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## Ocular Signs of COVID-19 Suggested by Internet Search Term Patterns Worldwide



Studies have suggested a possible association of coronavirus 2019 (COVID-19) with conjunctivitis, chemosis, and other ocular symptoms such as red or sore eyes.<sup>1–5</sup> The estimated proportion of those with ocular symptoms, some consistent with conjunctivitis, ranges widely, from less than 1% (Centers for Disease Control and Prevention Coronavirus 2019-Associated Hospitalization Surveillance Network) to more than 30%,<sup>1,5</sup> suggesting that conjunctivitis could be a disease feature and potentially a useful diagnostic sign. More precise characterization of clinical eye presentations associated with COVID-19 infection or social distancing measures may be hindered by a marked reduction in eye care clinical visit data as a result of sheltering in place. Moreover, observations of other life-threatening conditions take precedence in clinical documentation. Online search and social media data can reflect community seasonal clinical eye disease patterns and conjunctivitis epidemics.<sup>6</sup> We used Google Trends data, readily available outside of a clinic environment, to investigate whether public interest in search terms related to eye conditions might suggest a surge in COVID-19–related symptoms during the COVID-19 shelter-in-place months.

We assessed 18 search terms, including for proposed ocular<sup>1–5</sup> and known nonocular COVID-19 symptoms. Terms for allergy symptoms were included as well, in part as positive control measures. In consultation with native language speakers, similar terms in French, Spanish, and Italian also were included. Daily relative search frequency volume was obtained using the Google Timelines for Health API for the weeks of April 26, 2015, through April 24, 2020, using methods as described previously.<sup>6</sup> Table S1 (available at [www.aaojournal.org](http://www.aaojournal.org)) indicates search terms included from each language representing sore eyes, burning eyes, red eyes, conjunctivitis, allergy, and nonocular COVID-19.

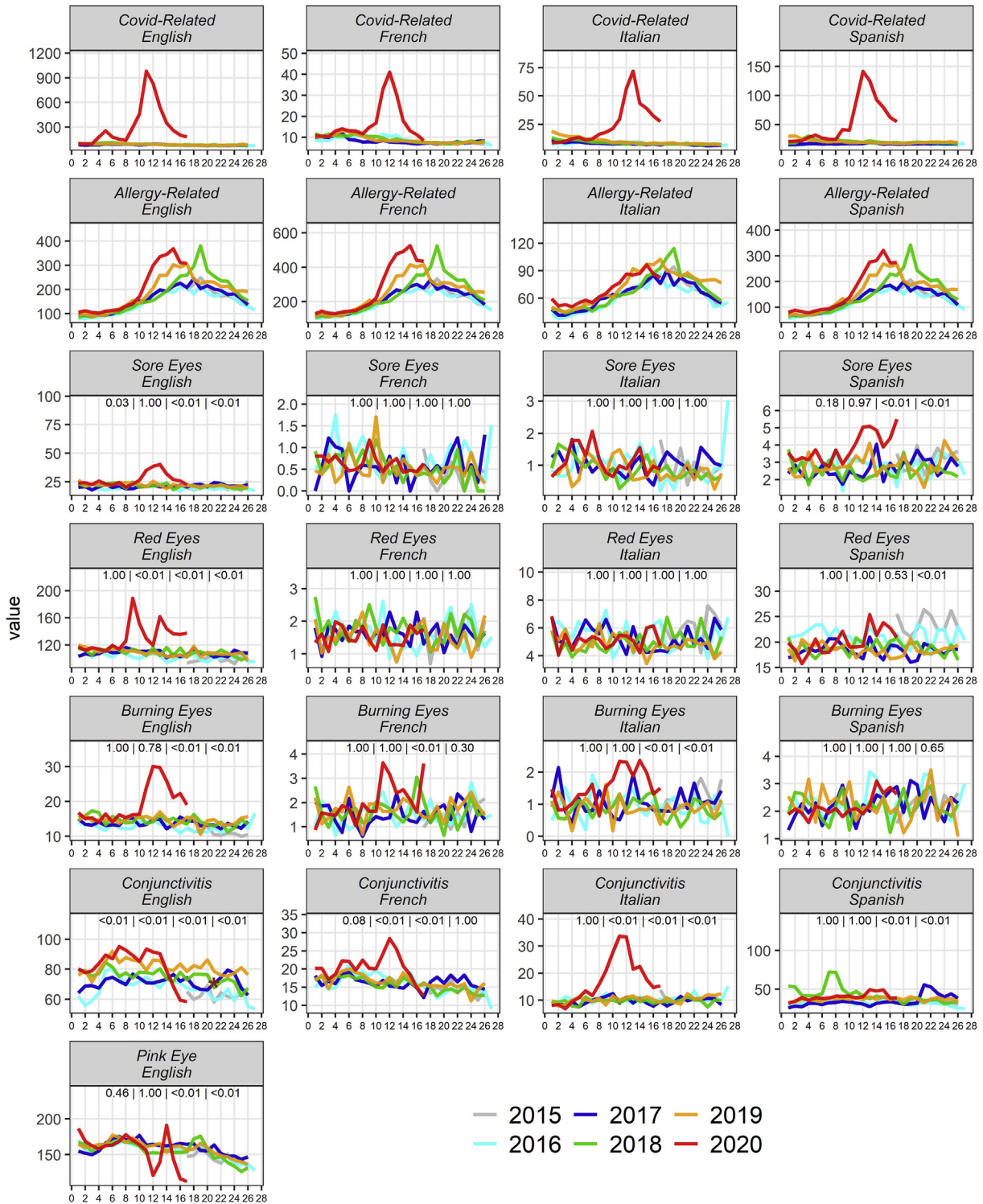
To reduce bias, before statistical analysis, actual search terms and languages in the dataset were numerically encoded (masked). We then fit linear regression models contrasting search interest in each month of 2020 with that month in prior years, yielding 2-sided  $P$  values ( $\alpha = 0.05$ ). Holm-Bonferroni correction was applied within each monthly analysis. For each month in 2020, the mean monthly search interest for each selected masked search term was compared with the mean in the same months of the prior 4 years. Search terms and languages then were unencoded (unmasked). In Figure 1, mean search interest (y-axis) for eye-related, allergy-related, and nonocular COVID-19 terms are plotted for weeks 1 through 27 (x-axis) of each year. In Table S1 (available at [www.aaojournal.org](http://www.aaojournal.org)),  $P$  values and change ratios indicate, for each term-per-month combination, if searches in 2020 were significantly higher or lower than in the same months in 2015 through 2019. Because our French language speakers had occasionally suggested multiple French translation term options, we also conducted post hoc a sensitivity comparison between French terms that had been assessed originally and alternate suggested terms that had not been included in the original analysis. This study was approved by University of California, San Francisco, Institutional Review Board (approval no. 14-14743) and adhered to the tenets of the Declaration of Helsinki.

Figure 1 and Table S1 (available at [www.aaojournal.org](http://www.aaojournal.org)) show that 2020 searches for terms representing conjunctivitis were significantly more frequent than for prior years in February through April in Italian (173%), French (48%), and Spanish (22%). In English, 2020 searches for *conjunctivitis* and *pink eye* increased slightly above the frequency for prior years in January and February. However, searches for the same English terms decreased significantly in March and April 2020 compared with prior years. This was despite significantly elevated 2020 English allergy-related searches. In addition, 2020 searches representing burning eyes were significantly higher in March through April for English (67%) and Italian (101%) and in March for French (56%). Searches in 2020 representing sore eyes were higher than prior years in January and in March through April for English and in March through April for Spanish. In English, searches representing red eyes also were higher in 2020 compared with prior years in February through April. Several allergy-related searches were higher in 2020 than in prior years in all languages including in January, and especially in March through April for English and French. Most nonocular COVID-19 terms were searched significantly more in spring 2020 (often well above 1000%) compared with prior years, some starting in January. We also observed that  $P$  values varied, but only slightly, between the optional French translations that we examined. For instance, use of *mal aux yeux* led to a slightly smaller adjusted  $P$  value (0.71) in March compared with that for *douleur des yeux* (1.0), and use of *yeux qui piquent* instead of *yeux piquent* yielded  $P < 0.001$  in both cases.

Increased search interest during the pandemic compared with the same months in prior years for terms representing conjunctivitis (especially in Italian) could suggest an association with COVID-19 infection, as has been suggested from isolated case reports on COVID-19 patients.<sup>1–4</sup> In English, despite a small early spring increase, *conjunctivitis* and *pink eye* searches decreased significantly in the later spring months of 2020 compared with prior years. This could suggest that although COVID-19 may be associated with conjunctivitis, any such English search interest was offset by a larger reduction in school-related conjunctivitis. That searches for *conjunctivitis* and *pink eye* (but no other eye symptoms) in English were significantly lower in March and April 2020 than in prior years supports the possibility that school closures and social distancing may have reduced the incidence of contagious conjunctivitis not related to COVID-19. This supports the public health policy of distancing for controlling conjunctivitis outbreaks.<sup>6</sup>

For terms representing sore, red, and burning eyes (especially in English and Spanish), elevated search frequency in spring 2020 compared with prior years aligns with reports associating these symptoms with COVID-19 infection in some patients.<sup>2,3,7</sup> Recent reports have suggested COVID-19 spread in the United States and Europe as early as December 2019. Our finding that search interest for allergy-related terms was elevated early in spring 2020 compared with prior years could be the result of the similarity between COVID-19 symptoms and allergy symptoms. Alternatively, this could signify an aggressive early 2020 allergy season combined later with excessive screen time as a result of working from home.

Our results suggest a relationship between the COVID-19 pandemic and internet search patterns for some ocular surface conditions, varying between languages. This study has several limitations. Additional, better non-English translations may exist for some



**Figure 1.** Graphs showing comparison of weekly search interest in spring 2020 versus 2015 through 2019 by category and language. Weekly mean search interest values for January through April are plotted for 2020 (red) and for 2015 through 2019 (other colors). *P* values indicate statistically significant search interest difference for spring 2020 months from prior spring months are shown at the top of each plot (January, February, March, and April). See [Table S1](http://www.aaojournal.org) (available online at [www.aaojournal.org](http://www.aaojournal.org)) for more details on search terms, *P* values, and ratios. Values for all nonocular coronavirus 2019 (COVID-19) terms are combined, as are allergy-related term values. A single term represents each ocular category. Note that a 2017 week-21 peak (brown asterisk; value = 150) for English conjunctivitis was not plotted simply to retain a y-axis scaled for convenient annual comparisons and that the scale bars for each term in [Figure 1](#) indicate that not all terms exhibited similar strength. The x-axis is the week number and the y-axis is the weekly mean search interest.

of the terms studied. Although some languages (Italian and French) can help to identify a region, overlap exists between regions and languages spoken. Because some reports suggest that distinct strains of COVID-19 could affect regions differently, future studies using search data from countries or smaller geographic regions could investigate whether search interest in ocular conditions related to COVID-19 varies regionally. Although we observed a significant increase in conjunctivitis searches in Italian, conjunctivitis searches did not surge consistently across all COVID-19-affected languages or more than other ocular (red, sore, burning eyes) or nonocular COVID-19 conditions, diminishing the likelihood that conjunctivitis is a global cardinal finding of COVID-19 infection. Increased search interest also could be triggered by news stories or case reports about eye conditions. However, because *conjunctivitis* and *pink eye* searches decreased in English and searches for more subjective ocular symptom terms increased (terms less likely to have appeared in news or publications), this explanation is less likely. As ambulatory visits and telemedicine increase capacity, comparing searches with clinical and epidemiologic data will help to assess alternate causes of search pattern changes and will help to support or refute our findings.

MICHAEL S. DEINER, PhD<sup>1,2</sup>  
 GERAMI D. SEITZMAN, MD<sup>1,2</sup>  
 STEPHEN D. MCLEOD, MD<sup>1,2</sup>  
 JAMES CHODOSH, MD, MPH<sup>3</sup>  
 DANIEL H. HWANG<sup>4</sup>  
 THOMAS M. LIETMAN, MD<sup>1,2</sup>  
 TRAVIS C. PORCO, PhD, MPH<sup>1,2,5</sup>

<sup>1</sup>F. I. Proctor Foundation, University of California, San Francisco, San Francisco, California; <sup>2</sup>Department of Ophthalmology, University of California, San Francisco, San Francisco, California; <sup>3</sup>Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts; <sup>4</sup>The Nueva School, San Mateo, California; <sup>5</sup>Department of Epidemiology and Biostatistics, Global Health Sciences, University of California, San Francisco, San Francisco, California

Financial Disclosure(s): The author(s) have made the following disclosure(s): G.D.S.: Consultant – Dompe Pharmaceutical J.C.: Consultant – United States Food and Drug Administration, American Academy of Ophthalmology, Santen Supported in part by the National Eye Institute, National Institutes of Health, Bethesda, Maryland (grant nos.: 1R01EY024608-01A1 [T.M.L.], EY002162); and Research to Prevent Blindness, Inc., New York, New York (unrestricted grant [S.D.M.]). The sponsor or funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: No human subjects were included in this study. The human ethics committees at the University of California, San Francisco, approved the study. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Deiner, Seitzman, Lietman, Porco  
 Analysis and interpretation: Deiner, Seitzman, McLeod, Chodosh, Lietman, Porco  
 Data collection: Deiner, Hwang, Porco  
 Obtained funding: McLeod, Lietman  
 Overall responsibility: Deiner, Seitzman, McLeod, Chodosh, Hwang, Lietman, Porco

Correspondence:

Travis C. Porco, PhD, MPH, F. I. Proctor Foundation, University of California San Francisco, 513 Parnassus, San Francisco, CA 94143. E-mail: [travis.porco@ucsf.edu](mailto:travis.porco@ucsf.edu).

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## Successful Strategic Management of *Pythium insidiosum* Keratitis with Antibiotics



Management of *Pythium insidiosum* keratitis has several challenges<sup>1–5</sup> due to the lack of information related to its clinical and microbiological features and availability of efficacious medical treatment. Except for a few anecdotal case reports, most of the studies recommend early therapeutic penetrating keratoplasty (ThPK) as the primary line of management. However, the recurrence rates of infection are high even after ThPK.<sup>6</sup> With the use of in vitro susceptibility testing, we managed few cases<sup>7</sup> with a novel combination of antibacterial drugs as the primary treatment for *Pythium insidiosum* keratitis. After successful outcomes in those cases, we managed all our cases (January 2017 to October 2018) on similar lines and evaluated their outcomes in the present study.

The study was approved by the Institutional Ethics Committee, L V Prasad Eye Institute, Hyderabad, India, and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. All consecutive cases with *Pythium insidiosum* keratitis were reviewed retrospectively. They were microbiologically confirmed by the observation of coenocytic aseptate/sparsely septate filaments suggestive of *Pythium insidiosum* on corneal scrapings or growth in culture. All these cases were treated hourly with a combination of topical linezolid 0.2% (Cipla Ltd., Mumbai, India) and topical