Review Article

Potential ocular and systemic COVID-19 prophylaxis approaches for healthcare professionals

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The COVID-19 pandemic has brought with it, innumerable challenges in healthcare, both through the direct burden of morbidity and mortality of the disease, and also by the curtailing of other essential albeit less emergency medical services to reduce the risk of community spread. Reports from around the world are showing mounting number of cases even in healthcare professionals spite of usage of adequate personal protective equipment. There are a number of factors which could account for this, be it the affinity of the virus to the respiratory and other mucosa or to patient risk factors for developing severe forms of the disease. In view of the growing need for resuming other medical services, it is essential to find newer ways to protect ourselves better, whether by systemic or topical mucosal prophylaxis with various medications or lifestyle changes promoting wellbeing and immunity. This article discusses additional prophylactic measures including drug repurposing or new indication paradigms to render protection. Certain medications such as chloroquine, trehalose, antihistaminics, and interferons used topically for various ocular conditions with reasonably good safety records are known to have anti-viral properties. Hence, can be harnessed in preventing SARS-CoV-2 attachment, entry, and/or replication in host cells. Similarly, use of hypertonic saline for nasal and oral mucosa and dietary changes are possible methods of improving our resistance. These additional prophylactic measures can be cautiously explored by healthcare professionals to protect themselves and their patients.

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The novel viral respiratory illness named COVID-19 caused by SARS-CoV-2, first reported in Wuhan, China,[1] has presented as one of the greatest challenges for disease control and eradication in modern history. The number of infected cases and the fatalities are increasing day by day with the latest WHO situation report-132 putting the number of infected cases as over 5.9 million with the death toll having crossed 367,000 worldwide.[2] Initially, all non-emergency healthcare services were advised to be withheld to try and control disease transmission.[3,4] However, given the scale of disease spread across countries, and the expected prolonged period before control, it is likely all healthcare services, both essential and elective, will need to resume amidst the ongoing pandemic. In this situation, it is important to consider plausible options of prophylaxis for high-risk groups and healthcare workers. As medical professionals, we are at a higher risk of being exposed to the virus as compared to the rest of the population,[5] as even among asymptomatic persons there is a high level of shedding of the SARS-CoV-2 virus, which increases the risk of transmission.[6] Thus, prophylaxis or prevention of infection is an important strategy in controlling this pandemic. Across the world, guidelines are being released with regard to use of personal protective equipment (PPE), out-patient, in-patient, and operating room procedures to reduce the risk of infection.[4,7] However, despite all the protective equipment and guidelines, the number of people infected by SARS-CoV-2 including healthcare professionals is rising by the day.[2] Hence, additional prophylactic strategies including the use of pharmacological agents, managing nutritional deficiencies, and adopting well-being practices need to be explored to mitigate the spread of the infection.

This article aims to provide a brief update on viral transmission at the mucosal surfaces and stratified approaches to mucosal and systemic prophylaxis against SARS-CoV-2 infection/COVID-19. We hypothesize that the following approaches that are based on peer-reviewed published scientific literature could possibly help decrease the chances of contracting the infection or reduce the severity of its sequelae.

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Update on viral transmission and systemic risk factors of severity

Severe acute respiratory syndrome associated coronavirus (SARS-CoV) is a part of a family of human coronaviruses (HCoV), which are enveloped, single-stranded RNA viruses.[8] It is transmitted primarily via the respiratory route, both by direct contact or via aerosols from infected people.[9] This has also been proven for the SARS-CoV-2 which causes COVID-19 wherein droplets and aerosols from nasopharyngeal and oropharyngeal tracts of infected people can be a source of infection.[10] As the SARS-CoV-2 has been found in feces as well, other modes of transmission such as a feco-oral route is also a biological plausibility.[11]

The status of the cells in mucosal surfaces contributes toward susceptibility to viral infection and the severity of the disease. Angiotensin-converting enzyme 2 (ACE2), TMPRSS2 and Cathepsin B/L are essential for the entry of SARS-CoV-2 into host cells[12-16] and hence are attractive targets for prophylaxis and therapeutics. SARS-CoV-2 binds to the host cells via the interaction of the spike protein, S of the virus to ACE2 on the host cells.[12] Post-binding, the viral entry into the cells are facilitated by proteolytic cleavage of virus S protein by two independent host proteases: (i) TMPRSS2, a transmembrane serine protease, facilitates the fusion of viral and host cell membranes at the target cell surface to facilitate entry; (ii) Cathepsin B and L are endosomal cysteine proteases that allows the fusion of viral and host endosomal membranes,[12-16] an event that precedes the release of viral genetic material into the host cell and subsequent replication of the virus.

The definite anatomical and host receptor links through the respiratory and ocular mucosa increase the tropism of respiratory viruses for these two areas. In addition, the anatomical connect formed by the nasolacrimal system and the distribution of permissive cellular receptors across both the respiratory tract and ocular mucosa increase the risk of infection.[17,18] Epithelial cell glycoproteins bearing terminal sialic acids (SA) like 2-6-linked SA and 2-3-linked SA serve as the cellular receptor for different respiratory viruses.[19,20] Though studies in the past were able to demonstrate the cell

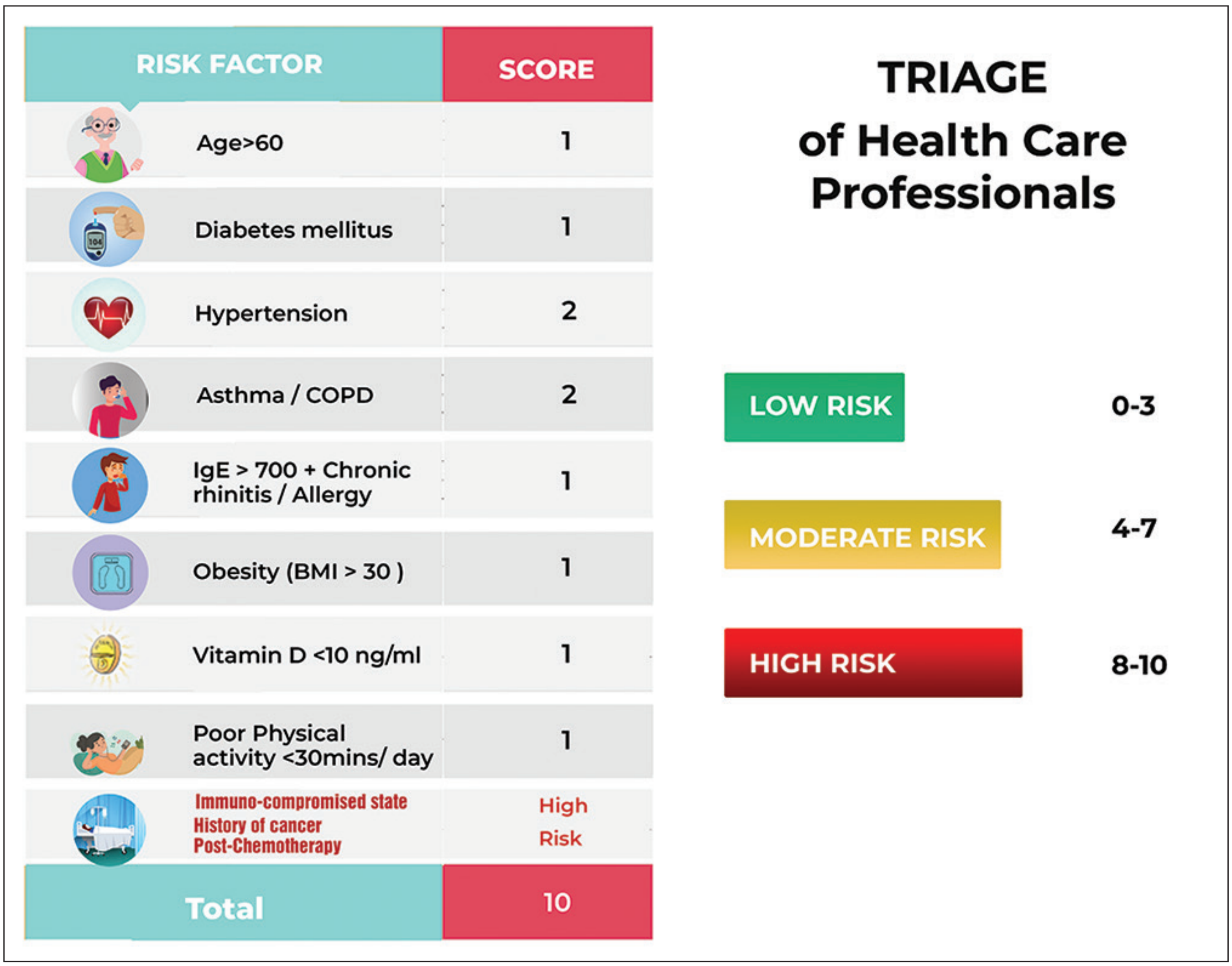

Figure 1: Scoring system to assess the risk of COVID-19 associated morbidity among healthcare professionals. This is will be used to triage the professionals and plan for appropriate additional prophylactic measures

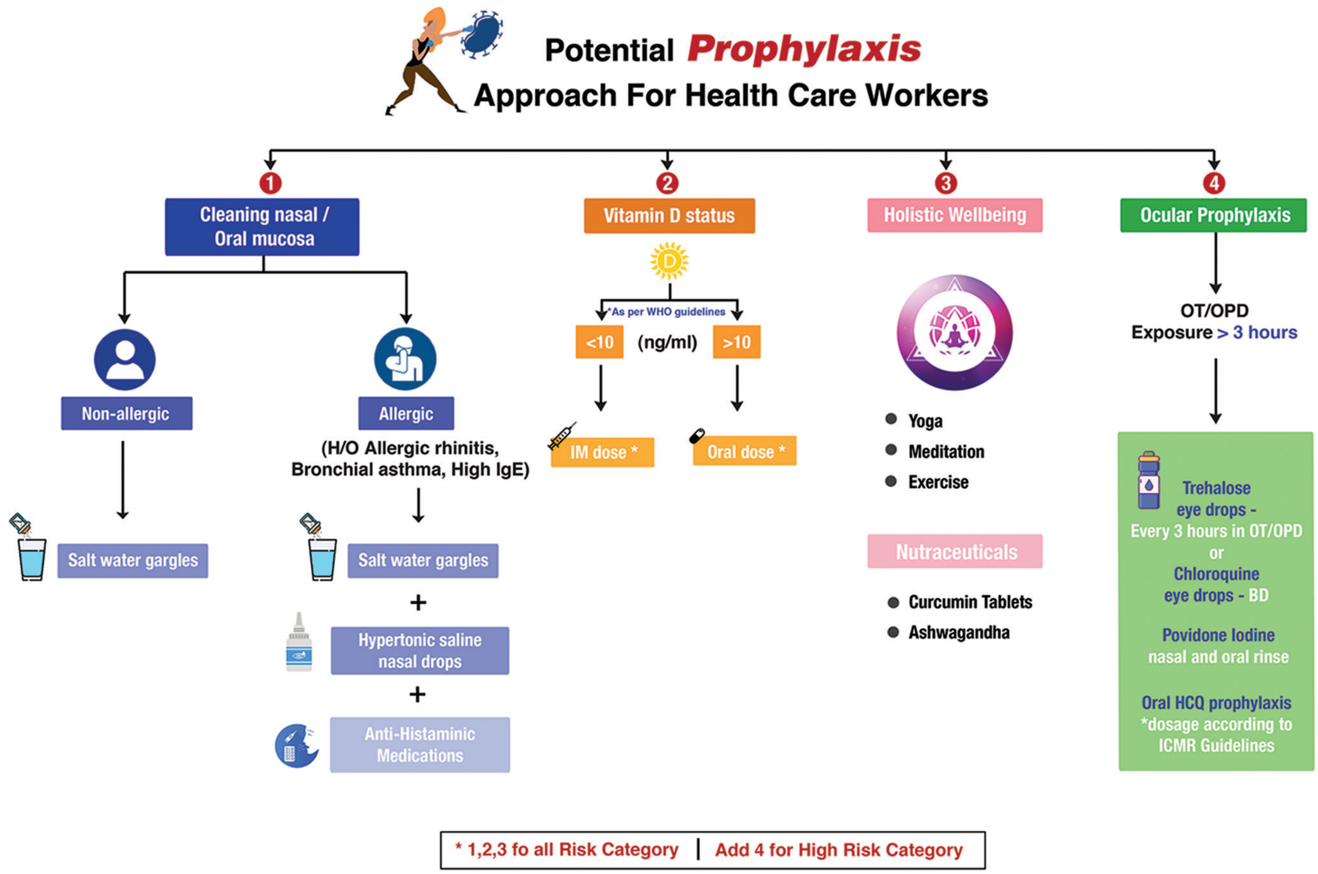

Figure 2: Prophylaxis strategies for healthcare workers based on the prevailing risk factors

surface ACE2 only in respiratory mucosa and posterior parts of the eyeball,[21] a recent study has shown the presence of these cell surface proteins in the conjunctiva and corneal epithelium as well.[22,22] Therefore, not surprisingly as in the previous SARS coronavirus outbreak,[24] the possibility of transmission of SARS-CoV-2 has also been reported through the ocular mucosa.[25] An ophthalmologist in China was reported to have conjunctivitis, which was followed by a systemic SARS-CoV-2 infection.[26] Following these initial reports, several studies were undertaken to study the possibility of transmission through the ocular surface and of tears being a carrier of the virus.[27-30] Though a study done at Singapore[27] could not find RT-PCR positivity for the virus in the tear fluid of COVID-19 patients, some other studies have been able to show RT-PCR positivity for the virus in tears.[29-31] In addition, different studies have reported varying proportions of COVID-19 infected patients showing conjunctival involvement.[27,29,30] The above findings show that the ocular surface could be infected through aerosols from infected patients and further transmit the infection to the respiratory tract through the nasolacrimal duct.[32] As conjunctivitis could potentially be a presenting symptom of COVID-19, guidelines to approach conjunctivitis during this pandemic have also been made.[33]

Another important finding from a recent meta-analysis published from China was that there is significantly higher odds of severe COVID-19 infections being associated with systemic comorbidities such as hypertension, diabetes, cardiovascular, and respiratory system disease.[34] Additionally, it has been shown that elderly and immunocompromised people are more severely affected by this illness.[35] Based on these, and a few other published associated risk factors, we have categorised healthcare workers into low, moderate, and high-risk groups [Fig. 1]. This would help decide on what level of prophylaxis they might need. On the basis of scientific evidence, we have tried to provide a comprehensive prophylaxis algorithm [Fig. 2]. All of these measures are recommended in addition to the use of PPE and existing guidelines and precautions suggested by literature from around the world. Targeted modulation with intent to enhance genes or activity of factors that would prevent viral entry and replication in the mucosa would severe as an ideal approach for pharmacological prophylaxis. The types of prophylaxis could either be a direct approach at the mucosal surfaces or indirectly via a systemic approach or both.

Respiratory mucosal prophylaxis

The viral endocytosis of the SARS-CoV in the human cells is shown to be pH dependent.[36] Irrigation of the nasopharynx and gargle of the oropharynx with hypertonic saline, twice daily or before and after patient exposure, could alter the pH of these environments and possibly decrease viral attachment and entry into cells.[37] Nasal hypertonic salt is easily available as sachets over-the-counter, which can be diluted in lukewarm water to make hypertonic saline for immediate use. A related concept was utilized previously in the development of a novel

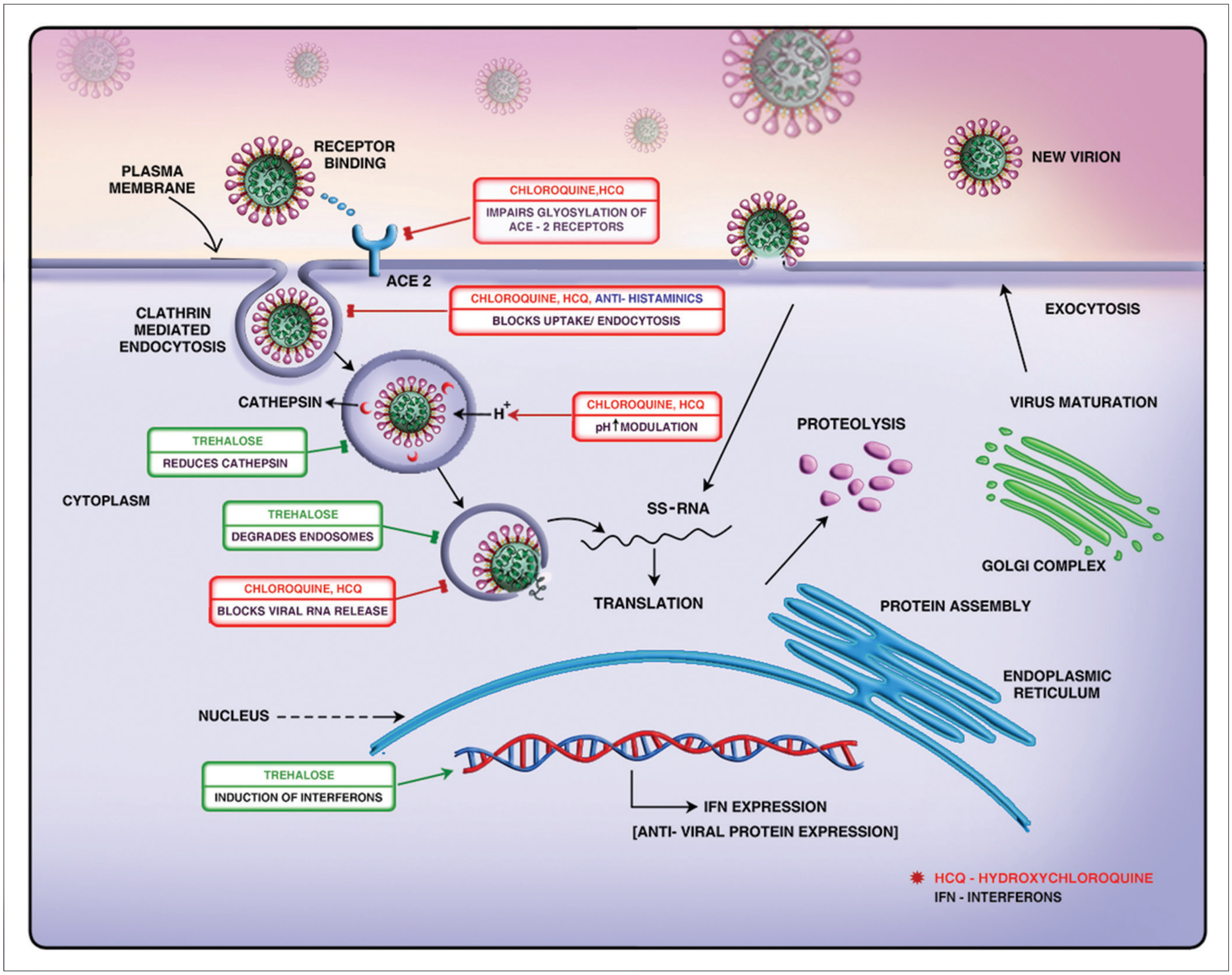

Figure 3: Schematic representation of mechanisms underlying various ocular pharmaceutical agents in preventing attachment and entry of SAR-CoV-2 in host cells. (i) Hydroxychloroquine prevents binding of SARS-CoV-2 to host cells by disrupting the interaction between viral S protein and ACE2 of host cells, by impairing glycosylation of ACE2 in host cells. (ii) Hydroxychloroquine and anti-histaminics prevent the uptake of virus by endocytosis. (iii) Hydroxychloroquine increases endosomal pH that would prevent the activation of cathepsins, an essential event for the fusion of viral and host endosomal membranes, necessary for viral entry, (iv) Trehalose facilitates endosome based degradation of virus, (v) Trehalose inhibits the activation of cathepsins, an essential event for the fusion of viral and host endosomal membranes, necessary for viral entry, (vi) Trehalose induces type 1 interferons in host cells and (vii) type 1 interferons induces interferon response genes that would prevent the viral replication and maturation

mask, which was incorporated with sodium chloride crystals to prevent viral aerosol transmission. The authors claim the mask has a very high filtration capacity and potential ability to deactivate the pathogen, thereby preventing spread of the virus from discarded masks.[38]

Anti-histaminic agents such as chlorpheniramine maleate (CPM) have been shown to effectively prevent viral transmission of a broad spectrum of influenza viruses through the respiratory mucosa.[39] They do not interfere with the viral attachment on to the cell surface, but inhibit the process of endocytosis, by which the virus enters into the host cell.[39] SARS-CoV-2 viruses, though they attach onto cells using a different cell surface protein,[12] have a similar process of endocytosis[40] and therefore CPM can lower the risk of acquiring the COVID-19 infection. In healthcare workers with allergies and high IgE, this can be potentially beneficial as a prophylaxis. Anti-histaminic drugs such as Olopatadine and Azelastine are also medications which selectively inhibit H1 histamine receptors, similar to CPM. Olopatadine, in addition, has a mast cell stabilizing property too. Both Azelastine and Olopatadine are also available as nasal sprays allowing for easy and targeted application to the nasal mucosa.[41,42] We recommend starting the medication in consultation with their allergy-immunology and ENT specialists as the dosage and generic drug has to be decided and titrated depending on individual requirements, tolerability and safety profile.

Ocular mucosal prophylaxis

Very recent findings confirm the expression of viral entry-associated genes ACE2 and TMPRSS2 in ocular mucosal surface cells (corneal and conjunctival) in addition to respiratory and intestinal epithelial cells, thus suggesting ocular surface as an additional route of SARS-CoV-2 transmission.[23,24] The anatomical connection of the ocular surface mucosa to the respiratory tract mucosa via the nasolacrimal duct as discussed previously further emphasizes the possibility of ocular-respiratory route of transmission. Hence, targeting these viral entry-associated proteins on the ocular surface would be beneficial in the prevention of SARS-CoV-2 infection via the surface of the eye. Certain medications used as eye drops for other conditions including hydroxychloroquine and trehalose may have beneficial prophylactic effects against SARS-CoV-2 by modulating the factors that facilitates viral entry. Hydroxychloroquine can prevent viral attachment and entry into host cells by impairing glycosylation of ACE2, thus disrupting the interaction between S protein and ACE2.[43,44] It also blocks clathrin-mediated viral endocytosis and prevents fusion of viral and host cell endosomal membranes by preventing endosomal acidification (by increasing endosomal pH), an event that is critical for Cathepsin B/L activity [Fig. 3].[45-48]

Trehalose, a simple plant based sugar known to modulate autophagy[49,50] is also a widely used ocular pharmaceutical agent that is used as an eye drop. It is known for its anti-viral properties, such as induction of type 1 interferons,[51] facilitating lysosomal degradation of intracellular virus,[52] reducing viral entry by decreasing the expression of host cell surface proteins that facilitates the attachment of virus to the cells[53] and reducing cathepsin activity [Fig. 3].[54] Autophagy induction is a newer phenomenon documented by several studies. Trehalose is one such drug which by means of induction of autophagy,[49,55] provides an anti-inflammatory milieu to the ocular surface. However, one study did report that trehalose-mediated autophagy impaired anti-viral response in airway epithelial cells.[56]

The anti-viral properties of ocular pharmaceutical agents discussed suggests that these agents can potentially prevent an aerosol based viral infection of the ocular surface. However, it is important to investigate the anti-viral potency at the doses used in ocular formulations. Both Trehalose 3% (4–6 times a day) and chloroquine 0.03% (twice a day) eye drops have been used in the treatment of dry eyes.[57,58] While the long-term use of these medications topically has been shown to be safe,[58-60] one report of probably excessive unmonitored use of chloroquine drops has been shown to result in a sterile corneal ulcer.[61] Trehalose eye drop has been shown to alter tear film thickness up to 240 min after instillation.[62] Considering this, Trehalose can either be used in a 3 h application or specifically around an hour before an expected exposure to a patient.

As discussed in the respiratory prophylaxis, anti-histamines could also be potentially used as an ocular prophylaxis. Anti-histamine eye drops, such as Olopatadine 0.1% eye drops (twice daily), is routinely used in patients with eye allergies. Even in long-term use and prophylactic use for ocular allergies, the drug is known to be safe.[63,64] In the context of COVID-19, medications such as this could potentially have a role in decreasing the ocular route of transmission.

Interferons (IFNs) are endogenous proteins which have anti-viral activity by blocking viral protein synthesis and degrading viral RNA.[65] The use of type 1 interferons (IFN) in the management of SARS-CoV and MERS-CoV has been well explored and has been found to significantly decrease viral shedding.[66,67] More recent work has shown the effectiveness of the IFNalpha in disease resolution in COVID-19 patients and for prophylaxis.[68] Another Type 1 IFN, Interferon alpha2b is already being used topically in the context of ocular surface squamous neoplasia (OSSN). Though it is relatively safe, adverse events such as follicular hyperplasia and corneal erosions have been documented.[69] By means of its anti-viral activity, though Type 1 IFN alpha2b eye drops could theoretically decrease the chance of ocular COVID-19 infection and viral shedding, further research on its safety as a prophylaxis in normal eyes is needed before it can be repurposed for this indication. Nevertheless, this could be one potential ocular prophylactic agent in the making.

Povidone-iodine has been shown to have potent virucidal activity against a number of viruses, including SARS-CoV and MERS-CoV coronaviruses.[70,71] It has been advocated for use as a prophylaxis for healthcare workers in addition to PPE in the form of nasal irrigation using 0.4% povidone-iodine solution and oral/oropharyngeal wash using 10 mL of 0.5% povidone-iodine solution.[72] To further reduce the risk of cross-infection in the operation theatre, the American Academy of Ophthalmology has advised ophthalmologists to continue the use of 5% povidone-iodine in the patient's eye prior to surgery. This would reduce the viral load in the eye and decrease the potential risk of aerosolizing viral particles.[73] However, care must be taken in refractive surgery as povidone-iodine is a potential cause for diffuse lamellar keratitis (DLK) post-laser *in situ* keratomileusis (LASIK).[74] Healthcare workers who work in close proximity to patients, and who are exposed to large aerosol loads and can potentially stand to benefit from these repurposed topical medications.

Systemic prophylaxis

There are a few systemic agents which have shown scientific basis for use as a prophylaxis against SARS/CoV-2.

Oral Hydroxychloroquine (HCQ) has been approved by ICMR (Indian Council of Medical research) for prophylactic use in healthcare workers at a starting dose of 400 mg twice a day on the first day, followed by 400 mg weekly for the next 7 weeks. At doses of <5 mg/kg, the drug is relatively safe and long-term irreversible side effects of retinal toxicity are noted only at doses >6.5 mg/kg/day over a cumulative period of over 5 years.[75] However, even at regular prescribed doses, those with cardiac arrhythmias, G6PD deficiency, pre-existing renal/hepatic/retinal damage, and those on tamoxifen therapy should exercise caution, while there is no ophthalmological concern in short-term use.[75,76] A basic medical evaluation is advisable for predisposing conditions of such life threatening adverse effects prior to initiating this prophylaxis.

Turmeric has been in dietary use in India since several centuries. Its active ingredient, Curcumin, has been studied extensively and has been shown to have anti-viral, anti-bacterial, anti-inflammatory, and anti-oxidant properties.[77-80] In a study published from Taiwan, curcumin has been found to exert mild inhibitory effect on the replication of SARS-CoV.[81] In addition, it also exerts positive effects in metabolic syndrome by lowering blood sugar and lipid levels,[77] thus controlling systemic risk factors for developing severe COVID-19 infection.[34] The allowable daily intake of curcumin is 3 mg/kg/day.[82] Also important to know that Curcumin in combination with black pepper has a 2,000% better bio-absorption of curcumin and is available as an oral supplement. When dosage exceeds over 500 mg/day, adverse effects as nausea, rash, diarrhoea, and headache have been reported.[82]

Recently, Amantadine, an FDA approved drug for treatment of influenza and Parkinson disease has shown potential repurposed application in the management of SARS/CoV-2 as it affects steps in the viral entry by altering cathepsin-mediated pathways.[83] Further studies are needed before it can come in to use as a prophylactic agent during this pandemic.

General wellbeing and vitamin D check

Multicentric data from North America and Europe on COVID-19 severity/mortality has shown low systemic vitamin D levels to be associated with higher COVID-19 severity due to a heightened cytokine storm.[84] Vitamin D has been shown to play an important role in immune response to infections, by modulating inflammatory cytokine production, monocyte differentiation among other actions.[85] Deficiency of Vitamin D has also been independently linked to increased viral respiratory infections.[86] Hence, Vitamin D supplementation should be considered an important prophylactic measure for COVID-19, particularly for Vitamin D deficient healthcare workers. Intramuscular or oral supplementation of Vitamin D should be initiated based on severity of deficiency. However, unregulated high doses are to be strictly avoided as it can lead to hypercalcemia and related complications.[87] It is also worthwhile to improve overall micronutrient status, such as Vitamin A, C, B6, B12 and trace elements such as iron, zinc, copper, and omega-3 fatty acids as they have been shown to play an important role in protecting against viral infections.[88] We have focussed on Vitamin D as it has been specifically studied in the context of COVID-19.[84] Adhering to recommended dosage of these micronutrients is important and overuse of such over the counter multivitamin tablets should be strictly avoided.

Systematic review of yoga and physical activity (>30 min/day) has been scientifically documented to improve the immune status/response in adults.[89,90] Meta-analysis has also shown that yoga can significantly decrease diastolic blood pressure and lipid levels, which are risk factors for severe form of COVID-19 infection.[91] Any form of yoga and physical activity suiting the individual's lifestyle is strongly encouraged to be undertaken to strengthen our ability to deal with the infection.[90]

Conclusion

All of the agents discussed and represented in Figs. 2 and 3 have shown scientific basis for a potential role as a prophylaxis against developing viral infections. During a pandemic, it is practically difficult to conduct large-scale randomized controlled trials (RCT) to generate scientific evidence. Hence, we can use allied research and existing scientific knowledge to derive possible therapeutic and prophylactic measures. At this point, they can be said to hypothetically decrease the risk of SARS-CoV-2 transmission and COVID-19 associated morbidity or mortality. Over time, these require more studies and data to validate them. These agents or measures have to be customized based on the health workers' risks and level of exposure. In summary, while adequate and appropriate use of PPE and avoiding inadvertent unprotected exposure to the virus are still the key stones in the approach to prevention, these additional prophylactic measures could play an adjunct role in stemming the spread of the infection.

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Conflicts of interest

There are no conflicts of interest.

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