

Work-Related Asthma

Jordan Minov*

Institute for Occupational Health of R. Macedonia, Balkans

***Corresponding author:** Jordan B. Minov, Department of Cardiorespiratory Functional Diagnostics, Institute for Occupational Health of R. Macedonia - WHO Collaborating Center and GA2LEN Collaborating Center, II Makedonska Brigada 43, 1000 Skopje, R. Macedonia, Tel: + 389 2 2639 637, Fax: + 389 2 2621 428, e-mail: minovj@hotmail.com

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ABSTRACT

Work-related asthma (**WRA**) is a form of asthma caused or aggravated by workplace agents or conditions. Substantial proportion of all adult asthma cases are related to work, i.e. WRA became the most common work-related respiratory disease in developed countries in the last three decades. WRA is not unique and homogeneous entity, but includes three types with significant difference in their pathogenesis, management, and legal aspects: occupational asthma (**OA**), work-exacerbated asthma (WEA) and asthma-like disorders. OA is defined as a new-onset asthma induced by causes and conditions attributable to a particular workplace environment and not by stimuli encountered outside the workplace. Two subtypes of OA are recognized, depending on whether it is induced by immunological or non-immunological stimuli from the workplace: sensitizer-induced OA and irritant-induced OA. Sensitizer-induced OA is a subtype of OA induced by sensitization to an occupational sensitizer and it accounts up to 90% of all OA cases. Irritant-induced OA is a new-onset asthma which develops following single or repeated exposure to high concentrations of irritant compounds at the workplace. WEA is defined as a pre-existing or

concurrent asthma aggravated or reactivated by work agents and conditions. Currently, all WRA types are a matter of growing interest, and not a little controversy. Epidemiology, risk factor, pathogenesis, diagnostics, management, and prevention of the WRA types are discussed in this review.

Keywords: Asthma-like disorders; Irritant-induced occupational asthma; Occupational asthma; Sensitizer-induced occupational asthma; Work-exacerbated asthma

INTRODUCTION

Occupational exposures may cause new-onset asthma in a healthy subject, aggravate pre-existing asthma in a symptomatic individual or reactivate asthma in an asymptomatic individual. All these disorders are covered by the term *work-related asthma (WRA)* or work-attributable asthma, i.e. asthma caused or aggravated by workplace agents or conditions [1,2]. In addition, based on the European Community Respiratory Health Survey (**ECRHS**) results, it was estimated that occupational exposures contribute to one in seven cases of severe exacerbation of asthma [3].

WRA became the most common work-related respiratory disease in developed countries in the last three decades. Substantial proportion of all adult asthma cases are related to work, varying from at least 10%, 10-20%, 21%, 2-26%, 21-29%, to 32.9% according to the results of the studies performed in this period [4-8].

WRA was found in 24.7% of all adult asthma cases in the age group 20-44, as it was documented in the study carried out in R. Macedonia at the beginning of last decade [9]. In addition, in Michigan, new cases of work-related asthma are identified in 140-150 workers each year, but it seems that this is an underestimate of the real incidence of WRA. It is estimated there are 228-801 individuals a year who develop WRA, and there are at least 500,000 adults with asthma in Michigan. Furthermore, 54.1% of Michigan adults with current asthma have ever told a health professional or were ever told by a health professional that their asthma was work-related [10]. Data for WRA prevalence vary markedly depending on the study design, the size and the structure of study population, the study protocol, etc. In addition, despite in the last decades WRA and their forms were defined as separate entities, definitions need to be clearer to allow valid comparisons between studies.

As it is mentioned above, WRA is not unique and homogeneous entity, but includes three forms with significant difference in their pathogenesis, management, and legal aspects:

- occupational asthma,
- work-exacerbated or work-aggravated asthma and
- asthma variants (asthma-like disorders).

OCCUPATIONAL ASTHMA

Occupational asthma (**OA**) is defined as a form of WRA characterized by airway inflammation, variable airflow obstruction and bronchial hyperresponsiveness (**BHR**) that are induced by causes and conditions attributable to a particular workplace environment and not by stimuli encountered outside the workplace [1,2,11]. Currently, OA is the most common occupational lung disorder in developed countries. On the other hand, many affected individuals remain undiagnosed as the diagnosis of OA remains one of the most difficult in respiratory medicine because of the large number of potential offending agents, the extremely diverse range of materials and processes that are involved in the workplace, and the variability in the temporal relationship of the pulmonary response and the workers exposure [12,13]. There is epidemiological evidence that 5-15% of all adult asthma cases are induced by occupational agents and conditions so OA should be suspected and evaluated in every patient with adult-onset asthma [14].

As in the cases of other occupational diseases, OA is included in the International Labour Organization (**ILO**) List of occupational diseases (revised 2010), as well as in the national lists of occupational diseases. Workers who developed OA should be compensated according to the certain national legislatures with the level of benefit usually depending on the severity of their disability.

Two types of OA are recognized, depending on whether it is induced by immunological or non-immunological stimuli from the workplace:

- sensitizer-induced OA, also referred to as allergic OA, immunological OA, classical OA and OA with latency period, which develops after a sensitization to certain occupational agent and
- irritant-induced OA, also referred to as non-allergic OA and OA without latency, which develops following exposure to occupational respiratory irritants (dusts, gases, fumes or chemicals) [11,15].

SENSITIZER-INDUCED OA

Definition and classification

Sensitizer-induced OA, defined as a form of OA induced by sensitization to an occupational sensitizer followed by development of chronic allergic inflammation in the airways, accounts up to 90% of all OA cases [15-17].

Depending on the molecular weight of the causal agent, sensitizer-induced OA is divided in two subtypes: sensitizer-induced asthma caused by high-molecular-weight (**HMW**) agents and sensitizer-induced asthma caused by low-molecular-weight (**LMW**) agents.

Epidemiology

A recent meta-analysis indicates that occupational factors account for approximately one in six cases of asthma in adults of working age [14]. According to the current evidence, sensitizer-

induced OA is more frequent in developed than in developing countries. Reported mean incidence of sensitizer-induced OA in developing countries is less than 2 cases per year in 100,000 working population, while in Scandinavian countries it is much higher, reaching 18 new cases per year in 100,000 working population [18]. The incidence of sensitizer-induced OA in R. Macedonia in the period 2005-2014 varied from 1.8/100,000 in 2013 to 2.8/100,000 in 2006 [19].

In regard to specific occupational exposures, there is an evidence that the prevalence of sensitizer-induced OA varies from 1 to 3% in food processing, 3 to 5% in wood industry workers exposed to dust from red west cedar, 7 to 9% in bakers and other workers exposed to flour, 3 to 30% in laboratory animal workers, 5 to 30% in automobile industry workers exposed to isocyanates to about 46% in workers exposed to platinum salts [20-22]. In addition, the high-risk occupations and industries associated with the development of sensitizer-induced OA vary depending on the dominant industrial sectors in a particular country. Namely, the highest prevalence of sensitizer-induced OA at the end of the last century in the United Kingdom was registered for that caused by isocyanates, in France for that caused by isocyanates and persulphates, in Finland for that caused by animal epithelium, in Italy for that caused by natural rubber latex, etc [23]. In the analysis of distribution of sensitizer-induced OA in R. Macedonia in the period 2005-2014, the highest prevalence of sensitizer-induced OA was registered among bakers and workers related to bakery, cleaners and textile workers [19].

Risk factors

The development of asthma as a consequence of occupational exposure is a matter of significant interest and importance, and not a little controversy. Most workers who are exposed to occupational respiratory sensitizers will not develop sensitizer-induced OA. As in the cases of other occupational diseases, the development of sensitizer-induced OA is based on interaction of host factors and factors from the work environment. Risk factors for sensitizer-induced OA include exposure to occupational sensitizers (type, level and duration of exposure), genetic factors, atopy, bronchial hyperresponsiveness (BHR), pre-existing asthma, occupational rhinitis (**OR**), etc.

Exposure to occupational sensitizers

Several studies have reported a clear association between occupational exposure and asthma in atopic and non-atopic individuals. Up to now, more than 400 sensitizers from the work environment are identified. As it is mentioned above, occupational respiratory sensitizers, i.e. occupational agents able to trigger allergic reaction and to produce respiratory symptoms, are divided in two groups based on their molecular weight: HMW (large molecules, proteins or glycopeptides) and LMW (chemicals with a molecular weight less than 1 kilodalton). HMW agents are complete sensitizing antigens, while LMW chemicals are incomplete antigens (i.e. haptens) that combine with a protein to produce a sensitizing antigen. The major causes of OA and occupations at risk are shown in Table 1.

Table 1: Major causes of occupational asthma and occupations at risk.

Occupational sensitizer	Occupation at risk
High-molecular-weight agents	
Plant proteins (wheat, grain dust, tea and coffee dust, cotton, latex)	Bakers, grain workers, food processors, textile workers, health care workers
Animal proteins (domestic and laboratory animals, fish, seafood)	Farmers, laboratory workers, food processors
Enzymes (trypsin, alpha-amylase, lipase, pectinase)	detergent manufacturers, pharmaceutical workers
Low-molecular-weight agents	
Isocyanates (toluene diisocyanate, diphenylmethan isocyanate)	Automobile spray painters, roofers, insulators, polyurethane workers
Anhydrides (trimellitic anhydride, phthalic anhydride)	Manufacturers of paints, epoxy resins, plastics
Glues and resins (acrylates, epoxi resins)	Manufacturers of plastics, chemical workers
Metals (potassium dichromate, nickel sulfate, platinum salts, vanadium)	Platters, metal workers, welders, construction workers
Wood dust (oak, maple, Western red cedar)	Wood workers, carpenters
Dyes and bleaches (persulfate, carmine, anthraquinone)	Hairdressers, fabric dyers
Amines	Cleaners, manufacturers of plastics
Aldehydes (formaldehyde, glutaraldehyde)	Laboratory workers, cleaners
Drugs (beta lactams, opiates)	Pharmaceutical workers, health care workers
Mixed exposure (high- and low-molecular-weight agents)	Farmers, bakers

The mechanism for sensitizer-induced OA caused by HMW agents and some LMW agents (e.g. beta lactams, platinum salts, etc.) is a type I or immediate type or IgE-mediated allergic reaction (IgE-mediated sensitizer-induced OA). Allergologic evaluation, i.e. skin prick tests and specific immunoglobulin E (IgE) levels, in this form of sensitizer-induced OA is helpful in identifying the occupational respiratory sensitizer which caused the disease. Sensitizer-induced OA caused by HMW agents is considered as a good model for understanding the pathogenesis of non-occupational allergic asthma.

The immunological mechanism of sensitizer-induced OA caused by LMW is still poorly defined. IgG antibodies, as well as cellular hypersensitivity, may be involved in the development of this form of sensitizer-induced OA (non-IgE-mediated sensitizer-induced OA or IgE-independent sensitizer-induced OA). Skin prick tests to occupational allergens, as well as specific IgE, in this form of sensitive-induced OA are negative and the causal agent can not be identified by allergologic evaluation.

Genetics

Several studies have examined whether genetic characteristics would explain why some exposed workers develop OA, while other exposed workers do not. Genes that have been implicated include human leukocyte antigen (HLA) class II molecules and polymorphisms in non-HLA genes (e.g. glutathione S-transferases, N-acetyltransferase, tumor necrosis factor alpha, prostaglandin-endoperoxide synthase) [11].

Atopy

Atopy, defined as skin prick reactions towards common inhalant allergens, is found to be risk factor in various occupations with exposure to HMW of biological origin. For sensitizers causing IgE-independent sensitizer-induced OA (majority of the LMW agents), atopy is not a risk factor. Wang et al. reported a significant association between atopic asthma and occupational exposure to HMW agents (e.g. wheat flour, latex, laboratory rats urine, etc.) and a significant association between non-atopic asthma and occupational exposure to LMW agents (e.g. cleaning agents and metal sensitizers), while agriculture was associated with both atopic and non-atopic asthma [24].

BHR and **pre-existing asthma** are also considered as a risk factor for the development of sensitizer-induced asthma caused by HMW. In addition, pre-existing asthma is a major risk factor for WEA and increases risk of sensitization to occupational agents. As in the case of non-occupational asthma, there is evidence of nasal and bronchial involvement in occupational respiratory allergy but it seems that this involvement depends on the type of occupational agents. However, results from epidemiological studies indicated that approximately 10% of individuals with **OR** develops OA [25]. OR usually precedes the onset of OA and the risk is highest in the year after the onset of OR [26].

Cigarette smoking

Cigarette smoking is considered as a risk factor for sensitization to some HMW occupational allergens, including coffee bean, castor beans, shrimp, and snow-crab, but not to laboratory animal allergens. Cigarette smoking is also considered as a risk factor for sensitization to a few low-molecular-weight (**LMW**) agents, such as platinum salts and phthalic anhydride, but appears to be less important in promoting sensitization to other LMW agents [27].

Pathogenesis

Both HMW and LMW agents cause OA by immunological mechanisms. The sensitization process does not occur after one exposure but develops over time (i.e. a latency period). Latency periods are variable and may be as short as several weeks or as long as 30 years depending on the type and the level of exposure, as well as on the individual susceptibility. If exposure is consistent, the period of greatest risk for sensitization of susceptible workers is the first two years of exposure but the risk does not go away after that but may be somewhat reduced. In addition, allergic sensitization in susceptible workers commonly develops to one occupational allergen [28].

Although no uniform dose-response relationship exists for allergens and other sensitizers (i.e. LMW), most well performed studies of workers show a positive association between the risk of asthma and increasing intensity of exposure [29]. *“The higher the degree of exposure to an agent, the higher the prevalence of asthma”* indicated by Chan-Yeung in 1990, was confirmed by results from many studies in this domain. A dose-response relationship between the exposure and both

the prevalence and incidence of OA has been demonstrated for both HMW and LMW including flour, natural rubber latex, laboratory rats urine, Western red cedar, isocyanates, colophony, acid anhydride, alpha-amylase, cow dander, etc. For most respiratory sensitizers the chances of become sensitized are much lower, but not completely absent, if the sensitizer is controlled below the occupational exposure level (OEL). There is evidence that allergic sensitization to wheat flour does not develop when exposure in the working environment is less than 0.5 mg/m^3 . In addition, the concentration of allergens of latex and laboratory rats urine in the work environment required for the development of allergic sensitization are estimated as 0.6 ng/m^3 and $0.7 \text{ }\mu\text{g/m}^3$, respectively [30-33].

In addition, there is limited evidence that sensitization to occupational contact allergens may cause respiratory allergy. Namely, animal studies have demonstrated that dermal exposure to occupational sensitizers can elicit respiratory inflammation after airway challenge. Case reports and limited epidemiological studies support this concept [34].

As in the case of allergic sensitization to non-occupational respiratory sensitizers, clinically manifested disease (i.e. occupational allergic rhinitis and/or OA) develops only in a part of the workers sensitized to respiratory occupational sensitizers. On the contrast to doses required for allergic sensitization, there is no threshold dose of certain occupational sensitizer required for triggering respiratory symptoms. Namely, once the sensitization has taken place, further exposure of the worker with sensitizer-induced OA, even to the smallest amounts of certain occupational sensitizer will produce symptoms, i.e. the OEL does not protect the worker already sensitized [28].

Chronic inflammation of the airways in asthma patients involves many inflammatory cells (T-2 helpers, B-lymphocytes, dendritic cells, mast cells, eosinophils, etc.) and over 100 different mediators (lipid and peptid mediators, chemokines, cytokines, and growth factors). The development and maintenance of the chronic airway inflammation are due to established allergic cascade independently of way of sensitization (IgE-mediated or IgE-independent), i.e. the airway inflammatory process is similar in IgE-mediated and IgE-independent sensitizer-induced OA. Multiple inflammatory effects (airway epithelial shedding, subepithelial fibrosis, bronchoconstriction, mucus hypersecretion, plasma exudation, sensory nerve activation, etc.) are the basis of variable bronchial obstruction and BHR which are the hallmark of both occupational and non-occupational asthma [20,35].

Clinical Manifestations

Clinical manifestations of IgE-mediated sensitizer-induced OA are the same manifested in non-occupational allergic asthma, i.e. typical nasal and lower respiratory symptoms induced by immediate type of allergic reaction: rhinorrhoea, sneezing, itching and watering of the eyes, dry cough, dyspnea, wheezing and chest tightness. These symptoms commonly occur at the entering of the workplace (i.e. early respiratory symptoms) and improve after the work shift. Clinical

manifestations of sensitizer-induced OA caused by LMW occupational agents often include isolated lower respiratory symptoms which may appear at the end or after the work shift (i.e. late respiratory symptoms) or combination of early and late respiratory symptoms. There is universal tendency for worsening of the symptoms in the periods at work and their improvement at the periods away from work (weekends, holidays, vacations, etc.), i.e. for their work relatedness. Besides the occurrence of work-related symptoms, the patients with sensitizer-induced OA also manifest typical asthma symptoms, such as night waking with cough and breathlessness and symptoms induced by non-specific triggers (cold air, physical exertion, tobacco smoke, traffic pollutants, perfumes, etc.). There is some epidemiological evidence that asthma caused by occupational agents is more severe than non-occupational asthma, as well as that severity of OA does not relate to the specific agent, i.e. the bigger problem probably is in the control of the disease [36,37].

Asthma exacerbations are acute or subacute episodes of worsenings of the symptoms accompanied with lung function deterioration. The most common causes of asthma exacerbations in sensitizer-induced asthma does not differ from those in non-occupational asthma, i.e. acute respiratory infections, exposure to occupational or environmental irritants, use of some drugs (aspirine, beta blockers, etc.), climatic changes, gastroesophageal reflux, emotional stress, etc. [38,39].

Diagnosis

Diagnostic work-up for sensitizer-induced OA in a worker with asthma diagnosed according to the actual recommendations includes occupational history, immunological evaluation, specific inhalation challenge (SIC) and serial measurements of peak expiratory flow rate (**PEFR**) and non-specific BHR at and away from work. It should be emphasized that none of the current diagnostic tests is perfect in isolation, and the diagnosis usually is established by results obtained from several tests [17,40,41].

Occupational history of working patients includes questions for their job, type of occupational exposure and its intensity and duration (being aware of occupations and exposures which carry particular risks) and their previous jobs. Work-relatedness of the asthma symptoms, i.e. their worsening in the periods at work following by improvement at the periods away from work indicates that the disease is work-related and that it should be assessed whether occupational exposure is a causal or an aggravating factor of the disease. In addition, assessment of occupational exposure, i.e. recognition and quantification of occupational respiratory hazards, is an important part of evaluating the worker' complaints.

Specific IgE assay or skin prick testing are high sensitive for agents causing IgE-mediated sensitizer-induced asthma (i.e HMW agents and some LMW agents), but a number of LMW cause IgE-independent sensitizer-induced asthma and sensitization to these agents can not be confirmed by the tests mentioned above.

Diagnosis of sensitizer-induced OA in routine practice usually is established by serial measurements of the peak expiratory flow rate (PEFR) and non specific BHR in the periods at and away from work in combination with other diagnostic tools mentioned above. The changes in daily PEFR variations or/and level of non-specific BHR reflect the changes in the intensity of airway inflammation in the periods when the worker is exposed and not exposed to offending occupational agent.

Serial PEFR measurements at and away from work are commonly used in routine diagnostics of sensitizer-induced OA. To provide an adequate representation of days at work and days away from work positive record included 2 weeks at work and 2 weekends away from work, and a negative record included 2 work periods separated by at least 10 days away from work. Serial PEFR measurements should be carried out after a teaching session on the use of a PEFR-meter. Workers should be instructed to perform three readings on each occasion, and to accept the highest reading only if the two best readings were within 20 L/min of each other. Readings should be carried out at least four times daily from waking to retiring to bed at similar times on days at and away from work. Interpretation of the readings may be done by analyzing graphic presentation of data obtained and calculating daily variation, or by computed-based analysis. Results from systematic review did not express preference for one method of interpretation over the other (i.e. the “eye-balling” plotted results by a physician experienced in interpreting such results *versus* the computerized interpretation system). The test should be considered positive when PEF varied by 20% or more (calculated as maximum PEFR minus minimum PEFR divided by maximum PEFR) during working days, as opposed to days off (Figure 1). Serial PEFR measurement is useful when the working patient is still working in a job with exposure to the suspect agent. In addition, relocation of a patient during the process of diagnosis is necessary only if symptoms are severe [26,42-46].

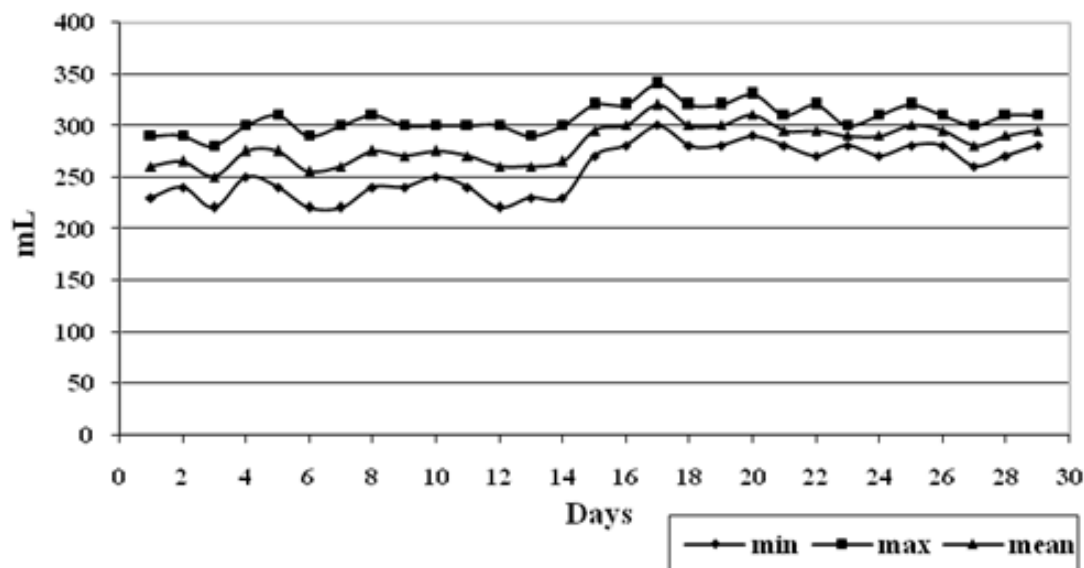


Figure 1: Serial peak expiratory flow rate (PEFR) measurements at and away from work in a herbal tea processor with sensitizer-induced OA.

Period at work days 1-14; mean daily PEFR variation = 23.4%

Period away from work days 15-29; mean daily PEFR variation = 8.9%

Source: Institute for Occupational Health of R. Macedonia, Skopje.

Serial measurements of non-specific BHR, i.e. serial non-specific bronchoprovocation (NSBP) test, at and away from work usually is performed to clarify the results obtained by serial PEFR measurements at and away from work when it is needed. By some authors, the serial measurements of non-specific BHR can be performed as a single test independently of serial PEFR measurements at and away from work and a combination of this test with a specific skin prick test or specific IgE is an appropriate alternative to SIC in diagnosing sensitizer-induced OA [47]. The serial metacholine/histamine challenge should be done on a work day and then non-specific BHR should be reassessed after at least two weeks away from work. The test is considered positive when BHR improved by at least 2 doubling concentrations of metacholine/histamine while away from work (Figure 2) [16,43].

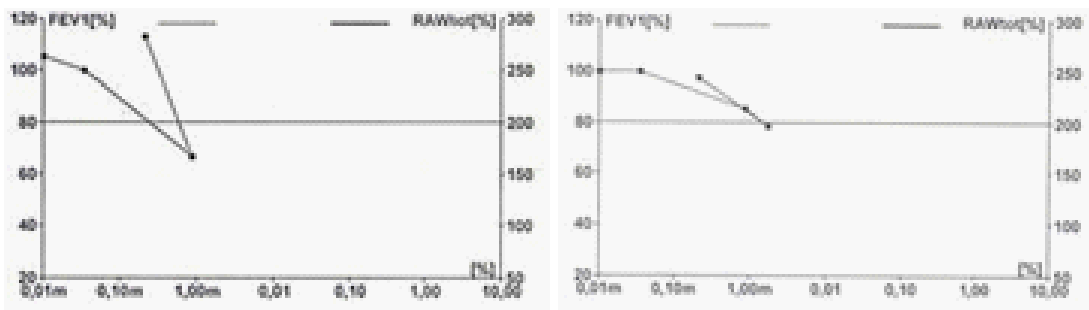


Figure 2: Serial measurements of non-specific bronchial hyper responsiveness (BHR) in a herbal tea processor with sensitizer-induced occupational asthma.

A. At work

Provocative concentration 20 (PC_{20}) = 0.43 mg/ml metacholine.

B. Away from work

Provocative concentration 20 (PC_{20}) = 2.76 mg/ml metacholine

Source: Institute for Occupational Health of R. Macedonia, Skopje.

Specific inhalation challenge (SIC), introduced by Pepys and Hutchcroft in middle 70s of the last century, is considered as a gold standard for diagnosis of sensitizer-induced OA but it is available in a few specialist centers only and the diagnosis of the disease can usually be made without this test. SIC can be performed in the workplace or laboratory and its performing can last four or more days. In addition, SIC can produce false negative results (inhalation challenge with occupational agent which did not cause the disease), as well as false positive results (inhalation of high concentrations of occupational agent which did not cause the disease). Furthermore, performing of SIC is associated with a risk of allergic reactions, life threatening in some cases [48]. Clinical indication for SIC (when available) is likely to be in cases where other tests were not performed or were inconclusive. Working patients with relevant clinical history, who have positive skin response to a certain occupational allergen and/or increased peak flow variability and/or increased metacholin/histamine responsiveness in the period at work compared with off-work period are unlikely to undergo SIC [49].

Despite there is a significant improvement in the diagnostics of sensitizer-induced OA, the disease is still under-diagnosed. The experts' opinion regarding this issue is that between-physician agreement on diagnosis is still not satisfactory, diagnosis takes too long, more sophisticated tests (induced sputum, SIC, etc.) should be introduced or performed more often in routine diagnostics, as well as the guidelines should become practice [17].

Management

Existing evidence indicates that early, complete and definitive avoidance of exposure to

the causal agent and pharmacological treatment that follows clinical-practice guidelines is the preferable approach to the management of sensitizer-induced OA.

Besides its health implications, diagnosis of sensitizer-induced OA is related with serious socioeconomic implications. Namely, cessation of exposure to offending occupational agent usually is associated with a decrease in asthma severity and in pharmaceutical expenses, but it is often associated with a deterioration of patient's socioeconomic status (professional downgrading and loss of work-derived income). Furthermore, many patients with sensitizer-induced OA have difficulties in finding a job without exposure. Reduction of exposure to the causal agent may be an alternative to the complete avoidance of exposure, but it seems that reduced exposure is less beneficial than exposure cessation. Conclusions from a Cochrane review confirmed benefit from stopping versus continuing exposure, but considered the data too limited to draw conclusions on reducing exposure [50]. There likely are some patients who can work with reduced exposure without significant worsening of their asthma and the phenotypes of such patients need to be examined. If patient elects to continue working in areas with lower exposure, he requires careful monitoring in regular intervals and appropriate interventions [15].

Pharmacological treatment of sensitizer-induced OA does not differ from pharmacological treatment of non-occupational asthma. The long-term goals of asthma management are: to achieve good control of symptoms and maintain normal activity levels and to minimize the further risk of exacerbations, fixed airflow limitation and side-effects of the used medications. The pharmacological options for long-term treatment fall into three main categories: controller medications, reliever (rescue) medications and add-on therapies for patients with severe asthma. Controllers (inhaled corticosteroids, leukotriene modifiers, long-acting inhaled β_2 -agonists, theophylline, cromones, systemic corticosteroids, etc.) are used for regular maintenance treatment. They reduce airflow inflammation, control symptoms and reduce future risks for exacerbations and decline in lung function. Relievers (short-acting inhaled β_2 -agonists, anticholinergics, systemic corticosteroids, theophylline, and short-acting oral β_2 -agonists) are provided for all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. Reducing or, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment [51].

Prognosis

According to the findings from studies on outcomes after removal from the offending environment, asthma symptoms and non-specific BHR persist several years in majority of patients with sensitizer-induced OA. The outcomes are best when the diagnosis is established early, the exposure is stopped, and the asthma is not yet severe. There is evidence that if cessation of exposure happens within the first two years of the development of the disease, complete recovering is possible. If exposure to the causal agent continues, there is a tendency for worsening of the disease. However, a cessation of exposure is nearly always of benefit [28].

In the study assessed clinical and functional outcomes of sensitizer-induced OA in bakers and textile workers three to five years after cessation of exposure to the causative occupational agent, Minov et al. found lower prevalence of respiratory symptoms as compared to their prevalence at the time of diagnosis. In addition, all study subjects were left with their non-specific BHR, although all of them improved [52]. Results from several studies indicated that approximately two-thirds of workers with sensitizer-induced OA never achieve full recovery of the symptoms and approximately three-quarters have persistent non-specific BHR. In addition, there is evidence that one-third of workers with sensitizer-induced OA removed from offending occupational exposure are unemployed three to five years after established diagnosis, with serious financial consequences [26,53,54].

Prevention

Similarly to the development of other occupational diseases, the development of sensitizer-induced OA is a matter of prevention. Despite there is sufficient understanding of the causation of sensitizer-induced OA, preventive action is inappropriate. Attempts are still unsuccessful that is largely due to non-scientific/technical obstacles. In addition, there are a limited number of studies reporting evaluation of preventive programmes. None of them is entirely rigorous but each suggests that primary and secondary prevention are both feasible and highly effective [53].

Primary prevention

Primary prevention of sensitizer-induced asthma includes methods of limiting exposure to respiratory sensitizers, methods to predict new sensitizers before their introduction in the workplace, implementation of legislated exposure limits, implementation of models to estimate relative validity of various ameliorative measures when completely avoidance of the sensitizer is not feasible, medical surveillance and education of the workers.

The level of exposure to a causative agent at the workplace is a major determinant of risk for the development of allergic sensitization and subsequent sensitizer-induced OA in susceptible workers so the measures of primary prevention should be focused on reducing exposure at source. The most important measures of reducing exposure to respiratory sensitizers include adequate engineering control (elimination/substitution, ventilation, isolation/enclosure, modification in work processes, etc.) and proper use of respiratory protective devices.

Elimination of the use of respiratory sensitizers is the ideal primary preventive measure. There is strong evidence that exposure elimination of latex (mainly powdered gloves) is associated with reduction in the sensitizer-induced OA prevalence among health care workers. On the other side, there are many working environments (e.g. bakery, cleaning or spray painting) which are technically and hygienically much more complex and such simple interventions are not possible. Furthermore, each industry is different, making effects of individual interventions extremely difficult to evaluate. In these cases, measures for reducing exposure mentioned above are substantial for reducing the risk of allergic sensitization and occurrence of clinical symptoms [56,15].

Prediction of new sensitizers before their introduction in the workplace should be based on the results from the studies on animal models, as well as on a computerized quantitative structure-activity program which is freely available and predicts the risk of sensitization according to the molecular structure [57].

Medical surveillance and education, especially for young individuals with asthma and new workers about to enter the workforce, have a great importance for protection of the workers from risks of the development of sensitizer-induced OA. Despite the increased risk for the development of sensitizer-induced OA caused by HMW agents, atopy and pre-existing BHR should not be used as a screening tool in high-risk workplaces because their positive predictive value for the subsequent development of symptoms is low [58].

Secondary prevention

Secondary prevention of sensitizer-induced OA includes measures for early detection of the disease and early intervention on its course. In the workers exposed to HMW agents, skin testing with these agents is feasible and can identify sensitized subjects who should be followed closely. In the workers exposed to LMW agents, early stages of the disease could be detected by the use of questionnaires and BHR measurements.

Tertiary prevention

Tertiary prevention of sensitizer-induced OA includes measures for management of advanced disease (i.e. re-employment to a job free from exposure and asthma medication as needed).

IRRITANT-INDUCED OA

Irritant-induced OA, a form of WRA developed at the workplace by non-immunological mechanisms, still is a field of many controversies that have to be clarified.

Definition and Classification

Irritant-induced OA also referred to as OA without latency, non-immunological OA and non-allergic OA, is a new-onset asthma which develops following single or repeated exposure to high concentrations of irritant compounds at the workplace [2,11,15]. Depending on the level of exposure, there are two forms of irritant-induced OA: reactive airways dysfunction syndrome (**RADS**) and non-RADS-irritant-induced OA (not-so-sudden-irritant-induced OA).

RADS is defined as a new onset asthma following single exposure to very high exposures to respiratory irritants. The inhalational accident usually occurs in occupational settings, but it also may occur outside the workplace (i.e. in the general environment).

Non-RADS-irritant-induced OA also referred to as not-so-sudden-irritant-induced OA and sub-acute irritant-induced OA, is a subtype of irritant-induced OA which occurs following repeated moderate-to-high level exposures of respiratory irritants over a days.

In addition, there are still some differences in the nomenclature and classification of asthma caused by non-immunological stimuli. Malo et al. used the term *acute irritant-induced asthma* (*acute IIA*) as a synonym for RADS [59]. Non-allergic OA by Milby is divided in two forms: RADS (asthma symptoms appear within 24 hours after single exposure to very high concentrations of respiratory irritants) and irritant-induced asthma (asthma symptoms appear after repeated, more-or-less tolerable exposures within several days, weeks, or even months). Both forms may develop as new-onset asthma, as well as in subjects with pre-existing asthma and negative history of asthma symptoms for at least two years prior to single or repeated exposure to respiratory irritants [60, 61].

Epidemiology

Most of the cases of OA are caused by specific sensitization to an occupational agent (i.e. sensitizer-induced OA). Nevertheless, there is a evidence that up to 10% of all OA cases are induced by non-immunological stimuli from the work environment.

Risk Factors

Occupational exposure to occupational respiratory irritants is the main risk factor for developing irritant-induced OA. Irritating properties of these agents depend on the type of the occupational agent, as well as on the level and duration of exposure.

There are many recognized occupational agents with irritating properties, and, many will be added as additional observations will be reported. Known occupational respiratory irritants capable of causing irritant-induced OA include chlore and its compounds, sulfur dioxide, ammonia, formaline, formaldehyde, fire/smoke, diesel exhaust, welding fumes, various acids, iodine, diisocyanates, hydrazine, phtalic anhydride, organic solvents, cleaning agents, sealing agents, bleaching agents, heated paints, pulverized paints, tear gas, mustard gas, phosgene, etc.

In addition, occupations at high risk for developing irritant-induced OA include: cleaning, firefighting, welding, metallurgy, chemical industry, construction, mining, agriculture, plastic manufacture, etc.

The role of genetic factors in the development of irritant-induced OA is still unknown.

By some authors, atopy and pre-existing asthma are risk factors of non-RADS-irritant-induced OA [60].

Pathogenesis

Mechanisms of the development of RADS are still poorly understood. The initial injury that activates mechanism leading to chronic inflammation of the airways seems to be a damage of the bronchial epithelium. Consequences of this damage are the loss of relaxing factors derived from epithelium, the exposure of nerve endings leading to neurogenic inflammation, the release of inflammatory mediators and cytokines after the non-specific activation of mast cells, and the secretion of growth factors that leads to remodeling of the airways [62,63].

Acute histological changes in irritant-induced OA include epithelial shedding and haemorrhage, whereas chronic changes include regeneration of epithelial cells, infiltration with lymphocytes and neutrophils, increased collagen deposition and thickness of the basement membrane. Such remodeling of the airways in patients with irritant-induced OA is probably cause of less expressed bronchial reversibility in these patients as compared to bronchial reversibility in the patients with sensitizer-induced OA [11,33].

The World Trade Center tragedy brought new insight in the understanding of irritant-induced asthma, suggesting that it can exhibit a prolonged interval between exposure and recognition of clinical symptoms and disease [64]. Expanding exposure criteria to moderate or long-term low-level irritant exposures causes difficulty in excluding transient irritant exacerbation of underlying asthma or coincidental onset of asthma during working life. In addition, there is evolving understanding from epidemiological studies that chronic exposures may be associated with an increased risk of developing asthma. Despite this recognition, the mechanisms and clinical case definitions of work-related asthma that might be caused by chronic exposures to irritants (vs. new-onset asthma that begins coincidentally to work exposures), remain unclear at present [65].

Clinical manifestations

The asthma-like symptoms in RADS occur 24 hours after inhalational accident and persist for at least three months and commonly for years, or even permanently. At the time of the acute event, coughing is generally predominant symptom. Pulmonary function tests may show airway obstruction, which response to bronchodilator is less expressed as compared to bronchial reversibility in the patients with sensitizer-induced OA, as it is mentioned above. Metacholine/histamine challenge is positive indicating the presence of non-specific BHR. As in the case of asthma-like symptoms, pulmonary functional abnormalities persist at least three months, commonly for years [33,61]=4 The symptoms in these patients may be triggered by inhalation of irritants from the workplace, as well as from the general environment (e.g. tobacco smoke, traffic pollution, etc.).

The persistent symptoms in non-RADS-irritant-induced asthma (accompanied by functional pulmonary abnormalities) occur after a prolonged exposure to moderate-to-high concentrations of respiratory irritants. The patients usually are still working when diagnosis is established, but they are not able to link the initial onset of their respiratory symptoms to any given accident or unusual event at the workplace [33].

Diagnosis

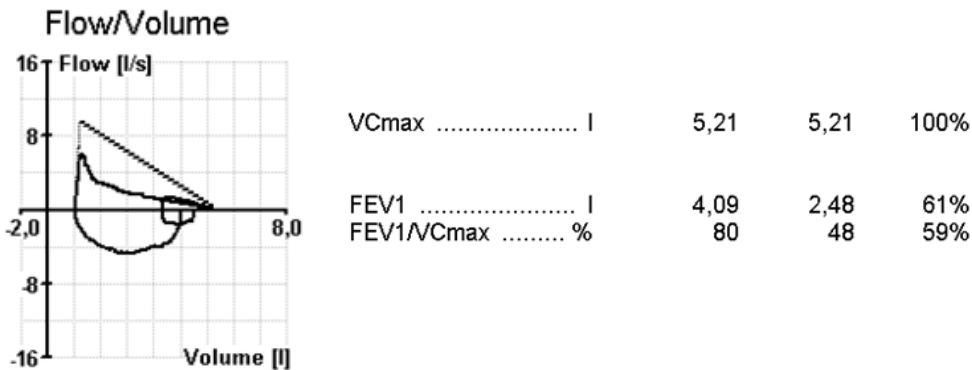
There is no gold standard for diagnosis of RADS, so its diagnosis is based on a compatible history and a demonstration of persistent non-specific BHR by positive bronchodilator test or non-specific bronchoprovocation test, i.e. on completion of diagnostic criteria.

Diagnostics of RADS is based on following diagnostic criteria:

- Documented absence of preceding chronic respiratory disease
- Occupational exposure to gas, smoke, fume or vapor with irritant properties in very high concentrations
- Onset of asthma symptoms in 24 hours after exposure
- Persistence of symptoms for at least three months
- Pulmonary function test may show airway obstruction
- Positive metacholine/histamine challenge
- Other diseases ruled out [66,67,68].

Figure 3 is shown positive bronchodilator test in iron smelter in whom the diagnosis of RADS was established regisrtered at his first visit after inhalation accident at work.

A. Native (pre-bronchodilator) spirometry.



B. Post-bronchodilator spirometry Δ FEV₁ = 16.4%.

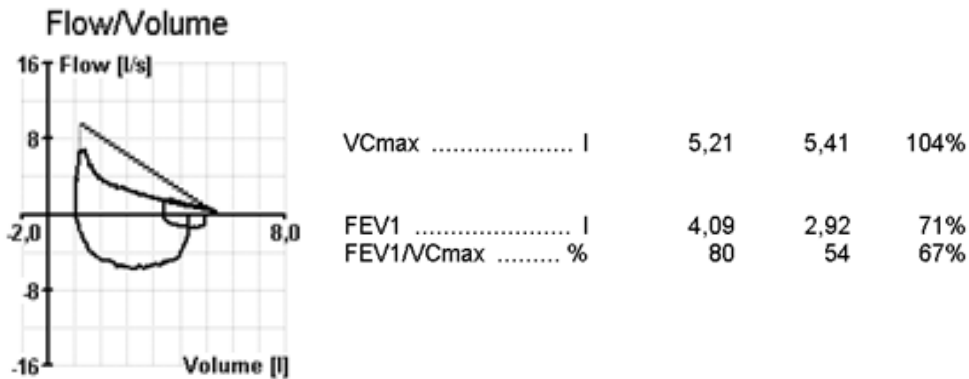


Figure 3: Bronchodilator test in iron smelter with reactive airways dysfunction syndrome (RADS).

Source: Institute for Occupational Health of R. Macedonia, Skopje.

There are cases in which a part of diagnostic criteria for RADS are not met. When most but not all criteria for RADS are met, then a diagnosis of irritant-induced asthma may also be considered to be “more probable than not” [65].

Diagnostic procedure for non-RADS-irritant-induced OA is still not standardized. According to some authors, diagnosis of this controversial entity should be considered in when the initiation of asthma symptoms is timely related to the irritant exposure (i.e. asthma symptoms should become clinically apparent during the period when the irritant exposure is taking place, although this exposure can be intermittent or continuous in nature) and the diagnosis of sensitizer-induced OA is excluded [60,61].

Management

On the contrast of sensitizer-induced OA, stop exposure to causal occupational agents in the working patients with irritant-induced OA is not necessary. Reduction of exposure to respiratory irritants, e.g. by changes in ventilation system or in work processes, move to a different work area, use of appropriate masks for short-term exposure, etc., obtains sufficient protection of triggering asthma symptoms in the working patient. If measures for reduction of exposure are not successful, the working patient should be removed to a workplace with fewer triggers [32,69].

Pharmacological treatment of irritant-induced OA includes asthma medications as needed according to the actual recommendations [51]. In addition, there is some evidence that high dose vitamin D added to recommended asthma treatment may be beneficial in the treatment of these patients.

Prognosis

There is a limited knowledge of the prognosis of irritant-induced OA as it has been investigated in a limited number of studies. In regard to short-term outcomes, Malo et al. found that 75% of patients with irritant-induced OA due to repeated exposure to chlorine were left with their BHR 2.5 years after inhalational accidents. In addition, in regard to long-term outcomes of irritant-induced OA, it seems that they are at least as poor as that found in patients with sensitizer-induced OA.

Prevention

Primary prevention of irritant-induced OA includes measures for reduction exposure to respiratory irritants, medical surveillance and education of the workers. Secondary prevention includes measures for early detection and early intervention in the case of non-RADS-irritant-induced OA, as RADS develops after acute inhalational accident. Tertiary prevention includes measures for management of advanced disease (i.e. eventually removal to workplace with few triggers and asthma medication as needed).

WORK-EXACERBATED ASTHMA

Definition

Work-exacerbated asthma (WEA), also referred to as work-aggravated asthma (WAA) is defined as a pre-existing or concurrent asthma aggravated or reactivated by work agents and conditions. Pre-existing asthma is asthma with onset before entering the worksite of interest (i.e. a new job or changes in exposure at an existing job due to introduction of new processes or materials. Concurrent or coincident asthma is asthma with onset while employed in the worksite of interest but not due to exposures in the worksite [70].

Epidemiology

The proportion of individuals with asthma who have worsening asthma symptoms at work is approximately 10 percent. This figure was derived from a meta-analysis of 43 risk estimates from 19 different countries [71]. In addition, by some authors, median WEA asthma prevalence is estimated as 18% of adults with asthma, 25% of working adults with asthma and 45% of all WRA cases [72].

Risk Factors

Occupational triggers are the main risk factor of WEA. WEA can result by variety of occupational triggers, such as:

- respiratory irritants and allergens (mineral dusts, construction dusts, cleaning agents, welding fumes, endotoxins, wood dusts, flour dust, sulfur dioxide, hydrogen sulfide, volatile organic compounds, ozone, environmental tobacco smoke, odours, perfumes, fragrances, pollens, molds, animal danders, latex, etc.),
- physical factors (cold and dry air, exercise, workplace temperature changes, etc.) and
- behavioral states (strong emotions and stress at the workplace).

In addition, as a consequence of a number of exposures that may triggered asthma symptoms, there is a wide range of worksites, i.e. from bakeries to hospitals, at risk for developing WEA.

Pathogenesis

The mechanisms of developing WEA are still not well recognized. There is limited evidence of the effects of exposures related to WEA (e.g. sulfur dioxide, chlorine, endotoxin, acetaldehyde, ozone, etc). The responses related to mentioned agents included inflammatory changes, increased BHR, lung function decline, and symptoms. Furthermore, these responses can be prevented or reduced by bronchodilators [73].

Regarding the airway inflammatory changes in workers with WEA related to occupational exposures, they are investigated in only few studies. On the contrast to workers with sensitizer-induced OA who showed an eosinophilic type of airway inflammation after SIC performed at the

workplace and in laboratory, workers with WEA showed no change or neutrophilic type of airway inflammation after SIC performed at their workplaces and no changes in airway inflammation after SIC performed in laboratory [74].

Clinical Manifestations

WEA is manifested with typical asthma symptoms (episodes of cough, dyspnea, wheezing and chest tightness) occurring in work-related pattern (worse at work and better away from work). Work-related pattern in the case of pre-existing asthma can also be registered in asthma medication use (more in working days and less in the periods away from work). Work-related nasal and eye symptoms can also be present. The symptoms in WEA may begin several minutes or hours after relevant workplace exposures, ranging from a single short-term worsening to daily consistent worsening [17].

There is evidence that compared to asthma unrelated to work, WEA is associated with more symptomatic days, a higher exacerbation rate, a greater utilization of health care services and a lower quality of life [70].

Diagnosis

WEA should be considered in any adult with asthma that is getting worse or who has work related symptoms. Diagnosis of WEA in working patient with established diagnosis of asthma (pre-existing or concurrent) is based on:

- asthma work-temporal relationship, i.e. worsening of asthma associated with work based on self-reporting symptoms or medication use related to work in workers with pre-existing asthma and worsening of lung function related to work,
- presence of conditions at the workplace that can trigger asthma symptoms and
- OA caused by occupational agents (primarily sensitizer-induced OA) is unlikely.

Distinction of WEA from OA is important, as actions required following a diagnosis differ at the individual and workplace levels. Although it is difficult to distinguish WEA from OA, a combination of tools (i.e. medical and occupational history, as well as lung function, allergy and challenge tests) will help clinician to make a diagnosis. SIC performed in the workplace or laboratory is considered as a gold standard to confirm diagnosis [75].

Skin prick tests or specific IgE are useful if a worker is exposed to HMW agents. A positive test may support, but could reflect exposure only in an atopic worker.

Serial measurements of PEFR at and away from work can not be used solely to differentiate WEA from OA (Figure 4). In the study aimed at comparison of PEFR variability between workers with WEA and workers with sensitizer-induced OA, Chiry et al. found that about a half of the cases with WEA had serial PEFR measurements that were more variable while working compared with periods away from work [76]. In addition, there is evidence based on chart reviews for a group of

WRA patients, test results to support the work-relatedness of asthma were more common for OA cases (76%) than for WEA cases (11%) [77].

Serial measurements of non-specific BHR also can not reliably distinct WEA from OA, but may help in making this distinction. There is evidence that certain exacerbating factors (e.g. cold air or strenuous physical exertion) are less likely to be associated with changes in non-specific BHR than respiratory irritants.

SIC to certain workplace sensitizers may be useful in distinction of WEA from OA. Despite some authors indicated that a negative test supported the diagnosis of WEA, it should be taken into account that SIC may have false negative results (e.g. use of incorrect occupational agent or removal from the offending workplace a long time prior to the SIC). In addition, as it is mentioned above, SIC is not widely available and this test is not commonly used in WRA types diagnostics.

Other tests, such as exhaled nitric oxide, induced sputum and sputum cellular examination, are still not standardized and validated that limit their use in this domain.

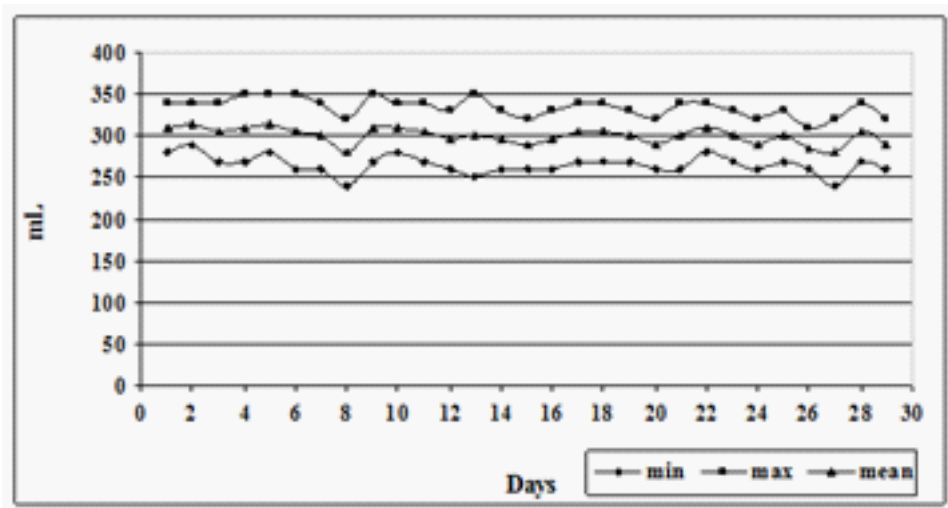


Figure 4: Serial peak expiratory flow rate measurements at and away from work in a textile worker with work-aggravated asthma.

Period at work days 1-14; mean daily PEFR variation = 23.5%

Period away from work days 15-29; mean daily PEFR variation = 18.2%

Source: Institute for Occupational Health of R. Macedonia, Skopje.

Management

Management of WEA includes achieving asthma control by reducing exposure to relevant asthma triggers both at work and off work, as well as use of asthma medication as needed. As in the case of irritant-induced OA, stop exposure to asthma triggers at the work environment is not

necessary. Reduction of exposure to asthma triggers by adequate engineering control and use of personal protective equipment obtains sufficient protection of triggering asthma symptoms in the most working patients. If measures for reduction of exposure are not successful, the working patient should be removed to a workplace with fewer triggers [17].

On the contrast of workers with OA, the workers with WEA are not supported by workers' compensation systems in national legislatures, with exception of province Ontario in Canada (does accept claims for WEA) [78].

Prognosis

There is limited evidence in regard to natural history of WEA. In addition, most of them indicated that avoidance or reduction of exposure often leads to improvement of asthma symptoms and pulmonary function abnormalities [70].

Prevention

Improving asthma control by intervention at the individual level (improving treatment, ensuring treatments are taken as prescribed and education regarding these issues) is effective personal intervention of the WEA primary prevention in the cases of pre-existing asthma. Workplace-based interventions include reduction in exposures to asthma triggers. Secondary prevention includes measures for early detection and early intervention of the working patients with WEA. Tertiary prevention includes measures for management of advanced disease (i.e. eventually removal to workplace with few triggers and asthma medication as needed) [17,75].

ASTHMA VARIANTS

Occupational Eosinophilic Bronchitis

Definition

Eosinophilic bronchitis is asthma-like disorder characterized by cough that is responsive to corticosteroids and eosinophilia detectable in the sputum (percentage of sputum eosinophils greater than 3%), without variable airflow obstruction or BHR [11]. Eosinophilic bronchitis can be regarded as an occupational respiratory disorder when it develops as a consequence of work exposures. Recently, exposure to certain occupational sensitizers, such as natural rubber latex, chloramine T (CLT), mushroom spores, bakery exposure, welding fumes, isocyanates, acrylates and an epoxy resin hardener, have been reported to cause eosinophilic bronchitis without asthma [79,80].

Pathogenesis

Mechanisms of developing occupational eosinophilic bronchitis are poorly understood. Furthermore, it still remains unclear whether this is a different disease or a different stage of asthma [17]. Several hypotheses have been put forward trying to explain why patients with

eosinophilic bronchitis do not have BHR. It is unknown whether eosinophilic bronchitis may progress to typical OA, or if eosinophilic airway inflammation may persist when asthma symptoms and BHR have waned after the cessation of exposure to the occupational agent [79].

Diagnosis and management

Chronic, work-related, bronchodilator-resistant dry cough is the common clinical manifestation of occupational eosinophilic bronchitis. Examination, spirometry and radiology are normal. Skin prick tests and specific IgE to certain occupational HMW agents are usually positive. There is no evidence neither of significant diurnal variations of PEFR, nor of BHR to metacholine/histamine. Negative results of PEFR and BHR monitoring exclude the diagnosis of OA. SIC to certain occupational agent is also negative, but there is significant increase in sputum eosinophils. There are also significant work-related changes in sputum eosinophils, so the examination of induced sputum should be added to the objective monitoring of lung function during periods at work and away from work, as well as before and after specific inhalation challenges with occupational agents.

Management of occupational eosinophilic bronchitis includes avoidance of exposure to the causal agent and use of inhaled corticosteroids [79,81].

Prognosis

According to the results from several longitudinal studies, symptoms of eosinophilic bronchitis and sputum eosinophilia often recur within a few months of inhaled corticosteroids use. In addition, some patients may develop classical asthma. Furthermore, patients resistant to standard therapy may develop progressive chronic airway obstruction in the absence of BHR [82].

Prevention

Primary prevention of occupational eosinophilic bronchitis includes measures for reduction of exposure, medical surveillance and education. Secondary prevention includes early identification and early intervention, whereas tertiary prevention includes removal from offending exposure and use of inhaled corticosteroids.

References

1. Blanc PD, Toren H. How much adult asthma can be attributed to occupational factors? *Am J Med* 1999; 107: 580-587.
2. Nemery B. ERS School Course – Occupational Asthma. Leuven. 2006; 22-24.
3. Henneberger PK, Mirabelli MC, Kogevinas M, Anto JM, Plana E, Dahlman-Hoglund, et al. The occupational contribution to severe exacerbation of asthma. *Eur Respir J*. 2010; 36: 743-750.
4. Youakim S. Work-related asthma. *Am Fam Physician* 2001; 64: 1839-1849.
5. Baggs J, Curwick C. Worker's Compensation Based Surveillance of Asthma, Hospitalized Burns, Adult Blood Lead Levels in Washington State 1994-1998. Washington State Department of Labor and Industries, 2000.
6. Milton DK, Solomon GM, Rosiello RA, Herrick RF. Risk and incidence of asthma attributable to occupational exposure among HMO members. *Am J Ind Med*. 1998; 33: 1-10.

7. Rosenman KD, Reilly MJ, Kalinowski DJ. A state-based surveillance system for work-related asthma. *JOEM*. 1997; 39: 415-425.
8. Harrison R, Filios MS, Schill DP. Work-related asthma. Occupational Health Surveillance Program. Massachusetts Department of Public Health, 2002.
9. Minov J, Cvetanov V, Karadzinska-Bislimovska J, et al. Epidemiological characteristics of bronchial asthma in R. Macedonia. *Mak Med Pregled*. 2003; 56: 156.
10. Lutzker LA, Rafferty AP, Brunner WM, Walters JK, Wasilevich EA, Green MK, et al. Prevalence of Work-Related Asthma in Michigan, Minnesota and Oregon. *Journal of Asthma*. 2010; 47: 156-161.
11. Cartier A, Bernstein D. Occupational asthma: Definitions, epidemiology, causes and risk factors. Updated February 2016.
12. McNutt GM, Schlueter DP, Fink JN. Screening for occupational asthma: a word of caution. *J Occup Med*. 1991; 33: 19-22.
13. Burge PS. Diagnosis, clinical assessment and management of occupational asthma. European Respiratory Society Postgraduate Course; Annual Congress 2002 Stockholm.
14. Toren K, Blanc J. Asthma caused by occupational exposures is common: a systematic analysis of the population attribute able fraction. *BMC Pulm Med*. 2009; 9: 1471-2466-9-7.
15. Tarlo SM, Malo J-L. An Official American Thoracic Society Proceedings: Work-related Asthma and Airway Diseases. *Ann Am Thorac Soc*. 2013; 10: S17-S24.
16. Vandenplas O, Malo J-L. Definition and types of work-related asthma: a nosological approach. *Eur Respir J*. 2003; 21: 706-712.
17. Tarlo SM, Malo J-L. An Official ATS Proceedings: Asthma in the Workplace. *Proc Am Thorac Soc*. 2009; 6: 339-349.
18. Jeebhay MF, Quirce S. Occupational asthma in the developing and industrialized world: a review. *Int J Tuberc Lung Dis*. 2007; 11: 122-133.
19. Minov J, Karadzinska-Bislimovska J, Vasilevska K, et al. Distribution of sensitizer-induced occupational asthma in R. Macedonia in the period 2005-2014 by occupation. *Glob J Allergy*. 2015; 1: 104.
20. Mapp CE, Boschetto P, Maestrelli P, Fabbri L. Occupational asthma. *Eur Respir Mon*. 2005; 172: 280-305.
21. Janson C, Anto J, Burney P, Chinn S, De Marco R, Heinrich J, et al. The European Community Respiratory Health Survey: What are the main results so far? *Eur Respir J*. 2001; 18: 598-611.
22. Minov J, Karadzinska-Bislimovska J, Vasilevska K, Risteska-Kuc s, et al. Occupational asthma in subjects occupationally exposed to herbal and fruit tea dust. *Arh Hig Rada Toksikol*. 2007; 58: 211-221.
23. Sigsgaard T, Nowak D, Annesi-Maesano I, Nemery B, Toren K, Vieqi G, et al. ERS position paper: work-related respiratory disease in the EU. *Eur Respir J* 2010; 35: 234-238.
24. Wang T-N, Lin M-C, Wu C-C, Leung SY, Huang MS, Chuang HY, et al. Risks of exposure to occupational asthmagens in atopic and non-atopic asthma. *Am J Respir Crit Care Med* 2010; 182: 1369-1376.
25. Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest* 2003; 123: 283-288.
26. Nicholson PJ, Cullinan P, Burge PS. Concise guidance: diagnosis, management and prevention of occupational asthma. *Clinical Medicine*. 2012; 12: 156-159.
27. Siracusa A, Marabini A, Folletti I, Moscato G. Smoking and occupational asthma. *Clin Exp Allergy*. 2006; 36: 577-584.
28. Health and Safety Authority. Guidelines on Occupational Asthma.
29. Newman Taylor AJ, Cullinan P, Burges PS, et al. BOHRF guidelines for occupational asthma. *Thorax*. 2005; 60: 364-366.
30. Baur X, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin Exp Allergy*. 1998; 28: 537-544.
31. Cullinan P, Cook A, Nieuwenhuijsen MJ, Sandiford C, Tee RD, Venables KM, et al. Allergen and dust exposure as determinants of work-related symptoms and sensitization in a cohort of flour-exposed workers; a case-control analysis. *Ann Occup Hyg*. 2001; 45: 97-103.
32. Heederik D, Houba R. An exploratory quantitative risk assessment for high molecular weight sensitizers: wheat flour. *Ann Occup Hyg*. 2001; 45: 175-185.
33. Malo JL, Chan-Yeung M. Agents causing occupational asthma. *J Allergy Clin Immunol*. 2009; 123: 545-550.
34. Arrandale VH, Liss GM, Tarlo SM, Pratt MD, Sasseeville D, Kudla L, et al. Occupational contact allergens: are they also associated with occupational asthma. *Am J Ind Med*. 2012; 55: 353-360.

35. Barnes PJ. Pathophysiology of asthma. *Eur Respir Mon.* 2003; 8: 84-113.
36. Moscato G, Dellabianca A, Maestrelli P, Paggiaro P, Romano C, De Zotti R, et al. Features and severity of occupational asthma upon diagnosis: an Italian multicentric case review. *Allergy.* 2002; 57: 236-242.
37. Le Moual N, Siroux V, Pin I, et al. Epidemiological study on the genetics and environment of asthma. Asthma severity and exposure to occupational asthmogens. *Am J Respir Crit Care Med.* 2005; 172: 440-445.
38. Nicholson PJ, Cullinan P, Burge PS, Boyle C. Occupational asthma: prevention, identification and management: systematic review and recommendations. London: British Occupational Health Research Foundation. 2010.
39. Lemiere C, Cartier A, Boulet L-P, Bernstein D. Occupational asthma: clinical features and diagnosis.
40. Beach J, Russel K, Blitz S, Hooton N, Spooner C, et al. A systematic review of the diagnosis of occupational asthma. *Chest.* 2007; 131: 569-578.
41. Jares EJ, Baena-Cagnani CE, Gomez RM. Diagnosis of occupational asthma: an update. *Curr Allergy Asthma Rep.* 2012; 12: 221-231.
42. Gannon PFG, Sherwood Burge P. Serial peak expiratory flow measurement in the diagnosis of occupational asthma. *Eur Respir J.* 1997; 24: 57-63.
43. Nemery B. Occupational asthma for the clinician. *Breath.* 2004; 1: 25-33.
44. Moore VC, Jaakkola M, Sherwood Burge P. A systematic review of serial peak expiratory flow measurements in the diagnosis of occupational asthma. *AoRM* 2009.
45. Minov J. Bolesti na belite drobovi i plevrata povrzani so profesionalnata ekspozicija [Lung and Pleural Diseases Related to Occupational Exposures, in Macedonian] Skopje: Pristop MK & Institut za medicina na trudot na R. Makedonija. 2009.
46. Oasys Research Group. Asking a patient for a serial peak flow record.
47. Beach J, Rowe b, Blitz S, Hooton N, Russell K, et al. Evidence Report/Technology Assessment No. 129. AHRQ Publication No. 06-E003-2. Rockville, MD: Agency for Healthcare Research and Quality, November. 2005.
48. Vandenplas O, Malo J-L. Inhalation challenge with agents causing occupational asthma. *Eur Respir J.* 1997; 10: 2612-2629.
49. Tarlo S, Rowe B, Liss GM, Catherine Lemiere, Jeremy Beach. Consensus on work-related asthma. *Occup Med.* 2009; 59: 213-215.
50. De Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwiers D, et al. Workplace interventions for treatment of occupational asthma. *Cochrane Database Syst Rev.* 2011; 5: 373-374.
51. Global Strategy for Asthma Management and Prevention: Revised. 2014.
52. Minov J, Karadzinska-Bislimovska J, Tutkun E, Vasilevska K, Stoleski S, et al. Clinical and functional outcomes of sensitizer-induced asthma in bakers and cotton workers after removal from exposure. *Arch Pulmonol Respir Care.* 2016; 2: 001-006.
53. Lin FJ, Dimich Ward H, Chan-Yeung M. Longitudinal decline in lung function in patients with occupational asthma due to western red cedar. *Occup environ Med.* 1996; 53: 753-756.
54. Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman Taylor A, et al. Outcome of occupational asthma after cessation of exposure: a systematic review. *Thorax.* 2007; 62: 147-152.
55. Cullinan P, Tarlo S, Nemery B. The prevention of occupational asthma. *Eur Respir J* 2003; 22: 853-860.
56. Heederik D, Henneberger PK, Redlich CA. Primary prevention: exposure reduction, skin exposure and respiratory protection. *Eur Respir Rev* 2012; 21: 112-124.
57. Seed M, Agius R. Further validation of computer-based prediction of chemical asthma hazard. *Occup Med* 2010; 60: 115-120.
58. Gautrin D, Infante-Rivard C, Dao TV, et al. Specific IgE-dependent sensitization, atopy, and bronchial hyperresponsiveness in apprentices starting exposure to protein-derived agents. *Am J Respir Crit Care Med.* 1997; 155:1841-1847.
59. Malo J-L, L'Archeveque J, Castellanos L, Lavoie K, Ghezzi H, et al. Long-term outcomes of acute irritant-induced asthma. *Am J Respir Crit Care Med.* 2009; 179: 923-928.
60. Brooks SM, Hammad Y, Richards I, Giovenco-Barbas J, Jenkins K, et al. The spectrum of irritant-induced asthma: sudden and not-so-sudden onset and the role of allergy. *Chest.* 1998; 113: 42-49.
61. Milby TH. Reactive Airway Dysfunction Syndrome & Irritant Induced Asthma.
62. Lemiere C, Malo J-L, Boulet M. Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment. *Eur Respir J* 1997; 10: 241-244.

63. Martin JG, Campbell HR, Iijima R, Gautrin D, Malo JL, et al. Chlorine-induced injury to the airways in mice. *Am J Respir Crit Care Med*. 2003 ; 168 : 568-574.
64. Prezant DJ, Weiden M, Banauch GI, McGuinness G, Rom WN, et al. Cough and bronchial responsiveness in firefighters at the World Trade Center site. *N Engl J Med*. 2002; 347: 806-815.
65. Tarlo SM. Irritant-induced asthma in the workplace. *Curr Allergy Asthma Rep*. 2014; 14 : 406.
66. Tarlo SM, Broder I. Irritant-induced asthma. *Chest*. 1989; 96: 297-300.
67. Alberts WM, do Pico GA. Reactive airways dysfunction syndrome. *Chest*. 1996; 109: 1618-1626.
68. Tarlo SM. Workplace respiratory irritants and asthma. *Occup Med* 2000; 15: 471-484.
69. Chatkin JM, Tarlo SM, Liss G, Banks D, Broder I, et al. The outcome of asthma related to workplace irritant exposure: a comparison of irritant-induced asthma and irritant-aggravated asthma. *Chest* 1999; 116: 1780-1785.
70. Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemi re C, et al. An Official American Thoracic Society Statement: Work-Exacerbated Asthma. *Am J Respir Crit Care Med* 2011; 184: 368-378.
71. Gautrin D, Ghezzi H, Infante-Rivard C, Malo JL. Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. *Eur Respir J* 2001; 17: 904.
72. Henneberger PK. Work-exacerbated asthma. *Curr Opin Allergy Clin Immunol*. 2007; 7 (2): 146-151.
73. Michel O, Olbrecht J, Moulard D, Sergysels R. Effect of anti-asthmatic drugs on the response on inhaled endotoxin. *Am Allergy Asthma Immunol*. 2000; 85: 305-310.
74. Girard F, Chaboillez S, Cartier A, C  t   J, Hargreave FE, et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med*. 2004; 170: 845-850.
75. Bradshaw L, Fishwick D. Work-aggravated asthma. A review of reviews.
76. Chiry S, Cartier A, Malo J-L, Susan M, Lemi re C, et al. Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. *Chest*. 2007; 132: 483-488.
77. Santos MS, Jung H, Peyrovi J, Lou W, Liss GM, et al. Occupational asthma and work-exacerbated asthma: factors associated with time to diagnostic step. *Chest*. 2007; 131: 1768-1775.
78. Lim T, Liss GM, Vernich L, Buyantseva L, Tarlo SM. Work-exacerbated asthma in a workers' compensation population. *Occup Med*. 2014; 64: 206-210.
79. Quirce S. Eosinophilic bronchitis in the workplace. *Curr Opin Allergy Clin Immunol*. 2004; 4: 87-91.
80. Krakowiak AM, Dudek W, Ruta U, Palczynski C. Occupational eosinophilic bronchitis without asthma due to chloramine exposure. *Occup Med*. 2005; 55: 396-398.
81. Burton C, Barber C. Occupational eosinophilic cough conditions.
82. Berry MA, Hargadon M, McKenna S, Shaw D, Green RH, et al. Observational study of the natural history of eosinophilic bronchitis. *Clin Exp Allergy*. 2005; 35: 598-601.