Occupational asthma: Pathogenesis

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INTRODUCTION

The label "asthma in the workplace" encompasses several entities: (1) asthma exacerbated at work by various environmental conditions; (2) occupational asthma; and (3) variants (eg, eosinophilic bronchitis) [1]. Occupational asthma is a disease characterized by variable airflow limitation, airway hyperresponsiveness, and inflammation resulting from an inciting agent only found in the workplace [2].

The pathogenesis and pathology of occupational asthma will be reviewed here. Issues related to other aspects of occupational asthma are discussed separately. (See "Occupational asthma: Definitions, epidemiology, causes, and risk factors" and "Occupational asthma: Clinical features, evaluation, and diagnosis" and "Reactive airways dysfunction syndrome and irritant-induced asthma".)

TYPES

Two main types of occupational asthma have been recognized [1,3]:

- Immunologically mediated. This type includes IgE and nonIgE-mediated responses following chronic exposure and respiratory sensitization to high or low molecular weight agents.

- Nonimmunologic, irritant-mediated, also called irritant-induced asthma. This type includes reactive airways dysfunction syndrome (RADS) caused by a single high level exposure to an irritant, irritant-induced asthma caused by multiple high level exposures to an irritant, and possibly asthma caused by chronic lower level of exposure, although the latter is controversial. (See "Reactive airways dysfunction syndrome and irritant-induced asthma".)
Some occupational agents, such as diisocyanates, may induce asthma through more than one mechanism. As an example, asthma may develop in subjects after a diisocyanate spill by causing acute airway injury and reactive airways dysfunction syndrome (RADS), while in others, respiratory sensitization to diisocyanate develops with lower levels of exposure. Exposure to high levels of diisocyanates causing irritant-induced occupational asthma can also promote the development of immunologic occupational asthma caused by diisocyanates. (See "Reactive airways dysfunction syndrome and irritant-induced asthma").

The various types of occupational asthma may include different phenotypes or endotypes [4]. As an example, in an analysis of 187 patients with diisocyanate asthma, different clusters were populated, similar to common asthma, with the largest cluster including the youngest patients with the shortest duration of exposure to the sensitizers, while another cluster included older male patients with worse lung function and longer occupational exposure [5]. This suggests that occupational asthma (as probably many others) is phenotypically heterogeneous. More research should be done to characterize the phenotypes/endotypes of occupational asthma.

This variation in features among patients with occupational asthma is supported by an international study of 1167 subjects with occupational asthma to high (n = 544) and low (n = 623) molecular weight agents, confirmed by specific inhalation challenges [6]. Multivariate logistic regression analysis showed significant associations between occupational asthma caused by high molecular weight agents and work-related rhinitis, conjunctivitis, atopy, and early asthmatic reactions. By contrast, occupational asthma to low molecular agents was associated with chest tightness at work, daily sputum production, and late asthmatic reactions. Although assessed in a lower proportion of subjects, baseline sputum inflammatory profiles were similar in the two groups, but occupational asthma caused by high molecular weight agents showed higher baseline blood eosinophils and a greater postchallenge increase in fractional nitric oxide. Postchallenge, a higher proportion of subjects with occupational asthma to high molecular weight agents showed a switch from a paucigranulocytic to an eosinophilic pattern in their sputum.

**PATHOLOGY**

In the case of immunologically mediated occupational asthma, the pathology in the airways at the time of exposure is similar to that seen in patients with nonoccupational asthma (see "Pathogenesis of asthma", section on 'Airway inflammation'). Nonimmunologic irritant mediated occupational asthma is discussed elsewhere. (See "Reactive airways dysfunction syndrome and irritant-induced asthma").

The pathologic abnormalities associated with occupational asthma persist for weeks to years after cessation of exposure. One study examined the bronchial biopsies of 18 subjects with occupational asthma after cessation of exposure for a period of 3 to 24 weeks [7]. Eleven subjects had disease due to exposure to high molecular weight compounds, and seven to low molecular
weight (LMW) compounds. Extensive epithelial desquamation, epithelial cell ciliary abnormalities, smooth muscle hyperplasia, and subepithelial fibrosis were found, and the numbers of total inflammatory cells, eosinophils, and lymphocytes were increased compared to healthy controls (picture 1). Similar findings were described in reports of subjects with isocyanate- and Western red cedar-related asthma [8,9]. Animal models have suggested that profibrotic cytokines such as interleukin (IL)-13, can be involved in these changes although a direct toxicity of some agents against epithelial cells can be involved in the remodelling process [10,11].

Subjects with isocyanate-induced asthma show a reduction in subepithelial fibrosis, but inflammatory cell infiltration of the airways after removal from exposure can persist for a period ranging from 5 to 21 months [12]. The course of airway hyperresponsiveness parallels that of airway inflammation, suggesting that airway inflammation contributes to the persistence of hyperresponsiveness. It is possible that inflammatory and remodeling airway changes precede the development of clinical features of occupational asthma, as shown in asthma induced by common allergens, but this remains to be further documented [13].

Persistent airway inflammation and remodeling exists even in subjects whose occupational asthma is presumed to be cured. In an observational study, 133 subjects with occupational asthma were evaluated at a mean of nine years after cessation of the exposure [14]. Among those from whom induced sputum was obtained (n = 84), eosinophils were increased (≥2 percent) in 18 percent, including 3 of the 20 subjects who were considered cured, based on resolution of symptoms, no need for respiratory medication, normal airway caliber, and nonallergic airway responsiveness. Neutrophils were increased (≥61 percent of cells in induced sputum) in 45 percent (including nine of those considered cured). Furthermore, 10 of the subjects considered cured, who had no evidence of bronchial eosinophilia on induced sputum, underwent bronchoscopy with bronchial biopsies at a mean of 14 years after cessation of exposure. Compared to controls, subjects with prior occupational asthma had more transforming growth factor (TGF)-beta1 and eosinophil cationic protein (ECP) positive cells, increased subepithelial fibrosis, and decreased distance between the epithelium and airway smooth muscle [15]. These findings suggest that permanent inflammatory and structural changes persist many years after stopping exposure to a respiratory sensitizer. The reason for the persistence of eosinophilic inflammatory changes many years after stopping exposure is unknown.

Acute changes in the airways of subjects with reactive airways dysfunction syndrome (RADS) or irritant-induced asthma consist of rapid denudation of the mucosa with fibrinohemorrhagic exudate and swelling in the submucosa (picture 2) [16]. This is followed by regeneration of the epithelium with proliferation of basal and parabasal cells and persistent subepithelial edema [16]. Similar findings have been described in an animal model of RADS due to chlorine exposure [17,18]. Furthermore, bronchial biopsies from subjects with persistent asthma symptoms two years following chlorine-induced RADS show a thickened basement membrane with reticulocollagenic fibrosis of the bronchial wall (picture 3) [19]. In irritant-induced asthma due to multiple exposures...
to an irritant, an inflammatory infiltrate with eosinophils and lymphocytes is found, as well as diffuse deposition with collagen fibers [20]. Even many years after the inhalational accident, induced sputum can show increased levels of mediators involved in inflammation and airway remodeling [21]. (See "Reactive airways dysfunction syndrome and irritant-induced asthma").

Evidence of eosinophilic and neutrophilic inflammation and also airway remodeling can persist for several years following acute irritant-induced asthma. Ten subjects with irritant-induced asthma (mean interval of 10.9 years, minimum of 4 years, since the inhalational accident) underwent bronchoscopy followed by bronchoalveolar lavage and bronchial biopsies [22]. The most significant difference in tissue morphometry was the increase in basement membrane thickness in subjects with irritant-induced asthma compared with the healthy controls and subjects with mild asthma. The detachment of epithelium was increased in subjects with irritant-induced asthma, although not significantly so. Also, the number of TGF-beta1 positive cells and ECP positive cells was increased by comparison with normal controls and comparable to subjects with common asthma. Finally, the levels of cells (neutrophils and eosinophils) and of several mediators that reflect an inflammatory and remodeling effect were significantly higher in the bronchoalveolar lavage than in normal controls and comparable or even higher than in subjects with common asthma.

**GENETICS**

Genetic loci associated with non-occupational asthma have been investigated as susceptibility markers for occupational asthma, primarily in workers with diisocyanate asthma [3]:

- Innate immunity and immunoregulation
- Th2-cell differentiation
- Epithelial biology and mucosal immunity
- Lung function (airway hyperresponsiveness), airway remodeling, and disease severity

The human leukocyte antigen (HLA) system, which is synonymous with the major histocompatibility complex (MHC), encodes a variety of cell surface markers, antigen-presenting molecules, and other proteins involved in immune function. Studies of genes involved in immunoregulation have shown associations between HLA Class II antigens and various types of occupational asthma [23]. Several examples of HLA associates (eg, DR3, DQ5, DQA1, DQB1, DR1) have been described in the case of workers exposed to diisocyanates, Western red cedar, platinum salts, laboratory animals, and anhydrides [24]. In a study of 140 diisocyanate-exposed workers, diisocyanate asthma was associated with HLA Class I (HLA-B and HLA-E) and Class II single nucleotide polymorphisms (SNPs), not identified in prior studies [25]. The associations with HLA antigens have biological implications in that they provide evidence for a specific immunological response and for T cell involvement in the development of occupational asthma caused by low molecular weight compounds.
Several studies support a role for antioxidant genes, such as the glutathione S-transferases (e.g., GSTP1 and GSTM1) and N-acetyltransferase (NAT1, NAT2), in the development of occupational asthma \[25,26\]. As examples:

- Glutathione S-transferases belong to a family of enzymes that detoxify chemical substances in the body. The GSTM1 null genotype is associated with an approximately two-fold increased risk of diisocyanate-induced asthma \[27\]. In addition, GSTM1 null and GSTM3 AA genotypes are significantly related to late asthmatic reactions induced by diisocyanates \[27\]. On the other hand, homozygosity for the GSTP1*Val allele may provide a protective effect against asthma in workers exposed to isocyanate \[3,27\].

- NAT1 also helps to metabolize drugs and chemicals. The slow acetylator genotype increases the risk of asthma in workers exposed to toluene diisocyanate (TDI) \[3,28\]. NAT2 SNPs and SNP combinations have been associated with a higher likelihood of diisocyanate asthma \[28,29\].

- Genetic variants in manganese superoxide dismutase (SOD2) and microsomal epoxide hydrolase (EPHX1) and their interactions may contribute to development of diisocyanate asthma \[30\].

Associations have also been found for other genes (e.g., toll-like receptors, IL-4 receptor, IL-13, CD14, neurokinin 2 receptor, alpha-catenin) in patients with occupational asthma due to diisocyanates \[31-33\]. An association between diisocyanate asthma and two linked alpha-catenin gene variants was identified by GWAS and confirmed in a second worker population \[34,35\]. In addition, genetic variations in tumor necrosis factor (TNF)-alpha, transforming growth factor (TGF)-beta1, prostaglandin-endoperoxide synthase (PTGS) 1, and PTGS2 are associated with diisocyanate asthma susceptibility \[36\].

Work-related exposure to occupational chemicals could result in epigenetic modification of specific genes associated with airway inflammation. The interferon (IFN)-gamma gene promoter region was significantly hyper-methylated in a study of workers with diisocyanate asthma in comparison to asymptomatic workers, suggesting that epigenetic effects could play an important mechanistic role \[37\].

Gene-environment interactions are difficult to study in the workplace. A cross-sectional study performed in laboratory animal workers demonstrated that those workers with high endotoxin exposure and a known CD14 endotoxin responsive genotype had significantly lower forced expiratory volume in one second (FEV\(_1\)), suggesting that workers with the latter genotype are at greatest risk \[38\].

An unbiased genome wide association study followed by next generation sequencing of workers with diisocyanate asthma identified five disease-associated variants (proximal to ATF3, cadherin...
17, FAM71A, and TACR1 genes) with gene regulatory effects [39]. Such an approach could help elucidate novel pathogenic mechanisms in the future.

**IMMUNOLOGIC MECHANISMS**

Agents that induce occupational asthma by immunologic mechanisms are characterized by a latency period between exposure and the development of symptoms. Immunologic occupational asthma affects only a small proportion of exposed subjects, but in these patients exposure to a minute quantity of the offending agent can lead to a severe asthmatic reaction. While some compounds, mostly metal salts and those containing protein, induce asthma through the production of specific IgE antibodies, the immunologic mechanism(s) that pertain to other agents (most chemicals) have not been identified.

Specific IgE-mediated responses to work-place sensitizers are considered to be involved in the majority of cases of occupational asthma, particularly when caused by high-molecular-weight agents [40]. Low molecular weight agents are, however, more likely to cause non-IgE-mediated disease. In this regard, bronchial biopsies obtained after inhalation challenge with diisocyanates did not reveal an expression of messenger RNA for IgE ε (epsilon) chains or interleukin (IL)-4, suggesting that IgE is not usually involved in this type of OA [41].

T lymphocytes appear to play a major role in the pathophysiology of occupational asthma. When causative agents are inhaled, antigen-presenting cells collect and process the antigen, and then migrate to regional lymph nodes where the antigen is presented to T helper cells, which are responsible for the initiation of the immune response. In a series of nonsmoking patients with occupational asthma, a triple-color immunohistofluorescence labelling technique was used on cryosections of bronchial samples to demonstrate a significantly increased bronchial density of regulatory T cells, effector T cells, proliferative T cells, and activated CD8+ T cells [42]. (See "The adaptive cellular immune response: T cells and cytokines".)

The most common route of exposure in occupational asthma is inhalational. However, skin exposure has also been incriminated in the onset of sensitization to diisocyanates [43].

**IgE-mediated** — High molecular weight (HMW) agents (eg, latex, animal proteins, and flour) act as complete antigens and induce the production of specific IgE antibodies. Certain low molecular weight (LMW) occupational agents, including platinum salts, trimellitic anhydride, and other acid anhydrides, can also induce specific IgE antibodies, probably by acting as haptens and binding with proteins to form functional antigens (table 1). Several human leukocyte antigen (HLA) associations have been described, but the results have not been convincingly reproduced [23].

Regardless of the characteristics of the inciting antigen, reactions between specific IgE antibodies and antigens lead to a cascade of events that results in an influx of inflammatory cells into the airway and the release of inflammatory mediators.
Inhalational challenge with culprit antigens in sensitized individuals generally results in an isolated early reaction, although inhalation challenge may sometimes result in a late reaction or a biphasic reaction (figure 1) [44,45]:

- An isolated early asthmatic reaction occurs within a few minutes after an inhalation challenge, reaches its maximum within one-half hour, and subsides within 1 to 1.5 hours.

- A late reaction occurs four to six hours after a challenge, reaches maximal intensity within eight to ten hours, and subsides after 24 to 48 hours.

- A biphasic reaction is a combination of an early and a late reaction.

Specific inhalation challenges can also cause atypical temporal patterns of airflow limitation [45]. Although occupational asthma due to high-molecular-weight agents is frequently if not always associated with increased levels of serum specific IgE antibodies, this test alone should not be considered as confirming the disease. Confirming the effect of exposure to the agent on airway function should always be recommended for diagnostic purposes [46].

**Detection of IgE** — The ability to detect specific IgE antibodies in patients with occupational asthma to low molecular weight agents may be technically difficult [47,48]. Specific IgE antibodies to toluene diisocyanate (TDI) have been reported in 0 to 50 percent of workers with TDI induced asthma [49]. This variation has been attributed to several factors:

- The short half-life of the specific IgE antibodies to TDI of about two days [50].

- The appearance of new antigenic determinants after the binding of specific IgE to TDI-human albumin conjugate [51].

- Use of different carrier proteins. As an example, human serum albumin is sometimes used for conjugation with TDI, while keratin, which is found in the lungs and skin, has been found to conjugate with hexamethylene diisocyanate in studies using human epithelial cell lines and endobronchial biopsy samples [52]. Whether the TDI-keratin conjugate would give a higher proportion of specific IgE antibodies in patients with TDI induced asthma remains to be seen.

- The different methods of conjugation of the haptenic low molecular weight antigen with a carrier and the methods of assay [52].

- Pathogenic mechanisms other than IgE mediation are causing occupational asthma. (See 'Non-IgE mediated reactions' below.)

Workers with the AA genotype of the 46 A>G polymorphism of the beta 2-adrenergic receptor gene (ADRB2) who were exposed to TDI had significantly higher serum levels of TDI-albumin-specific IgE than those with GG genotype, suggesting that ADRB2 polymorphism may affect IgE-specific sensitization to TDI [53].
Non-IgE mediated reactions — Many LMW agents can induce occupational asthma after a latent period (e.g., acid anhydrides, certain metals, diisocyanates), suggestive of immunologic mediation. Some LMW agents produce pathogenic IgE via conjugation with a hapten (see 'IgE-mediated' above). However, many LMW agents are NOT associated with production of specific IgE. The exact nature of the non-IgE immunologic mechanisms remains unclear.

The ability of a LMW agent to induce asthma may depend upon its chemical structure [54,55]. As examples, certain transitional metals form coordination complexes that may chelate human proteins (e.g., chromium, cobalt, nickel, platinum), and some organic substances have two or more reactive chemical groups (e.g., amines, cyanates) that are highly reactive with human macromolecules. The agents with two or more reactive chemical groups, also known as bifunctional bases, (e.g. diisocyanate) have a much higher propensity to induce asthma than those with a single reactive group, also known as a monofunctional base (e.g., monoisocyanates) [55].

Evidence against IgE mediation — Evidence against IgE mediation in occupational asthma induced by LMW agents includes the following observations: affected workers are typically nonatopic, the pattern of airflow limitation following inhalational challenge is different from that of IgE-mediated occupational asthma, and the IgE molecules identified lack the ability to cause passive sensitization.

Specific inhalation challenge tests with LMW agents generally induce an isolated late asthmatic reaction or a biphasic reaction, rather than the predominantly early reaction of IgE-mediated occupational asthma [45]. Atypical reactions are often observed with LMW agents (figure 2): a progressive type with onset during or minutes after exposure, progressing to a maximum reaction five to six hours later, a continuous asthmatic reaction with no remission between the early and the late phases (square-waved), and a prolonged immediate reaction. (See "Bronchoprovocation testing", section on 'Antigen challenge'.)

Patients with occupational asthma due to non-IgE mediated reactions may produce IgE antibodies that are reflective of prior exposure, rather than being integral to disease pathogenesis. As an example, Western red cedar-related asthma, caused by sensitization to the LMW agent plicatic acid, results in production of IgE antibodies to plicatic acid in approximately 20 percent of affected subjects [56]. However, these antibodies do not passively sensitize human lung fragments [56,57]. Based on the high proportion of patients without evidence of specific IgE production and the lack of passive sensitization, it is likely that non-IgE mechanisms are responsible for the majority of plicatic acid-induced occupational asthma.

In contrast, among workers with suspected diisocyanate-induced asthma, having a higher level of specific IgE to diisocyanates is highly specific for identifying those affected with occupational asthma as confirmed by specific inhalation challenges [50].
Evidence for cell mediated responses — Most studies have found that cellular mediated immunological mechanisms contribute to the pathogenesis of non-IgE mediated immunologic (low molecular weight antigen) occupational asthma. Bronchial biopsies from subjects with diisocyanate and red cedar-related asthma show large numbers of activated T lymphocytes adjacent to bronchi, suggesting that these cells play a direct role in mediating airway inflammation [8, 9].

Diisocyanate-induced asthma, a non-IgE mediated disease in most instances, appears to be associated with increased recruitment and activation of pulmonary lymphocytes:

- Monocyte chemoattractant protein-1, a T cell chemoattractant, is elaborated in increased amounts by peripheral blood mononuclear cells from patients with occupational asthma due to diisocyanates [58]. Among workers exposed to diisocyanate, production of monocyte chemoattractant protein-1 (MCP-1) by peripheral blood mononuclear cells in response to stimulation with diisocyanate-human serum albumin (DIISO-HSA) was more sensitive and specific for diisocyanate-induced asthma than serum levels of specific IgE [58].

- When bronchial biopsy specimens were obtained by fiberoptic bronchoscopy 24 hours after diisocyanate inhalational challenge, bronchial recruitment of IL-5, CD25 (soluble IL-2 receptor), and CD4 positive cells was noted in patients with diisocyanate-induced asthma [41].

- In contrast to most studies that suggest mediation by CD4 T cells, one study of bronchial biopsies from patients with diisocyanate-induced asthma found that the majority of T cells exhibited the CD8 phenotype and produced IFN-gamma and IL-5, with very few clones producing IL-4 [59]. However, there was evidence of an eosinophilic involvement.

- In another study, bronchial biopsies of workers with occupational asthma to methylene diphenyl diisocyanate (MDI) demonstrated an increase in eosinophil cationic protein and increased basophil release of histamine [60]. Sputum eosinophil counts correlated with IL-8 and MMP-9 levels.

Other evidence that T lymphocytes play a role in occupational asthma induced by LMW compounds comes from studies of peripheral blood cells obtained from patients with occupational asthma due to various LMW agents.

- In patients with asthma associated with Western red cedar, nickel, or cobalt, proliferation of peripheral blood lymphocytes occurs following incubation with the appropriate antigen, suggesting the presence of a cell-mediated hypersensitivity reaction [61, 62].

- In diisocyanate-induced asthma, CD8-positive T lymphocytes and eosinophils are increased in the peripheral blood of subjects during late asthmatic reactions induced by challenge with the agent [63].
Specific IgG antibodies — Exposure to occupational allergens can induce specific IgG responses, and specific IgG antibodies may play a role in low molecular weight agent-induced occupational asthma, although their exact role is unknown. As an example, specific IgG antibodies have been identified in patients with occupational asthma due to diisocyanates [58]. However, they may represent an immunological response to current or past exposure and may not be directly related to the pathogenic mechanisms in diisocyanate-induced asthma [65].

Animal models — Animal models have been developed to examine the physiopathology of immunologic occupational asthma [66]. Unique effector mechanisms may exist for different antigens or types of antigens (haptens versus protein antigens) [67]. The species, strain, age, dose of allergen, and routes of sensitization and challenge may influence the model. Effector mechanisms may also differ depending on the asthmatic reaction being considered (ie, airway obstruction or eosinophil infiltration).

Data from animal models support a role for Th2 lymphocytes and their cytokines in some forms of occupational asthma [68,69]. As an example, T regulator lymphocytes (Tregs) isolated from TDI-sensitized mice, were significantly more suppressive than those from nonsensitized controls, supporting a role for Tregs in TDI sensitization [70]. When Tregs were depleted before sensitization, the sensitization response was enhanced.

NONIMMUNOLOGIC MECHANISMS

Agents that induce asthma by nonimmunologic mechanisms are characterized by the absence of a latency period. Three mechanisms may explain the development of symptoms in these patients:

- Subjects without any prior respiratory difficulties develop symptoms of asthma within a few hours of acute, high level irritant exposure, and may have evidence of nonspecific airway hyperresponsiveness for more than three months. Acute airway injury from accidental exposure to high dose of irritants such as chlorine, ammonia, smoke, or acetic acid may lead to reactive airways dysfunction syndrome (RADS). Furthermore, the development of irritant-induced asthma due to diisocyanates may promote sensitization to these compounds [71,72]. (See "Reactive airways dysfunction syndrome and irritant-induced asthma".)

The underlying mechanism of RADS is not known, but it has been postulated that extensive denudation of the epithelium results in airway inflammation because of a loss of epithelial derived relaxing factors, exposure of the nerve endings leading to neurogenic inflammation, and nonspecific activation of mast cells with release of inflammatory mediators and cytokines.
Epithelial damage may also result in the marked airway remodeling observed in these patients, particularly the intense subepithelial fibrosis which is probably responsible for the reduced reversibility of airflow obstruction observed in this condition [19].

• Some low molecular weight agents have pharmacologic properties that may cause bronchoconstriction. As examples, diisocyanates may block beta-2 adrenergic receptors, and plicatic acid in high concentrations may activate complement [71,74].

• Diisocyanates and other occupational agents may stimulate sensory nerves to release substance P and other neuropeptides and may inhibit the neutral endopeptidases that normally inactivate these substances [75]. Neuropeptides affect a variety of cells in the airways, resulting in cough, smooth muscle contraction, and mucus production [76].

The role of long-term irritant exposure at work in the development of asthma remains to be elucidated, but some observations suggest an effect of such exposure in work-related asthma. The proposed underlying mechanisms include oxidative stress, neurogenic inflammation, and dual irritant and adjuvant effects [77].

In regard to occupational asthma induced by exposure to laboratory animals, exposure to endotoxins is associated with a higher prevalence of wheezing, but not with asthma, as assessed with mannitol challenge or self-reported asthma [78].

Some agents can induce asthma through both immunological and nonimmunological mechanisms. Diisocyanate is the best example. Toluene diisocyanate-induced asthma (through sensitization) has been reported in individuals who have previously been heavily exposed during a chemical spill [72,79]. While the immune system plays an important role in occupational asthma, inflammation may be a secondary response rather than the underlying cause of pathogenesis. Multiple mechanisms involving airway epithelial injury and repair, structural remodeling, oxidative stress, and neurogenic factors may also contribute to the pathogenesis [65].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Occupational asthma".)

SUMMARY

• Occupational asthma is a disease characterized by variable airflow limitation, airway hyperresponsiveness, and inflammation resulting from exposures to agents present in the workplace. (See 'Introduction' above.)
Two main types of occupational asthma have been recognized: immunologically mediated (with or without evidence of participation of IgE), and nonimmunologic, irritant mediated. (See 'Types' above.)

In the case of immunologically mediated occupational asthma, the pathology in the airways is similar to that seen in patients with nonoccupational asthma. The pathologic changes may persist for weeks to years after cessation of exposure. For nonimmunological occupational asthma, there is a predominance of denudation of epithelium in the acute phase with a long-term increase in basement membrane thickness. (See 'Pathology' above.)

High molecular weight agents (eg, animal proteins and flour) act as complete antigens and induce the production of specific IgE antibodies, which are felt to play a key role in disease pathogenesis, similar to that of common inhalant allergens (eg, dust mite) in allergic asthma. (See 'Immunologic mechanisms' above.)

Certain low molecular weight occupational agents, including platinum salts, trimellitic anhydride, and other acid anhydrides, also induce specific IgE antibodies, probably by acting as haptens, binding with proteins to form functional antigens. Most low molecular weight agents may also cause occupational asthma through non-IgE mediated mechanisms. (See 'Immunologic mechanisms' above.)

Occupational asthma due to exposure to irritants (eg, chlorine, ammonia, smoke) may result from nonimmunologic mechanisms such as denudation of the airway epithelium, direct beta-2 adrenergic receptor inhibition, or elaboration of substance P by injured sensory nerves. Nonimmunologic occupational asthma is characterized by the absence of a latency period and by exposure to a high level of the irritant agent. (See 'Nonimmunologic mechanisms' above and "Reactive airways dysfunction syndrome and irritant-induced asthma".)


74. Chan-Yeung M, Giclas PC, Henson PM. Activation of complement by plicatic acid, the chemical compound responsible for asthma due to western red cedar (Thuja plicata). J Allergy Clin Immunol 1980; 65:333.


Bronchial biopsy of a patient with occupational asthma after removal from exposure, showing partial desquamation of the epithelium, thickened basement membrane, and some cellular infiltration.

*Courtesy of Lemiere, C, Malo, JL, Boulet, M.*

Graphic 60266 Version 1.0

**Normal lung**

Low power photomicrograph of normal lung tissue shows open alveoli with thin, capillary-containing interstitial spaces. An artery (A) is identifiable by its thick, muscular wall; the accompanying bronchus (B) contains mucoid material and is lined by columnar respiratory epithelial cells.

*Courtesy of Steven E Weinberger, MD.*

Graphic 54820 Version 1.0
Irritant-induced asthma

Bronchial biopsy taken three days after acute accidental inhalation of high concentration of chlorine showing almost complete desquamation of bronchial mucosa (upper part) with fibrinohemorrhagic deposits (dark pink) and inflammatory influx of neutrophils (dark purple spots in the middle and upper portions). Normal smooth muscle is shown in the lower portion. Weigert-Masson stain.

_Courtesy of Lemiere, C, Malo, JL, Boulet, M._

Graphic 53602 Version 1.0

Normal lung

Low power photomicrograph of normal lung tissue shows open alveoli with thin, capillary-containing interstitial spaces. An artery (A) is identifiable by its thick, muscular wall; the accompanying bronchus (B) contains mucoid material and is lined by columnar respiratory epithelial cells.

_Courtesy of Steven E Weinberger, MD._

Graphic 54820 Version 1.0
Irritant-induced asthma

Bronchial biopsy taken two years after an acute accidental inhalation of chlorine showing severe desquamation of epithelial cells. Smooth muscle cells are surrounded by reticulocollagenic fibrous tissue seen in the center part of the figure. Weigert-Masson trichrome stain.

*Courtesy of Lemiére, C, Malo, JL, Boulet, M.*

Normal lung

Low power photomicrograph of normal lung tissue shows open alveoli with thin, capillary-containing interstitial spaces. An artery (A) is identifiable by its thick, muscular wall; the accompanying bronchus (B) contains mucoid material and is lined by columnar respiratory epithelial cells.

*Courtesy of Steven E Weinberger, MD.*
### Major causes of occupational asthma and rhinitis

<table>
<thead>
<tr>
<th>Low molecular weight chemicals</th>
<th>Occupation at risk</th>
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<tbody>
<tr>
<td>Isocyanates (eg, toluene diisocyanate, diphenylmethane diisocyanate, hexamethylene diisocyanate)</td>
<td>Polyurethane workers, roofers, insulators, painters</td>
</tr>
<tr>
<td>Anhydrides (eg, trimellitic anhydride, phthalic anhydride)</td>
<td>Manufacturers of paint, plastics, epoxy resins</td>
</tr>
<tr>
<td>Metals (eg, chromic acid, potassium dichromate, nickel sulfate, vanadium, platinum salts)</td>
<td>Platers, welders, metal and chemical workers</td>
</tr>
<tr>
<td>Drugs (eg, beta-lactam agents, opiates, other)</td>
<td>Pharmaceutical workers, farm workers, health professionals</td>
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<tr>
<td>Wood dust (eg, Western red cedar, maple, oak, exotic woods)</td>
<td>Carpenters, woodworkers</td>
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<tr>
<td>Dyes and bleaches (eg, anthraquinone, carmine, henna extract, persulfate, reactive dyes)</td>
<td>Fabric and fur dyers, hairdressers</td>
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<tr>
<td>Amines (eg, chloramine, quaternary amines)</td>
<td>Chemists, cleaners, plastic manufacturers</td>
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<tr>
<td>Glues and resins (eg, acrylates, epoxy)</td>
<td>Plastic manufacturers</td>
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<tr>
<td>Miscellaneous (eg, formaldehyde, glutaraldehyde, ethylene oxide, pyrethrin, polyvinyl chloride vapor)</td>
<td>Laboratory workers, textile workers, paint sprayers, health professionals</td>
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<th>High molecular weight organic materials</th>
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<tr>
<td>Animal proteins (eg, domestic and laboratory animals, fish and seafood)</td>
<td>Farmers, veterinarians, poultry processors, fish and seafood processors</td>
</tr>
<tr>
<td>Flours and cereals</td>
<td>Bakers, food processors, dock workers</td>
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<tr>
<td>Enzymes (eg, pancreatic extracts, papain, trypsin, <em>Bacillus subtilis</em>, bromelain, pectinase, amylase, lipase)</td>
<td>Bakers, food processors, pharmaceutical workers, plastic workers, detergent manufacturers</td>
</tr>
<tr>
<td>Plant proteins (eg, wheat, grain dust, coffee beans, tobacco dust, cotton, tea, latex, psyllium, various flours)</td>
<td>Bakers, farmers, food and plant processors, health professionals, textile workers</td>
</tr>
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Inhalation challenge testing

Types of specific asthmatic reactions after specific inhalation challenge testing: immediate, early late, isolated late, and dual (immediate and late). Mean and standard deviation of percent change in FEV1 (ordinate) are shown as a function of time (abscissa) from the challenge test.


Graphic 56482 Version 1.0
Inhalation challenge testing

Atypical asthmatic reactions after specific inhalation challenge testing.


Graphic 65163 Version 1.0
Contributor Disclosures

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Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy