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Occupational Allergy (S Quirce and J Sastre, Section Editors)

United Airway Disease in Occupational Allergy

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Opinion Statement

The term "united airway disease" has been used since 2000 to describe the strong association between asthma and rhinitis. Although this term is not extensively used, it refers to the fact that asthma and rhinitis are frequently associated and share common risk factors, causal agents and mechanisms. Similarly, since 2010 the term occupational united airway disease has been used to describe the strong association between occupational asthma and rhinitis. Rhinitis and occupational rhinitis are less severe diseases but more frequent than asthma and occupational asthma, respectively. Every year several case reports and epidemiological studies enhance the long list of agents responsible for occupational asthma and rhinitis with new agents or occupations. Primary, secondary and tertiary prevention strategies are aimed at reduction of the onset and severity of work-related respiratory diseases. Primary prevention mainly includes avoiding/reducing exposure to known sensitizing/irritant agents. Secondary prevention or early detection should focus on medical surveillance of individuals at risk, health and safety education and training of workers, and recognition of early bronchial/nasal symptoms. Tertiary prevention includes early recognition and diagnosis, appropriate removal from further exposure and pharmacologic treatment. Unfortunately, pharmacologic treatment has seldom been studied in occupational asthma and rhinitis, and it usually refers to the international guidelines of management of asthma and rhinitis aimed to achieve control of the two diseases. For simultaneous treatment of asthma and rhinitis, the anti-IgE monoclonal antibody omalizumab, effective in occupational asthma and rhinitis, is available. Immunotherapy has been shown to be effective in health care workers with occupational asthma

due to natural rubber latex, in workers with occupational asthma due to laboratory animals and in baker's asthma. A limitation of immunotherapy, however, can be systemic reactions after subcutaneous injections of sometimes non-standardized and non-purified extracts.

Introduction

The term "united airway disease" has been used in the last 15 years to highlight the strong association between asthma and rhinitis shown in epidemiological, clinical and experimental studies [1•, 2]. Asthma and rhinitis are frequently associated and share common risk factors, causal agents and mechanisms [1•, 2]. Rhinitis is two to four times more frequent than asthma, and the strength of their association remained stable between 1990 and 2008 [3•]. The prevalence of asthma in subjects with rhinitis varies from 10% to 40%; the majority of asthma patients have rhinitis, and this often occurs before the onset of asthma [4•]. The association of asthma and rhinitis may cause impairment of asthma control [4•].

Similarly, the term "occupational united airway disease" has been used to describe the strong association between occupational asthma (OA) and rhinitis (OR), which is supported by clinical and epidemiological studies [5•, 6•, 7•, 8•]. OA and OR share agents, risk factors and mechanisms [9•, 10•]. Many agents, both high and low molecular weight, were identified as causes of OA and OR, but the mechanism of united airways disease development is not entirely clear. OR tends to be three times more frequent than OA, and its onset tends to occur before OA onset [9•].

The incidence of nasal and respiratory symptoms is higher in the first 2-3 years of occupational exposure [11••, 12•]. In workers exposed to laboratory animals, the prevalence of OR remained stable over time while that of OA declined by 1.6% every 10 years [13•]. When OA is associated with OR asthma severity seems to increase [14•].

OA and OR were found concomitantly present in many epidemiological studies done in laboratory workers, farmers, grain elevators, bakers, health care, pharmaceutical, fish/seafood and chemical workers [7•, 8•, 9•, 15, 16].

New causes and workplace settings responsible for OA and OR have been reviewed [17]. Between January 2012 and June 2014, ten new agents were identified: seven were high-molecular-weight compounds (two new enzymes used as detergents, food additives, arthropods contaminating food, earthworms used as aquarium fish food, orange fruit and orange zest), and three were low-molecular-weight agents (spruce wood dust, the biocide 4,4-methylene-bismorpholine and potassium tetrachloroplatinate) [17]. Moreover, eight new workplace settings (food processing, garbage work, screen printer, hand-crafted guitar maker, nurses, plumbers, nail art operator and eyelash extension glue) were identified [17].

Table 1 shows six case reports and one small epidemiological study that in the last 2 years have enhanced the long list of agents responsible for OA and OR with new agents or occupations [19–25].

Nguyen et al. have proposed an integrated diagnostic approach when OA and OR are associated [18•]. The first step is a detailed medical and occupational history and physical examination, followed by immunologic tests (i.e., skin prick tests and serum IgE, if available) for occupational agents. The diagnosis of OA and OR is confirmed by inhalation challenges with parallel assessment of nasal and bronchial responses. In workers with symptoms of OR and negative immunologic tests, especially if they are exposed to high-molecular-weight agents, a local OR should be considered [26].

Treatment

Prevention

Review articles on OA and OR summarize primary, secondary and tertiary prevention strategies aimed at the reduction of the onset and severity of work-related respiratory diseases [10•, 27••]. Primary prevention includes avoiding/

Table 1. Occupational asthma or rhinitis due to new agents/occupations (2015-2016)

Reference/ country	Study design	Patients (n)	Occupation/ activity	Agent/molecular weight	Age (years)	WR symptoms	Duration of exposure before WR respir. symptoms	Prevention	Diagnostic findings	Mechanism
Liccardi et al., 2014/Italy [19]	Case report	1	Part-time magician	Rabbit/HMWA	30	Upper and lower airway WR symptoms	Not stated	Avoidance of workplace exposure to rabbit	Atopic history. Positive SPT for rabbit dander, *Parietaria* and house dust mite	IgE-mediated
Cannon et al., 2015/UK [20]	Case report	1	Pharmacist employed in a pharmaceutical industry	Tafenoquine (novel anti-malarial compound)/LMWA	38	Upper and lower airway WR symptoms	2	Avoidance of workplace xposure to tafenoquine	Atopic history. Positive SPT for grass pollen and cat fur. Negative serum IgE to tafenoquine. Positive SIC with 1% tafenoquine dust	Allergic non-IgE-mediated
Gómez Torrijos et al., 2015/Spain [21]	Case report	1	Farmer	LTP in flower/leaves of melon plant and in rind of melon fruit/HMWA	46	WR conjuntival, upper and lower airway symptoms, and contact urticaria	Not stated	Not stated	Positive SPT and serum IgE to peach LTP. Positive conjuntical test and SIC	IgE-mediated
Paris et al., 2015/France [22]	Small crosssectional study	9	Workers employed in a cosmetic factory	Argan (*Argania spinosa*) powder/HMWA	35 (28-45)	3 with lower and 1 with upper aiway WR symptoms		Not stated	Crossreaction between argan and hazelnut allergens. 3 with positive SIC to argan powder	Probable IgE-mediated
Poussel et al., 2015/France [23]	Case report	1	Technician in a manufacturing facility working for the cosmetic industry	*Moringa oleifera* seed powder preparation/HMWA	32	Upper and lower airway WR symptoms	1	Not stated	Positive SPT and SIC to *Moringa oleifera* seed powder	IgE-mediated
Henriquez-Santana et al., 2016/Spain [24]	Case report	1	Employed in a pharmaceutical laboratory	Ranitidine/LMWA	41	WR conjuntival and upper airway symptoms, and urticaria	19	Not stated	Positive SPT for grass pollen, negative SPT, intradermal tests and oral challenge tests with ranitidine.	Allergic non-IgE-mediated

Table 1. (Continued)

Reference/ country	Study design	Patients (n)	Occupation/ activity	Agent/molecular weight	Age (years)	WR symptoms	Duration of exposure before WR respir. symptoms	Prevention	Diagnostic findings	Mechanism
Jiang et al., 2016/China [18•]	Case report	1	Employed in a sausage processing factory	Papain/HMWA	53	Upper and lower airway WR symptoms. Oral allergy syndrome and laryngeal edema after eating kiwi and fig fruit	2	Suggested avoidance of workplace exposure to papain	Positive SIC to ranitidine Positive SPT to fresh kiwi fruit and papain. Positive serum IgE to Kiwi fruit, papain and chymopapain	Non-IgE-mediated

reducing exposure to known sensitizing/irritant agents and educating workers in the use of safe work practices. Especially in the first 3 years after first exposure, secondary prevention (early detection) should focus on medical surveillance of individuals at risk, health and safety education and training of workers, and recognition of early bronchial/nasal symptoms. Tertiary prevention (appropriate treatment) includes early recognition and diagnosis, appropriate removal from further exposure and pharmacologic treatment, if necessary.

The level of exposure to sensitizing agents is the most important determinant of IgE-mediated sensitization, OA and OR [9•, 27••]. Therefore, reducing or eliminating workplace exposure to sensitizing agents, i.e., primary prevention, should be the most effective approach to minimize the onset of sensitization, OA and OR.

As regards prevention of OA, it has unanimously been recommended that primary prevention must include the avoidance of workplace exposure [27••]. Sometimes it is possible to replace a known sensitizer with a non-sensitizing agent, for example, substitute natural rubber latex gloves with non-latex gloves [27••]. When it is not feasible to replace a sensitizer, e.g., flour in bakeries, various interventions can reduce exposure to sensitizers, such as improved ventilation, personal protective equipment and education of workers in the use of safe work practices [27••]. For example, reduction of exposure was shown to be effective in reducing OA onset in enzyme detergent production, platinum refinery workers, laboratory and health care workers [28–31]. Workers with sensitization to occupational agents must undergo close medical surveillance because of the risk of onset of OR and OA.

Secondary prevention includes early diagnosis of OA and OR by means of medical surveillance. In workers with confirmed OR, regarded as a less severe disease, reduction of exposure is considered an acceptable alternative to complete avoidance [10•]. Close medical surveillance is mandatory because of the risk of OA onset.

In workers with confirmed OA a complete removal from further exposure is strongly suggested [27••]. However, complete avoidance of exposure often implies considerable professional changes for affected workers and is associated with adverse socioeconomic effects [32]. When avoidance of workplace exposure is not feasible or not acceptable by workers, every effort to reduce exposure must be made. For example, the study of Laoprasert et al. showed that a laminar flow helmet was effective in reducing latex-induced symptoms [33].

Pharmacologic treatment

OA and OR are responsible for financial loss in society because of direct and indirect costs. Workers affected by OA and OR often discontinue their occupation. Effective management and treatment of these occupational diseases are recommended [34]. International guidelines have established that the objective of asthma and rhinitis management is to achieve control of the two diseases. The pharmacologic treatment has a key role in obtaining good control of asthma and rhinitis [4•, 35]. Treatment of asthma and rhinitis using a single approach has been discussed [4•, 36]. Oral H_1 antihistamines are effective in rhinitis but not in asthma, and intranasal corticosteroids are slightly/not effective in asthma [4•]. For simultaneous treatment of asthma and rhinitis with one drug two options are available: leukotriene receptor antagonists, such as

montelukast, and the anti-IgE monoclonal antibody omalizumab, both effective in asthma and rhinitis [4•].

In many workers with OA/OR avoidance strategies may not be sufficient or feasible in controlling symptoms, and pharmacological treatment is needed. However, pharmacologic treatment has seldom been studied in OA and OR. Malo and co-workers evaluated a 1-year inhaled corticosteroid treatment in 32 subjects with OA, observing a small but significant improvement of respiratory symptoms, lung function and quality of life [37]. Marabini et al. studied 20 subjects with OA still exposed to the work environment and treated with inhaled corticosteroids and long-acting beta2-agonists [38]. In the 3-year follow-up the pharmacologic treatment seemed to prevent respiratory deterioration during work exposure. Several reviews on OA and OR include pharmacologic treatment in general, without mentioning specific studies on OA and OR [39–43].

Biological therapy

A new treatment for moderate and severe asthma with the monoclonal anti-IgE antibody omalizumab is used in Europe and the USA with significant clinical benefits for patients, improvement of quality of life, reduction of steroid intake and improvement of lung function. This therapy should be recommended in moderate-severe asthma (evidence A) [35]. One drawback is the high cost of therapy. Nasal, ocular and skin allergic symptoms are also well controlled by omalizumab.

Leynadier et al. demonstrated an improvement of allergic symptoms in 16 health care workers who had work-related latex allergy (i.e., rhinitis, conjunctivitis and/or mild/moderate asthma). After 32 weeks of omalizumab therapy the latex glove challenge test was negative in 73% of workers [44••]. Case reports of baker's asthma have shown that in workers exposed to flour dust at the workplace, the omalizumab therapy allowed them to continue work, improve quality of life and reduce asthma exacerbation and oral/inhaled steroids [45••, 46•]. Recently, Lavaudet al. published a follow-up study of ten patients affected by severe uncontrolled OA due to high- and low-molecular-weight agents and treated with omalizumab [47••]. Workers who remained exposed to the causal agent at a lower level after environmental intervention had a decrease in the number of exacerbations and in oral steroid consumption and improvement of FEV_1. Seven workers were able to continue their job.

Omalizumab is administered in a hospital setting once or twice monthly subcutaneously for 3-5 years, and the dose is related to the patient's total serum IgE level and weight. Figure 1 reports the administration doses. As only few data showed the effectiveness of omalizumab on OA treatment, the level of evidence for this therapy cannot be recommended.

Immunotherapy

Another option for simultaneously treating asthma and rhinitis is specific immunotherapy (SIT). SIT is the administration of gradually increasing doses of

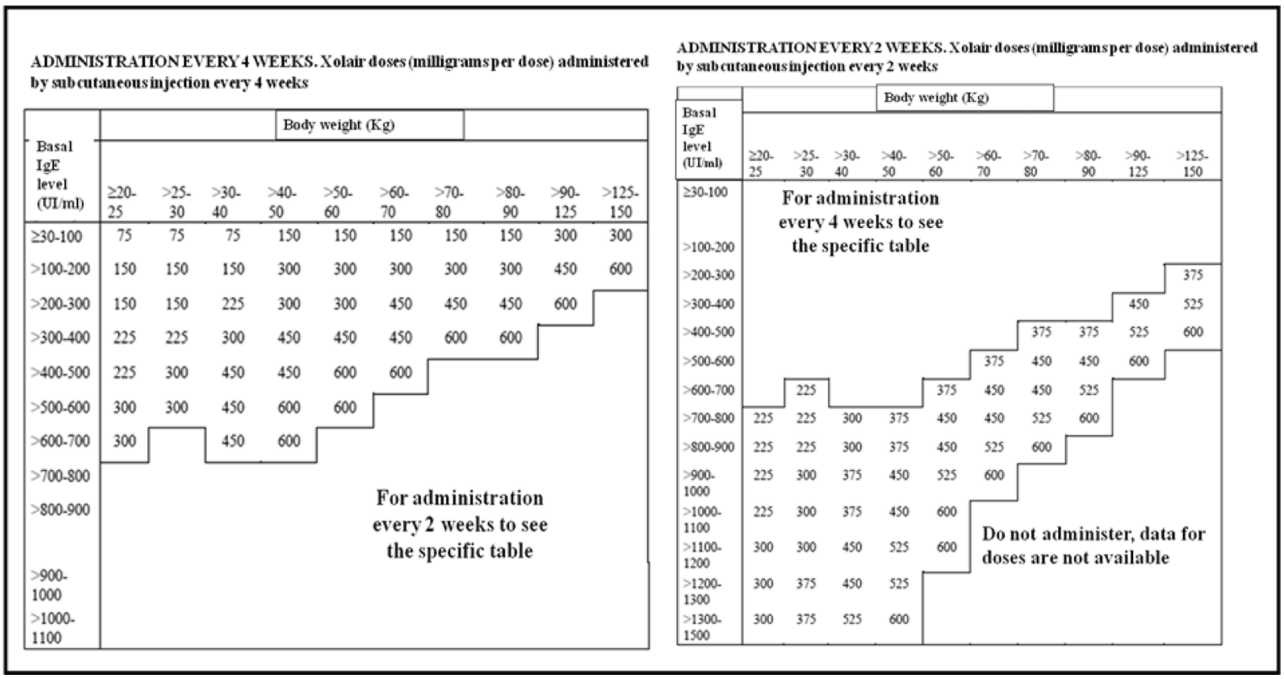

Fig. 1. Administration doses of omalizumab (adapted from the Xolair drug sheet).

allergen extract to induce the patient/worker immunological system tolerance. SIT can modify the natural history of allergic respiratory diseases, with improvement of rhinitis and asthma symptoms for a variable time. SIT is particularly appropriate when asthma and rhinitis are associated. It can also prevent the onset of asthma in patients with allergic rhinitis [4•]. When an IgE-mediated mechanism has been clearly confirmed, SIT can be administered by the subcutaneous (SCIT) or sublingual (SLIT) route (evidence A for rhinitis and D for asthma) [4•, 35].

SIT in OA and OR has been reviewed [10•, 48]. In OA and OR it has only been used for a few sensitizers, such as latex, flour and laboratory animals. Occupational allergy due to natural rubber latex (NRL) has been an important risk in health care workers and in other occupations, such as cleaners, processing foods, etc. Workers with allergy to NRL experience rhinitis, asthma, conjunctivitis, urticaria and, less frequently, anaphylactic reaction. Primary prevention is complete avoidance of exposure but, in some cases, as in the health care setting, this may not be feasible. SCIT with standardized NRL extract was administered in workers affected by OA and/or OR due to natural rubber latex in randomized double-blind placebo control studies, and significant improvement of symptoms was demonstrated, but systemic side effects related to SCIT have also been recorded. Because of frequent side effects, SCIT in NRL allergy has been abandoned; instead, SLIT is now used because of its better safety profile (very few side effects and significant clinical benefits). Latex immunotherapy has been reviewed by Nettis et al. [49]. NRL SLIT is commercially available in Europe.

OA and OR due to flour sensitization are among the most frequent IgE-mediated occupational allergies, and bakers are among the most frequently affected. The main allergen responsible for sensitization is white flour. Only a few case reports have been published. A double-blind placebo control study published in 1990 showed a significant improvement of symptoms and a decrease in skin sensitivity, serum level IgE and bronchial hyperresponsiveness to methacholine in workers treated with SIT [50]. Case reports and a retrospective study performed in patients with baker's asthma reported an improvement of asthma and rhinitis symptoms [50–52]. Bakers were able to continue their job for several years after 4 years of SCIT with wheat flour extract. Unfortunately, available extracts for diagnosis of baker's asthma are not standardized, and thus a correct diagnosis and treatment are not always feasible [53, 54].

Few studies have investigated treatment with SIT in workers affected by OA and OR due to animal allergens. Two studies evaluated SIT in workers with laboratory animal allergy. Wahn et al. treated 11 asthmatic workers with SIT for mouse, rat or rabbit and showed a significant improvement of the symptoms and IgG dose-related level [55]. Hansen et al. showed relief of symptoms in a biologist affected by OA due to rat epithelium after 18 months of SIT [56]. Recently, a case report of a cow breeder affected by OR and mono-sensitized to cow dander showed a mild improvement of rhinitis symptoms after 4 weeks of SIT [57]. SIT can also be effective in OA and OR due to horse, cat and dog sensitization, but there are no available studies in the occupational setting. As only few data showed the effectiveness of SLIT on OA and OR treatment, the level of evidence for this therapy cannot be recommended.

Conclusions

Asthma and rhinitis are often associated, and this association is often named “united airway disease” to highlight that they share common risk factors, causal agents and mechanisms. For the same reason the term “occupational united airway disease” has often been used. This frequent association in the occupational and non-occupational setting gives us the chance to use definition, classification and diagnostic tests, such as immunological tests and inhalation challenges, which are common for both diseases. Moreover, management—such as prevention, pharmacologic treatment, biologic therapy and immunotherapy—can simultaneously be used and is effective for asthma and rhinitis. As regards the occupational setting, prevention, especially primary prevention, is the most effective approach to minimize the onset of occupational sensitization, asthma and rhinitis. Pharmacologic treatment has been studied very little, but we strongly suggest following the international guidelines on the management of asthma and rhinitis also for occupational asthma and rhinitis. Very promising, although expensive, is the biologic therapy with omalizumab, effective for both occupational asthma and rhinitis. Finally, pilot studies on immunotherapy for natural rubber latex, flour and laboratory animals have shown effectiveness for both diseases, although there is little if no interest by industry in making standardized extracts commercially available.

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Compliance with Ethical Standards

Conflict of Interest
Dr. Folletti, Dr. Paolocci, Dr. Muzi and Dr. Siracusa declare that they have no conflicts of interest.

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

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