



New causes of immunologic occupational asthma, 2012–2014

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Purpose of review

The objective of this study was to review all new causes of well documented immunologic occupational asthma (IOA) published in the English and French medical literature between January 2012 and mid-2014.

Recent findings

Ten case reports of new causes of IOA were reported during that period. The diagnosis was either confirmed by specific inhalation challenges ($n=5$) or a combination of peak expiratory flow monitoring at and off work, confirmation of specific sensitization, and asthma ($n=3$). These involved both high (mites contaminating cured ham, various enzymes used as detergents and food additives, aquarium fish food, and orange allergens) and low-molecular-weight agents (spruce wood dust, a biocide, and an halogenated platinum compound used in cytotoxic drugs). Furthermore, eight studies reported cases of IOA with agents already known as airway sensitizers but in working environments that were unusual and reported for the first time.

Summary

There are more than 400 known causes of IOA and the list grows continuously with the development of new technologies and better recognition of the diagnosis by physicians. IgE-mediated sensitization was confirmed in all new cases involving high-molecular-weight agents and in two of the three new cases involving low-molecular-weight agents. Symptoms of rhinitis were often associated with both types of agents. Physicians should stay alert and suspect occupational asthma in any adult with new-onset asthma or with newly uncontrolled asthma.

Keywords

causative agents, occupational allergy, occupational asthma, specific inhalation challenges

INTRODUCTION

Asthma is among the leading causes of occupational lung diseases in industrialized countries and about 10–15% of adult-onset asthma is thought to be because of the work [1,2]. Work-related asthma can be defined as work-exacerbated asthma and occupational asthma [1,3]. While work-exacerbated asthma, also called work-aggravated asthma, is pre-existing or concurrent asthma that is exacerbated by workplace exposure, occupational asthma is defined as asthma (a disease characterized by airway inflammation, variable airflow limitation, and airway hyperresponsiveness) caused by conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace [4]. Occupational asthma can be further distinguished between immunologic or nonimmunologic types, according to whether there is a latency period necessary to acquire an immunologic sensitization – this is called immunologic occupational asthma (IOA) – or not, as asthma develops within hours

of a single exposure to high levels of inhaled irritants – variants of this type of asthma have been described following multiple exposures to irritants and it is now called irritant-induced asthma.

There are more than 400 agents known to be associated with IOA and/or non-IOA and the list steadily grows each year with the development of new industrialized processes and better recognition by physicians. Recently, Baur [5,6] reviewed the various causes responsible for immunologic and nonimmunologic asthma published by August 2011. The objective of this study is to review the list of all new agents recognized as a cause of IOA and described in the literature between January

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KEY POINTS

- Workers exposed to HMW agents who develop occupational asthma have frequently other allergic manifestations such as rhinoconjunctivitis or contact urticaria.
- Physicians should be aware that new causes of occupational asthma are still reported each year, stressing the importance of inquiring about work-related symptoms in any worker with newly uncontrolled or new-onset asthma.
- HMW but particularly LMW agents may be found in many different occupational settings, often unsuspected.
- New causes of occupational asthma should ideally be confirmed by SICs.

2012 and June 2014. Epidemiological studies reporting an increased prevalence of chest symptoms in various work forces and for whom the diagnosis of IOA was not confirmed objectively will not be discussed.

METHODS

Medline was searched for publications in English or French using the key words 'occupational asthma', 'occupational allergies', and 'asthma and work' in 2012, 2013, and in the first 6 months of 2014. This review refers to studies that reported new causes of well documented IOA or to studies reporting known causes of IOA encountered in new occupational environmental conditions. However, the level of evidence for causation varied between the studies [7–9], specific inhalation challenges (SICs) being considered the reference standard.

REVIEW

The following sections describe new agents associated with IOA, new occupational settings associated with IOA and an overview of the various investigations which led to the diagnosis.

New agents

Between 2012 and mid-2014, 10 new agents were identified as airway sensitizers causing IOA. The diagnosis of IOA first relies on a good history with the demonstration that asthma is caused by work exposure, ideally with identification of the responsible agent [1,7,8]. However, the latter may not always be possible and workers might be exposed to several sensitizers at work. A combination of confirmed asthma, temporal relationship of symptoms with workplace exposures and objective tests

such as confirmation of immunological sensitization by skin prick tests (SPTs) or specific IgE (sIgE), monitoring of peak expiratory flows (PEFs) at and off work, nonallergic bronchial hyperresponsiveness (BHR), and sputum counts cells have various probability levels of accuracy [1,7,8,10]. SICs are considered the reference standard for the diagnosis of occupational asthma, and, when done in the laboratory, they allow identification of the responsible agent [1,7,8].

Table 1 [11[■],12–14,15[■],16,17[■],18–20] lists all new causes of IOA according to their molecular weight, that is, high (>5–10 kD, usually a protein or glycopeptide) or low, as well as the type of job involved (workplace setting), the number of subjects and their clinical characteristics (age, sex, atopic status, and smoking history when known), associated work-related symptoms (rhinoconjunctivitis and contact urticaria or dermatitis), immunological findings specific to the relevant agent (SPT and sIgE) when done, functional tests used to confirm the diagnosis of asthma (defined by variable airflow obstruction or increased BHR) and work relatedness including monitoring of PEFs at and off work, and finally results of SICs.

The majority of new causes of IOA were seen with high molecular agents: new enzymes used as detergents [11[■],12] or food additives [13], arthropods contaminating food (cured ham) [14], earthworms used as aquarium fish food [15[■]], and orange fruit [tree aeroallergen [16] and flavedo (zest) [17[■]]], and only three agents having a low molecular weight (LMW) (spruce wood dust [18], the biocide 4,4-methylene-bis(morpholine) [19], and the halogenated platinum compound K_2PtCl_4 [20]). Although savinase is not a truly new agent as it belongs to the subtilisin family, like other enzymes such as maxatase or alcalase, the cases presented here [11[■],12] were the first cases described with this specific protease enzyme derived from *Bacillus amyloliquefaciens*. The diagnosis was well documented in eight subjects by either SIC (n=5) and/or combining PEF monitoring at and off work, objective evidence of asthma, and specific sensitization (positive SPT or sIgE) (n=3). For two agents (bacterial α -amylase Termanyl and microbial transglutaminase), the diagnosis relied only on history, evidence of asthma, and specific sensitization, which make the diagnosis highly probable.

Not surprisingly, most cases of occupational asthma to high-molecular-weight (HMW) agents were associated with other allergic manifestations, such as rhinoconjunctivitis or contact urticaria, the latter being less common [1]. Rhinitis was also often associated to LMW agents-induced IOA (2/3). Previous studies [21,22] had shown that both

Table 1. New causes of occupational asthma

Substances	Reference	Workplace setting	No. of cases	Symptoms	Clinical characteristics	Immunological tests (specific)	Functional tests	SIC	Comments
HMW agents									
Savinase (subtilase family)	[11 [■]]	Process operator in a dishwashing tablets factory and exposed to enzymes including savinase	1	A	51, F, nonatopic, NS	SPT ND sIgE +	BHR +	Late (increase in sp_{PEF} post-S(C))	Savinase is an endopeptidase of the subtilase family, produced by <i>Bacillus</i> sp. different from subtilisin; negative sIgE to α -amylase (and SPT), alkalase and maxatase. Diagnosis based only on history, positive sIgE, and confirmed asthma
Genetically engineered bacterial α -amylase TERNMyl	[12]	Production and packaging of detergents	1	A, R, C	60, M, nonatopic, NS	SPT ND sIgE +	Reversible airflow obstruction	ND	Also exposed to savinase (sIgE +); negative sIgE to alkalase, cellulase, fungal α -amylase. Diagnosis based only on history, positive SPT/sIgE, and confirmed asthma
Microbial transglutaminase	[13]	Superintendent in company commercializing ingredients for food industry	1	A	40, M, nonatopic, S	SPT + sIgE +	Reversible airflow obstruction BHR +	ND	Used as an additive in food industry to improve texture, flavor, appearance, shelf-life, resistance ... Diagnosis based only on history, positive SPT/sIgE, and confirmed asthma-associated COPD
<i>Tyrophagus putrescentiae</i> (dust mite)	[14]	Driver of van transporting dry-cured ham (contaminated floor of the van)	1	A, R, C, pruritus	43, M, atopic	SPT + (<i>Ty. putrescentiae</i> crust of ham) sIgE +	BHR + (significant change on return to work)	Immediate	Also allergic to shrimp – cross-reactivity between shrimp and <i>Ty. putrescentiae</i>
<i>Tubifex tubifex</i> , a tubificid segmented earthworm	[15 [■]]	Aquarium fish food production – packing and canning; exposed to Red midge larvae, <i>Gammarus</i> species and <i>Tu. tubifex</i>	1	A, R, C	28, M, NS	SPT + sIgE +	PEF + BHR +	ND; Specific nasal challenge +	8/10 workers of the plant had a presumptive diagnosis of asthma/rhinitis to either <i>Gammarus</i> sp (n=5), Red midge larvae (n=7), or <i>Tu. tubifex</i> (n=1); symptoms particularly when canning. Diagnosis based on PEF monitoring, positive SPT/sIgE, BHR, and history
Cit s 3 (orange tree aeroallergen)	[16]	Farmer – working in his fields during the months that orange trees bloom, especially when pruning, grafting, or rolling	1	A, U	21, M, atopic	SPT + (peach LPT; orange tree branch, leaf, and blossom; orange pulp and peel) sIgE + (orange tree branch, leaf, and blossom)	PEF +	ND	Immunoblot showed a 9–10 kDa-binding band in all three extracts, corresponding probably to Cit s 3. Diagnosis based on positive PEF monitoring, SPT/sIgE, and history
Orange zest (flavono)	[17 [■]]	Handling and peeling oranges	1	A	22, W, atopic; previous history of allergic asthma and rhinitis	SPT + sIgE +		Immediate	Negative SPT to orange albedo, pulp, and juice. Immunoblot showed two IgE-binding bands of ~9–10 kDa (Cit s 3) and 23 kDa (Cit s 1)
LMW agents									
Spruce wood dust	[18]	Sawmill owner	1	A	31, M, nonatopic, NS	SPT not valid sIgE +	Reversible airflow obstruction PEF +	ND	Also allergic to acetyl salicylic acid. Diagnosis based on PEF monitoring, positive sIgE, and history

(Continued)

Table 1 (Continued)

Substances	Reference	Workplace setting	No. of cases	Symptoms	Clinical characteristics	Immunological tests (specific)	Functional tests	SIC	Comments
4,4-Methylene-bis(morpholine) (biocide additive)	[19]	Machine tool setter operator – exposed to semisynthetic metalwork fluid	1	A, R	54, M, atopic; NS	SPT + sIgE ND	PEF + BHR – increase in sp eo on work exposure	Dual: metalworking fluid; Late: 4,4-methylene-bis(morpholine) (with immediate rhinitis)	SIC done with metalwork fluid (dual) and 4,4-methylene-bis(morpholine) (isolated late asthmatic response with immediate nasal response; significant increase in BHR post-SIC)
Potassium tetrachloroplatinate [K ₂ PtCl ₆ – halogenated platinum compound] (cytotoxic drugs)	[20]	Production of cisplatin	1	A, R	22, M, atopic; NS; previous history of allergic asthma and rhinitis	SPT: dermatographism sIgE: ND	BHR +	Immediate	No change in BHR post-SIC

COPD, chronic obstructive pulmonary disease; HMW, high molecular weight; LMW, low molecular weight; LPT, lipid protein transfer; ND, not done; SIC, specific inhalation challenge; sp eo, sputum eosinophils. Symptoms (A: asthma; R: rhinitis; C: conjunctivitis; U: contact urticaria; D: contact dermatitis). Clinical characteristics: age, gender, atopic status, smoking history (NS: never smoker; ES: ex-smoker; S: current smoker) if given. Immunologic tests (specific to the offending agent): sIgE, specific IgE; SPT, skin prick test. Functional tests: BHR, nonspecific bronchial hyperresponsiveness; PEF, monitoring of peak expiratory flows at and off work.

HMW and LMW agents can induce IOA but that rhinitis is usually more severe with HMW agents. Contact dermatitis is less often seen although it may be associated with IOA [23].

New workplace settings

In the same period, IOA was reported in new workplace settings for eight known airway sensitizers. Table 2 [24–33] list studies reporting IOA to known sensitizers found in unusual and new working environments, either with HMW agents (squid [24] and *Aspergillus fumigatus* [25]) or LMW agents (carmine red [26], Western red cedar [27], chlorhexidine [28], polyvinyl chloride [29], acrylic resins [30], and cyanoacrylate [31]). The diagnosis of IOA was confirmed by SIC in seven of eight cases or a combination of evidence of asthma and PEF monitoring at and off work.

Overview

All HMW agents have the potential to cause IgE sensitization and typical allergic responses. This mechanism of sensitization was confirmed in all new causes of HWM agents-induced IOA. As commercial or standardized extracts are rarely available, most allergens used for SPT or sIgE were made locally, and prick-to-prick skin tests were often performed. Interestingly, specific IgE sensitization was also confirmed in four cases of IOA caused by LMW agents (chlorhexidine, carmine red, the biocide additive 4,4-methyl-bis(morpholine), and spruce wood dust). LMW agents are incomplete antigens (i.e. haptens) that must bind to autologous or heterologous proteins to become immunogenic [34] and the mechanism of sensitization often cannot be demonstrated to be IgE mediated.

For HMW agents, the patterns of bronchial response to SIC were usually typical, that is, immediate or dual, although the enzyme savinase induced an isolated late response that is unusual with HMW agents [35], although we had previously shown a similar pattern in a worker exposed to another subtilisin [36]. The bronchial response to LMW agents was either late, dual, or atypical as previously shown [35], only one worker having an immediate response (with carmine red).

Except for one study [26] in an aquarium fish food production plant, where 80% (8/10) of the workers developed occupational asthma and rhinitis to various HMW agents due to high exposure in small and poorly ventilated premises without any respiratory protection, the prevalence of occupational asthma in workplaces where these cases were reported is not known. The potential for sensitization of an agent is surely related to the level of exposure and how the workers are exposed (dust,

Table 2. New workplace settings of known causes of occupational asthma

Substances	Reference	Workplace setting	No. of cases	Symptoms	Clinical characteristics	Immunological tests (specific)	Functional tests	SIC	Comments
HMW agents									
Squid (<i>Loligo vulgaris</i>)	[24]	Food processing – preparing frozen meals, containing seafood, mainly squid	1	A, R, C, U	33, M; S	SPT +; sIgE ND	Reversible airflow obstruction	Dual response	Previous cases of occupational asthma seen in a cook [32]; SPT also positive to oysters and mussels
<i>Aspergillus fumigatus</i>	[25]	Garbage sorter of packaging material and driver in same plant	1	A, R	36, M; atopic; S	SPT + and sIgE + to <i>A. fumigatus</i>	BHR +	Immediate	First case of occupational asthma in a garbage worker; possible occupational asthma and hypersensitivity pneumonitis in another case with no objective evidence of work-related asthma
LMW agents									
Carmine red (E120) natural red pigment	[26]	Screen printer (serigraphy or screen printing)	1	A, R, C	48, F	SPT +	PEF +	Immediate (with nasal obstruction)	Well known cause of occupational asthma in workers manufacturing natural dyes, at spice blenders and butcher shops
Western red cedar	[27]	Hand-crafted guitar maker	1	A	22, M; nonatopic; S	SPT –	BHR + (negative after work withdrawal)	Late	Well known cause of occupational asthma but unusual occupational setting
Chlorhexidine (antiseptic and disinfectant)	[28]	Nurses Working on medical wards	2	#1: A #2: A, R	#1: 23, W, nonatopic; #2: 34, W, nonatopic	#1: SPT + sIgE +; #2: SPT – sIgE +	#1: BHR +; #2: BHR +	#1: atypical with increase in sputum eosinophils; #2: atypical, increase in BHR and sputum eosinophils post SIC	Previous occupational asthma in a nurse confirmed by SIC (immediate) but no immunological tests. One nurse (#2) had concomitant confirmed occupational asthma, R and U to latex; a third case showed an anaphylactic reaction to chlorhexidine
PVC powder in adhesive	[29]	Plumber using an adhesive containing PVC powder and traces of methyl methacrylate	1	A	48, M; nonatopic	SPT: ND; sIgE: ND	BHR +	Late to adhesive; dual to PVC powder; dual to methyl methacrylate	Previous cases seen with degradation products or handling bottle caps and packaging (meat wrappers' asthma). Methacrylate was not listed in safety data sheets. Decrease of PC2OM post SIC to PVC powder – ND with other agents
Acrylic resin	[30]	Nail art operator, using acrylic resins	1	A, D	33, W; nonatopic	Patch test + to several acrylates	PEF + at work; BHR +	Not done	Well known cause of occupational asthma but in a new occupational setting; previous cases in two nail makers – published in Finnish [33]
Cyanoacrylate	[31]	Eyelash extension glue	A, R, D	37, W; nonatopic; ES	sIgE –	PEF +	Late	Well known cause of occupational asthma but not previously described in this setting	

HMW, high molecular weight; LMW, low molecular weight; ND, not done; PVC, polyvinyl chloride; SIC, specific inhalation challenge. Symptoms (A: asthma; R: rhinitis; C: conjunctivitis; U: contact urticaria; D: contact dermatitis). Clinical characteristics: age, gender, atopic status, smoking history (NS: never smoker; S: current smoker) if given. Immunologic tests (specific to the offending agent): sIgE, specific IgE; SPT, skin prick test. Functional tests: BHR, nonspecific bronchial hyperresponsiveness; PEF, monitoring of peak expiratory flows at and off work.

fumes, aerosols). Furthermore, individual risk factors such as atopy and smoking may play a role [37]. For LMW agents, exposure is also critical but some agents are clearly more sensitizing than others, highly reactive side chains increasing the potential of sensitization. Agius *et al.* [38] have developed and validated a quantitative structure–activity relationship model to predict the potential of LMW organic agents to cause asthma due to sensitization, as determined by the hazard index [39,40]. This model was applied in the case of IOA to a biocide as described by Walters *et al.* [19], the occupational hazard index of 4,4-methylene-bis(morpholine) reaching 0.95; comparatively, diisocyanates, the most frequent cause of occupational asthma in industrialized countries, have a hazard index of 1 [41]. However, even with a hazard index of 1, chlorhexidine is an uncommon cause of IOA probably because of the nature of its exposure as it is less aerosolized in vapor form than diisocyanates.

CONCLUSION

The list of agents causing IOA is continuously growing in our industrialized countries and clinicians should always suspect the diagnosis in new-onset adult asthma or in subjects with newly uncontrolled asthma. In 2012–2014, 10 new agents (seven HMW and three LMW agents) were reported as airway sensitizers whereas new occupational environmental exposures were reported for eight known airway sensitizers. A good medical history is critical for the diagnosis but it should always be combined with objective evidence of work-related asthma. The documentation of any new case of occupational asthma should be considered as a sentinel health event [1] leading to proper assessment of the workers' environment and reduction of exposure in other workers.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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