

# Hypersensitivity pneumonitis

Melissa M. Watts, M.D. and Leslie C. Grammer, M.D.

## ABSTRACT

Hypersensitivity pneumonitis (HP), also referred to as extrinsic allergic alveolitis, is characterized by non-immunoglobulin E mediated inflammation of the parenchyma, alveoli, and terminal airways of the lung initiated by inhaled antigens in a susceptible host. Etiologic agents of HP are either organic high-molecular-weight compounds (e.g., bacteria, fungi, amoebae, plant and animal proteins) or inorganic low-molecular-weight haptens (e.g., isocyanates) and drugs (including amiodarone, nitrofurantoin, and minocycline). Six significant predictors have been identified that provide approximately 95% diagnostic accuracy. These six predictors are (1) exposure to a known offending allergen, (2) positive precipitating antibodies to the offending antigen, (3) recurrent episodes of symptoms, (4) inspiratory crackles on lung auscultation, (5) symptoms that occur 4–8 hours after exposure, and (6) weight loss. HP is staged into acute, subacute, and chronic. In the acute stage, after direct exposure to the antigen, there are fever, chills, nonproductive cough, dyspnea, malaise, and myalgias, all of which resemble influenza. However, if obtained, a chest radiograph demonstrates nodular infiltrates, and pulmonary function testing is restrictive (unless the cause is avian, in which case, obstruction or obstruction with restriction is present). In the chronic stage, fever and chills are absent, but weight loss can occur. The immunologic response includes activated macrophages and CD8<sup>+</sup> cytotoxic lymphocytes, and bronchoalveolar lavage fluid reveals marked lymphocytosis with a ratio of CD4<sup>+</sup> to CD8<sup>+</sup> cells of <1. Activated macrophages have increased expression of CD80/CD86, and T cells have increased expression of its counter-ligand, CD28, evidence for heightened antigen presentation.

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Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is characterized by non-immunoglobulin E (IgE) mediated inflammation of the parenchyma, alveoli, and terminal airways of the lung initiated by inhaled antigens in a susceptible host. Historically, since the 1930s, HP was primarily associated with occupational exposures to, for example, *Thermophilic actinomyces*, which results in farmer's lung. Residential contact with agents responsible for HP now accounts for most new cases of the disease, with pet birds, contaminated heating and cooling units, and household indoor molds as the most frequent sources of exposure.<sup>1</sup>

The mechanism of inflammation in HP is not fully understood. The inflammation is non-IgE mediated and seems to be driven by activated alveolar macrophages and CD8<sup>+</sup> cytotoxic lymphocytes, which are unable to suppress macrophage activity.<sup>2</sup> The Gell and Coombs type III immune complex and IV cell-mediated reaction are the best way to explain the mechanisms that result in HP. Elevated antibody production, primarily IgG, is seen in HP and is thought to be

secondary to CD4<sup>+</sup> T-helper lymphocyte stimulation of plasma cells.<sup>1</sup>

Etiologic agents of HP are either organic high-molecular-weight compounds (e.g., bacteria, fungi, amoebae, plant and animal proteins) or inorganic low-molecular weight haptens (e.g., isocyanate) and drugs (including amiodarone, nitrofurantoin, and aripiprazole). Some etiologic agents are listed in Table 1; however it is not a comprehensive list because > 300 agents have been identified.<sup>1–4</sup> Examples include the following: *T. actinomyces*, found in decomposing hay and causing farmer's lung; *Naegleria gruberi*, in contaminated humidifiers and causing ventilation pneumonitis; avian protein in bird droppings and causing bird-fancier's lung; and acid anhydrides in plastics and causing plastic worker's lung (Table 1).

The epidemiology of HP varies with the etiologic agent, population, genetic risk factors, and environment. Although *T. actinomyces* and avian proteins cause most cases of HP in the United States, the incidence varies by region and season, with farmer's lung more common in humid regions and seasons. In Japan, summer-time mold contamination of homes with *Trichosporon cutaneum* or *Cryptococcus albidus* is the most common cause of HP. However, new cases of HP and new causative agents continue to emerge. Biologics, e.g., rituximab, have been linked to HP.<sup>3</sup>

HP presents in an acute, subacute, or chronic form, depending on the amount and duration of exposure and the level of host reactivity. The acute form typically occurs within 6 to 12 hours of an intense expo-

From the Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

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Address correspondence to Leslie C. Grammer, M.D., 211 E. Ontario Street, no. 1000, Chicago, IL 60611

E-mail address: l-grammer@northwestern.edu

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Table 1 Some antigens of hypersensitivity pneumonitis

| Disease or Condition                                                                                    | Source of Antigen                                                                                                        | Antigen                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Farmer's lung, bagassosis                                                                               | Moldy hay, compost, silage, grain, moldy sugarcane                                                                       | <i>Thermophilic actinomycetes</i> ,<br><i>Saccharopolyspora rectivirgula</i>                                                                                       |
| Bird fancier's disease, pigeon breeder's disease, budgerigar disease, plucker's lung, duck fever        | Droppings, feather bloom                                                                                                 | Avian proteins                                                                                                                                                     |
| Summer-type hypersensitivity pneumonitis                                                                | Moldy homes in Japan                                                                                                     | <i>Trichosporon cutaneum</i>                                                                                                                                       |
| Ventilation pneumonitis, humidifier lung                                                                | Air conditioner, humidifier                                                                                              | <i>Bacillus</i> , <i>Klebsiella</i> , <i>Cytophaga</i> ,<br><i>Naegleria gruberi</i>                                                                               |
| Chemical worker's lung, plastic worker's lung, bathtub refinisher's disease, paint refinisher's disease | Paint and/or chemical catalyst, varnish, lacquer, polyurethane foam plasticizer, spandex fibers, polyurethane elastomers | Isocyanates (TDI, HDI, MDI)                                                                                                                                        |
| Machine operator's lung                                                                                 | Contaminated metal-working fluids                                                                                        | <i>Pseudomonas</i> , <i>Acinetobacter</i>                                                                                                                          |
| Yacht-maker's lung                                                                                      | Chemicals used in making yachts                                                                                          | Dimethyl phthalate or styrene                                                                                                                                      |
| Saxophonist's lung                                                                                      | Moldy reed                                                                                                               | <i>Candida</i>                                                                                                                                                     |
| Laboratory worker's lung                                                                                | Rats, other mammals                                                                                                      | Urine antigens                                                                                                                                                     |
| Cheese worker's lung                                                                                    | Moldy cheese                                                                                                             | <i>Penicillium</i>                                                                                                                                                 |
| Hot tub lung; metal worker lung                                                                         | Hot tub, metal-working fluids                                                                                            | Nontuberculous<br><i>Mycobacterium</i>                                                                                                                             |
| Drug-induced Hypersensitivity pneumonitis                                                               | Drugs administered to patients                                                                                           | Drugs such as amiodarone, gold, sulfonamide, nitrofurantoin, minocycline, leflunomide, methotrexate, fluoxetine, sirolimus, HMG-CoA reductase inhibitor, rituximab |

TDI = toluene diisocyanate; HDI = hexamethylene diisocyanate; MDI = methylene diphenyl diisocyanate; HMG-CoA = 3-hydroxy-3-methylglutaryl-Coenzyme A.

sure, with symptoms of fever, dyspnea, and nonproductive cough. The chronic form is associated with continuous low-level exposure and presents with insidious onset of shortness of breath that particularly occurs with exertion, productive cough, and weight loss. Fever is not typical for chronic HP. The subacute form has features of both the acute and chronic forms. Additional information that distinguishes the three forms of HP can be found in Table 2.<sup>2,4,5</sup>

The overall prevalence and incidence is considered low; however, there must be a high index of suspicion for HP because it is frequently misdiagnosed as a viral illness or asthma. In addition, the reported mortality is increasing in the United States.<sup>6</sup> There is no single confirmatory test for HP. Physicians must

identify exposure to an agent capable of causing HP with an appropriate temporal relation to symptoms. Diagnostic tests are used to support the diagnosis. Six significant predictors have been identified that provide approximately 95% diagnostic accuracy. These six predictors are (1) exposure to a known offending allergen, (2) positive precipitating antibodies to the offending antigen, (3) recurrent episodes of symptoms, (4) inspiratory crackles on lung auscultation, (5) symptoms that occur 4–8 hours after exposure, and (6) weight loss.<sup>2,4</sup> For the acute form of HP, an inhalation challenge can clearly establish exposure and an appropriate temporal relation to symptoms, but it is rarely done because severe respiratory reactions may occur.

Table 2 Clinical presentations of hypersensitivity pneumonitis: acute, subacute, chronic\*

| Feature                         | Acute                                                                                            | Subacute                                                                                 | Chronic                                                                  |
|---------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Fever, chills                   | +                                                                                                | ±                                                                                        | –                                                                        |
| Dyspnea                         | +                                                                                                | +                                                                                        | +                                                                        |
| Cough                           | Nonproductive                                                                                    | Productive                                                                               | Productive                                                               |
| Malaise, myalgia                | +                                                                                                | +                                                                                        | +                                                                        |
| Weight loss                     | –                                                                                                | –                                                                                        | +                                                                        |
| Rales                           | –                                                                                                | +                                                                                        | +                                                                        |
| Chest film                      | Nodular infiltrates                                                                              | Nodular infiltrates                                                                      | Fibrosis                                                                 |
| PFTs                            | Restrictive                                                                                      | Mixed                                                                                    | Mixed                                                                    |
| DLCO                            | Decreased                                                                                        | Decreased                                                                                | Decreased                                                                |
| High-resolution CT of the chest | May have normal CT of the chest; or, some ground-glass opacities with centrilobular micronodules | Ground-glass opacities with a centrilobular micronodular pattern (<5 mm), mosaic pattern | Parenchymal fibrosis, including honeycombing and traction bronchiectasis |

+ = usually present; ± = variably present; – = usually not present; PFT = pulmonary function test; DLCO = diffusing capacity for carbon monoxide; CT = computed tomography.

\*Adapted with permission by Grammer LC. Occupational Allergic Alveolitis. *Ann Allergy Asthma Immunol.* 1999; 83:602–606.

Skin testing is not useful because HP is not an IgE-mediated disease. The presence of serum precipitating IgG antibodies to the offending antigen are found in HP but are not diagnostic because many individuals with exposure but no disease may have precipitating antibodies. In addition, the absence of precipitating antibodies does not exclude the diagnosis. The results of a physical examination, radiographic imaging, and pulmonary function tests differ, depending on the form of HP. Details of the differences are shown in Table 2. A lung biopsy specimen is not diagnostic but is often characterized by poorly formed granulomas, alveolar-wall infiltration with lymphocytes; plasma cells; and neutrophils; and, in the chronic form of HP, fibrosis. Usual interstitial pneumonia patterns may be seen.<sup>4</sup>

The cornerstone of management in HP is early diagnosis and avoidance of the offending agent. Avoidance often requires a change in occupation or parting with a beloved pet bird. Therefore, there frequently are emotional, psychological, social, and economic factors that lead to noncompliance. Prednisone at a dose of 0.5 mg/kg/day can decrease symptoms in the acute and subacute forms but has no benefit in terms of disease progression. It is recommended to not treat a patient with more than a brief course of oral steroids in the setting of continued antigen exposure. The majority of patients with HP enjoy a complete recovery once the offending agent is identified and avoided. However, deaths have been reported if exposure continues.<sup>4,6</sup>

## IMMUNOLOGY

- The inflammation in HP is not IgE mediated.
- Activated macrophages and CD8<sup>+</sup> cytotoxic lymphocytes are key mediators of inflammation in HP.
- Bronchoalveolar lavage fluid typically reveals a lymphocytosis with a ratio of CD4<sup>+</sup> to CD8<sup>+</sup> cells of <1.
- Activated macrophages have increased expression of CD80/CD86, and T cells have increased expression of its counter-ligand, CD28.
- Although HP is classically thought of as a T-helper (Th) type 1 disease, a Th2 profile may be involved in those patients with chronic HP.
- Levels of Th1 cytokines are increased, including interleukin (IL) 12, IL-18, and tumor necrosis factor  $\alpha$ .
- IL-17, a proinflammatory cytokine that increases the number and activation of neutrophils, may also be an important participant in HP.

## CLINICAL PEARLS

- HP is a clinical diagnosis that requires a high index of suspicion to detect; mortality is increasing in the United States.
- Levels of precipitating antibodies to the inciting antigen are identified; however, the absence of precipitating antibodies does not exclude the diagnosis.
- Residential exposures to causative agents are responsible for some new cases of HP.
- HP can result from medications.

- Clinical features and diagnostic test results differ in the acute, subacute, and chronic forms of HP.
- Skin testing is not useful because HP is not an IgE-mediated disease.
- The cornerstone of management in HP is early diagnosis and avoidance of the offending agent.
- Prednisone will decrease symptoms in the acute and subacute phases but will not impact disease progression in most cases.<sup>4,6</sup>

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