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

Asthma and Cleaning: What's New?

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Abstract

Professional and domestic cleanings are associated with work-related asthma (WRA). Increased risk of asthma has been shown in many epidemiological and surveillance studies, and several case reports describe the relationship between exposure to one or more cleaning agents and WRA. Moreover, exposure to cleaning chemicals could be associated with severe uncontrolled asthma. Cleaning sprays, bleach, ammonia, disinfectants, mixing products, and specific job tasks have been identified as specific causes and/or triggers of asthma or airway respiratory diseases. Their measurements at the workplace could be interesting but hardly feasible. It is still under controversy whether cleaning products are airway irritants or sensitizers. The social consequence of unemployment in this population is one of the most important limitations to the management of occupational in cleaning professionals. The prognosis of the disease depends of removal from exposure, with avoidance of high-risk cleaning products, even at home.

Introduction

Occupational asthma is a frequent disease that represents 15% of total asthma in adults [1]. Cleaners represent a large professional group with a majority of women with mean ages between 44 and 48 years [2, 3]. It is mostly a low income population with many migrants. Occupational asthma in cleaning professionals is a public health issue with important socio-economic consequences that has not yet received enough attention from health agencies and employers. It is of importance to diagnose asthma in cleaners since an early removal could help to recover.

Cleaning agents and exposure

Cleaning products are defined as any material used for cleaning or disinfecting surfaces in general work environments. These products have become an indispensable part of modern life, as they are used on daily basis in nearly all workplaces and homes. A wide array of cleaning agents has been developed to facilitate dust and dirt removal, and for disinfection and surface maintenance [4•]. Most the cleaning chemicals are low-molecular-weight agents.

Some cleaning products have been found to be strong irritants like chlorine bleach, ammonia, hydrochloric acid, or alkaline agents [4•, 5, 6]. The main sensitizers contained in cleaning products are disinfectants, quaternary ammoniums, amines, and fragrances (containing pinene and limonene) [4•]. New chemical components are continuously added to the list of irritants and/or sensitizers.

Cleaning professionals are exposed to a large variety of cleaning products and chemicals, often mixed together. Chemicals contained in cleaning products are often irritants or sensitizers [7, 8, 9••]. There are three elements in chemicals that play a role in the development of asthma and respiratory symptoms: (i) the intrinsic sensitizing and irritant nature of chemicals, (ii) the condition of exposure, and (iii) the personal susceptibility of the cleaning professionals.

Among these two first elements, cleaning professionals should pay peculiar attention to the type, frequency, and duration of cleaning tasks with high risk chemicals, the application procedures (spraying or mopping), and the volatility and concentration (dilution) of products, an associated important domestic use [3].

Quirce et al. [4•] listed the principle chemicals involved in work-related respiratory symptoms.

Sensitizers
- Amine compounds (eg, monoethanolamine)
- Disinfectants (eg, aldhydes)
- Quaternary ammonium compounds (eg, benzalkkonium chloride)
- Scents containing terpenes (eg, pinene d-limonene), eugenol
- Isothiazolinones, formaldehyde (preservatives)
- Others: natural rubber latex

Irritants
- Chlorine (bleach)
- Ammonia
- Hydrochloric acid
- Monochloramine
- Mixing bleaching and or ammonia
- Sodium hydroxide (caustic soda)
- Quaternary ammonium compunds
- Monoethanolamine

The intensity of exposure to chemicals is one of the most important factors, but the threshold of each product for being at risk of developing asthma is unknown. We actually do not know if there is a "no effect level" and whether cumulative doses are more at risk than peak exposures. Accidental high-exposures usually seem to cause irritant-induced exacerbations of asthma or asthma-like symptoms, called reactive airways dysfunction syndrome. Inappropriate mixtures of two or more chemicals are also associated with a higher release of chlorine and chloramine components, which are strong irritants [4•. People with prolonged exposures to moderate and low concentration of irritant or sensitizing chemicals may be at risk of developing new onset asthma and work-related asthma [4•, 10, 11].

The use of cleaning sprays increases the respiratory exposure to chemicals and consequently the inhalation risk [12, 13]. Many low-molecular-weight agents are volatile organic solvents and can become airborne during the cleaning tasks [10].

The measurement of airborne quaternary ammonium compounds was not possible until recently [14]. Using mass spectrometry, measurable levels of quaternary ammonium could be found in the air of a bedroom at the Strasbourg University Hospital (unpublished data). For chlorine and ammonia, it has been demonstrated that cleaning bathrooms or kitchens induced peak levels of chlorine and ammonia far above the threshold value (0.5 and 35 ppm, respectively) [15].

Most of the times, cleaning professionals are also exposed to other allergens. They are usually exposed to latex, house dust mite, molds, animal dander, and cockroaches especially while cleaning in damp environments [2, 16]As chemicals are released slowly from the cleaned surfaces other people in the building can be exposed to moderate or low doses of chemicals and common allergens [7, 17, 18].

Epidemiology

Since 1990's, several programs of surveillance indicated that healthcare workers and cleaners emerged as most frequently reported jobs among all cases of work-related asthma (WRA). The studies of the European cohort ECRHS showed the highest risk of asthma for cleaners compared to workers not using cleaning products (1.71 (IC 95% [0.92–3.17]) [19]. Nurses and cleaners had the highest relative risks for new onset asthma [20]. In a recent cross-sectional study of 34,000 adults in Estonia, cleaning and health-related occupations were among the job categories associated with asthma: OR adjusted respectively 2.07 [1.25–3.42] and 1.77 [1.24–2.53] [21]. In this study, these jobs were mainly occupied by women. Seventy-seven percent of the total workforce in the cleaning industry are women who work generally part time, 30% are migrant workers [22]. In consequence, women are more exposed than men to cleaning products.

The risk of WRA affecting individuals exposed to cleaning products does not seem dependent on atopic status, whereas smoking increases the risk of asthma for cleaners [23] In recent studies, poor psychosocial working conditions seem to contribute to the high prevalence of asthma for Peruvian cleaners [24] and in Northern Europe, early life disadvantage, like maternal smoking, may increase airway vulnerability to harmful exposure from cleaning agents later in life [25].

A study of respiratory work disability showed that cleaners were at risk to change of work because of respiratory symptoms [26]

A study group comprised 50 professional cleaning women with suspicion of occupational asthma showed that work-related asthma was frequent (46% of cases) and disinfectants played an important role as a causative agent [27]. Exposure to cleaning agents (both at home and in the workplace) plays an important role in adult-onset asthma, and an association was observed between uncontrolled adult-onset asthma and exposure to cleaning agents (OR 2.0, 95% CI 1.2–3.3) with stronger associations for long-term exposures [3] About specific exposure, professional use of bleach is associated with asthma and respiratory symptoms. Recently, the link between the use of bleach for domestic cleaning and asthma was studied. The use of bleach for domestic cleaning is associated with non-allergic asthma in women and for women without allergic sensitization, with bronchial hyperresponsiveness, asthma-like symptoms, and chronic cough. In contrast, no association was observed between bleach use and allergic asthma [28].

At the healthcare professional, specific exposure to cleaning products were characterized by self-reported exposure or job-exposure matrix JEM. A job-task-exposure (JTEM) matrix was recently developed to assess occupational exposure to disinfectants among US nurses. The JTEM may provide more accurate estimates about occupational exposure than the JEM, especially for nursing jobs with heterogeneous tasks [29]. Disinfectant use among healthcare workers has been associated with asthma [30]. About 8851 nurses, differences about disinfectant use, (and in fact about occupational exposure), was noticed according to workplace characteristics (size of the hospital, numbers of beds) and region (west, north of USA) [31•]. About nurses with asthma, use of disinfectants to clean medical instruments was associated with poorly (OR 1.37; 95% CI 1.05–1.79) and very poorly (OR 1.88, 95% CI 1.38–2.56) controlled asthma (p_{trend} = 0.004, after adjustment for potential confounders). Using JTEM estimates, exposure to formaldehyde, glutaraldehyde, hypochlorite bleach, hydrogen peroxide, and enzymatic cleaners was associated with poor asthma control (all $p_{trend} < 0.05$); exposure to quaternary ammonium compounds and alcohol was not [32]. Nurses with a baseline history of asthma were more likely to move to jobs with lower exposure to disinfectants (HR 1.13 (1.07 to 1.18)), especially among those with more severe asthma [33].

Pathophysiology

While the mechanisms of common asthma have been studied more and more in the past few years, the physiopathology of occupational asthma remains unclear, especially in cleaning professionals. Multiple factors may influence the initiation and the evolution of the disease, like genetic, environmental, or behavioral factors. According to the USA Occupational Safety and Health Administration, irritants are non-corrosive substance that causes a temporary inflammation on direct contact. If the intensity or the duration of the exposure is sufficient, irritant substances could induce inflammatory and remodeling processes. The upper and lower respiratory tract seems to be an important exposure location and the main site for inflammatory response in cleaning professionals exposed to chemicals. However sensitization could occur through

other ways, like by dermal exposure [34, 35]

Work-related asthma to cleaning products can be induced through both immunological and non-immunological mechanisms [9••, 36, 37]

Some studies found an increased IgE synthesis to cleaning products in cleaners with occupational asthma but the IgE production was low [30, 38]However, an adjuvant effect on atopy has been described in pig farmers using quaternary ammoniums to clean their piggery [39, 40]. An increased bronchial epithelial permeability and a Th_2-mediated immune response were also shown with dual irritant and adjuvant effects [41, 42].

Cleaners with a positive specific inhalation challenge had a more severe asthma with higher blood eosinophilia corresponding to a Th_2 high immune response [43•].

However, several studies did not find any Th_2 high effect in symptomatic cleaners. Atopy did not seem to play a role in the mechanisms of asthma in cleaning professionals as described by Zock et al. [44]. Moreover, occupational asthma to low-molecular weight agents were more frequent in non-atopic patients who have low eosinophilic and sometimes high neutrophilic counts in blood and sputum and rare bronchial reversibility after ß2-mimetics [5, 11, 13, 44, 45] A possible limitation of these studies could be the difficulty to distinguish asthma-like symptoms from asthma.

A perturbed secretion of different factors can also be seen, like lack of relaxing epithelial factors, an increased secretion of epithelial cells growth factors, a release of inflammatory mediators and pro-inflammatory cytokines [36]. Components like smooth muscle cells, fibroblasts and matrix can also be damaged by the inflammatory response [36].

High exposure to irritant chemicals leads to an injured bronchial epithelium. The pathophysiological pattern for damaged epithelium consists in an infiltration and activation of inflammatory cells from innate and adaptive immunity, an increased sub-epithelial collagen volume with bronchial hyperresponsiveness, and an exposure of nerve endings with neurogenic inflammation [9••]. In neurogenic inflammation, the Transient Receptor Potential (TRPA1) is activated in neurons, in lung cells and in mast cells [46].

Epithelial injuries induced by irritant chemicals also seem to cause oxidative damages to epithelial cells, smooth muscle cells, and immune cells. On mice, exposure to chlorine caused bronchial hyperresponsiveness and local oxidative stress in the airways [47]. A nitration of amino acids and the synthesis of nitrotyrosine are one of the ways to produce reactive oxygen species after exposure to chlorine [48]. A production of reactive oxygen species could take place in damaged epithelial cells as well as in inflammatory immune cells (macrophages, neutrophils), due to an imbalance between oxidizing and reducing systems [49]. Reactive oxygen and nitrogen species have shown to play a major role in the physiopathology of asthma [50], and we recently found an increased mitochondrial function in immune peripheral blood cells with an increased production of reactive oxygen species in severe exacerbated asthma (data not shown). Zock et al. [51] recently studied the interactions between genetic polymorphisms of genes involved in oxidative stress and an exposure to low-molecular-weight molecules on new onset asthma. Eight single nucleotide polymorphisms (SNPs) by exposure interactions at five loci were positively associated with new onset asthma. These genes are likely to play a role in the NF-κB pathway that is known to be involved in the general inflammatory

process. A few of these SNPs may also be involved in regulatory mechanisms. Further studies on genetics in occupational asthma especially in cleaning professionals are needed in order to get a better understanding of the disease.

In conclusion, occupational asthma in cleaning professionals seems to depend on an immunological sensitization and at least a part of airway irritation. There is still much to learn on the underlying mechanisms of asthma in cleaning professionals, to determine specific risk factors and biomarkers.

Diagnosis

Occupational asthma is a condition where asthma is provoked de novo or worsened by occupational exposure. This term regroups two different entities, which are new onset asthma and work-exacerbated asthma. New onset asthma is an induction of the disease induced by an exposure to irritant or immunogenic substances at work. Work-exacerbated asthma consists in a preexisting asthma that is exacerbated by at least one specific exposure at work [5, 52].

There is a third category of work-related respiratory symptoms but that is not associated with actual asthma. These asthma-like respiratory symptoms are called airway sensory hyperreactivity. These airway symptoms are often induced by strong smelling products and cannot be related to asthma or immune reactions and scents are not related to irritancy and toxicity [4]. Such patients seem to have an increased sensitivity to capsaicin [53, 54] Airway sensory hyperreactivity does not seem to be associated with asthma nor psychiatric morbidity [55].

Cleaning professionals experiencing asthma or respiratory symptoms should be taken care by occupational physicians specialized in asthma. However, most of the time, asthma in cleaning professionals is under-diagnosed and few patients access to specialized care [16].

The diagnosis should begin as usual with a complete medical questioning and clinical examination. Physicians should focus on the exposition at the workplace and at home. Symptoms should be related to working shift demonstrating a delirious effect of work exposure on respiratory symptoms, with or without a latency period [45]. There should be also a relation between respiratory symptoms and the exposure to chemicals.

Exposure characteristics should be specified: type and number of products, repeated use, frequency of use, exact type of tasks, use of sprays and mixtures, and dilution of different mixtures. A detailed occupational history has to be recorded. Clinicians should inquire about the prevention used at work like the use of gloves, protective masks, training and education about risks, and the proper use of cleaning products. Exposure should be quantified as far as possible with the support of employers.

The remaining questioning should interrogate for non-occupational asthma. Questions should be asked on atopic profile, presence of rhinitis, conjunctivitis, gastro-intestinal symptoms, episodes of wheezing, dyspnea, chest tightness, and cough. Lower respiratory tract symptoms and chronic bronchitis seem to be frequent for cleaning professionals [4, 44, 56•]A thorough personal and familial medical history should be noted with drug intake, possible other toxic or allergen exposure. The Asthma Quality-of-Life Questionnaire should also be fold out to measure the handicap induced by asthma.

Socio-economic situation and gender also seem to worsen the exposure, as for more female cleaning professionals report more respiratory symptoms than male [57]

Clinical examination should follow the allergic asthma model with a search for seriousness signs and different auscultation sounds. Other irritation symptoms should also be searched for: checking eyes, nose, sore, throat, and dry cough. A complete skin examination, especially on hands (risk of irritation dermatitis [35, 56•], skin rash or chemical burns [57] and a complete rhinological and eye examination should be conducted looking for help from dermatologists, oto-rhino-laryngologists, or ophthalmologists if needed. After examination the peak expiratory flow has to be reported. All these informations should appear in the patient's medical file.

Guidelines about managing occupational asthma are available but not specifically for cleaning professionals [58, 59, 60•]. For affected cleaning professionals further biological and radiological tests should be conducted as in every asthma assessment.

As a higher prevalence of bronchial hyperresponsiveness and a lower lung function were found at cleaning professional with asthma [4, 44], a spirometry has to be done with FVC, FEV_1, and FEV_1/FVC (with a reversibility test after ß2-mimetics) as well as a methacholine challenge has to be performed at and off work. A spirometry and peak expiratory flow measurements (at least four times a day) should be done as far as possible at the workplace during the exposure period take in account a possible latency period.

Specific provocation tests to chemicals seems to have an important place in the diagnosis of occupational asthma especially in cleaning professionals, but has to be done in specialized centers. Provocation test for quaternary ammoniums proved to be useful in the diagnosis of occupational asthma [38, 61•] but in the case of chlorine these tests seem to be more difficult to interpret [62, 63]. Patients responding to specific provocation test seem to have more severe asthma with high blood eosinophilia and a Th_2 immune response [43•].

At the beginning of medical cares, blood gas measurement, chest radiography, and complete blood count should also be done.

For cleaning professionals specific IgE levels seem to be low, whereas total serum IgE levels increased significantly [11]. Skin prick or specific IgE blood tests are available for a few low-molecular-weight agents but no standardized allergens for clinical use are commercially available.

FeNO measurements should be conducted as several studies mention it being significantly higher for cleaning professionals with asthma and respiratory symptoms [16].

Currently, there is no proper biomarker for occupational asthma in cleaning professionals.

For now, there is no routine biomarker available for occupational asthma in cleaning professionals. Cytokines, growth factors, and determinants of oxidative stress (H2O2, 8-isoprostrane, 4-hydroxynonenal) did not allow the evaluation of the inflammation process. However, higher total IgE, increased FeNO and lower FEV_1 were associated with asthma in cleaning professionals [16, 48]. Different biomarkers could give information on an irritant or a sensitizing process, but it is not possible to differentiate one from the other with the biomarkers that have been tested thus far. There is a need to conduct other studies based in environmental

monitoring in order to find better biomarkers for occupational asthma in cleaning professionals.

Treatment

Medical treatment in occupational asthma does not differ from the regular treatment of asthma [58].

The most important measures are an early diagnosis, an early and a total eviction of the cause which means in this case avoidance to exposure at chemicals. Most of the time, this means a change of activity for the cleaning professional. If such a change is not possible, cleaning professionals with asthma should be relocated to low or occasional exposure areas and have extended health controls. Patients must be informed that avoidance of exposure is the only way for an improvement of their asthma and that the respiratory symptoms and airway damages can subsist several years after eviction [64•].

Workplace interventions are important for primary prevention of occupational asthma in cleaning professionals [9••]. For example cleaning professionals should wear protections such as respiratory protective masks, non-latex non-powdered gloves, and long-sleeve clothing. Time of exposure should be as short as possible and bleach, cleaning sprays, ammonia, disinfectants, and mixing products should also be avoided as much as possible. Proper ventilation of the cleaning space seems crucial. This can be achieved best by crossed-ventilation between open windows and technical ventilation [7, 10]. The labelling of cleaning products should be improved and cleaning professionals should receive a proper education and information on the risks and adequate use of chemicals. Green products should be purchased and disinfections should be done only when necessary. Quantitative measurements at workplace of irritant and sensitizer chemicals should also be done. A collaboration between scientific communities, health agencies, and employers of cleaning professionals should exist.

Health surveillance programs at work are important for an early diagnosis of asthma for cleaning professionals and contribute to a better prognosis of the disease.

One of the most important limitations of medical care for cleaning professionals with asthma is a possible job loss. Most cleaning professionals have a narrow socio-economic background (13) and cannot afford unemployment. This is a possible reason why asthma in cleaning professionals is underdiagnosed.

Conclusions

Improving the physiopathological knowledge, the management and the prognosis of occupational asthma in cleaning professionals still remains a challenging issue. Specific causal exposures, cleaning tasks, and chemicals need to be better identified. Thresholds would be useful to establish safety protocols for exposed cleaning professionals. For that idea, exposures at work need to be better quantified.

Health surveillance at work should focus on occupational asthma, respiratory, and cutaneous symptoms in cleaning workers. If diagnosed early,

occupational asthma has a better prognosis. Even if the medications are similar to allergic asthma, primary and secondary prevention measures seem to be crucial in this population. There is a need for more information and training of cleaning professionals on the risks and adequate uses of their cleaning products. Healthcare comities and employers should have a better communication in order to improve working conditions and as far as possible avoid high-risk chemicals while remaining productive and cost-effective. Further studies are needed to help understanding immune and pathological mechanisms of occupational asthma and to help identify/quantify causal agents and tasks.

Compliance with ethical standards

Conflict of interest

Frederic de Blay reports grants from STALLERGENES-GREER, grants from CHIESI, personal fees from ALK, personal fees from MUNDIPHARMA, personal fees from NOVARTIS, during the conduct of the study; other from STALLERGENES-GREER, other from NOVARTIS, other from ALK, other from MUNDIPHARMA, other from MEDAPHARMA, other from BOEHRINGER, other from ASTRAZENECA, outside the submitted work.
Carole Ederle declares that she has no conflict of interest.
Carole Donnay declares that she has no conflict of interest.
Naji Khayath declares that he has no conflict of interest.
Marie Mielcarek declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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