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COVID-19: Ocular Manifestations and the APAO Prevention Guidelines for Ophthalmic Practices

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Abstract: The World Health Organization declared the Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 a "Pandemic" on March 11, 2020. As of June 1, 2020, Severe Acute Respiratory Syndrome Coronavirus 2 has infected >6.2 million people and caused >372,000 deaths, including many health care personnel. It is highly infectious and ophthalmologists are at a higher risk of the infection due to a number of reasons including the proximity between doctors and patients during ocular examinations, microaerosols generated by the noncontact tonometer, tears as a potential source of infection, and some COVID-19 cases present with conjunctivitis. This article describes the ocular manifestations of COVID-19 and the APAO guidelines in mitigating the risks of contracting and/or spreading COVID-19 in ophthalmic practices.

Key Words: COVID-19, SARS-CoV-2, ocular involvement, preventive measures, ophthalmic practice

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Coronavirus Disease 2019 (COVID-19) can affect patients' eyes in a number of ways. First, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) could directly infect the ocular surface tissue leading to conjunctivitis, which has been reported in the literature since the beginning of the pandemic.[1–4] Both the conjunctiva and cornea are found to express molecule ACE2, which is the target of SARS-CoV-2[5]; viral keratitis is also a theoretically possible ocular manifestation of COVID-19. In a case report, a patient later diagnosed with COVID-19 first presented to the ophthalmologist with keratoconjunctivitis, retrospective analysis of the eye swab taken earlier revealed SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR).[6]

Second, the ocular involvement could be part of the systemic problems. The more severe COVID-19 patients require intensive care in hospital. Many of them developed chemosis, conjunctival injection, exposure keratopathy, and secondary infectious keratitis due to the positive pressure from mechanical ventilation, electrolyte imbalance, and fluid imbalance between body compartments, and so on.[7–9]

Third, the treatment of COVID-19 infection could have ocular side effects, such as Bull's eye maculopathy secondary to the use of considerably higher than safe doses, although over a short period of time, of chloroquine and hydroxychloroquine.[10–13] There is also the potential drug-induced uveitis secondary to the use of anti-viral medications.[14,15] Marmor, who led the American Academy of Ophthalmology revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy, has commented in his editorial that short-term trials (<2 weeks) will have negligible risk even with doses 5 to 6 times the usual 5 mg/kg/day maximum hydroxychloroquine recommendation. His editorial emphasized that retinopathy is not a serious concern with respect to chloroquine and hydroxychloroquine usage for coronavirus.[16] More recently, Marinho et al[17] reported the presence of hyper-reflective lesions in the ganglion cell layer and inner plexiform layers of 12 COVID-19 patients in optical coherence tomography, although these lesions were described as the vascular occlusive conditions. Thus, it still remains uncertain whether these hyper-reflective lesions are due to viral infections or secondary to the vascular complications of COVID-19.

The following sections describe the ocular manifestations, eye as a potential route of spread, and a proposed set of guidelines to mitigate the risks of SARS-CoV-2 spread in the ophthalmic practices.

OPHTHALMOLOGICAL INVOLVEMENT AND MANIFESTATIONS

Conjunctivitis has been reported to be the primary ocular manifestation of COVID-19, with the prevalence ranging from 0.8% to 31.6% of patients.[1,4] In the largest retrospective study involving 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals across 30 provinces in China, the rate of

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conjunctivitis is 0.8%.[1] Wu et al[4] reported 12 (31.6%) of 38 COVID-19-positive patients had conjunctival hyperemia, chemosis, epiphora, or increased secretions, and attributed these to conjunctivitis, although only 2 patients had positive RT-PCR detected on the conjunctival swabs. Wan et al,[18] however, commented on the reported high prevalence (31.6%) of conjunctivitis in Wu et al' article since two-thirds of these patients were in critical conditions; ocular surface disease and ventilator eye could account for a significant proportion of these ocular manifestations in intensive care unit setting. Another 2 studies reported the prevalence of conjunctivitis as 5.9% and 6.6%, respectively, in their confirmed cases of COVID-19.[2,3] Rare neuro-ophthalmic presentations such as diplopia, ophthalmoplegia, and nystagmus secondary to Miller Fisher syndrome and cranial nerve palsies have been reported.[19,20]

Although secondary conjunctivitis is the main ocular manifestation in COVID-19, primary viral conjunctivitis is rare. Nonetheless, because acute red eye is a very common condition that brings patients to clinics or hospitals, general practitioners and eye doctors, should be especially vigilant for other signs of early COVID-19 infection. Ideally, patients should be screened for symptoms, exposure, history, and fever before entering the health facility. Any potential concerns that arise during the examination should be meticulously detailed. Every patient with red eye should be managed as if they were asymptomatic carriers of SARS-CoV-2 or of infectious conjunctivitis.

CAN THE EYE BE A ROUTE OF INFECTION?

SARS-CoV-2 could be present in tears of COVID-19 patients with or without conjunctivitis. Xia et al recruited 30 COVID-19 patients in which only one of them had conjunctivitis. The authors collected 2 conjunctival swab samples at least 1 day apart from each patient for RT-PCR. The virus could only be identified in the 2 samples from a single patient, who was the only subject with conjunctivitis.[21]

In contrast, Zhou et al reported positive RT-PCR results on conjunctival swabs from 2 (1.8%) of their 113 patients without ocular symptoms.[3] However, although the chances of having the virus in tears is small, ophthalmologists and health care workers need to be vigilant still, since COVID-19 patients can possibly have no respiratory symptoms and most importantly, red eye is a very common eye complaint which may possibly bring a SARS-CoV-2 carrier to eye clinics.

It has recently been demonstrated that both the conjunctival and corneal epithelium showed expressions of ACE2 and TMPRSS2, in which the former is the receptor of SARS-CoV-2 and the latter is a protease that facilitates viral entry.[5] However, SARS-CoV-2 is noted to be more infective to conjunctiva than SARS-CoV and it is believed that both the airway and conjunctiva are the main routes of infection of COVID-19.[22]

Aerosols and droplets could potentially be generated in ophthalmic practices such as air-puff noncontact tonometry, syringing of nasolacrimal duct, phacoemulsification, and so on. If the virus-containing droplets/aerosols come into contact with health care personnel, their conjunctival epithelium could be a potential site of viral infection. Moreover, the virus in tears could, in theory, get into the nasopharynx through the suction effect of nasolacrimal system, subsequently infecting the cells lining the airway. Among 64 tear samples obtained from 17 patients without ocular symptoms during the first 3 weeks of presentations, all were tested negative on viral isolation and RT-PCR.[2] Therefore, we believe that COVID-19 could spread through eyes; however, chances of tears harboring virus appear to be relatively negligible in cases without conjunctivitis.

Among eye professionals, staffs with higher seniority, higher rate of contact with confirmed or suspected COVID-19 cases, reporting higher rate of sleep deprivation, and a lack of PPE are at an increased risk of developing COVID-19.[23] In view of the increased risk of conjunctival exposure to virus among eye care professionals, we suggest the routine use of protective goggles by all staff in ophthalmic practices.

Before universal vaccinations or definite treatment become readily available, or herd immunity can be achieved, we will need to co-exist with COVID-19. At present, the incidence of COVID-19 is still escalating worldwide. Herein, we have reviewed the literature on COVID-19 preventions and guidelines from majority ophthalmology societies, that is, American Academy of Ophthalmology, American Society of Retinal Specialist, and United Kingdom Royal College of Ophthalmologists.[2,24–26] In addition, we share our infection control protocols at Prince of Wales Hospital, Hong Kong, in 2003 in response to the SARS epidemic.[27] In this guideline, we are reporting the current common practices of the eye institutions from Asia-Pacific regions: Hong Kong Eye Hospital, Hong Kong; the C-MER Eye Centers, Hong Kong; C-MER Eye Hospitals, China; and Singapore National Eye Center. The guidelines have also been endorsed by the Asia-Pacific Academy of Ophthalmology (APAO) as its official guidelines. We hope that these guidelines will help institutions in the Asia-Pacific regions mitigate the risks of COVID-19 for the patients and health care personnel.

THE APAO GUIDELINES TO PREVENT COVID-19 INFECTION IN OPHTHALMIC PRACTICES

These guidelines are written for consideration of application during the active phase of the pandemic; however, some of these guidelines may still be considered as "New Normal" in ophthalmic practice until the vaccine for COVID-19 is available.

Administrative Measures, Triage, and Preconsultation Measures

1. Pre-appointment screening by telephone call or online channels should be performed shortly before the date of visit to confirm patient and their accompanying person(s) do not have fever, respiratory symptoms; the presenting eye symptoms/complaints are also asked. A travel history should be inquired, but by this time into the pandemic, when almost all nations worldwide are affected, a recent history of travel may be less useful as an indicator for risk assessment, except for travels to specific highest-risk areas.
   a. In case of positive in any part of the screening, the patient shall be advised to self-quarantine at home and defer the appointment unless ophthalmic emergencies are suspected; these patients shall also be advised to seek medical help in case of persistent or worsening symptoms.
   b. Accompanying person should be limited to one except for special circumstances.
   c. Remind the patients regarding the requirement of face mask inside the ophthalmic practice.

2. Triage station could be set up at the entrance for the followings:
   a. Nontouch measurement of body temperature with infrared devices if appropriate.
   b. Questionnaire and declaration for respiratory symptoms, travel history [for both patient and accompanying person(s)].
   c. Hand hygiene with alcohol hand rub before entering the premise.
   d. Remind patients and accompanying persons that wearing face mask is required all the time during their stay in the clinic/hospital, except when being asked by doctors to take off for examination purposes.
   e. Check for evidence of mandatory quarantine (eg, wrist band/bracelet as an identifying sign of person under quarantine in Hong Kong, or an applet on the Wechat platform as an identifying sign of person under quarantine in mainland China).
   f. In cases of patients with significant risk of infection, but requiring urgent attendance, these patients shall be directed to designated consultation room without passing through the general waiting area if possible; and the minimal number of doctor and nurses shall be assigned to provide care to those patients, in a focused manner. Keep a log on personnel entry.
   g. Consider referring high-risk patients to hospital with adequate facilities (eg, negative pressure isolation rooms) for patients and staff safety.
3. Waiting area
   a. Educational materials such as posters of hand hygiene and respiratory hygiene on walls to remind patients of importance of hygiene.
   b. Spacing out patients with special arrangement of sofa/chairs and the use of shields.
   c. Alcohol hand rub and rubbish bins shall be made easily accessible in the clinic.
   d. Clean and disinfect fomites including sofa, door handles, and elevator buttons from time to time (eg, every 2 hours).
   e. Maintain good ventilation within the waiting area. Air purifier could be considered.
4. Suspension of nonurgent services such as electrodiagnostic studies, contact lens clinics, and so on.
5. All staff are required to measure their body temperature, report any respiratory symptoms, and travel or contact history before entering the clinic/ward.
6. Administrative and clinical meetings
   a. Consider video conferences to reduce unnecessary contacts between staff.

Consultation Rooms

1. Commercially available or custom-made slit lamp breath shield[28,29] can be installed on each slit lamp to reduce 46% to 97% of the overspray from a simulated sneeze. Breath shields of comparable sizes mounted more anteriorly at the objective arm are more effective than those hung posteriorly at the oculars.
2. Potential droplets- or aerosol-generating procedures should be avoided as much as possible such as:
   a. Noncontact air puff tonometry
   b. Syringing and probing
   c. Nasal endoscopy
   d. Subconjunctival injection
3. Cleaning and disinfection of equipment
   a. Use disposable instrument if possible.
   b. Immersion of apparatus that comes into contact with patient's ocular surface (eg, prisms of Goldmann Applanation Tonometer, diagnostic contact lens) in 1:10 bleach solution with sodium hypochlorite, or 3% hydrogen peroxide or 70% isopropyl alcohol for at least 5 minutes.
   c. Ophthalmic instruments such as slit lamp, autorefractor, trial lens set, and so on, shall be disinfected with 70% to 75% ethanol or isopropyl alcohol immediately after use.
   d. Wiping and cleaning of chairs, desk, door handle after each patient.
   e. Plastic wrapping of electronic office instruments such as computer keyboards, telephones, vision testing hand remote so that the plastic wrapped surface can be disinfected after each use. Otherwise, disinfectant will enter the device or crevasses will be difficult to access.
4. One-in-one-out policy for patient

Operating Theatre

1. Defer elective operations if necessary
2. Number of staff shall be kept to minimal
3. Avoid general anesthesia since intubation is an aerosol-generating procedure.
   a. If general anesthesia is inevitable, consider a delay in the use of the operating theatre after intubation and extubation to minimize spread of disease by aerosols.
4. Only minimal number of personnel shall stay in the operating theatre.
5. Operations involving high-speed devices (eg, Phacoemulsification, Pars Plana Vitrectomy) are preferably to be performed by senior ophthalmologists to minimize the operating time and risks of needles and blades injuries. Turn on the infusion only after the phacoemulsification handpiece is inside the anterior chamber to minimize potential aerosol generation.
6. Patients should be asked to wear a new face mask underneath the surgical drape to minimize spread of respiratory droplets. Adhesive tapes around the upper edge to ensure tight blockage of droplets from patients' expiration, coughing, or sneezing should be used.
7. In cases of patients with suspected or confirmed infectious diseases who need urgent operations
   a. Doctors and nurses shall wear full personal protective equipment including N95 respirators, gowns, visors or protective goggles, gloves, surgical caps, and shoe covers.
   b. High-risk patients shall be scheduled as the last case of the session to reduce risks of cross-infection.
   c. For vitreoretinal surgeries, consider using silicone oil tamponade, when appropriate, to reduce the number of postoperative visits and risk of early re-operation.
   d. In semiurgent or elective procedures for suspected or high-risk individuals, RT-PCR of nasopharyngeal swabs or deep throat saliva can be considered as a more sensitive tool of risk assessment.
8. Surgical instruments are sterilized according to standard protocol.

Personal Protective Measures

1. All staff of the ophthalmic practice shall be given a refresher lesson on infection control, including routes of infectious

disease transmission and the proper sequence in donning and doffing protective gowns, goggles, gloves, face masks/N95, and surgical cap.
2. Routine use of protective goggles by all staff.
3. Doctors are asked to use alcohol hand rub or proper hand washing with soap/disinfectant after seeing each patient as usual as routine standard precaution.
4. Alcohol hand rubs should not be applied on gloved hands.

CONCLUSIONS

The pandemic is starting to plateau in some nations by this time into the pandemic. There has yet to be a definitive treatment or effective vaccine for COVID-19. Until these become readily available, COVID-19 is not going to just magically disappear. "Normal" ophthalmology service is starting to resume now in the "New Normal" era. Precautionary and mitigation strategies will continue to evolve as more evidence becomes available on the virus tropism and mode of transmission. The role of new technologies using artificial intelligence, 5G, and Internet will become more and more important.[30–36]

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