



Diagnostic approach to occupational rhinitis: the role of nasal provocation tests

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Purpose of review

The diagnosis of occupational rhinitis is a challenge. Underdiagnosis is substantial as the clinical presentation is nonspecific and often no occupational history is taken. Detection of occupational rhinitis can be improved by including screening questions on occupational exposure in the assessment of every patient with adult-onset rhinitis.

Recent findings

Case reports, case series and epidemiological studies continuously demonstrate new sensitizers and irritants capable of inducing allergic or nonallergic (irritant-induced) occupational rhinitis. Recent reviews have focused on the value of immunological tests with specific IgE, skin prick tests or basophil activation tests in demonstrating sensitization to occupational agents. Nasal provocation tests (NPT) can establish a definite diagnosis of allergic occupational rhinitis. Several NPT guidelines have been published, however, focusing exclusively on standardized high-molecular weight allergens. When performing NPT with nonstandardized agents – like most occupational sensitizers – adapted protocols are needed.

Summary

We provide pragmatic guidance to clinicians taking care of rhinitis patients on how to diagnose occupational rhinitis, based on recent insights from the literature. We focus on the challenges in the diagnostic work-up, on how to identify suspected causes, and on the role of NPT.

Keywords

irritant-induced rhinitis, nasal allergen challenge, occupational exposure, occupational health, work-related rhinitis

INTRODUCTION

Occupational rhinitis is defined as an inflammatory disease of the nose, characterized by intermittent or persistent symptoms (nasal obstruction, sneezing, rhinorrhea, itch), caused by a particular work exposure [1]. Occupational rhinitis can be distinguished from ‘work-exacerbated rhinitis’, which refers to preexisting rhinitis exacerbated by workplace exposure [1,2].

The diagnosis of occupational rhinitis is a challenge. The nonspecific clinical presentation and frequent lack of occupational history result in substantial underdiagnosis [3]. Improving detection of occupational rhinitis is important because stopping – or diminishing – causal exposure can reduce symptoms and prevent negative socioeconomic consequences [4,5]. Additionally, detecting a sentinel case might lead to workplace interventions and prevent occupational rhinitis in coworkers. Occupational asthma is frequently preceded by

occupational rhinitis and should always be excluded. Whether early detection of occupational rhinitis and exposure control can prevent the development of occupational asthma is still unclear [6].

Occupational rhinitis can be classified into allergic and nonallergic occupational rhinitis (Fig. 1). Allergic occupational rhinitis is an immunologically mediated hypersensitivity reaction resulting from

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KEY POINTS

- Occupational rhinitis can be caused by high-molecular weight or low-molecular weight sensitizers (allergic occupational rhinitis) or by irritants (nonallergic occupational rhinitis).
- As the clinical presentation is nonspecific, thinking about the possibility of occupational rhinitis is key.
- A brief occupational history in every patient with adult-onset rhinitis can improve the detection of occupational rhinitis without requiring detailed knowledge of toxicology, neither from the clinician, nor from the patient.
- Immunological tests, such as specific IgE, skin prick tests, or basophil activation tests can be helpful to demonstrate sensitization to occupational agents but there are several potential pitfalls.
- Performing nasal provocation tests (NPT) with occupational agents generally requires adapted protocols as recent guidelines focus exclusively on NPT with standard high-molecular weight allergens.

antibody-mediated or cell-mediated mechanisms [1]. A latency period is necessary to acquire sensitization. Note that this definition of allergic occupational rhinitis encompasses both IgE and non-IgE-mediated sensitization and is broader than the classical definition of 'allergic rhinitis', considered to be exclusively IgE-mediated [7^{***}]. Sensitizers are grouped into high-molecular-weight (HMW; ≥ 5 kDa) and low-molecular weight agents (LMW; < 5 kDa). HMW agents are mainly biological agents causing IgE-mediated sensitization. LMW agents are generally synthetic chemicals. Although some induce IgE-mediated sensitization, most act through less well known mechanisms.

Nonallergic occupational rhinitis is caused by occupational agents through irritant, nonimmunological, nonspecific mechanisms. The relation between irritant exposures and rhinitis is complex. Irritants can cause acute, but *transient*, nasal irritation. Preexisting nasal inflammation increases susceptibility to irritation [8,9^{*}]. Moreover, irritants may increase the risk of allergic sensitization [2]. However, the term nonallergic occupational rhinitis is generally reserved for *persistent* nasal symptoms induced by irritant exposures (irritant-induced rhinitis). Persistent rhinitis can be induced by a single high-level irritant exposure, such as an accidental chemical spill (reactive upper airway dysfunction syndrome; RUDS [10]) or by prolonged moderate-level irritant exposures, such as cleaning products, grain and cotton dust, formaldehyde, or

combustion products. The neurogenic system presumably plays a role in the pathophysiology. Irritants interact with trigeminal nerve endings in the nasal mucosa, resulting in the release of various neuropeptides including substance P, neurokinin A and B, causing local neurogenic inflammation. These neuropeptides can not only directly activate mucus-producing cells (rhinorrhea) and endothelial cells causing vasodilation (nasal congestion) but also activate mast cells. The release of these mediators is mostly initiated via the activation of transient receptor potential cation channel (TRP) subfamily V receptor 1 (TRPV1) or TRPA1 present on afferent nerves [11]. Increased activation of TRPV1 and/or TRPA1 is found in idiopathic rhinitis [12] and allergic asthma [13]. It remains to be elucidated whether irritants can upregulate TRP channels.

In this article, we provide pragmatic guidance to clinicians taking care of rhinitis patients on how to diagnose occupational rhinitis, incorporating recent insights from the literature. An example of a case of occupational rhinitis is shown in the Supplementary Box, <http://links.lww.com/COAI/A19>.

RECENT EPIDEMIOLOGICAL STUDIES

The prevalence of occupational rhinitis in the general population is largely unknown. A recent Finnish study showed that in nonsmokers, unexposed to occupational irritants, 31.8% had chronic nasal symptoms, whereas in occupationally exposed nonsmokers, the prevalence was 46.4% and in occupationally exposed smokers even 55.1% [14^{*}]. Wang *et al.* [15^{*}] showed in a Scandinavian general population cohort that dampness or molds at work increased the onset of rhinitis symptoms (odds ratio 1.31).

Most studies on occupational rhinitis look at specific working populations. In an extensive literature review, Jeebhay *et al.* [16^{***}] described an increased risk of occupational rhinitis in a wide range of workers in food handling and processing (cereals, plants, seeds, mushrooms, farm products, seafood [17]). In an interesting outbreak investigation in a chemical factory, Suojalehto *et al.* [18^{***}] identified a new LMW sensitizer [3-(bromomethyl)-2-chloro-4-(methylsulfonyl)-benzoic acid] causing occupational asthma, rhinitis, and contact urticaria; among 85 workers, 7 had positive skin prick tests, 6 had rhinitis, and 3 out of 4 tested had a positive nasal provocation test (NPT). A Brazilian study demonstrated high exposures to particulate matter (PM_{2.5}) in sugarcane workers because of the burning of sugarcane to facilitate the harvesting. Prevalence of nasal symptoms was higher after 3 months of harvesting (53.4%), compared with nonharvesting

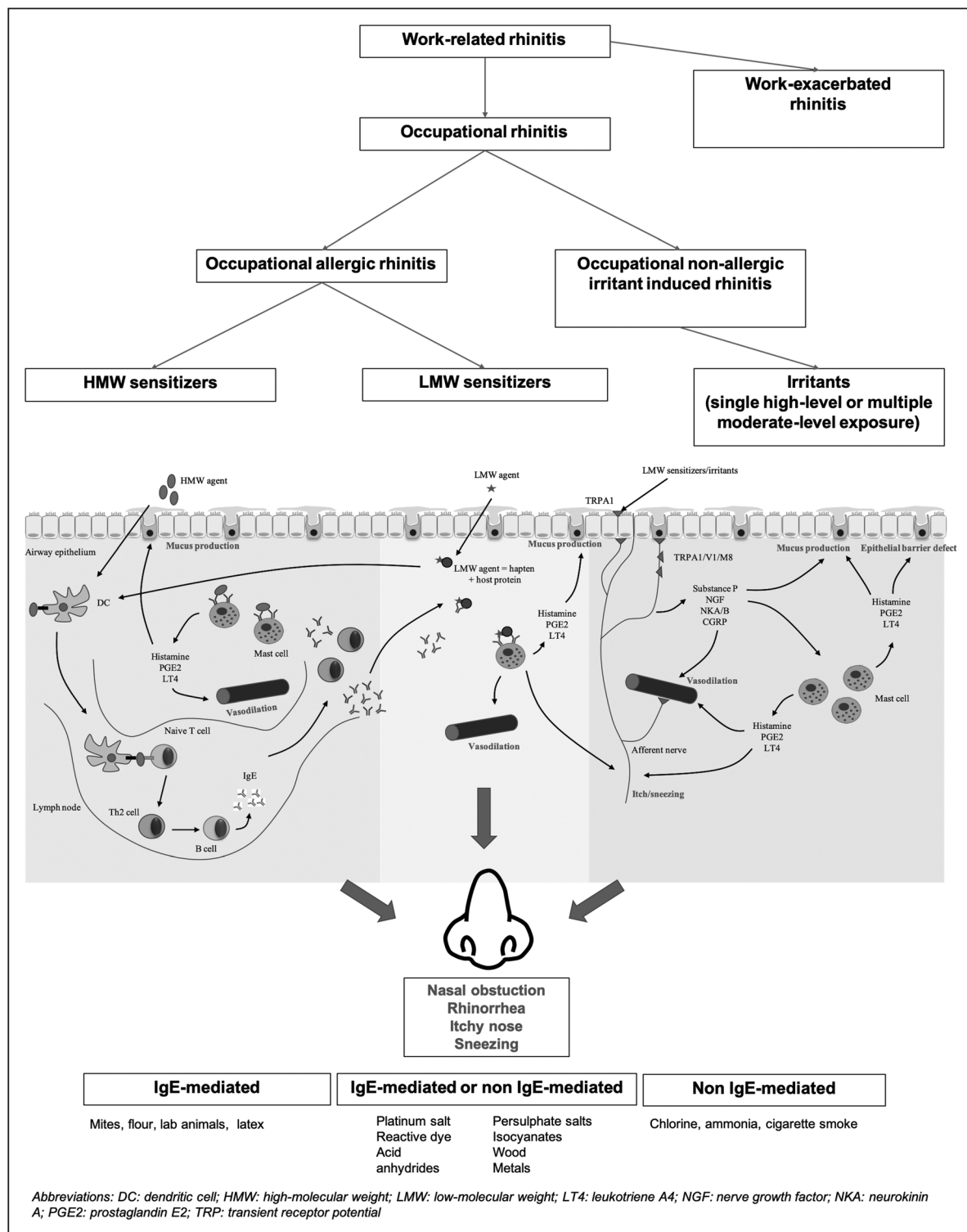


FIGURE 1. Classification and mechanisms of occupational rhinitis.

(26.7%), and IL-6 in nasal lavage had increased [19[¶]]. In a pilot study in 3D printing workers, 37% reported nasal symptoms, mainly nasal obstruction (26%), rhinorrhea (20%) and itch (20%) but less sneezing (2%), with higher prevalence among those working more than 40 h per week [20[¶]]. Two recent

studies in farmers showed increased odds of having rhinitis when using herbicides or insecticides [21[¶],22]. A literature review by Dumas *et al.* [23] suggested an association between trichloroethylene exposure and rhinitis. An overview of recently published case reports is shown in Table 1.

Table 1. Recent reports on agents causing occupational rhinitis

Causal agent	Description of the study
HMW	
<i>Hoya compacta</i> (horticultural workers) [24]	Three cases: SPT+, NPT+ (simulating working conditions in challenge chamber)
Pork (slaughterhouse workers) [25 [■]]	Two cases: SPT+ (negative with commercial pig dander allergen), NPT + (drops with raw pork meat extract 10–20% w/v)
Gum Arabic (candy factory worker) [26 [■]]	One case: sIgE+, SPT+, NPT+
<i>Psocoptera</i> spp. (book lice; old book shop worker) [27]	One case: SPT+
Senna (phytopharmaceutical warehouse worker) [28 [■]]	One case: SPT+, conjunctival provocation test +
Casein (microbiology laboratory worker) [29 [■]]	One case: sIgE+, SPT+
Irritants	
Diesel engine exhaust [30]	One case

HMW, high-molecular weight agent; NPT, nasal provocation test; SPT, skin prick test.

DIAGNOSTIC WORK-UP

When to consider occupational rhinitis?

Nasal symptomatology of occupational rhinitis does not differ from other forms of persistent rhinitis [7[■]]. Ideally, occupational rhinitis is considered in all patients with adult-onset rhinitis – not only newly diagnosed patients but also patients who received another diagnosis but do not improve despite adequate treatment. Sensitization to common aeroallergens should certainly not exclude the possibility of occupational rhinitis [31]. Occupational rhinitis could not only present as perennial but also as seasonal allergic rhinitis, because working conditions might vary over the year. Additionally, occupational exposures have been shown to be a risk factor for chronic rhinosinusitis [32].

More specifically, two situations should trigger further diagnostic steps. Firstly, when patients have ‘at-risk’ occupations, such as laboratory animal workers, healthcare workers, cleaners, hairdressers and workers in wood, chemical, pharmaceutical or food industry [1,7[■],16[■]]. Secondly, when there seems to be a time-relation between nasal symptoms and specific tasks or exposures at work. In addition to asking if symptoms are worse at work, it might be more efficient to ask if symptoms get better during weekends or holidays [31]. However, sometimes the temporal relationship is not obvious, and might become blurred in longstanding occupational rhinitis.

Confirming work-relatedness

A simple way to document work-relatedness – even without suspecting a specific cause – is a ‘work removal – work resumption test’. The patient is

assessed after a period of a few weeks away from the suspected exposure and is reassessed again a few weeks after work resumption [3]. A work-related effect on nasal patency can be visualized by asking the patient to register symptoms [e.g. on visual analog scales (VAS)] and to measure peak nasal inspiratory flow (PNIF) 2-hourly during periods of normal work and days off [33] and by plotting the mean PNIF for each day. A consistent work-related decline could support the presence of a trigger at work. However, unlike in the field of occupational asthma no validated cutoffs or expert system exist to analyze sequential PNIF measurements [34].

Identification of the suspected cause

Except for some jobs with well known exposures, it is often challenging to find out precisely what a worker is exposed to. In our experience, the likelihood of encountering potential causes can be increased by approaching the exposure from different perspectives, questioning job title, tasks, and exposure to vapors, gases, dust, fumes, or chemicals (Table 2). Questions about what the patient is *doing* at work are easier to answer than inquiring about specific job *exposures*. For example, a patient working in a car garage knows exactly what tasks he is doing but is probably unaware that car spraying leads to exposure to isocyanates, well known potent LMW sensitizers found in many spray paints. Inquiring about workplace protective measures can be useful. However, the use of masks does not necessarily imply adequate protection. When work-related rhinitis is suspected but no cause is identified, referral to the workplace’s occupational physician or an occupational medicine clinic should be considered.

Table 2. Screening questions and examples of typical patients with occupational rhinitis

	Job title	Job tasks	Exposures
Questions	Where do you work? What is your job title? When did you start working there?	What do you do? What does a typical workday or workweek look like? What do your co-workers do? Any changes in work processes or materials preceding the onset of rhinitis?	Are you exposed to vapors, gasses, dust, fibers or chemicals? Are Safety Data Sheets available of the products you work with?
Examples	PhD student in biology	Mouse experiments	Dust containing urinary mouse allergens (HMW) from cleaning the cages
	Baker	Artisanal baking; manual mixing	Dust from flour, including dough improver alpha-amylase (HMW)
	Car workshop	Spray painting	Spray aerosol containing hexamethylene diisocyanate (LMW)
	Hairdresser	Hair bleaching and dyeing	Bleaching agents containing ammonium persulphate (LMW and irritant)
	Domestic cleaner	Cleaning homes	Household cleaning products, including bleach (irritants and possibly LMW sensitizers, such as quaternary ammonium salts)

HMW, high-molecular-weight agent; LMW, low-molecular-weight agent.

Confirming the suspected cause in allergic occupational rhinitis

In allergic occupational rhinitis, the suspected cause might be confirmed by demonstrating sensitization with a skin prick test (SPT) or serum sIgE. However, this is only possible for HMW – and some LMW – agents. False negatives could occur because of variability in the quality and low sensitivity of commercial sIgE and SPT solutions, especially in LMW agents [35[¶]]. Performing SPT with material brought from the patient's workplace might be useful but should be performed with caution as most of these agents are potentially skin irritants, thus producing false-positive results. Also, a negative SPT and absence of serum sIgE do not exclude regional IgE-mediated allergy, as in local allergic rhinitis, with sIgE production confined to the nasal mucosa [7^{¶¶}].

Component-resolved diagnosis has been investigated for few occupational allergens, such as latex and cereal flour [36[¶]], but its value for diagnosing occupational rhinitis is unknown [37]. Basophil activation tests (BAT) might offer an alternative to detect sensitization and could reduce the need for NPT [38]. BAT has been applied for the investigation of occupational asthma and, to a lesser degree, occupational rhinitis with several allergens, including wood allergens, latex, persulphates, and pharmaceuticals [39,40[¶]].

Diagnosing irritant-induced rhinitis

Irritant-induced nonallergic occupational rhinitis is more difficult to diagnose firmly than (sensitizer-induced) allergic occupational rhinitis. As no sensitization is involved, immunological tests are not

helpful to identify the causal agent. When, after a single, well documented exposure to a high-level irritant, a previously healthy person develops acute-onset but persistent nasal hyperreactivity a confident diagnosis can be made. Nasal hyperreactivity can be detected, for example, by a cold dry air provocation exposing the patient to cold ($<-10^{\circ}\text{C}$), dry ($<10\%$ humidity) air for 15 min. With a 20% decrease in PNIF as cutoff point, nasal hyperreactivity is detected with a sensitivity of 66.7% and specificity of 100% [9[¶],41]. When the irritant exposure is moderate but prolonged, and the onset of nasal symptoms is not acute but insidious, the individual attribution of rhinitis to the exposure becomes more problematic.

NASAL PROVOCATION TESTS IN OCCUPATIONAL RHINITIS

A suggestive clinical history with a positive immunological test for a well standardized extract could be considered as *probable* occupational rhinitis. However, when immunological tests for sensitization are not available or considered unreliable, when local allergic rhinitis is suspected, or when a *definite* diagnosis of occupational rhinitis is needed, a nasal provocation test (NPT) may be indicated. The required level of certainty of the diagnosis may vary according to the purpose of the evaluation, the therapeutic implications, and the expected socio-economic impact [1].

NPT can be considered the gold standard for diagnosing allergic occupational rhinitis. With NPT, an agent's causal role can be demonstrated on an individual basis by directly observing the

relation between exposure and the induction of rhinitis symptoms. NPT is regarded as well tolerated and reproducible [42]. Recently, an EAACI Position paper proposed a unified protocol for NPT with commercially available HMW allergens, provoking immediate reactions [43²²]. Performing an NPT with other agents requires adaptations to the protocol regarding the preparation of the agent, the exposure method, and the timing of the assessment of the nasal response – as delayed reactions can be expected with LMW agents.

Contraindications to NPT include previous anaphylactic reaction to the allergen, acute inflammation of the nose or paranasal sinuses, uncontrolled lower airway disease, pregnancy, and other severe comorbidities [43²²]. Any medication interfering with nasal response should be discontinued for a given washout period of at least 1 week. NPT is time consuming and, especially in the case of nonstandardized agents, involvement of experts in occupational medicine and occupational hygiene may be needed to create an adapted protocol [1,44,45²²].

Methods of exposure

Ideally, NPT is performed in a hospital setting under controlled conditions (or at work under usual working conditions). The delivery method depends largely on the nature of the agent [1].

Water-soluble HMW agents can be administrated as aqueous solutions directly to the nasal mucosa. Whenever available, standardized allergenic extracts should be used and delivered bilaterally with a pump aerosol spray, applying two puffs (of 50 µl/puff) per nostril, one in the inferior meatus and one towards the middle turbinate [43²²,46]. For many occupational HMW agents, extracts should be prepared using material the patient brings from the workplace. As a safety measure it is recommended to begin with a low starting concentration of 1:100(w/v) of the concentration that produces a skin reaction or 1:10,000 if SPT is negative [46]. If the initial allergen application is negative, then the concentration can be increased by 3-fold to 10-fold every 15–60 min. Before testing the suspected agent, a control challenge should be performed with the same diluent that is used to prepare the allergen solutions to exclude irritant or nonspecific hyperresponsiveness [43²²].

For LMW and water-insoluble agents, the method of exposure depends on the chemical properties and the physical state of the agent. Sprays, aerosols, drops, powders, or impregnated paper discs can be used. Ideally, the workplace exposure is mimicked as closely as possible, delivering the agent as a gas, fume, liquid, or particle aerosol [1]. Sometimes, this can be achieved by asking patients to

reproduce their usual work tasks in a dedicated challenge room – for example, grinding a piece of wood or applying a liquid on a surface. In this scenario, the delivered dose can be gradually increased by prolonging the duration of exposure, if necessary, over the course over several days [44]. Concentrations should be controlled and maintained below permissible threshold levels [1].

Assessment of nasal response

To evaluate the outcome of the NPT after challenge, a combination of subjective and objective parameters should be used. Objective measurements alone are poor predictors of the subjective symptoms experienced by the patient [43²²].

For assessing symptoms, Lebel score or VAS can be used to evaluate sneezing, nasal pruritus, rhinorrhea, nasal obstruction, and ocular symptoms [43²²]. For objective assessment of nasal patency, PNIF is the easiest and cheapest method, which correlates well with subjective nasal congestion, but is strongly dependent on patients' collaboration and lung function [47]. Also, acoustic rhinometry, active anterior rhinomanometry and four-phase-rhinomanometry are established methods to assess nasal patency [43²²]. A clearly positive subjective measure, a clearly positive objective measure or a combination of a moderately positive subjective measure and a moderately positive objective measure can all define a positive NPT (Fig. 2). When performing NPT with nonstandardized methods of exposure, it is recommended to assess lower respiratory symptoms and perform spirometry for safety as well as diagnostic purposes.

Changes in mediators and blood cells in peripheral blood have been reported after NPT [48]. Some evidence suggests that assessment of inflammatory cells (eosinophils), mediators of inflammation (eosinophil cationic protein and tryptase) or local IgE in nasal secretions could increase the specificity of NPT and could reduce patient misclassification [49²²,50]. However, at present, nasal sampling for inflammatory markers remains predominantly a research tool [33].

For NPT with an HMW agent, assessing the response after 10 min (and if necessary, also after 20 min) is sufficient [43²²]. The timing of the nasal reaction to LMW agents is more difficult to predict and can be immediate, late or dual [51]. There is no consensus on the duration of the assessment of the nasal response after NPT with LMW agents. Several authors propose protocols with periodical assessment until 6–24 h after provocation [52,53] (Fig. 2).

The possibility of a false-negative result should be considered because of using the wrong agent. To

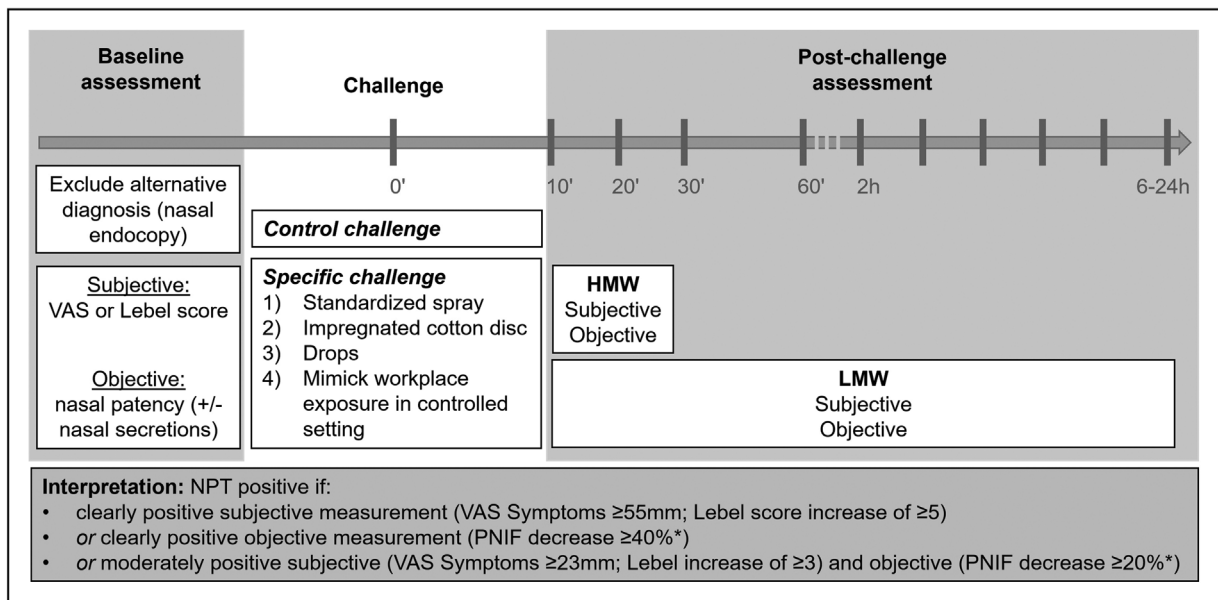


FIGURE 2. Performing a nasal provocation test with high and low-molecular weight sensitizers [1,43^{***},52,53]. *Also, significant changes in nasal patency can be measured by Acoustic Rhinometry (AcRh), Active Anterior Rhinomanometry (AAR) or 4-phase-rhinomanometry (4PR); see EAACI Position paper for interpretation [43^{***}]. HMW, high-molecular weight; LMW, low-molecular weight; PNIF, peak nasal inspiratory flow; VAS, Visual analog scale.

exclude a positive nasal reaction because of irritant effects, especially when testing a nonstandardized agent, an NPT could be performed on a healthy unexposed person [18^{***}].

CONCLUSION

Occupational rhinitis is a diagnostic challenge. Occupational rhinitis should be considered in every patient with adult-onset rhinitis – not only in new patients but also in patients who fail to improve despite adequate treatment. NPT can establish a definite diagnosis of occupational rhinitis but is not always needed. When performing NPT with nonstandardized agents, adapted protocols should be created.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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