



## Special report

# Eye and SARS-CoV-2 in 2022

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### HIGHLIGHTS

Although ocular symptoms are relatively rare in COVID-19 patients, the most common are conjunctivitis and retinal lesions in more severe cases. COVID-19 vaccinations may be associated with ocular adverse events.

### ABSTRACT

The ocular symptoms of COVID-19 are rare, however, the most common is conjunctivitis. Retinal changes, including dilated veins, tortuous blood vessels, intraretinal hemorrhages, and cotton balls are much less common. In addition, there may be swelling of the eyelids, their irritation, most often in combination with conjunctival hyperemia. Moreover, COVID-19 infection may be accompanied by different neuro-ophthalmic disorders and, in rare cases, by mucormycosis. Various ocular complications have been reported following vaccination against COVID-19, including facial nerve palsy, abduction nerve palsy, acute macular neuro-retinopathy, superior ocular vein thrombosis, corneal transplant rejection, membrane inflammation vascular eye disease, central serous chorioretinopathy, reactivation of Vogt-Koyanagi-Harada disease and onset of Graves' disease. Chemical eye injuries in children caused by hand sanitizers have also been reported. Although numerous studies have confirmed the antiviral activity of benzalkonium chloride, its role in this regard requires further research.

**Key words:** ocular signs, SARS-CoV-2, COVID-19

## INTRODUCTION

COVID-19 pandemic continues to pose serious health and economic challenge worldwide. After 2 years, attempts can be made to summarize the accumulated knowledge on the transmission and ocular symptoms of SARS-CoV-2 infection, post-vaccination ocular manifestations, antiseptics-related ocular damage in children and antiviral activity of some substances commonly found in eye drops, such as benzalkonium chloride (BAK). The following article is a discussion of the literature review on the above issues in the years 2020–2021.

## OCULAR PENETRATION OF THE VIRUS

The angiotensin converting enzyme 2 (ACE2) receptor, the major SARS-CoV-2 binding protein, is present in relatively high concentrations in the conjunctiva, cornea, and retina, allowing viral tropism to the eye and potentially transmission to ocular structures [1, 2]. Although the main route of SARS-CoV-2 transmission is through the respiratory tract, transmission of the virus to the eye may also occur in rare cases. Initial reports from Wuhan, China in 2019 described the spread of SARS-CoV-2 among physicians wearing N95 masks but without eye protection [3]. The proposed mechanism of transmission to the eye involves binding of the virus to ACE2 receptors on the surface of the conjunctiva, followed by transmission to the airways via the nasolacrimal duct [4].

However, the likelihood of SARS-CoV-2 transmission to the eye is generally considered low. The published conjunctival smear rates in patients with SARS-CoV-2 have ranged from 0% to 16.7% and are probably even lower in patients without ocular symptoms, suggesting limited viral titers in the eye. Patients with confirmed SARS-CoV-2 infection usually did not show excretion of virus particles in tear secretions [5]. Certain conjunctival enzymes, including ADAR-1 and APOBEC3A, are thought to provide natural antiviral protection, reducing virus titers in the conjunctiva and minimizing the risk of their further transmission [6]. It is currently recommended that goggles or face shields be worn by healthcare workers with a high potential risk of transmission to the eye, as well as slit lamp shields [5, 7–9]. Ophthalmologists may be particularly exposed to SARS-CoV-2 particles during aerosolization procedures, including tonometry testing, as well as slit lamp examination.

## OCULAR LESIONS IN THE COURSE OF COVID-19 (TAB. 1)

TABLE 1

The most common ocular manifestations associated with SARS-CoV-2 infection.

- Conjunctivitis and conjunctival congestion
- Eyelid lesions
- Retinal and choroidal pathologies
- Inflammatory pathologies (keratitis, epididymitis, uveitis)
- Neuro-ophthalmic pathologies
- Naso-orbital mucormycosis

The most common ocular manifestation of COVID-19 is conjunctivitis, particularly conjunctival congestion and discharge from the conjunctival sac [2, 10, 11]. These occur in 4.8–7.7% of COVID-19 patients [2, 12, 13] and up to 32% of hospitalized patients [14].

Conjunctivitis usually begins 1–2 weeks after the onset of symptoms [14]. Interestingly, it may be the only symptom present in otherwise asymptomatic children [15, 16]. Although conjunctivitis itself is largely benign and self-limiting, it can occur in up to 55% of children with COVID-19-related polyarthritis, a more serious condition requiring urgent attention. Therefore, children with conjunctival symptoms should be investigated for other associated symptoms, including rash, lymphadenopathy, and limb edema [17]. Swelling of the eyelids was found in 0.9% of COVID-19 patients, their irritation in 4.9% of individuals, most often in combination with conjunctival congestion [11, 18–20].

Retinal lesions were mainly observed in hospitalized COVID-19 patients with moderate to severe disease [5]. The pathomechanism of retinal damage is still not understood, but it may result from direct cytotoxic effects of the virus or, in the case of microangiopathy and vasculitis, from endothelial cell damage [1, 5].

One cross-sectional study of asymptomatic COVID-19 patients showed dilated venous vessels (27.7%), tortuous blood vessels (12.9%), intraretinal hemorrhages (9.3%), and cotton wool spots (7.4%) [21]. Edema of the optic nerve disc and whitish retinal staining have also been described in isolated cases [22–25]. Systemic inflammation and propensity for venous and arterial thromboembolic complications in COVID-19 predisposes patients to the development of arterial or venous retinal obstruction, as described in several patients with severe COVID-19 [22, 26–28].

Inflammatory conditions of the eye, including cornea, epithelium, or uvea, are rarely described as occurring in COVID-19 patients [11, 29–31]. The absence of SARS-CoV-2 in the conjunctiva in most cases of this type of inflammation suggests that a cytokine-induced inflammatory response (rather than direct viral action) may play a major role in the pathogenesis. Furthermore, it is worth remem-

bering that dysregulated and systemic immune responses in patients with COVID-19 may also predispose to the development of inflammatory ocular pathologies such as uveitis.

Neuro-ophthalmic manifestations in COVID-19 patients are usually rare and may result from direct viral neuroinvasion, virus-induced immune responses and cytokine storms, and delayed post-infectious immune activation [32]. These include optic nerve disc edema, optic neuritis in young patients after COVID-19 has resolved (may reflect a para-infectious demyelinating syndrome) [33], cranial nerve neuropathies (most commonly, paralysis of the inferior alveolar nerve) [34–37], double vision (possibly due to inflammatory demyelinating neuropathy) [34].

Most patients did not require specific treatment, and symptoms resolved spontaneously within 1–2 weeks in the vast majority of cases.

Double vision, ophthalmoplegia and eyelid drooping have also been described in the course of Guillain-Barré and Miller-Fisher syndromes, probably caused by post-viral inflammation with COVID-19 [38–41]. Many of these patients experienced at least partial resolution of symptoms after intravenous immunoglobulin treatment.

Mucormycosis is a life-threatening infection caused by filamentous molds that most commonly causes localized nasal or nasal-orbital symptoms or, less commonly, disseminated infection. These infections are classically associated with immunocompromised and diabetic patients. Patients with severe COVID-19 often have comorbidities that may predispose them to mucormycosis, and the use of systemic corticosteroids as standard therapy likely further contributes to its development [42–45].

## OCULAR ADVERSE EVENTS FOLLOWING COVID-19 VACCINATION

There are a growing number of reports in the literature on ocular adverse events following COVID-19 vaccination. One major review of this issue discussed 23 articles reporting ocular lesions associated with COVID-19 vaccination [46]. Ocular complications were reported in 74 patients-including facial nerve palsy, paralysis of the abducens nerve, acute adrenomyeloneuropathy (AMN), superior ocular vein thrombosis, corneal graft rejection, uveitis, central serous chorioretinopathy, reactivation of Vogt-Koyanagi-Harada syndrome (VKH) and onset of Graves-Basedow disease [46]. Complications occurred in 7 cases after AZD1222 vaccine, Oxford/AstraZeneca, 15 cases after BNT162b2 vaccine, Pfizer-BioNTech, and 1 case after BBIBP-CorV vaccine, Sinopharm [46]. The published descriptions primarily include retrospective case groups or single case reports and inherently provide insufficient information to establish association or causality. Never-

theless, the described presentations resemble the reported ocular manifestations of COVID-19. Therefore, it appears that the human immune response to COVID-19 vaccination may be involved in the pathogenesis of ocular side effects after COVID-19 vaccination.

A recently published original article involving a retrospective analysis of cases from a region in Italy identified 34 patients with uveitis and other ocular complications after COVID-19 vaccination [47]. Three cases of herpetic keratitis, two anterior scleritis, five (AU), three retinitis due to toxoplasma, two reactivations of VKH syndrome, two pars planitis, two retinal vasculitis, one bilateral uveitis and onset of Behçet's disease, three multiple evanescent white dot syndromes (MEWDS), one acute AMN, five retinal vein occlusions (RVO), one non-arteritis anterior ischemic optic neuropathy (NAION) three activations of inactive choroidal neovascularization (CNV) secondary to myopia or uveitis and one central serous chorioretinopathy (CSCR). The mean time between vaccination and onset of ocular complications was 9.4 days (range 1–30 days). 23 cases occurred after Pfizer-BioNTech vaccination (mRNA BNT162b2), 7 after Oxford/ AstraZeneca vaccination (ChAdOx1 nCoV-19), 3 after ModernaTX vaccination (mRNA-1273) and 1 after Janssen Johnson & Johnson vaccination (Ad26.COV2) [47]. It should be noted, that the number of reported cases of ocular adverse events after vaccination is extremely small – at the end of 2021, approximately 60% of the world population was vaccinated and approximately 10 billion vaccinations were performed [48].

## UNINTENTIONAL OCULAR CONSEQUENCES OF HAND DISINFECTANT USE

Numerous eye injuries in children due to inadvertent contact with alcohol-based hand sanitizers have been described [49, 50]. Martin et al. found a sevenfold increase in eye exposure in children in 2020, with a corresponding increase in the number of corrective surgeries [49].

Children's exposure is most likely due to the placement of the sanitizer dispenser near their face. Dispensers, often pressure-controlled with a pedal, allow for unit doses of disinfectants. However, they typically placed about 1 m high, i.e., at the eye level of young children. In addition, the delay in eye washing due to the lack of access to water or the viscosity of some formulations is very harmful to the ocular surface [49]. Therefore, efforts should be made to isolate automatic disinfectant dispensers from children. Where possible, it is important to redesign dispensers. Signage warning of the potential danger of eye contact must be placed. In addition, education regarding conduct in the event of an injury needs to be introduced – in an emergency, any clear liquid can be used to rinse the eye after exposure to chemicals. Furthermore, parents need to know the

importance of examining their child's eyes after a chemical injury, as early diagnosis and treatment will reduce the long-term consequences of eye damage.

## EFFICACY OF BENZALKONIUM CHLORIDE (BAK) AGAINST CORONAVIRUSES

Benzalkonium chloride is a substance classified as a quaternary ammonium compound (QAC). It is a surfactant whose activity changes the structure of the lipid layer – it is absorbed by negatively charged phosphate heads of phospholipids in the lipid layer. An increase in the concentration of BAK causes a decrease in the fluidity of the bacterial cell membrane, hydrophilic gaps are formed in it, which consequently leads to increased permeability and its damage [51]. Features of BAK that give it an advantage over alcohol-containing disinfectants include lower toxicity, less skin irritation, and non-flammable nature.

According to the US Center for Disease Control and Prevention (CDC) [52], there is currently no better alternative for skin disinfection than agents containing ethanol over 60% or isopropanol 70%. Benzalkonium chloride, along with ethanol and isopropanol, is approved by the US Food and Drug Administration (FDA) for use in hand disinfectant formulations for medical personnel. However, the CDC reports that available scientific evidence indicates that BAK is less effective against certain bacteria and viruses compared to the above-mentioned alcohols.

The authors reviewed recent scientific literature to evaluate the antiviral efficacy of BAK. Schrank et al. presented microbiological data obtained with BAK at different concentrations and highlighted its variable efficacy in reducing viral activity [53]. Furthermore, the researchers summarized the available data on the efficacy of BAK in inactivating different strains belonging to coronaviruses. Among others, they reported that in a study by Pratelli et al. that analyzed the effect of disinfectants on coronavirus present in dogs, the authors noted that BAK did not reduce viral load, although it induced significant morphological damage to the virus [53]. In addition, Ansaldi et al. demonstrated that BAK 1% reduced SARS-CoV-2 virus replication after 5 min of treatment; however, viral RNA was detectable by RT-PCR even after 30 min of exposure [53]. A study by Meister et al. on the antiviral efficacy of oral rinses against SARS-CoV-2 showed that a product containing BAK 0.035% significantly reduced virus infectivity up to undetectable levels [54].

Another study on three surface disinfectants (two of which contained BAK 0.5%) demonstrated the efficacy of BAK. Exposure times were 30 min and 60 min in three parallel experiments conducted on three organic materials: albumin 0.3%, fetal calf serum 10%, and albumin 0.3% with sheep erythrocytes. Agents containing BAK 0.5% showed a more than fourfold reduction of SARS-CoV-2 virus, re-

sulting in inactivation below its detection level [55]. Kampf et al. collected available data on the effects of different disinfectants on the inactivation efficiency and persistence of viruses (SARS, MERS, HCoV) on different surfaces [56]. BAK at concentrations of 0.05–0.2% was found to be less effective than other antiviral agents tested [56].

Ogilvie et al. analyzed the efficacy of alcohol-free disinfectants and highlighted that a hand sanitizer containing BAK effectively inactivates SARS-CoV-2 [57]. On this basis, it was approved by the FDA for hand disinfection in COVID-19 prevention. Pedreira et al. summarized the effectiveness of disinfection and control of SARS-CoV-2 in the food industry [58]. According to the authors, BAK is effective in controlling and inactivating coronaviruses, although it requires much longer exposure to achieve the desired effect [58].

Hirose et al. analyzed the efficacy of various disinfectants including ethanol, isopropanol, BAK, and chlorhexidine in inactivating SARS-CoV-2 and influenza A virus. Studies have been performed in vitro and on a skin model collected during autopsy procedures [59].

### Antiviral efficacy of benzalkonium chloride in vitro [59]:

- BAK was significantly less effective compared with ethanol at concentrations of 80%, 60% and 40% and isopropanol at concentration of 70%, whose logarithm of viral load reduction was above 4 in each case.
- BAK at a concentration of 0.05% was least effective at all three application times, i.e., after 5 s, 15 s, and 60 s, and the logarithm of viral load reduction was 1.33, 1.75, and 2.17, respectively.
- BAK at a concentration of 0.2% was ineffective at short application times, i.e., after 5 s and 15 s, during which the logarithm of viral load reduction was 1.83 and 2.42, respectively. Application of BAK for 60 s increased the eradication efficiency of SARS-CoV-2 virus (logarithm of reduction was 3.00).

### Antiviral efficacy of benzalkonium chloride in a skin model study [59]:

- The study showed that BAK has higher efficacy in inactivating novel coronavirus on skin model than in vitro.
- The efficacy of BAK at a concentration of 0.05% was low at all three application times, i.e., after 5 s, 15 s and 60 s, and the logarithm of viral load reduction was 2.03, 2.19 and 2.36, respectively.
- Increasing the concentration of BAK to 0.2% resulted in an increase in disinfection efficiency at all three application times. The logarithm of reduction for 5-, 15-, and 60-second applications was 2.72, 2.92, and 3.19, respectively.



- As in vitro, ethanol at concentrations of 80%, 60% and 40% and isopropanol 70% proved to be most effective in eradicating the virus on the skin model (logarithm of reduction above 4).

In conclusion, the literature review conducted on the efficacy of BAK against coronaviruses is ambiguous and inconclusive. Some studies have confirmed that BAK is effective in deactivating the virus; however, it is significantly less effective than alcohol formulations. The efficacy of BAK increases with concentration and with time of application; however, this may be influenced by its toxicity or adverse effects.

#### CORRESPONDENCE

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#### CONCLUSIONS

- Although ocular manifestations in COVID-19 patients are relatively rare, conjunctivitis and retinal changes in more severe cases are among the most common (tab. 1).
- The ophthalmologist is potentially exposed to SARS-CoV-2 virus infection, so personal protection in the form of goggles and a slit lamp shield is recommended.
- COVID-19 vaccination may be accompanied by ocular adverse events.
- In recent years, an increasing number of cases of hand-sanitizer chemical trauma to children's eyes have been observed, necessitating appropriate preventive measures.
- Although numerous studies have demonstrated the antiviral activity of BAK, its role in this regard needs further investigation.

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