical efficacy would require the agent(s) to have adequate mechanisms of target or viral cellular infiltration along with routes of delivery and medium suspension to reach the pathologic areas. Cellular absorption enhancement agents may also be needed to increase effectiveness. And as with any therapeutic agent, proper safety profiles for intranasal use are important. This article summarizes the current knowledge

478 from the literature regarding intranasal drug delivery and its potential applications in combating
479 the SARS-CoV-2 pandemic and other future viral epidemics.

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REFERENCES

1. Chin AWH, Chu JTS, Perera MRAet al. Stability of SARS-CoV-2 in different environmental conditions. The Lancet Microbe 2020.
2. Arons MM, Hatfield KM, Reddy SCet al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. New England Journal of Medicine 2020.
3. Lytras T, Dellis G, Flountzi Aet al. High prevalence of SARS-CoV-2 infection in repatriation flights to Greece from three European countries. Journal of Travel Medicine 2020.
4. Nishiura H, Kobayashi T, Miyama Tet al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). International Journal of Infectious Diseases 2020; 94:154-155.
5. He X, Lau EHY, Wu Pet al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020.
6. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19) *StatPearls*. Treasure Island (FL), 2020.
7. Fehr AR, Perlman S. Coronaviruses: An Overview of Their Replication and Pathogenesis: Springer New York, 2015:1-23.
8. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020; 24:91-98.
9. Shang J, Ye G, Shi Ket al. Structural basis of receptor recognition by SARS-CoV-2. Nature 2020.
10. Chan JF-W, Kok K-H, Zhu Zet al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging Microbes & Infections 2020; 9:221-236.
11. Loeffelholz MJ, Tang Y-W. Laboratory diagnosis of emerging human coronavirus infections – the state of the art. Emerging Microbes & Infections 2020; 9:747-756.
12. Wang W, Xu Y, Gao Ret al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. Jama 2020.
13. Pittet D, Allegranzi B, Boyce J. The World Health Organization Guidelines on Hand Hygiene in Health Care and Their Consensus Recommendations. Infection Control & Hospital Epidemiology 2009; 30:611-622.
14. Rabenau HF, Kampf G, Cinatl J, Doerr HW. Efficacy of various disinfectants against SARS coronavirus. Journal of Hospital Infection 2005; 61:107-111.
15. Siddharta A, Pfaender S, Vielle NJet al. Virucidal Activity of World Health Organization–Recommended Formulations Against Enveloped Viruses, Including Zika, Ebola, and Emerging Coronaviruses. The Journal of Infectious Diseases 2017; 215:902-906.
16. Cdcgov. CDC Statement for Healthcare Personnel on Hand Hygiene during the Response to the International Emergence of COVID-19 | CDC. 2020-04-03T08:51:28Z. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/hand-hygiene.html.
17. Kratzel A, Todt D, V'kovski Pet al. Efficient inactivation of SARS-CoV-2 by WHO-recommended hand rub formulations and alcohols. Emerg Infect Dis 2020.
18. Steed LL, Costello J, Lohia S, Jones T, Spannhake EW, Nguyen S. Reduction of nasal Staphylococcus aureus carriage in health care professionals by treatment with a nonantibiotic, alcohol-based nasal antiseptic. American Journal of Infection Control 2014; 42:841-846.

19. Eggers M. Infectious Disease Management and Control with Povidone Iodine. Infect Dis Ther 2019; 8:581-593.
20. Safety & Efficacy Information 3M Kin and Nasal Antiseptic (Povidone-Iodine Solution 5% q/q [0.5% available iodine] USP) Patient Preoperative Skin Preparation. Available at: https://multimedia.3m.com/mws/media/716788O/3m-skin-and-nasal-antiseptic-safety-and-efficacy-brochure.pdf. Accessed April 24, 2020.
21. Rezapoor M, Nicholson T, Tabatabaee RM, 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; 32:2815-2819.
22. Kim JH, Rimmer J, Mrad N, Ahmadzada S, Harvey RJ. Betadine has a ciliotoxic effect on ciliated human respiratory cells. The Journal of Laryngology & Otology 2015; 129:S45-S50.
23. 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. International Forum of Allergy Rhinology 2020.
24. Mady LJ, Kubik MW, Baddour K, Snyderman CH, Rowan NR. Consideration of povidone-iodine as a public health 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 Oncology 2020:104724.
25. Kirk-Bayley J, Combes J, Sunkaraneni S, Challacombe S. The Use of Povidone Iodine Nasal Spray and Mouthwash During the Current COVID-19 Pandemic May Reduce Cross Infection and Protect Healthcare Workers 2020.
26. Hwang PH, Vukkadala N. PVP-I Nasal Sprays and SARS-CoV-2 Nasopharyngeal Titers (for COVID-19) - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04347954. Accessed May 4, 2020.
27. Khan FR. A Clinical Trial of Gargling Agents in Reducing Intraoral Viral Load Among COVID-19 Patients - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04341688. Accessed May 4, 2020.
28. Mimoz O, Seguin S. Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Naso- Pharyngeal Viral Load in Patients With COVID-19 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04371965. Accessed May 4, 2020.
29. Rickert S, Moses L. Gargling and Nasal Rinses to Reduce Oro- and Nasopharyngeal Viral Load in Patients With COVID-19 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04344236. Accessed May 4, 2020.
30. Eccles R, Winther B, Johnston SL, Robinson P, Trampisch M, Koelsch S. Efficacy and safety of iota-carrageenan nasal spray versus placebo in early treatment of the common cold in adults: the ICICC trial. Respir Res 2015; 16:121.
31. Ludwig M, Enzenhofer E, Schneider Set al. Efficacy of a Carrageenan nasal spray in patients with common cold: a randomized controlled trial. Respiratory Research 2013; 14:124.
32. Gern JE, Mosser AG, Swenson CAet al. Inhibition of rhinovirus replication in vitro and in vivo by acid-buffered saline. J Infect Dis 2007; 195:1137-1143.
33. Brown CM, Nwokeji E, Rascati KL, Zachry W, Phillips GA. Development of the burden of prior authorization of psychotherapeutics (BoPAP) scale to assess the effects of prior

authorization among Texas Medicaid providers. Administration and policy in mental health 2009; 36:278-287.
34. Rennie P, Bowtell P, Hull D, Charbonneau D, Lambkin-Williams R, Oxford J. Low pH gel intranasal sprays inactivate influenza viruses in vitro and protect ferrets against influenza infection. Respir Res 2007; 8:38.
35. Ramalingam S, Graham C, Dove J, Morrice L, Sheikh A. A pilot, open labelled, randomised controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. Sci Rep 2019; 9:1015.
36. Ramalingam S, Cai B, Wong Jet al. Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypochlorous acid levels. Sci Rep 2018; 8:13630.
37. Kanjanawasee D, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K. Hypertonic Saline Versus Isotonic Saline Nasal Irrigation: Systematic Review and Meta-analysis. American journal of rhinology & allergy 2018; 32:269-279.
38. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. Journal of Hospital Infection 2020; 104:246-251.
39. Goyal SM, Chander Y, Yezli S, Otter JA. Evaluating the virucidal efficacy of hydrogen peroxide vapour. Journal of Hospital Infection 2014; 86:255-259.
40. Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. The Lancet Gastroenterology & Hepatology 2020.
41. Lehtinen MJ, Hibberd AA, Mannikko Set al. Nasal microbiota clusters associate with inflammatory response, viral load, and symptom severity in experimental rhinovirus challenge. Sci Rep 2018; 8:11411.
42. Kanmani P, Clua P, Vizoso-Pinto MGet al. Respiratory Commensal Bacteria Corynebacterium pseudodiphtheriticum Improves Resistance of Infant Mice to Respiratory Syncytial Virus and Streptococcus pneumoniae Superinfection. Front Microbiol 2017; 8:1613.
43. Zelaya H, Tada A, Vizoso-Pinto MGet al. Nasal priming with immunobiotic Lactobacillus rhamnosus modulates inflammation-coagulation interactions and reduces influenza virus-associated pulmonary damage. Inflamm Res 2015; 64:589-602.
44. Rosen PL, Palmer JN, O'Malley BW, Jr., Cohen NA. Surfactants in the management of rhinopathologies. American journal of rhinology & allergy 2013; 27:177-180.
45. Numata M, Mitchell JR, Tipper JLet al. Pulmonary surfactant lipids inhibit infections with the pandemic H1N1 influenza virus in several animal models. The Journal of biological chemistry 2020; 295:1704-1715.
46. Voelker DR, Numata M. Phospholipid regulation of innate immunity and respiratory viral infection. The Journal of biological chemistry 2019; 294:4282-4289.
47. Wang J, Li P, Yu Yet al. Pulmonary surfactant-biomimetic nanoparticles potentiate heterosubtypic influenza immunity. Science (New York, NY) 2020; 367.
48. Kimura K. Impact of Nasal Saline Irrigations on Viral Load in Patients With COVID-19. Available at: https://clinicaltrials.gov/ct2/show/NCT04347538. Accessed May 12, 2020.
49. Turner JH, Wu J, Dorminy CA, Chandra RK. Safety and tolerability of surfactant nasal irrigation. International forum of allergy & rhinology 2017; 7:809-812.
50. Kemény L, Koreck A. Ultraviolet light phototherapy for allergic rhinitis 2007; 87:58-65.

51. Koreck AI, Csoma Z, Bodai Let al. Rhinophototherapy: a new therapeutic tool for the management of allergic rhinitis. The Journal of allergy and clinical immunology 2005; 115:541-547.
52. Cingi C, Cakli H, Yaz A, Songu M, Bal C. Phototherapy for allergic rhinitis: a prospective, randomized, single-blind, placebo-controlled study. Ther Adv Respir Dis 2010; 4:209-213.
53. Dulguerov N GN, Courvoisier D, Landis BN, Lacroix JS, Hauser C. Rhinophototherapy in chronic rhinosinusitis: a double blind randomized placebo-controlled trial. Rhinology journal 2017; 55:106.
54. Koreck A, Szechenyi A, Morocz Met al. Effects of intranasal phototherapy on nasal mucosa in patients with allergic rhinitis. J Photochem Photobiol B 2007; 89:163-169.
55. Mitchell D, Paniker L, Sanchez Get al. Molecular response of nasal mucosa to therapeutic exposure to broad-band ultraviolet radiation 2010; 14:313-322.
56. Apuhan T, Terzi, E. H., Kükner, A., & Gök, Ü. . Histopathological evaluation of the effect of intranasal phototherapy on nasal mucosa in rabbits. Journal of Photochemistry and Photobiology B: Biology 2011; 105:94–97.
57. Fujii T, Kitamura Y, Mizuguchi Het al. Effects of irradiation with narrowband-ultraviolet B on up-regulation of histamine H1 receptor mRNA and induction of apoptosis in HeLa cells and nasal mucosa of rats. J Pharmacol Sci 2018; 138:54-62.
58. Yurttas V, Şereflican, M., Erkoçoğlu, M., Terzi, E. H., Kükner, A., & Oral, M. Histopathological effects of intranasal phototherapy and nasal corticosteroids in allergic rhinitis in a rabbit model. Journal of Photochemistry and Photobiology B: Biology 2015; 149:289–291.
59. Husain Q, Banks C, Woodworth BA, Bleier BS. Lightening in a bottle: comparison of ultraviolet light to traditional sterilization in saline irrigations bottles. International forum of allergy & rhinology 2020; 10:53-58.
60. Keil SD, Ragan I, Yonemura S, Hartson L, Dart NK, Bowen R. Inactivation of severe acute respiratory syndrome coronavirus 2 in plasma and platelet products using a riboflavin and ultraviolet light-based photochemical treatment. Vox Sang 2020.
61. Kraissl CJ, Cimiotti JG, Meleney FL. CONSIDERATIONS IN THE USE OF ULTRAVIOLET RADIATION IN OPERATING ROOMS 1940; 111:161-185.
62. Setlow RB, Grist E, Thompson K, Woodhead AD. Wavelengths effective in induction of malignant melanoma. Proceedings of the National Academy of Sciences 1993; 90:6666-6670.
63. Balasubramanian D. Ultraviolet radiation and cataract. J Ocul Pharmacol Ther 2000; 16:285-297.
64. Ponnaiya B, Buonanno M, Welch D, Shuryak I, Randers-Pehrson G, Brenner DJ. Far-UVC light prevents MRSA infection of superficial wounds in vivo. PLOS ONE 2018; 13:e0192053.
65. Buonanno M, Randers-Pehrson G, Bigelow AWet al. 207-nm UV Light - A Promising Tool for Safe Low-Cost Reduction of Surgical Site Infections. I: In Vitro Studies. PLoS ONE 2013; 8:e76968.
66. Winther B, Buchert D, Turner RB, Hendley JO, Tschaikin M. Decreased rhinovirus shedding after intranasal oxymetazoline application in adults with induced colds compared with intranasal saline. American journal of rhinology & allergy 2010; 24:374-377.
67. de Weerd NA, Samarajiwa SA, Hertzog PJ. Type I interferon receptors: biochemistry and biological functions. The Journal of biological chemistry 2007; 282:20053-20057.

68. Ziegler CGK, Allon SJ, Nyquist SKet al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 2020.
69. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. Lancet 2003; 362:293-294.
70. Sun Y, Jiang J, Tien P, Liu W, Li J. IFN-lambda: A new spotlight in innate immunity against influenza virus infection. Protein Cell 2018; 9:832-837.
71. Lin H, Huang L, Zhou Jet al. Efficacy and safety of interferon-alpha2b spray in the treatment of hand, foot, and mouth disease: a multicenter, randomized, double-blind trial. Arch Virol 2016; 161:3073-3080.
72. Djukanovic R, Harrison T, Johnston SLet al. The effect of inhaled IFN-beta on worsening of asthma symptoms caused by viral infections. A randomized trial. Am J Respir Crit Care Med 2014; 190:145-154.
73. Zhongji Meng TW, Li Chen, Xinhe Chen, Longti Li, Xueqin Qin, Hai Li, Jie Luo. An experimental trial of recombinant human interferon alpha nasal drops to prevent coronavirus disease 2019 in medical staff in an epidemic area 2020.
74. David S IL. Absorption Enhancers for Nasal Drug Delivery. Clin Pharmacokinet 2003; 42:1107-1128.
75. M. Ways T, Lau W, Khutoryanskiy V. Chitosan and Its Derivatives for Application in Mucoadhesive Drug Delivery Systems. Polymers 2018; 10:267.
76. Hong S-S, Oh KT, Choi H-G, Lim S-J. Liposomal Formulations for Nose-to-Brain Delivery: Recent Advances and Future Perspectives. Pharmaceutics 2019; 11:540.
77. Bodratti A, Alexandridis P. Formulation of Poloxamers for Drug Delivery. Journal of Functional Biomaterials 2018; 9:11.
78. Snidvongs K, Thanaviratananich S. Update on Intranasal Medications in Rhinosinusitis. Current Allergy and Asthma Reports 2017; 17.
79. Djupesland PG, Skretting A. Nasal Deposition and Clearance in Man: Comparison of a Bidirectional Powder Device and a Traditional Liquid Spray Pump 2012; 25:280-289.
80. Harvey RJ, Debnath N, Srubiski A, Bleier B, Schlosser RJ. Fluid residuals and drug exposure in nasal irrigation 2009; 141:757-761.
81. Aderibigbe BA, Naki T. Design and Efficacy of Nanogels Formulations for Intranasal Administration. Molecules 2018; 23.
82. Dayal P, Shaik MS, Singh M. Evaluation of different parameters that affect droplet-size distribution from nasal sprays using the Malvern Spraytec. J Pharm Sci 2004; 93:1725-1742.
83. Geisthoff U, Blum A, Ruppclassen M, Plinkert P. Lipid-based Nose Ointment for Allergic Rhinitis 2005; 133:754-761.

Table 1. Evidence for topical intranasal antiviral therapies. (+): yes, there is evidence. (-): no, there is evidence against statement; NS: not studied; adverse reactions tested: mucosal or skin irritation (I), smell and taste disturbance (ST), headaches (H), allergic reactions (A), nasal bleeding (B), fungal infection or colonization (F), and rhinosinusitis (RS); HFMD: Hand Foot Mouth Disease

Agents (antiviral mechanism)	**SARS-CoV-2**			***Other Viruses***			**Adverse Reactions**	**Conclusion**
	In vitro activity	***In vivo activity***	***Clinical efficacy***	***In vitro activity***	***In vivo activity***	***Clinical efficacy***		
Alcohol and Isopropanol (virucidal)	+	NS	NS	+ SARS-CoV-1 MERS-CoV	NS	NS	Y: I NS: ST, H, A, B, F, RS	Alcohol and Isopropanol surface preparations have rapid virucidal effects on SARS-CoV-2 and other viruses, but they can cause nasal irritation. An intranasal swab application has shown antibacterial properties without nasal irritation.
Hydrogen peroxide (virucidal)	+	NS	NS	+	NS	NS	NS: I, ST, H, A, B, F, RS	H2O2 has long been used as a disinfecting agent and has efficacy against SARS-coV-2 and other viruses *in vitro*. Intranasal safety profile is unknown.
Povidone-Iodine (virucidal)	+	NS	NS	+ MERS-CoV SARS-CoV-1 H1N1	NS	NS	Y: I (≥5%), A N: I (≤0.5%) NS: ST, H, A, B, F, RS	Anterior nasal formulations are tolerated well. *In vitro* preparations have shown rapid virucidal effects to SARS-CoV-2 and other viruses. Human adverse effect profile is incomplete. PI may have ciliotoxic effects and

								smell/taste loss has not been evaluated.
Carageenan (prevents viral attachment)	NS	NS	NS	+ Rhinovirus Enterovirus Influenza	+ Rhinovirus	+ Rhinovirus	NS: ST, H, A, B, F, RS	Carageenan nasal sprays have shown efficacy in reducing viral loads and symptoms versus placebo in several RCTs. No nasal irritation were noted, but other adverse effects were not evaluated.
Acid-Buffered Saline (virucidal)	NS	NS	NS	+	+ Rhinovirus Influenza	+ Rhinovirus	NS: ST, H, A, B, F, RS	Acid-buffered saline nasal gels have been used in several studies demonstrating ability to reduce viral load and symptoms.
Hypertonic Saline (promotes innate antiviral immune response)	NS	NS	NS	+	+ Common cold	+ Common cold	Y: I, H, B NS: ST, A, F, RS	Hypertonic saline irrigation is well tolerated with minor discomfort in many other diseases and has been shown to reduce symptoms, viral shedding, and transmission of the common cold.
Probiotics (may promote innate immunity and antibody production)	NS	NS	NS	+	+	+ Rhinovirus Influenza	Y: I NS: ST, H, A, B, F, RS	Nasal probiotics have been shown to be well tolerated in CRS but have not been studied for antiviral purposes. Oral probiotics have shown efficacy in animal and human studies with common upper respiratory viruses
Surfactants/Shampoo (prevents viral plasma membrane fusion)	NS	NS	NS	+	+ H1N1 Influenza	NS	Y: I, ST NS: H, A, B, F, RS	Surfactant has been shown *in vitro* and *in vivo* (lungs) to have antiviral properties. Nasal surfactant or shampoo rinses are usually well tolerated but

								have had reports of nasal irritation and reversible smell loss. Intranasal surfactant efficacy against viruses has not been studied.
UV (virucidal)	+	NS	NS	+	NS	NS	NS: I, ST, H, A, B, F, RS	UV-C radiation is virucidal to SARS-coV-2, but its use intranasally and its safety profile has not been studied. Far UV-C light may be less harmful but retain its antimicrobial properties.
Oxymetazoline and Xylometazoline (unknown)	NS	NS	NS	NS	+	+	Y: I NS: ST, H, A, B, F, RS	Small study shows that nasal decongestant may reduce viral shedding temporarily in rhinovirus. Extended use is known to cause mucosal irritation and rebound nasal congestion.
Interferon (multiple pathways)	NS	+	+	+ SARS-CoV-1	+ HFMD Influenza	+ HFMD	NS: ST, H, A, B, F, RS	Systemic interferon induces multiple side effects, but intranasal preparations have been shown to have antiviral properties and well tolerated. Topical nasal drops were used as prophylaxis in healthcare workers in Hubei, China during the beginning of the epidemic with no infections recorded in this population.

FIGURE LEGENDS

Figure 1. Mind map graphically displaying the ideas and concepts of intranasal drug delivery in the setting of antiviral disease, including SARS-Co-V-2. The central topic has branches extending in a radial fashion to connect subtopics. Each subtopic is connected to key concepts.

Figure 2. Structure of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Reprinted from Shereen, et al. 2020.[8]

Figure 3. The life cycle of SARS-CoV-2 in host cells. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment. Reprinted from Shereen, et al. 2020.[8]

Figure 4. Gamma camera image information from the nasal cavity superimposed on the corresponding sagittal MRI section presenting deposition two minutes after delivery using: (**A**) a traditional liquid spray, (**B**) the breath-powered powder device, and (**C**) the breath-powered liquid spray device incorporating the same spray pump. Reprinted from Djupesland, et al. 2012.[79]

Figure 5. Potential applications of intranasal drug delivery.

Figure 1

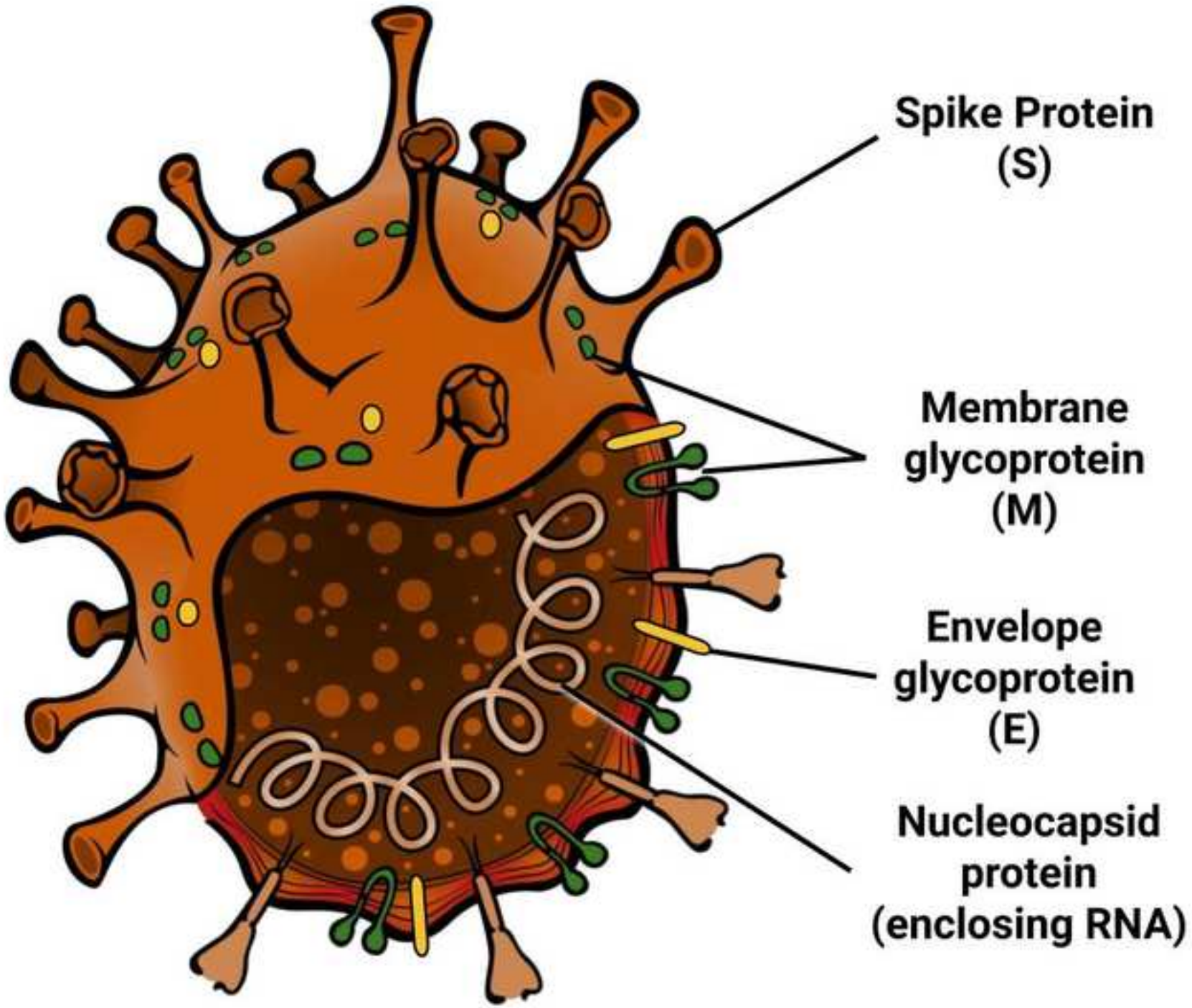

Figure 2

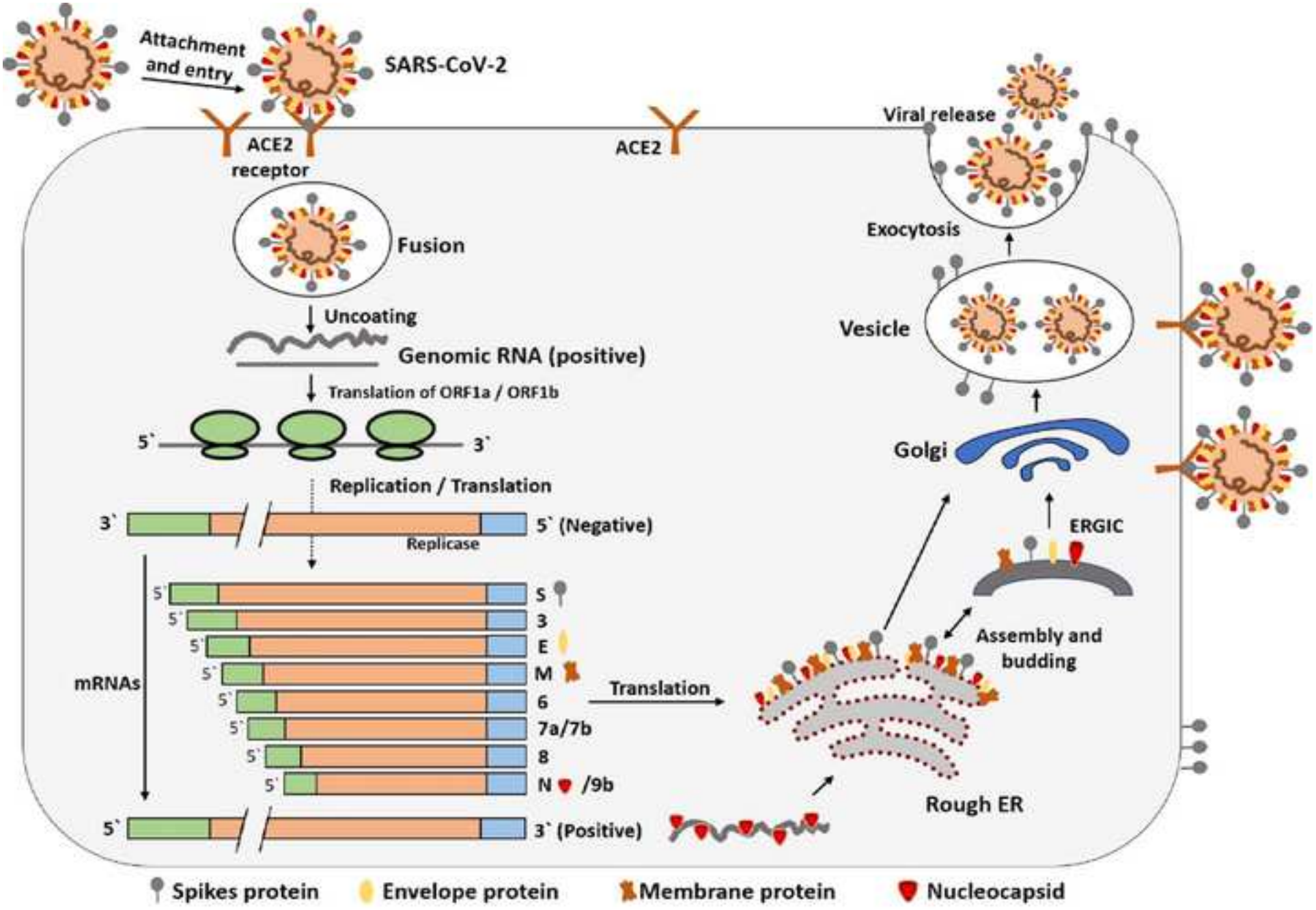

Figure 3

Click here to access/download;Figure;Figure 3 - Mind Map - Intranasal COVID19.jpg

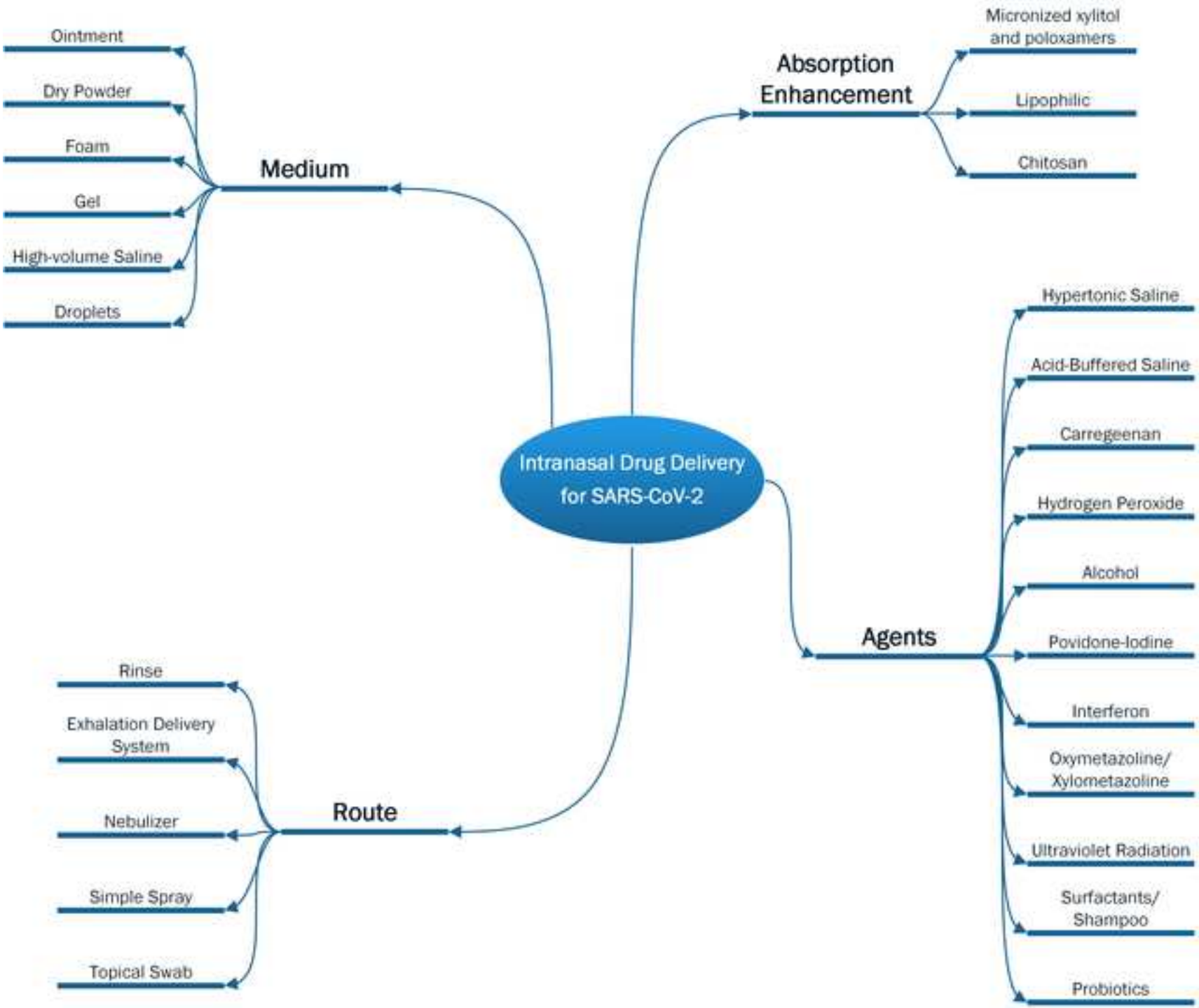

Figure 4

Click here to access/download;Figure;Figure 4 - Gamma camera image - CC free to use.jpg

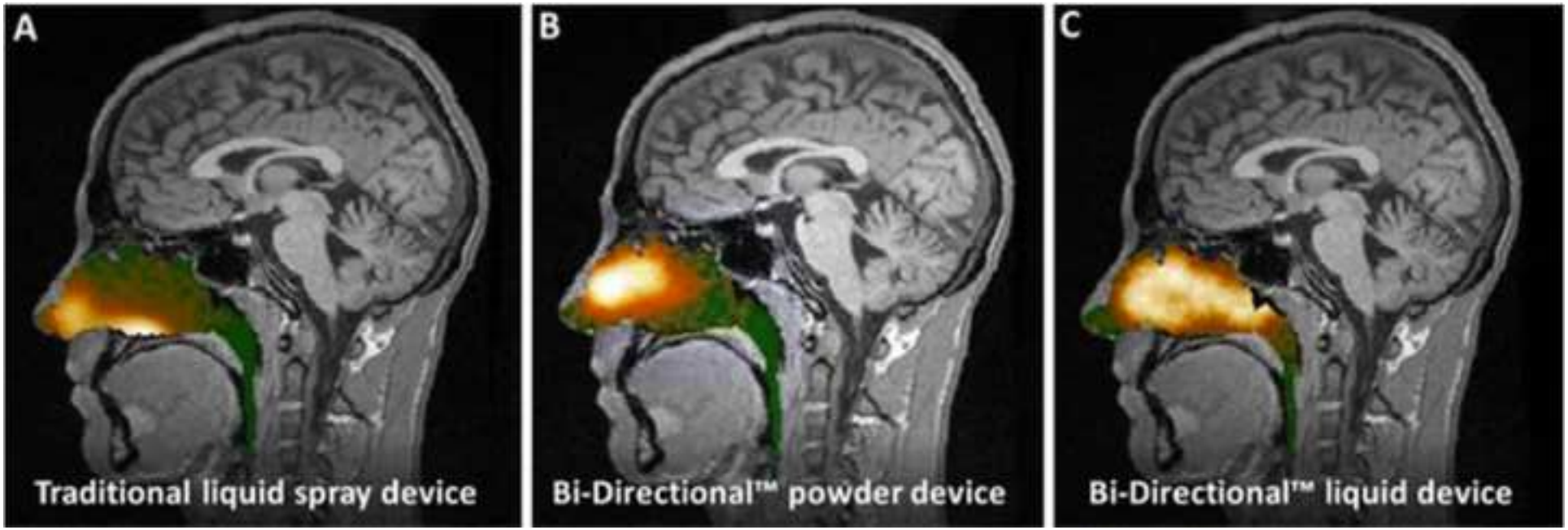

Figure 5