Clinical Management Review

Occupational Rhinitis

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There is convincing evidence that tight relationships between the upper and lower airways also apply to the workplace context. Most patients with occupational asthma (OA) also suffer from occupational rhinitis (OR), although OR is 2 to 3 times more common than OA. OR most often precedes the development of OA, especially when high-molecular-weight protein agents are involved, and longitudinal cohort studies have confirmed that OR is associated with an increased risk for the development of OA. The level of exposure to sensitizing agents at the workplace is the most important determinant for the development of IgE-mediated sensitization and OR. Atopy is a risk factor for the development of IgE-mediated sensitization only to high-molecular-weight agents. In workers with work-related rhinitis symptoms, documentation of IgE-mediated sensitization to a workplace agent via skin prick testing or serum specific IgE confirms a diagnosis of probable OR, whereas specific nasal provocation testing in the laboratory remains the reference method to establish a definite diagnosis of OR. Complete avoidance of exposure to the causal agent is the most effective therapeutic option for controlling work-related nasal symptoms and preventing the development of OA. If complete elimination of exposure is expected to induce meaningful adverse socioeconomic consequences, reduction of exposure can be considered as an alternative approach, but it is important to consider the individual risk factors for the development of OA to implement a more personalized management of OR. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:3311-21)

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INTRODUCTION

The various dusts, gases, fumes, and vapors present in the workplace environment can induce or trigger different phenotypes of work-related rhinitis (WRR) through immunologic or irritant, nonimmunologic mechanisms (Figure 1).[1-6] Considering that the concept of "united airway disease" and the tight interactions between the upper and lower airways also apply in the context of the workplace, a task force of the European Academy of Allergy and Clinical Immunology proposed a nosologic approach for disentangling subphenotypes of WRR[1] similar to that used for work-related asthma.[7-9] *Occupational rhinitis* (OR) was defined as "an inflammatory disease of the nose, which is characterized by intermittent or persistent symptoms (ie, nasal congestion, rhinorrhea, sneezing and itching), and/or variable nasal airflow limitation due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace."[1] OR can be induced by either immunologic sensitization to a specific substance, which is termed sensitizer-induced OR, or exposure to high levels of irritants at work, which is termed irritant-induced rhinitis (IIR). Sensitizer-induced OR—hereafter simply referred to as OR—can be caused either by high-molecular-weight (HMW) proteins of vegetable or animal origin acting through an IgE-mediated mechanism or by low-molecular-weight (LMW) agents such as reactive chemicals, metals, and wood dusts. A few LMW agents induce the production of specific IgE (sIgE) antibodies while the immunologic mechanisms involved in OR due to most of the LMW agents remain uncertain.

IIR refers to transient or persistent symptoms of rhinitis that develop after a single (ie, the reactive upper airway dysfunction syndrome)[10] or multiple acute exposures[11,12] to high concentrations of irritant compounds, such as chlorine, chlorine dioxide, sulfur dioxide, ozone, and hydrogen sulfide. It is currently acknowledged that not only acute inhalation of high concentrations of irritants may have detrimental effects on the nasal mucosa but long-term exposure to irritants, even in concentrations within occupational exposure limits, may also induce a chronic form of IIR.[3,4,13] Various occupational exposures have been associated with an increased risk of rhinitis symptoms. The few available data on the pathophysiology of IIR suggest a combined role of innate immune response with the nasal sensory nervous system (nonadrenergic, noncholinergic). Inhalation of irritants can directly harm the nasal epithelium, resulting in the generation of reactive oxygen species and the release of several

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Abbreviations used
HMW- High molecular weight
IIR- Irritant-induced rhinitis
LMW- Low molecular weight
OR- Occupational rhinitis (sensitizer-induced)
QOL- Quality of life
sIgE- Specific IgE
sNPT- Specific nasal provocation test
SPT- Skin prick test
WER- Work-exacerbated rhinitis
WRR- Work-related rhinitis

damage-associated molecular patterns, IFN-γ, and proinflammatory cytokines.[4] Irritants can also directly activate the trigeminal nonadrenergic, noncholinergic nerve fibers that express irritant detectors such as the transient receptor potential A1 channel.[4] The activation of these receptors induces a local release of neuropeptides, leading to mucus secretion, nasal congestion, sneezing, and even the recruitment and activation of leukocytes.

OR should be distinguished from work-exacerbated rhinitis (WER), which refers to the worsening of nasal symptoms temporally related to work exposure in subjects with preexisting or coincident rhinitis that was not caused by the workplace environment.[1] Respiratory irritants at work as well as other nonspecific stimuli (eg, cold air, cigarette smoke, exercise, and temperature changes) may trigger—through the activation of chemoreceptors on the trigeminal nonadrenergic, noncholinergic nerve fibers—rhinitis symptoms in individuals with nasal hyperreactivity, which is highly prevalent in allergic and nonallergic rhinitis.[14-16]

This review aimed to provide a comprehensive overview of current knowledge pertaining to the different aspects of OR with a focus on diagnostic approaches, societal burden, and management options. The purpose was also to provide practical guidance to clinicians who are faced with the assessment and management of WRR symptoms.

EPIDEMIOLOGY

Prevalence and incidence

The burden of OR in the general population has not been thoroughly explored. A systematic review of cross-sectional epidemiological studies conducted among various workforces concluded that OR is 2 to 3 times more frequent than occupational asthma (OA).[17] An analysis of OR cases reported to the Finnish Register of Occupational Diseases (1986-1991) failed to provide incidence estimates in the general population but identified occupations at increased risk (ie, bakers, livestock breeders, food processing workers, veterinarians, farmers, electronic/electrical products assemblers, and boat builders).[18] A questionnaire survey of a large sample of workers employed in various industrial sectors in the French-speaking part of Belgium found that a substantial proportion (6.3%) of the workers (ie, 28% of those with current rhinitis) experience WRR defined by the presence of 2 or more nasal symptoms at work.[19] However, inherent to its questionnaire-based design, this survey failed to distinguish between OR and WER. In addition, this random sample of workers might not have been accurately representative of the whole workforce and the full spectrum of occupations with a high risk of OR.

A number of cross-sectional surveys of workforces exposed to HMW and LMW sensitizing agents documented high prevalence rates of WRR symptoms ranging from 3% to more than 60%, whereas the rates of OR documented by skin prick tests (SPTs) or sIgE antibodies were usually much lower.[1,17] For instance, a systematic review of cross-sectional studies of workers exposed to laboratory animals found that the prevalence of WRR symptoms ranged from 7% to 42%, whereas OR documented by immunologic tests was approximately 2-fold lower, ranging from 3% to 19%.[20] These differences might reflect the presence of both allergens and nonallergic irritant triggers in these work environments.

Prospective cohort studies of subjects exposed to HMW agents (ie, laboratory animals, wheat flour, pepper bell pollen, and latex) reported incidence rates of WRR symptoms ranging from 1.4 to 13.1 cases per 100 person-years, whereas the incidence of nasal symptoms associated with IgE-mediated sensitization to workplace-specific allergens ranged from 0.7 to 6.3 cases per 100 person-years (Table I).[21,23-31] Of note, the highest incidence rates of IgE-mediated sensitization to work-specific agents and OR were observed within the first 2 years after entering exposure to the HMW sensitizing agent.[21,24,31]

Risk factors

The level of exposure to sensitizing agents has been the most consistently identified environmental risk factor for the development of IgE-mediated sensitization and OR.[17,32] However, atopy is an important individual risk factor for IgE-mediated sensitization to HMW agents. There is some suggestion that preexposure sensitization to common allergens that are related to workplace allergens, such as pets in laboratory animal workers[30] and grass pollen in workers exposed to flour,[31] could be a stronger predictor of OR than atopy.

RELATIONSHIPS WITH OA

Clinical studies have consistently documented that most patients with OA also suffer from OR and that OR most often precedes the onset of OA (Table II).[33-39] These associations between OR and OA are more frequent when HMW agents are involved.[33-35] Interestingly, in workers with OA induced by trimellitic anhydride, an LMW agent associated with the production of sIgE, most of the patients (88%) also reported OR, and in 77% of these cases, rhinitis symptoms preceded asthma.[37] This observation indicates that a strong association between OR and OA is more likely when an IgE-mediated mechanism is involved, irrespective of the molecular weight category of causal agents. Nevertheless, a recent study found that acrylate-induced OA was significantly more frequently associated with WRR symptoms than OA due to isocyanates, although IgE-mediated sensitization to acrylate compounds has never been documented.[40] Of note, there is also an association between WER and work-exacerbated asthma (Table III).[34,43] However, in subjects with work-exacerbated asthma, WRR symptoms seemed to be less frequent, less severe, and less often preceded the onset of asthma than in those with sensitizer-induced OA.[34]

In addition, longitudinal cohort studies have provided convincing evidence that OR is a strong risk factor for the subsequent development of OA (Table III),[22,41,42] similar to what has been documented for nonoccupational rhinitis and asthma.[44,45] These longitudinal studies further confirmed that

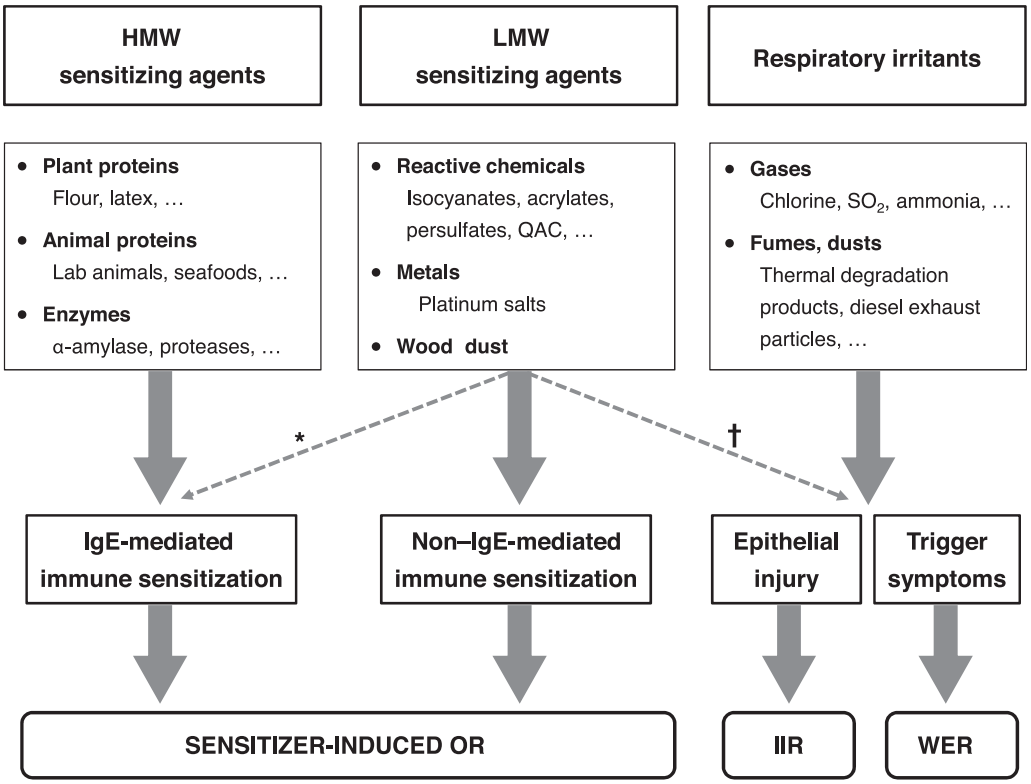

FIGURE 1. Illustration of the WRR phenotypes and their causal exposures and mechanisms. *QAC*, Quaternary ammonium compounds (biocides). *A few LMW agents (ie, platinum salts, acid anhydrides, reactive dyes, and obeche wood) are associated with demonstrable sIgE sensitization. †LMW agents with a sensitizing potential may have irritant properties at high concentrations.

OR is 1.2 to 10 times more common than OA, although with some exceptions.[24,29]

CAUSAL AGENTS

The workplace agents capable of causing OR are almost the same as those identified as inducing OA.[46] These agents are traditionally distinguished into 2 broad categories: HMW agents (<1 kDa) and LMW agents. HMW agents are biological substances derived from plants or animals, as well as enzymes from various sources. LMW agents include mainly reactive chemicals, metals, and wood dusts.

The distribution of causal agents may vary between different geographical areas, depending on the pattern of industrial activities.[47,48] Among 3637 ascertained cases of OR reported to the Finnish Register of Occupational Diseases between 1988 and 1999, the most frequently involved agents were animal allergens (29.0%), flour (12.2%), acid anhydrides (1.1%), cleaning products (0.6%), and persulfates (0.5%).[41] The principal agents causing OR in a large European cohort of subjects with OA ascertained by a specific inhalation challenge during the period 2006 to 2018 are presented in Table IV.[49,50]

PATHOPHYSIOLOGY

The united airway disease concept has been introduced to highlight the strong association and interactions between asthma and rhinitis, both allergic and nonallergic, and to support the concept that asthma and rhinitis are different clinical manifestations of a single disease process. Considering that clinical and epidemiological studies have also documented strong associations between rhinitis and asthma related to the workplace environment,[51] it is expected that OR and OA share common pathophysiological mechanisms, although very few studies have been conducted to support this assumption.

HMW proteins and a few LMW compounds (ie, platinum salts, reactive dyes, acid anhydrides, sulfonechloramide, and some wood species) act through the production of sIgE antibodies and induce a T_H2 immune response. In contrast, for most LMW agents, the immunologic mechanisms leading to upper airway sensitization remain largely unknown, even though they induce similar clinical symptoms. It has been demonstrated that LMW agents, such as acid anhydrides (eg, trimellitic anhydride and phthalic anhydride), can act as haptens by binding to autologous proteins (eg, HSA) to form allergens. Such LMW agents causing OA and OR are typically highly reactive electrophilic compounds that are capable of combining with amino acid residues on airway proteins.[52,53]

The resulting airway inflammatory process seems similar for OR and OA and is predominantly characterized by the presence of eosinophils.[54] An influx of eosinophils in the nasal mucosa has been demonstrated in nasal lavage fluid or nasal blown secretions after specific nasal provocation tests (sNPTs) with both HMW[55-57] and LMW[38,58,59] agents in subjects with OR. Interestingly, eosinophilic inflammation of the nasal mucosa has been documented in subjects with OA due to persulfate salts who did not experience clinical manifestations of rhinitis, further supporting the concept of united airway disease in the occupational setting.[38]

TABLE I. Incidence of OR

Occupational agent	Population (no. of subjects)	Follow-up (y)	Incidence of work-related nasal symptoms (per 100 person-years)	Incidence of OR (per 100 person-years)	OR/OA ratio	Reference
Laboratory animals	Laboratory workers (n = 342)	3	7.3	2.4*	1.5*	Cullinan et al[21]
Laboratory animals	Animal health technology apprentices (n = 373)	2.7-3.3	10.3	5.7*	2.1*†	Gautrin et al[22]
Laboratory animals	Laboratory workers (n = 495)	12.3	2.0	NA	4.8	Elliott et al[23]
Flour/α-amylase	Bakery and flour mill workers (n = 300)	Median 3.3	11.8	2.3*	0.8*	Cullinan et al[24]
Flour	Pastry-making apprentices (n = 188)	1.4	13.1	1.3*	10.1	Gautrin et al[25]
Flour	Baker apprentices (n = 287)	2.0	8.0	6.3*	1.4‡	Walusiak et al[26]
Flour	Baker apprentices (n = 114)	1.7	22.1	NA	2.2	Skjold et al[27]
Bell pepper pollen	Greenhouse workers (n = 280)	8	1.4	0.6*	1.2*	Patiwael et al[28]
Latex	Dental hygiene apprentices (n = 110)	2.7	NA	0.7*	0.4†	Archambault et al[29]

NA, Not available.
*Work-related nasal or asthma symptoms associated with IgE-mediated sensitization to work-specific allergens.
†OA defined by the onset of skin reactivity to a work-specific allergen associated with a >3.2-fold decrease in the provocative concentration of methacholine causing a 20% decline (PC_{20}) in FEV_1.
‡Occupational rhinitis and asthma demonstrated by a positive provocation test result.

TABLE II. Association between WRR and work-related asthma

Type of work-related asthma and agent	WRR			Reference
	Prevalence (%)	Severity	Onset before asthma (%)	
OA				
HMW agents (n = 24)	92*	NA	58	Malo et al[33]
LMW agents (n = 14)	71*	NA	25	
HMW agents (n = 110)	92*	6 (4-7)†	48	Vandenplas et al[34]
LMW agents (n = 62)	55*	4 (0-6)†	28	
HMW agents (n = 174)	74‡	NA	52	Ameille et al[35]
LMW agents (n = 381)	51‡	NA	39	
HMW agents (n = 22)	20§	NA	NA	Castano et al[36]
LMW agents (n = 21)	10§	NA	NA	
Acid anhydride (n = 25)	88	NA	77	Grammer et al[37]
Persulphate salts (n = 26)	54‖	NA	34	Moscato et al[38]
Flour (n = 175)	54‖	NA	NA	Wiszniewska et al[39]
Work-exacerbated asthma				
HMW agents (n = 24)	71*	4 (2-6)†	32	Vandenplas et al[34]
LMW agents (n = 81)	65*	4 (2-6)†	12	
Flour (n = 63)	32§	NA	NA	Wiszniewska et al[39]

NA, Not available.
*OR defined by at least 2 nasal symptoms at work.
†Median (25th-75th percentile) of overall rhinitis severity score calculated by summing the severity of individual nasal symptoms (ie, sneezing/itching, rhinorrhea, and nasal blockage) graded on a 0-3 scale.
‡Physician-based diagnosis of OR.
§Among 43 subjects with work-related asthma symptoms who completed specific inhalation challenge, concomitant positive nasal and bronchial responses were more frequent in subjects challenged with HMW agents than with LMW agents (n = 2/21).
‖OR documented by work-related nasal symptoms and a positive nasal provocation test result (ie, significant increase in total symptom score and in nasal lavage fluid eosinophils).

Few studies have compared the pattern of nasal immune response induced by HMW and LMW occupational agents. Castano et al[60] reported that, in subjects with OR, challenge exposure to HMW agents was associated with higher nasal lavage levels of the acute-phase reactants (ie, fibrinogen and haptoglobin), vascular cell adhesion molecule 1, vascular endothelial growth factor, and vitamin D binding protein compared with LMW agents. Suojalehto et al[61] performed a proteomic analysis of nasal brush samples collected from subjects with work-related asthma and WRR due to HMW agents, isocyanates, or welding fumes. The changes in protein expression revealed biological activities related to airway inflammation, oxidation-reduction,

TABLE III. Risk of asthma in subjects with OR

Causal agent	Population	Study design	Outcome	Reference
Laboratory animals	Animal health technology apprentices (n = 417)	• Prospective cohort study • FU: 2.7-3.3 y • OR defined by questionnaire and positive SPT	• Positive predictive value for OA*: 11.4%	Gautrin et al[22]
Various occupations	Compensated OR (Finnish Register of Occupational Diseases, 1988-1999; n = 3637) vs other occupational diseases	• Linkage with national health insurance register (reimbursement of asthma medication) • Mean FU: 6 y	Adjusted RR for asthma or OA†: 5.4 (95% CI, 4.8-6.2)	Karjalainen et al[41]
Laboratory animals	• Laboratory workers in a pharmaceutical company (n = 603; 2527 person-years)	• Surveillance program by annual questionnaire • FU = 12.3 y • OR defined by questionnaire	• Adjusted HR for work-related asthma symptoms: 7.4 (95% CI, 3.3-16.6)	Elliott et al[42]

FU, Follow-up duration; *HR*, hazard ratio; *RR*, risk ratio.
*OA based on questionnaire, positive SPT results for occupational allergens, and presence of nonspecific bronchial hyperresponsiveness to methacholine.
†Among incident cases of asthma, 37% of the subjects developed ascertained and compensated OA.

TABLE IV. Principal agents causing OR

HMW agents	n (%)*	LMW agents	n (%)*
Flour, grains	411 (39.8)	Isocyanates	108 (10.5)
Latex	34 (3.3)	Persulfate salts	83 (8.0)
Enzymes	27 (2.6)	Wood dusts	36 (3.5)
Seafood, fish	10 (1.0)	Metals	30 (2.9)
Rodents	10 (1.0)	Quaternary ammonium compounds	29 (2.8)
		Acrylate compounds	24 (2.3)
		Cleaning products, disinfectant (NOS)	18 (1.7)
		Welding	18 (1.7)
		Aldehydes	14 (1.4)
		Drugs	12 (1.2)
		Acid anhydrides	12 (1.2)
		Metal working fluids	10 (1.0)
		Epoxy resins	9 (0.9)
		Amines	9 (0.9)
Total cases of OR	586	Total cases of OR	447

NOS, Not otherwise specified.
Note. A physician-based diagnosis of OR was established in 586 of 685 (85.5%) subjects with OA caused by HMW agents and 447 of 817 (54.7%) of those with OA due to LMW agents. OA was ascertained by a positive specific inhalation challenge. (European network for the PHenotyping of OCcupational Asthma, unpublished data, 2006-2018).
*Percentage of total identified agents (n = 1033).

tissue matrix turnover, and inflammatory signaling. HMW agents and isocyanates induced similar nasal proteome responses, whereas the proteome of subjects exposed to welding fumes resembled healthy controls, suggesting different underlying mechanisms. An interesting murine model of toluene diisocyanate–induced rhinitis showed that mice exposed to toluene diisocyanate vapor showed predominantly eosinophilic inflammation of the nasal mucosa associated with a mixed T_H1/T_H2 immune response, features that are similar to nonoccupational allergic rhinitis.[62]

DIAGNOSTIC ASSESSMENT

An accurate diagnosis is essential in the management of OR because advising avoidance of exposure or other environmental interventions is associated with substantial professional, psychosocial, and financial consequences. The different steps involved in the investigation of OR are the clinical history, nasal examination, immunologic testing, and sNPT in the laboratory or assessment of nasal parameters at the workplace (Figure 2).

Clinical history

Taking a detailed medical and occupational history is the first step for diagnosing OR. The purpose of the clinical history is to confirm the existence of rhinitis and to evaluate its temporal relationship with work exposure by carefully gathering information on the important items that are presented in Table V. Nevertheless, the clinical history is not specific enough to establish a diagnosis of sensitizer-induced OR. Indeed, epidemiological surveys have found that WRR symptoms were associated with IgE sensitization to specific workplace agents in less than half of symptomatic subjects exposed to laboratory animals[21,31,63] and flour[24,25] (Table I). Hence, objective tests confirming the causal relationship between WRR symptoms and

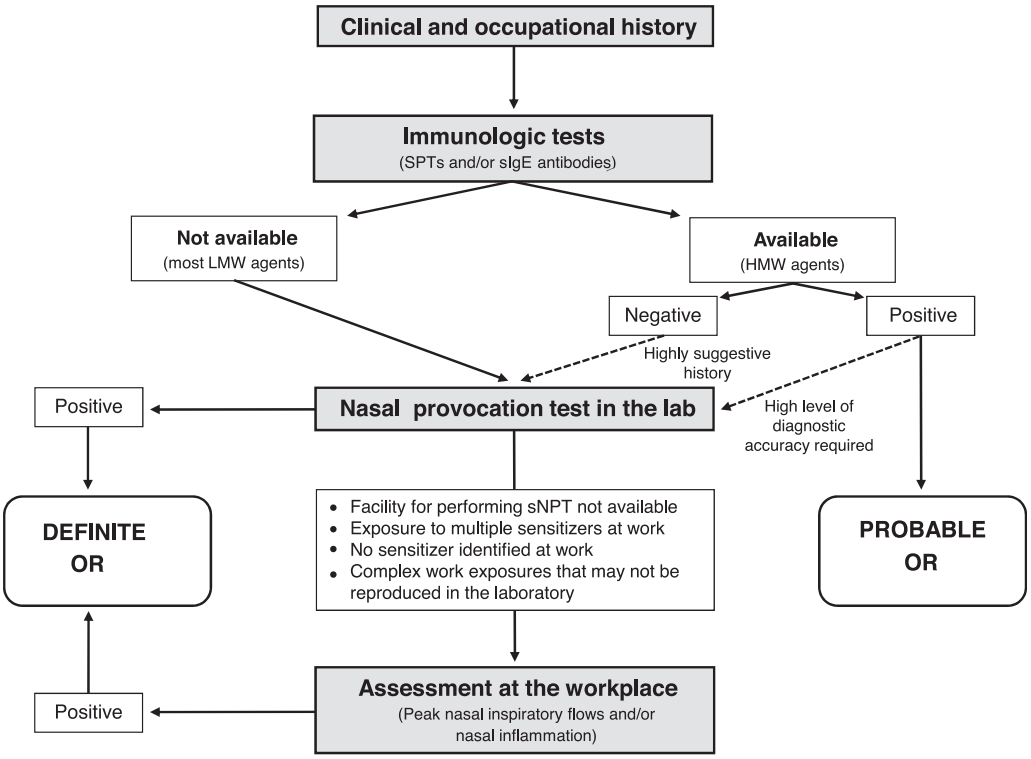

FIGURE 2. Proposed algorithm for diagnosing OR.

exposure to a specific agent at the workplace are necessary for establishing a definite diagnosis of OR.

Nasal examination

Inspection of endonasal cavities, preferably through nasal endoscopy, should be performed to identify associated disorders (eg, mucosal swelling, crusting, polyps, atrophic rhinitis, and septal perforation) and anatomical abnormalities that can interfere with the nasal function (eg, choanal atresia and septal deviation).[64]

Immunologic tests

IgE-mediated sensitization to occupational agents can be assessed by SPT and/or assessment of sIgE. The major limitation of *in vivo* and *in vitro* immunologic tests is the unavailability of standardized antigens for SPT and serum sIgE to most occupational agents, especially LMW agents.[65,66] In addition, there is scarce information to validate the sensitivity and specificity of immunologic tests compared with the results of sNPTs. For instance, only 10 of 24 (42%) subjects with WRR symptoms and positive results of SPT to laboratory animals showed a positive sNPT response to the handling of laboratory animals and litter.[63] Among 47 bakery apprentices who developed WRR symptoms over a 2-year period, sNPT result was positive in the 36 subjects with IgE sensitization to flour but also in 2 subjects with negative immunologic test results.[26] Extrapolating available data pertaining to OA,[66,67] immunologic tests would yield a high sensitivity for diagnosing OR caused by HMW agents and a few LMW agents (ie, platinum salts, reactive dyes, acid anhydrides, and obeche wood). It is noteworthy that positive sIgE testing (especially SPTs) may occur in a substantial proportion of asymptomatic exposed individuals,[68-71] so that the specificity of immunologic tests may be lower than expected. Nevertheless, in clinical practice, documentation of IgE-mediated sensitization by SPT or elevated sIgE is considered sufficient to establish a diagnosis of probable OR in subjects with a consistent history.

Assessment of the causal relationship with workplace agents

The sNPT aims at reproducing the nasal reaction occurring at the workplace under controlled conditions and, as such, these tests represent the reference standard for establishing a causal relationship between WRR symptoms and exposure to a specific occupational agent.[1,64,72,73] An sNPT may also be considered when a "local OR" is suspected in workers who report a clinical history highly suggestive of OR but demonstrate negative immunologic test results.[74] However, local allergic rhinitis due to occupational agents has not yet been formally demonstrated.

The sNPT with occupational agents is still poorly standardized, and the technical details are largely variable among centers.[1,64,72,73] Before challenging the subject with the suspected occupational agent, a sham provocation test is recommended to exclude nasal hyperreactivity and nonspecific irritant responses to occupational agents. The subjects should be carefully evaluated for the possibility of associated asthma, and if this is confirmed, lung function parameters should be monitored for at least 6 hours after the sNPT to detect an asthmatic reaction.[73] The method for delivering occupational agents during sNPT should be adapted to their chemical and physical properties (ie, gas, liquid, particles, or aerosol) as well as the mode of usage at the workplace.[75,76]

A positive sNPT result in a controlled laboratory setting is deemed to establish a diagnosis of definite OR. Alternatively, a

TABLE V. Clinical history checklist

Personal and/or familial history of allergy to ubiquitous allergens
Nature of nasal symptoms: rhinorrhea, nasal blockage, sneezing, itching
Relationship between nasal symptoms and occupational exposure
Duration of exposure at current job before onset of symptoms (latency period)
Pattern of symptoms in relation to daily work: immediate or late onset
Improvement after the workshift, during weekends, or prolonged periods off work
Identification of a specific product or task inducing symptoms
Associated disorders and their temporal relationship with work exposure
Conjunctivitis: itching, redness, watery eyes
Rhinosinusitis: postnasal drip, mucopurulent rhinorrhea, facial pressure, and altered olfaction and taste
Nonoccupational allergic rhinitis: symptoms associated with pollen seasons or exposure to indoor aeroallergens (eg, house-dust mite and pets)
Nasal hyperreactivity: nasal symptoms on exposure to environmental stimuli, such as cigarette smoke, temperature/humidity changes, and strong odors/fragrances
Asthma: wheezing, cough, chest tightness, breathlessness, and phlegm
Severity of nasal/ocular symptoms and their impact on daily life and sleep
Occupational history
Current job tasks description
Processes in adjacent work areas
Identification of direct and indirect exposures (safety data sheets)
Recent changes in work processes or materials
Workplace hygiene conditions: ventilation and personal protective equipment
Accidental high-level exposure(s)

"workplace challenge" demonstrating work-related nasal symptoms associated with increased nasal obstruction and/or enhanced nasal inflammation while exposed to the suspect causal agent may provide strong evidence supporting a diagnosis of definite OR. Workplace challenges should be considered in the following settings: (1) facility and expertise for performing sNPT is not available; (2) the subject is exposed to multiple potential sensitizers at work; (3) no potential airway sensitizer has been identified at work; and (4) the conditions of exposure at work cannot be reliably reproduced in the laboratory in case of complex industrial processes.

The nasal response to the sNPT and workplace challenge can be evaluated in different ways: (1) nasal symptom score or visual analog scale; (2) weighting nasal secretions; (3) evaluation of nasal patency (ie, nasal peak flow meter, acoustic rhinometry, or rhinomanometry); and/or (4) assessment of nasal inflammation through the analysis of nasal blown secretions, nasal lavage fluid, nasal scraping/brushing, or the assessment of nasal nitric oxide concentration.[1,64,77] There is general agreement that both subjective and objective indices must be considered,[72,78,79] although available studies provide conflicting results regarding the correlation between objective measurements of nasal patency using rhinomanometry and acoustic rhinometry and the subjective sensation of nasal blockage.[80] Unlike bronchial provocation tests,[75] the criteria for defining a positive nasal response have been seldom compared or validated.[81] The measurement of peak nasal inspiratory flow has been proposed as a simple tool for evaluating nasal airway patency in the same individual over time at the workplace.[82-85] The method is, however, effort-dependent and yields substantial variability.[84] There is accumulating evidence that assessment of eosinophilic inflammation in nasal secretions could increase the specificity of nasal responses during sNPT or challenge at work.[38,55-59] In this respect, studies have shown that a 4% increase in eosinophils recovered in nasal lavage or nasal blown secretions should be an adequate cutoff value for defining a significant inflammatory response.[86,87]

Differential diagnosis

The most challenging aspect of the differential diagnosis for OR is to distinguish this condition from WER. Epidemiological and clinical studies have consistently found that a high proportion of subjects who report WRR failed to demonstrate IgE-mediated sensitization to work-specific HMW agents (Table I)[88,89] or a positive nasal response to sNPT[63] and actually should be considered as having WER. The possibility of nonoccupational allergic and nonallergic rhinitis, such as vasomotor rhinitis and nonallergic rhinitis with eosinophilia, should be carefully considered because these conditions are associated with nonspecific nasal hyperreactivity that could make the affected workers more susceptible to WER.[14-16]

Overall, the clinical features of WER are similar to those of OR. Hence, a diagnosis of WER should be considered only after careful exclusion of OR through appropriate diagnostic procedures. The demonstration of an IgE-mediated process and/or the occurrence of an eosinophilic inflammatory response on exposure to an occupational agent are strongly supportive of a diagnosis of OR. Nevertheless, WER and OR are not mutually exclusive because workers with OR may experience work-related worsening of their symptoms because of nonspecific effects of occupational irritants. Nasal airway hyperactivity can be documented using specific questionnaires and/or nasal provocation tests, preferably with cold dry air.[15,16] However, these tests are available only in specialized centers, and their clinical relevance in diagnosing WER has not yet been explored.

In cases of acute-onset IIR, evidence supporting the diagnosis and the causal relationship with the workplace can be drawn only from the temporal association between exposure to unusually high levels of irritants and the development of persistent rhinitis symptoms (or other objective indices of the disease). In contrast, establishing a causal relationship between chronic workplace irritant exposures and the development of IIR is elusive on an individual basis.

HEALTH AND SOCIOECONOMIC IMPACT

In contrast to the significant literature on the burden of allergic and nonallergic rhinitis on quality of life (QOL) and work productivity,[90-92] there is only limited information on the specific impact of WRR on these outcomes.

Quality of life

Studies of workers with IgE-mediated OR reported either a greater[93] or a similar level of impairment[94] in rhinitis-specific QOL as compared with adults with nonoccupational rhinitis. However, a Finnish study reported a worse general health-related QOL in workers with OR due to protein allergens compared with control subjects with allergic rhinitis and healthy controls without rhinitis.[94] A cross-sectional questionnaire survey of a large sample of the general workforce in Belgium demonstrated that WRR, defined by the presence of at least 2 rhinitis

symptoms at work, is associated with an incremental adverse impact on both rhinitis-specific and general health-related QOL as compared with rhinitis unrelated to work.[19]

Work productivity

Follow-up studies of bakers and greenhouse workers showed that WRR was associated with a higher rate of job changes compared with asymptomatic workers.[88,95,96] In a clinical series of patients diagnosed with allergic OR in Tunisia,[97] the mean work time missed and the mean impairment while working due to OR assessed using the Work Productivity and Activity Impairment Questionnaire were similar (10% ± 21% and 47% ± 33%, respectively) to the estimates provided by a systematic review of nonoccupational.[92] In contrast, the aforementioned Belgian workforce survey found that the overall work productivity was more impacted in WRR than in rhinitis unrelated to work. Of note, the financial consequences resulting from either avoiding or reducing exposure to causal agents have never been investigated in workers suffering from OR alone.

OUTCOME AND MANAGEMENT

The management of OR aims not only to minimize nasal symptoms and their impact on patients' QOL, but may also offer the opportunity to prevent the development of OA. Complete avoidance of exposure to the sensitizing agent is considered the most rational management approach because it has been convincingly demonstrated that OR is associated with a high risk for the development of OA in workers who remain exposed to the offending agent (Table III).[22,41,42] A cross-sectional questionnaire study assessed 119 Finnish patients at an average of 10 years after a diagnosis of IgE-mediated OR from various agents.[94] Health-related QOL scores were impaired among workers with persistent workplace exposure, whereas among those removed from exposure, QOL was similar to that in healthy controls. Other follow-up studies of workers with OR confirmed that avoidance of exposure resulted in a significant improvement in nasal symptom score and QOL.[96,98]

However, complete avoidance of exposure to the causal agent is likely to require considerable professional changes for affected workers, which is most often associated with substantial socioeconomic consequences. Among greenhouse workers, those with OR at baseline were more likely to leave bell pepper cultivation for another job.[96] Reduction of exposure to the causal agent is often considered a pragmatic alternative to complete avoidance because of its lower socioeconomic impact for affected workers.[99] Reduction of exposure has been documented as resulting in a substantial improvement in the severity of OR symptoms due to laboratory animal allergens,[100] platinum salts,[101] and latex,[102-105] but the long-term efficacy of this approach has not yet been evaluated.

Hence, it is currently difficult to decide whether a worker suffering from OR should be immediately and completely removed from the causal exposure because of the lack of quantitative estimates of the long-term risk of asthma. The beneficial effects of complete avoidance of exposure to the sensitizing occupational agent must be balanced against the potential socioeconomic consequences. Epidemiological studies have identified risk factors for the development of OA that could be considered for a more personalized management approach to minimize the socioeconomic impact of the disease. The female sex[41,42] and a familial history of allergy or asthma[42] have been associated with a 3 times higher risk of subsequent OA. However, atopy (especially polysensitization to common allergens), severe OR symptoms, and the presence of asymptomatic nonspecific bronchial hyperresponsiveness may also be associated with an increased risk of OA because these characteristics were important cofactors in determining the risk of developing asthma among individuals with nonoccupational rhinitis[45,106-108] In these patients, complete removal from exposure should be more strongly recommended. Workers with OR who remain exposed to lower levels of the sensitizing agent must be medically monitored for the development of OA, which would then dictate more aggressive interventions.

Pharmacological treatment of OR (ie, intranasal corticosteroids and intranasal, ocular, or oral antihistamines) should be adapted to the severity of symptoms according to international guidelines issued for the management of rhinitis in general. However, information on the long-term efficacy of these medications is lacking because WRR/conjunctivitis symptoms are currently not specifically assessed in treatment trials. Specific allergen immunotherapy has been evaluated for a few occupational agents, such as latex, flour, and laboratory animals,[109] but it remains unknown whether this approach can alter the long-term course of the disease and reduce the risk of OA when workers with OR remain exposed to the causal agent. In addition, allergen immunotherapy is currently limited by the unavailability of standardized extracts.[109]

Because OR is often a harbinger of OA, its recognition in a worker as a sentinel event presents opportunities for implementation of both primary and secondary prevention efforts in the workplace. Primary preventive strategies aimed at reducing the development of immunologic sensitization to occupational agents and subsequent OR should focus on reducing or eliminating exposure to potentially sensitizing agents.[1-6] Observational studies and historical data provided evidence that prevention strategies, most often multicomponent programs targeting education, control of exposure, and medical surveillance, were effective in reducing the incidence of IgE-mediated sensitization to various occupational agents, including natural rubber latex in health care workers,[110] enzymes,[111,112] flour,[113] and laboratory animals.[114]

CONCLUSIONS

The key lesson clinicians should take from the scarce available data is that OR is likely to remain largely unrecognized and inappropriately investigated, although there is increasing evidence that this condition imposes a substantial health and socioeconomic burden. An early and accurate diagnosis of OR is crucial for improving the management and outcome of this prevalent work-related condition, and all patients with rhinitis should be asked about the possible work-relatedness of their symptoms and their impact on QOL. Consensus algorithms for diagnosing OR need to be developed and validated. An essential pathway to enhance the diagnostic process of OR is to promote the use and availability of the most appropriate diagnostic tests through the implementation of specialized referral centers. Early and complete avoidance of further exposure to the sensitizing occupational agent should still be recommended as the most effective treatment, although the beneficial effects of this option must be weighed against its potential adverse socioeconomic impact. There is a need to further investigate the risk factors for

the development of OA that should be taken into account to allow for a more personalized management of OR. In the context of the united airway disease model, further research should focus on determining the mechanisms involved in the expression of OR alone or in association with OA for HMW and LMW agents.

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