Clinical reviews in allergy and immunology

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Occupational asthma: Current concepts in pathogenesis, diagnosis, and management

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List of Design Committee Members: *Authors:* Mark S. Dykewicz, MD

Activity Objectives

1. To become familiar with the revised classification and nomenclature for occupational asthma (OA) outlined in recent consensus guidelines.
2. To review the various subtypes of respiratory illnesses categorized under the board heading of work-related asthma (WRA).
3. To review current theories of the pathogenesis and risk factors of WRA.
4. To provide evidence-based recommendations for diagnosis and management of OA.
5. To review prognostic indicators of OA.

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Occupational asthma (OA) may account for 25% or more of *de novo* adult asthma. The nomenclature has now better defined categories of OA caused by sensitizing agents and irritants, the latter best typified by the reactive airways dysfunction syndrome. Selecting the most appropriate diagnostic testing and management is driven by assessing whether a sensitizer is involved, and if so, identifying whether the sensitizing agent is a high-molecular-weight agent such as a protein or a low-molecular-weight reactive chemical such as an isocyanate. Increased understanding of the pathogenesis of OA from reactive chemical sensitizers is leading to development of better diagnostic testing and also an understanding of why testing for sensitization to such agents can be problematic. Risk factors for OA including possible genetic factors are being delineated better. Recently published guidelines for the diagnosis and management of occupational asthma are summarized; these reflect an increasingly robust evidence basis for recommendations. The utility of diagnostic tests for OA is being better defined by evidence, including sputum analysis performed in relation to work exposure with suspected sensitizers. Preventive and management approaches are reviewed. Longitudinal studies of patients with OA continue to show that timely removal from exposure leads to the best prognosis. (J Allergy Clin Immunol 2009;123:519-28.)

Key words: *Occupational asthma, irritant-induced asthma, sensitizer-induced asthma diagnosis, isocyanates, management, guidelines, RADS*

Several terms are now used to define subsets of patients with *work-related asthma* (WRA), a broad term that refers to asthma that is exacerbated or induced by inhalation exposures in the workplace. The nomenclature of work related asthma has been evolving, so medical literature and studies must be considered in that context. Occupational asthma (OA), a subset of WRA, has been the subject of a number of recently published reviews and guidelines.[1-7] As defined by the 2008 Guidelines of the American College of Chest Physicians (ACCP), WRA includes OA that refers to *de novo* asthma or the recurrence of previously quiescent asthma induced either (1) by sensitization to a workplace substance, termed s*ensitizer-induced OA*, or (2) by exposure to an

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Abbreviations used
ACCP: American College of Chest Physicians
ENO: Exhaled nitric oxide
HMW: High molecular weight
HSA: Human serum albumin
LMW: Low molecular weight
MSDS: Material Safety Data Sheet
OA: Occupational asthma
PEFR: Peak expiratory flow rate
RADS: Reactive airways dysfunction syndrome
SIC: Specific inhalation challenge
TDI: Toluene diisocyanate
TMA: Trimellitic anhydride
WEA: Work-exacerbated asthma
WRA: Work-related asthma

inhaled irritant at work, termed *irritant-induced OA*. Previously, OA was defined to refer only to sensitizer-induced OA. A distinct subset of WRA is work-exacerbated asthma (WEA), defined to be present in workers with pre-existing or concurrent asthma that is triggered by work-related factors (eg, aeroallergens, irritants, or exercise), but not considered to be OA. Estimates of the incidence and prevalence of OA vary. It has generally been accepted that at least 9% to 15% of adult asthma can be attributed to workplace exposures, although recent data indicate that 25% or more of *de novo* asthma may have an occupational basis.[1,2] WRA results in considerable morbidity to affected individuals, but also results in tremendous costs to society.[2] Failure to recognize OA in a timely fashion can lead to permanent respiratory impairment, underscoring the need for early diagnosis and intervention.

TYPES OF OA

Sensitizer-induced OA

Occupational asthma from sensitizers typically presents with a latent period of exposure, followed by the onset of clinical disease. After sensitization, airway reactions develop from levels of exposure to the sensitizing agent that were tolerated before sensitization. Although the mechanism causing OA from some sensitizers has been demonstrated to have an immunologic basis (IgE antibody–mediated or otherwise), no immunologic mechanism has been demonstrated for some suspected sensitizers (eg, colophony). OA sensitizers (Table I) may be categorized on the basis of their molecular weight. By convention, high-molecular-weight (HMW) sensitizers are >10 kd, with common examples being inhaled protein agents. HMW agents typically cause occupational asthma by IgE antibody–mediated mechanisms. Low-molecular-weight (LMW) sensitizers are often reactive chemicals that act as haptens in that they can only induce an adaptive immune response and be recognized as antigens after combining with self-proteins to form immunogenic conjugates after inhalation. Some LMW agents have been demonstrated to cause sensitization via IgE-mediated mechanisms, whereas have not. There are more than 250 reported workplace sensitizers.

Irritant-induced OA

Not previously considered a form of occupational asthma, *de novo* asthma caused by exposure to inhaled irritants at work now is commonly termed *irritant-induced OA*.[2]

The existence of the reactive airways dysfunction syndrome (RADS) resulting from a single episode of a high level exposure to an irritant agent (usually from an occupational accident) has long been recognized.[2,8] Examples of agents reported to cause RADS include chlorine gas, hydrochloric acid, anhydrous ammonia, hydrogen sulfide, fumigating fog, heated acids, and smoke by inhalation. In 1984, a toxic cloud of methyl isocyanate gas released from a chemical plant in Bhopal, India, killed thousands of people, and caused thousands more to develop persistent respiratory disease, some with reversible airway obstruction. After the collapse of the World Trade Center towers in New York City during the 2001 terrorist attacks, a complex mixture of airborne dusts and pollutants was elaborated that has been associated with RADS (and other respiratory disorders) in exposed rescue and recovery workers and residents of the surrounding area.[9]

The 2008 ACCP consensus guidelines retain use of the RADS term, but consider it to be a form of irritant-induced asthma.[2] By definition, the diagnosis of RADS can be made only when defined criteria are satisfied and should not be made in patients with pre-existing asthma (Table II). This leaves open another debate about how to define worsening of pre-existing asthma caused by inhalation of high levels of irritants or worsening of pre-existing smoking-related chronic obstructive pulmonary disease.

There is still controversy about whether chronic lower-level exposure to irritants can cause OA.[2,5] Repeated peak exposure to irritant gases in the pulp industry has been shown to increase the risk for both adult-onset asthma and wheezing.[10] There is also a report that asthma symptoms developed in 3 patients after repetitive exposure to irritants that occurred over several days to months.[11] According to the 2008 ACCP guidelines, cases that do not meet the stringent criteria for RADS (eg, when there is several-day lag before the onset of symptoms, or when there is no single massive exposure but rather repeated exposures over days or weeks, less massive exposures, or a shorter duration of symptoms) are all classified under the general category of irritant-induced asthma. Specific examples include meat wrapper's asthma, pot room asthma, asthma from professional cleaning materials, and asthma from exposure to ozone, endotoxin, formaldehyde, and quaternary ammonium compounds.

PATHOPHYSIOLOGY

Pathophysiology of sensitizer-induced OA

OA from HMW sensitizers. High-molecular-weight agents such as proteins and glycoproteins (Table I) characteristically act as complete antigens that cause sensitizer OA through a classic IgE antibody–mediated mechanism. The allergens responsible for OA from some HMW agents have been well characterized—for example, in detergent workers who develop asthma from exposure to *Bacillus subtilis* enzymes, or in egg processing workers. However, identifying the actual protein sensitizers in complex plant or animal materials can be problematic, confounding studies about the pathogenesis of OA and development of appropriate agents for diagnostic testing. For example, baker's asthma caused by wheat inhalation typically does not occur because of sensitization to wheat ω-5 gliadin [Tri a 19], an allergen commonly important for wheat allergy from oral ingestion such as food allergy in children or wheat-dependent exercise-induced anaphylaxis. Instead, baker's asthma may be caused by an increasingly recognized number of other allergens present in wheat flour (eg, α-amylase inhibitors, thioredoxins cross-reactive with grass allergens, a wheat lipid transfer protein, Tri a 14, a wheat serine proteinase inhibitor, and baking additives such as fungal α-amylase