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93

OCCUPATIONAL LUNG DISEASE

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Occupational lung diseases include a wide spectrum of respiratory disorders with symptoms, signs, and diagnostic test results that often present with features similar to nonoccupational diseases (Table 93-1). For example, adult-onset asthma (Chapter 87) may be occupational asthma, presumed sarcoidosis (Chapter 95) may actually be chronic beryllium disease, apparent idiopathic pulmonary fibrosis may be asbestosis, or a suspected viral pneumonia (Chapter 97) may be hypersensitivity pneumonitis from an occupational cause such as contaminated metal-working fluid.

When evaluating any respiratory disease, the clinician should consider the possibility of an occupational cause or contribution (see E-Fig. 18-1 in Chapter 18; see Table 93-1). The onset of disease after an occupational exposure may occur with a short latency period, as for an acute toxic inhalation injury, or over a period of months to years, as for occupational asthma or hypersensitivity pneumonitis. Latency can be 20 years or more in chronic beryllium disease or lung cancer from chromium, asbestos, or other carcinogens. The most relevant job and occupational exposure history will therefore depend in part on the type of lung disease: for acute syndromes, the recent job exposure is most relevant; for asthma or hypersensitivity pneumonitis, the exposures at the onset of symptoms and ongoing exposures are most relevant; but for chronic diseases or diseases that may result from a long latency exposure, a full working history is essential. Consideration also should be given to potentially relevant exposures that may be related to a patient's hobbies or avocations (e.g., woodworking, model building, or insect collecting).

The clinical relevance of a correct occupational attribution is most apparent for diseases with a close temporal relationship between exposure and the onset of symptoms because intervention to reduce or remove exposure may reverse the disease or prevent progression. In addition, interventions in the workplace may reduce or prevent disease in other workers. However, even for diseases with a potential long latency, such as chronic beryllium disease, identification of disease in one worker should be regarded as a sentinel event that can lead to investigation of the workplace exposures and introduction of preventive measures. With the assistance of their physicians, workers with occupational lung diseases also often can qualify for workers' compensation.

EPIDEMIOLOGY

No reliable figures exist for the total incidence or prevalence of occupational lung diseases, and regional variation in occupations and exposures is substantial. Work-related asthma has become the most common chronic occupational lung disease in developed countries, where occupational asthma (asthma caused by work) accounts for about 15% of all adult-onset asthma, and work-exacerbated asthma occurs in 25 to 52% of asthmatic workers. The occupational contribution of workplace dusts, fumes, and gases to chronic obstructive pulmonary disease (COPD) is estimated at 15%.

In contrast, pneumoconiosis from silica or coal dust, although still important in developing countries, is declining in incidence in developed countries (E-Fig. 93-1) as a result of occupational hygiene measures. For example, approximately 100,000 Americans received benefits from the Federal Black Lung Program in 2005, compared with about 500,000 in 1980, and the percentage of coal miners with pneumoconiosis has fallen from 11% in the mid-1970s down to 3%. However, newer exposures that lead to silicosis include the textile industry's use of jet silica blasting of denim jeans, reported from Turkey. Newly recognized asbestos-related diseases continue to occur, owing to the long latency period between exposure and clinical disease, despite the declining exposure to asbestos in developed countries. Although annual deaths from asbestosis have now reached a plateau in North America and will likely decline, new cases of mesothelioma, which has a latency of up to 35 years or more, are not estimated to plateau until 2020.

Chronic beryllium disease declined in frequency and severity after the elimination of beryllium from fluorescent lightbulbs in the 1950s, but then increased because of the increasing use of beryllium in nuclear facilities, aerospace, electronics, dental ceramics, metal alloys, recycling of metals, and products such as golf clubs and bicycles. The beryllium lymphocyte proliferation test can identify beryllium sensitization, which can be found in up to 10% of exposed workers and facilitates earlier diagnosis of chronic beryllium disease.

SPECIFIC OCCUPATIONAL LUNG DISORDERS

Occupational lung diseases are often misdiagnosed as other common nonoccupational diseases, but a careful history and appropriate investigations can lead to a correct diagnosis. For many occupational lung diseases, the diagnosis can significantly improve prognosis and lead to measures to prevent illness in other workers.

Work-Related Asthma

Work-related asthma includes both occupational asthma that is caused by work and asthma that is not caused by work but is exacerbated by work exposures.

SENSITIZER-INDUCED OCCUPATIONAL ASTHMA

EPIDEMIOLOGY

Occupational asthma is most commonly associated with a specific immune response to a high- or low-molecular-weight sensitizer (Table 93-2). Sensitizer-induced occupational asthma usually affects no more than 5 to 10% of workers exposed to the sensitizing agent, but exposure to complex platinum salts or detergent enzymes may result in symptoms in about 50% of highly exposed workers. In most studies, higher levels of exposure are associated with higher rates of sensitization in the exposed populations, but there is no clear threshold exposure below which all workers are protected from the risk of sensitization.

PATHOBIOLOGY

Genetic factors increase the risk of sensitization, but the risks appear to be polygenic and may differ for different allergens and sensitizers. Underlying atopy, as exemplified by a history of allergy or positive skin tests to common environmental allergens (Chapter 257), carries an increased risk of

TABLE 93-1 EXAMPLES OF OCCUPATIONAL RESPIRATORY DISEASES THAT COULD BE MISDIAGNOSED AS COMMON NONOCCUPATIONAL RESPIRATORY DISEASE

DISEASE THAT IS MIMICKED	POSSIBLE OCCUPATIONAL DISEASE	EXAMPLES OF SUGGESTIVE FEATURES LEADING TO A CORRECT DIAGNOSIS
Asthma	Occupational asthma from a work sensitizer	Asthma symptoms begin and are worse during a working period, with some improvement on days or weeks off work. Exposure to a high- or low-molecular-weight workplace sensitizer
	Occupational asthma—irritant-induced, including reactive airways dysfunction syndrome	Asthma begins within days after a high-level (accidental) workplace exposure
	Work-exacerbated asthma	Asthma usually began before starting the job or exposure, but severity is worse on days of work, or work exposures to expected asthma triggers or common allergens at work
COPD	Occupational COPD	Prolonged exposure at work to dusts, fumes, or gases
Pneumonia	Acute hypersensitivity pneumonitis	Symptoms typically resolve within days and recur on re-exposure to the same work trigger (e.g., metal-working fluid, moldy hay, humidifiers)
Acute viral respiratory illness or pneumonia	Humidifier fever, organic dust toxic syndrome, metal fume fever, polymer fume fever, cotton dust fever	Exposure triggers the episodes
Sarcoidosis	Chronic beryllium disease	History of exposure to beryllium dust or fumes up to 30 years or more before onset of disease
	Silicosis	History of exposure; typical radiographic findings of rounded opacities with upper lobe predominance and progressive massive fibrosis, biopsy
Idiopathic pulmonary fibrosis	Asbestosis	History of moderate or high previous asbestos exposure and appropriate latency period, often with other markers of asbestos exposure, such as radiographic evidence of pleural plaques
	Chronic hypersensitivity pneumonitis	± Work exposure to a known trigger, ± improvement during periods away from exposure
	Flock-worker's lung	Lymphocytic bronchiolitis and interstitial lung disease from nylon/synthetic textile microfibers
Idiopathic pulmonary fibrosis or hypersensitivity pneumonitis	Hard metal disease	History of exposure to hard metal (tungsten, cobalt), and histologic findings of giant cell pneumonitis on lung biopsy
Chest infections	Occupational causes of chest infections, e.g., SARS or TB in health care workers, histoplasmosis in construction workers, anthrax in wool workers or farmers	History of occupation and exposures
Pleural effusion	Asbestos-related benign pleural effusion	Previous asbestos exposure with appropriate latency; pleural plaques commonly present
Incidental pulmonary nodule	Rounded atelectasis from asbestos	Previous asbestos exposure with appropriate latency; pleural plaques commonly present
Multiple nodules	Silicosis or pneumoconiosis	History of exposure, distribution of nodules, presence of progressive massive fibrosis
Lung cancer	Occupational lung cancer	History of exposure to carcinogens at work, with an appropriate latency period (e.g., asbestos, radon, chromium)
Bronchiolitis obliterans	Popcorn lung	History of working with microwave popcorn or flavorings

COPD = chronic obstructive pulmonary disease; SARS = severe acute respiratory syndrome; TB = tuberculosis.

sensitization to the high-molecular-weight allergens, and smoking (Chapter 31) has been reported as a risk factor for sensitization to complex platinum salts. Currently, no host factors are sufficiently specific to justify exclusion of workers from settings with exposure to potential sensitizers.

Occupational asthma from a high-molecular-weight allergen is associated with specific immunoglobulin E (IgE) antibody production. Low-molecular-weight sensitizers may act as haptens or may induce neoantigens by reacting with proteins in vivo, but specific IgE antibodies have been demonstrated with only a few low-molecular-weight sensitizers, such as complex platinum salts and acid anhydrides used in epoxy compounds.

CLINICAL MANIFESTATIONS

Sensitizer-induced occupational asthma has a latency period ranging from weeks to several years before it develops, but most patients develop symptoms within the first few years of exposure. Once a patient has become sensitized and has developed asthma, even very small subsequent exposures can trigger asthma, sometimes including exposures that may be below the limit of measurable detection. Pulmonary function and histologic changes are similar to those in nonoccupational asthma (Chapter 87). Sensitizer-induced occupational asthma from a high-molecular-weight agent sensitizer typically causes a prompt asthmatic response within minutes after exposure with or without a late asthmatic response starting 4 to 6 hours after exposure. By comparison, responses to low-molecular-weight sensitizers typically start 4 to 6 hours after exposure.

DIAGNOSIS

The diagnosis of sensitizer-induced occupation asthma is clinically suspected by history and should be considered in all cases of new-onset asthma in patients who work. Supportive features include symptomatic improvement when away from work, such as weekends off work or holidays, but not necessarily in the evenings after a work shift, when symptoms from a late asthmatic response may occur. In patients who are exposed to high-molecular-weight sensitizers, allergic rhinitis or conjunctivitis associated with work frequently appears before the development of asthma. A detailed occupational history (Chapter 18) or review of material safety data sheets or occupational hygiene reports may reveal a known occupational sensitizer. However, more than 300 occupational respiratory sensitizers are currently known, and new agents or exposures are reported each year; as a result, the absence of a recognized sensitizer does not exclude occupational asthma.

Although the history can be very helpful, the evaluation should always include objective pulmonary function testing (Chapter 85) to confirm asthma, either when the patient has symptoms or within 24 hours of the typical suspected work exposure (Fig. 93-1). Allergy skin-prick tests, blood samples, or both should be obtained to test for specific IgE antibodies to any relevant sensitizer if feasible. Serial monitoring of peak expiratory flow rates, symptom diaries, or use of rescue inhalers can provide supportive information. The results of a methacholine challenge test (Chapter 87) toward the

TABLE 93-2 COMMON CAUSES OF SENSITIZER-INDUCED OCCUPATIONAL ASTHMA

OCCUPATION	ALLERGEN BY SETTING
Bakers	Wheat, rye, fungal amylase in flour
Laboratory workers	Animal allergens, e.g., proteins in rat urine, mouse or rabbit dander
Detergent-making, medical instrument cleaning, pharmaceuticals or laboratory workers	Enzymes: e.g., *Bacillus subtilis*, pancreatic enzymes
Farmers	Grains, plant, and animal allergens; mites
Greenhouse workers and florists	Pollen, fungi, mites
Food workers	Airborne food allergens, e.g., powdered milk or eggs and vegetables
Some office workers	Fungal allergens in moldy or "sick" buildings
Health care workers	Latex allergens from gloves, glutaraldehyde, orthophthaldehyde, aerosolized medications
Factory or other industrial workers	Chemicals in spray paints, glues, polyurethane, coatings and spray insulation, adhesives
Electronic workers	Soldering flux with colophony

end of a typical work week can help when compared with results after 10 days or more without exposure. A comparison of eosinophil counts in induced sputum at work and after a period away from exposure, showing higher levels when exposed, provides supportive diagnostic information. If the diagnosis is still in doubt, a carefully controlled specific inhalation challenge with the suspected workplace sensitizer can be performed. Each investigation can be falsely positive or negative, so a combination of investigations is advised while the patient continues to work until the diagnosis is confirmed. Given the specialized nature of many of these studies, consultation with a specialist is recommended. The main differential diagnosis for patients with confirmed asthma is the coincidental onset of asthma with subsequent work-exacerbated asthma. Other conditions, such as vocal cord dysfunction, may explain symptoms or may coexist with asthma and confound the diagnosis.

TREATMENT AND PREVENTION

Rx

The optimal management of patients with sensitizer-induced occupational asthma includes complete removal from further exposure to the sensitizer and cross-reacting agents combined with the usual pharmacologic approach to the treatment of asthma (Chapter 87) and advocacy for appropriate workers' compensation. Consideration of the other exposed workers typically includes communication with the workplace or public health officials, in the hope that measures may be instituted to protect other workers from similar exposures and symptoms. Recommendations for primary prevention have been to reduce exposures to occupational sensitizers as far as possible, removing unnecessary sensitizing agents (e.g., removing high-powdered and high-protein latex gloves) and limiting exposures to sensitizers with occupational hygiene measures. Ongoing medical surveillance measures in the workplace may also be of value.

PROGNOSIS

Outcome is best if an early diagnosis results in removal from further exposure while asthma is relatively mild. Improvement may continue to occur up to 10 years after removal from exposure, but asthma does not completely resolve in most patients. For patients with occupational asthma from natural rubber latex, use of powder-free, low-protein latex gloves by coworkers and direct avoidance of natural rubber products by the sensitized worker results in improvement that is similar to the improvement in patients who are completely removed from work.

Work-Exacerbated Asthma

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Work-exacerbated asthma is defined as asthma that is not caused by work but is aggravated or exacerbated by work conditions. Asthma may have been present before starting employment or may begin coincidentally during employment, but it is not caused by work. Work exposures that commonly exacerbate asthma include extreme temperature or humidity, exertion, dusts, fumes, and gases. Patients may be exposed at work to common environmental allergens (e.g., fungal allergens in an office setting or dust mites or animals in domestic settings) that exacerbate asthma in patients who are sensitized to these allergens. Symptoms of work-exacerbated asthma may occur transiently with an unusual work exposure (e.g., during renovation in a work building) or may occur on a daily basis (e.g., daily exposure to fumes while performing physical exertion in an industrial setting).

DIAGNOSIS AND TREATMENT

Rx

Transient work-exacerbated asthma is commonly diagnosed on the basis of the history of work exposures and the associated increase in asthmatic symptoms, medication requirements, or unscheduled physician visits. The recommended evaluation of patients with daily or frequent work exacerbations of asthma is similar to that for patients with suspected occupational asthma. Work-related changes in serial peak flow recordings mimic those seen in occupational asthma, but sputum eosinophil counts typically show less of a work-related increase than is observed with occupational asthma. If the workplace exposure includes a potential work sensitizer, immunologic testing or a controlled challenge exposure may confirm whether respiratory sensitization has occurred.

Management includes the same pharmacologic measures as for non-work-related exacerbations, including the optimization of pharmacologic asthma management (Chapter 87) and, when needed, adjusting the work exposures to avoid ongoing exacerbations. Occupational hygiene measures can reduce exposures, but some patients require a change in job description or work area. Workers' compensation may be available for some patients who miss work owing to work-exacerbation of asthma.

IRRITANT EXPOSURE AND REACTIVE AIRWAYS DYSFUNCTION SYNDROME

A high level of usually accidental exposure to an irritant agent can cause asthma. Although the clinical manifestations can be dramatic, irritant-induced occupational asthma represents a relatively small proportion of all occupational asthma. The most definitive criteria for this condition are those applied to the term *reactive airways dysfunction syndrome*: the onset of asthma symptoms within 24 hours of the exposure, generally severe enough to lead to an unscheduled physician visit; exposure to a single high-level irritant; asthma symptoms that persist for at least 3 months; pulmonary function testing that confirms asthma with a significant beneficial response to bronchodilators or a bronchoconstrictor response to a methacholine challenge; and the lack of preexisting lung disease or other conditions to explain the symptoms. When these criteria are not completely met (e.g., symptoms start later than 24 hours after exposure or resolve within weeks after exposure), the term *irritant-induced asthma* is commonly applied, recognizing that this diagnosis is less certain than reactive airways dysfunction syndrome.

Irritant-induced asthma and reactive airways dysfunction syndrome may clear after weeks or months. Management is the same as for other causes of asthma (Chapter 87), although these patients are often less responsive to the usual pharmacologic treatment.

Occupational hygiene measures at the workplace should be improved to prevent similar future exposures. Affected patients may need a modified work environment to prevent subsequent exacerbations of asthma.

OCCUPATIONAL CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic exposure to dusts, fumes, and gases can cause occupationally induced COPD, with pathophysiologic changes essentially identical to those seen in COPD that is related to smoking (Chapter 88). Symptoms of chronic bronchitis, including chronic cough and sputum production, may occur with or without changes on pulmonary function testing. Causes include mineral dusts such as silica and organic dust exposures such as those of farmers and woodworkers; particulate matter in diesel exhaust fumes; and nitrogen oxides, ozone, and ultrafine particles in welding fumes.

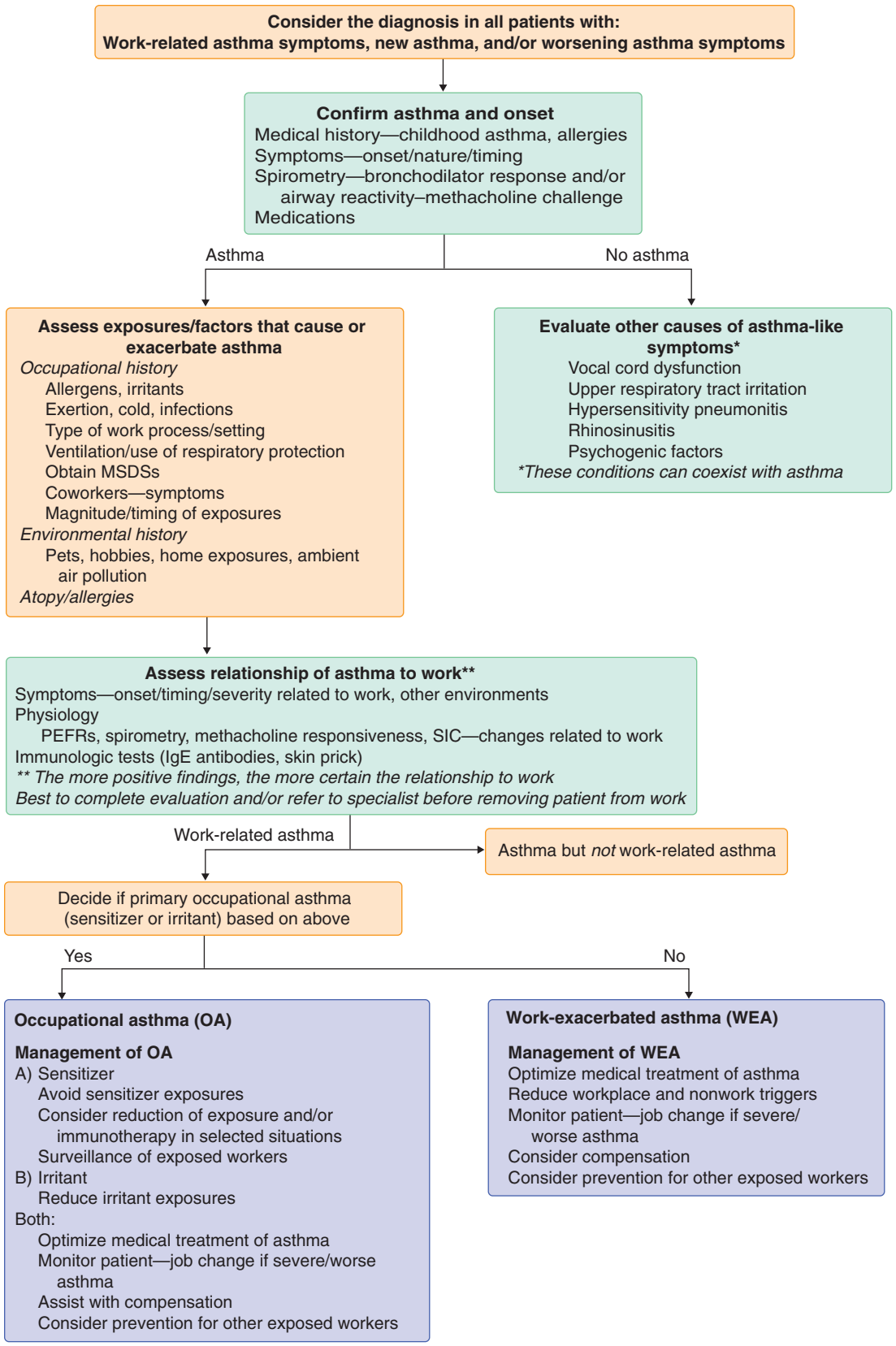

FIGURE 93-1. Clinical evaluation and management of work-related asthma. IgE = immunoglobulin E; MSDS = Material Safety Data Sheets; PEFR = peak expiratory flow rates; SIC = specific inhalation challenge. (From American College of Chest Physicians. Consensus statement: diagnosis and management of work-related asthma. *Chest.* 2008;134:1S-41S.)

No specific diagnostic tests distinguish an occupational from a nonoccupational cause of COPD. The history of exposure, with objective documentation, is helpful. Confirmation of the absence of a smoking history can assist in determining probability of an occupational cause, but a positive smoking history does not exclude an occupational contribution.

Management is the same as for patients with nonoccupational COPD (Chapter 88). In addition, however, further exposure to dusts, fumes, and gases that are likely to worsen disease should be minimized.

HYPERSENSITIVITY PNEUMONITIS

Many exposures that lead to hypersensitivity pneumonitis (Chapter 92) occur in the workplace, and several bear the name of the occupation or job associated with them: farmer's lung; maple bark stripper's lung; cheese washer's lung; thatcher's lung; mushroom worker's lung, and metal-working fluid hypersensitivity pneumonitis (Table 93-3). Occupational causes also include exposure to contaminated humidifiers (with protozoa or fungi) in factories

TABLE 93-3 EXAMPLES OF OCCUPATIONAL CAUSES OF HYPERSENSITIVITY PNEUMONITIS

OCCUPATION	CAUSE
Farmer	Thermophilic actinomycetes in moldy hay
Metal worker	Contamination of metal-working fluids with microorganisms such as *Mycobacteria immunogens* or fungi
Worker exposed to humidifiers	Contamination with microorganisms such as protozoa or fungi
Sugarcane worker	Moldy sugarcane (bagassosis)
Maple bark stripper	Fungi
Chicken or turkey worker	Avian proteins
Pharmaceutical worker	Penicillin
Food handler	Soybeans
Office worker	Microorganisms contaminating air conditioners or humidifiers
Swimming pool attendant	Fungal contamination in sprays around pool area
Animal worker	Rat proteins
Mushroom worker	Fungi
Wheat farmer or handler	Weevil-infested flour
Greenhouse worker	Fungi
Workers spraying urethane paint or adhesives/sealants (or less often, other workers using diisocyanate)	Methylene diphenyl diisocyanate, hexamethylene diisocyanate, toluene diisocyanates
Chemical worker using plastics, resins, paints	Trimellitic anhydride

or office buildings (humidifier lung), as well as lifeguards exposed to sprays of water from pool fountains contaminated with microorganisms. Metal workers or machinists can develop hypersensitivity pneumonitis from recirculated coolants that can become contaminated with gram-negative bacteria or atypical mycobacteria, which then are aerosolized in the coolant mist and inhaled.

PATHOBIOLOGY

Most antigenic exposures that lead to hypersensitivity pneumonitis are organic, especially thermophilic actinomycetes (Chapter 337), fungi, atypical mycobacteria (Chapter 333), and protozoa. Other common antigens include avian and rat proteins. Less commonly, hypersensitivity pneumonitis can be induced by low-molecular-weight chemical antigens, such as penicillin or methylene diphenyl diisocyanate (MDI), which is used as a sealant or binder. Small particles, commonly 3 to 5 μm in mass median aerodynamic diameter, reach the small airways and alveoli, where the immune response leads to hypersensitivity pneumonitis. This immune response is associated with specific IgG antibodies and T lymphocytes, and it recurs with repeated exposures.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The acute form of disease manifests as cough, dyspnea, chills, and malaise, typically 4 to 8 hours after exposure and clearing by 12 to 24 hours. On examination, patients typically are febrile and tachypneic, with reduced chest expansion and basal crackles. Neutrophilia is common, and the chest radiograph shows acute infiltrates. Pulmonary function testing may show a restrictive pattern, with a reduced diffusing capacity, and arterial blood gases may show hypoxemia owing to ventilation-perfusion mismatch.

Chronic hypersensitivity pneumonitis may follow repeat acute episodes or start de novo. It causes a chronic dry cough, progressive dyspnea, and often significant weight loss. The physical examination typically reveals reduced chest expansion and basal crackles. Results on pulmonary function testing and radiographic findings may be similar to nonspecific idiopathic pulmonary fibrosis (Chapter 92), and ground-glass opacities are often seen on a computed tomography (CT) scan of the chest. Bronchoalveolar fluid typically shows an increase in the lymphocyte count, and there may be a predominance of CD8 T lymphocytes (Chapter 85).

The specific occupational cause for hypersensitivity pneumonitis may be suspected from a temporal relationship to work exposures. The differential diagnosis in the chronic form includes idiopathic pulmonary fibrosis, although clubbing is less common in hypersensitivity pneumonitis. Radiographic and pulmonary function test findings may also mimic idiopathic pulmonary fibrosis, but a distinguishing finding is often a bronchoalveolar lavage that shows lymphocytes as high as 60 to 80% of the cells, usually with a predominance of $CD8^+$ T lymphocytes, but sometimes with $CD4^+$ cells in chronic forms of disease.

Laboratory investigations include determining the presence of serum IgG antibodies to the suspected antigen. However, IgG antibodies may also be present in exposed individuals who do not have disease and are therefore not specific to the diagnosis. Conversely, failure to demonstrate specific antibodies is not uncommon in hypersensitivity pneumonitis because the limited number of antigens used for testing may not include the relevant occupational antigen. Specific challenge with the suspected antigen in a laboratory setting is occasionally needed if the diagnosis is in doubt.

Some patients can safely undergo "work challenge" that monitors changes in symptoms, fever, blood neutrophil count, radiographic findings, and pulmonary function with and without exposure to the suspected agent. Lung biopsy, if performed, may show granulomas and foreign body giant cells. If other findings are supportive of hypersensitivity pneumonitis, however, open biopsy and challenges usually are not needed.

TREATMENT AND PROGNOSIS

Rx

Treatment principles are the same as for nonoccupational hypersensitivity pneumonitis (Chapter 94). Removal from exposure to the causative agent is the primary treatment measure. As with occupational asthma from a sensitizer, the removal must be complete and often requires a change in work if the causative agent cannot be removed. Reduction of exposure by use of respiratory protective devices is generally not practical and not effective, with the exception of air-supplied helmet respirators for occasional short-term exposures. Patients with acute hypersensitivity pneumonitis may not require any medications in addition to removal from antigen exposure, but if acute episodes are severe, they may need supportive measures, including corticosteroids (e.g., 20 to 60 mg of prednisone orally per day), supplemental oxygen, and intensive care (Chapter 94). Chronic hypersensitivity pneumonitis may require additional oral corticosteroid treatment (e.g., 5 to 10 mg of prednisone orally per day) as for nonoccupational chronic hypersensitivity pneumonitis, and severe end-stage fibrosis may lead to need for lung transplantation. Prognosis is better with early diagnosis and complete removal from exposure to the causative agent. Preventive measures include occupational hygiene measures to avoid contamination of aerosolized fluid or dusts with bio-organisms and use of appropriate respiratory protective devices.

CHRONIC BERYLLIUM DISEASE

EPIDEMIOLOGY AND PATHOBIOLOGY

Acute toxic pneumonitis was described in workers who had high exposure to beryllium in the manufacture of fluorescent lightbulbs in the 1940s, and a hypersensitivity response causing chronic beryllium disease was described in the 1950s. Acute toxic effects are now rare, but chronic beryllium disease remains a problem because of the expanded use of beryllium (Table 93-4) and better recognition of sensitization by development of an immunologic blood test.

Chronic beryllium disease is a hypersensitivity disease with a strong genetic association with HLA-DPB1 gene variants that code for Glu69 and that have been identified in 83 to 97% of patients with disease. However, this gene variant occurs in 30 to 48% of the general population and, as a result, is not useful as a screening test.

CLINICAL MANIFESTATIONS

The pulmonary clinical features of chronic beryllium disease are similar to those of sarcoidosis (Chapter 95), ranging from asymptomatic histologic or radiographic findings, to potential progression, to severe granulomatous restrictive lung disease. Onset can occur up to 20 years or more after exposure to beryllium, even if the patient no longer is exposed. The clinical history in all patients with apparent sarcoidosis must include inquiry about possible beryllium exposure, even many years ago.

DIAGNOSIS AND TREATMENT

Rx

The chest radiograph shows changes that appear identical to sarcoidosis with enlarged hilar or mediastinal lymph nodes or multiple lung nodules, or both (Fig. 93-2). Sensitization to beryllium can be detected by a beryllium lymphocyte proliferation test that demonstrates the presence of sensitized lymphocytes in blood or bronchoalveolar lavage fluid. This test also can detect sensitization to beryllium among asymptomatic exposed workers, who can then be evaluated to assess possible chronic beryllium disease and provided with advice for reducing or eliminating further work exposures.

After disease develops, removal from exposure is advised, but the disease may still worsen. Progressive deterioration in lung function is treated similarly to sarcoidosis (Chapter 95), with oral corticosteroids and supportive measures.

ASBESTOS-RELATED DISEASES

Although the use of asbestos has declined, and better protective equipment has been mandated, asbestos-related disease has continued to occur owing to the long latency between exposure and disease. Chrysotile asbestos has less effect on the lungs than other forms of asbestos, that is, amphiboles. Effects of exposure include benign and malignant disease.

Benign asbestos disease is often asymptomatic and identified on chest imaging. Pleural thickening and pleural plaques, commonly with calcification, can occur 20 to 30 years after first exposure and may initially appear on the chest radiograph as calcified linear opacities over the hemidiaphragms and cardiac border (see Fig. 84-10 in Chapter 84). If extensive, it may be difficult to exclude intrapulmonary opacities except by CT scan. Pleural plaques are a marker of asbestos exposure but do not occur in all workers with significant asbestos exposure. They generally do not cause significant changes in lung function, except diffuse pleural thickening may result in exertional dyspnea and extrapulmonary restrictive lung disease. Pleural thickening may cause rounded atelectasis (Chapter 90) when encasement of a portion of the peripheral lung tissue by thickened pleura causes an apparent lung nodule, typically with a "comet sign" showing the thickened pleura. Benign pleural effusion can develop, typically about 10 to 15 years after asbestos exposure. It requires further investigation because the differential diagnosis includes malignant pleural effusion (Chapter 99).

Asbestosis is the term for interstitial lung disease caused by asbestos. The clinical presentation is usually with dry cough and dyspnea on exertion. Physical examination usually reveals digital clubbing and basal crackles on lung auscultation. Chest imaging shows basal interstitial lung disease, with or without additional pleural changes as described earlier. Pulmonary function testing shows restrictive lung disease (Chapter 85), and histologic findings are the same as in usual interstitial pneumonia (Chapter 92). Findings supporting the diagnosis of asbestosis rather than usual interstitial pneumonia include a significant duration and level of exposure to asbestos, an appropriate latency of usually 20 to 40 years after first exposure, and the finding of ferruginous asbestos bodies in sputum or lung tissue (Fig. 93-3). Unfortunately, pharmacologic treatment is not effective, and the lung disease may progress to end-stage fibrosis. Management is supportive, including supplemental oxygen and consideration for lung transplantation (Chapter 101). As with the other diseases of long latency, preventing exposure is paramount.

Mesothelioma (Chapter 197), a malignant tumor of the pleura, peritoneum, or both, is the one complication of asbestos exposure that can occur after even relatively minor exposure, such as second-hand exposure from dust on clothing in the families of those working with exposure. It typically occurs 30 to 40 years after exposure to asbestos and may present incidentally on chest imaging or with chest pain or weight loss. Radiographs show pleural thickening, and a pleural effusion may be present. Mesothelioma often is difficult to distinguish from benign pleural thickening without a biopsy. No treatment has proved effective (Chapter 197), so routine screening to detect mesothelioma in exposed persons is not currently recommended. The risk of lung cancer (Chapter 197) increases after significant exposure to asbestos, with a usual latency period of 20 to 30 years. Smoking and asbestos exposure have multiplicative effects on the risk of lung cancer.

TABLE 93-4 POTENTIAL EXPOSURES TO BERYLLIUM

OCCUPATIONAL EXPOSURES
Metal and alloy production (alloys of aluminum, copper, and nickel; recently includes golf clubs and metal pen clips)
Ceramic manufacturing
Metal casting, including dental technicians (crowns, bridges)
Electronics, including computer components, transistors, microwave and x-ray windows, heat sinks, telecommunications
Aerospace and atomic engineering (rocket fuels, heat shields, nose cones, and metal parts)
Aircraft manufacture and repair
Nuclear reactors, nuclear weapons and defense industry
Coating of cathode ray tubes for radar and similar installations
Laboratories
Extraction from ore
Metal reclamation and recycling
NONOCCUPATIONAL EXPOSURES
Family members exposed to dust from workers' clothing
Breakage of old fluorescent lamps (made before 1950 in North America)
Downwind exposure from industrial accidents (e.g., from a nuclear processing plant in Kazakhstan, in the former Soviet Union in 1990)

From Tarlo SM, Rhee K, Powell E, et al. Marked tachypnoea in siblings with chronic beryllium disease due to copper-beryllium alloy. *Chest.* 2001;119:647-650.

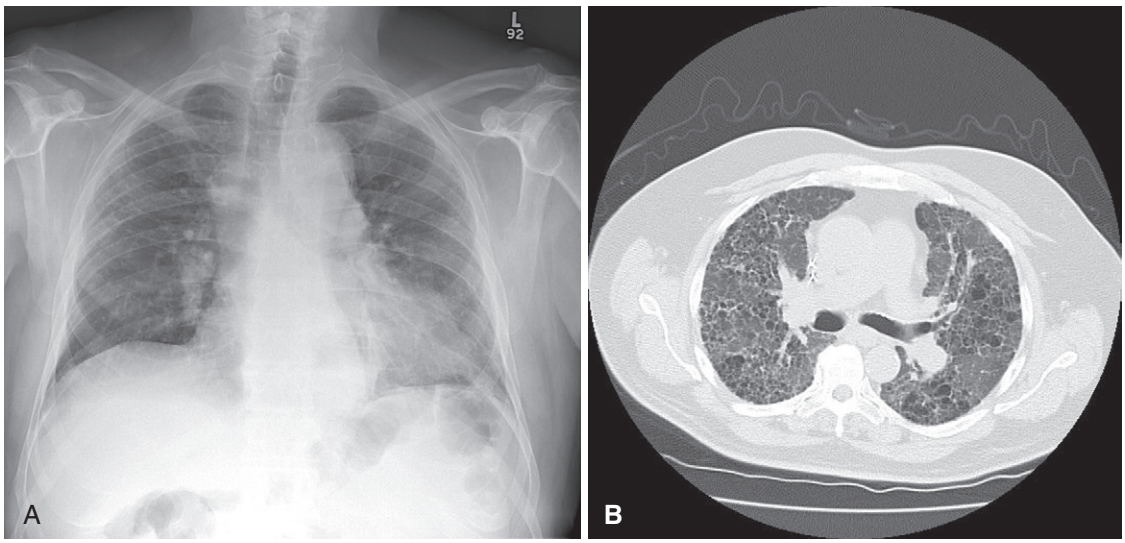

FIGURE 93-2. Posteroanterior chest radiograph (A) and high-resolution computed tomography scan (B) from patients with chronic beryllium disease. The chest radiograph demonstrates hilar adenopathy and infiltrates, and the scan shows air space destruction and infiltrates.

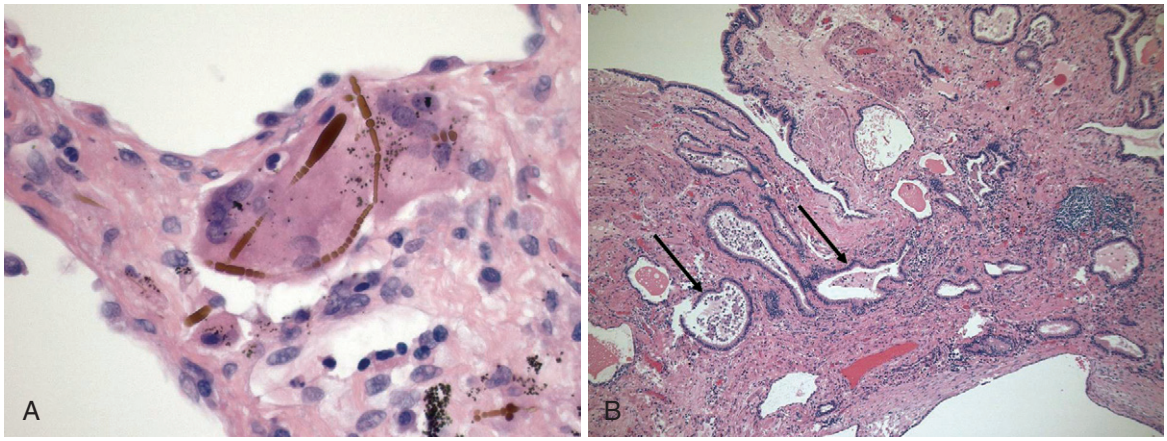

FIGURE 93-3. Histology from a lung biopsy showing asbestos bodies. Ferruginous bodies consisting of asbestos fibers coated by iron-protein-mucopolysaccharide material with typical golden-brown, beaded appearance. The two longest asbestos bodies at the centre of the figure are present within a multinucleated giant cell. (Hematoxylin and eosin stain, × 400). (Courtesy of Dr. David Hwang, Toronto General Hospital.)

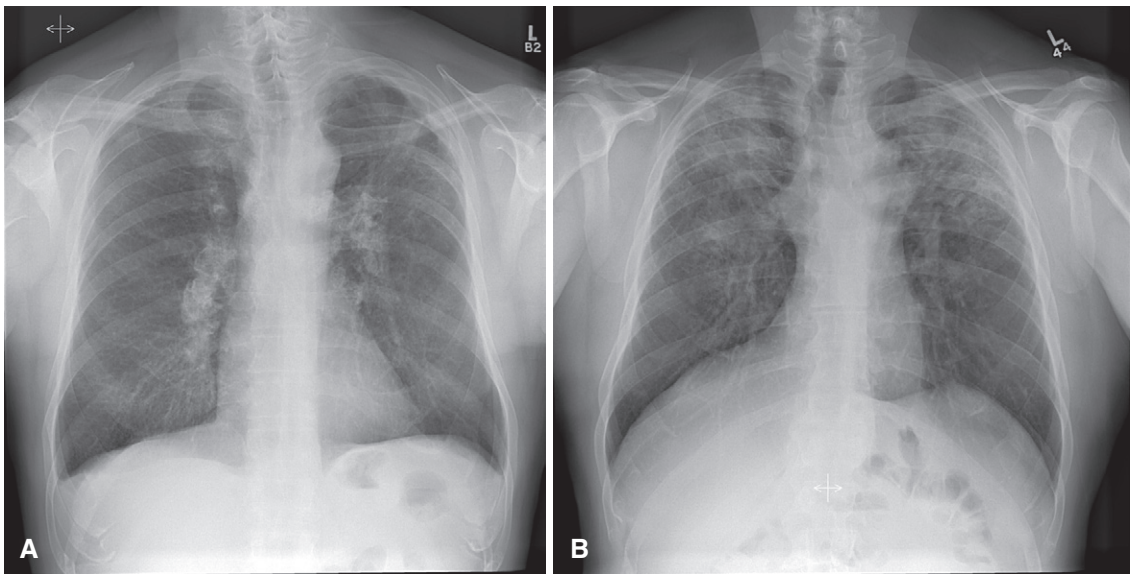

FIGURE 93-4. Posteroanterior chest radiographs from two patients with silicosis. A, Small nodules and eggshell calcification of hilar lymph nodes. **B**, Progressive massive fibrosis of the upper lung zones with compensatory emphysema.

SILICOSIS AND OTHER PNEUMOCONIOSES

The incidences of silicosis and other inorganic dust diseases of the lungs (Table 93-5) have declined substantially in recent decades owing to better worksite protection in mines, sandblasting, and other settings. There is an association between silicosis and the development of collagen-vascular disease, especially rheumatoid arthritis. Patients with pneumoconiosis and rheumatoid arthritis may be at higher risk of developing rheumatoid nodules in the lung, so-called Caplan's syndrome, and mycobacterial infections.

Patients may initially be identified incidentally during a medical surveillance program or by a chest radiograph that shows multiple small lung nodules, often with enlarged mediastinal lymph nodes that can mimic sarcoidosis (Fig. 93-4). Nodules can coalesce and lead to progressive massive fibrosis, especially in the upper lungs, with compensatory emphysema in the lower lung fields. On chest imaging, mediastinal lymph nodes may have a characteristic "eggshell" calcification in silicosis. Treatment is supportive. Patients with exposure to silica or coal dust may develop COPD from the dust exposure. Patients who develop end-stage lung disease may be considered for lung transplantation.

TABLE 93-5 JOBS THAT CAN LEAD TO SILICOSIS

Mining: surface or underground mining (tunneling)
Milling: ground silica for abrasives and filler
Quarrying
Sandblasting: e.g., of buildings, preparing steel for painting
Pottery; ceramic or clay work
Grinding, polishing using silica wheels
Stone work
Foundry work: grinding, molding, chipping
Refractory brick work
Glass making: to polish and as an abrasive
Boiler work: cleaning boilers
Manufacture of abrasives

ACUTE FEBRILE SYNDROMES

A variety of occupational exposures can cause acute febrile respiratory syndromes that may mimic acute viral respiratory illnesses (Table 93-6). The mechanism of these syndromes is incompletely understood, but they are associated with systemic neutrophilia and cytokine activation, often with increased interleukin-6 (IL-6) and IL-8.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Typically, chills, fever, malaise, dry cough, and chest tightness start about 6 to 8 hours after onset of an exposure at work and generally resolve by the next day. Occasionally, shortness of breath and other respiratory symptoms are

TABLE 93-6 OCCUPATIONAL CAUSES OF AN ACUTE FEBRILE SYNDROME

SYNDROME	CAUSE
Polymer fume fever or Teflon fever	Polytetrafluoroethylene and other fluorocarbon polymer fumes
Metal fume fever	Zinc fumes from welding of galvanized steel, less commonly other metal fumes
Cotton mill fever	Dust and endotoxins from bacterial contamination of unprocessed cotton, flax, and hemp
Humidifier fever	Microorganisms found in reservoirs, e.g., humidifiers, air conditioners, aquariums
Organic dust toxic syndrome	Grain dust, moldy wood chips

severe enough for patients to seek emergency medical attention. Infiltrates on the chest radiograph can occur with neutrophilia and hypoxemia that can mimic acute pneumonia or acute hypersensitivity pneumonitis. Symptoms and signs generally resolve in 24 to 48 hours without antibiotics and recur with further exposures, although the clinical manifestations generally become milder with repeated daily exposures (e.g., Monday morning fever in cotton mill workers). Workers are often familiar with the syndrome because it commonly affects up to 30% of exposed workers. If the diagnosis is not provided by the patient, however, careful elicitation of potential work exposures is needed.

TREATMENT

Rx

Treatment is supportive. If the causative exposure can be removed (e.g., cleaning a contaminated humidifier), symptoms can be prevented. If the cause cannot be removed and symptoms are severe, the patient may need reduction or change of the work exposure.

OCCUPATIONAL LUNG CANCER

A significant duration and level of exposure to a recognized carcinogen such as asbestos, hexavalent chromium (as in chromate production and the pigment industry), soluble radon compounds or radon gas, polycyclic aromatic hydrocarbons, chloromethyl ethers, arsenic, or silica can increase the risk of lung cancer (Chapter 197). Such a history should be elicited in all patients. The International Agency for Research on Cancer provides a listing of occupational lung carcinogens and the likelihood of their association with cancer (*http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php*).

SUGGESTED READINGS

CDC NIOSH Work-Related Lung Disease (WoRLD) Surveillance System. http://www2.cdc.gov/drds/WorldReportData. Accessed Oct. 27, 2010. *Information on the prevalence of occupational lung diseases in the United States.*

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