ATS Interstitial Lung Disease Primer: Hypersensitivity Pneumonitis
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List of abbreviations and acronyms

**CT:** computed tomography
**DLCO:** diffusion capacity of lung for carbon monoxide
**FVC:** forced vital capacity
**GERD:** gastroesophageal reflux
**HLA:** human leukocyte antigen
**HP:** hypersensitivity pneumonitis
**IA:** inciting antigen
**ILD:** interstitial lung disease
**IVD:** isovaleryl-CoA dehydrogenase
**MUC5B:** mucin 5B
**NSIP:** nonspecific interstitial pneumonia
**TNF:** tumor necrosis factor
**OBFC1:** oligonucleotide/oligosaccharide-binding folds containing one gene
Definition

- HP is a complex immunologically mediated form of lung disease that occurs in susceptible individuals resulting from repeated inhalation of and sensitization to a large variety of environmental and/or occupational organic and nonorganic inciting antigens (Table 1). HP is not an atopic disease or cryptogenic. Several drugs are associated with radiologic and histological HP-like reactions (e.g., ILD with granulomas) and must be excluded.
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<th>Common inciting antigen(s)</th>
<th>Source</th>
<th>Exposure setting HP term</th>
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<td><strong>Organic antigens: bacteria, fungi / yeast</strong></td>
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<td><em>Aspergillus spp</em>, <em>Thermophillic actinomycetes</em>, <em>Thermoactinomyces vulgaris</em>, <em>T. sacchari</em>, <em>F. rectovirgula</em></td>
<td>Moldy hay, silage, grain</td>
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<td><em>M. avium complex</em>, <em>M. immunogenenum</em></td>
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<td><em>Alternaria alternate</em>, <em>Aureobasidium spp.</em></td>
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<td><em>Candida spp</em>, <em>M. chelonae</em>, <em>Fusarium spp.</em></td>
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<td><em>Saccharomyces cerevisiae</em>, <em>A. fumigatus</em></td>
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<td><strong>Organic antigens: animal protein</strong></td>
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<tr>
<td>Anhydrides</td>
<td>Heated epoxy resin</td>
<td>Chemical worker’s lung, epoxy resin lung</td>
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Incidence / prevalence

- The 1-year prevalence rates for HP in the US ranged from 1.67 to 2.71 per 100,000 persons, and 1-year cumulative incidence rates ranged from 1.28 to 1.94 per 100,000 persons between 2004 and 2013.\(^{(1)}\)

- HP prevalence estimates based on ILD registry data (population between 330 and 2,245 ILD cases) from Europe, the Middle East, and India range from 2 to 47% in these communities.\(^{(2)}\)

- Throughout Europe, the estimated incidence of HP has been reported to range between 0.12 and 0.9 per 100,000 persons per year.

- Variations in HP epidemiology correlate with age, geography, occupation, season and host risk factors.\(^{(3-5)}\)
  > In one study, the prevalence increased with age, ranging from 1.48 per 100,000 among 35- to 44-year-olds to 11.2 per 100,000 among those aged 65 years and older.\(^{(1)}\) Between 56% and 68% of HP cases in each year were classified as chronic and 36–48% of chronic HP cases were classified as having fibrotic disease.\(^{(1)}\)

  > Farmer’s lung and bird related HP are among the most common forms of HP globally. Farmer’s lung is prevalent during late winter and the early spring cattle feeding period and after the harvest season.

  > There are reports of occupational outbreaks in specific settings such as workers exposed to various low-molecular-weight chemicals, contaminated metalworking fluids, and water humidification systems.\(^{(6)}\)
Clinical presentation

- In some patients, HP is antigen-specific, whereas in other patients HP might represent a reaction to several IAs (inciting antigen) emerging either from single or various environments.
- Exposure to the IA may have ceased before the recognition of the disease or evidence of disease progression.\(^\text{7}\)
- HP can occur at any age, with most patients presenting after the fourth decade of life.
- The extent and severity of respiratory symptoms and the presenting disease course of patients with HP are variable.
- During lung auscultation, inspiratory crackles and/or high-pitched inspiratory squeaks are usually heard.

Genetic factors

- Polymorphisms in genes of the major histocompatibility complex, including HLA-DR and HLA-DQ, transporter-associated antigen processing, tissue inhibitors of matrix metalloproteinases, immunoproteasomes, and the TNF-\(\alpha\) promoter are associated with an increase susceptibility to HP.\(^\text{8-12}\)
- Common IPF genetic risk variants in \textit{TERT}, \textit{MUC5B}, and \textit{IVD} have been associated with fibrotic HP, while common genetic variants in \textit{OBFC1} are associated with nonfibrotic HP.\(^\text{13}\)
- Short leukocyte telomere length has been associated with histopathological features of usual interstitial pneumonia and reduced survival.\(^\text{14}\)
- Familial clustering of patients with HP living in different environments and the development of HP in monozygotic twins has been reported.\(^\text{15}\)
Diagnosis and evaluation

- HP is classified based on the presence or absence of radiologic or histological lung fibrosis, IA exposure likelihood, and the confidence level of imaging and pathologic findings.\(^{(16, 17)}\) Both fibrosis and IA characterization have implications for diagnosis, prognosis, and treatment.

- The diagnosis of HP requires the exclusion of alternative etiologies and thorough multidisciplinary evaluation. HP can present occasionally with emphysema, and in patients with autoimmune features.

- No single test is diagnostic in all scenarios, and the histological diagnosis is no longer regarded as the gold standard or required in all cases during the diagnostic process.

Exposure assessment

- The first step in determining the likelihood of diagnosis is characterizing the occupational and environmental IA exposure type(s), extent and source(s) by a comprehensive history and exposure questionnaire. A structured questionnaire incorporated during the clinical evaluation can prevent the premature conclusion that the exposure history is negative, aid patient recall, save time when completed before a scheduled clinic visit, and ensure consistency.\(^{(16)}\) In the course of evaluating a suspected HP case, a thorough history and use of a structured exposure questionnaire during periodic evaluations may help uncover relevant exposures. The association between the IA exposure and HP is informed by causal inference such as the temporal relationship of symptoms with work and non-occupational exposures.

- The categorization of the IA exposure can be based on exposure likelihood: identified, indeterminate (evidence is suggestive of an association), or unidentified.\(^{(16)}\)

- Antigen-specific immunological tests should not be used in HP cases with identifiable IA exposure, particularly in patients unwilling to avoid and remove the antigen source despite the adverse clinical consequences.\(^{(16)}\) Negative results may help support patient bias towards no antigen avoidance. Patient education regarding management goals, exposure avoidance and testing is essential.
• An unidentified exposure (~20-50% cases, predominantly in fibrotic HP) does not rule out the diagnosis.

• A history indicating clinical improvement with IA remediation or worsening with IA re-exposure may suggest the diagnosis of HP but does not rule it out if absent.

• Consultation with an occupational medicine expert and an environmental hygienist should be considered, especially when the IA exposure is thought to arise in a workplace setting and patients with disease progression and suspicion for ongoing indeterminate IA exposure or multiple IA sources. (16)

Figure 1: Typical nonfibrotic HP pattern on HRCT

Figure 2: Sparse centrilobular nodules in a patient with nonfibrotic HP

1: Profuse, diffuse centrilobular nodules of ground glass attenuation in a patient with nonfibrotic HP. The centrilobular location is indicated by the clear zone between the nodules and the fissural and parietal pleura. This CT appearance is typical for HP.

2: This CT appearance is compatible with but not diagnostic of HP. Differential diagnosis might include other forms of inflammatory bronchiolitis such as smoking-related respiratory bronchiolitis.
Laboratory testing
- The detection of serum antigen-specific antibodies by quantitative (e.g., ELISA) or qualitative methods (e.g., double diffusion) is indicative of previous exposure but is not a confirmation of the presence of HP.
- Pulmonary function tests are non-diagnostic but are a reliable tool in quantifying the severity of the underlying pulmonary impairment, in addition to monitoring disease progression and response to therapy.

Imaging features

Nonfibrotic HP
- The typical nonfibrotic HP pattern (Figure 1) is characterized by any of the following: 1) Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones, 2) Inspiratory mosaic attenuation with density sign (i.e., combination of lung lobules of decreased attenuation, normal lung, and areas of increased ground-glass lung opacification), (18) 3) Inspiratory mosaic attenuation and air trapping associated with centrilobular nodules, and 4) lack of features to suggest an alternative diagnosis.
- A compatible nonfibrotic HP pattern (Figure 2) is characterized by any of the following: 1) centrilobular nodules of ground glass attenuation that are not profuse or diffuse, and not associated with mosaic attenuation or lobular air-trapping, 2) patchy or diffuse ground-glass opacity, 3) mosaic attenuation and lobular air-trapping without centrilobular nodules or ground glass abnormality and 4) lack of features suggesting an alternative diagnosis.

Fibrotic HP
- A typical fibrotic HP pattern (Figure 3) is characterized by CT signs of fibrosis (reticular or ground-glass abnormality with traction bronchiectasis or bronchiolectasis; lobar volume loss; honeycombing) with either of the following: 1) profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones, 2) inspiratory mosaic attenuation with three-density sign, and 3) lack of features suggesting an alternative diagnosis.
**Figure 3: Typical fibrotic HP pattern on HRCT**

3A: Inspiratory CT shows subpleural reticular abnormality with three-density sign (lobules of decreased attenuation (red circle) interspersed with ground glass attenuation (green circle) and normal attenuation (blue circle). 3B: Expiratory CT accentuates the areas of decreased attenuation.

**Figure 4: Findings compatible with fibrotic HP**

4A: Inspiratory CT shows multiple foci of mosaic attenuation (arrows). Three density sign is not present. 4B: Expiratory CT accentuates the foci of decreased attenuation.
A compatible fibrotic HP pattern (Figure 4) includes any of the following: 1) patchy or diffuse ground-glass opacity, 2) patchy, non-profuse centrilobular nodules of ground-glass attenuation, 3) mosaic attenuation and lobular air-trapping that do not meet criteria for typical fibrotic HP, and 4) lack of features suggesting an alternative diagnosis.

The category indeterminate for fibrotic HP (Figure 5) is used when CT signs of fibrosis are seen without other features suggestive of HP.

An upper and midlung zone pattern is suggestive of fibrotic HP. However, the fibrotic HP pattern is commonly diffuse or lower lung predominant in the craniocaudal plane.

Histological features

- BAL fluid lymphocytosis may increase diagnostic confidence and is most useful when the clinical context, exposure history, or high-resolution CT findings are indeterminate.

- BAL with lymphocyte cellular analysis - or lung biopsy - should not be done as a confirmatory test in all subjects, particularly in those with a compelling exposure history within the appropriate clinical context and a chest HRCT pattern typical for HP.\(^{15}\)
• Lymphocytic alveolitis is not consistently present in patients with fibrotic HP and specific ranges (e.g., BAL lymphocyte count between 20-30%) or its absence does not exclude the diagnosis. The diagnostic performance characteristics of the BAL fluid CD4+/CD8+ ratio in HP are unclear.

**Nonfibrotic HP**

• The typical nonfibrotic HP pattern (Figure 6) is characterized by four major features in at least one lobe and the lack of features suggesting an alternative diagnosis. The four major features include: 1) small airway centered distribution involving bronchioles and/or alveolar ducts (bronchiocentricity), 2) relatively diffuse and uniform cellular interstitial inflammation of alveolar walls and bronchioles (cellular bronchiolitis), 3) inflammation consisting mostly of lymphocytes with few plasma cells, and 4) interstitial poorly formed granulomas and/or multinucleated giant cells that are often peribronchial in location. In addition, minor features represent nonspecific findings that can be seen in HP but are not part of the diagnostic criteria. These include small foci of organizing pneumonia, foamy macrophages, Schaumann bodies and calcium oxalate crystals.

• A biopsy demonstrating a pattern compatible with nonfibrotic HP (Figure 7) is characterized by the first three major features of a typical HP pattern but both granulomas and features of an alternative diagnosis are lacking.

• The category indeterminate for nonfibrotic HP (Figure 8) refers to biopsies that show an ILD pattern that does not meet criteria for nonfibrotic HP, compatible with nonfibrotic HP, or an alternative diagnosis.

**Fibrotic HP**

• A typical fibrotic HP pattern (Figure 9) requires the presence of three major features in at least one of the sampled lobe(s) and the lack of features suggesting an alternative diagnosis 1) areas of small airway centered fibrosis with or without widespread peribronchiolar metaplasia (> 50% the bronchioles), 2) chronic fibrosing interstitial pneumonia with regions showing one or more of the following patterns: a) NSIP-fibrosing pattern, b) UIP-pattern, c) a fibrosing pattern that is difficult to classify, and d) fibrosis that is solely peribronchial, and 3) poorly formed interstitial noncaseating granulomas and/or multinucleated giant cells.
While bronchiolocentric fibrosis is often associated with HP, it may be seen in other forms of lung diseases, including connective tissue disease related ILDs and drug-induced ILD. Clues in favor of connective tissue related ILD include prominent lymphoid follicles with germinal centers, pleuritis and an inflammatory infiltrate that includes a much greater proportion of plasma cells than lymphocytes. The best distinguishing feature between drug reactions with granulomas and HP relies on a detailed history of administration of a drug associated with ILD and granulomas and the presence of extrapulmonary signs (e.g., rash) and laboratory abnormalities (e.g., peripheral eosinophilia).\(^{20}\)

A pattern compatible with fibrotic HP (Figure 10) shows the features #1 and #2, but both poorly formed noncaseating granulomas and features of an alternative diagnosis are absent.

Similar to nonfibrotic HP, the category of Indeterminate (Figure 11) for fibrotic HP pattern shows a pattern of fibrosing ILD that by itself does not meet the pathologic criteria for the pattern of typical fibrotic HP, compatible with fibrotic HP, or an alternative diagnosis.

**Multidisciplinary consensus diagnosis**

The degree of diagnostic confidence for HP requires integrating the clinical context, exposure history, chest CT pattern, and histology data when available: confident vs. provisional diagnosis, or unlikely.

A consensus diagnostic approach by a multidisciplinary team with expertise in ILD can enhance the accuracy and confidence of diagnosis and help determine whether more invasive diagnostic procedures may be needed to support the diagnosis in patients with a provisional HP diagnosis.
6A: This biopsy shows a bronchiolocentric cellular chronic inflammatory infiltrate (arrows).

6B: The wall of this bronchiole (arrow) is involved by chronic inflammatory cells that also infiltrate the peribronchiolar interstitium. 6C: Chronic inflammation infiltrates the wall of this bronchiole and extends into the surrounding interstitium. A poorly formed granuloma (arrows) is present in the peribronchiolar interstitium. A small focus of organizing pneumonia (arrowhead) involves an airspace. 6D: This loose cluster of epithelioid histiocytes surrounded by lymphocytes comprises a poorly formed granuloma.
**Figure 7: Compatible with nonfibrotic HP**

7A: Patchy chronic inflammatory infiltrates involve bronchioles (arrows). 7B: The infiltrate is centered on this bronchiole (arrow) and alveolar duct (arrowhead). Granulomas are absent.

**Figure 8: Indeterminate for nonfibrotic HP**

8A: This biopsy was initially felt to have nonspecific findings with minimal focal, patchy interstitial chronic inflammation (arrows) and organizing pneumonia (arrowhead). 8B: Because the CT showed features of typical nonfibrotic HP, reevaluation of the biopsy revealed vague collections of epithelioid histiocytes that in retrospect were felt to be a poorly formed granuloma (arrowhead and insert), leading to reinterpretation of the biopsy to favor an HP pattern.
**Figure 9: Typical fibrotic HP**

9A: This fibrotic HP shows fibrosis centered on bronchioles (arrows) as well as patchy subpleural fibrosis (arrowheads) with fibroblastic foci (insert) consistent with a UIP pattern. 9B: Multiple bronchioles are surrounded by fibrosis and mild chronic inflammation (arrows). Within the interstitium, loose rounded collections of epithelioid histiocytes comprised poorly formed granulomas (insert).

**Figure 10: Compatible with fibrotic HP**

10A: Patchy subpleural fibrosis causing remodeling of the lung architecture with fibroblastic foci (insert and arrow) in this biopsy represented a UIP pattern of fibrosis. 10B: A bronchiolocentric pattern (arrows) of fibrosis, lacking any granulomas was present in a separate lobe from the same patient. The diagnosis of HP was supported by CT scan showing features of typical HP. Despite the focal UIP pattern on biopsy the diagnosis of idiopathic pulmonary fibrosis is excluded by the CT features and areas of bronchiolocentricity in the biopsy.
Figure 11: Indeterminate for fibrotic HP by surgical lung biopsy

11A: This biopsy shows diffuse thickening of alveolar walls by mild to moderate interstitial fibrotic thickening. No bronchiolocentricity is seen. These features fit for a fibrosing pattern of NSIP. No granulomas or honeycombing are seen. 11B: This CT shows classical features of typical HP characterized by the three-density sign (predominant ground glass attenuation with areas of normal attenuation and mosaic attenuation) with mild reticulation and traction bronchiectasis. These CT findings from the same patient as the biopsy shown in Figure 11A, are compatible with the diagnosis of HP rather than idiopathic NSIP.

Treatment

Antigen avoidance

- Eliminating the IA at an early stage may reduce the risk of disease progression and impact survival.
- Referral to and collaboration with an occupational medicine specialist should be considered in suspected occupational cases.
- When remediation or complete avoidance is not possible, removing the patient from the likely antigen containing environment should be considered, particularly in patients with disease progression.
Pharmacotherapy

- Systemic corticosteroid therapy with a tapering schedule is commonly initiated in patients with severe clinical presentation, acute respiratory exacerbation and/or evidence of disease progression despite IA avoidance (Figure 12).

- Clinical improvement with immunosuppressive treatment appears to occur less frequently in fibrotic HP. If clinical response is noted or prolonged corticosteroid treatment is required, or if intolerable corticosteroid side effects transitioning to corticosteroid-sparing drugs can be considered (e.g., azathioprine, mycophenolic acid, mycophenolate mofetil).

- Patients should routinely be evaluated for complications of corticosteroids (e.g., diabetes, hypertension, cataract formation, osteoporosis) and corticosteroid-sparing drug use (e.g., transaminitis, leukopenia). Bone mineral-preserving therapies and pneumocystis prophylaxis should be strongly considered.

- In patients with progressive fibrotic HP, antifibrotic therapy should be considered. Nintedanib has been shown to slow the rate of decline in FVC in non-IPF patients with a progressive fibrotic ILD: defined as a relative decline in the FVC of at least 10%; a relative decline in the FVC of 5 to <10% and worsening of respiratory symptoms or an increased extent of fibrosis on HRCT; or worsening of respiratory symptoms and an increased extent of fibrosis.\(^\text{21}\)

Adjunctive care

- In addition to antigen avoidance, other nonpharmacological interventions in HP include the use of supplemental oxygen to help maintain normoxia in hypoxic patients; pulmonary rehabilitation to improve exercise endurance, capacity, and quality of life; smoking cessation; appropriate vaccination to prevent infection; early referral for lung transplant evaluation; appropriate treatment of comorbid conditions (e.g., coronary artery disease, sleep apnea, obesity, GERD, pulmonary hypertension); disease education, symptom management (e.g., cough) and palliative care when appropriate.
Monitoring

- Surveillance for IA re-exposure and patient education focused on IA avoidance at every visit is the highest priority for all patients.
- Physiologic, imaging and symptomatic monitoring every 3 to 6 months or sooner to assess both response to pharmacological therapy and drug toxicity, and evaluation of disease behavior while off pharmacological therapy is advisable.
- Fibrotic HP is a heterogenous disease with an unpredictable clinical progression.
- During follow-up, comorbidities should be screened for and managed as appropriate, as they can contribute to respiratory symptoms.

Prognosis

- Factors associated with increased risk of mortality include:
  - Unidentified antigen exposure, continuing long term exposure to the IA, older age, male sex, auscultatory crackles on lung examination, lower FVC and DLCO and progressive decrease in lung function from baseline (e.g., 10% decline in FVC), and acute exacerbation. Conserving lung function and reducing respiratory-related hospitalizations are essential goals of management.
  - A history of cigarette smoking. Smokers are less likely than non-smokers to develop nonfibrotic HP, attributed to a reduced immune response to IA exposure. However, cigarette smokers diagnosed with fibrotic HP have a worse prognosis.
  - Peripheral blood leukocyte telomere lengths less than the tenth percentile for age.
The presence and extent of fibrosis on CT and the rate of progression of fibrosis from baseline on CT. However, inspiratory mosaic attenuation and expiratory air-trapping on CT may indicate a better prognosis.\(^{(22)}\)

The presence and extent of lung fibrosis on histology at the time of diagnosis.

- In addition to lung fibrosis, common contributors of HP-related morbidity and mortality include cardiovascular disease, chronic obstructive pulmonary disease and malignancies.\(^{(23)}\)
References


Notes
To improve health worldwide by advancing research, clinical care and public health in respiratory disease