

**In Reply** It is certainly great to see the adaptation of our initial design<sup>1</sup> with use of a Bookwalter retractor by Yarlagadda and Anderson. One of our aims in development of the negative pressure aerosol cover was to use materials and instruments commonly available at most medical centers. The use of the widely available Bookwalter retractor undoubtedly follows in the spirit of this goal. Key to our continued success in managing the current global pandemic is the responsiveness and resourcefulness of our community in identifying issues and developing solutions to these shared challenges. It is our hope that fellow otolaryngologists and the greater medical community continue to rise to adapt to these challenging times with ingenuity and vigor.

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1. Bertroche JT, Pipkorn P, Zolkind P, Buchman CA, Zevallos JP. Negative-pressure aerosol cover for COVID-19 tracheostomy. *JAMA Otolaryngol Head Neck Surg*. 2020;146(7):672–674. doi:[10.1001/jamaoto.2020.1081](https://doi.org/10.1001/jamaoto.2020.1081)

## Understanding COVID-19–Related Olfactory Dysfunction

**To the Editor:** We read with interest the article by Boscolo-Rizzo et al<sup>1</sup> titled “Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19.” We would like to commend the authors for this important work in the documentation of the natural history of olfactory dysfunction in patients with COVID-19. We concur that the pattern of symptoms reported suggests a sensorineural cause of the olfactory dysfunction.

Postviral anosmia, most frequently investigated among patients with the influenza virus, is often attributed to infection and consequent apoptosis of olfactory neurons. In contrast, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been hypothesized to affect olfactory function via infection of the sustentacular, perivascular, and stem cells in view of its affinity with the angiotensin-converting enzyme 2 (ACE2). These cells, and not the olfactory sensory neurons, have been shown to have high expressions of ACE2 and TMPRSS2.<sup>2</sup> Bryce et al<sup>3</sup> reported that SARS-CoV-2 infection of the sustentacular cells resulted in massive infiltration of immune cells and damage to the olfactory ciliary layer within a short period of 2 days in a golden Syrian hamster model. They further reported partial restitution of the ciliary structure at 14 days after infection, which is postulated to reflect differentiation of progenitor cells to sustentacular cells and mature olfactory receptor neurons.<sup>4</sup> In contrast, other studies have shown functional recovery at 45 days and odorant receptor expression at 90 days after olfactory neuronal damage.<sup>5</sup>

The authors have described a high proportion of recovery of olfactory function at 4 weeks from the initial diagnosis

of COVID-19.<sup>1</sup> However, the timing of onset and recovery of olfactory dysfunction was unclear in the article. Being able to establish a proper timeline of olfactory symptoms would help to further shed light on the pathogenesis of olfactory dysfunction. We would therefore like to suggest considering critical testing time points of 2 to 3 days,<sup>3</sup> 14 days,<sup>3</sup> and 1 to 3 months<sup>5</sup> after infection.

To further complicate matters, recent data have emerged showing that SARS-CoV-2 may be able to infect apparently ACE2-negative cell types<sup>5</sup>—either via other participative molecules such as BSG, neuropilin-1, and PIKfyve, or perhaps that very low-level ACE2 expression is sufficient to mediate infection.

Having a clear account of the symptomatology and evolution of olfactory dysfunction at regular intervals would allow researchers to compare and correlate post-COVID-19 olfactory dysfunction with other olfactory disorders on a cellular level. This may play an important role in furthering our understanding of the pathogenesis of SARS-CoV-2.

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1. Boscolo-Rizzo P, Borsetto D, Fabbris C, et al. Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg*. Published online July 2, 2020. doi:[10.1001/jamaoto.2020.1379](https://doi.org/10.1001/jamaoto.2020.1379)

2. Brann D, Tsukahara T, Weinreb C. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *BioRxiv*. Accessed October 13, 2020. <https://www.biorxiv.org/content/10.1101/2020.03.25.009084v4>

3. Bryce B, St Albin A, Murri S, et al. Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. *Brain Behav Immun*. 2020;S0889-1591(20)31358-1.

4. Bilinska K, Butowt R. Anosmia in COVID-19: a bumpy road to establishing a cellular mechanism. *ACS Chem Neurosci*. 2020;11(15):2152–2155. doi:[10.1021/acscchemneuro.0c00406](https://doi.org/10.1021/acscchemneuro.0c00406)

5. Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the chemical senses: supporting players take center stage. *Neuron*. 2020;107(2):219–233. doi:[10.1016/j.neuron.2020.06.032](https://doi.org/10.1016/j.neuron.2020.06.032)

**In Reply** We thank Chee and Wang for their appreciation of our original investigation titled “Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19.”<sup>1</sup>

We agree that it would be useful to include more frequent evaluation of olfactory function; this was not possible in this current study owing to the overwhelming demands on clinicians at the peak of the pandemic, but hopefully future studies will be able to recruit patients and evaluate with both self-reported and psychophysical testing of olfactory function at more frequent intervals.

We encourage the self-reported evaluation of anosmia because it has as a baseline parameter of comparison to the sub-

jective perception of smell preceding the onset of COVID-19; although it has been shown to lack sensitivity in mild hyposmia. In contrast, evaluation by psychophysical tests, although essential to better characterize the olfactory dysfunction, may overestimate the prevalence of COVID-19-related smell disorders because it can detect preexisting impairment unrelated to SARS-CoV-2 infection. In older adults, for example, the prevalence of objective olfactory impairment in the setting of no reported deficit is 15%.<sup>2</sup>

Furthermore, a long-term evaluation of chemical senses both in patients with mild-to-moderate COVID-19 and those with severe disease, the latter apparently having less frequently an altered sense of smell during the acute phase of the disease, is mandatory to estimate the burden of persistent smell disturbance following SARS-CoV-2 infection.

Nonetheless, based on evidence showing the absence of expression of ACE2 and TMPRSS2 in neurons, current data suggest that SARS-CoV-2 is not directly neuroinvasive, with the alteration of chemical perception being a consequence of targeting nonneuronal support cells by SARS-CoV-2.<sup>3</sup> Much remains to be learned, and there is still much work to be done to evaluate the pathophysiological mechanisms of olfactory function, looking at patients with anosmia/hyposmia, including imaging studies, postmortem examination, and in vivo histopathological assessment. Finally, a more accurate evaluation of the sense of taste to discriminate between real loss, if any,<sup>4</sup> and loss of retronasal olfaction as well as an assessment of chemesthesis is fundamental. This will better direct therapeutic strategies for the large and increasing numbers of patients experiencing ongoing symptoms.

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1. Boscolo-Rizzo P, Borsetto D, Fabbris C, et al. Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg*. Published online July 2, 2020. doi:10.1001/jamaoto.2020.1379.
2. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA*. 2002;288(18):2307-2312. doi:10.1001/jama.288.18.2307
3. Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the Chemical Senses: Supporting Players Take Center Stage. *Neuron*. 2020;107(2):219-233. doi:10.1016/j.neuron.2020.06.032
4. Hintschich CA, Wenzel JJ, Hummel T, et al. Psychophysical tests reveal impaired olfaction but preserved gustation in COVID-19 patients. *Int Forum Allergy Rhinol*. 2020;10(9):1105-1107. doi:10.1002/alr.22655

## Regarding Use of Topical Steroids in Patients With COVID-19–Associated Olfactory Loss

**To the Editor** We read with interest the recent Invited Commentary by our friend and colleague, Dr Joshua Levy, on the treatment of postviral olfactory dysfunction titled “Treatment Rec-

ommendations for Persistent Smell and Taste Dysfunction following COVID-19—the Coming Deluge.”<sup>1</sup>

Although we agree with Dr Levy that there is a frustrating dearth of interventions that can help everyone who suffers from postviral or postinfectious olfactory loss, we cannot help but completely disagree with his discussion surrounding the use of oral and topical corticosteroids in this patient population.

He asserts that there is a lack of demonstrated efficacy of topical steroids for this patient population. We would direct him to our recent randomized clinical trial (RCT), followed by a systematic review of the evidence, addressing this very topic.<sup>2,3</sup>

We first demonstrated in our RCT<sup>2</sup> that placing a topical steroid, in particular budesonide, in a rinse formulation, used along with olfactory training, added significant benefit to patients with idiopathic or postviral olfactory dysfunction.

In addition, in our systematic review,<sup>3</sup> we confirmed that topical steroid nasal sprays should not be used in this patient population because there is good evidence showing no benefit, while also examining the conflicting data regarding oral corticosteroid use in this patient population.

Topical steroid sprays should not be used to treat patients with postviral olfactory dysfunction, coronavirus disease 2019 (COVID-19) related or otherwise, because it will not help them. Alternatively, rinsing with a topical steroid irrigation can be helpful for these patients. Finally, we simply do not have enough data currently to advise or recommend for or against use of oral corticosteroids in this patient population, although a cohort study is currently underway to answer this particular question in patients with COVID-19.

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**Conflict of Interest Disclosures:** Dr Patel reported being a consultant for Medtronic, Stryker, and Optinose.

1. Levy JM. Treatment recommendations for persistent smell and taste dysfunction following COVID-19—the coming deluge. *JAMA Otolaryngol Head Neck Surg*. Published online July 2, 2020. doi:10.1001/jamaoto.2020.1378
2. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. *Int Forum Allergy Rhinol*. 2018;8(9):977-981. doi:10.1002/alr.22140
3. Yan CH, Overdevest JB, Patel ZM. Therapeutic use of steroids in non-chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2019;9(2):165-176. doi:10.1002/alr.22240

**In Reply** I thank Dr Patel for her contribution to my recent Invited Commentary, “Treatment Recommendations for Persistent Smell and Taste Dysfunction following COVID-19—the Coming Deluge.”<sup>1</sup> A thoughtful analysis of available evidence is essential in determining appropriate treatment recommendations in any context, and her voice is welcome as we refine care pathways for patients with persistent olfactory dysfunction following coronavirus disease 2019 (COVID-19).

There is an ongoing need for additional high-quality studies evaluating the use of topical corticosteroid sprays and/or irrigations for the treatment of postviral olfactory dysfunction (PVOD). Although the findings introduced by Dr Patel and members of her esteemed research team represent 2 of the higher-quality studies adding evidence to this debate, they are limited by study designs that include patients with olfactory dysfunction not related to viral illness. This potential source of confounding is significant because less than 50% of enrolled participants in their randomized clinical trial had a post-viral etiology associated with their symptoms.<sup>2</sup> Among this subgroup of 62 patients, only 20 (32%) showed clinical improvement. In addition, the distribution of these patients between the budesonide and control groups is unclear. Although this in no way diminishes the importance of their findings among patients with olfactory dysfunction not related to chronic rhinosinusitis (CRS), further study and nested analysis is needed to tease out outcomes among unique etiologies of olfactory dysfunction, including PVOD.

The consideration of topical corticosteroid sprays for PVOD in the setting of COVID-19 is an ongoing and welcome debate with expert recommendations both for and against their routine use.<sup>3,4</sup> Factors considered when recommending these sprays include their relative safety, low cost, efficacy in olfactory dysfunction related to CRS and the available evidence supporting the use of these same medications in topical irrigations. It is also important to note the emergence of an exhalation corticosteroid delivery system with improved sinonasal penetration vs traditional sprays.<sup>5</sup> Although the current lack of evidence supporting corticosteroid sprays in PVOD must be acknowledged,<sup>6</sup> it is my belief that future studies with increased power and the use of emerging devices with improved sinonasal distribution have the potential to demonstrate benefit, especially when used with olfactory training. It is for these reasons that I recommend both topical corticosteroids (with discussion of sprays vs irrigations) and olfactory training to patients with persistent PVOD.

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1. Levy JM. Treatment recommendations for persistent smell and taste dysfunction following COVID-19—the coming deluge. *JAMA Otolaryngol Head Neck Surg*. Published online July 2, 2020. doi:10.1001/jamaoto.2020.1378
2. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. *Int Forum Allergy Rhinol*. 2018;8(9):977-981. doi:10.1002/alr.22140
3. Whitcroft KL, Hummel T. Olfactory dysfunction in COVID-19: diagnosis and management. *JAMA*. 2020;323(24):2512-2514. doi:10.1001/jama.2020.8391
4. Walker A, Pottinger G, Scott A, Hopkins C. Anosmia and loss of smell in the era of covid-19. *BMJ*. 2020;370:m2808. doi:10.1136/bmj.m2808
5. Sher MR, Steven GC, Romett JL, et al. EXHANCE-3: a cohort study of the exhalation delivery system with fluticasone for chronic sinusitis with or without nasal polyps. *Rhinology*. 2020;58(1):25-35.
6. Yan CH, Overdevest JB, Patel ZM. Therapeutic use of steroids in non-chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2019;9(2):165-176. doi:10.1002/alr.22240

## CORRECTION

**Error in Author Byline Order:** The Clinical Challenge titled, “A Young Patient With Painless Neck Swelling,” published online October 1, 2020, in *JAMA Otolaryngology–Head & Neck Surgery*, included an error in the author byline order. The article has been corrected.

1. Mei J, Bello JA, Shifteh K. A young patient with painless neck swelling. *JAMA Otolaryngol Head Neck Surg*. Published online October 1, 2020. doi:10.1001/jamaoto.2020.1595

**Errors in Age Ranges:** In the Original Investigation titled “Association of Patient Age With Progression of Low-risk Papillary Thyroid Carcinoma Under Active Surveillance: A Systematic Review and Meta-analysis,” published in the June issue of *JAMA Otolaryngology–Head & Neck Surgery*, there were errors in the age ranges of some of the individuals from the pooled data. In the Findings of the Key Points and in the Results section of the abstract and text, “individuals aged 40 to 50 years” should actually be referred to as “individuals aged 40 to 50 years or older,” “adults aged 40 to 45 years” should actually be referred to as “adults aged 40 to 45 years or older,” and/or “patients aged 40 to 45 years” should actually be referred to as “patients aged 40 to 45 years or older.” This article was corrected online.

1. Koshkina A, Fazelzad R, Sugitani I, et al. Association of patient age with progression of low-risk papillary thyroid carcinoma under active surveillance: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2020;146(6):552-560. doi:10.1001/jamaoto.2020.0368

**Error in Figure:** In the Original Investigation titled “Association of Hypertension With the Risk and Severity of Epistaxis” that was published online September 10, 2020,<sup>1</sup> the total number of eligible participants in the National Sample Cohort by the Korean National Health Insurance Service given in the Figure should be 1 025 797, not 1 025 340. This error did not affect the research process or the results. The article has been corrected online.

1. Byun H, Chung JH, Lee SH, Ryu J, Kim C, Shin JH. Association of hypertension with the risk and severity of epistaxis. *JAMA Otolaryngol Head Neck Surg*. Published online September 10, 2020. doi:10.1001/jamaoto.2020.2906