A primer on viral-associated olfactory loss in the era of COVID-19

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Abstract

Early reports have suggested that smell loss may be an early symptom associated with the pandemic known as COVID-19. The possibility that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might cause olfactory dysfunction is certainly plausible. Patients presenting to specialized smell clinics are commonly diagnosed with upper

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respiratory infection (URI)-associated olfactory loss and most are presumed to be viral related. In acute phases of infection, it is common to experience some smell loss as a result of nasal inflammation, mucosal edema, and obstruction of airflow into the olfactory cleft. In most cases, these episodes of smell loss are self-limiting and coincide with resolution of URI symptoms. However, in some cases the smell loss persists for months to years and this is presumed to occur through a more direct olfactory insult by the virus. It remains too early to know whether infection with SARS-CoV-2 causes persistent olfactory dysfunction. However, given the scale of this pandemic, if SARS-CoV-2 does cause chronic olfactory loss in even a small portion of those infected, then the overall population prevalence could be quite large. This review provides a brief, practical overview of viral-associated olfactory loss, realizing that evidence related to COVID-19 will likely not be clear for some time. Our goal is to highlight the existence and importance of this condition and provide information geared for both providers and patients. Practical suggestions regarding evaluation and treatment will be provided, realizing that there may be constraints on medical resources and the nature of this pandemic remains dynamic.

A primer on viral-associated olfactory loss in the era of COVID-19

Introduction

Early reports have suggested that acute smell loss may be an early symptom associated with the worldwide pandemic known as COVID-19[1-5]. In addition, smell and/or taste loss has been noted in the absence of other known symptoms of the disease. Although these reports are occurring at an alarmingly high frequency both abroad and in the United States (US), they have yet to be verified with hard data, including testing of both smell function and/or COVID-19. The possibility that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might cause olfactory dysfunction is certainly plausible. Another closely related coronavirus, the 2004-2005 pandemic SARS-CoV, has also been linked with prolonged anosmia[6], while experimental introduction of a 'common cold' variant coronavirus(229E) has been shown to cause impaired olfactory ability in human subjects[7]. Patients presenting to specialized smell and taste clinics are commonly diagnosed with upper respiratory infection (URI)-associated olfactory loss and most are presumed to be viral related. In acute phases of infection, it is very common to experience some smell loss as a result of nasal inflammation, mucosal edema, and obstruction of airflow into the olfactory cleft. In most cases, these episodes of smell loss are self-limiting and coincide with resolution of URI symptoms. However, in some cases the smell loss persists for months to years and this is presumed to occur through a more direct olfactory insult by the virus. Although the onset of viral-associated olfactory loss is often sudden, patients rarely pay attention to this symptom acutely given the common co-occurrence of associated URI symptoms. Therefore, there is often a significant delay between onset of olfactory loss and presentation to a provider's office for evaluation, with one study documenting an average of 3 years between symptom onset and olfactory testing.[8] This delay is likely related to a lack of awareness of this condition among both patients and medical providers. It remains too early to know whether infection with SARS-CoV-2 causes persistent olfactory dysfunction. In fact, early anecdotal reports have noted return of function within 14 days, although this has not been demonstrated yet in a population-based study. However, given the scale of this pandemic, if SARS-

CoV-2 does cause chronic olfactory loss in even a small portion of those infected, then the overall population prevalence could be quite large.

Until recently, olfactory loss was often considered innocuous, something that might be annoying to patients but rarely life threatening or life altering. However, a number of high-profile studies have found an association between olfactory loss and increased 5-year mortality rates.[9-11] This association persists even after controlling for neurologic disease (known to impact olfaction) and weight loss (presumably from dietary modification). Whether olfactory loss truly contributes to increased mortality, or is simply an associated factor, is still unknown, but these studies suggest that loss of smell is important, nonetheless. Additionally, there are many studies demonstrating that olfactory dysfunction impacts quality of life, as this loss affects food enjoyment, social interaction, and incidence of depression.[12-14]

The purpose of this primer is to provide a brief, practical overview of viral-associated olfactory loss, realizing that evidence related to COVID-19 will likely not be clear for some time. Our overall goal is to highlight the existence and importance of this condition and provide information geared for both providers and patients on presentation, natural history, and available treatments. Practical suggestions regarding evaluation and treatment will be provided, realizing that there may be constraints on medical resources and the nature of this pandemic remains dynamic.

Presentation and evaluation

The diagnosis of viral-associated olfactory loss is made primarily via patient history. Classically, a patient will lose ability to smell during the course of a viral URI. Most often, the subjective loss of smell will not be realized by the patient until after the infection has resolved. Because smell loss can be insidious, months may go by before they realize there is a problem. Patients may or may not appreciate the relevance of the infection unless asked directly, as not all illnesses are particularly severe or otherwise noteworthy. Because smell informs the flavor of food, patients may also complain of altered taste, describing food as bland. A detailed history would also rule out other causes of ongoing olfactory loss or symptoms that are indicative of more worrisome pathology (Table 1). Physical examination for any suspected etiology of smell loss should include nasal endoscopy, usually performed by an otolaryngologist, and would be expected to be normal in cases with viral-associated olfactory loss. Imaging is rarely done unless symptoms and examination suggest an alternative diagnosis such as chronic rhinosinusitis or a mass lesion. Formal smell testing is an important aspect of the evaluation in order to document the precise degree of olfactory loss as compared to population norm which reflects an overall diminishing ability to smell as age advances. The most common forms of smell testing are the Smell Identification Tests and the Sniffin' Sticks battery of tests, the latter of which evaluates threshold, discrimination, and identification.[15] These tests allow the degree of smell loss to be quantified into hyposmia (some smell present but less than normal) and anosmia (no discernible smell). Unfortunately, these tests are not widely available in general otolaryngology offices and thus formal, objective olfactory testing is unlikely to be feasible during or shortly after the COVID-19 pandemic for most patients.

Natural history

At the time of diagnosis, roughly two-thirds of patients will have hyposmia by testing, and one-third will be anosmic; however, most of this data comes from specialized smell and taste centers and thus may be skewed toward patients who failed to improve.[8] The natural history of viral-associated smell loss is for there to be some degree of spontaneous recovery. The exact degree of improvement is hard to capture on a population level since few patients immediately present to centers capable of

testing. Available data suggests that 40-60% of patients will have some spontaneous improvement in the years following initial diagnosis.[8,16] In one of the largest series, the percentage of anosmic and hyposmic patients exhibiting clinically significant improvement was 46% and 35%, respectively.[16] Unfortunately, only 15% of those who present with anosmia will achieve normal smell levels, whereas 25% of those with hyposmia improve to normal over time.[8]

Mechanisms of disease and viral pathogens

In typical viral-associated olfactory loss it is assumed there has been direct damage to the olfactory system. The site of damage is widely believed to be at the level of the olfactory epithelium, with biopsy studies revealing abnormal findings of increased respiratory metaplasia and neuroma formation.[17-19] However, animal models have demonstrated direct damage to the olfactory bulb with minimal epithelial damage.[20] Noting the high rates of spontaneous improvement in smell function over time, an epithelial based etiology is more likely given the known ability for the olfactory receptor neurons to regenerate after damage.

Without further data at the time of this writing, the effect of SARS-CoV-2 on the olfactory epithelium is unknown. If the vast majority of smell loss cases resolve in a matter of weeks, it could be assumed that the virus caused an inflammatory response in the nasal cavity that temporarily impedes odorants from reaching the olfactory receptor neurons. Damage to olfactory neurons would require a longer period of regeneration and axon regrowth to make useful synapses with the olfactory bulb. In addition, a recent report identifying cells expressing the SARS-CoV-2 receptor, ACE2, notes higher levels in respiratory epithelial cells compared to olfactory epithelium. However, olfactory epithelial cells did express ACE2, including supporting cells and horizontal basal cells but not olfactory receptor neurons.[21] Transmission of the virus could occur via other methods and routes potentially damaging the olfactory bulbs directly. For example, intranasal inoculation of mice transgenic for human ACE2 with the SARS-CoV virus results in rapid propagation of viral particles into the olfactory bulb and subsequently other areas of the brain[22]. In any case, making assumptions without hard evidence could be dangerous. During the polio epidemic, wrong assumptions were made that the virus spread through olfactory axons to the brain, which led to purposeful damaging of olfactory epithelium with resulting permanent smell loss.[23] Only later was it realized that transmission occurs through the oral/GI route.

Pharmacologic treatment

Many different medications have been proposed to treat viral-associated olfactory loss, including oral corticosteroids, topical corticosteroids, zinc sulfate, alpha lipoic acid, theophylline, caroverine, vitamin A, Ginkgo biloba, and minocycline. A recent systematic review failed to identify any high-level evidence to support these treatments, noting that most studies were small in size and failed to include a control group, which is critical considering that some degree of spontaneous recovery is expected.[24] Although there is some data to suggest possible benefit of corticosteroids in non-sinus related olfactory loss, many of these studies include patients with non-viral etiologies which limits conclusions.[25] A recent position paper on olfactory dysfunction comprised of olfactory experts from across the world echoed these findings, suggesting that definitive evidence was lacking for any specific medical treatment of non-sinus related olfactory loss.[15]

Olfactory Training

In the absence of proven pharmacotherapy, olfactory training (OT) has emerged as a primary treatment strategy for viral-associated olfactory loss. The concept behind olfactory training is analogous to physical therapy after a stroke or other neurologic insult. Faced with an injury and

resultant deficit, existing neural pathways can be strengthened and "retrained" in order to compensate.[26] Otolaryngologists are most familiar with balance therapy for vestibular disease or audiologic training after cochlear implantation. Olfactory training is thought to be similar, retraining the brain to correctly interpret the neurologic signals received as odorants generate unique impulses that travel through the olfactory nerves, olfactory bulb, and olfactory cortex. In addition, animal models have shown an activity-dependent survival of olfactory receptor neurons during development and regeneration.[27,28]

Traditional olfactory training utilizes twice daily training sessions involving 4 odors specifically chosen from distinct chemical classes of odorants. For each odor, the patient inhales through the nostrils for 15 seconds, concentrating on the odor and its intended smell. After a short break of 10 seconds, the next odor is inhaled and the process repeated for all odorants.[29] The duration of therapy is usually a minimum of 6 months, although therapy is often continued longer if the patient is demonstrating progress.

Studies examining outcomes after olfactory training have consistently demonstrated significant improvements in objective olfactory testing, including those with post-traumatic, post-viral, and age-related olfactory loss.[30] This includes 2 randomized controlled studies focused specifically on those with viral-associated olfactory loss.[31,32] These studies both showed more improvement in those undergoing olfactory training versus the control interventions. Damm et al found that olfactory function improved in 15/24 participants (63%) of the high-concentration training group and in 6/31 participants (19%) of the low-concentration training group (P = .03) in subjects with a duration of olfactory dysfunction of <12 months.[31] Altundag et al found improvement with both classic (four different odors) and modified (3 sets of four odors changed every 4 months) olfactory training compared with control, with the greatest improvement with a modified regimen.[32]

There are a couple of caveats worth discussing when considering olfactory training for patients with olfactory loss. The first is that expectations should be managed, as it would be rare for olfactory training alone to dramatically improve someone's sense of smell. Therefore, someone with complete anosmia should not on average expect complete normalization. The typical improvement is in the range of 4-6 points on the Sniffin' Sticks composite scale; which is above the minimal clinically important difference but is still nonetheless considered to be a modest improvement.[33] For example, a patient with complete anosmia may regain some smell function but remain subjectively diminished or conversely, a patient with mild hyposmia may potentially improve into normal range. The second point is that many providers recommend "modified" olfactory training. Modified olfactory training involves rotating odors periodically, usually monthly or at least every 3 months. At least one study has demonstrated superiority of modified olfactory training over traditional olfactory training and most patients find it more interesting to vary odors to keep the therapy from getting stale.[32] Lastly, actually obtaining odorants to perform training can be a practical limitation.[34] Proprietary smell retraining kits can be purchased, although these are still not widely available nor easy to obtain. For many patients, it is easiest to utilize essential oils or various household items (e.g. coffee, cinnamon, vanilla) for therapy. Providing patients with a list of odorants, instructions for therapy, and a diary to document progress is helpful to augment compliance. Lastly, scheduled follow-up with repeated objective olfactory testing gives patients something to look forward to and a quantifiable way to measure progress.

Practical Recommendations

1. Patients experiencing sudden complaints of smell and/or taste loss irrespective of co-existing symptoms should be considered suspicious for COVID-19.

Frequent reports of smell/taste complaints in patients who have tested positive for COVID-19 supports a cautious approach in using this symptom as a possible indicator of infection. In addition, the symptom of smell loss may be a useful indicator of COVID-19 infection in those with mild cases that may otherwise act unwittingly as a vector for spread without proper isolation measures. Nasal endoscopy and/or imaging would not be recommended in the acute setting, as findings are unlikely to impact treatment recommendations and these evaluations risk unnecessary exposure of healthcare workers.

2. Patients with acute loss of smell and taste after COVID-19 should assume they may have viral-associated smell loss

If a patient loses their smell after suffering from COVID-19 and it fails to improve after recovery of other symptoms, it is reasonable to assume they have viral-associated smell loss, provided there are no other concerning symptoms (Table 1). Although evaluation by an otolaryngologist is ideal and ultimately should be done, this may not be feasible during or shortly after the COVID-19 pandemic. Furthermore, the scarcity of medical resources and potential risks of nasal endoscopy may limit the availability of objective olfactory testing, nasal endoscopic examination, and imaging in the near future.

3. Oral and/or topical corticosteroids should not be given to treat acute smell loss in a patient with active COVID-19

The use of systemic corticosteroids to treat COVID-19 has been controversial. Early commentary and recommendations from the US Centers for Disease Control suggested corticosteroids "should be avoided unless indicated for other reasons, such as management of chronic obstructive pulmonary disease exacerbation or septic shock." [35,36] However, more recent reports and expert recommendations have suggested judicious use of short courses of systemic corticosteroids may be beneficial in those with severe lung injury.[37,38] In our opinion, acute smell loss would not be an appropriate indication given lack of proven benefits and possible risks. Recommendations are less clear for the patient with persistent smell loss who has definitely recovered from COVID-19. Traditionally, clinicians might consider a short course of oral and/or topical steroids in the setting of viral-associated olfactory loss despite the limited evidence showing benefit, usually weighing risks and benefits on a case-by case-basis. At this point in time, we would advise caution prescribing corticosteroids until data is available with regard to efficacy and risks specific to the COVID-19 population.

4. Olfactory training therapy can be started prior to formal medical evaluation

If loss of smell persists for several weeks following resolution of other COVID-19 symptoms, than one should be concerned that smell loss has become persistent. Although data is limited, there is some indication that there may be a finite period of time during which spontaneous recovery could be expected to occur after viral-associated smell loss. Certainly, those with loss >5 years do not often see further improvement. Additionally, at least one study of olfactory training found that patients receiving the greatest benefit from training were those with smell loss for less than 12 months.[31] Therefore, it makes sense to start olfactory training sooner rather than later.

5. For those patients with persistent loss of smell, formal evaluation by an otolaryngologist should be considered when safe to do so from a public health standpoint

The above recommendations are made with the expectation that formal evaluation by an otolaryngologist may not be immediately feasible for many patients with viral-associated smell loss

during the COVID-19 pandemic, particularly for those in severely impacted regions. Additionally, available medical care may be initially focused on more pressing medical needs. However, it is important to recognize other potential causes of olfactory loss, including chronic rhinosinusitis and in rare instances nasal or intracranial tumors. For those patients who fail to normalize and/or have any concerning symptoms, formal evaluation by an otolaryngologist should take place so that objective smell testing can be performed and other etiologies ruled out.

Table 1: Symptoms that could suggest an alternative diagnosis

Symptom	Typical Smell Loss Characteristics	Possible condition	Endoscopic exam
Nasal congestion and/or drainage	Fluctuating smell loss	Chronic sinusitis or rhinitis	Mucosal inflammation
Nasal congestion and/or bleeding	Gradual smell loss	Sinonasal tumor	Unilateral mass/polyp
Headache or neurologic changes/vision changes	Gradual smell loss	Intracranial tumor	Normal
Memory problems	Gradual smell loss	Dementia	Normal
Tremor, bradykinesia, muscular stiffness	Gradual smell loss	Parkinson's disease	Normal

Bibliography

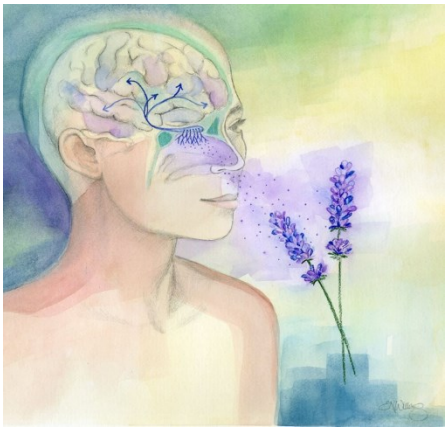
1. Bagheri SHR, Asghari AM, Farhadi M, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak. *medRxiv.* 2020:2020.2003.2023.20041889.
2. Rabin RC. Lost sense of smell may be peculiar cluse to coronavirus infection. https://www.nytimes.com/2020/03/22/health/coronavirus-symptoms-smell-taste.html. Published 2020. Accessed.
3. Stone J. There's an unexpected loss of smell and taste in coronavirus patients. https://www.forbes.com/sites/judystone/2020/03/20/theres-an-unexpected-loss-of-smell-and-taste-in-coronavirus-patients/#5a90a8d51017. Published 2020. Accessed.
4. Bienkov A. If you've lost your sense of smell or taste, you could be a 'hidden carrier' of the coronavirus. 2020.
5. Hopkins C, Kumar N. Loss of sense of smell as marker of Covid-19 infection. https://www.entuk.org/sites/default/files/files/Loss%20of%20sense%20of%20smell%20as%20marker%20of%20COVID.pdf. Published 2020. Accessed.
6. Hwang CS. Olfactory neuropathy in severe acute respiratory syndrome: report of A case. *Acta neurologica Taiwanica.* 2006;15(1):26-28.
7. Akerlund A, Bende M, Murphy C. Olfactory threshold and nasal mucosal changes in experimentally induced common cold. *Acta oto-laryngologica.* 1995;115(1):88-92.
8. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol.* 2008;63(2):159-166.
9. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One.* 2014;9(10):e107541.

10. Liu B, Luo Z, Pinto JM, et al. Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults: A Cohort Study. *Ann Intern Med.* 2019;170(10):673-681.
11. Van Regemorter V, Hummel T, Rosenzweig F, Mouraux A, Rombaux P, Huart C. Mechanisms Linking Olfactory Impairment and Risk of Mortality. *Front Neurosci.* 2020;14:140.
12. Miwa T, Furukawa M, Tsukatani T, Costanzo RM, DiNardo LJ, Reiter ER. Impact of olfactory impairment on quality of life and disability. *Arch Otolaryngol Head Neck Surg.* 2001;127(5):497-503.
13. Croy I, Symmank A, Schellong J, et al. Olfaction as a marker for depression in humans. *J Affect Disord.* 2014;160:80-86.
14. Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The Association Between Olfaction and Depression: A Systematic Review. *Chem Senses.* 2016;41(6):479-486.
15. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinol Suppl.* 2017;54(26):1-30.
16. Cavazzana A, Larsson M, Munch M, Hahner A, Hummel T. Postinfectious olfactory loss: A retrospective study on 791 patients. *Laryngoscope.* 2018;128(1):10-15.
17. Yamagishi M, Fujiwara M, Nakamura H. Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. *Rhinology.* 1994;32(3):113-118.
18. Holbrook EH, Leopold DA, Schwob JE. Abnormalities of axon growth in human olfactory mucosa. *Laryngoscope.* 2005;115(12):2144-2154.
19. Holbrook EH, Rebeiz L, Schwob JE. Office-based olfactory mucosa biopsies. *Int Forum Allergy Rhinol.* 2016.
20. Schwob JE, Saha S, Youngentob SL, Jubelt B. Intranasal Inoculation with the Olfactory Bulb Line Variant of Mouse Hepatitis Virus Causes Extensive Destruction of the Olfactory Bulb and Accelerated Turnover of Neurons in the Olfactory Epitheliumof Mice. *Chem Senses.* 2001;26(8):937-952.
21. Brann D, Tsukahara T, Weinreb C, Logan DW, Datta SR. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. 2020. doi:https://doi.org/10.1101/2020.03.25.009084. Published March 28, 2020.
22. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *Journal of virology.* 2008;82(15):7264-7275.
23. Doty RL. The olfactory vector hypothesis of neurodegenerative disease: is it viable? *Ann Neurol.* 2008;63(1):7-15.
24. Harless L, Liang J. Pharmacologic treatment for postviral olfactory dysfunction: a systematic review. *Int Forum Allergy Rhinol.* 2016;6(7):760-767.
25. 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.
26. Kollndorfer K, Fischmeister FP, Kowalczyk K, et al. Olfactory training induces changes in regional functional connectivity in patients with long-term smell loss. *Neuroimage Clin.* 2015;9:401-410.
27. Zhao H, Reed RR. X inactivation of the OCNC1 channel gene reveals a role for activity-dependent competition in the olfactory system. *Cell.* 2001;104(5):651-660.
28. Watt WC, Sakano H, Lee ZY, Reusch JE, Trinh K, Storm DR. Odorant stimulation enhances survival of olfactory sensory neurons via MAPK and CREB. *Neuron.* 2004;41(6):955-967.
29. Hummel T, Rissom K, Reden J, Hahner A, Weidenbecher M, Huttenbrink KB. Effects of olfactory training in patients with olfactory loss. *Laryngoscope.* 2009;119(3):496-499.
30. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. *Rhinology.* 2017;55(1):17-26.

31. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope.* 2014;124(4):826-831.
32. Altundag A, Cayonu M, Kayabasoglu G, et al. Modified olfactory training in patients with postinfectious olfactory loss. *Laryngoscope.* 2015;125(8):1763-1766.
33. Pekala K, Chandra RK, Turner JH. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. *International forum of allergy & rhinology.* 2016;6(3):299-307.
34. Patel ZM, Wise SK, DelGaudio JM. Randomized Controlled Trial Demonstrating Cost-Effective Method of Olfactory Training in Clinical Practice: Essential Oils at Uncontrolled Concentration. *Laryngoscope Investig Otolaryngol.* 2017;2(2):53-56.
35. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395(10223):473-475.
36. CDC. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Published 2020. Updated March 20, 2020. Accessed.
37. Zheng C, Wang J, Guo H, et al. Risk-adapted Treatment Strategy For COVID-19 Patients. *Int J Infect Dis.* 2020.
38. Surviving Sepsis Campaign. COVID-19 Guidelines. https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19. Published 2020. Updated March 20, 2020. Accessed.

Appendix 1: Olfactory Training

This technique of **olfactory training** is based on the idea that the nerves responsible for providing our sense of smell can be strengthened through exercise. **Olfactory training** has been shown to be effective in multiple clinical studies. However, these results are averaged across multiple patients and it should be remembered that each individual person may improve by different amounts. The improvement in smell is often slow and occurs over many months, even up to 2 years.



Technique:

A. The training consists of smelling four different odors: **rose**, **eucalyptus**, **lemon**, and **clove**, twice a day and every day.

1. Choose one odor and smell it for approximately 15 seconds while trying to remember what it once smelled like.
2. Rest for about 10 seconds.
3. Smell the next odor for approximately 15 seconds.
4. Rest for about 10 seconds.
5. Repeat until all 4 odors have been sampled.

B. After **3 months** switch to a new set of odors: **menthol, thyme, tangerine,** and **jasmine** and train with them as described above.

C. After **3 months** switch to another new set of odors: **green tea, bergamot, rosemary,** and **gardenia** and train with them again as described above.

Note: If there is a particular smell you want to be able to smell again, you can add this to your training. The actual substance is not required to produce an effect. Most people purchase essential oils containing the odors listed above. The advantage is ease of use and ability to cap the bottles to prevent gradual decreasing strength of the odor. These can be purchased through multiple on-line vendors, some holistic medicine shops, and health foods stores.

Appendix 2: Patient Education: Losing Your Sense of Smell After a Viral Upper Respiratory Infection

- A viral infection of the nose or sinuses is one of the reasons people may suddenly lose their smell. Sometimes patients will recall having had a cold or a flu just prior to losing their smell. Other times these viral infections are so mild, the person may not remember much at all about having been ill.

- COVID-19 is one of the viral infections that could lead to smell loss, but there are also lots of other types of viruses (for example, other types of coronaviruses, rhinoviruses and influenza viruses) that can cause smell loss.

- When people lose their sense of smell, they often feel like they've also lost their sense of taste. Because the flavor of food (the ability to make out the difference between watermelon versus cherry) is dependent on our ability to smell it. The only "tastes" left are the basic ones of sweet/salty/sour/bitter that our tongue delivers directly to our brain.

- People are sometimes able to recover their sense of smell after a viral infection. If this is going to happen, the majority of recovery usually happens in the first several months after being sick. A slower recovery could possibly still happen over the next year or so. Unfortunately, there are many people who are not able to recover on their own.

- Losing your smell and taste can really affect a person's quality of life. It may be hard to enjoy food and drink. It may be hard to judge personal hygiene. It may be hard to detect dangerous things like smoke, natural gas, and food that has turned bad.

- Unfortunately, no medications have been proven to help people recover their smell after a virus. There are even some types of medications and sprays that can further harm your smelling ability. The best thing to do if you have smell loss that persists beyond the time of your cold or flu is to seek treatment from a medical doctor. The type of doctor that will likely know most about smell loss is an otolaryngologist (also known as an ENT doctor).

- Even though medications may not be helpful, there is a treatment called "olfactory training" that can be helpful. Olfactory training is a very simple protocol that a person can do themselves at home to help retrain their brain to smell again. Olfactory training actually has high-level evidence showing that it works. Olfactory training may not bring all the smell back, but it is simple and can help many improve. See the attached Olfactory Training sheet for details.

- In this time of the COVID-19 pandemic, it may not be easy for you to visit your doctor in person about this symptom, but even a telemedicine visit with an otolaryngologist may be a helpful starting point. If this symptom occurs during a time when the hospital systems near you are at capacity and you cannot be seen, even via telehealth, starting with olfactory training until you can get a visit is a good idea. One last important consideration during this time is that, based on information we have currently, losing your sense of smell and taste can be an early sign of COVID-19 infection (and is sometimes the only symptom people have). If this happens to you without any other symptoms, consider self-isolating if possible, so you do not carry the infection to others. If you develop other symptoms of COVID-19 in addition to your smell loss, contact your doctor to be screened and possibly tested.