COVID-19: Update on Its Ocular Involvements, and Complications From Its Treatments and Vaccinations

Timothy P.H. Lin, MBChB*, Chung-Nga Ko, PhD†, Ke Zheng, MD‡,
Kenny H.W. Lai, FCOPhtHK, FHKAM(Ophthalmology)*†,
Raymond L.M. Wong, FCOPhtHK, FHKAM(Ophthalmology)*†,
Allie Lee, FCOPhtHK, FHKAM(Ophthalmology)§, Shaochong Zhang, MD∥,
Suber S. Huang, MD, MBA¶#,
Kelvin H. Wan, MBChB, MRCS*, and Dennis S.C. Lam, MD, FCROphth**

Abstract: The coronavirus disease 2019 (COVID-19) came under the attention of the international medical community when China first notified the World Health Organization of a pneumonia outbreak of then-unknown etiology in Wuhan in December 2019. Since then, COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has appalled the world by spreading at a pandemic speed. Although ophthalmologists do not directly engage in the clinical care of COVID-19 patients, the ophthalmology community has become aware of the close ties between its practice and the pandemic. Not only are ophthalmologists at heightened risk of SARS-CoV-2 exposure due to their physical proximity with patients in routine ophthalmic examinations, but SARS-CoV-2 possesses ocular tropism resulting in ocular complications beyond the respiratory tract after viral exposure. Furthermore, patients could potentially suffer from adverse ocular effects in the therapeutic process. This review summarized the latest literature to cover the ophthalmic manifestations, effects of treatments, and vaccinations on the eye to aid the frontline clinicians in providing effective ophthalmic care to COVID-19 patients as the pandemic continues to evolve.

Key Words: complications from treatment, COVID-19, ocular involvement, vaccine-related eye problems

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The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one of the worst pandemics the world has witnessed, continues to evolve since its advent in December 2019 with the emergence of novel variants.1 As of September 2021, the case count of the COVID-19 pandemic has surpassed 200 million, with a death toll of 5 million. Ophthalmology, like all other medical specialties, has been substantially impacted by the pandemic in its practice.2,3 As the pandemic unfolded, the literature has consistently reported the tropism of the SARS-CoV-2 for the ocular surface and retina due to the extra-pulmonary expression of ACE2 and TMPRSS2 receptors.4,5 This tropism renders the eye a potential portal of entry for SARS-CoV-2.6

Early in the course of the outbreak, it was reported that conjunctivitis could be the first and only clinical manifestation among COVID-19 patients.4,7,8 The SARS-CoV-2 has also been isolated from ocular surface specimens such as tears and conjunctival swabs from patients with COVID-19.9,10 As these initial observations raised cautions against the ocular involvement of COVID-19, there was a surge in reports of ophthalmic manifestations at additional anatomical locations of the eye beyond just the ocular surface directly exposed to the coronavirus in the environment.11,12

Given the devastating effect of the COVID-19 pandemic on public health and its disastrous socioeconomic impact, there has been a relentless search for effective treatment strategies and vaccines to contain the pandemic. Chloroquine (CQ) and hydroxychloroquine (HCQ), which are known to result in retinal toxicity, have initially been proposed as a treatment of COVID-19.13 Steroids used in COVID-19 were also associated with different ocular side effects such as ocular hypertension and endogenous endophthalmitis.14 With the emergency use authorization of novel vaccines, adverse ocular outcomes have also been reported in the latest literature. Although ophthalmologists are rarely engaged in the clinical management of COVID-19 patients, it remains crucial to promptly recognize the ocular findings in these contexts. This review summarized results and data from the latest literature regarding the ophthalmic manifestations of COVID-19 and the adverse ocular outcomes secondary to treatment and vaccination to update ophthalmologists in the face of such patients.

METHODS

A systematic search of the literature on PubMed for articles about ophthalmic manifestations of COVID-19, adverse ocular effects from COVID-19 treatment, and vaccination were conducted. The following key words were used for searching the database: (“coronavirus” OR “covid-19” OR “sars-cov-2”) AND...
RESULTS

A total of 3767 studies were initially identified after searching according to the search strategy above. After title and abstract screening, 295 studies were chosen for full-text evaluation. Finally, 88 studies were included in this study. The ophthalmologic manifestations of COVID-19 in different parts of the eye, and the adverse ocular effects resulting from COVID-19 treatment and vaccination were discussed in the following sections. The ocular findings, management, and outcomes in these cases were summarized in Tables 1 and 2.

Ocular Manifestations

Ocular Surface

The ocular surface was postulated to be a portal of entry and potential route of transmission of SARS-CoV-2 early in the course of the pandemic. Notably, the expression of ACE2 and TMPRSS2 was observed in conjunctival and corneal tissues.1–4 ACE2 serves as the key cell-surface receptor which binds the viral spike protein of SARS-CoV-2,5,6 and the subsequent viral entry involves TMPRSS2, a cell-surface-associated protease.6 In view of the ocular surface susceptibility to the virus, it was hypothesized that primary viral infection of the ocular surface could induce local immune or inflammatory responses and resulting in the reported spectrum manifestations such as conjunctival hyperemia, tearing, and chemosis.17

Coronavirus is known to cause conjunctivitis in humans,18 and conjunctivitis was the most commonly reported ophthalmic manifestation of COVID-19.19 The prevalence of conjunctivitis varied from <1% to 63.6%.20,21 Although conjunctivitis were the initial presenting symptoms of mild COVID-19 cases which were otherwise asymptomatic,22 it was also reported as a late manifestation and on the more severe spectrum of the disease.23,24 A meta-analysis concluded that the overall rate of conjunctivitis in COVID-19 was 1.1%, and it was 3% and 0.7% in severe and nonsevere COVID-19 patients, respectively.25

The common symptoms of conjunctivitis associated with COVID-19 infection included conjunctival hyperemia, foreign body sensation, hypersecretion, chemosis, and epiphora.25 The differential diagnosis of conjunctivitis associated with COVID-19 includes all causes of red eye before the COVID-19 era. In the current context, it may also reflect either the direct viral or immune response to SARS-CoV-2, or ocular surface disturbances in the setting of COVID-19 patients admitted to the intensive care unit (ICU).26 As many cases of conjunctivitis in COVID-19 were the initial or sole clinical feature of the infection, it presents a diagnostic challenge for frontline clinicians to ascertain a diagnosis of COVID-19–associated conjunctivitis. Although it is possible to perform real-time polymerase chain reaction (RT-PCR) of tears and conjunctival secretions, the detection rate of SARS-CoV-2 from ocular surface specimens was low. Wu et al reported that the detection rate of conjunctival SARS-CoV-2 was only 16.7%, as compared with 91.7% from nasopharyngeal swabs in COVID-19 patients with ocular abnormalities.17 Similar findings were confirmed by Zhou et al.27 The low yield of SARS-CoV-2 detection in ocular surface specimens could be attributed to the inclusion of patients with asymptomatic or mild diseases.27 Alternatively, in a recent study that included only patients with moderate to severe COVID-19 without ocular involvement, it has reported a SARS-CoV-2 detection rate of up to 24%.28 This implied the presence of SARS-CoV-2 in the ocular surface was likely related to the disease severity, and the absence of ocular manifestations does not safely exclude the possibility of viral shedding from tears. Therefore, clinicians ought to maintain a high index of suspicion for patients presenting with conjunctivitis or signs of ocular surface inflammation and exercise contact precaution during ocular examination in the COVID-19 era.29 Almost all cases of conjunctivitis related to COVID-19 were self-limiting in nature, which resolved with conservative management without subsequent ocular or systemic sequelae.30

Besides conjunctivitis, ocular surface manifestations of COVID-19 reported in the literature also include keratoconjunctivitis31–33 and episcleritis.34,35 It is notable that as SARS-CoV-2 infection of the ocular surface induces immune and inflammatory dysregulations and can potentially compromise the ocular immune privilege,36 cases of acute corneal graft rejection in patients with COVID-19 have also been reported in the literature.37

Orbit

Although orbital involvement in COVID-19 infection remained uncommon, cases of orbital cellulitis as the presenting clinical feature of COVID-19 in pediatric patients have been reported.38 More severe orbital complications could occur in COVID-19 patients with concomitant systemic comorbidities and the use of immunosuppressive agents such as steroids. Various cases of development of rhino-orbital mucormycosis were reported in COVID-19 patients with pre-existing diabetes mellitus (DM) and subjected to parenteral broad-spectrum antibiotics and steroids.39–46 In these patients, ophthalmic examination revealed extensive edema of the periorbital region with soft tissue necrosis along the eyelids, proptosis, conjunctival edema, exposure keratopathy, decreased visual acuity, and restricted extraocular movement.47 Fatal cases resulting from rhino-orbital cerebral mucormycosis in COVID-19 have also been documented.48 Of note, there was a case series of 13 previously immunocompetent and nondiabetic patients developing new-onset DM complicated by rhino-orbital mucormycosis following COVID-19 infection, in which aggressive surgical intervention including orbital exenteration was necessary.49 Among these 13 cases, 6 received no steroids or immunomodulators.49 Therefore, ophthalmologists and clinicians involved in the care of COVID-19 patients ought to be aware of the possibility of recent-onset diabetes and its potentially devastating orbital consequences.

Uvea

As the ACE2 receptors which bind the SARS-CoV-2 viral spike proteins are also found in other anatomical locations of the eye besides the ocular surface, it is also possible for the virus to produce ophthalmic manifestations at these sites. Following an initial episode of conjunctivitis, panuveitis with the presence of decreased visual acuity, anterior chamber cells, posterior synechiae, vitritis, optic nerve swelling with peripapillary subretinal fluid and choroidal folds was reported as a presenting clinical feature in a patient who was subsequently diagnosed with COVID-19.50
### TABLE 1. Summary of Ophthalmic Manifestations in COVID-19

| Site                     | Manifestation/Diagnosis | Ocular Findings                                                                 | Management                                                                                      | Outcome                                                                 |
|--------------------------|-------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Ocular Surface           | Conjunctivitis          | Conjunctival hyperemia, epiphora, chemosis, foreign body sensation              | Cold compresses, ocular lubricants                                                              | Self-limiting; complete recovery after treatment                         |
|                          | Keratoconjunctivitis    | Ocular discomfort/pain, epiphora, mucus discharge, photophobia, foreign body    | Artificial tears, cyclopelgic eye drops, eye bagging, topical fluorometholone                   | Complete recovery after treatment                                        |
|                          |                         | sensation, erythema and edema of the eyelid, blepharospasm, corneal epithelial defects on fluorescence test |                                                                                                  |                                                                         |
|                          | Episcleritis            | Episcleral injection, epiphora, foreign body sensation, photophobia, positive  | Artificial tears/ocular lubricants, topical fluorometholone                                      | Complete recovery after treatment                                        |
|                          |                         | phenylephrine blanching test                                                   |                                                                                                  |                                                                         |
|                          | Acute corneal graft rejection | Ocular pain, red eye, decreased visual acuity; the presence of keratic precipitates, and microcystic and stroma edema involving the corneal graft | Repeat corneal transplant (penetrating keratoplasty)                                             | Best-corrected visual acuity improved to 20/40 (baseline: 20/80), and the new corneal graft remained clear without signs of rejection |
| Orbit                    | Orbital cellulitis      | Periorbital edema and erythema, chemosis, proptosis, ophthalmoplegia; CT/MRI  | Broad-spectrum parenteral antibiotics, followed by endoscopic sinus surgery, and surgical       | Near resolution of orbital findings and ocular motility                  |
|                          |                         | findings suggestive of paranasal/subperiosteal abscesses                       | drainage of orbital and subperiosteal abscesses                                                 |                                                                         |
|                          | Rhino-orbital mucormycosis | Periorbital edema with soft tissue necrosis, complete proptosis, proptosis,   | Management of hyperglycemia; Systemic antifungal agents; Aggressive surgical interventions including endoscopic sinus debridement surgery and orbital exenteration | Usually poor; fatal cases have been documented                           |
|                          |                         | conjunctival edema, exposure keratopathy, ophthalmoplegia, decreased visual acuity |                                                                                                  |                                                                         |
| Uvea                     | Uveitis                 | Decreased visual acuity, presence of anterior chamber cells, posterior synechiae, vitritis, optic nerve swelling with peripapillary subretinal fluid and choroidal folds | High dose oral prednisone, topical steroid eyedrops and mydriatics | Severe optic atrophy                                                   |
| Retina                   | Abnormal OCT findings   | Hyper-reflective lesions at the level of retinal ganglion cells and inner plexiform layers | Not reported in the literature                                                                 | Not reported in the literature                                           |
|                          | Abnormal fundus examination | Ischemic changes (cotton wool spots, microhemorrhage along the retinal arcade), flame-shaped hemorrhage, macular hemorrhage with hard exudates | Not reported in the literature                                                                 | Not reported in the literature                                           |
|                          | Atypical acute retinal necrosis due to Varicella-Zoster Virus | Decreased visual acuity, papaveutis, necrotizing retinitis | Intravitreal foscarnet and oral valaciclovir                                                   | Significant visual improvement in one eye but residual visual impairment in another eye Complete recovery after treatment |
| Neuro-ophthalmodony     | Miller Fisher Syndrome  | Ophthalmoplegia, ataxia, areflexia                                             | Intravenous immunoglobulin                                                                     | Complete recovery after treatment: residual neurologic deficit suggestive of denervation has also been reported11 |
|                          | Cranial Nerve Palsy     | Palsy of the third, fourth or sixth nerve                                      | Intravenous immunoglobulin                                                                     | Complete recovery after treatment: residual neurologic deficit suggestive of denervation has also been reported11 |
|                          |                         |                                                                                 | Oral prednisone and intravenous immunoglobulin                                                  | Complete recovery after treatment: residual neurologic deficit suggestive of denervation has also been reported11 |
|                          | Myasthenia Graves       | Fluctuating diplopia, ptosis, positive Cogan lid twitch test                   | Intravenous immunoglobulin and oral pyridostigmine methyldinosolone followed by oral prednisone taper | Significant recovery after treatment                                   |
|                          | Neurotomylosis optica   | Bilateral optic neuritis (subacute vision loss, painful extraocular movement, papillodema, relative afferent pupillary defect) | Intravenous immunoglobulin and oral pyridostigmine methyldinosolone followed by oral prednisone taper | Rapid improvement after treatment                                      |
|                          | Ophthalmic artery occlusion (OAO); central retinal artery/vein occlusion (CRAO; CRVO) | Acute painless vision loss, relative afferent pupillary defect, absent accommodation reflex; Also in OAO: Retinal edema, attenuated retinal vessels, papillodema Also in CRAO: cherry-red spot, retinal whitening, retinal arterial narrowing Also in CRVO: dilated and tortuous retinal veins, macular edema, retinal hemorrhage, papillodema; areas of hypofluorescence, vessel wall staining and leakage in fluorescein angiogram | OAO: not reported in the literature CRAO: not reported in the literature CRVO: intravitreal anti-VEGF injection, systemic anticoagulation, systemic steroid | Ophthalmic artery occlusion: not reported in the literature CRAO: not reported in the literature CRVO: significant improvement after treatment |
|                          |                         |                                                                                 |                                                                                                  |                                                                         |
|                          | Ischemic optic neuropathy | Acute painless vision loss                                                      | Aspirin and statin for secondary prevention                                                     | Spontaneous improvement                                                 |
|                          | Cortical visual impairment | Bilateral acute painless vision loss                                           | Systemic anticoagulation followed by dual antiplatelet therapy (oral prednisone)                  | No significant improvement in vision                                     |
|                          | Adie pupil              | Enlarged tonic pupil with poor response to light, cholinergic hypersensitivity | Oral prednisone                                                                                 | Full recovery                                                            |

CT indicates computed tomography; MRI, magnetic resonance imaging; OCT, optical coherence tomography.

**Retina**

OCT changes of the retina were also reported in COVID-19 with hyper-reflective lesions at the level of retinal ganglion cells and inner plexiform layers.51 Fundus examination revealed cotton wool spots and microhemorrhages along the retinal arcade suggestive of ischaemic changes, flame-shaped hemorrhage, and macular hemorrhage with hard exudates.31–53 Despite the presence of retinal manifestations, these patients have no visual symptoms. There was also a report of sight-threatening atypical acute retinal necrosis due to Varicella-Zoster Virus occurring...
## TABLE 2. Summary of Adverse Ocular Outcomes of Interventions and Vaccinations in COVID-19

| Intervention/Vaccine | Adverse Ocular Outcomes | Ocular Findings | Management | Outcomes |
|----------------------|--------------------------|----------------|------------|----------|
| **Pharmacological Treatment** | | | | |
| Remdesivir | Not reported in the literature | | | |
| Anti-SARS-CoV-2 monoclonal antibodies | Not reported in the literature | | | |
| Steroid | Ocular hypertension | Elevated intraocular pressure | Topical glaucoma therapy | IOP returned to the normal level after treatment |
| | Central serous chorioretinopathy | Decreased visual acuity, absent foveal reflex with serous elevation of the retina with ring reflex at the macula; hyper-reflective dots in the posterior vitreous and altered foveal contour with serous detachment in the macular and with pigment epithelial detachment on OCT; hyperfluorescent spots in macular which increased in size and intensity in later films in an inkblot pattern on fluorescein angiography | Cessation of steroid therapy | Spontaneous improvement after cessation of steroid therapy |
| | Endogenous endophthalmitis | Ophthamolplegia, chemosis, exposure keratopathy, Descemet membrane folds, scleral abscess, anterior chamber cells, vitritis | Pars plana vitrectomy with intravitreal antifungal injection, followed by systemic antimicrobial agents | | |
| Hydroxychloroquine/Chloroquine | Unlikely to produce retinal toxicity with short term use in COVID-19; no longer supported by the latest evidence and treatment guidelines for use in COVID-19 | | | |
| **Nonpharmacological Intervention** | | | | |
| Mechanical ventilation | Orbital emphysema | Subcutaneous emphysema involving the conjunctiva and eyelids, palpable crepitus in periorbicular region | Nil | Spontaneous resolution |
| | Exposure keratopathy | Lagophthalmos, chemosis, corneal epithelial changes (punctate epithelial erosions, macroepithelial defects, stromal whitening in the presence of epithelial defects, stromal scar, microbial keratitis) | Not reported in the literature | Not reported in the literature |
| | Mask | Nontraumatic orbital hemorrhage | Ocular irritation and discomfort, exacerbation of pre-existing dry eye disease | Not reported in the literature |
| | Dry eye | Methanol-induced toxic optic neuropathy | Not reported in the literature | Not reported in the literature |
| | Inappropriate ingestion of sanitizer | Bilateral acute painless loss of vision, mid-dilated and nonreactive pupils, optic disc pallor; thinning of the retinal nerve fiber layer in both eyes on OCT; extinguished visual evoked potentials (VEP) in both eyes | | |
| | Vaccination | Pfizer-BioNTech vaccine | Horizontal diplopia, esotropia, abduction deficit | Not reported in the literature | Not reported in the literature |
| | | Moderna vaccine | Decreased visual acuity, ocular pain, red eye, photophobia, cells in the anterior chamber and vitreous | Systemic and topical steroid | Complete resolution or significant improvement after treatment |
| | | AstraZeneca vaccine | Anterior chamber inflammation, cells in the vitreous, retinal folds and subretinal fluid on OCT; Exudative retinal detachment on fluorescein angiography; hyperfluorescent dark dots on indocyanine angiography | Aggressive immunosuppression (intravenous methylprednisolone followed by oral prednisone with concomitant cyclosporine, mycophenolic acid, and infliximab) | Complete resolution after treatment |
| | | Johnson & Johnson vaccine | Arteritic anterior ischemic optic neuropathy | | |
| | | SinoPharm vaccine | Acute loss of vision, relative afferent pupillary defect, optic disc pallor | Systemic steroid and subcutaneous tocilizumab | Not reported in the literature |
| | | | Decreased visual acuity, ocular pain, red eye, photophobia, thickened cornea, Descemet folds | Systemic and topical steroid | Complete resolution or significant improvement after treatment |
| | | | Non-specific nasal field defect, photopsia; Outer retinal layer segmental disruption on OCT | Intravitreal dexamethasone implant | Not reported in the literature |
| | | | Paracentral scotoma; Oval parafoveal hyperreflective lesions on infrared reflectance imaging | Not reported in the literature | Not reported in the literature |
| | | | Progressive bilateral corneal melting, decreased visual acuity | Tetanic penetrating keratoplasty | Not reported in the literature |
| | | | Bilateral acute vision loss, cells in the anterior chamber and vitreous, serous retinal detachment, optic disc hyperemia | Systemic steroid | Complete resolution or significant improvement after treatment |
| | | | Scleral hyperemia, ocular pain, positive phenylephrine test | Topical steroid | Complete resolution after treatment |
concomitantly in COVID-19 patients who had received immunosuppressive agents.\textsuperscript{54}

**Neuro-ophthalmology**

Neuro-ophthalmic manifestations of COVID-19 have also been reported in the literature.\textsuperscript{55} COVID-19 could result in ophthalmoplegia, diplopia, cranial nerve palsies, acute vision loss, and defective pupillary responses as described in the cases below.

Miller Fisher syndrome (MFS), characterized by a triad of ophthalmoplegia, ataxia, and areflexia, may also be associated with COVID-19 infection. MFS is a variant of Guillain-Barre syndrome, defined as an acute peripheral neuropathy after exposure to various viral, bacterial, or fungal pathogens. Classical development of MFS with bilateral ophthalmoplegia, ataxia, and hyporeflexia subsequently improved upon treatment with intravenous immunoglobulin have been reported in COVID-19 patients.\textsuperscript{56,57}

Diplopia and ophthalmoplegia due to cranial nerve palsies in COVID-19 patients have also been reported. Dinkin et al\textsuperscript{58} reported a case of unilateral oculomotor nerve palsy with magnetic resonance imaging (MRI) demonstrating T2 hyperintensity and enlargement of the left oculomotor nerve following COVID-19 development. Falcone et al reported a case of unilateral abducens nerve palsy with MRI findings of lateral rectus muscle atrophy in a middle-aged patient 5 weeks after COVID-19 development.\textsuperscript{59} Similar findings of ophthalmoplegia due to cranial nerve palsies were reported in later studies,\textsuperscript{60–63} and complete recovery was possible upon treatment and recovery from COVID-19.\textsuperscript{64} Alternatively, COVID-19 infection could also result in diplopia due to the development of postinfectious myasthenia gravis. In such case, acetylcholine receptor antibodies were detected serologically alongside antibodies against SARS-CoV-2 one month following COVID-19; the patient showed improvement with the administration of intravenous immunoglobulin and pyridostigmine.\textsuperscript{65} Bilateral subacute vision loss secondary to neuromyelitis optica were present in a young patient simultaneously positive for SARS-CoV-2 and myelin oligodendrocyte glycoprotein (MOG) IgG antibodies.\textsuperscript{66} The patient’s visual acuity improved rapidly after administration of intravenous methylprednisolone followed by oral prednisolone taper.

Infection of SARS-CoV-2 was also associated with systemic inflammatory response and coagulation activation. The binding of SARS-CoV-2 to ACE2 receptors within vascular endothelial cells was hypothesized to result in systemic endothelial dysfunction and a state of hypercoagulability. The state of hypercoagulability has important implications to the eye as occlusion of retinal blood vessels by thromboembolism could result in serious ophthalmic complications.\textsuperscript{66} Acute vision loss in COVID-19 patients attributed to vascular complications of COVID-19 has been reported in the literature. These could manifest as an ophthalmic artery or central retinal artery/vein occlusion and ischemic optic neuropathy.\textsuperscript{67–72} Furthermore, hypercoagulability can also result in vascular occlusion beyond the retina at the central nervous system and manifest as bilateral acute vision loss due to infarct of the visual cortices in bilateral occipital territories.\textsuperscript{76}

Finally, pupillary involvement such as Adie pupil was also documented as a complication following COVID-19 infections.\textsuperscript{77–79}

**Ocular Side Effects Arising From Treatment and Prevention**

As frontline clinicians directly involved in the care of patients, besides promptly recognizing ophthalmic manifestations of COVID-19 so that timely diagnosis and interventions can be arranged, ophthalmologists need to be aware of the potential side effects that may arise from treatments or preventive measures of COVID-19.\textsuperscript{80,81} Currently, therapeutic strategies for COVID-19 patients depend on the disease severity. General management of nonhospitalized patients with mild to moderate disease involves supportive care, isolation, and serial follow-up. In hospitalized patients, among patients with severe COVID-19 requiring supplemental oxygen for respiratory support, there is evidence supporting the use of the antiviral remdesivir, dexamethasone, and monoclonal antibodies.\textsuperscript{82} Bamlanivimab, etesevimab, casirivimab, and sotrovimab are anti–SARS-CoV-2 monoclonal antibodies that have received emergency use authorizations from the Food and Drug Administration of the United States.\textsuperscript{82}

At the time of review, there have been no reports on adverse ocular effects of remdisivir and anti–SARS-CoV-2 monoclonal antibodies in the literature. Steroid is well known to produce ocular hypertension, which may necessitate glaucoma therapy to reduce the intraocular pressure (IOP) to eliminate the symptoms associated with the acute surge in IOP and prevent potential visual field loss.\textsuperscript{83} The administration of steroids for treatment of COVID-19 was also reported to result in central serous choroiditis.\textsuperscript{84} In a series of 7 COVID-19 cases complicated by endogenous endophthalmitis, 6 cases were secondary to mucormycosis-associated sinusitis or systemic fungal infections, and all had received intravenous corticosteroid for COVID-19.\textsuperscript{85} As

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**TABLE 2.** (Continued)

| Intervention/Vaccine | Adverse Ocular Outcomes | Ocular Findings | Management | Outcomes |
|----------------------|------------------------|----------------|------------|----------|
| Sinovac vaccine\textsuperscript{112} | Acute macular neuroretinopathy | Acute vision loss, hyperreflectivity of the outer plexiform layer, Henle fiber layer, and outer nuclear layer on OCT nasal to the unchanged pigment epithelium detachment | Conservative treatment | Complete resolution |
| | Paracentral acute middle maculopathy | Inferior scotoma, dot hemorrhage superior to the fovea; superior enlargement of the foveal avascular zone on OCT angiography | Not reported in the literature | Not reported in the literature |
| | Episcleritis | Details not provided in the literature | / | / |
| | Subretinal fluid | Details not provided in the literature | / | / |
| | Bilateral transient visual field defect | Left congruous hemianopia | Nil | Spontaneous resolution |

IOP indicates intraocular pressure; OCT, optical coherence tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
predispose patients to the development of dry eye.95

The use of HCQ and CQ during the early COVID-19 period sparked heated debates within and beyond the ophthalmology community. There were initial concerns regarding its potential retinal toxicity and the development of Bull’s eye maculopathy associated with its use.13 Nevertheless, it is uncommon to develop retinopathy before 10 or more years of using such medications at the American Academy of Ophthalmology’s recommended dosage of <5 mg/kg real weight.86 As HCQ and CQ use in COVID-19 is only within a short period, it is extremely unlikely to produce such ocular complications.13,87 However, most of the evidence has shown no benefit of HCQ as compared to the standard of care across the different severities of COVID-19, and both drugs are no longer recommended by the latest evidence and treatment guidelines.82,88,89

Complications from nonpharmacological interventions for COVID-19 patients have also been reported in the literature. Patients who developed severe pneumonia and respiratory failure related to COVID-19 often required intensive care and ventilatory support. The development of orbital emphysema extending from the chest to the face and periocular crepitus has been documented in COVID-19 patients placed on positive end-expiratory pressure ventilation.90,91 Furthermore, in patients who require advanced ventilatory support in the intensive care unit, exposure keratopathy was previously reported to develop in >50% of mechanically ventilated patients.92 This can be attributed to the use of sedation and neuromuscular blocking agents which reduces the orbicularis muscle tone and prone positioning of the patients, both of which increase the risk of exposure keratopathy.26,93

The World Health Organization (WHO) has endorsed face masks to prevent transmission of COVID-19. Nevertheless, inappropriate use of masks can result in ocular complications. Nontraumatic orbital hemorrhage presented as sudden orbital-protrusion from the palpebral fissure has been reported in COVID-19 patients with positive end-expiratory pressure ventilation.93,94 Furthermore, patients who require advanced ventilatory support in the intensive care unit, exposure keratopathy was previously reported to develop in >50% of mechanically ventilated patients.92 This can be attributed to the use of sedation and neuromuscular blocking agents which reduces the orbicularis muscle tone and prone positioning of the patients, both of which increase the risk of exposure keratopathy.26,93

At the beginning of the rapidly evolving pandemic, public fear and confusion regarding appropriate public health measures and behaviors to eliminate COVID-19 transmission have fuelled the dissemination of erroneous information and false beliefs. A patient developed bilateral complete vision loss within 24 hours following intentional ingestion of alcohol-based sanitizer solution.95 Alcohol-based sanitizers usually contain ethanol, isopropyl alcohol, n-propyl alcohol, or their combinations as the major component. These agents had not been previously reported to result in vision loss. Retrospective investigation revealed that the patient in this case likely ingested a sanitizer that contained methyl alcohol (methanol), which is rapidly absorbed and metabolized into formaldehyde to produce ocular toxicity.

Conclusions

The SARS-CoV-2 emerged in late 2019 when the entire world knew little of it. As the pandemic continues to evolve with the advent of new viral variants, the medical community also witnesses a boom in knowledge and information covering all
facets of the pathogen. This review summarized the ophthalmic manifestations and adverse ocular effects resulting from therapeutic and preventive measures of COVID-19, which can guide ophthalmologists in their clinical encounters of COVID-19 patients in the battle ahead.

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