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RHINOLOGY: TASTE AND SMELL DISORDERS (C PHILPOTT, SECTION EDITOR)

Ask the Experts: An International Consensus on Managing Post-Infectious Olfactory Dysfunction Including COVID-19

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Abstract

Purpose of Review To summarise the current understanding of post-infectious olfactory dysfunction (PIOD) and provide a consensus on management of the condition through an evidence-based approach, critically reviewing the available management options.

Recent Findings New studies investigating the pathophysiology of PIOD in COVID-19 patients have found that in those with persistent symptoms there is an association with lower tissue perfusion in the orbital and medial regions of the frontal lobe. Recent meta-analyses have listed olfactory training as the first line management for PIOD.

Summary Olfactory training remains the most recommended management option for PIOD. The use of systemic corticosteroids to treat PIOD is not encouraged due to poor evidence.

Keywords Post-infectious olfactory dysfunction · COVID-19 · Olfactory training

Introduction

Olfactory dysfunction has been a frequent occurring complaint in adults [1], though awareness of this complaint has become more prevalent in the public eye with the emergence of the SARS-CoV2 (COVID-19) virus [2]. Pre-pandemic, post-infectious olfactory dysfunction (PIOD) was identified as a significant cause of persistent olfactory dysfunction with 11% of all cases attributed to it [3]. This rises to between 20 and 30% in specialised olfactory clinics [4]. Post-pandemic, the proportion of olfactory dysfunction cases caused by PIOD is likely to be much higher.

PIOD has a variable prognosis, dependent on a number of factors. One meta-analysis indicated that almost 50% of anosmic and a third of hyposmic patients displayed clinically significant improvement of their symptoms within 2 years [5], and in a separate study one-third of patients also had spontaneous improvement of symptoms within 12–18 months [6].

Although most patients will display some recovery within 2 to 3 years [5], loss of olfaction can have a significant psychological effect on patients, including loss of satisfaction and enjoyment of food and drink, safety perception—which helps avoid environmental hazards such as fire or rotten food, as well as some psychosocial function—recognition of family and other interpersonal relationships [7, 8]. This may lead to social anxiety and/or depression [9].

Regarding modalities of treatment for PIOD, olfactory training (OT) has emerged as one of the most promising options. Multiple meta-analyses since 2009 have concluded that OT has the best efficacy compared to other management options, including non-PIOD etiologies [10]. There are no specific pharmacological treatments for PIOD but the use of topical and systemic corticosteroids, theophylline, sodium citrate, alpha lipoic acid, vitamin A, minocycline and zinc sulphate have all been trialled and investigated [11, 12]. The

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aim of this review is to summarise current understanding of PIOD and offer clinicians a guide on managing the typical PIOD patient.

Pathogenesis of Non-COVID-Related PIOD

Disruption of the normal olfactory mechanisms begins post-infection with the acute onset of inflammation in the nasal mucosa resulting in nasal congestion. This impairs the airflow across the olfactory epithelium, resulting in reduced detection of odorants. In the majority of patients, olfactory function would return once this acute process settles. If olfactory dysfunction persists, however, the likely cause is neuroepithelial injury [12].

Alongside coronavirus, rhinovirus is the most common virus found in patients with PIOD, with parainfluenza and Epstein-Barr virus also commonly identified [13]. These viruses, amongst others, have been found to damage olfactory function via a number of different methods. The viruses can cause partial loss to olfactory receptor neurons, found in the olfactory epithelium, which are involved in detecting odorants [14]. Viruses have also been shown to cause cellular changes to the olfactory epithelium leading to a significantly disorganised epithelium when compared to patients with normal olfactory function [15]. This ultimately leads to a much-reduced area dedicated to odour detection. Other studies have found that viruses induce neurogenesis as a response, resulting in the majority of neurons being immature. The dendrites in patients with PIOD have also been shown to be truncated and struggle to reach the surface layer of the epithelium, again causing an impact on the sense of smell [16].

Imaging studies have found that viruses can cause changes further along the olfactory pathway also, with the olfactory bulb in particular affected [17]. This is significant as the presence of smell dysfunction is associated with a reduced olfactory bulb volume [18]. The host immune response to the virus can also be a potential cause of PIOD, with damage to neuroepithelial cells caused by a neutrophil-mediated response [19].

Pathogenesis of COVID-19-Related PIOD

The olfactory dysfunction related to COVID-19 has been noted to be much more profound with accompanying loss of taste, which tends to be to bitter foods [20]. As mentioned above, olfactory loss due to post-viral infections can occur anywhere along the olfactory pathway. The PIOD associated with COVID-19 tends to predominate in the olfactory epithelium rather than the central nervous system [21]. Angiotensin-converting enzyme 2 (ACE2) has been found to play a key role in the pathogenesis of PIOD in COVID-19 patients. Viral entry through the ACE2 receptors causes olfactory dysfunction when the sustentacular supporting cells are infected, leading to cell death. The sustentacular cells support olfactory function via a number of different methods. This includes providing glucose to the cilia and absorbing odorant-binding proteins. Damage to these cells could explain why in the majority of patients with PIOD, symptoms tend to resolve as the olfactory sensory neurons are not directly damaged and it is only the support system for smell affected [22, 23].

A recent study investigating persistent PIOD in COVID-19 patients using multimodal MRIs found that olfactory dysfunction was associated with lower tissue perfusion in the orbital and medial frontal regions of the brain. It should be noted that whether these findings were a result of a reduction of input signalling from the peripheral olfactory system or simply due to central nervous system damage cannot be reliably made [24••].

Evaluating Olfactory Dysfunction

Olfactory dysfunction has numerous different aetiologies and therefore a thorough history and examination are essential. This review will focus on evaluating PIOD. Nasal endoscopy should always be used to assess the patency of the olfactory cleft and middle meatus; and for evidence of nasal inflammation which can include, but are not limited to, secretions, polyps and turbinate hypertrophy. Findings can be documented via a validated scoring system such as the Lund-Kennedy or Olfactory Cleft Endoscopy scale [25]. Clinicians should note that intranasal anaesthesia, usually used before nasal endoscopy can influence self-assessment of smell and odour discrimination [26]. It is therefore advised that endoscopy is carried out after subjective olfactory tests.

There are three different approaches to assessment of olfactory dysfunction. The first involves a subjective assessment, usually via validated questionnaires such as the Questionnaire for Olfactory Dysfunction. These tests can be useful for evaluating progress during treatment and for measuring the impact on quality of life. When used in isolation, they can be unreliable, however, for quantifying actual olfactory dysfunction compared to other methods [27].

One of the difficulties with subjective assessment is that patients struggle to accurately reflect the degree of olfactory dysfunction. This can be due to a number of factors, such as age and cognition [28]. Psychophysical tests can accurately reflect olfactory function in patients. They work by introducing an olfactory stimulus to the patient and recording their response as the outcome. There are different types of olfactory testing, such as suprathreshold and threshold assessment. Suprathreshold assessment can include odour

discrimination (able to distinguish between different odours non-verbally), odour identification (correctly recognising stimulus and conveying its identity) and odour memory (remembering and recalling an odour). Threshold assessment asks the patient the lowest concentration of an odour they can detect [12]. Studies have shown that suprathreshold testing and odour threshold are important in the diagnostic work up of psychophysical assessment. Currently, there is no consensus on whether odour threshold, discrimination and identification all need to be tested as part of the psychophysical assessment [29]. In patients with PIOD related to COVID-19, it should be noted that odour threshold may be more compromised than odour identification [30]. Specific validated tests that can be used include the Sniffin' Sticks test [31], Smell Diskettes [32] and the University of Pennsylvania Smell Identification Test [33].

MRI scanning forms a non-subjective form of assessment of olfactory function by allowing accurate measurements of olfactory bulb volume and sulcus depth. This is important as numerous studies have shown a positive correlation between olfactory function and olfactory bulb volume [34]; some studies have also found the olfactory sulcus depth to be smaller in patients with PIOD [35]. MRIs can also be useful in assessing olfactory-related cortical activity [36] and can also provide information on the aetiology of non-infectious causes of olfactory dysfunction though the cost–benefit of routine MRIs in this patient cohort would be debatable [37].

Management of PIOD–Conservative

The rate of recovery from PIOD is dependent on a number of factors. These include the patient's age, length of symptoms and the degree of dysfunction [38]. Taking this into consideration, studies have shown that around one-third of patients who present to clinicians with PIOD spontaneously recover without the need of treatment [39]. This seems to be the case regardless of the aetiology [38]. Olfactory function can recover when symptoms of acute inflammation or nasal congestion clear, but insults to the olfactory epithelium will take longer to recover as complete neurogenesis will need to take place to replace the damaged cells [40]. With COVID-19-related PIOD, there seems to be a higher incidence of recovery and occurs over a shorter period of time. As explained earlier, this may be due to COVID-19 affecting the sustentacular cells rather than the sensory neurons of the olfactory epithelium [23].

Patients need to be counselled on an individual basis taking into account factors that are specific to them (aetiology, age, duration of symptoms etc.) The risk of no recovery and possible deterioration is also present for those who choose to forgo treatment and this must be a consideration when making treatment decisions.

Management of PIOD–Corticosteroids

The use of corticosteroids (CS) to treat PIOD (both COVID-19 and non-COVID-19) is controversial. Although there have been numerous studies done investigating different doses, routes and formulations of steroids, these do not include randomised controlled trials (RCT) focussing on PIOD [12].

An RCT in 2016 found that patients given a 4-week course of oral prednisolone, either by itself or combined with Ginkgo biloba, displayed significant improvement in their threshold testing scores [41]. Oral steroids were also shown to significantly improve olfactory function in a retrospective study done comparing oral versus topical steroids [42]. Several studies have accredited the positive effects of oral CS to their action on any underlying sinonasal inflammation [43]. A possible explanation for the poor performance of topical CS in several studies could be the method of delivery, with patients unsure of the best head position to ensure the steroids reach the olfactory cleft [44]. Conversely, Yan et al. found very poor evidence to support systemic CS use in patients with the non-sinonasal disease [43]. A further review found that CS use, either topical or systemic, could only be recommended as 'optional' because of the shortage of high-quality studies [45].

Numerous studies have looked into the potential benefits of using systemic CS to treat COVID-19-related PIOD, especially after the World Health Organisation recommended their use in patients with severe illness to reduce 28-day mortality [46]. High-quality evidence, however, is lacking and combined with the high rate of spontaneous recovery associated with COVID-19, that this is simply the natural progression of the disease must be considered [47••]. Chiesa-Estomba et al. carried out a prospective study and found that both topical and systemic CS had no impact on the prognosis of olfactory dysfunction [48].

Management of PIOD–Olfactory Training

Classical olfactory training (COT) involves patients smelling four sets of odours (phenyl ethyl alcohol, eucalyptol, citronella and eugenol) for 12 weeks [49]. Modified olfactory training (MOT) is a 36-week process, with the 12-week COT odorants course followed by 12 weeks of a different set (menthol, thyme, tangerine and jasmine), followed by another 12-week course of the final set of odorants (green tea, bergamot, rosemary and gardenia). MOT was found to leave patients with superior odour discrimination and identification in one study [50], though this has been disputed in numerous other studies [51]

OT has generated a significant amount of attention since its inception and has been heavily researched. Although it has been found to achieve improvement in olfactory dysfunction in patients of all aetiologies, the most significant results appear in patients with PIOD [10]. Three meta-analyses and numerous prospective controlled studies have all found that OT benefits olfactory function [10, 52, 53], with a shorter duration of olfactory loss being a good indicator of greater recovery [45].

Management of PIOD–Other Medical Management

Studies have been done on numerous other potential management options for PIOD with some options showing more promise than others. Vitamin A was noted to show improvement in olfactory function as far back as 1962 [54] and is believed to help the regeneration of the olfactory epithelium. Hummel et al. also observed improvement in patients given 10,000 IU of intranasal vitamin A when compared to the control group but, as this was a retrospective study, the fact that the variables between the two groups could not be controlled may affect the results [55].

Although theophylline in one study displayed a statistically significant improvement in olfactory function in over 50% of total patients (312), the study did use olfactory tests that were not validated, had numerous treatment arms and also had changes in treatment [56, 57]. The exact mechanism of action is not completely understood, though it is believed to help the regeneration of the olfactory epithelium by inhibiting phosphodiesterase [57]. It should be noted that there are no specific studies on theophylline for patients with PIOD.

Intranasal sodium citrate in a 2017 study had a statistically significant improvement in odour thresholds for phenyl ethyl alcohol, 1-butanol and eucalyptol with effects lasting for up to 2 h [58]. However, Whitcroft et al. in their study of 60 patients concluded that sodium citrate had no effect on patients with PIOD [59].

Minocycline and zinc sulphate have both been the subject of many studies and were found to have no statistically significant improvement in olfactory function [12].

Recommendations for Managing PIOD Patients in a Non-ENT Setting

Managing PIOD patients can present quite a challenge for clinicians. Olfactory dysfunction as a symptom in itself is not often given importance, particularly in the context of COVID-19, when more emphasis is rightly given to survival and organ impairment. This does not mean that the impact olfactory dysfunction can have on a patient's quality of life should not be appreciated. A further difficulty lies in the lack of validated testing. Most clinicians rely on their patients' subjective assessment of olfactory dysfunction and this can be difficult to quantify.

And finally, both the availability of treatment options and the limited evidence for them can lead to difficulties in both deciding and obtaining treatment.

Figure 1 (adapted from Addison et al. [12]) shows a schematic chart for the management of PIOD in the primary care setting

History and examination

A full and thorough history should be carried out, focussing on:

- Onset and duration of symptoms
- Specific precipitating factors (head trauma, COVID, other viral illnesses)
- Fluctuations
- Specific changes (separating smells from basic tastes)
- Impact on quality of life
- Past medical history including allergies
- Medications
- Previous episodes of sinusitis, nasal obstruction due to polyps, epistaxis
- Smoking and alcohol history
- Exposure to toxins
- Family history

Examination should involve a full head and neck assessment (including anterior rhinoscopy), a neurological examination and a respiratory examination (for any evidence of an upper respiratory infection). For patients with a sudden onset smell loss, COVID-19-related precautions must be taken.

Olfactory Testing

Assessment of olfactory function is an essential component of the initial work up of PIOD patients. Subjective testing can be misleading and variable between patients so a psychosocial test will help assess impact of disease and the success of any clinical intervention. Realistically, for clinicians in the community, olfactory assessment could be achieved through the use of validated questionnaires (Questionnaire for Olfactory Dysfunction) or validated tests such as the Sniffin' Sticks test [31].

Recommendations for Treatment

Olfactory training has been the treatment option with the best-reviewed evidence base and therefore forms the cornerstone of initial treatment. This is a very cost-effective option, which

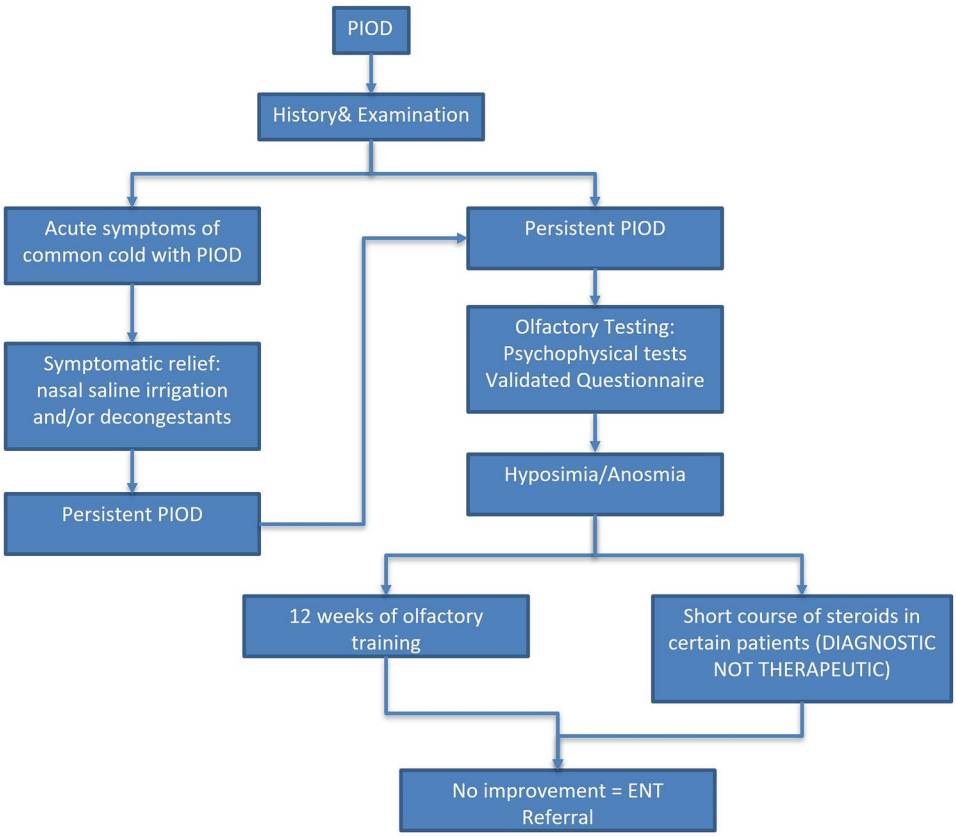

Fig. 1 Management flow chart for treating PIOD in primary care. (Adapted from: Addison AB et al. Journal of Allergy and Clinical Immunology. 2021 May 1;147 (5):1704–19, with permission from Elsevier) [12]

patients can perform at home and it should also be noted that the earlier olfactory training is commenced the better the chances of recovery. The method and schedule of olfactory training, using the four specific odours, are described below:

1. Place each specific odour material into a separate bowl or jar, or, alternatively, into your hands
2. Naturally inhale: do not sniff too quickly or deeply as this will have a detrimental effect on registering the smell
3. Repeat the gentle sniffing for 20 to 30 s
4. Move onto the next smell and repeat the previous steps
5. Record your findings and document any changes into a daily diary or log (available at https://www.fifthsense.org.uk/smell-training)
6. This programme should be at least 12 weeks in duration

Steroids are currently not recommended as a treatment option for PIOD [47••]. They can be initially trialled for diagnostic use to rule out nasal congestion, which can occur alongside PIOD and can limit the efficacy of clinical interventions and spontaneous recovery. Patients should be counselled on the use of steroids, specifically the potential side effects that may occur (increased risk of hip fractures and decompensating glaucoma) [60] and the lack of evidence for its use in PIOD [45]. Topical steroids may be better in this aspect, as they have a better profile for adverse reactions but instructions on the proper method of delivery should be given, to ensure the olfactory cleft is reached.

Clinicians should also provide advice and counselling to patients about the impact olfactory dysfunction can have on their quality of life and refer them to help and support groups and online charities such as Fifth Sense.

Referral to Tertiary Care

As the evidence-based management of PIOD is still limited, we would recommend that primary care clinicians refer to ear, nose and throat (ENT) for further management if olfactory training has been unsuccessful.

Conclusion

PIOD (both COVID-related and non-COVID-related) presents significant challenges to clinicians and can have a detrimental impact on patients' quality of life. The aim of this review was to provide a brief understanding on the pathophysiology of PIOD and guide current recommendations on management. The emphasis on olfactory testing cannot be understated, as is the need to start olfactory training as

early as possible. There is no evidence to suggests systemic steroids should be given to patients with PIOD and further research into their use needs to be done.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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