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Guidelines for Occupational Asthma

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Introduction

Occupational asthma (OA) is the most common occupational disease in industrialized countries and it is estimated that approximately 15% of all adult asthma is occupational in origin. Correct diagnosis and early management are key factors affecting disease prognosis and socioeconomic consequences. The individual patient is not the only one affected when measures are taken; the consequent changes in working conditions can also prevent the appearance of other cases at the patient's workplace or other sites. Thus, the benefits are important for the health of the workforce and also for the economy, both of individual companies and of society in general.

Given the widespread importance of OA, the scientific committee of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) placed a group of highly experienced professionals from the SEPAR Working Groups on Occupational Respiratory Diseases (EROL) and Asthma under the supervision of Dr Ramon Orriols Martínez to prepare these guidelines, which are intended to provide clear and concise advice for the diagnosis and subsequent management of patients with suspected OA.

Definition

OA is a disease characterized by variable obstruction of airflow and/or airway hyperresponsiveness attributable to factors associated with the workplace rather than to stimuli found outside that environment.[1-4]

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Classification

The following types of OA are distinguished according to the pathogenesis of the disease[1-4]:

1. Immunologic OA or OA caused by hypersensitivity. This requires a period of time for sensitization to the causative agent to develop, and therefore, there is a latent period between exposure and the appearance of symptoms. The following subtypes are distinguished according to the substances responsible for causing the disease:

– Immunologic OA caused by high molecular weight substances. This usually occurs via an immunologic mechanism involving immunoglobulin (Ig) E.

– Immunologic OA caused by low molecular weight substances. In this case, there is generally no clear involvement of IgE.

2. Nonimmunologic OA or irritant-induced OA. This type of OA occurs as a result of irritation or toxicity. Two subtypes can be distinguished:

– Reactive airways dysfunction syndrome (RADS). This is caused by single or multiple exposures to high doses of an irritant. Its onset, however, is linked to a single exposure. It is also known as OA without a latent period, since the symptoms appear within 24 hours of exposure.

– OA caused by low doses of irritants. This occurs after repeated contact with low doses of the causative agent. It is a condition of particular current relevance but that is still under discussion.[3-5]

3. Other variants of OA. This category includes OA with special or distinctive characteristics:

– Asthma-like disorders. These are due to exposure to plant-derived dust (grain, cotton, and other textile fibers) and also to dust from confined animals.

– Potroom asthma. This occurs in workers involved in the production of aluminium.

TABLE 1
High Molecular Weight Agents That Cause Immunologic Occupational Asthma

Type	Agent	Product, Occupation, Industry
Cereals	Wheat, barley, rye, oats, maize, sunflower, soya, etc	Baker's shop, bakery, cake shop, mill, transport, agriculture
Flowers	Sunflowers, decorative flowers, etc	Florist, greenhouse, gardener
Seed or grain	Coffee, castor-oil plant, pea, carob, soya, sesame, fennel, etc	Oil industry, food processing industry, bakery, meat product industry, etc
Rubber	Acacia, tragacanth, gutta-percha, guar, gum arabic, etc	Printing, rubber industry, dental hygienist, etc
Enzymes	*Bacillus subtilis*, trypsin, papain, pepsin, amylase	Bakery, pharmaceutical, plastics, and detergents industries, etc
Fungi	*Aspergillus, Cladosporium, Trichoderma* species, etc	Baking, agriculture, domestic tasks, technicians, saw mill workers, etc
Animals	Rat, guinea pig, rabbit, etc	Laboratory workers
	Cow, pig, chicken, egg, lactalbumin, casein, etc	Farmers, dairy workers, butchers, cake shops, tanneries, etc
	Beetle, locust, cockroach, cricket, fly, butterfly, silkworm, etc	Museum, laboratory, fishing, agriculture, cosmetics, entomology, silkworm farms, etc
	Crustaceans, fish, coral, molluscs, etc	Fisherman, fish farms, and feed, coral, and mother of pearl industries
Others	Latex, dust mites, henna	Health care workers, production of gloves and condoms, etc, manipulation of grains, hairdressing

TABLE 2
Low Molecular Weight Agents That Cause Immunologic Occupational Asthma

Type	Agent	Product, Occupation, Industry
Diisocyanates	Toluene, methylene, and hexamethylene diisocyanates	Polyurethane, plastic varnishes, insulation material, spray paints
Acid anhydrides	Phthalic acid, trimellitic acid anhydride, hexahydrophthalic acid, tetrachlorophthalic acid, pyromellitic dianhydride	Plastics and resins, adhesives, chemical industry, flame retardants
Metals	Platinum salts, cobalt sulfate, chromium sulphate and chromium salts, potassium dichromate, tungsten carbide	Platinum refinery, polishers, silver and chrome-containing paints, tanners, emery polish
Antibiotics	Penicillin, spiramycin, tetracycline	Pharmaceutical industry
Amines	Piperazine, ethanolamine, dimethyl propanolamine, ethylene diamine, aliphatic amines, aminoethanolamine, hexamethylene tetramycin	Chemical industry, spray paints, ski manufacture, polishes, photography, rubber, solder, cables
Woods	Red cedar, rosin	Woods, electronic solder
Miscellaneous factors	Glutaraldehyde, persulfate salts, cyanoacrylate, methylmethacrylate, polyethylene, chloramine, polypropylene	Nursing/endoscopy, hairdressing, orthopedics, glues, paper packaging, plastic bags, sterilizer in food and pharmaceutical industries

Causes

More than 300 agents have been implicated in the development of OA (Tables 1-3). A complete list of those agents can be found in certain research articles and reviews[6-13] and webpages.[14-16]

TABLE 3
Agents That Cause Nonimmunologic Occupational Asthma

Type	Agent	Product, Occupation, Industry
Bleach	Chlorine	Cleaning, paper, sewage treatment, bleach industry, etc
Smoke	Fire-related products	Emergency services
Gases	Products derived from metal galvanization	Metalwork
Other products	Resins, hydrochloric acid, sodium hydroxide, acetic acid	Chemical, cleaning, and health industries

Prevalence and Incidence

Notable discrepancies are found in the data on prevalence and incidence currently available in the medical literature. Differences in the design of epidemiologic studies, the definition of OA, the study population, and the country in which the study was

performed account for some of the discrepancies and the consequent difficulty in making comparisons. Some of the data can be found in a recent review article.[4] It has been reported that 4% to 58% of all cases of asthma may be occupational in origin. A recent review of the literature estimated a mean value of 15%.[17] Immunologic OA caused by high molecular weight substances is the most common form. The prevalence of the disease varies depending on the causative agent and it has been shown to occur in 4% to 12% of animal laboratory workers, 79% of bakers, and 1% to 7% of health care workers exposed to latex.[18] The prevalence of OA caused by sensitization to low molecular weight substances is less clear, although some authors estimate it at around 40% of all cases of OA.[7] The agents most frequently implicated in the disease in industrialized countries have generally been the isocyanates, which cause asthma in 2% to 10% of workers.[7] In British Colombia, Canada, where the wood industry is very extensive, another agent, cedar wood, is more common and is responsible for causing asthma in 10% of workers.[19] Other substances such as glutaraldehyde, cleaning products, and persulfates are emerging as disease-causing agents in workers involved in the health care, cleaning, and hairdressing industries.[20-22] RADS is estimated to occur in 36% of cases referred to hospital for assessment of OA.[23-26] In addition, 11% to 15% of all work-related asthma is reported to be caused by irritants.[27-29]

Monitoring through the use of registries allows the incidence of OA to be estimated. Such programs have been developed in many different countries. In Spain, the registry started in 2002 in Asturias, Catalonia, and Navarre obtained respective incidences of 48.4, 77.2, and 75.8 cases per million inhabitants per year. Given that the registries are still in their initial stages, comparisons with the incidences of 92 and 22 cases per million inhabitants per year reported from registries in Canada[19] and the United Kingdom,[30] respectively, should only be made with caution. Results for prevalence and incidence in different countries are available in a recent article.[4]

Pathogenesis

Genetic predisposition. Atopy is a risk factor for asthma induced by high molecular weight substances.[31] For instance, OA in health care workers exposed to latex is more common in atopic than nonatopic individuals.[32] The same is true of workers exposed to laboratory animals or detergents.[18] The phenotype of individuals with OA appears to be generated through the involvement of genes of the major histocompatibility complex on chromosome 6p coding for class II human leukocyte antigen (HLA) molecules.[4] In the case of isocyanates, an association has been described between this disease and the HLA-DQBQ0503 allele and protection in the presence of the HLA-DBQ0501 allele. The marker for susceptibility is the substitution of the aspartate residue at position 57 of HLA-DBQ.[33] In the case of asthma caused by red cedar, an increase in the HLA-DQBI*0603 and HLA-DQBI*0302 alleles and a decrease in the DQBI*050134 allele has been observed.[34] Other authors have reaffirmed that HLA class II alleles contribute to the susceptibility of the individual to suffer from asthma caused by low molecular weight substances.[35] However, the associations are not sufficient to generate preventative recommendations. Genes of the glutathione S-transferase and N-acetyltransferase superfamilies also appear to be involved in OA, especially that caused by isocyanates.[4]

Causative agent. The high molecular weight substances that are able to generate sensitization are proteins that behave as complete antigens.[36] In addition, there is evidence that some of those proteins have enzymatic activity that could aid antigen penetration.[37] In contrast to the allergenic proteins, the low molecular weight substances that are able to cause OA are generally incomplete antigens (haptens) that must combine with other molecules to trigger an immune response.[36] These agents are known to be highly reactive and capable of binding certain specific sites on proteins in the airway.[38] In the case of RADS, it is reasonable to assume that the higher or lower irritant capacity of an agent would be involved in the pathogenesis of the disease.[8]

Type of exposure. The level of exposure appears to be the main determinant in the development of OA caused by agents that act through IgE-mediated mechanisms, such as the majority of high molecular weight substances but also certain low molecular weight substances such as platinum salts and acid anhydrides.[39,40] The risk of developing OA is highest just after the first year of exposure to the causative agent and if symptoms of occupational rhinoconjunctivitis appear prior to bronchial symptoms.[4] Evidence also exists supporting an interaction between irritants and sensitizing agents. Smoking has been linked to an increase in sensitization to tetrachlorophthalic anhydride and platinum salts,[41] and exposure to ozone may potentiate the development of bronchial hyperresponsiveness to hexachloroplatinate.[42] In addition to the causative agent itself, the intensity of the exposure also appears to be an important determinant in the appearance of RADS.[8]

Pathophysiology (Table 4)

IgE-dependent mechanisms. Most high molecular weight substances that cause OA are animal- or vegetable-derived proteins or glycoproteins that act via a mechanism involving IgE. These proteins behave as complete antigens that stimulate the production of IgE. Nevertheless, some low molecular weight substances (eg, acid anhydrides and platinum salts) can function as haptens and combine with carrier proteins to form a hapten-protein complex that will also stimulate IgE production. When these substances are inhaled they bind the specific IgE found on the surface of mast cells and basophils, triggering a sequence of cellular events that leads to the release of preformed or de novo synthesized mediators and the recruitment and activation of

TABLE 4
Types of Occupational Asthma According to the Mechanism Involved and the Principal Characteristics*

Characteristics	Immunologic OA		Nonimmunologic OA
	IgE-Mediated	Non-IgE-Mediated	RADS
Clinical			
Interval between onset of exposure and symptoms (latency)	Long	Shorter	Short (<24 h)
Typical response to bronchial challenge	Immediate, dual	Late, dual, atypical	Not determined
Epidemiologic			
Prevalence in exposed population	<5%	>5%	Unknown
Predisposing factors	Atopy, smoking	Inconclusive	Inconclusive
Histopathologic			
Epithelial desquamation	++	++	+++
Subepithelial fibrosis	++	++	+++
Basement membrane thickening	++	++	++
Eosinophils	+++	+++	+/–
Lymphocytes	++	++	+/–

*OA indicates occupational asthma; Ig, immunoglobulin; RADS, reactive airways dysfunction syndrome.

inflammatory cells that ultimately provoke an inflammatory reaction in the airways characteristic of asthma.[36]

IgE-independent mechanisms. Most low molecular weight substances that cause OA act via a mechanism that, while probably immunologic, does not involve IgE.[36] Specific IgG and IgG_4 antibodies appear to be associated more with the level of exposure than with the disease itself.[43] It is possible that cellular or delayed hypersensitivity is involved in these cases.[44] CD4 lymphocytes play a supporting role in the production of IgE by B lymphocytes and may also induce inflammation by secreting interleukin (IL) 5. IL-5 is a potent stimulator and activator of eosinophils and is the main cytokine involved in the recruitment and activation of eosinophils during delayed asthmatic responses.[45] Increased numbers of activated T lymphocytes (which express the receptor for IL-2), activated eosinophils, and mast cells have been observed in bronchial biopsies from patients with OA caused by low molecular weight substances.[46,47]

In addition, those substances can have nonimmunologic proinflammatory effects. If they bind glutathione, they cause intracellular glutathione deficiency, which can reduce defense against oxidizing agents.[48] In fact, it has been reported that exposure to isocyanates is associated with elevated intracellular concentrations of peroxide.[49] Damage to cells of the bronchial mucosa caused by such a process could amplify or initiate a response to low molecular weight substances.

Irritation or toxicity. The mechanisms underlying RADS deserve special mention.[8] The massive initial epithelial lesion would probably be followed by direct activation of sensory nerves that would give rise to neurogenic inflammation. This would not only induce changes in vascular permeability but would also provoke an increase in mucosal secretion that would contribute to the chronic inflammation seen in biopsy material. During the process of recovery the inflammation would be resolved, leading to recovery of the epithelium, inhibition of neuronal activity, and improvement of vascular integrity. However, complete recovery would not always be achieved and sequelae of the inflammatory response would persist in the form of hyperreactivity and bronchial obstruction.

Diagnosis and Treatment of Immunologic Occupational Asthma

Diagnosis of immunologic OA requires a series of steps (Figure).[40,50]

Clinical History

A clinical history is essential for the diagnosis of OA. The patient should be questioned not only about the existence of bronchial symptoms but also about nasal symptoms and symptoms of the eyes, skin, and upper airways. Those symptoms often precede the appearance of asthma, particularly when high molecular weight antigens are involved. Prior to entering the symptomatic period of the disease there is normally a highly variable period of time that can last from a few weeks to a number of years. Therefore, diagnosis should not be ruled out by a worker having performed the same job for years without presenting symptoms. Sudden-onset asthma in an adult with no history of respiratory or allergic disease may be cause for suspicion of OA. It is important to be able to link asymptomatic periods with absence of exposure and symptomatic periods with exposure. Sometimes the patient will spontaneously report the presence of symptoms minutes after exposure to the causative

agent. In other cases, however, the symptoms are noted in the evening or only during the night. In those cases, it is less likely that patients will associate the symptoms with their daytime activities. In general, improvements are observed at the weekend or during holidays, but this is not always the case. In fact, this association is more common at the onset of clinical symptoms, since as the symptoms progress they often become more persistent and recurrent and this can prevent the patient from associating their asthma with work. Nevertheless, questions about the improvement of asthma symptoms during the weekend and especially during holidays display a greater diagnostic yield than those relating to the worsening of symptoms at work.[51] Sometimes, as occurs with red cedar and isocyanates, the symptoms continue for months or years after exposure is discontinued.[52] Furthermore, in some industries the chemical and operational processes are complex and cause the release of substances that remain completely unnoticed. For this reason, one of the keys to the diagnosis of OA is a year by year work history and awareness of the products found in the workplace that can cause asthma. It is useful to review the safety information provided with the products used by the worker and determine whether the causative agent thought to be involved has been previously linked to asthma of occupational origin. A clinical history indicative of OA is not sufficient to establish the diagnosis, since the opinion of the physician only coincides with a true diagnosis of OA in slightly more than half of suspected cases.[53]

Physical Examination, Chest Radiography, Standard Workup, and Lung Function Testing

Physical examination, chest radiography, standard workup, and lung function testing do not differ in OA from those performed in any other asthmatic patient. However, they should be used because, firstly, they allow a diagnosis of asthma to be made, and secondly, they allow OA to be differentiated from other work-related conditions with which the disease can be confused. It must be taken into account that often when patients attend the clinic they are completely asymptomatic and only report a sensation of dyspnea or tightness in the chest, sometimes without wheezing or other symptoms. A test to reveal nonspecific bronchial hyperreactivity, such as the methacholine or histamine test, is necessary when the bronchodilator test is negative due to the absence of bronchial obstruction at that time. This test, along with clinical assessment by the physician, is a useful approach to diagnosis of bronchial asthma in patients whose history, physical examination, or lung function are indicative of atopy.[54] In addition, if the methacholine or histamine test is negative, the existence of OA can be ruled out in practice, so long as the test is performed when the patient is working, since airway hyperresponsiveness can normalize following a variable period without exposure to the causative substance.[55-57]

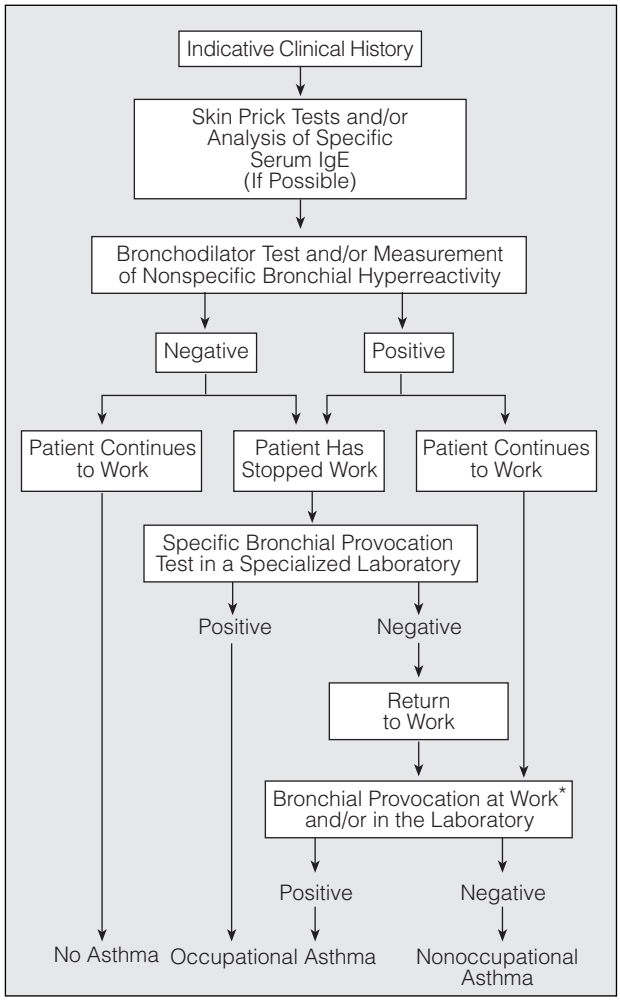

Figure. Diagnostic algorithm for immunologic occupational asthma. Ig indicates immunoglobulin. *May require measurement of exposure.

Immunologic Tests

The results of immunologic tests can indicate exposure and sensitization but by themselves are unable to confirm a diagnosis of OA. A positive test does not always imply the existence of clinical signs. To prevent erroneous interpretations, the sensitivity and specificity of each of the antigens used must be known when any such tests are performed, since various substances can give rise to false positive or negative reactions. Either in vivo (prick test) or in vitro (analysis of specific IgE antibodies) techniques can be used. Sometimes allergen extracts have to be prepared in the laboratory due to a lack of commercial availability. In general, high molecular weight substances display a high sensitivity and in some cases the absence of a reaction allows the possibility that the substance with which the test was performed is responsible for the symptoms of the patient to be ruled out.[58] Most low molecular weight substances are irritants and, therefore, prick tests are not appropriate. Likewise, if there is no clear IgE mediated immunologic mechanism, this antibody cannot be

detected, and if it can be, low sensitivity means that it is almost always of very little use. Only some low molecular weight substances, such as isocyanates, appear to display a good specificity.[59] When a positive result is obtained, the possibility of an accurate diagnosis of OA should once again be considered in case of uncertainty or when a diagnosis of OA has previously been rejected.

Bronchial Provocation in the Workplace

Bronchial provocation can confirm clinical suspicion of bronchial asthma caused by an agent that is present in the workplace or produced by work activities. The measurement relates the occupation to the disease but does not indicate which specific substance or agent is involved.[60] However, if it is known that in that particular occupation a product is used that is commonly linked to OA, or if evidence of sensitization of the patient to a particular agent can be obtained through immunologic tests, diagnosis of OA caused by that agent is highly likely. The test must be performed during or after a period of time in which the patient is working and during or after another period in which the individual is not. Those periods must generally be at least 2 weeks long and interference in the test due to factors such as use of bronchodilators, presence of exacerbations, etc, should be prevented. In some cases, such as when it is suspected that irritant concentrations of particular substances are reached in the workplace, it may be necessary to measure the concentrations of the agent under suspicion. Measurement of the changes between 2 periods can be performed in various ways. The method that is most widely used and probably possesses the greatest diagnostic efficiency is serial monitoring of peak expiratory flow (PEF) during periods of exposure and lack of exposure, although serial monitoring of forced expiratory volume in 1 second (FEV_1) during both periods or periodic monitoring of FEV_1 or nonspecific bronchial hyperreactivity at the end of each period can also be useful.[61] In any case, they are not incompatible with each other and sometimes a method such as testing of nonspecific bronchial hyperreactivity can reinforce the diagnosis obtained using another method such as serial monitoring of PEF.[60] Although there is some lack of consensus regarding what represents a significant change, a difference of more than 20% in PEF or FEV_1, or a reduction of at least 3 fold in the concentration of agent that causes a reduction of at least 20% in FEV_1 (PC_{20}) between the 2 periods would be considered definitively positive.[4,60,62] It is noteworthy that qualitative visual analysis of serial PEF recordings by an expert has a very high sensitivity and specificity, the highest among the different systems mentioned.[61] Serial PEF recordings must nevertheless be performed according to a method.[60] Measurement 4 times per day is usually acceptable for most patients.[63] Using that method, 4 types of response have been identified: *a)* deterioration during the working day, such that on returning the following day the patient has completely recovered; *b)* progressive deterioration over the course of the week with recovery at the weekend; *c)* week-by-week deterioration with recovery only after at least 3 days away from work; and *d)* maximal deterioration on Monday with recovery over the course of the week. Sometimes different patterns can also be observed, such as periodic reductions when the worker is exposed to a specific substance only occasionally over the course of the day or only on particular days. However, as with other respiratory function tests, experience and correct interpretation of the data can draw attention to manipulations or tricks on the part of individuals seeking work or financial advantages. Nowadays, however, apparatus is available in which the use of a computer program allows the information to be stored and prevents it being manipulated.[64]

Specific Bronchial Provocation Test

Although specific bronchial provocation tests are considered the gold standard for diagnosis of OA, in most cases they cannot be considered for routine diagnosis.[4] They may be indicated in the following situations: *a)* when there is a new agent that may be a possible cause of asthma; *b)* to identify the causative agent from among various substances to which a worker is exposed; *c)* when severe asthmatic reactions may occur when the individual returns to work; and *d)* when diagnosis is still doubtful after other tests have been performed.

Exposure to the agent can be performed in 2 ways, always in specialized clinics[65]:

1. Via nebulization when the agents are soluble and the immunologic mechanism is mediated by IgE. Antigen solutions are administered as aerosols at increasing concentrations. The concentration at which the technique is initiated is calculated using a formula based on the PC_{20} (mg/mL) for methacholine and the lowest concentration that generates a positive response in skin prick tests. Forced spirometry is performed 10 minutes after each nebulization. The test result is positive if there is a reduction in FEV_1 of at least 20%. The results are expressed as the PC_{20} of the allergen, or as the PD_{20} of the allergen if a dosimeter is used. If the result is negative a higher concentration is administered. During the 24 hours following inhalation it is important to monitor FEV_1 every hour to identify delayed responses.

2. In a challenge chamber, when the agents are insoluble. The test involves exposure of the patient to a nonirritant concentration of the suspected causative agent. For this reason, means of measuring the concentration of those agents should be available if possible. The length of exposure varies according to the agent and the characteristics of the patient. The test results are positive if there is a greater than 20% reduction in FEV_1, or a positive response or significant decrease in the PC_{20} compared with that performed prior to exposure.[56,57] If the test is negative, exposure is repeated for a longer period of time or with a higher concentration of the product on successive days.

When non-water-soluble dust is used, it can be passed from one tray to another mixed with lactose to produce a cloud of dust. The use of lactose alone allows a placebo test to be performed.[21] Drug-inhalation devices that employ capsules containing a specific amount of dust have also been used.[66]

When gases or fumes are tested, the methods used to generate a given concentration can be classified as static or dynamic (continuous flow).[65,67,68] In the static systems, a known quantity of gas is mixed with another of air to produce a given concentration. In dynamic systems, the airflow and the addition of gas is controlled to produce a specific dilution. These systems offer a continuous flow and allow rapid and predictable changes in the concentration to be made, favoring good mixture and minimizing loss through adsorption to the walls of the chamber.

As an alternative or to avoid the use of a challenge chamber, some hospitals have developed equipment for closed-circuit exposure, which in theory offers greater control over exposure and makes it safer for health care personnel.[68]

Treatment and Prognosis

In most cases of immunologic OA it appears to be obligatory to recommend discontinuation of exposure to the processes or substances responsible.[4,69] Wherever possible, the solution lies in a change of work situation. If that is not possible and the worker continues to be exposed, the safety procedures of the company should be assessed and exposure should be avoided as far as possible through protection of the airways. In such cases, the effectiveness of the intervention must be demonstrated on a regular basis through respiratory function tests.[51] Limitation of contact through the use of protective masks in animal care facilities and the pharmaceutical industry has been associated with a certain improvement in clinical condition and respiratory function.[70,71] A beneficial effect has also been observed with the use of inhaled bronchodilators and antiinflammatory drugs in this type of patient.[72]

Discontinuation of exposure to the causative agent is associated with an improvement in symptoms and lung function that does not normally exceed 50% in affected individuals. Lung function is only normalized and nonspecific bronchial hyperreactivity stopped in around 25% of individuals. In general, the prognosis of a given patient in whom contact with the causative agent is removed depends on the severity of the condition when diagnosis was established. On the other hand, if exposure to the causative agent continues, it almost always leads to clinical and functional deterioration of the patient.[69,72]

Following diagnosis of OA, available information indicates that from a socioeconomic perspective there is a substantial deterioration if the patient stops work, since the system of support appears to be insufficient in Western countries. In fact, a third of workers do not discontinue exposure to the causative agent following diagnosis to avoid adverse financial consequences.[4,73,74]

Diagnosis and Treatment of Nonimmunologic Occupational Asthma

Reactive Airways Dysfunction Syndrome

Even though cases had already been described, the term RADS was not used until 1985, when Brooks et al[23] described a series of 10 patients. The diagnostic criteria for RADS established by those authors continue to be used[3,4,25,75]:

1. Absence of prior respiratory symptoms
2. Exposure to a gas, smoke, or vapor present at high concentrations and with irritant qualities
3. Onset of symptoms within the first 24 hours of exposure and persistence for at least 3 months
4. Symptoms similar to asthma with cough, wheezing, and dyspnea
5. Objective evidence of bronchial asthma
6. Other types of lung disease ruled out

RADS occurs through direct toxic mechanisms. Destruction of the respiratory epithelium and inflammation have been demonstrated to take place during the acute phase and with collagen regeneration and proliferation in subsequent phases. Once exposure has occurred, only treatment appears able to influence the course and prognosis of the disease. Reports of experience with a small number of cases have indicated that early treatment with high doses of corticosteroids can improve prognosis.[76,77] However, many patients with RADS continue to present symptoms of bronchial irritation and hyperreactivity years after exposure. Consequently, once stabilized following the acute phase, patients should be treated as asthmatics. On the other hand, since they do not display any greater susceptibility than other asthmatic patients to reexposure to nonirritant doses of the causative agent, they can return to work so long as preventative measures remove the possibility of contact with products at irritant concentrations.[8,26]

Occupational Asthma Caused by Low Doses of Irritants

The appearance of cases with symptoms of asthma following repeated exposure to moderate or low concentrations of irritants is currently of particular interest. In 1989, Tarlo and Broder,[24] upon introducing the term "irritant-induced asthma," already included workers who developed asthma following single or multiple exposure to the irritant, even if exposure was at low concentrations. Chan-Yeung et al[78] also described cases of asthma with those characteristics. The terms "low-dose RADS" and "delayed RADS" were later proposed.[8,79] However, it was not clearly demonstrated in those case series that multiple moderate-intensity exposure could cause asthma, and furthermore, other studies have demonstrated that repeated moderate inhalation of an irritant is not associated with persistence of airway hyperresponsiveness, whereas such persistence is observed with exposure to higher concentrations, even in the case of single exposure.[80,81]

As admitted by Tarlo,[5] there is currently a genuine debate regarding the existence of asthma produced by low or moderate doses of irritants.[3,4] Further studies will be necessary to clearly establish and characterize the condition.

Other Variants of Occupational Asthma

Asthma-Like Syndromes

Asthma-like syndromes can present certain differential characteristics: systemic symptoms are present, the severity of the symptoms decreases over the course of the week, changes in expiratory flow as a result of exposure are less pronounced, airway hyperresponsiveness is not so notable or persistent, and neutrophilic inflammation is present in the airways.[1,4]

Byssinosis. Byssinosis develops in textile-industry workers exposed to dust from cotton, flax, hemp, jute, and pita thread.[82] The main agent responsible for byssinosis seems to be a high concentration of endotoxin from gram-negative bacilli present in the air, although this is not certain.[83] In Europe and the United States of America, the prevalence of the condition in individuals working in areas of production that generate the most dust has decreased from 50% to around 3%. In developing countries the prevalence remains high at around 30% to 50%.[82,83]

Byssinosis in its classical form is characterized by the appearance of a set of systemic and respiratory symptoms, generally following more than 10 years of exposure. Fever, asthenia, loss of appetite, tightness in the chest, dyspnea, and cough are characteristic symptoms on the first day of the working week (following absence from the textile plant for 48 hours). The symptoms diminish during the following working days despite continued exposure. As the disease progresses, the symptoms also begin to present later in the week, although with less intensity, and eventually they appear every day of the week, including the weekend. The onset of symptoms during a shift can occur either at the beginning of the shift (60%) or during the second half (40%). Those symptoms are accompanied by lung function abnormalities, such as the following:

1. Reduced FEV_1 at the end of the working day (compared with the value obtained prior to beginning work); the reduction is more marked on the first day of work[83]

2. Presence of nonspecific bronchial hyperresponsiveness (78% of cases of byssinosis, 38% of workers with respiratory symptoms not associated with byssinosis, and 17% of asthmatic workers[83,84])

3. Long-term reduction in spirometry values[85,86]

The main determining factor in the diagnosis is the patient's history, in particular confirmation that symptoms typically appear or display the greatest severity on the first working day of the week. Diagnosis of byssinosis cannot be ruled out in patients who do not exhibit acute or chronic changes in lung function; likewise, the presence of such changes is insufficient to establish a diagnosis.[87]

Asthma caused by exposure to grain dust. Asthma caused by exposure to dust from cereal grain occurs mainly in workers involved with grain silos, mills, or bakeries but is also seen in agricultural workers.[88] The specific cause is unknown but could be a component of the cereal, of parasitic fungi such as smut or rust, of saprophytes such as *Aspergillus* species, of organisms such as weevils or mites, or of gram-negative bacteria.

The reported prevalence varies markedly in different studies. The asthma is often mild and the individual's work is not affected. In close to 50% of cases the symptoms improve or disappear spontaneously, suggesting a process of desensitization in some cases.

Asthma in livestock workers. A higher rate of nonatopic asthma has been demonstrated in farm workers who are exposed to livestock, particularly birds, cattle, and pigs. This type of asthma is associated with exposure to endotoxins, fungal spores, and ammonia.[89-91]

Asthma in aluminium potroom workers. Asthma is produced in aluminium foundry workers during production of the metal from an aluminium oxide such as corundum, in electrolytic cells. In this variant of OA, increased airway hyperresponsiveness is not normally observed upon exposure and various immunologic and nonimmunologic mechanisms may be involved. Although excessive concentrations of fluoride have been implicated, the cause remains to be elucidated.[4,92]

Differential Diagnosis

Work-Aggravated Asthma

The term work-aggravated asthma refers to the situation in which there is evidence of worsening of preexisting asthma as a consequence of environmental exposure in the workplace. Although it manifests as an increase in the frequency and/or severity of asthma symptoms and/or an increase in the medication required to control the disease during working days, diagnosis should be performed on the basis of changes in bronchial diameter, the degree of bronchial hyperresponsiveness, or the extent of inflammation of the airway in relation to workplace exposure.[75]

However, demonstrating such changes in a patient with asthma prior to workplace exposure is not always easy. As a consequence, some authors have suggested that work-aggravated asthma be distinguished from symptoms of asthma aggravated by work. The second entity appears to be much more common than the first, although few publications have looked at its pathogenesis, treatment, and course.[93]

Eosinophilic Bronchitis

Eosinophilic bronchitis causes chronic cough, expectoration, dyspnea, and on rare occasions, wheezing. Its main characteristic is the presence of a large number of eosinophils in sputum and the absence of variable airflow obstruction and/or bronchial hyperresponsiveness.[94,95] It should be noted that cases of eosinophilic bronchitis have been described associated with exposure to certain workplace-related substances.[96] In such cases, and in the absence of recognizable bronchial hyperresponsiveness, diagnosis is provided when significant reproducible changes in the number of eosinophils in sputum are seen to be associated with workplace exposure.

Some authors have classified eosinophilic bronchitis as a variant of OA[3,4]; however, the condition clearly does not fulfill the criteria that define bronchial asthma.

Bronchiolitis

The term bronchiolitis applies to various diseases involving inflammation of the bronchioles. The symptoms will depend on the underlying disease, although the majority of patients present cough, dyspnea, tightness of the chest, and occasionally, expectoration and/or wheezing.[97,98]

As an occupational disease, constrictive bronchiolitis has been associated with the inhalation of various agents found in the workplace, such as nitrogen dioxide, sulfur dioxide, ammonia, or hydrochloric acid, and more recently it has been described in workers in a popcorn factory, probably due to exposure to diacetyl, an organic chemical used in the preparation of that product.[99]

Inhalation of asbestos, iron oxide, aluminium oxide, talc, mica, silica, silicates, and carbon can cause bronchiolitis secondary to inhalation of mineral dust. The condition is characterized by inflammation of the respiratory bronchioles and occasionally of the alveoli, leading to airflow obstruction. These changes can occur in the absence of concomitant pneumoconiosis.

Finally, lymphocytic bronchiolitis has recently been described in workers in the nylon industry.[100]

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is a lung disease that occurs as a result of inhalation of antigens to which the patient has been previously sensitized. Many of those antigens may be present in the workplace and cause occupational disease.[101-103] It is important to distinguish this condition from OA, taking into account that both the causative agents and the clinical symptoms may on occasions be the same. Thus, it is known that an appreciable percentage of patients with hypersensitivity pneumonitis present wheezing, airway hyperresponsiveness, and a normal chest radiograph.[104,105] Nevertheless, the diagnosis of hypersensitivity pneumonitis, unlike asthma, is suspected and/or confirmed in the presence of systemic symptoms, reduced diffusing capacity with or without functional restriction, diffuse radiographic abnormalities, lymphocytosis in bronchoalveolar lavage, granulomatous pathologic reactions, and/or positive alveolar response to specific challenge test.[103]

Vocal Cord Dysfunction

Vocal cord dysfunction is characterized by paradoxical vocal cord adduction during inhalation. This anomalous adduction causes airflow obstruction that can be manifested as stridor, wheezing, tightness of the chest, dyspnea, and/or cough.[106] Differential diagnosis with asthma is difficult and it is possible that many patients with vocal cord dysfunction are misdiagnosed and treated as if they were suffering from asthma. The disease is suspected if flattening of the inspiratory flow profile is seen in forced spirometry. Diagnosis is confirmed by fiberoptic bronchoscopy on observation of anomalous adduction of the vocal cords during inhalation.

Although the condition has been associated with various psychiatric disorders, it has recently been proposed that certain types of workplace exposure, especially to irritants, can cause vocal cord dysfunction.[107] Distinguishing this condition is important, since the treatment is radically different from that prescribed for asthma. Patients with vocal cord dysfunction can benefit from educational treatment aimed at training the muscles that cause the laryngeal dysfunction. Inhaled or systemic corticosteroids and bronchodilators have not been proven to be of benefit.

Multiple Chemical Sensitivities Syndrome

Multiple chemical sensitivities syndrome is a condition acquired following a documented toxic exposure and is usually characterized by recurrent symptoms that affect multiple organ systems.[108] Those symptoms appear in response to exposure to unrelated chemical compounds at doses lower than those known to be toxic in the general population. The following criteria are used to establish diagnosis: *a)* the symptoms are reproduced with repeated chemical exposure; *b)* the disease is chronic; *c)* a low level of exposure causes the syndrome; *d)* the symptoms improve or disappear when the triggers are removed; *e)* the symptoms occur in response to multiple chemically unrelated substances; *f)* the symptoms affect multiple organ systems; and *g)* not all of the symptoms can be explained by a multiorgan disease.

The symptoms reported by the patients are highly variable, although the most frequent are neurologic, digestive, and respiratory. In relation to the respiratory system, patients usually report cough, dyspnea, tightness of the chest, and presternal pain during inhalation. Clinical examination is usually normal, as are the various complementary tests, including tests of lung function and bronchial hyperresponsiveness.

The agents most commonly implicated in this syndrome are petrochemical-derived products, pesticides, synthetic fragrances, cleaning products,

paints, and detergents. It is important to note that the symptoms can occur in response to a wide variety of agents, commonly leading to a substantial reduction in patient quality of life. Since there is no specific treatment for this syndrome, many authors favor encouraging patients to carry on with their lives as normally as possible, including the work activities that have caused the disease, and to learn to live with the symptoms, since to date it has not been demonstrated that this leads to deterioration of any organ in particular.

Environmental Monitoring of Chemical Agents

The measurement of possible causative agents of OA in the environment may be important for a number of reasons[109]: *a)* it is sometimes necessary to confirm a diagnosis of OA in the laboratory or workplace; *b)* monitoring should be used to ensure that exposure to high concentrations of certain agents is prevented to guard against the development of OA in the workforce; and *c)* since workers who have developed OA should not continue to be exposed to the causative agent, it may sometimes be necessary to monitor the agent following introduction of safety measures or workplace changes.

However, it is important to bear in mind that measurements of possible causative agents should not be considered in isolation and should form part of the general principles of industrial safety. Within this process, the following elements are often necessary:

1. Diagram of the processing or flow of the primary materials until the final product is obtained. This involves exhaustive monitoring of the primary material from the moment it enters the company and as it passes through the processes that alter it and may involve other chemicals that could lead to the appearance of intermediate substances or other byproducts before the final product or products are obtained.

2. Inventory and identification of substances that may be present in the working environment. In addition to our own knowledge of a possible agent's presence in a working environment, we should look at manufacturer's safety data sheets, which nearly always provide the necessary information on the substances used. The possibility should also be considered that it is not one of the substances normally present in the production process but rather a substance produced by an anomalous industrial process or a substance that does not form part of the process but for one reason or another is used, sometimes temporarily, in the company; such substances may include cleaning products, coolants, paints, fuels, etc.

3. Assessment of the aggregation state of the agent as a dust, aerosol, gas, or vapor, since this can affect its interaction with the body and the way in which it must be analyzed.

Prior to sampling and analysis it is usually indispensable to first focus suspicion on a specific causative agent. Otherwise, it is difficult, and sometimes impossible, to identify the agent. It must be remembered that a specific agent normally requires a particular type of sampling in order to then use the appropriate analytic technique. The web pages of various organizations publish sampling methods and analytic techniques for a variety of chemicals.[110-112]

Sampling Techniques

Sampling involves collecting a sample of air to be taken to the laboratory, where the agent it contains is identified and characterized, or alternatively passing a volume of air through a support that retains the contaminants of interest.

Sampling of gases is performed in plastic, Teflon, or aluminium bags into which air is pumped. The flow and time of use of the pump allow the concentration of the agent studied to be calculated. Sampling in bags is limited to stable gases that do not react with the material of the bag and that are not absorbed by it.

Sampling of volatile organic components is usually undertaken through adsorption on a solid such as activated charcoal or silica gel. This can be performed actively through the use of a pump or passively as a result of diffusion by simple exposure of the support to the agent present in the air.

If the substance is in the form of an aerosol, dust, or smoke, it can be captured using filters or membranes made of materials such as Teflon, cellulose, polyvinyl chloride, or glass fiber. The filter is located in a plastic container connected to a pump that passes room air through the filter.

Analytic Techniques

Various analytic techniques exist, such as gas chromatography, high performance liquid chromatography, atomic absorption, ultraviolet, and/or infrared spectrophotometry, spectrometry, ion chromatography, and mass spectrometry.

It should be noted that industrial hygiene equipment has now been developed that collects and simultaneously carries out analysis of air for various chemical substances such as isocyanate monomers, anhydrides, and formaldehyde. Such equipment should be used with caution in the workplace due to the possibility of interference from the environmental conditions and other contaminants.

Various organizations, such as the Spanish national occupational safety commission (Instituto Nacional de Seguridad e Higiene en el Trabajo) have established limits for exposure to protect workers from the toxic effects of chemical contaminants.[113] These limits appear to be inadequate either for prevention of immunologic OA or for protection of workers who have already developed the disease. However, they may be sufficient to protect a worker who has suffered RADS and waited a sufficient period to achieve a certain stability.

Environmental Monitoring of Protein Aeroallergens

Quantification of environmental allergens has various applications that can also be useful in the diagnosis of OA. Specifically, their quantification allows *a)* monitoring of specific concentrations of allergens in the workplace or the environment; *b)* confirmation of exposure to a given allergen as the cause of disease; and/or *c)* occasionally, establishment of the concentrations of a given allergen that represent a risk.[114]

Sampling Techniques

When analyzing environmental allergens it should be taken into consideration from the outset that the process involves various stages that can generate variability in the results obtained and that it is therefore important to undertake the necessary standardization. Firstly, samples must be taken of particles present in the air, a process that requires environmental sampling equipment. Such equipment contains an aspirator that pulls a known volume of air through filters on which the allergen particles are deposited. Accurate standardization of the characteristics of the sampling (time and airflow) are important in order to collect sufficient allergen on the filter to allow subsequent quantification. The volume of filtered air usually varies between 0.5 and 1000 m^3, although in many cases the airflow is fixed and it is the sampling time that is varied. Extended sampling times present the problem that it is impossible to detect temporal changes in the concentration and what is measured is the mean concentration over the sampling period.

Various types of sampler exist for the different environments in which an allergen might be measured and it is important to choose the most appropriate one. Area samplers operate with an airflow of 1 to 3 L/s, can measure and confirm the presence of a given allergen, and can work for extended periods. Built-in particle-size analyzers (cascade impactors) allow the quantity of biologically active allergen to be determined. Personal samplers allow measurements to be made that are related to an individual's specific workplace. However, cascade impactors and personal samplers can have the disadvantage of not collecting a sufficient quantity of allergen for subsequent detection since they work at flow rates that are lower than area samplers.

Extraction of Allergens

The second step involves extraction of soluble allergens from the filter with buffered aqueous solutions. The choice of filter is also essential. It must offer low resistance to airflow along with efficient retention of breathable particles. In addition, it should prevent denaturation of proteins, should not absorb the allergen, and should allow extraction in small volumes in order for the sensitivity of the assay to allow detection of the proteins. The best filters are made from polytetrafluoroethylene, Teflon, or glass fiber. During the development and validation of a measurement method for a new allergen, it is necessary to determine the stability of the allergen on the filter and the efficiency of extraction. In addition, sample storage is also important. The filters can generally be stored for a number of months at -20ºC. Although it is also possible to store the eluted allergen, in some cases the allergen is less stable in aqueous solution due to protease activity; in those cases it is possible to lyophilize the extract to improve storage.

Analytic Techniques

Various techniques are used to measure the environmental conservation of aeroallergens. Quantification of some airborne pollens, which display a characteristic morphology, can be performed by optical microscopy based on morphologic criteria. Those techniques, along with culture methods, are also employed for environmental quantification of microorganisms; they are highly sensitive and offer the advantage of also allowing taxonomic classification.[114] However, in most cases the air samples are made up of complex mixtures that contain, among other substances, amorphous allergenic substances that cannot be visually identified. Such cases require the use of specific immunoassay techniques such as radioimmunoassay and enzyme-linked immunosorbent assay (ELISA), which can be classified as capture (also known as sandwich methods) or competitive (inhibition ELISA or inhibition radioallergosorbent test [RAST]).

Those methods are currently used for the analysis of many different aeroallergens, including those derived from dust mites (*Dermatophagoides pteronyssinus*),[115] domestic cats (*Felis domesticus*),[116] laboratory animals,[117] enzymes such as α-amylase,[118] and latex.[119] The most recently described include an immunoassay developed to analyze the environmental concentration of phytase, an enzyme used as an additive in animal feed.[120]

Capture immunoassays display an acceptable reproducibility and sensitivity, since they can detect protein concentrations of between 100 pg/mL and 1 ng/mL; consequently, they can be used to assess the relative environmental concentrations of most protein aeroallergens, which in many cases are low, particularly when allergens are measured in the atmosphere. This type of analysis requires 2 specific monoclonal antibodies that recognize 2 different epitopes of the allergen, or alternatively purified polyclonal antibodies. Analysis using monoclonal antibodies offers substantial advantages: higher specificity and reproducibility, as well as the possibility of unlimited production of the antibodies if the producing cell line is maintained.[121] However, there are disadvantages to their use when analyzing complex material such as environmental samples because they are designed to detect only a single component of the mixture and not all of the allergens present.[122] Capture immunoassays that employ polyclonal antibodies have the advantage that the antibodies can be prepared using various animal species and are easier to obtain. Furthermore, they are

particularly useful for the analysis of denatured proteins since they recognize multiple epitopes.[121]

When monoclonal antibodies and/or purified polyclonal antibodies are unavailable, competition or inhibition assays are recommended for the quantification of environmental allergens. The most common inhibition methods are inhibition RAST and inhibition ELISA.[123,124]

A disadvantage of inhibition methods is that in most cases there is no international standardization and they are considered semiquantitative methods with potential problems of long-term reproducibility caused by the use of antibody mixtures (eg, human antibodies).[123] This makes it difficult to compare absolute values between different laboratories and makes it necessary to establish the efficacy of the technique for each allergen. The antisera used in those methods made up of IgG antibodies from animals offer advantages over the use of those made up of human IgE antibodies, since they are used at 10-fold to 1000-fold dilutions. However, the use of human IgE antibodies ensures measurement of the disease-causing substance (ie, those allergens that are of clinical importance), particularly when the identity of the allergenic molecules is unknown or powders are used that contain complex mixtures of allergens.[114]

Is It Possible to Establish an Environmental Limit for Allergens?

The goal of monitoring environmental concentrations of aeroallergens is not only to aid diagnosis but also to establish the safe limit below which sensitized individuals will not display symptoms. However, to establish a safety limit in the case of allergens is more complex than with toxic materials, since the concentration that provokes symptoms in sensitized individuals can vary and depends upon the titers of specific IgE the patient has against the allergen and the degree of bronchial hyperresponsiveness to methacholine or histamine.[114] In addition, 2 environmental allergen concentrations should be taken into consideration: the sensitizing level and the level that provokes symptoms in sensitized individuals. Various authors report that the quantity of allergen necessary for sensitization is around 100 to 1000 ng/m^3, while that necessary to provoke symptoms once an individual is sensitized is around 10 ng/m^3 or less.[114] Furthermore, various studies analyzing sensitization to allergens such as *D pteronyssinus* report that concentrations above 80 μg per gram of domestic dust could even sensitize healthy individuals.[125] A safe limit to prevent sensitization and allergy has only been established for a few allergens, such as wheat flour, latex, and α-amylase.[126]

Analysis of Inflammatory Markers

Inflammation can be assessed in patients with OA by analyzing bronchial biopsy material obtained by fiberoptic bronchoscopy. That technique is invasive, however, and it cannot be used systematically in OA patients despite its high diagnostic yield. Currently, noninvasive methods that are relatively easy and economical are available for the assessment of bronchial inflammation; the tests display good reproducibility and they do not present complications for the patient. Such methods include analysis of induced sputum and exhaled breath condensate, and quantification of nitric oxide (NO). Although those methods were initially used for research, they are of increasing importance in clinical practice.

Induced Sputum

Sputum induction is a safe technique that can be applied without complications in day-to-day clinical practice. Sputum samples containing cells and cellular and extracellular products can be obtained with this technique. The most widely used method was described by Pizzichini et al.[127] It involves pretreatment of the patient with inhaled salbutamol 10 minutes prior to nebulization of increasing concentrations of hypertonic saline solution (3%, 4%, and 5%) over a period that generally ranges from 5 to 7 minutes. Prior to and after the first nebulization and following each subsequent nebulization, patients are asked to blow their nose and rinse their mouth with water to minimize contamination with nasal secretions or saliva. The patient is then asked to cough (effective cough) and sputum is obtained from the lower airways in a sterile container. The test is considered complete after 3 nebulizations. The procedure is stopped if at any point a reduction of more than 20% is observed for FEV_1.

Subsequently, sputum is processed in the laboratory to separate the cell pellet from the liquid supernatant. The pellet can be used to obtain a complete cell count and a differential cell count (eosinophils, neutrophils, lymphocytes, and macrophages). The supernatant can be used to analyze inflammatory mediators produced by those cells.

Various authors have described the usefulness of induced sputum in the diagnosis and monitoring of OA. Some studies have demonstrated that an increase in the number of eosinophils in sputum when the patient is working compared with rest days can aid the diagnosis of the disease.[128] In addition, a recent study reported that additional analysis of cells in induced sputum increases the specificity of PEF monitoring.[129] Finally, it has also been demonstrated to be useful during specific challenge tests. In this context, Lemière et al[130] observed a significant increase in the number of eosinophils and neutrophils following specific bronchial challenge in patients with OA caused by both high and low molecular weight substances.

Exhaled Nitric Oxide

Various studies have reported abnormalities in the concentrations of NO in respiratory diseases characterized by inflammatory processes. This marker has been extensively studied in asthma and it has been

observed to be correlated with the number of eosinophils and the concentration of eosinophil cationic protein in sputum. It is produced by both constitutive NO synthase (to mediate physiologic processes) and inducible NO synthase (in pathologic processes).[131] The systems currently used for analysis vary in complexity but are based on chemiluminescence techniques. The concentration of NO is measured in air samples as parts per billion (ppb) and the equipment calculates the concentration of the gas over a preselected period of time based on the guidelines of the European Respiratory Society and the American Thoracic Society.[132,133]

Although the measurement of NO has been demonstrated to be useful for the diagnosis and follow-up of patients with asthma,[134] its usefulness in the case of OA is less clear. Some authors have suggested that elevation of this marker is involved in the pathophysiologic mechanism through which different agents cause OA. Thus, elevated concentrations of NO have been observed in asthma mediated by immunologic mechanisms involving IgE; this association is less clear in patients whose asthma is nonimmunologic, mediated by irritants.[131] In addition, the possibility has recently been reported that measurement of NO during specific bronchial challenge tests may be useful to establish a positive test result independently of the reduction in FEV_1.[135]

However, since smokers may have lower NO concentrations than nonsmokers, administration of inhaled corticosteroids interferes with NO synthesis, and higher NO concentrations may be observed in the context of other pulmonary diseases or viral infections, the use of this marker for diagnosis of OA cannot yet be generally applied.

Exhaled Breath Condensate

Exhaled breath contains aerosols and water vapor that can be condensed by freezing. The method used to collect the condensate by passing exhaled breath through a condenser, which freezes it, is noninvasive, simple, and safe. The equipment that is currently available can collect 1 to 2 mL of condensate in approximately 15 minutes, although the volume collected depends mainly on the total volume of breath exhaled and the temperature of the condenser.[136,137]

This water vapor can carry nonvolatile substances arising from the respiratory system and it is possible to analyze volatile oxidants such as hydrogen peroxide, neutrophil chemoattractants such as leukotriene B4, changes in pH, concentration of nitrites and nitrates, etc.[134,137] There is currently increasing interest in the use of exhaled breath condensate for proteomics studies. Thus, some studies have reported the detection of various cytokines in this type of sample; however, due to the high dilution, to perform such studies it must be remembered that methods with a very high sensitivity must be used.

In summary, analysis of exhaled breath condensate is a noninvasive technique that can be repeated in order to monitor inflammation and that allows longitudinal studies to be undertaken. However, analysis of this type of sample must be subjected to extensive standardization to allow future comparison of data obtained in different laboratories and assessment of its possible usefulness in patients with OA.

Impairment and Disability: Medicolegal Considerations

The concept of workplace prevention is relatively recent compared with that of compensation for injury caused to workers. European countries, led by Switzerland, Germany, and Austria, began to provide compensation for industrial injury at the end of the 19th century and later other countries followed suit. According to this system, employees agree not to take legal action for workplace injuries against the company that contracts them in return for financial compensation, medical treatment, and rehabilitation paid for by private or state insurance schemes. Diseases caused by inorganic material, particularly silicosis, were the first and have been the most frequent motives for compensation. However, OA is currently surpassing it as a motive for compensation in many industrialized countries.

The regulations affecting compensation policies vary according to the country or region. The difficulties associated with definition and diagnosis of the disease, the involvement of factors such as atopy or smoking in causing asthma or the difficulty in detecting the cause, the possibility of prior asthma, the variability of the disease, and its persistence following discontinuation of work represent some factors that complicate the development of regulations. Consequently, some countries prepared lists or tables of types of asthma, occupations, and causes in order to establish when compensation should be provided for OA. These were soon found to be too restrictive and they were not updated often enough in response to new scientific tests that would have obliged changes to be made. Even today, although many countries accept claims for any occupational disease, obtaining appropriate compensation is still problematic.[138]

In Spain, although the diagnosis of OA is not subject to rigid criteria, when associated disability is proposed, certain premises and recommendations are usually considered:

1. Confirmation of occupational disease, defined as disease contracted as a result of work activities performed as an employee and that fall within established regulations, whenever the disease involves substances or elements that are indicated for each occupational disease within the aforementioned regulations (article 116 of the Spanish social security law [Ley General de la Seguridad Social] of June 20, 1994). Currently, self-employed or freelance workers are also covered by the same regulations (Spanish Royal Decree 1273/2003, of October 20, 2003).

2. Consideration of a series of diagnostic criteria.[139] Notably, a positive bronchial challenge test is not required as a criterion.

3. Consideration of a series of causative agents. OA appears in the section covering occupational diseases caused by chemical agents (up to 43 agents are included) and in those diseases caused by inhalation of agents not included in other categories.[140] Thus, it is an open list that will soon be adapted to the recommendations of the European Commission and that can already be consulted at the web site of the Spanish Health Ministry (Ministerio de Sanidad y Consumo).[141]

Once diagnosis of OA has been made, the best option is to relocate the patient in the workplace to a role in which they are no longer exposed to the causative agent if the OA is caused by hypersensitivity, or return the worker to their original role once stabilized, so long as the patient is not unable to perform the job and the safety conditions are appropriate, if the asthma was caused by irritants. In this last case it would also be acceptable to relocate the worker to a post in which they were exposed to lower levels of irritants.

If those options are not possible, disability should be assessed. At this point, it is important to realize that there is one set of terminology that is medical and another that is legal. The latter is specific to each country and is essentially the concept on which compensation is based.

In relation to medical terminology, the World Health Organization has established 3 terms[142,143]:

1. Impairment refers to functional deficit or loss, which in asthma would be assessed quantitatively by spirometry and the measurement of nonspecific bronchial hyperreactivity.

2. Disability refers to the difficulty or inability to perform a job (occupational disability) or day to day activities (general disability). This is a difficult concept to quantify since it involves assessment both by the doctor and the worker.

3. Handicap refers to the negative repercussions of impairment and disability in the life of the individual. Assessment of handicap does not generally form part of the evaluation for possible industrial compensation.

Regarding legal terminology in Spain, the current legal provisions relating to these areas can be obtained at the web site of the Ministerio de Trabajo y Asuntos Sociales,[144] where Decree 3158/66 and Spanish Royal Decree 1/1994 of June 20, 1994 can be consulted along with their subsequent modifications.

From a legal standpoint, while suffering from OA the worker may be in the following situations:

1. Temporary occupational disability, when the worker is temporarily disabled for the purposes of work. This is normally an observation period whilst further studies are performed or whilst the individual awaits a new work position. The maximum length of this period is 12 months, extendable for up to 6 more in receipt of benefits. Periods of temporary occupational disability for the same disease are added together until the maximum period is reached, even when periods of work are interspersed, so long as those periods are less than 6 months.

2. Permanent total disability for the individual's usual occupation, when the individual can undertake a different one. This occurs when the individual cannot be transferred to another position in the company without continuing to be exposed to the causative agent. The level of compensation would correspond to 55% of the calculation basis.

3. Qualified total permanent disability, when the circumstances of the beneficiary suggest that they will have difficulty in obtaining a different type of work. This can be accessed from the age of 55 years and the amount can reach 75% of the calculation basis.

4. Absolute permanent disability, when the worker is unable to undertake any occupation. The amount of the compensation would be 100% of the calculation basis. In the case of OA, this would occur if the disease caused symptoms that prevented the individual from undertaking any task. In such cases, the worker would have to be evaluated once he or she were stable, receiving appropriate treatment, and at least 2 years after diagnosis and without exposure to the causative agent, after which time it is assumed that functional improvement would have plateaued. Various guidelines are available for assessment of asthma-related disability. Tables 5A and 5B show the guidelines of the American Thoracic Society.[145]

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TABLE 5A
Assessment of Occupational Disability in Asthma*

Score	FEV_1, %	Percentage Change in FEV_1	Degree of Hyperresponsiveness PC_{20} (mg/mL)	Requirement for Medication
0	>80	<10	>8	No medication
1	70-80	10-19	8-0.6	Occasional bronchodilators or chromoglycate
2	60-69	20-29	0.6-0.125	Daily bronchodilators or chromoglycate, or inhaled corticosteroids
3	50-59	>30	<0.125	Bronchodilators, inhaled corticosteroid,† or 3 courses of systemic corticosteroids per year
4	<50			Bronchodilators, inhaled corticosteroids,‡ oral corticosteroids daily or on alternate days

*FEV_1 indicates forced expiratory volume in 1 second; PC_{20}, concentration in the challenge test that leads to a reduction in FEV_1 of at least 20%.
†800 µg beclomethasone or equivalent.
‡1 µg beclomethasone or equivalent (>800 µg budesonide; >500 µg fluticasone; >2 mg flunisolide or triamcinolone; or >400 µg ciclesonide)

TABLA 5B
Assessment of Occupational Disability in Asthma

Class	Disability	Overall Score
1	0%	0
2	10%-25%	1-5
3	6%-50%	6-9
4	51%-100%	10-11, or uncontrolled asthma despite maximum treatment

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