Azzolini and colleagues that SARS-CoV-2 transmission may be mediated by ocular fluid and that attention should be given to the possibility of ocular disease in patients with suspected COVID-19 infection.

Letters

COMMENT & RESPONSE

Live and Replication-Competent SARS-CoV-2 in Ocular Surfaces

To the Editor We read with great interest the research by Azzolini and colleagues. From the virologic perspective, the authors showed that SARS-CoV-2 RNA was found on the ocular surface in 52 of 91 patients with COVID-19 (57.1%; 95% CI, 46.3-67.5), and 10 of 41 patients with nasopharyngeal swab results available the same day or within 2 days had positive results with conjunctival swab and negative results with nasopharyngeal swab. We believe it is useful to elucidate the role of the ocular apparatus and lacrimal secretions in COVID-19 pathogenesis, both in the interest of infection control and diagnosis. To this end, more in-depth bibliographic research may be of help as the scientific interest on ocular involvement in COVID-19 and its route of transmission has been high since the beginning of the pandemic. As shown by Roehrich et al, among others, both corneal and conjunctival epithelium specimens obtained from cornea donors express ACE2, DC-SIGN or DC-SIGNR, and TMPRSS2, which are recognized cell receptors for SARS-CoV-2. This evidence points to the SARS-CoV-2 tropism for ocular apparatus. In addition, the viral replication competence in conjunctival mucosa has been demonstrated in ex vivo and in vitro cultures, suggesting that the conjunctiva is a potential virus reservoir for SARS-CoV-2 infection and may represent an additional portal of infection with implications for both transmission and contagion.

We have previously reported that live and replication-competent virus was isolated directly from the ocular fluid collected from 1 of the COVID-19 patients in Italy who was admitted to the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome, Italy, at the end of January 2020. The presence of infectious virus and the prolonged detection of SARS-CoV-2 RNA in longitudinal ocular samples (when viral RNA was at lower levels or even undetectable in nasal swabs) suggest a sustained viral replication in the ocular compartment. Overall, these data corroborate the conclusions of Azzolini and colleagues that SARS-CoV-2 transmission may be mediated by ocular fluids and that attention should be given to the possibility of ocular disease in patients with suspected COVID-19 infection.

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In Reply We read with great interest the letter from Colavita and colleagues on our article, and we add some considerations here in light of newly available literature. Colavita and colleagues demonstrated the presence of the replication-competent virus from external ocular fluids at the beginning of the pandemic. Our study found the virus in 52 of 91 patients with COVID-19 (57.1%), and these findings were possible thanks to strict procedural measures. It is interesting to note that very similar percentages have recently been found in SARS-CoV-2 RNA prevalence in the corneas of patients with COVID-19 viremia, albeit in small samples (6 of 11 eyes [55%]). Given the new evidence available in the literature, it should be noted that, as conjunctival swabbing has been performed by a rolling technique, it is possible that part of the RNA found by reverse transcription-polymerase chain reaction does not come only from fluid tears but also from the cytoplasm of conjunctival cells lysed and collected during swab procedures. New perspectives could come from other investigations, including genetic studies. For example, we started considering our samples stored at ~80°C to evaluate the expression of specific membrane markers in patients with SARS-CoV-2 infection and the activation of the local immune system.

There are 2 pathways by which ocular exposure could lead to systemic transmission of the SARS-CoV-2 virus. The first is direct infection of the ocular tissues, including cornea, conjunctiva, lacrimal gland, and meibomian glands, from virus exposure. There is evidence now that SARS-CoV-2 can infect conjunctiva in vitro, but how often this occurs in patients and whether this can lead to transmission of the virus systemically is still unknown, in part because there is evidence of interindividual variability in the expression of the receptor. Histopathologic findings in conjunctiva demonstrate alteration in goblet cells and epithelial cells, suggesting an interaction between the virus and the conjunctiva.

The other pathway of systemic transmission is through tears. Although it has been established that tears are a
potential reservoir for SARS-CoV-2, we still lack knowledge on the path of systemic contagion in vivo through the lacrimal lake, the lacrimal canals, and the nasolacrimal duct, the physiological channel for the outflow of tears from the conjunctiva into the throat. Many in vivo parameters can alter tear outflow, such as dry eye syndrome, the variability of blinking, or occlusions of tear outflow passages causing a lower tear viral load toward the throat. The conjunctiva also hosts several bacterial species in its fornix, and it is specifically equipped with immune-acquired defense mechanisms mediated by conjunctival tissue (ie, lymphatic follicles).

For these reasons, systemic contagion from the ocular surface can be variable. Further studies will be necessary to understand the infectivity potential of tears in different situations and better modulate ocular protections.

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CORRECTION

Labeling Errors in Figure: In the Original Investigation titled “Assessment of Cumulative Incidence and Severity of Primary Open-Angle Glaucoma Among Participants in the Ocular Hypertension Treatment Study After 20 Years of Follow-up,” published in the May 2021 issue of JAMA Ophthalmology, 4 rows in the table below the graph in Figure 2A were incorrectly labeled. The rows labeled “Observation” should have been labeled “Medication,” and the rows labeled “Medication” should have been labeled “Observation.” This article was corrected online.