# SARS-COV-2 PANDEMIC FROM THE OPHTHALMOLOGIST`S PERSPECTIVE. A REVIEW

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## SUMMARY

In December 2019, a novel coronavirus (CoV) epidemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged from China. Coronaviruses belong to enveloped ssRNA viruses and are classified into four genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus and Delta coronavirus. It is assumed that SARS-CoV-2 is spread primarily during a personal contact via bigger respiratory droplets. These droplets with viruses can be directly inhaled by other people or can lend on the surfaces with the possibility of further spreading. The ocular surface has been suggested as one of possible infection entries. Human eye has its own renin-angiotensin system with present ACE2 receptors, which bind the virus through spike protein. The most common symptoms of the SARS-CoV-2 infection are fever, cough and dyspnoea. Several clinical entities, such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis have been associated with this infection. The most common ophthalmologic symptom associated with COVID-19 disease is conjunctivitis. Some studies indicate that eye symptoms are commonly present in patients with severe COVID-19 pneumonia and that it is possible to detect viral RNA from the conjunctival sac of these patients.
In ophthalmologic praxis, we manage not only the therapy of the eye structures` inflammation in relation with this infection, but also the overall management of the visits and the supervision of the patients who are at risk and positive for coronavirus. Ophthalmologists could potentially have a higher risk of SARS-CoV-2 infection due to personal communication with the patients, frequent exposure to tears and eye secrets and the use of devices. We would like to provide an ophthalmologist`s perspective on this topic.
**Key words:** ACE2, COVID-19, SARS-CoV-2, conjunctivitis, coronavirus, ocular surface

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## INTRODUCTION

Since December 2019, the whole world has been struggling to cope with a serious acute respiratory coronavirus disease (COVID-19), caused by a strain of the coronavirus known as severe acute respiratory syndrome causing coronavirus 2 disease (SARS-CoV-2). The WHO first became aware of this new virus on 31st December 2019, following a report on a cluster of cases of "viral" pneumonia in Wuhan, the People's Republic of China. The breathing difficulties caused by this type of virus are well investigated. However, the ophthalmic symptoms are still under investigation.

While most human coronaviruses (HCov) cause relatively mild upper respiratory tract infections (common colds), two zoonotic viruses named severe acute respiratory syndrome (SARS) CoV (Corona Virus) and Middle Eastern Respiratory Syndrome (MERS) CoV are associated with severe lower respiratory tract infections and are a threat to public health [1].

Coronaviruses are classed among enveloped ssRNA viruses with a genome of 27–32 kb, belonging to the Nidovirales family and are classified into 4 genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus and Delta coronavirus [1]. Each serological type is characterised by a specific range of host that it can infect, as well as a specific genome sequence. The most pathogenic is SARS-CoV, which can cause life-threatening pneumonia [2]. The virus is likely to use animals as hosts and may be transmitted to humans by zoonotic transmission [3]. In humans, coronaviruses cause a variety of health problems, including gastroenteritis, respiratory problems and conjunctivitis [4].

Several studies have highlighted the fact that one-third of COVID-19 patients had eye abnormalities (common

manifestation in patients with a more severe course of the disease). Although the virus is excreted in tears in relatively small quantities, transmission through conjunctival secretions is possible [5].

## AETIOLOGY AND PATHOGENESIS OF COVID-19

Coronaviruses are generally able to cause a wide range of upper respiratory tract infections (colds): alpha-coronavirus HCoV-229E, alpha-coronavirus HCoV-NL63, beta-coronavirus HCoV-OC43 and HCoV-KHU1, while other beta-coronaviruses such as SARS-CoV and MERS-CoV are responsible for more aggressive respiratory problems, considered as atypical pneumonia. Different sites of infection are probably related to the presence of a virus' spike, composed of glycoprotein dipeptidyl peptidase 4, which binds to its receptor called ACE2 present in the lower respiratory tract. However, due to the above-mentioned glycoprotein spike, SARS-CoV-2 binds to ACE2 receptors with a 10–20 times higher affinity [7].

The moment SARS-CoV-2 enters the alveolar cells, it begins to replicate quickly. This replication will trigger a very strong immune response, causing cytokine storm syndrome and later lung tissue damage [8]. Cytokine storm syndrome generally causes an increase in the level of pro-inflammatory cytokines. These cytokines are an important cause of ARDS syndrome and multi-organ failure. In addition, the number of T cells (CD4 and CD8) decreases in patients infected with SARS-CoV-2, indicating a decrease in immune function. This allows superinfection, which could aggravate the pre-existing respiratory symptoms [9]. Both viral infection itself and immunological insufficiency can lead to ophthalmic manifestations such as: conjunctivitis, uveitis, retinitis, and others. The pathogenesis of the eye impairment is difficult to determine. As the virus has been cultivated from conjunctival secretions, it is more likely that the COVID-19 eye disability is related to the viral infection itself, rather than to the superinfection caused by immunological insufficiency [10].

## TRANSMISSION OF SARS-COV-2

While animals are considered to be the original source of the infection, SARS-CoV-2 is thought to be spread primarily via personal contact through larger respiratory droplets (on average larger than 5 μm) on which gravitational forces act [11]. These droplets can be directly inhaled by other people, or they can land on surfaces (which other people may come into contact with), where the virus can remain viable from a few hours to several days. Respiratory particles can be spread by breathing, talking, coughing, or sneezing. Airborne transmission occurs when infectious droplets of less than 5 μm circulate in the air over an extended period of time. Viral particles can be absorbed through the respiratory mucosa and potentially through the conjunctiva. The coronavirus is not yet considered airborne, unless the virus creates droplets. Viral RNA has also been found in stool samples of infected patients, indicating possible transmission by the faecal-oral route. The transmission of SARS-CoV-2 may also occur from an asymptomatic patient, making prevention difficult [11].

In 2014, Loon et al. showed the presence of SARS-CoV-2 in tears. Tear samples taken from 36 patients suspected of COVID-19 were sent for RT-PCR analysis. SARS-CoV-2RNA was identified in three patients [12]. It is controversial whether the virus can be transmitted through tears [13]. The exposed surface of the eye may serve as a possible gateway for respiratory droplets, but, according to the study of 120 patients, the risk of such transmission is extremely low [14].

Considering the reported cases suggesting a nosocomial transmission in healthcare professionals, there is a presumption that ophthalmologists might be at higher risk of acquiring a coronavirus infection [13].

The most common manifestations of infection are fever, cough, and shortness of breath. Others include blocked nose, headache, sore throat, mucus, fatigue, myalgia, arthralgia, nausea, vomiting, diarrhoea, loss of taste, loss of smell and conjunctivitis. Despite this huge number of symptoms, a significant number of patients can be asymptomatic.

## EYE SYMPTOMS

**1. Conjunctivitis**

The most common eye symptom related to COVID-19 is conjunctivitis [5,10,15].

The human eye has its own renin-angiotensin system with ACE2 receptors [16]. This system is currently of interest in the development of anti-glaucoma drugs [17]. As mentioned above, the main receptor for SARS-CoV-2 is the ACE2 receptor, suggesting that aqueous fluid could be the target of COVID-19 infection. However, no information is yet available on eye tissue infection via ACE2 receptors.

In one of the studies, Xia et al. analysed 30 patients with confirmed COVID-19 pneumonia. An RT-PCR test of lacrimal and conjunctival secretions was used in this study. The authors showed that SARS-CoV-2 was present in the tears and conjunctival secretions of the patients with coronavirus pneumonia and conjunctivitis at the same time, but no virus was detected in conjunctivitis-free patients. These results suggest that lacrimal and conjunctival secretions are not a common route of transmission of the coronavirus, since most patients with COVID-19 do not show signs of conjunctivitis. This finding should be considered in the differential diagnosis of conjunctivitis, particularly if conjunctivitis is accompanied by other respiratory problems or fever [19].

**2. Impairment of retina**

The first reported retinal disability was in the study conducted by Marinho et al. [20], who investigated 12

COVID-19 positive patients by OCT examination. All these patients showed COVID-19 symptomatology, and anosmia was observed in addition in 11 patients. The patients showed hyper-reflective lesions at ganglion cell level in both eyes. Four of these patients also had micro bleedings along the retinal arcades, seen in a photo of the fundus. No signs of eye inflammation were observed, and visual acuity and pupillary reflexes were intact. Subsequently, Vavvas et al. highlighted the fact that the observed hyper-reflective areas on the OCT are most likely to represent normal retinal vessels [21].

COVID-19 infects the host by means of the ACE2 receptor, which is expressed in several organs, including retinal endothelial cells [22]. Inflammation of the endothelial cells causes their oedema, overload, and thrombosis, which eventually leads to ischaemia. COVID-19 RNA was also detected in the retina of affected patients [23]. This finding suggests that COVID-19 can cause retinal vasculitis and ischaemia. Viral infection is a rare cause of retinitis, but relevant cases have already been reported [24].

In another cross-sectional clinical study, Invernizii et al. examined the changes in retinal vessels in 54 patients. Bleeding, dilated veins and arteries were observed. The mean arterial diameter and mean venous diameter were compared with 133 unexposed patients. COVID-19 has been shown to induce changes, especially at the level of retinal veins, and these changes were directly correlated with the severity of the disease. It is therefore possible that the diameter of the retinal vessels may be a useful parameter of monitoring the inflammatory response. Due to the non-invasive nature of the examination of the eye background, the change in retinal vessels should be further investigated to understand their possible use in the diagnosis and treatment of COVID-19. The above-mentioned evidence suggests that retinal disability in COVID-19 is more than likely. This should be particularly considered in higher risk patients (i.e. diabetic or hypertensive). It should also be considered that both diabetes and high blood pressure are risk factors for COVID-19. Given the scale of the current pandemic and the major challenges in terms of diagnosis and management, we should emphasise the better reporting of clinically significant eye symptoms, to further explore the possibility of retinal involvement [25].

**3. Uveitis**

As a part of the multisystem inflammatory response during COVID-19 infection, uveitis may also occur. Uveitis, defined as intraocular inflammation, is the fifth leading cause of vision loss in the United States and causes 10–15 % of visual impairment in the Western world [26,27].

**4. Myopia**

Myopia is one of the main health problems worldwide. The WHO estimates that one-half of the world's population may be short-sighted by 2050. In recent years, insufficient time spent on outdoor activities has been considered a major risk factor for myopia [28].

The research focuses mainly on the impact of quarantine measures and lockdown, related to a longer time spent in front of digital screens and the emergence and determination of myopia. According to the United Nations Educational, Scientific and Cultural Organization, some 1.37 billion students (80 % of the world´s student population) from more than 130 countries are affected by these measures, and normal teaching methods in the classroom are replaced by digital or e-learning practices. There is a possibility that the long-term fight against pandemics may lead to an increase in myopia, by shaping long-term behavioural changes leading to the emergence and progression of myopia [29]. The meta-analysis comprising 12 cohort studies and 15 cross-sectional studies involving 25 025 children aged 6–18 years has recommended that the time spent tracking a mobile, laptop, etc. be reduced, to lessen the risk of myopia [30]. This means that there is considerable evidence to support this recommendation. In the cross-sectional study of 123 535 children, Wang et al. recorded a significant myopic shift (-0.3 D) in children aged 6–8 years after staying at home due to COVID-19 [31]. Myopia prevalence increased 1.4–3 times in 2020, compared to the previous 5 years. The refractive state of younger children may be more sensitive to changes in the external environment than older children, as younger individuals are more susceptible to the development of myopia. Further studies are needed to accurately assess these findings and to observe these children in the long term. The WHO recommends that children aged 1–5 years spend less than 1 hour per day behind a screen. The American Academy of Paediatrics recommends limiting screen time to 1 hour per day for children aged 2–5 years and suggests consistent limits for children aged 6 years and older, but does not specify the limits for this age group [31,32].

What can be done to mitigate the myopic behaviour that occurs during the COVID-19 pandemic?

**Firstly**, in the long term, public education is important to raise parents' awareness of the effects of indoor work and reduced outdoor time on the occurrence and progression of myopia. Parents need to understand the importance of following the correct eye habits during and after the lockdown, including frequent breaks from work and limiting the use of electronic screens for leisure activities [29].

**Secondly**, government agencies for healthcare and eyecare professionals should continue to work with schools to shape a coherent home curriculum that promotes creative learning, not only when reading and studying at home, but also one that includes frequent breaks and physical activities, as well as household chores such as cooking, baking, cleaning, etc. [29].

**Thirdly**, children should be encouraged to perform leisure activities outdoors in the form of sport or to

play at an appropriate social distance (if it is safe and in accordance with the law). The recommended 2–3-hour outdoor time should be easier to reach, thanks to the flexibility of distance learning. COVID-19 should not suppress the benefits of outdoor activities on children's health [33].

While it is important to take strict measures (lockdown and home quarantine) to slow or stop the spread of the coronavirus, multidisciplinary cooperation and close partnerships among ministries, schools and parents are also essential in order to minimise the long-term collateral impact of COVID-19 on the emergence and progression of myopia, which was already a major public health problem before the pandemic [29].

Concerning the severity of COVID-19, patients with ocular symptoms are more likely to have a higher leukocyte count and higher levels of CRP, PCT and LDH than those without eye symptoms [5].

There is now growing evidence that COVID-19 can also affect the nervous system. Recent studies suggest that neurotropic potential is one of the typical features of the coronavirus family [34]. The mechanism of infection and neurotropism previously seen in coronaviruses such as MERS and SARS-CoV-2 could also be seen in SARS-CoV-2. Regarding the clinical characteristics, the study in Wuhan showed that 77 of the 214 patients (36 %) hospitalised for COVID-19 developed neurological symptoms or secondary strokes. Further studies reported several categories of central and peripheral neurological disorders in COVID-19 patients. Reported non-specific and systemic neurological symptoms included: headache, myalgia, dizziness, fatigue, hyposmia, hypogeusia and visual disturbances [34,35]. These symptoms occur in 30–40 % of patients and are more common in more severe stages of the disease. Other serious neurological manifestations reported in relation to COVID-19 were encephalopathy, epilepsy, paralysis and disturbances of consciousness, cerebrovascular events (ischaemic event, intracerebral haemorrhage, sinus thrombosis), as well as acute necrotising encephalopathy and meningitis. Predicted mechanisms of microinvasion and manifestations on the nervous system include spreading through the cribriform plate and spread of the virus into the brain through the olfactory nerve. Another possible mechanism of transmission is the haematological pathway and ACE2 receptors on neurons and glia cells, which make these cells a potential target for SARS-CoV-2. The virus can also interact with ACE2 on capillary endothelium, which could damage the blood-brain barrier. Due to neuro-invasive and neurotropic properties, we can assume that SARS-CoV-2 may also affect other neuronal structures, including the optic nerve, sub-basal plexus, corneal nerve, and the nerves innervating the extraocular muscles [34].

## OPHTALMOLOGICAL PREVENTION

According to many authors, ophthalmologists could have a higher risk of developing SARS-CoV-2 infections, due to personal communication with patients, frequent exposure to tears and eye secretions, and the necessary use of devices. Recently, some guidelines have been published to minimise the risk of infection.

**1. Before a patient's visit**

There should be a strict timetable for patients, to avoid clustering of patients in the waiting room. Telephone contact and online platforms (website) should be the primary way of calling patients for examinations. Telephonic assistance could be useful in helping the patient to distinguish between urgent and non-urgent conditions, to recommend treatments for other than urgent diseases, and as a tool to remind patients to use personal protective equipment (PPE) before arriving for an examination, as well as to answer questions about possible symptoms in relation to COVID-19. A triage system is also important to identify patients with fever, respiratory symptoms and/or acute conjunctivitis and those who have recently travelled to outbreak areas. It is also recommended that prescribed medicines be supplied and ordered online, in particular for medicines for long-term use in chronic diseases [36].

**2. During a patient's visit**

The number of accessible entrances to the hospital should be reduced and there should be a check-in at each entrance. Patients should be measured for body temperature, and screened for COVID-19 symptoms. A history of contact with other confirmed or suspected COVID-19 patients in the last 14 days should be taken. Patients should be provided with a protective mask or respirator without an exhalation valve filter, upon request. Patients with conjunctivitis or other similar infections should be placed in a separate outpatient clinic with a separate waiting room. Patients should be tested for SARS-CoV-2 RNA in the conjunctival sac and in tears more than 2 times. Examination rooms should have a limited number of persons (1 doctor and 1 patient), except for visually impaired patients, patients with communication/mobility disorders or young children. The room should be well ventilated, and the devices/tools used should be disinfected immediately after each patient's visit. A protective shield should be placed on all examination devices, disinfection of the equipment should be frequent, and the staff should protect their eyes (goggles, shields). For staff, it is necessary to cover the upper respiratory tract, including the nose and mouth, with protective masks, maintain hand hygiene and keep a distance of more than 2 metres. A direct examination with an ophthalmoscope is not recommended and should be replaced by Volk lenses with examination by slit lamp, optical coherent tomography, or fundus photography [36].

**3. Inpatient care and surgical procedures**

All healthcare professionals should be provided with training in infection control. Strict hand hygiene is essential, and gloves should be changed regularly. One pair of latex gloves should not be used for an extended period [36].

Preoperative screeding of infection and a detailed epidemiological history is recommended in hospitalised patients, especially before surgery. General anaesthesia should be avoided, and local anaesthesia is preferred to prevent contamination. Any urgent operation of a COVID-19 positive patient should be performed in an operating theatre with negative pressure. If such a theatre is not available, the patient should be sent to another qualified hospital equipped with such a theatre. Operations on healthy patients may be performed in an area with an overpressure laminar flow [36].

**4. Disinfection**

According to current evidence, the human coronavirus is able to remain infectious on non-living surfaces for up to 9 days. The WHO recommends cleaning the surfaces with water and detergent and using common disinfectants such as sodium hypochlorite. Bleach is typically used in the dilution of 1:100 5% sodium hypochlorite, which ultimately gives a concentration of 0.05%. on small surfaces; 62–71% ethanol showed an efficacy against the coronavirus. Other bactericidal substances such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective [37].

## TREATMENT OF EYE COMPLICATIONS IN PATIENTS WITH COVID-19

There is little evidence of the treatment of COVID-19-related viral conjunctivitis. During the outbreak, a number of antiviral systemic agents (antivirals) such as: umefenovir, lopinavir and ritonavir were used, but not specifically for eye complications. Chen et al. reported the possibility that eyedrops containing ribavirin may help in the treatment of eye symptoms. Treatment of viral conjunctivitis is mostly supportive. Nevertheless, it is important that ophthalmologists reduce the possible viral load on the conjunctiva and reduce the potential for transmission by tears and eye secretions. Some general recommendations for viral conjunctivitis could apply to COVID-19 patients, in terms of both the reduction of transmission rate and possible complications, including hygiene measures:

- Frequent hand washing (especially when using eyedrops or wearing contact lenses)
- Do not touch or rub your eyes
- Regular change of pillowcases/sheets
- Do not share personal belongings

**Chloroquine (CQ) and hydroxychloroquine (HCQ) in the treatment of COVID-19**

The FDA has approved chloroquine and hydroxychloroquine for the treatment of COVID-19, based on limited clinical data and these medicines are used in some countries as an off-label indication [38]. The treatment was authorised, despite a lack of randomised clinical trials supporting the safety and efficacy of these medicinal products. The observational study of 1 376 COVID-19 patients in New York City showed that HCQ administration was not associated with either a significantly increased nor significantly reduced risk of intubation and death. The American Association of Ophthalmologists (AAO) recommended the maximum daily HCQ use ≤ 5.0 mg/kg of weight, with the risk of developing dose dependency during usage [20]. With this dosage, retinopathy occurs rarely after 10 or more years of treatment. However, in the treatment of COVID-19, higher doses of HCQ are used than those recommended by the AAO. Therefore, Marble et al. suggested that ophthalmic screening is not necessary for COVID-19 patients who have been taking CQ or HCQ for less than two weeks, as the likelihood of retinal damage is very low, even at high doses [39].

Although CQ and HCQs are still used in many countries, taking into account the latest data reported from the recent studies indicating an absence of benefit or even an increased risk of HCQ-related death, at the end of May 2020 several European countries suspended the use of HDQs for the treatment of COVID-19 [40].

Although there is still no consistent evidence of the clinical efficacy of HCQ and CQ in the treatment of COVID-19, these 2 medicines have been widely used in clinical practice and, in addition, several new clinical trials are exploring the role of HCQ and CQ in the treatment of COVID-19. Given these facts, the toxicity of HCQ and CQ could pose a considerable problem in future. In this respect, further clinical studies could provide more detailed evidence of HCQ- and CQ-related retinal toxicity in COVID-19 patients, in order to improve the management from an ophthalmological point of view [41].

Several studies should be carried out to introduce specific antiviral eye treatment, aimed at reducing viral loads on the conjunctival tissue of patients (if present) and reducing the transfer rate from an ophthalmological point of view. However, it is very difficult to establish a specific treatment, as there are still many doubts about the ophthalmic consequences of infection with SARS-CoV-2 [42].

**Vitamin D**

Vitamin D is best known for its effects on calcium homeostasis. Vitamin D deficiency is associated with the development of autoimmune diseases close to uveitis, including: IBD, juvenile idiopathic arthritis, SLE and Sjogren´s syndrome [43]. An active form of vitamin D can induce the expression of ACE2 and regulate the immune system through various mechanisms: it maintains the integrity of the epithelium barrier by restoring connections: tight junctions, gab junctions and adherence junctions [44]. In addition, it increases congenital immunity by increasing the production of antimicrobial peptides such as cathelicidin in the respiratory epithelial cells, which have the ability to disrupt bacterial membranes

by electrostatic interactions [45]. Vitamin D also induces cellular immunity by increasing the production of anti-inflammatory cytokines and suppressing pro-inflammatory cytokines, such as TNF-alpha and interferon gamma. This prevents the development of a cytokine storm, which is responsible for ARDS syndrome in COVID-1. In addition, it also affects adaptive immunity by reducing inflammatory Th1- and Th2-mediated responses and suppresses Th17 pro-inflammatory cells as well [46]. In their study of 151 patients, Chiu Zelia et al. showed significantly reduced serum vitamin D levels in patients with active uveitis. They found that vitamin D supplementation is related to uveitis activity in the same way as sun exposure in vitamin D-deficient patients. It therefore seems logical to provide prophylactic supplementation and adjuvant therapy with vitamin D, in order to strengthen the immune system and to prevent and reduce the severity of COVID-19 infection, especially in the elderly population with comorbidities [47].

**Dexamethasone**

In recent decades, corticoids have been used to suppress the immune system's response in various diseases, including rheumatoid arthritis, SLE and others. In the fight against coronavirus infection, the immune system is activated, and then an inflammatory response is triggered. However, occasionally there may be an overreaction of the immune system (cytokine storm), which can lead to respiratory failure, coagulopathy and finally to multiorgan failure and death [48]. The use of corticosteroids is related to the suppression of the immune system and therefore their use is not supported in the initial stage of infection, as it would lead to the suppression of congenital immunity [49]. After several clinical studies investigating the effect of corticosteroids on COVID-19, corticoids have been shown to significantly contribute to the reduction of patient mortality [50]. Dexamethasone reduces the risk of death by one- third in patients with pulmonary ventilation, and by one-fifth in oxygen-dependent patients. Dexamethasone suppresses the immune response, helps in the treatment of inflammations, swellings, such as in allergic and asthmatic patients with inflammation in the airways and lungs, or in patients with painful and inflammatory disease of the joints. Other benefits include a long-lasting effect (with a half-life of about 36 hours), allowing once-daily dosing [51].

A breakthrough in the fight against COVID-19 came from the randomised evaluation of COVID-19 treatment on 16th June 2020. This randomised study was launched in March 2020 as a clinical study to evaluate potential therapeutic treatment options for COVID-19. More than 11 500 patients with confirmed COVID-19 were enrolled in 175 hospitals in the UK. The OXFORD RECOVERY study tested low doses of dexamethasone, lopinavir-ritonavir, hydroxychloroquine, and azithromycin in a randomised manner. Only dexamethasone managed to reduce COVID-19-related mortality rates. The use of dexamethasone at a dosage of 6 mg daily started on 8th June 2020 over a 10-day period, to evaluate the clinical efficacy in 2 014 patients, compared to 4 321 patients who did not receive dexamethasone [52]. The use of dexamethasone did not cause any serious adverse reactions and was ineffective in patients with mild disease progression. However, the OXFORD RECOVERY study has limitations regarding the potential adverse effects and efficacy of dexamethasone in patients with co-morbidities. Concomitant administration of corticosteroids should be limited to patients with severe cytokine storm-related conditions, including ARDS, renal failure, acute cardiac events and elevated serum D-dimer levels. On 19th September 2020, the WHO issued guidance on the use of dexamethasone and other corticosteroids (hydrocortisone or prednisone) for the treatment of COVID-19. The Guideline recommended the use of corticosteroids in serious and critical patients [53].

## CONCLUSION

Some studies suggest that eye symptoms commonly occur in patients with severe COVID-19 pneumonia and that the viral RNA can be detected from the conjunctival sac of these patients. Ophthalmological symptomatology does not appear to be a common manifestation of coronavirus infection in patients with a non-serious course of COVID-19. Despite the fact that conjunctivitis is generally a benign condition, it is an important route of transmission of the virus, and therefore its prevention is the most important aspect that healthcare professionals should remember in order to protect both patients and themselves.

## LITERATURE


1. Nakagawa K, Lokugamage K, Makino S. Viral and cellular mRNA translation in coronavirus--infected cells. Adv Virus Res. 2016;96:165-192. doi: 10.1016/bs.aivir.2016.08.001
2. Lai MM. SARS virus: the beginning of the unraveling of a new coronavirus. J Biomed Sci. 2003;10(6):664-675. doi: https://doi.org/10.1007/BF02256318
3. Martina BE, Haagmans BL, Kuiken T, et al. SARS virus infection of cats and ferrets. Nature. 2003;425(6961):915-915. doi: https://doi.org/10.1038/425915a
4. Van Der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med. 2004;10(4):368-373. doi: https://doi.org/10.1038/nm1024
5. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138(5):575-578. doi: https://doi.org/10.1001/jamaophthalmol.2020.1291
6. Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. Jama. 2020;323(8):707-708. doi: https://doi.org/10.1001/jama.2020.0757
7. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-1263. doi: 10.1126/science.abb2507.
8. Villar J, Zhang H, Slutsky AS. Lung repair and regeneration in ARDS: role of PECAM1 and Wnt signaling. Chest. 2019;155(3):587-594. doi: 10.1016/j.chest.2018.10.022
9. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion

of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827. doi: https://doi.org/10.3389/fimmu.2020.00827
10. Chen L, Liu M, Zhang Z, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. Br J Ophthalmol. 2020;104(6):748-751. doi: https://doi.org/10.1136/bjophthalmol-2020-316304
11. Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. BioRxiv. 2020; doi: https://doi.org/10.1101/2020.01.30.927806
12. Loon S, Teoh S, Oon L, et al. The severe acute respiratory syndrome coronavirus in tears. Br J Ophthalmol. 2004;88(7):861-863. doi: https://doi.org/10.1136/bjo.2003.035931
13. Sadhu S, Agrawal R, Pyare R, et al. COVID-19: limiting the risks for eye care professionals. Ocul Immunol Inflamm. 2020;28(5):714-720. doi: 10.1080/09273948.2020.1755442
14. Zhang X, Chen X, Chen L, et al. The evidence of SARS-CoV-2 infection on ocular surface. 2020; doi: 10.1016/j.jtos.2020.03.010
15. McIntosh K, Dees JH, Becker WB, Kapikian AZ, Chanock RM. Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc Natl Acad Sci U S A. 1967;57(4):933-940. doi: 10.1016/j.jtos.2020.03.010
16. Holappa M, Vapaatalo H, Vaajanen A. Many faces of renin-angiotensin system-focus on eye. Open Ophthalmol J. 2017;11:122-142. doi: https://doi.org/ 10.2174/1874364101711010122
17. Vaajanen A, Vapaatalo H. Local ocular renin-angiotensin system-a target for glaucoma therapy? Basic Clin Pharmacol Toxicol. 2011;109(4):217-224. doi: 10.1111/j.1742-7843.2011.00729.x
18. Seah I, Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. Ocul Immunol Inflamm. 2020;28(3):391-395. doi: 10.1080/09273948.2020.1738501
19. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. 2020;92(6):589-594. doi: https://doi.org/10.1002/jmv.25725
20. Marinho PM, Marcos AA, Romano AC, Nascimento H, Belfort R. Retinal findings in patients with COVID-19. The Lancet. 2020;395(10237):1610. doi:https://doi.org/10.1016/S0140-6736(20)31014-X
21. Vavvas DG, Sarraf D, Sadda SR, et al. Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication. 2020; doi: 10.1038/s41433-020-1084-9
22. Senanayake P deS, Drazba J, Shadrach K, et al. Angiotensin II and its receptor subtypes in the human retina. Invest Ophthalmol Vis Sci. 2007;48(7):3301-3311. doi: 10.1167/iovs.06-1024
23. Casagrande M, Fitzek A, Püschel K, et al. Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. Ocul Immunol Inflamm. 2020;28(5):721-725. doi: https://doi.org/10.1080/09273948.2020.1770301
24. Karampelas M, Dalamaga M, Karampela I. Does COVID-19 Involve the Retina? Ophthalmol Ther. 2020;9(4):693-695. doi: 10.1007/s40123-020-00299-x
25. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19: results from the SERPICO-19 study. EClinicalMedicine. 2020;27:100550. doi: https://doi.org/10.1016/j.eclinm.2020.100550
26. Bettach E, Zadok D, Weill Y, Brosh K, Hanhart J. Bilateral anterior uveitis as a part of a multisystem inflammatory syndrome secondary to COVID-19 infection. J Med Virol. 2021;93(1):139-140. doi: https://doi.org/10.1002/jmv.26229
27. John H Kempen, Michael M Altaweel, Janet T Holbrook, et al. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. Ophthalmology. 2011;118(10):1916-1926. doi: 10.1016/j.ophtha.2011.07.027
28. He M, Xiang F, Zeng Y, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. Jama. 2015;314(11):1142-1148. doi: 10.1001/jama.2015.10803
29. Wong CW, Tsai A, Jonas JB, et al. Digital Screen Time During the COVID-19 Pandemic: Risk for a Further Myopia Boom? Am J Ophthalmol. 2021;223:333-337. doi: 10.1016/j.ajo.2020.07.034
30. Huang H-M, Chang DS-T, Wu P-C. The association between near work activities and myopia in children-a systematic review and meta-analysis. PloS One. 2015;10(10):e0140419. doi: 10.1371/journal.pone.0140419
31. Wang J, Li Y, Musch DC, et al. Progression of Myopia in School-Aged Children After COVID-19 Home Confinement. JAMA Ophthalmol. 2021; doi:1 0.1001/jamaophthalmol.2020.6239
32. Chassiakos YLR, Radesky J, Christakis D, Moreno MA, Cross C. Children and adolescents and digital media. Pediatrics. 2016;138(5). doi: 10.1542/peds.2016-2593.
33. Enthoven CA, Tideman JWL, Polling JR, Yang-Huang J, Raat H, Klaver CC. The impact of computer use on myopia development in childhood: The Generation R study. Prev Med. 2020;132:105988. doi: 10.1016/j.ypmed.2020.105988
34. Abboud H, Abboud FZ, Kharbouch H, Arkha Y, El Abbadi N, El Ouahabi A. COVID-19 and SARS-Cov-2 Infection: Pathophysiology and Clinical Effects on the Nervous System. World Neurosurg. 2020. doi: 10.1016/j.wneu.2020.05.193
35. Xu X-W, Wu X-X, Jiang X-G, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. bmj. 2020;368. doi: https://doi.org/10.1136/bmj.m606
36. Yu A-Y, Tu R, Shao X, Pan A, Zhou K, Huang J. A comprehensive Chinese experience against SARS-CoV-2 in ophthalmology. Eye Vis. 2020;7:1-9. doi: 10.1186/s40662-020-00187-2
37. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246-251. doi:https://doi.org/10.1016/j.jhin.2020.01.022
38. Lenzer J. COVID-19: US gives emergency approval to hydroxychloroquine despite lack of evidence. bmj. 2020;369(10.1136). doi: https://doi.org/10.1136/bmj.m1335
39. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;382(25):2411-2418. doi: 10.1056/NEJMoa2012410
40. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016;123(6):1386-1394. doi: 10.1016/j.ophtha.2016.01.058
41. Nicolò M, Desideri LF, Bassetti M, Traverso CE. Hydroxychloroquine and chloroquine retinal safety concerns during COVID-19 outbreak. Int Ophthalmol. 2020;1-7. doi: https://doi.org/10.1007/s10792-020-01593-0
42. Lan Q, Zeng S, Liao X, Xu F, Qi H, Li M. Screening for novel coronavirus related conjunctivitis among the patients with corona virus disease-19. Zhonghua Yan Ke Za Zhi Chin J Ophthalmol. 2020;56:E009-E009. doi:10.3760/cma.j.cn112142-20200322-00213
43. Rosen Y, Daich J, Soliman I, Brathwaite E, Shoenfeld Y. Vitamin D and autoimmunity. Scand J Rheumatol. 2016;45(6):439-447.doi: 10.3109/03009742.2016.1151072.
44. Zhang Y, Wu S, Sun J. Vitamin D, vitamin D receptor and tissue barriers. Tissue Barriers. 2013;1(1):e23118. doi: 10.4161/tisb.23118
45. Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol. 2009;4(9):1151-1165. doi: 10.2217/fmb.09.87
46. Khemka A, Suri A, Singh NK, Bansal SK. Role of Vitamin D Supplementation in Prevention and Treatment of COVID-19. Indian J Clin Biochem. 2020;35(4):502-503. doi: 10.1007/s12291-020-00908-3
47. Chiu ZK, Lim LL, Rogers SL, Hall AJ. Patterns of vitamin D levels and exposures in active and inactive noninfectious uveitis patients. Ophthalmology. 2020;127(2):230-237. doi: 10.1016/j.ophtha.2019.06.030
48. Gulick RM, Sobieszczyk ME, Landry DW, Hollenberg AN. Prioritizing clinical research studies during the COVID-19 pandemic: lessons from New York City. J Clin Invest. 2020;130(9). doi: https://doi.org/10.1172/JCI142151
49. Isidori A, Arnaldi G, Boscaro M, et al. COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency. J Endocrinol Invest. 2020;43(8):1141-1147. doi: 10.1007/s40618-020-01266-w
50. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506. doi:https://doi.org/10.1016/S0140-6736(20)30183-5
51. Jiang K, Weaver JD, Li Y, Chen X, Liang J, Stabler CL. Local release of dexamethasone from macroporous scaffolds accelerates islet

transplant engraftment by promotion of anti-inflammatory M2 macrophages. Biomaterials. 2017;114:71-81. doi: 10.1016/j.biomaterials.2016.11.004
52. Horby P, Lim WS, Emberson J, et al. RECOVERY Collaborative Group. Dexamethasone Hosp Patients Covid-19-Prelim Rep N Engl J Med. 2020;1-11. doi: 10.1056/NEJMoa2021436
53. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39:2085-2094. doi: 10.1007/s10067-020-05190-5