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

Occupational Asthma, Not a Trivial Disorder and a Source of Fatal and Near-Fatal Events

Ignacio Esteban-Gorgojo, MD[1,*]
Isabel Coman, MD[2]
Manuel Jorge Rial, MD[3]

Address
[*,1]Department of Allergy, Hospital General de Villalba, Carretera de Alpedrete a Moralzarzal M-608 Km 41, Collado Villalba, 28400, Madrid, Spain
Email: igestebang@gmail.com
[2]Department of Allergy, Hospital Universitario La Paz, Madrid, Spain
[3]Department of Allergy, Fundación Jiménez Díaz, Madrid, Spain

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Opinion statement

Purpose of review Asthma is one of our society's heaviest health burdens, which is estimated to be responsible for 250,000 deaths every year. Whenever severe asthma with fatal or near-fatal events is described, occupational asthma is not specifically mentioned, but its importance should not be underestimated.
Recent findings Occupational asthma (OA) is the most prevalent work-related pulmonary disease. Therefore, it is a very important concern for health prevention and occupational health professionals. Although asthma treatments and earlier diagnosis have improved this condition's control, severe exacerbations with unpredictable consequences still occur. Early diagnosis and allergen avoidance are the two main objectives in our approach to this disease. Obtaining a correct diagnosis and recognizing the responsible allergen is not an easy task to achieve, but it should be the clinician's biggest concern. Severe exacerbations can be caused by many different triggers and their identification usually requires a well-trained expert in the field. Allergen avoidance should be the primary goal to avoid fatal or near-fatal asthma events, but good asthma control also is necessary to decrease OA future risk. The asthmagens involved in severe reactions are heterogeneous, making their identification difficult, but necessary. As these agents are used in very different industries and can be ubiquitous, OA should be considered in every patient with work-related asthma exacerbations or symptoms.
Summary Severe events have been described with many types of agents and allergenic sources; therefore, every patient should be treated to obtain a good illness control, regardless of the responsible allergenic source.

Introduction

Asthma is the 14th most important disease in the world and the most prevalent in childhood [1]; thus, it should be a real concern in our society. Its prevalence has been estimated around 14% in children [2] and 8.6% in adults [1]. The two main problems in the determination of this prevalence are the variation in the criteria used for asthma diagnosis and the inadequate access to medical care in many countries. Nowadays prevalence estimation varies from the 235 million asthmatics given by the WHO [1] and the 335 million stablished by the Global Asthma Report 2014 [3].

Although asthma has a significant prevalence worldwide, its mortality rate is not very high with 250,000 annual attributable deaths [4], out of which only 50,000 occur in developed countries. The highest mortality rates are found among subjects over 70 years old [3]. However, these subjects also have comorbidities that represent confounding factors in the identification of the true cause of death, leading to an overdiagnosis that ranges from 39 to 80% [5–8].

On the other hand, fatal asthma (FA) and near-fatal asthma (NFA) usually affects youngsters and adults below 50 years of age [9•, 10]. However, despite its relevance in terms of epidemiology and social impact, FA is not yet fully understood and effectively prevented. In fact, on clinical grounds, it includes several phenotypes, characterized by variable causes and risk factors. Thus, asthma mortality still represents a critical issue in the management of the disease.

Occupational triggers of asthma are not taken into account in most asthma studies, despite the fact that OA is the second most common occupational pulmonary disease in underdeveloped countries and the most common in the developed world [11]. Moreover, work-related asthma (WRA) is estimated to affect between 15 and 25% of asthmatic adults [12] and it mainly affects the under 50-year-old group who also may experience FA and NFA events, showing that a deeper research is needed in this field.

In this review, we performed an in-depth analysis of occupational FA and NFA. In order to do so, we used *Medline*, through the portals *PubMed* http://www.ncbi.nlm.nih.gov/pubmed/ and *SciELO* (http://www.scielo.br) as bibliographic database, using "severe asthma," "severe occupational asthma," "severe work related asthma," "near fatal asthma," "fatal asthma," "asthma mortality," and "asthma deaths" as keywords. Case reports and books were also considered. All near-fatal and fatal events directly related to work exposure were selected and analyzed.

Occupational asthma

WRA is a clinical entity that includes both OA and work-exacerbated asthma (WEA). OA can be induced by a sensitizing (sensitizer-induced OA or allergic OA) or irritant agent found in the workplace (irritant-induced OA), with reactive airway dysfunction syndrome (RADS) being the most characteristic form of irritant-induced OA (Fig. 1). WEA implies a pre-existing or concurrent diagnosis of asthma that is exacerbated, or whose severity is increased, by an agent found in the workplace [13•, 14] (Fig. 1).

In allergic OA, the causative agent may either be a high- (HMW) or low-molecular weight (LMW) agent. Sensitization to HMW agents is considered to be due to an IgE-mediated mechanism. Although specific IgE antibodies are less often detected in OA induced by LMW than HMW agents, some studies have suggested the implication of immunological mechanisms in LMW-OA, as well as non-IgE-mediated responses resembling delayed hypersensitivity reactions.

OA is the most important work-related pulmonary disease in developed countries and second most important in underdeveloped countries [11]. However, underreporting and underdiagnosis of OA are two major obstacles to the accurate determination of its prevalence. Workplace exposures are only

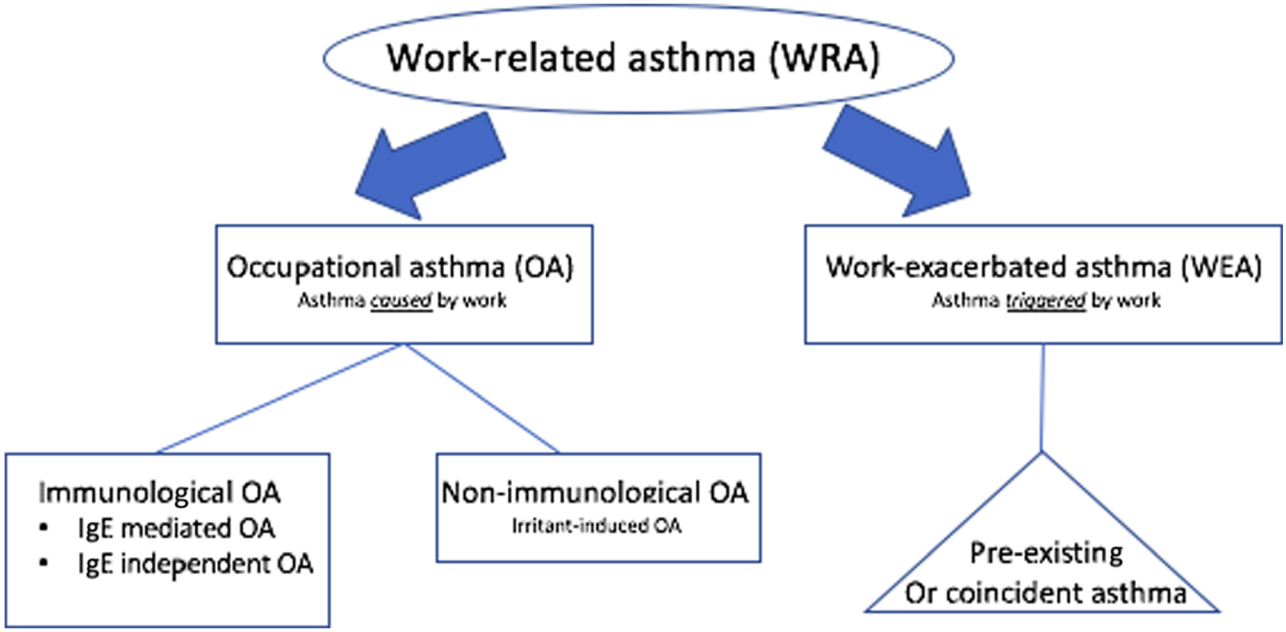

Fig. 1. Modified from Malo JL and Vandenplas O. Definitions and Classification of Work-Related Asthma. Immunol Allergy Clin North Am 2011 [13•].

documented in 7 to 15% of evaluations of adults with new-onset asthma [15], and larger asthma population studies do not always take workplace exposures into account. As diagnostic tools are not widely available, less than half of subjects with OA go through the proper evaluation for diagnosing OA [16]. In fact, even though the specific inhalation challenge (SIC) is the reference standard for OA diagnosis, it is not available in all tertiary centers. Hence, OA diagnosis relies on the clinician's ability to relate the disease's development and exacerbations to a workplace exposure. Nevertheless, studies have reported OA prevalence rates of 4–58% with a median of 15% [17•, 18]. The prevalence of WEA is even more uncertain than that of OA, but is considered to be similar [19].

Severity

The ERS/ATS and GINA guidelines define severe asthma as a subtype of asthma which requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids in order to prevent it from becoming uncontrolled, or that remains uncontrolled despite optimal therapy [20, 21]. Accordingly to the Global Asthma Report 2014, 10% of asthma cases can be considered as severe [3], but according to GINA, severe asthma represents 20% of cases, 50% of which is uncontrolled [20]. Due to the discrepancies between the prevalence of severe asthma found in different studies, together with OA underdiagnosis, it is very difficult to establish the prevalence of severe OA.

Nevertheless, it should be pointed out that most NFA and FA events happen among youngsters and subjects under 50 years old and it is among this population that occupational exposures occur. Therefore, although OA is not usually considered as an individual cluster in asthma severity studies and is markedly

underdiagnosed, it might be an important eliciting factor for severe asthma. Thus, future studies should look into this specific subgroup more deeply and evaluate its real prevalence and relevance.

Since OA asthma etiology and severity are related to the type and persistence of exposure to the causative agent, this exposure should be carefully analyzed. Early cessation of allergen exposure is associated with a better prognosis and milder OA severity [22••], finding which was also highlighted in a systematic review by Vandenplas and Lemière [23] on the cessation and reduction of exposure in OA. Meca et al. [24] suggested that OA induced by LMW agents is more severe than OA caused by HMW agents. These authors retrospectively studied 78 patients diagnosed with OA, where HMW agents were responsible for 23 (mostly cereal flour 48%) and LMW for 55 cases (mainly isocyanates 36% and persulfates 24%). After analyzing asthma severity according to GINA classification, they found a significantly higher risk for asthma severity and increased bronchial hyperresponsiveness for LMW agents. Of note, baseline lung function, hospitalizations, and emergency visits did not differ between the two groups of patients with OA.

A study undertaken by Le Moual et al. [25] also examined the relationship between asthma severity and exposure to occupational agents. In total, 148 subjects with OA and 228 controls with non-occupational asthma were categorized according to asthma severity using a clinical severity score combining the frequency of asthma attacks, symptoms between attacks, and hospitalizations. A significant association was found between exposure to any sensitizing agent (LMW agents, HMW agents, or mixed environments) and severe adult-onset asthma with an overall odds ratio (OR) of 4 (LMW 4.4 OR/HMW 3.7 OR), but not between exposure to irritants and asthma severity. Although the criteria used to define severity in this study relate to asthma control more than to treatment required to achieve control as per GINA guidelines, the results remained significant when analyzed using a variety of alternative severity definitions. Moreover, in order to avoid biased estimates of exposition, the study did not rely on self-reported exposure, but combined a job-exposure matrix and a standardized review step to give reliable exposure estimates.

This relation between exposure to LMW/HMW and asthma severity was also studied in The European Community Respiratory Health Survey (ECRHS) [26], where random samples of workers aged 22–44 years completed respiratory health-related questionnaires and underwent investigations including lung function testing, non-specific bronchial hyperresponsiveness testing, and specific IgE determination. Previous 12-month and 10-year occupational exposures were determined according to an asthma-specific job-exposure matrix and expert re-evaluation. Significant associations were found between uncontrolled asthma and past 12-month exposure to any HMW or LMW agent or to cleaning agents. The association was stronger when using the past 10-year exposures than 12-month exposures and no correlation was observed with irritants.

Occupational exposures seem to be an important cause of severe and/or uncontrolled asthma, and OA tends to be more severe than other types of asthma [27]. A longer latency between symptom onset and OA diagnosis is also related to a worse prognosis in terms of persistence and severity of OA [23]. Neutrophilic inflammation was also identified as a risk factor for refractory asthma in an Australian study performed in asthmatic workers with persistent occupational exposures [28]. Other OA biomarkers, such as fractional exhaled

nitric oxide, have not been shown to correlate with disease severity [29]. We should keep in mind that OA and occupational rhinitis frequently occur simultaneously and their severity is related [30].

Severe exacerbations

Exacerbations are the main cause of fatal and near-fatal events and therefore should be closely analyzed in order to implement preventive measurements and treatments to avoid them. The agents associated with exacerbations include work-specific agents such as gases, fumes, and spills, but also non-specific agents such as common aeroallergens, stress, exercise, and extreme temperature [31].

Henneberger et al. [32] performed different studies analyzing occupational risk factors associated with severe asthma exacerbations. They performed a study in 2010 with 998 patients where they found a higher risk for severe exacerbations among bakers and blue-collar workers (drivers, sculptors, painters, and art-related works). Cumulative incidence of severe asthma exacerbations was elevated for high exposure to any dust, gas, or fume in the workplace. The authors determined that 14.7%, or one in seven severe exacerbations, was induced by occupational exposures and could possibly be prevented by eliminating high dust, gas, and fume exposures. Later, another study [33] was carried out in 557 workers, of which 29% had presented a severe exacerbation in the previous year. Seven types of exposures were associated with severe exacerbations: LMW agents such as epoxy resins (prevalence ratio [PR] 2.50, $p = 0.046$), other highly reactive agents (PR 1.93, $p < 0.03$), and isocyanates (PR 3.11, $p = 0.001$) and irritant agents such as inorganic dusts (PR 3.61, $p < 0.001$), metalworking fluids (PR 2.84, $p = 0.005$), combustion particles (PR 1.52, $p = 0.07$), and environmental tobacco smoke (PR 1.88, $p < 0.001$). Although the study focused on the severity of the exacerbations, not the severity of asthma as such, when the analysis was limited to subjects whose asthma onset was prior to the start of the job, the results remained unchanged. This also suggests that continuous exposure affects the severity of exacerbations, which is also supported by the results of Lemière's prospective cohort study of 154 subjects described earlier [34]. In this study, the only predictor of severe asthma exacerbations in the 2 years of follow-up was the persistence of work exposure in subjects with WEA and OA (OR 0.2, 95% CI 0.05–0.6).

Unlike other types of asthma, OA has specific workplace triggers that induce all the symptoms. Thus, avoiding the causative allergen and early diagnosis are the cornerstones of OA management [35]. OA outcomes are best when the diagnosis is established early, the exposure is stopped, and the asthma is not yet severe [22••]. Besides avoidance and early diagnosis, OA treatment does not differ from other asthma phenotypes. Inhaled corticosteroids are the mainstay of treatment, but new therapeutic approaches such as immunotherapy and biological treatments can also be used [36].

Fatal and near-fatal asthma reports

Proper diagnosis and management of OA are of crucial importance, as the lack of an early diagnosis or proper disease management can lead to severe asthma and FA or NFA events. These events are not limited to specific triggers and have

Table 1. Occupational asthma related death reports (modified and updated from Ortega et al. [37])

Age	Year	Agent	Industry	Tenure (years)	Atopy	Time from start of symptoms to death (years)	Specific IgE and SIC	Autopsy
52	1958	Gum arabic [38]	Printing	20	NA	12	NA	Yes
26	1962	Bicycloheptadine dibromide [39]	Pharmacology laboratory	> 3	NA	3	NA	Yes
26	1962	Bicycloheptadine dibromide [39]	Pharmacology laboratory	> 2	No	2	NA	Yes
45	1978	Papain powder [40] positive	Laboratory Yes	3.5	no	2	sIgE	
40	1985	Isocyanates, anonymous	Car painting	NA	NA	NA	NA	NA
43	1988	Toluene diisocyanates [41] positive to TDI	Car painting Yes	> 20	Yes	20	SIC	
34	1997	Diphenylmethane diisocyanates [42] negative SIC positive to MDI	Steel foundry Yes	> 6	No	6	sIgE	
45	2005	Diphenylmethane diisocyanates [43]	Spray-on truck bedliner application	> 10	Yes	10	NA	Yes
NA	1995	Green coffee dust (2) [44••]	Food processing	NA	NA	NA	NA	No
42	1995	Flour [45] negative to flour, positive to wheat and maize SIC positive to flour	Bakery No	20	No	5	sIgE	
38	2002	Shark cartilage [46••]	Milling	8	NA	6 months	NA	Yes
75	2005	Chloramine gas [47]	Dairy farming	NA	NA	NA	NA	NA

NA not available

happened with a remarkable variety of allergens and among different industries (Table 1).

As it is shown in Table 1, fatal events are widespread among different jobs, but in all cases, persistence of exposure to the offending allergens and a long duration of asthma are observed. Moreover, most cases had presented previous exacerbations related to the same exposure. Patient ages range from 26 to

75 years old and the delay between the onset of OA symptoms and death ranges from 6 months to 20 years.

Autopsy was performed in most fatal events to confirm the cause of death, but allergic tests such as specific bronchial challenge, specific IgE measurements, or skin prick tests were not so consistently undertaken prior to the fatal event, leading to a lack of a proper diagnosis to prevent the event.

Reported cases

Among these FA and NFA events, isocyanates were the trigger in four cases. These events occurred in car spray painting [41] or with truck bedliner application [43]. In addition, a FA event with diphenylmethane diisocyanates occurred in a foundry worker, in a plant where this substance was used to produce metal belts and tank pieces [42].

While isocyanates seem to be the most common trigger in the reported FA and NFA events, other substances induce severe exacerbations as well. Two deaths were reported in food industries, where green coffee dust was considered as the responsible allergen [44••] and three cases occurred in laboratories; two cases were caused by bicycloheptadine dibromide in pharmacology laboratories [39] and a third case was caused by papain powder [40]. Bakers are at high risk of OA and a fatal event has also been reported in a baker [45]. Milling and printing industries have also been affected by fatal events, with shark cartilage [46••] and gum arabic [38] as the respective triggers.

NFA events have also been described in the literature. Hairdressers are one of the most frequently affected collectives. Severe events have been described among hairdressers, but also in ordinary dye exposure with no occupational relation [48]. Finally, NFA events have also been described in dairy processors; one event caused by locust bean gum was recently reported [37] and in a further past, a FA event while cleaning a bulk milk tank was documented [47]. In the latter, the occupational trigger was not studied prior to the fatal event, but the report suggests that the chloramines released by the combination of ammonia and acid was the probable cause of the fatal event. While it is unclear whether the patient had a previous asthma diagnosis (WEA) or started presenting symptoms after repeated occupational exposure (OA), we should not forget that exposure to gas, dust, and other unspecific irritants is also responsible for FA or NFA events.

Conclusions

OA is a recognized as an asthma phenotype that should not be underestimated by clinicians. This type of asthma is of particular importance among adult late-onset severe asthma. Early diagnosis, recognition of specific triggers, and allergen avoidance are the cornerstones of management. However, diagnosis is not always easy to perform and every patient with WRA should be studied by a clinician with experience in OA. Identifying this asthma phenotype is of utmost importance in the differential diagnosis of adult-onset asthma.

WRA is divided into OA and WEA that should be differentiated because its management differs. FA or NFA events can occur in both WRA subtypes, and both conditions should be properly studied and treated to avoid asthma

worsening and recurrent exacerbations. Late diagnosis and untreated or uncontrolled asthma are the main risks for FA and NFA events in any subjects with asthma. However, in OA, not achieving complete allergen avoidance, prolonged exposure to the allergen, and not preventing the development of severe asthma seem to be the main risk factors for FA and NFA. Despite some studies suggesting that LMW agents induce more severe asthma than other substances, others have shown that severe OA can be induced by LMW and HMW agents as well as mixed environments.

In conclusion, OA is an asthma phenotype that is susceptible of causing FA and NFA events regardless of the offending allergen involved. FA and NFA events can be prevented with a correct and timely diagnosis, which implies the accurate identification of the culprit agent and early cessation of exposure.

Compliance with Ethical Standards

Conflict of Interest
Ignacio Esteban-Gorgojo declares that he has no conflict of interest. Isabel Coman declares that she has no conflict of interest. Manuel Jorge Rial declares that he 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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. World Health Organization. WHO Projections of mortality and burden of the disease 2004–2030. Available at: http://www.who.int/healthinfo/global/burden_disease/Dth6_2030.xls.
2. Carvajal-Ureña I, García-marcos L, Busquets-Monge R, Suárez-Varela MM, De Andoni NG. Variaciones geográficas en la prevalencia de síntomas de asma en los niños y adolescentes españoles. Int StudAsthma Allergies Child (ISAAC). 2005;41:659–66.
3. The Global Asthma Report 2014 [Internet]. Available at: http://www.globalasthmareport.org/burden/burden.php.
4. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach [Internet]. Available at: http://apps.who.int/iris/bitstream/10665/43776/1/9789241563468_eng.pdf.
5. Jenkins MA, Rubinfield ARR, Robertson CS, Bowes G. Accuracy of asthma deaths statistics in Australia. Aust J Public Health. 1992;16(4):427–9.
6. Wright SC, Evans AE, Sinnamon DG, Mac Mahon J. Asthma mortality and death certification in Northern Ireland. Thorax. 1994;49(2):141–3. https://doi.org/10.1136/thx.49.2.141.
7. Reid DWEC, Hendrick VJ, Aitken TC, Berrill WT, Stenton SC, Hendrick DJ. Age-dependent inaccuracy of asthma death certification in Northern England, 1991–1992. Eur Respir J. 1998;12(5):1079–83. https://doi.org/10.1183/09031936.98.12051079.
8. Richards GN, Kolbe J, Fenwick J, Rea HH. Demographic characteristics of patients with severe life threatening asthma: comparision with asthma deaths. Thorax. 1993;48(11):1105–9. https://doi.org/10.1136/thx.48.11.1105.
9.• Serrano-Pariente J, Rodrigo G, Fiz JA, Crespo A, Plaza V. Identification and characterization of near fatal asthma phenotypes by cluster analysis. Allergy. 2015;70:1139–47.

A cluster analysis is performed on the NFA events over 2 years on 179 Spanish hospitals. Three different NFA phenotypes

were described. This phenotype identification can lead to a reduction on the NFA events on the future.

10. Campbell DA, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM, et al. A comparison of asthma deaths and near fatal asthma attacks in South Australia. Eur Respir J. 1994;7(3):490–7. https://doi.org/10.1183/09031936.94.07030490.
11. Jeebhay M, Quirce S. Occupational asthma in the developing and industrialised world: a review. Int J Tuber Lung Dis. 2007;11:122–33.
12. Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest. 2008;134(3):1S–41S. https://doi.org/10.1378/chest.08-0201.
13.• Malo JL, Vandenplas O. Definitions and classification of work-related asthma. Immunol Allergy Clin North Am. 2011;31:645–62.

WRA is described and classified into its different phenotypes, describing their features and analyzing existing data and its controversies.

14. Vandenplas O, Malo JL. Definitions and types of work-related asthma: a nosological approach. Eur Respir J. 2003;21(4):706–12. https://doi.org/10.1183/09031936.03.00113303.
15. Shofer S, Haus BM, Kuschner WG. Quality of occupational history assessments in working age adults with newly diagnosed asthma. Chest. 2006;130(2):455–62. https://doi.org/10.1378/chest.130.2.455.
16. Breton CV, Zhan Z, Hunt PR, Pechter E, Davis L. Characteristics of work related asthma: results from a population based survey. Occup Environ Med. 2006;63(6):411–5. https://doi.org/10.1136/oem.2005.025064.
17.• Johnson AR, Dimich-Ward HD, Manfreda J, Becklake J, Ernst P, et al. Occupational asthma in adults in six Canadian communities. Am J Respir Crit Care Med. 2000;162:2058–62.

Population of six Canadian communities was studied determining prevalence, population attributable risk, and clinical characteristics of occupational asthma.

18. Tarlo SM, Leung K, Broder I, Silverman F, Holness DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. Chest. 2000;118(5):1309–14. https://doi.org/10.1378/chest.118.5.1309.
19. Fishwick D. Work aggravated asthma; a review of the recent evidence. Br Med Bull. 2014;110(1):77–88. https://doi.org/10.1093/bmb/ldu004.
20. GINA [internet]. Available at: http://ginasthma.org.
21. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Resp J. 2014;43(2):343–73. https://doi.org/10.1183/09031936.00202013.
22.•• Tarlo SM, Lemière C. Occupational asthma. N Engl J Med. 2014;370:640–9.

Existing data on OA is critically reviewed in order to define its clinical features, diagnostic approach, and specific management.

23. Vandenplas O, Dressel H, Wilken D, Jamart J, Heecerik D, et al. Management of occupational asthma: cessation or reduction of exposure? A systematic review of available evidence. Eur Respir J. 2011;38(4):804–11. https://doi.org/10.1183/09031936.00177510.
24. Meca O, Cruz MJ, Sánchez-Ortiz M, González-Barcala FJ, Ojanguren I, Munoz X. Do low molecular weight agents cause more severe asthma than high molecular weight agents? Plos One. 2016;11(6):e0156141. https://doi.org/10.1371/journal.pone.0156141.
25. Le Moual N, Siroux V, Pin I, Kauffmann F, Kennedy SM, Epidemiological Study on the Genetics and Environment of Asthma. Asthma severity and exposure to occupational asthmogens. Am J Respir Crit Care Med. 2005;172(4):440–5. https://doi.org/10.1164/rccm.200501-111OC.
26. The European Community Respiratory Health Survey (ECRHS). [Internet] Available at: http://www.ecrhs.org/.
27. Malo JL. Asthma may be more severe if it is work-related. Am J Respir Crit Care Med. 2005;172(4):406–7. https://doi.org/10.1164/rccm.2506006.
28. Simpson JL, Guest M, Boggess MM, Gibson PG. Occupational exposures, smoking and airway inflammation in refractory asthma. BMC Pulm Med. 2014;14(1):207. https://doi.org/10.1186/1471-2466-14-207.
29. Coman I, Lemière C. Fractional exhaled nitric oxide (FeNO) in the screening and diagnosis work-up of occupational asthma. Curr Treat Options Allergy. 2017;4(2):145–59. https://doi.org/10.1007/s40521-017-0122-8.
30. Moscato G, Pala G, Folletti I, Siracusa A, Quirce S. Occupational rhinitis affects occupational asthma severity. J Occup Health. 2016;58:310–3.
31. White GE, Mazurek JM, Storey E. Employed adults with asthma who have frequent workplace exposures. J Asthma. 2015;52(1):46–51. https://doi.org/10.3109/02770903.2014.944984.
32. Henneberger PK, Mirabelli MC, Kogevinas M, Antó JM, Plana E, et al. The occupational contribution to severe exacerbation of asthma. Eur Respir J. 2010;36(4):743–50. https://doi.org/10.1183/09031936.00135109.
33. Henneberger PK, Liang X, Lillienberg L, Dahlman-Höglund A, Torén K, Andersson E. Occupational exposures associated with severe exacerbation of asthma. Int J Tuberc Lung Dis. 2015;19(2):244–50. https://doi.org/10.5588/ijtld.14.0132.
34. Lemirère C, Boulet LP, Chaboillez S, Forget A, Chiry S, et al. Work-exacerbated asthma and occupational asthma: do they really differ? J Allergy Clin Immunol. 2013;131(3):704–10. https://doi.org/10.1016/j.jaci.2012.08.024.
35. Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma.

Occup Environ Med. 2005;62(5):290–9. https://doi.org/10.1136/oem.2004.016287.
36. Esteban-Gorgojo I, Rial MJ, Sastre J. Infrequent treatments for occupational asthma: immunotherapy and biological treatments. Curr Treat Options Allergy. 2017;4(2):118–28. https://doi.org/10.1007/s40521-017-0125-5.
37. Hawley B, Cummings KJ, Mohammed M, Dimmock AE, Bascom R. Allergic sinusitis and severe asthma caused by occupational exposure to locust bean gum: case report. Am J Ind Med. 2017;60(7):658–63. https://doi.org/10.1002/ajim.22725.
38. Groetschel HWE. Death of a printer from bronchial asthma after working with wet sprays. Arch Gewerbepath Gewerbehyg. 1958;16:375–86.
39. Murray JF, Fink A. Toxicity from certain brominated alkylating agents. Arch Environ Health. 1962;5(1):5–11. https://doi.org/10.1080/00039896.1962.10663234.
40. Flindt MLH. Respiratory hazards from papain. Lancet. 1978;311(8061):430–2. https://doi.org/10.1016/S0140-6736(78)91216-3.
41. Fabbri L, Daniell D, Cresciol S, et al. Fatal asthma in a subject sensitized to toluene diisocyanate-4. Am Rev Respir Dis. 1988;137(6):1494–8. https://doi.org/10.1164/ajrccm/137.6.1494.
42. Carino M, Aliani M, Licitra C, Sarno N, Ioli F. Death due to asthma at workplace in a diphenylmethane diisocyanate-sensitized subject. Respiration. 1997;64(1):111–3. https://doi.org/10.1159/000196653.
43. Chester DA, Hanna EA, Pickelman BG, Rosenman KD. Asthma death after spraying polyurethane truck bedliner. Am J Ind Med. 2005;48(1):78–84. https://doi.org/10.1002/ajim.20183.
44.•• NIOSH. 1996. Preventing asthma and death from diisocyanate exposure. Atlanta, GA, Centers for Disease Control and Prevention.
Seven cases of severe respiratory disease and deaths due to diisociaate exposure, showing the importance of health prevention measurements to offending allergens.
45. Ehrlich RI. Fatal asthma in a baker: a case report. Am J Ind Med. 1994;26(6):799–802. https://doi.org/10.1002/ajim.4700260608.
46.•• Ortega HG, Kreiss K, Schill DP, Weissman DN. Fatal asthma from powdering shark cartilage and review of fatal occupational asthma literature. Am J Ind Med. 2002;42:50–4.
A FA event due to shark cartilage is reported and described placing it among other FA events and analyzing the characteristics and risk factors for these events to happen.
47. Michigan Fatality Assessment & Control Evaluation, M. 2005. Fatal asthma while cleaning bulk milk tank. East Lansing, MI: Michigan State University, Department of Medicine, Occupational and Environmental Medicine, HA#6; 2005:1
48. Fukushima C, Shimoda T, Matsuse H, et al. Fatal asthma with rhabdomyolysis induced by hair dye. Acta Med Nagasaki. 1998;43:58–62.