

The SARS-CoV-2, tears, and ocular surface debate: What we know and what we need to know

“No great advance has ever been made in science, politics, or religion, without controversy,” so said the 18th century American Reformer Lyman Beecher. The same holds for the subject of this editorial. The significance of accurately knowing the ocular tropism of the SARS-CoV-2 virus, the preferred locations, the viral load, eye to eye transmission, eye to respiratory transmission and vice-versa, cannot merely be overemphasized. A proper search for any answer begins with framing the right questions and qualifying them where needed. What do we know about the cellular interactions of the virus with ocular tissues? Is the conjunctivitis really virus related? Are coronaviruses routinely shed in tears? What is the detection window? What are the plausible mechanisms for the virus transfer between the respiratory and ocular tissues? How good are our detections systems? How reliable is the current evidence with its several limitations? How would this knowledge impact our practice? The confusion and haze can be cleared to a reasonable extent if a serial and scientific dissection of this issue is carried out logically.

It would be useful to start the analysis by combining the beginnings and the end. In this context, interactions of the virus with conjunctival epithelial cells would be the beginning, and conjunctival transmission would be the end. SARS-CoV-2 is known to interact with two major players on the cell surface for its entry into the host cells; Angiotensin-converting enzyme 2 receptor (ACE2) and transmembrane protease serine 2 (TMPRSS2).^[1,2] The conjunctival and corneal epithelia have demonstrated the presence of both ACE2 and TMPRSS2, which led to the speculation of direct virus infection and transmission.^[1-3] Interestingly, if this were true, conjunctivitis would not have been so low (0.8%) in huge series, and conjunctival route transmission could have been a major transmission mode. How can this discrepancy be explained? There is evolving evidence that not only are the number of ACE2 receptors less on the ocular surface as compared to the pulmonary tissue but also their binding capacity is low.^[3-5] Besides, the lactoferrin in tears is known to prevent attachment of SARS-CoV to heparan sulfate proteoglycans, an important assistant to subsequent ACE2 receptor binding.^[6] Also, the Serum IgA may be playing a role in neutralizing the viruses as evident in earlier animal models of coronaviruses.^[7,8] However, subsequent mutant variants of SARS-CoV-2 may be able to invade conjunctival epithelial cells and potentially change the disease pathogenesis.

The plausible mechanisms for the presence of a virus on the ocular surface could be exogenous (aerosol contact), self-inoculation, or poorly fitted masks, where the exhaled air can frequently come in contact with the ocular surface, and hematogenous infection of the lacrimal gland during viremia. Viral detection in the tears and ocular surface would depend on numerous factors, including viral shedding, viral load, sampling techniques, sampling timing related to the disease, investigative modality, and the host immune response. Several studies have demonstrated that either very few patients or none have viruses in tears and conjunctival surfaces.^[7,9-11] Is the yield low? Is something wrong with the techniques? Does the presence of the virus on the ocular surface translate to clinical infection? Can conjunctiva transmit SARS-CoV-2 systemically?

These questions have interesting answers. The viral load is much less in conjunctival samples than nasopharyngeal, and this should not be surprising.^[12] RT-PCR is a common modality to detect the viruses and the ocular results should be studied in the context that its specificity is high, but the sensitivity is significantly low (around 50–60%).^[5,7,13] The absence of a virus on RT-PCR does not necessarily mean the virus is absent in tears or conjunctival surface. Conversely, virus may not be detected in the presence of conjunctival symptoms.^[10,14] The window for detection of the virus in the conjunctival cul-de-sac is also controversial. Some advocated 3 days window in a positive patient, while others have persistently found them up to 2 weeks.^[9,15,16] The mere presence of the virus on the ocular surface or in tears does not appear to translate into an infection necessarily.^[17] Also, there is no direct evidence of virus replication on the ocular surface.^[15] Animal studies have shown that following SARS-CoV-2 exposure to the conjunctiva, it could be detected in the respiratory and intestinal tissues for a few days.^[18] However, the same was not true for virus isolation from the conjunctival swabs, which led to speculation of its transmission via the nasolacrimal duct. While it is surely possible that the nasolacrimal duct can transfer viruses both ways between the ocular surface and respiratory tract, it would be unfair to bring in the issue of nasolacrimal duct obstruction (NLDO). The belief in the literature that NLDO can exacerbate the ocular retention and periocular contamination is far-fetched.^[19] Besides, the cytopathic effects of the virus on the nasolacrimal duct are unknown. Summarizing these aspects, the current evidence does not show conjunctiva as either a favored route of entry or preferred tissue for SARS-CoV-2.

Certain perceptions about conjunctivitis in COVID-19 mostly appears to be an extrapolation beyond data. There are multiple reasons for it to be so. One, the reported prevalence in large series is quite low.^[20,21] Second, there is no strong evidence of the virus invasion and multiplication to cause direct effects. Third, the possibility of an abnormal autoimmune response is currently, at best, speculation.^[15] Fourth, COVID-19 conjunctivitis is often seen with the lens of the past, conjunctivitis experience with other coronaviruses in the past.^[22,23] The fundamentals of any disease pathogenesis are often ignored in times of such pandemics. To prove a conjunctival transmission, three criteria should be fulfilled. One, the virus replicates within the conjunctival epithelial cells. Two, it induces demonstrable cytopathic changes and virus particles, and three, its isolation from the epithelial cells. In the absence of these demonstrable changes, and the literature review, it would be safe to presume that transmission of SARS-CoV-2 through the conjunctiva is less likely. However, it is equally important to remember that the situation is fluidic, and the evidence is constantly evolving, and this may be subject to change in the future.

The current evidence at the most suggests only a low-risk of transmission through conjunctival surfaces and tears and hence it is advisable to have eye protection, slit-lamp breath shields, and meticulous disinfection. While we take all the precautions and remain vigilant, the paranoia associated with conjunctival transmission is uncalled for, amongst the Ophthalmologists.

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