Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction

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Background: Respiratory tract viruses are the second most common cause of olfactory dysfunction. As we learn more about the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the recognition that olfactory dysfunction is a key symptom of this disease process, there is a greater need than ever for evidence-based management of postinfectious olfactory dysfunction (PIOD).

Objective: Our aim was to provide an evidence-based practical guide to the management of PIOD (including post–coronavirus 2019 cases) for both primary care practitioners and hospital specialists.

Methods: A systematic review of the treatment options available for the management of PIOD was performed. The written systematic review was then circulated among the members of the Clinical Olfactory Working Group for their perusal before roundtable expert discussion of the treatment options. The group also undertook a survey to determine their current clinical practice with regard to treatment of PIOD.

Results: The search resulted in 467 citations, of which 107 articles were fully reviewed and analyzed for eligibility; 40 citations fulfilled the inclusion criteria, 11 of which were randomized controlled trials. In total, 15 of the articles specifically looked at PIOD whereas the other 25 included other etiologies for olfactory dysfunction.

Conclusions: The Clinical Olfactory Working Group members made an overwhelming recommendation for olfactory training; none recommended monocycline antibiotics. The diagnostic role of oral steroids was discussed; some group members were in favor of vitamin A drops. Further research is needed to confirm the place of other therapeutic options. (J Allergy Clin Immunol 2021;147:1704-19.)

Key words: *Olfaction, olfactory disorders, viral infections, hyposmia, anosmia, parosmia therapy, COVID-19*

Loss of smell is a common complaint in adults; yet, it has been underestimated.[1] Anosmia, complete loss of smell, is thought to affect at least 1% of the population, with the overall estimated prevalence of olfactory disorders now thought to be more than 20%.[2-4] Upper respiratory tract infections are usually associated with decreased smell during their acute phase.[5-7] Postinfectious olfactory dysfunction (PIOD) represents an important frequent cause of persistent olfactory dysfunction,[1] accounting for 11% of all cases[8] but 20% to 30% of cases in specialized smell and taste clinics[9,10] and typically (before coronavirus disease 2019 [COVID-2019]) affecting women older than 50 years of age. Olfaction plays important roles in daily life, ranging from safety perception (the ability to detect hazardous substances, fire, and rotten foods) to psychosocial functions (such as recognition of kin or emotions mediated through body odors) and enjoyment of food and drink.[11] Olfactory dysfunction may therefore lead to significant morbidity in the form of nutritional disturbance, social anxiety, or depression.[11-13]

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Abbreviations used

ALA: α-Lipoic acid
COVID-19: Coronavirus disease 2019
ENT: Ear, nose, and throat
MRI: Magnetic resonance imaging
OB: Olfactory bulb
OT: Olfactory training
PIOD: Postinfectious olfactory dysfunction (also known as postviral olfactory loss/dysfunction)
PTOL: Posttraumatic olfactory loss
RCT: Randomized controlled trial
TDI: Threshold, discrimination, identification
T&T: Toyota and Takagi
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
VAS: Visual analog scale

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, with its devastating global effects, has brought public awareness to the impact of viral infections on olfactory function.[14,15] There is now an emerging cluster of new patients with PIOD—those infected with the SARS-CoV-2 virus as part of the pandemic. With smell loss now an official World Health Organization symptom of COVID-19, it is estimated that more than 60% of those contracting the virus are affected by this symptom,[16-19] including those who are otherwise asymptomatic.[20] Extrapolating from this figure, it is therefore possible that nearly 20 million people globally will have experienced smell loss due to COVID-19 by October 2020. COVID-19 infection appears to have a different pattern of smell loss than typical PIOD cases, with a more profound loss of smell and with taste loss, specifically loss of bitter taste, which has been identified as a discriminating feature.[21] In another study SARS-CoV-2, mainly affected odor thresholds, possibly suggesting that the major cause of loss of smell lies at the level of the olfactory neuroepithelium rather than in the central nervous system.[20] Current thinking regarding the mechanism of chemosensory dysfunction in COVID-19 infection suggests that it is caused by viral entry via angiotensin-converting enzyme 2 receptors, with infection and death of sustentacular cells in the olfactory epithelium; this does not necessarily lead to infection, damage, death, or the need for regeneration of olfactory receptor neurons in the majority of cases, and hence, such patients appear to recover within 4 weeks of the onset.[22] The current data suggest that 10% to 17% of patients have continued smell loss (ie, COVID-19–related PIOD) and do not recover spontaneously.[23,24] Notably, many of these patients report parosmia during recovery.[25] The persistence of olfactory dysfunction in these cases may be attributed to a larger area of the olfactory epithelium being affected by the coronavirus, possibly with cellular death of a larger number of olfactory receptor neurons; further evidence is required to support this theory.[22]

The current understanding and pathogenesis of non–COVID-19 olfactory dysfunction following a viral upper respiratory tract infection begins with inflammation of the nasal mucosa as a result of the acute infection. This disrupts the natural airway conduction through the nasal cavity, hence inhibiting the transport of odorants to the olfactory epithelium. Impaired olfaction may also result from dysfunction at the level of the olfactory receptor neuron, although the precise pathophysiologic mechanism is virus dependant. Rhinoviruses, for instance, cause a selective neutrophil and monocyte recruitment to occur. The inflammatory cascade that ensues includes an increase in bradykinin, cytokine, chemokine, and sICAM-1 concentrations.[26] The response in an immunocompetent individual involves T-lymphocyte activation, allowing the viral pathogen to be eliminated. Viral pathogens other than rhinoviruses that have been implicated in PIOD include parainfluenza virus and EBV, with the frequency of virus found in individual studies varying[27]; for example, parainfluenza accounted for 88% of viral pathogens in 1 study.[28]

With specific respect to the olfactory apparatus, these viruses appear to cause some partial loss of olfactory receptor neurons in the olfactory epithelium. Ultrastructurally, studies have revealed a markedly disorganized epithelium with a decrease in the number of olfactory receptor cells and nerve bundles, with squamous metaplasia occurring in a few cases.[29] This reduction in the number of olfactory receptor neurons means that at the epithelial surface, there is a lack of dendrites and vesicles and, therefore, a decrease in the area available for detection of odor molecules.[30] Jafek et al reported that especially in patients with anosmia, the few dendrites that were present did not reach the epithelial surface and appeared shrunken.[31] Patients with PIOD have also been found to have reduced olfactory bulb (OB) volume and patchy distribution of neuroepithelia, perhaps because of the process of remodeling and replacement.[32] Calculation of the OB volume studied through magnetic resonance imaging (MRI) scanning in coronal T2 sequences has demonstrated an overall reduced OB volume on both sides even if normalized to age and sex. An OB volume greater than 40 cm^3 for 1 OB shows a trend for a good prognosis for recovery. This must be considered in conjunction with the age and sex of the patient, the duration between the onset of the symptoms and the period when the test has been performed, and other potential toxins to which the patient would have been exposed.[32]

The prognosis of PIOD is variable; it has been suggested that up to one-third of patients presenting at specialized, tertiary smell and taste clinics undergo spontaneous recovery over a period of 12 to 18 months.[33] The presence of parosmia has recently been demonstrated to be associated with a more favorable prognosis for recovery.[34] Different treatment modalities have been tried, ranging from smell training through to a variety of medical treatments, both topical and systemic.[35] This consensus document aims to combine the collective experience of the Clinical Olfactory Working Group with the current evidence base to establish guidance for medical and nonmedical treatments for patients with PIOD.

In general, evaluation of olfactory dysfunction can be performed by 3 different methods: subjective, patient-reported assessment; psychophysical testing; and less biased measures, such as olfactory event–related potentials or functional MRI.

Subjective assessment is performed by using various methods, including visual analog scales (VASs) and questionnaires. Although olfactory-specific questionnaires such as the Questionnaire for Olfactory Dysfunction can be used to differentiate between normosmia and hyposmia, they tend to be unreliable compared with psychophysical testing and are best used to assess impact on quality of life.[36] Subjective testing can be a valuable tool in monitoring the clinical effect of treatment, and it should therefore be used in conjunction with other objective testing.[1] Ideally only validated questionnaires should be used when assessing patients with olfactory dysfunction, and these should be used with other psychophysical tests, given their lack of accuracy when used alone.[36]

Apart from olfactory testing, clinical evaluation should always include nasal endoscopy focusing on the patency of olfactory cleft and the presence of findings suggesting nasal inflammation such as polyps, turbinate hypertrophy, edema, and purulent secretions. Assessment in this way should ideally be quantified by using a validated scoring system, such as the Lund-Kennedy or Olfactory Cleft Endoscopy scale.[37] In a certain percentage of patients with PIOD an underlying inflammatory process in the nose may already exist, and its recognition, if not already diagnosed, could modify the treatment options. Obviously, this has been problematic during the COVID-19 pandemic, when face-to-face contact and nasal endoscopy have been avoided wherever possible. Measures may need to be taken to screen patients for COVID-19 to reduce the potential for transmission of infection to the health care team. Where any doubt regarding COVID-19 status exists, appropriate personal protective equipment should be worn.

Psychophysical assessment of olfactory function involves the use of an olfactory stimulus presented to the patient; the outcome of the test is dependent on the patient's response. It requires a patient who is cooperative and understands and follows instructions.[1] Different aspects of olfactory testing, including threshold and suprathreshold assessment, can be performed. Odor threshold is the lowest concentration of an odorant that is detectable to a participant and does not require odor identification.[38] Odor discrimination describes the nonverbal ability to differentiate between different odors. Odor identification involves both recognition of a stimulus and communication of its correct identity (ie, the ability to name an odor from a list of descriptors). Odor identification requires previous exposure to odor stimulus and may therefore be culturally specific; hence, these tests need to be adapted for different communities.[1] The usefulness of testing for multiple psychophysical components of olfaction (eg, threshold, discrimination, and identification) when assessing olfactory dysfunction is debated. There is, however, good evidence that both odor threshold and suprathreshold testing add to the diagnostic value of psychophysical assessment[39]; odor threshold detection may be more affected by COVID-19 than odor identification is.[20]

There are various commercially available tests that measure either just 1 aspect of olfaction or multiple components, such as the Sniffin' Sticks test (Burghart, Tinsdaler, Germany),[40,41] Smell Diskettes (Novimed, Dietikon, Switzerland),[42] and the University of Pennsylvania Smell Identification Test (Sensonics, Philadelphia, Pa).[43] Other noncommercial tests have also been validated; they include the Connecticut Chemosensory Clinical Research Centre Test[44] and the Toyota and Takagi (T&T) olfactometer (Japan).[45] The U-Sniff has been validated for children,[46,47] and the European retronasal test for smell perception when eating.[48]

Retronasal olfaction can be tested by asking patients to identify flavored powders. Such tests are useful where there is diagnostic uncertainty. For example, it has been demonstrated that in cases of sudden-onset olfactory dysfunction, such as posttraumatic loss of olfaction, both orthonasal and retronasal functions decline concurrently. However, more progressive dysfunction, such as is seen in sinonasal disease, may preferentially affect the orthonasal route, whereas retronasal olfaction may be preserved.[49,50] As part of a full olfactory assessment, screening of gustatory function should be undertaken. This can be achieved by using liquids applied to the tongue for sweet, salty, sour, or bitter (umami is not commonly screened for, as it is poorly identified).

Electrophysiologic studies include electroencephalography and electroolfactography (the recording of generator potentials via an electrode in contact with the olfactory neuroepithelium). As electroencephalography and electroolfactography are both event-related, delivery of a known concentration of odorant must be precisely controlled by using an olfactometer, which requires certain equipment and specific technical expertise, which limits the use of such testing for routine clinical purposes.[51]

MRI scanning allows for calculation of OB volume, olfactory sulcus depth, and upstream volumetric assessment of olfactory eloquent regions, all of which have been linked to olfactory function.[52,53] In addition, computed tomography and MRI provide information regarding inflammation of nasal and paranasal mucosa in the event of a history suggestive of concomitant inflammatory pathology in cases in which endoscopy was not conclusive. They may also reveal evidence of central pathology contributing to smell dysfunction, such as sequelae of prior head trauma or microvascular disease. Functional MRI can provide dynamic assessment of olfactory-related cortical activity, but its use in individual patients is limited.[54]

METHODS

Literature review

A comprehensive electronic database search based on the updated guidelines for systematic reviews of the Cochrane Collaboration Review Group[55] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis was performed.[56] The population, intervention, comparisons, outcomes, and study design algorithm guided data extraction.[57]

On July 6, 2020, a systematic search of electronic databases (PubMed, Google Scholar, Cochrane database, Web of Science, Scopus, and Embase) was conducted. The Cochrane methodologic filter for randomized controlled trials (RCTs) was combine with a search of Medical Subject Heading key words and other relevant terms, including *anosmia*, *hyposmia*, *dysosmia*, *parosmia*, *pharmacotherapy*, *olfactory dysfunction*, *postviral*, *postinfectious*, *olfactory impairment*, *olfactory disturbance*, *olfactory loss*, *smell disorder*, *viral infection*, *virus*, *viral disease*, *common cold*, and *respiratory tract infection*, to identify primary comparative studies on treatment and management options for postviral olfactory loss. Further cross screenings of the references were performed to complement the initial search results. Comparative studies of any design examining the outcome of management of patients with postviral olfactory loss were included.

The level of evidence was established for each publication, and the risk of bias was analyzed for each of the included studies. The Modified Cochrane Collaboration Tool for Assessing Risk of Bias was applied to level 1 and level 2 studies, and The Newcastle-Ottawa Quality Assessment Scale was applied for studies in the level 3 and level 4 categories. By following the modified Grading of Recommendations, Assessment, Development, and Evaluation quality assessment, the quality of evidence for the treatment option was graded and recommendations (Table I) were provided when there was sufficient high-level evidence for a particular intervention. Each subsequent author reviewed, critiqued, and amended the recommendations, and any discrepancies between the authors were discussed until a consensus was reached.

Inclusion criteria

All published studies on treatment of PIOD, including

- RCTs,
- Cohort studies, and
- Preliminary results of ongoing research.

TABLE I. Grade of recommendation for PIOD

Intervention	Grade of recommendation	Effect
Olfactory training	B	Positive
Steroid	B	Positive
Theophylline	B (not specific for patient with PIOD)	Positive
Sodium citrate	B	Positive
N-methyl D-aspartate antagonist (caroverine)	C (hyposmic patients improved)	Positive
Traditional Chinese acupuncture	C	No effect
α-Lipoic acid	C	Positive
Vitamin A or B	C	Mixed
Monocycline	C	No effect
Zinc sulphate	C	No effect

Exclusion criteria

- Case reports, letters to the editor, and book chapters;
- Non–English language publications; and
- Studies of subjects with olfactory loss secondary to etiologies not including PIOD (eg, posttraumatic, congenital, etc).

RESULTS

The search resulted in 467 citations, from which the relevant studies were selected for review and duplicates were removed. In total, 107 articles were fully reviewed and analyzed for eligibility. In all, 40 citations fulfilled the inclusion criteria; they included 11 RCTs (Table II[58-97]). In total, 15 of the articles specifically looked at PIOD whereas the other 25 included other etiologies for olfactory dysfunction. All of the articles dealt with human studies related primarily to the outcomes of management in patients with PIOD (see the flowchart [Fig 1])

The combined total number of patients included in this review was 4983; of these patients, 2352 (47.2%) had PIOD. The patients with PIOD were diagnosed on the basis of self-reported history of a preceding (viral) upper respiratory tract infection. A diagnosis of PIOD should be made in line with international guidelines.[1] The most commonly used test kit was the Sniffin' Sticks (n = 18 studies). Other tests utilized included the University of Pennsylvania Smell Identification Test, T&T olfactometer, Cross-Cultural Smell Identification Test, Connecticut Chemosensory Clinical Research Centre test, butanol threshold testing, and VAS and/or additional subjective scales.

DISCUSSION

Conservative management

Studies have shown that at least one-third of patients presenting for evaluation of persistent PIOD had spontaneous recovery of their sense of smell without any treatment; this is in addition to the fact that many more patients will never present to a clinician on account of spontaneous resolution, even if the time course of an acute upper respiratory tract infection is longer than usual. In 2006, Reden et al studied 262 patients with PIOD and showed a 32% spontaneous recovery rate, although 6% of the cohort had worsening olfactory function after 14 months of follow-up.[33] In a 2007 study of 542 patients, London et al demonstrated that regardless of etiology, more than a third of patients had spontaneous improvement of olfaction.[98] The rate of recovery was dependent on the degree of initial loss, patient age, and duration of olfactory loss.[98] Hence, an individualized discussion about the prognosis and likelihood of spontaneous recovery should be undertaken with all patients. Especially in the case of COVID-19 infection, spontaneous recovery seems to be faster and with higher incidence, and this information would be valuable to be explained in those patients. Similarly, the possible deterioration of patients' sense of smell without any treatment should also be explained so that they can make an informed decision.

Quantification of recovery will depend on the study, but in most studies, improvement is defined as an improvement in psychophysical olfactory test results. In the Sniffin' Sticks test, for example, this would be a change of 5.5 points or more in the threshold, discrimination, identification (TDI) score.[39]

OT

There is good evidence to suggest that olfactory training (OT) improves olfactory function in patients with PIOD. There are 3 meta-analyses[99-101] and several prospective controlled studies using long-term (>32 weeks), high-concentration odorants that have shown improved olfactory function in patients who had OT. The classic OT involves a 5-minute exposure to 4 different odorants twice a day.[67] These 4 odorants (phenyl ethyl alcohol, eucalyptol, citronella, and eugenol) are said to represent 4 of the 6 most significant odor qualities of the olfactory spectrum and have been shown to improve olfactory loss after training of 12 weeks or more.

The concept of modified OT was first published by Altundag et al in 2015.[62] The 4 odorants used in the classic OT were initially used for 12 weeks. This was followed by a second set of odorants (menthol, thyme, tangerine, and jasmine) for a further 12 weeks and subsequently followed by a third set of odorants (green tea, bergamot, rosemary, and gardenia) for the final 12-week period. The study was able to demonstrate better odor discrimination and identification in patients treated with the modified technique than with the classic technique ($P < .001$).

Smoking cessation

Smoking has been shown to increase the prevalence and severity of olfactory dysfunction.[2,102] However, the role of smoking in olfactory loss remains a contentious issue, as other studies suggest a possible protective effect.[103] Although the most recent meta-analysis on the topic concluded that current smoking was associated with increased risk of olfactory dysfunction,[104] data specifically on the effects of smoking in PIOD are sparse. In a recent retrospective study, no association between smoking status and olfactory function was found in 1313 patients with PIOD.[105] However, as smoking cessation seems to have a positive effect on olfactory function,[106] undertaking it may be beneficial for some patients.

Oral and intranasal corticosteroids

Studies exploring the use of various formulations, routes, and doses of steroids in the treatment of patients with PIOD have shown some favorable outcomes.[69,77,79,85,107] There are, however,

TABLE II. PIOD clinical trials

Study	Study design	Patients/ etiology	Olfactory function test	Intervention	Follow-up (wk)	Results	Level of evidence
OT							
Choi et al, 2020[58]	Prospective controlled trial	104 with PIOD	Korean version of Sniffin' Sticks	OT	12	Significant improvement in threshold and identification in OT group. No change in discrimination	3
Kim et al, 2018[59]	Prospective case series	82 with PIOD	BTT and CCSIT	Korean odorants for OT	24	Improved BTT and CCSIT score	3
Poletti et al, 2017[60]	Prospective single-blinded trial	70 with PIOD; 26 with PTOL	Sniffin' Sticks	OT with HMW odorant (>150 g/mol; n=48) vs LMW odorant (<150 g/mol; n = 48) for 5 mo	20	Overall significant improvement in olfaction (PIOD > PTOL) No difference between HMW and LMW	2B
Konstantinidis et al, 2016[61]	Prospective controlled trial	111 with PIOD	Sniffin' Sticks	OT (12-wk training course vs 56-wk training course vs control)	56	Long-term training yields better function	2B
Altundag et al, 2015[62]	Prospective controlled trial	85 with PIOD	Sniffin' Sticks	OT	36	Longer OT with change of odor was effective in terms of odor discrimination and identification	2B
Damm et al, 2014[63]	Prospective single-blinded RCT	144 with PIOD	Sniffin' Sticks	High concentrations of 4 odors vs very low concentrations ("quasi-placebo")	38	OT was significantly more effective with high concentration of odors and dysfunction <12 mo	2B
Geißler et al, 2014[64]	Prospective study	39 with PIOD	Sniffin' Sticks	Suprathreshold concentrations of 4 odors	32	Longer duration of training (≥32 wk) increased effectiveness of training	2C
Konstantinidis et al, 2013[65]	Prospective study	N = 119, including 81 with PIOD	Sniffin' sticks	OT group vs control	16	Significant improvement training groups	2C
Kollndorfer et al, 2012[66]	Prospective case series	7 with PIOD	Sniffin' Sticks	OT with 4-6 odorants twice daily for 12 wk	13	Significant improvement in threshold but no change in discrimination or identification	4
Hummel et al, 2009[67]	Prospective controlled trial	N = 56, including 35 with PIOD	Sniffin' Sticks	OT group vs no-training group	12	Significant improvement in training groups with average TDI scores of 10.3 points higher after training	3
Saatci et al, 2020[68]	Prospective controlled trial	60 with PIOD	Sniffin' Sticks	Classical OT group vs OT ball group	12	Significant improvement in the OT ball group compared with in the classical OT group	3
Medical management							
Nguyen et al, 2018[69]	Prospective RCT	N = 133, including 62 with PIOD	UPSIT	OT with saline irrigation vs OT training with budesonide irrigation	32	Statistically significant improvement in the budesonide group	1B
Wang et al, 2018[70]	Retrospective cohort study	N = 288, including 158 with PIOD	UPSIT	Various bacteriostatic antibiotics vs bactericidal vs no antibiotics	52	No negative effect. No improvement in either antibiotic group. Odor thresholds better in bactericidal group	3
Whitcroft et al, 2016[71]	Prospective randomized cohort study	Hyposmia (n = 57, including 7 with PIOD)	Sniffin' Sticks	Topical sodium citrate (3.5 g/140 mL; pH 7.4; 298 mOsmol/L) vs placebo (sodium chloride)	30 min	Statistically significant improvement in PVOD	2B
Philpott et al, 2017[72]	RCT	N = 55, including 46 with PIOD	Threshold tests: phenyl ethyl alcohol, acetic acid, eucalyptol, 1-butanol	0.5 mL of 9 % sodium citrate versus placebo (sterile water)	120 min	32% improved odor sensitivity in treated arm	1B

(Continued)

TABLE II. *(Continued)*

Study	Study design	Patients/ etiology	Olfactory function test	Intervention	Follow-up (wk)	Results	Level of evidence
Whitcroft et al, 2017[73]	RCT	49 with PIOD	Sniffin' Sticks	1 mL of sodium citrate solution (3.5 g/140 mL; pH7.4; 298 mOsmol/L) versus placebo (1 mL of physiologic sodium chloride solution)	30 min	Statistically significant (but not clinically significant) improvement in composite threshold + identification scores following treatment with sodium citrate compared with placebo.	1B
Hummel et al, 2017[74]	Retrospective cohort study	N = 170, including 102 with PIOD	Sniffin' Sticks	Topical vitamin A 10,000 IU/d for 8 wk + OT vs OT for 12 wk	45	Significant improvement in vitamin A group (37%)	2B
Henkin et al, 2017[75]	Prospective controlled trial	N = 44, including 11 with PIOD	Olfactometry (odor detection and recognition for 4 odors)	Theophylline, 200-800 mg once per day for 2-10 mo	40	Increased nasal mucus sonic hedgehog levels associated with improved detection and perception of smell	2B
Dai et al, 2016[76]	Prospective cohort study	PIOD (n = 50 who failed steroid and vitamin B treatment)	UPSIT	TCA with acupoints at the nasolabial groove and middle turbinates	12	Improved UPSIT score in the TCA group from 18.24 to 22.08 vs in the observation group (from 17.36 to 18.64); subsequent analysis dismissed these findings	2B, high risk of bias
Kim et al, 2017[77]	Retrospective study	Olfactory dysfunction (N = 491, including 178 with PIOD)	Connecticut Chemosensory Clinical Research Center test (threshold test) and CCSIT	Oral prednisolone, 40 mg, reducing in third week by 5 mg/d vs mometasone furoate topical 2 sprays vs combination of oral and topical steroid	4	59.6% recovery in all group. Combination and single oral steroid statistically better than topical steroid alone	4
Schöpf et al, 2015[78]	Prospective controlled pilot study	<10 with PIOD	Sniffin' Sticks	Intranasal insulin, 40 IU (0.2 mL/nostril) vs saline placebo	55	Immediate improvement in threshold and discrimination. No clinically significant improvement. Small numbers. Patients with higher BMI performed better	4
Blomqvist et al, 2003[79]	RCT	40 with PIOD	Butanol threshold test score of < 8	40 mg of prednisolone, reducing dose; then topical fluticasone propionate for all patients; then randomized to the placebo, control, or continuation of flucticasone proprionate group	24	Initial 40 mg of prednisolone leads to improvement	2B
Henkin et al, 2009[80]	Open label prospective study	Multiple etiologies; N =312, including 97 with PIOD	Olfactometry (odor detection and recognition for 4 odors)	Patients who had suboptimal response to oral theophylline (200-800 mg) where treated with intranasal theophylline, 20 μg/d per nostril	4	Statistically significant improvement in olfactory function in this subgroup	2C
Reden et al, 2012[81]	RCT	PIOD and PTOL (N = 54)	Sniffin' Sticks	Systemic vitamin A (10,000 IU capsule, once per day for 3 mo vs placebo)	20	No statistical significance in either PVOD or PTOL groups	1B
Schriever et al, 2012[82]	Retrospective cohort study	All etiologies (N = 425, including 27 with PIOD)	Sniffin' Sticks	Oral methylprednisolone, 40 mg, reducing dose for 2 wk	2	Statistically significant improvement in sniffing sticks score by 6 points or more	2C

(Continued)

TABLE II. *(Continued)*

Study	Study design	Patients/ etiology	Olfactory function test	Intervention	Follow-up (wk)	Results	Level of evidence
Reden et al, 2011[83]	RCT	55 with PIOD	Sniffin' Sticks	Monocycline, 100 mg twice per day, vs placebo	28	No statistical difference although 15% improved in treated group against 20% spontaneously improved	1B
Vent et al, 2010[84]	Prospective study trial	30 with PIOD	Sniffin' Sticks	TCA with the following injection points: DuMai 16 and 20, Di20, Lu 7 and 9, Ma 36, and Ni3) repeated weekly for 10 wk vs oral vitamin B complex for 12 wk	12	Statistical improvement in TCA group (8/15) compared to Vitamin B group (2/15)	2C
Seo et al, 2009[85]	RCT	71 with PIOD	Butanol threshold test (anosmia score between 0 and 3), CCSIT	Monotherapy (prednisolone, 30 mg/d for the first 3 d, 20 mg/d for 4 d, and 10 mg/d for 7 d) combination (prednisolone/ginkgo biloba, 80 mg 3 times per d for 4 wk) + all given mometasone furoate for 4 ws	4	Statistically significant improvement BTT (4.8-6.9) and CCSIT	1B, no control group
Gudziol et al, 2009[86]	Prospective longitudinal pilot study	N = 19, including 4 with functional hyposmia	Sniffin' Sticks	200 mg of intravenous or oral pentoxifylline	2 d	Increased olfactory sensitivity in younger patients	2C
Fleiner and Goktas, 2011[87]	Prospective case series	N = 18, including 8 with PIOD	Sniffin' Sticks	250 μg of beclomethasone dipropionate spray directed to olfactory cleft using a specific nozzle	4	2 out of the 8 had improved TDI>6	4
Stenner et al, 2008[88]	Retrospective case series	N = 89, including 31 with PIOD	Sniffin' Sticks	Oral betamethasone, 3 mg, followed by intranasal budesonide (1.5 mg) vs intranasal budesonide (1.5 mg) + neomycin	12	Oral steroid TDI > 3; topical steroid alone = 1 patient steroid + neomycin = 2 patients	4
Fukazawa et al, 2005[89]	Prospective study	133 with PIOD	T&T olfactometer and VAS	5-mg intranasal injection of dexamethasone or betamethasone every 2 wk for 8 wk	12	49.6% improvement with use of T&T olfactometer and VASs	2C
Heilmann et al, 2004[90]	Prospective study	N = 92, including 22 with PIOD	Sniffin' Sticks	40 mg of oral prednisolone, reducing dose for 3 wk vs topical mometasone propionate for 3 mo	12	Oral steroids improved significantly. No significant improvement in topical	2C
Quint et al, 2002[91]	RCT	N = 77, including 38 with PIOD	Sniffin' Sticks and BTT	120 mg/d of caroverine vs zinc sulfate (control) for 4 wk	4	Anosmic patients improved, but significant improvement in hyposmic patient	1B-
Hummel et al, 2002[92]	Prospective clinical trial	23 with PIOD	Sniffin' Sticks	ALA, 600 mg/d for 3-11 mo	16	Statistically significant improvement in olfactory function especially younger patients	2B
Aiba et al, 1998[93]	Retrospective cohort study	N = 426, including 48 with PIOD	VAS	300 mg of zinc sulfate/d for 1 mo vs zinc + steroid (topical) + vitamin B vs top steroid + vitamin B	2	No significant improvement in PVOD group	2C
Mori et al, 1998[94]	Observational study	N = 889, including 244 with PIOD	T&T olfactometer Alinamin test/self-reporting	Topical steroids, not otherwise stated	2-48 wk	58% improvement self-reported	4

(Continued)

TABLE II. *(Continued)*

Study	Study design	Patients/ etiology	Olfactory function test	Intervention	Follow-up (wk)	Results	Level of evidence
Ikeda et al, 1995[95]	Observational study	N = 21, including 9 with PIOD 9	T&T olfactometer (OT & IT) and intravenous thiamine propyl disulfide (10 mg)	10-14 d of oral prednisolone for patients with PIOD who failed to improve following intranasal betamethasone	6-12 mo	No improvement	4
Henkin et al, 1976[96]	Double-blinded RCT - crossover design	N = 106, including 45 with PIOD	Olfactometry, VAS	One group received 2 courses of zinc sulphate 100 mg per day (in 4 divided doses), the second group received 2 courses of placebo, the third group received zinc followed by placebo, the fourth had placebo followed by zinc. Each course was 3 mo	24	No improvement in any of the groups	1A
Duncan et al, 1962[97]	Prospective case study	N = 56, including 21 with PIOD	Self-reporting	Vitamin A, 100,000 IU, for 6 wk followed by 50,000-150,000 IU of oral preparation for ≤12 wk	12	16 patients had marked improvement	3

BMI, Body mass index; *BTT*, butanol threshold testing; *CCSIT*, Cross-Cultural Smell Identification Test; *HMW*, heavy-molecular-weight; *LMW*, light-molecular-weight; *TCA*, traditional Chinese acupuncture; *UPSIT*, University of Pennsylvania Smell Identification Test.

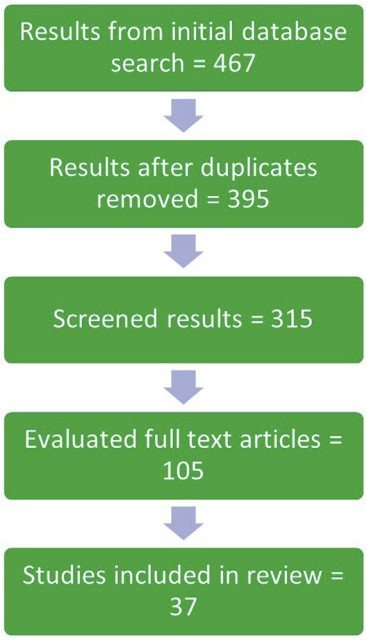


FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart based on our predefined inclusion and exclusion criteria.

no large RCTs focused on patients with PIOD. In 2018, Nguyen et al were able to show clinically and statistically significant ($P = .024$) improvement in olfactory function in randomized patients treated with OT combined with budesonide irrigation compared with the control group (which received OT plus saline irrigation).[69] Whether the improvement in olfactory function after the 8-month follow-up was due to spontaneous recovery or steroid effect was not clear from this study, however, as patients had to have had anosmia for only 6 months to be included in the study. Nor was there clarity regarding the method for ruling out inflammatory contribution to smell loss, which would improve with the topical steroid rinses. Various comparative studies have shown improvement in olfactory function in 25% to 55% of patients following treatment with steroids. In an RCT by Seo et al in 2016, 40 mg of oral prednisolone as monotherapy or in combination with 80 mg of ginkgo biloba for 4 weeks was shown to have significant improvement ($P < .001$) with use of both butanol threshold testing and Cross-Cultural Smell Identification Test scores.[85] The treatment response rate was 33% in the combination therapy group compared with 14% in the monotherapy group ($P = .08$). This study did not include a placebo or control group to ascertain whether the improvement was statistically significant in comparison with that in an untreated group.

In 2017, the question of oral versus topical steroids was evaluated by Kim et al in a retrospective study of 491 patients, of which 178 had PIOD.[77] This study showed that the combination of oral and topical steroids or an oral steroid as monotherapy significantly improves olfactory function versus monotherapy with topical steroids and there was no significant difference between monotherapy consisting of oral steroids or as a combination with a topical steroid ($P = .978$). In an unblinded study in 2004, Heilmann et al demonstrated a significant improvement in patients with PIOD treated with oral prednisolone ($P = .05$) but also showed no significant improvement in the group treated with mometasone propionate.[90] It has been suggested that the favorable effect of oral corticosteroids in PIOD could be attributed to their efficacy on any underlying sinonasal inflammation,[1,108] possibly because of the mucosal effects of an upper respiratory tract infection; there is no definitive evidence of any additional effect on the olfactory neuroepithelium.

It has, however, been suggested that the technique of delivery of topical steroids may be the reason for the poor response to topical steroids; the Kaiteki position (patients lie on the side with their head tilted and chin turned upward) allows nasal drops to reach the olfactory cleft in 96% of decongested noses and 75% in the nondecongested nose.[109]

Interestingly, intranasal injection of a steroid has also been shown to significantly improve the olfactory function in this group of patients. In a 2005 Japanese study, Fukazawa injected the nasal mucosa around the olfactory cleft, using dexamethasone at intervals of every 2 weeks on 8 to 10 occasions and was able to show a 49.6% improvement in 162 patients using VAS scores. This was a nonrandomized study, and although the T&T olfactometer was also used as an investigative tool, no results regarding its use was provided.[89]

Although there are no data for post–COVID-19 PIOD, there is increasing support for the use of corticosteroids to treat respiratory distress or systemic cytokine storm in severe cases of COVID-2019,[110-112] suggesting some potential value for managing respiratory system inflammation. Although evidence for using steroids in post–COVID-2019 PIOD is lacking and there is the confounding problem of steroid administration in severe disease, awareness that the treatment is safe and potentially valuable for COVID-2019 may tilt things in favor of an empirical trial for COVID-2019 PIOD.[113] Patients with a brief history of anosmia as potentially positive in SARS-CoV2 should not take oral steroids until the full clinical presentation of the infection can be recognized. In any case, the decision to initiate steroid therapy should be based on a multidimensional risk-benefit assessment and a detailed discussion with the patient regarding respiratory failure that includes consideration of existing comorbidities, imaging findings, and the implications of taking a short course of steroids.

Nonsteroidal medical management

Theophylline. The mechanism of action of theophylline on the olfactory neuroepithelium is not fully understood. Theophylline is suggested to inhibit phosphodiesterase and increase secondary messengers such as cyclic adenosine monophosphate and cyclic guanosine monophosphate, therefore aiding olfactory neuroepithelium regeneration.[80,114] There are no specific studies of theophylline in patients with PIOD. In 2009, Henkin et al evaluated 312 patients with hyposmia with multiple etiologies that was treated with 200 mg to 800 mg of theophylline; they were able to show that 50.3% of patients had statistically significant improvement in olfactory function. These patients were followed up for 6 to 72 months.[80] In an unblinded pilot study in 2012, the same group was also able to show improvement in olfactory function after treatment with intranasal theophylline.[115] Interpretation of these results should be viewed with caution, as the study's methodologic flaws include having been performed in only center and having used nonstandardized olfactory tests, multiple treatment arms, and changes in treatment.[80,114]

Sodium citrate. Intranasal sodium citrate, by virtue of its ability to sequester calcium ions, is thought to reduce free mucosal calcium, with subsequent reduction in negative feedback and increasing sensitivity to odorants. In 2016, Whitcroft et al performed a prospective placebo-controlled trial of monorhinal treatment with sodium citrate versus with sodium chloride for patients with olfactory loss (multiple etiologies [n = 57]); the study showed improved olfactory threshold and identification only in the PIOD cohort (n = 7).[71] In 2017, Philpott et al compared a single application of 0.5 mL of 9% sodium citrate per nostril versus sterile water (n = 55) in an RCT; the study showed statistically significant improvement in olfactory function with use of olfactory thresholds for phenyl ethyl alcohol, 1-butanol, and eucalyptol, with thresholds measured up to 2 hours after intervention showing an effect lasting between 30 and 120 minutes after application.[72] In the latter study, the response rate was 1 in 3 members of the treatment group as compared with 0 members of the control group. More recent studies have provided mixed results.[116]

N-Methyl D-aspartate antagonist. The mechanism of the N-methyl D-aspartate antagonist caroverine on the olfactory neuroepithelium is not entirely clear. Its mode of action is probably through inhibition of the OB feedback mechanism. In 2002, Quint et al conducted an RCT on 71 patients with nonconductive loss (including 38 patients with PIOD).[91] The treatment group (n = 51) received 120 mg per day of caroverine, and the control group (n = 26) received 140 mg per day of zinc sulfate. The study included 38 patients with PIOD; both groups were treated for 4 weeks, with the treatment group demonstrating statistically significant improvement in odor identification ($P = .042$) and odor threshold ($P = .005$) in patients with both anosmia and hyposmia. This therapeutic option certainly lends itself to further evaluation in a well-designed RCT.

α-Lipoic acid. α-Lipoic acid (ALA) is a fatty acid used mainly in the treatment of diabetic neuropathy. It stimulates the expression of nerve growth factors, substance P, and neuropeptide Y, and it has antioxidative and neuroprotective capabilities. In a 2002 uncontrolled prospective study of 23 patients with PIOD treated with ALA in a dose of 600 mg per day for an average of 4.5 months, Hummel et al showed at least moderate improvement in olfaction in 61% of the participants.[92]

Vitamin A. Vitamin A is known for its regenerative ability and has been suggested to improve olfaction by aiding regeneration of olfactory neuroepithelium. In 1962, Duncan and Briggs[97] reported marked improvement of olfactory function in 38 of 52 patients (with mixed causes of olfactory loss) and 16 of 21 patients with PIOD following systemic treatment with vitamin A (50,000-150,000 IU per week, intramuscularly). In 2012, however, Reden et al[81] found no improvement in olfactory function in patients with PIOD or patients with pottraumatic olfactory loss (PTOL) following oral administration of 10,000 IU per day of vitamin A for 3 months in a double-blinded, placebo-controlled trial using the Sniffin' Sticks olfactory test. More recently (in 2017), Hummel et al reported statistically improved olfaction in patients with PIOD and PTOL in a retrospective cohort study using Sniffin' Sticks test assessment (n = 124 in the treatment group, which received OT with 10,000 IU of intranasal vitamin A, and n = 46 in the control group, which received OT alone). Of the patients with PIOD who were treated in this study, 33% improved compared with 23% of the controls ($P = .03$)[74]; however, this study, had the inherent problem of any retrospective study, in that the inability to control the differences between the groups may have confounded the results.

Minocycline. Minocycline has been shown to act as an antiapoptotic agent, which may improve olfactory function. In a 2011 randomized, prospective, placebo-controlled, double-blinded study in which minocycline was administered orally in

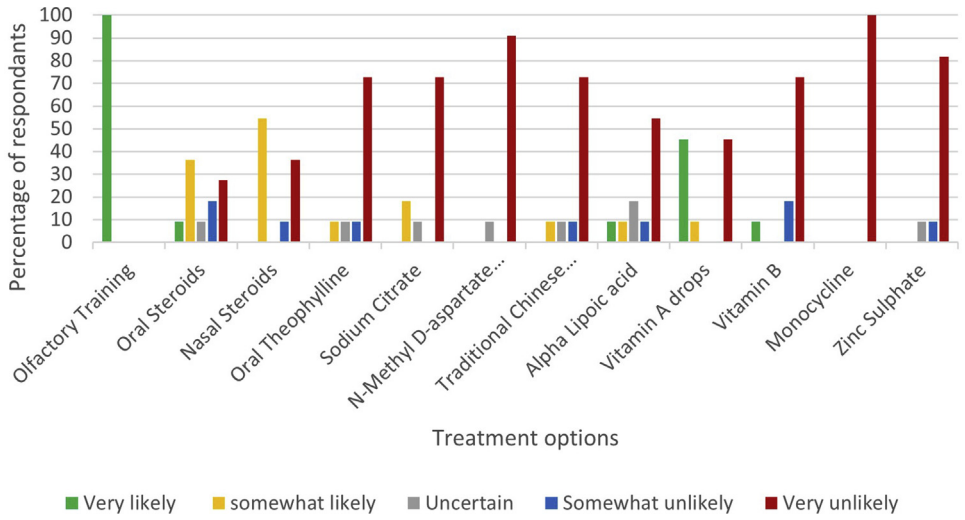


FIG 2. Results of survey of Clinical Olfactory Working Group members of recommendation of treatment options for PIOD. There is a strong recommendation for OT.

a dose of 50 mg twice daily versus placebo for 3 weeks, Reden et al found no statistical difference between the 2 groups.[83]

Zinc sulfate. All of the studies using zinc sulfate have reported no statistically significant improvement in olfactory function after treatment, especially in patients with PIOD.[93,94] Various doses, ranging from 120 mg daily to 300-mg daily doses, have been used. In 1998, Aiba et al performed an RCT with 3 groups (group A was treated with 300 mg of oral zinc sulfate only; group B was treated with zinc sulfate, 300 mg, and topical mometasone prioponate; and group C was treated with topical mometasone propionate and vitamin B); they reported no improvement in PIOD group, although the PTOL group showed statistically significant improvement with zinc sulfate.[93] In 1976, Henkin et al also found statistically significant improvement in 45 patients with PIOD in an RCT using zinc sulfate versus placebo.[96] In the aforementioned study of 26 patients with nonconductive loss, including PIOD, which was conducted by Quint et al, 140 mg of zinc sulfate per day had no effect on olfactory function.[91]

Nonmedical management

Traditional Chinese acupuncture. A nonrandomized prospective study conducted by Vent et al in 2010 was able to show significant improvement in patients with PIOD treated with traditional Chinese acupuncture (n = 15) versus in those treated with vitamin B (n = 15).[84] As stated in Table II, this study had a high risk of bias. However, a reanalysis of their data conducted by Doty et al did not support any improvement, and on the basis of current evidence, it appears that this treatment is not supported.[117]

Survey of the experts

The survey was designed to ascertain how members of the Clinical Olfactory Working Group recommend the treatment options identified from the literature review in clinical practice. Fig 2 shows the results obtained from the survey, which clearly shows an overwhelming recommendation for OT and definitely no recommendation for monocycline antibiotics.

There was some discordance regarding oral steroids, with similar numbers of experts likely and unlikely to recommend it. The consensus was that perhaps 3 to 4 days of oral steroids may be used as a diagnostic tool, in that if the patient were to respond to this treatment, then a conductive component *might* be present and a full course of steroids either for 1 week or in a reducing regimen might prove to be useful; however, the risks and benefits of this need to be discussed with the patient. A prescription of prednisolone should be written for a dose of 0.5 mg/kg; therefore, a typical adult would receive 40 mg per day for 1 to 2 weeks, followed by a course reduced by 5 mg per day over 1 week until it has been stopped. If complete recovery occurs after 1 week of oral steroids, this should lead the clinician to reconsider the diagnosis of PIOD. The group's opinion with regard to recommendation of a nasal steroid was similar to that in the case of oral steroids. But the fact that the side effect profile of nasal steroids is better than that of systemic steroids means that this would perhaps be a safer option to recommend. However, attention should be given to delivery instructions, as nasal steroids are better applied in the olfactory cleft area when sprayed by means of special nozzles (such as a laryngeal mucosal atomization device) or as nasal drops in specific head positions (eg, the Kaiteki position,[111] with the head in a dependent position).

With the exception of vitamin A, the other treatment options, including theophylline, zinc sulfate, sodium citrate, caroverine, and ALA, were all less likely to be recommended by the expert panel. Interestingly, a fair number of the experts would recommend using vitamin A drops for treatment of PIOD compared with sodium citrate. Although sodium citrate and vitamin A drops have shown promise in the treatment of PIOD, the only RCT investigating use of oral vitamin A did not show a significant difference between vitamin A and placebo, although significant improvement was seen in the vitamin A group. Topical vitamin A has shown more promise; however, further RCTs are required to underpin the existing data. Sodium citrate has been shown in the literature to

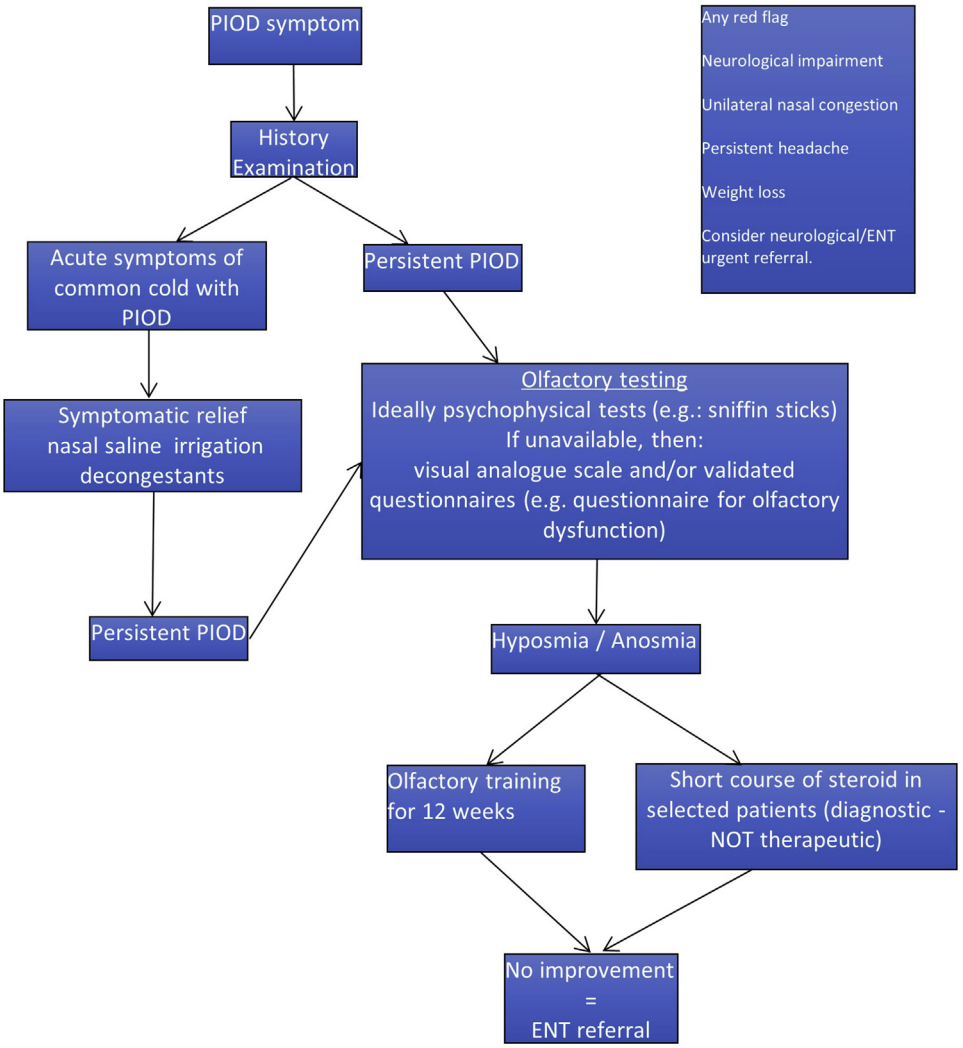


FIG 3. Schematic chart of the PIOD management scheme for primary care. The link for the questionnaire for olfactory disorder is https://images.app.goo.gl/fpNXCqBY.

improve odor threshold and identification to varying degrees, with the PIOD group showing the best responses.

Practical challenges to management

1. Perceived lack of clinical importance. The negative effect of olfactory dysfunction on patients' quality of life is not widely appreciated and is often ignored or trivialized.[13] This is particularly important in the COVID-2019 era, in which priorities are placed on initial survival, organ impairment, and transmissibility. Various surveys of patients with olfactory dysfunction have shown the significant morbidity associated with this disability, including problems with hazard avoidance, food-related problems, problems with managing odors, and social isolation.[11-13,118] Yet, the vast majority of clinicians do not place the same order of importance when it comes to treating this problem. An example of this is highlighted in the American Medical Association's guide to evaluation of permanent impairment, which quantifies permanent olfactory loss as 1% to 5% impairment compared with deafness or visual loss, which are quantified as 35% and 85% impairment, respectively.[119]

2. Lack of testing. Most general practitioners and even otolaryngology departments do not offer standardized qualitative or quantitative assessments for patients who present with olfactory dysfunction,[38] and therefore, they have no way of monitoring improvements. In general, a full ear, nose, and throat examination is performed in the clinical setting; in addition to anterior rhinoscopy, nasal endoscopy should also be performed (ideally, with a 0-degree Hopkins rod lens endoscope [4 mm in diameter or smaller] to start, after which a 30-degree endoscope may be used to facilitate visualization of the olfactory cleft).[1] Some patients may have MRI scans, depending on their presenting symptoms, but a significant number of patients may not have any subjective or psychophysical testing, which is key to offering management options.[1]

3. Availability of treatment. During the expert discussion, it was clear that some of the aforementioned treatments were not readily available for clinical use. This therefore provides a challenge in treating patients with these drugs. The bureaucracy surrounding the ability to obtain these medications for the number

of patients who present with olfactory dysfunction is making it increasingly difficult to offer treatment options for patients. Consequently, most of these treatment options are not widely used in the clinical situation. Oral and topical steroids are cheap and widely available, making their use more practical in most settings.

4. Limited evidence for available interventions. The relatively few patients accrued in the studies referenced in Table II underscore the challenges to date for studies of PIOD. Single institutions may be unlikely to recruit enough patients with a clear etiology of olfactory dysfunction of recent occurrence and enrolment criteria appropriate to power placebo-controlled studies. However, the current COVID-2019 pandemic offers a rare opportunity to pursue such studies for the benefit of patients with COVID-2019, in which case findings may be extended to other cases of PIOD in the future.

Practical guide for general practitioners

Fig 3 sets out a flowchart for management in primary care.

1. History and examination. A thorough history should be undertaken and should focus on the specifics of impairment (qualitative or quantitative, gustatory attributes (specifically, distinguishing aroma from basic tastes, etc), onset, duration, any fluctuations, effects on the quality of life, medication history, past medical history, allergies, previous episodes of sinusitis, smoking, alcohol consumption (liver cirrhosis),[120-122] exposure to toxins, prior significant head trauma, and family history.[123] If sudden onset of smell loss has occurred, then clinicians should assume that in the midst of the COVID-19 pandemic, SARS-CoV-2 infection is possible and the necessary precautions should be taken; this includes swab testing and personal protective equipment if face-to-face contact is needed.

2. Examination. Full head and neck examination should be carried out, and any evidence of upper respiratory infection should be noted. Basic neurologic examination should also be performed. However, we note that many general practitioners are now performing remote consultations, in which case this is not feasible; however, if face-to-face contact is made, then a basic nasal examination (anterior rhinoscopy) should be the minimum assessment.

3. Olfactory testing. We would consider that olfactory assessment in patients reporting olfactory dysfunction with a psychophysical test to be mandatory owing to the poor correlation between subjective assessment and test performance but also to fully determine disease burden and clinical impact of interventions.[1] However, we recognize that in general practice, this is not usually practically possible (especially with remote consultations), and thus ideally, validated questionnaires (such as the Olfactory Disorders Questionnaire)[36,118,124] should be used. But if this is not possible, a recognized form of assessment, possibly quantitative and/or anchored (such as a VAS), should be used. A quick screening test, such as the Q-Sticks test, could be used.[125]

4. Treatment options. Although there is limited evidence for the treatment options available, some treatment options have shown promise and may be useful in selected patients.

A. OT at home. Recent research suggests that early OT aids olfactory recovery in patients with PIOD. The classical method of OT may also be useful; it involves the steps described in Box 1. The classical OT method involves the use 4 odorants for 12 weeks, following a rigorous schedule as described in Box 1.

Box 1. Advice to patients undergoing smell training

The advice is not that patients "sniff odors as often as possible." The odors for this training include rose, eucalyptus, clove, and lemon.

1. Place each item into a separate bowl or jar, or take just the raw material into your hands.
2. Slowly and gently, inhale naturally; sniffing too quickly and deeply is likely to result in you not being able to detect anything.
3. Repeat this sniffing for 20 to 30 seconds.
4. Move on to the next smell and repeat as already stated.
5. Record your experience, noting any changes (ie, what you notice) in your Smell Ability Diary Log (available at https://www.fifthsense.org.uk/smell-training/).

B. Steroids. As already discussed, a trial of oral steroids can aid the diagnosis of PIOD and may be used in carefully selected patients, following careful explanation of potential side effects and the limited existing data supporting its use. Diagnostic (*not* therapeutic) oral steroid trials for a limited number of days can help to rule out concomitant residual congestion that may accompany PIOD and impair other therapeutic attempts (smell training, spontaneous recovery). Topical steroids have the benefit of a better side effect profile than that of systemic option; hence, a trial of this may be appropriate.

5. Referral to an ENT specialist. Most general practitioners will defer to the advice of a specialist (in this case an ear, nose, and throat [ENT] specialist) rather than prescribe oral steroids, so we recognize that this may be the next step if smell training has not helped.

6. Counseling on the hazards of smell disturbances. Such counseling should be undertaken at any opportunity, including when providing advice on labeling food and having gas detectors in the home environment.[12,13] Further help and support can be found through online forums, such as that of the charity Fifth Sense (www.fifthsense.org.uk).

Practical guide for otorhinolaryngologists

Fig 4 sets out a flowchart for the management in secondary care.

1. History and examination. As we have already stated, however, it is important that all patients referred to the ENT department undergo thorough examination, including anterior rhinoscopy and nasoendoscopy with rigid or flexible endoscopes to achieve complete visualization of the olfactory cleft and thereby permit exclusion nasal tumors and concomitant inflammatory conditions—especially when a short diagnostic trial of steroids elicits a positive response. The examination results should be quantified by using validated clinical scoring systems, where available, for comparative purposes.

2. Assessment. In patients reporting olfactory dysfunction, psychophysical olfactory assessment is mandatory not only to confirm quantitative olfactory loss and fully determine disease burden but also to determine the clinical impact of interventions. Where possible, validated questionnaires should be used in

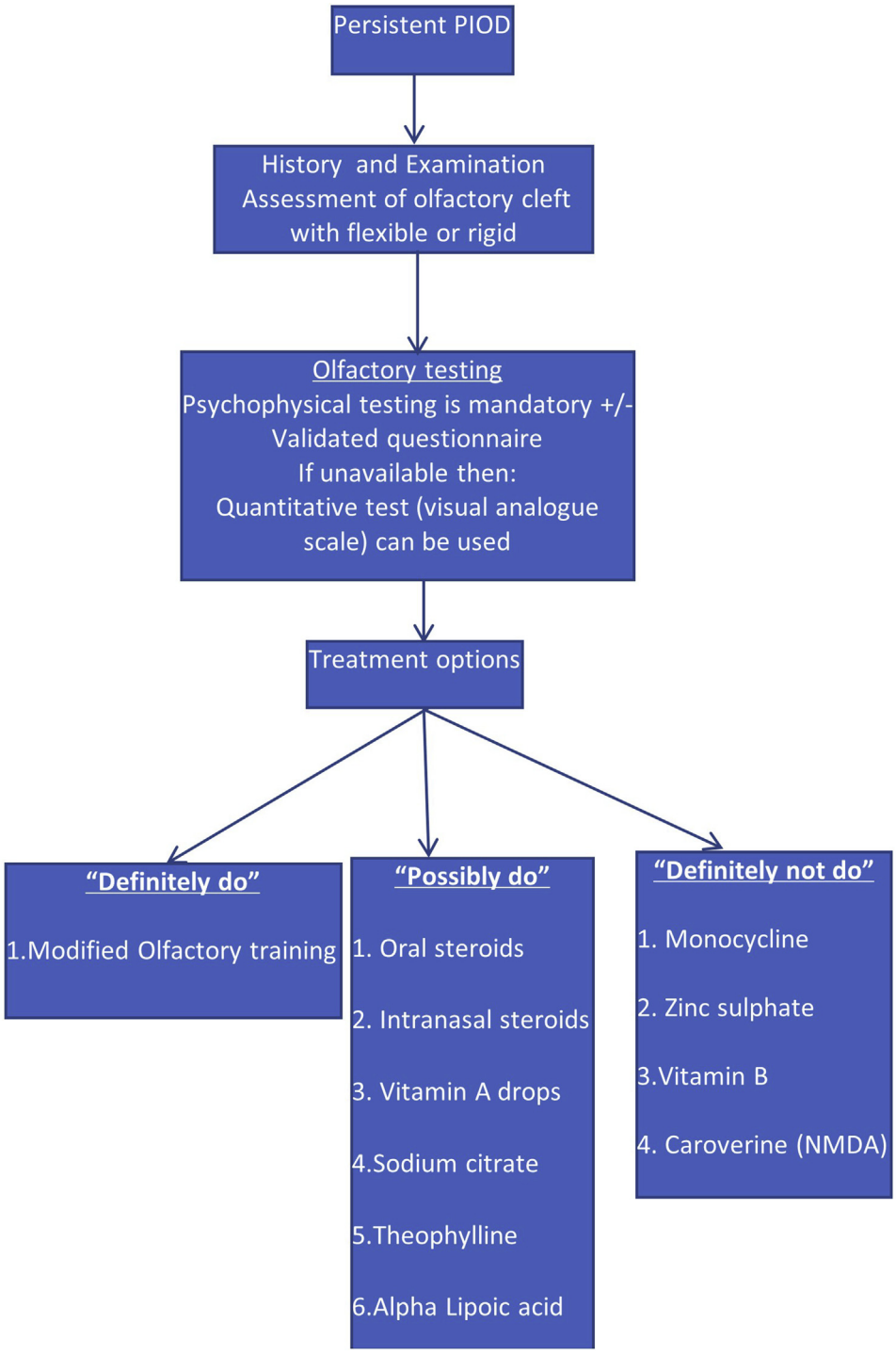


FIG 4. PIOD management scheme for otorhinolaryngologists.

addition.[36,118,126] In cases in which this is not possible, a recognized form of assessment, possibly quantitative and/or anchored, such as a VAS, should be used. Subjective olfactory assessment should not be undertaken in isolation, given its poor accuracy.

3. Modified OT. Recent evidence suggests that use of this method over a 24- to 36-week period is superior to performing the classical training. This training method involves use of the classical regimen for 12 weeks and then switching first to menthol, thyme tangerine, jasmine for 12 weeks and then to green tea, rosemary, bergamot, and gardenia for 12 weeks.

4. Treatment options. For treatment options, please see Fig 4.

Conclusion

The olfactory loss experienced by some patients who have been infected by the SARS-CoV-2 has brought to light the need for

good evidence-based management for patients with PIOD. This review highlights the importance of OT in the treatment of PIOD. The evidence for the use of medical treatment in PIOD is quite weak, but it is clear that there are additional management options available for motivated patients. Oral and topical steroids may still have a role in management with vitamin A and sodium citrate as an alternate treatment option. Nonmedical options such as acupuncture need to be investigated further. The ENT research community now needs to convince funding bodies of the need to deliver more RCTs that can usefully inform clinicians regarding the place of these therapies and help to treat this much-maligned group of patients. With an expectedly large number of patients with a common etiology (COVID-19) and increasing awareness of PIOD, the opportunity for rigorous study is apparent.

Clinical implications: Patients with COVID-19 and other infection-related olfactory dysfunction should be guided through olfactory rehabilitation and be signposted to specialists for other treatments in refractory cases.

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