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# Hypersensitivity Pneumonitis: A Comprehensive Review

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## ■ Abstract

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a complex pulmonary syndrome mediated by the immune system and caused by inhalation of a wide variety of antigens to which the individual has been previously sensitized. The pathobiology of the disease is not fully understood, but in addition to the triggers that initiate the disease, host/genetic factors are likely to be important, as only a minority of exposed individuals develop HP. Due to the lack of a diagnostic gold standard, the diagnosis of HP is not straightforward and relies on the integration of a number of factors, including history of exposure, precipitating antibodies to the offending antigen, clinical features, bronchoalveolar lavage, and radiological and pathologic features. However, in the appropriate setting, a high index of suspicion is critically important and may obviate the need for more invasive tests.

Clinical presentation and natural history vary widely. Acute forms generally resolve without sequelae, while chronic forms, which are caused by persistent low-grade exposures, are associated with poor prognosis. Corticosteroids may be useful in acute episodes for symptomatic relief or in chronic and progressive disease, but their long-term efficacy has never been validated in prospective clinical trials. Ideally, patients with HP should be referred to centers with expertise, as the overlap with other forms of interstitial lung disease may be substantial. Making the correct diagnosis has critical therapeutic and prognostic implications.

**Key words:** Hypersensitivity pneumonitis. Extrinsic allergic alveolitis. Idiopathic pulmonary fibrosis. Interstitial lung disease. Pathogenesis. Differential diagnosis. Management.

## ■ Resumen

La neumonitis por hipersensibilidad (NH), también conocida como alveolitis alérgica extrínseca, es un síndrome pulmonar complejo mediado por el sistema inmune y provocado por la inhalación de una amplia variedad de alérgenos frente a los cuales el paciente está previamente sensibilizado. La patogénesis de la enfermedad se conoce parcialmente; sin embargo, además de los activadores iniciales que dan lugar al desarrollo de la enfermedad hay factores genéticos que tienen importancia también, de tal forma que solo una minoría de los individuos expuestos desarrollan la enfermedad. Debido a la falta de un "gold estándar" para el diagnóstico de NH, se hace necesaria la integración de un número de factores, entre los que se encuentran la historia de exposición al alérgeno, la presencia de anticuerpos precipitantes frente al Ag ofensor, datos clínicos y datos patológicos en el lavado broncoalveolar, y radiológicos. En cualquier caso un alto índice de sospecha clínica es crítica y puede obviar la necesidad de otros test más invasivos. La presentación clínica y la historia natural de la enfermedad puede variar ampliamente desde las formas agudas que generalmente se resuelven sin secuelas a las formas crónicas fibróticas que son provocadas por la exposición de grado bajo mantenida y que se asocian con un peor pronóstico. Los corticosteroides pueden ser útiles en el tratamiento sintomático de los episodios agudos o en la enfermedad crónica progresiva, pero su eficacia a largo plazo nunca ha sido validada en ensayos clínicos diseñados para ese fin. La dinámica adecuada debe dirigir a los pacientes con NH a centros especializados expertos, dado que puede haber otras formas solapadas de enfermedad pulmonar y el diagnóstico correcto es crítico para la aplicación de un correcto tratamiento y un mejor pronóstico.

**Palabras clave:** Neumonitis por hipersensibilidad. Alveolitis alérgica extrínseca. Fibrosis pulmonar idiopática. Enfermedad pulmonar intersticial. Patogénesis. Diagnóstico diferencial. Manejo.

## Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a complex syndrome that results from repeated inhalation of and sensitization to a wide variety of aerosolized antigens [1]. Clinical presentation and disease course are highly variable, and depend on factors such as intensity and duration of exposure to the causative antigen, the nature of the antigen, and host factors [2]. The immunopathogenesis of HP is poorly understood, although T-cell hyperreactivity and immune complex formation and deposition appear to play a prominent role. Notably, the disease develops in only a minority of individuals exposed to potential disease-causing antigens (ie, the majority of individuals with the same exposure are either sensitized but healthy, or do not even become sensitized), suggesting the existence of a genetic predisposition to HP [3].

According to data from registries of interstitial lung diseases (ILDs) in 3 European countries, HP accounts for 4% to 15% of all ILD cases [4], but this figure falls to 2% according to a population-based study conducted in New Mexico [5]. However, the incidence and prevalence of HP are difficult to estimate with precision, mainly because of the number of cases that are misdiagnosed or not recognized, and a lack of uniform diagnostic criteria. In addition, disease prevalence varies from country to country (and even within countries) owing to geographic, seasonal, and climatic factors [6]. For instance, farmer's lung—the prototype of HP with seasonal and geographic variations in incidence—occurs most frequently in late winter (when stored hay is used to feed cattle), and in regions with both heavy rainfall and severe winter conditions [7]. It is estimated that between 1% and 19% of farmers exposed to moldy hay develop farmer's lung [8] and that between 6% and 20% of individuals exposed to bird droppings develop bird fancier's lung [9]. These 2 conditions

are the most common type of HP, and can affect all age groups, including children [1].

## Disease Definition

There is no universally agreed upon definition of HP [10,11]. However, there is consensus on the following key features of the disease: 1) HP is a pulmonary disease which may or may not be accompanied by systemic manifestations (eg, fever and weight loss); 2) It is caused by the inhalation of an antigen to which the individual is sensitized and hyperresponsive; and 3) It is defined by exposure to a given antigen, sensitization to this antigen, and the presence of clinical symptoms. Indeed, many exposed individuals develop an antigen-specific immune response limited to the presence of serum IgG antibodies and an increased number of lymphocytes in the lung [12], but they never develop the disease [13].

## Causative Agents

Agents capable of inducing HP are found in a number of settings, including the workplace, home, and recreational environments. A wide and increasing variety of antigens can cause the disease, although similar antigens may induce different types of disease in different settings. In addition, although HP is caused by specific antigens, additional “triggers” (either genetic or environmental) may be needed to induce the disease [14], possibly explaining why, despite the universal and wide distribution of the offending antigens, only a few individuals develop HP. HP-inducing antigens are commonly classified in 5 broad categories represented by disease prototypes (Table 1) [15]. The most common causes of HP are avian antigens and microbial agents [16,17]. However,

Table 1. Common Types of Hypersensitivity Pneumonitis According to Major Classes of Antigens

| Class of Antigens | Specific Antigens   | Sources  | Type of Disease   |
|-------------------|---|--|---|
| Bacteria          | <i>Saccharopolyspora rectivirgula</i> ,<br><i>Thermoactinomyces vulgaris</i>  | Moldy hay, grain   | Farmer's lung   |
| Fungi, yeasts     | <i>Aspergillus</i> species<br><i>Aspergillus</i> species<br><i>Trichosporon cutaneum</i><br><i>Penicillium</i> species<br><i>Penicillium casei</i><br><i>Alternaria</i> species | Moldy hay, grain<br>Moldy compost and mushrooms<br>Contaminated houses<br>Moldy cork<br>Moldy cheese or cheese casings<br>Contaminated wood pulp or dust | Farmer's lung<br>Mushrooms worker's lung<br>Japanese summer-type HP<br>Suberosis<br>Cheese washer's lung<br>Woodworker's lung |
| Mycobacteria      | <i>Mycobacterium avium-intracellulare</i><br><i>Mycobacterium avium-intracellulare</i>  | Mold on ceiling, tub water<br>Mist from pool water, sprays<br>and fountains  | Hot tub lung<br>Swimming pool lung  |
| Animal proteins   | Proteins in avian droppings and serum<br>and on feathers<br>Avian proteins<br>Silkworm proteins   | Parakeets, budgerigars, pigeons,<br>parrots, cockatiels, ducks<br>Feather beds, pillow, duvets<br>Dust from silkworm larvae<br>and cocoons               | Pigeon breeder's lung,<br>bird fancier's lung<br>Feather duvet lung<br>Silk production HP                                     |
| Chemicals         | Diisocyanates, trimellitic anhydride  | Polyurethane foams, spray paints,<br>dyes, glues   | Chemical worker's lung  |

in recent years, a number of exposures (eg, mycobacterial antigens, which are typically encountered in hot tubs, pools, or metal working fluids) have also been recognized as an established cause of HP [18,19]. The latency between exposure and onset of disease is variable, and ranges from months to decades [20], making it challenging for the clinician to detect the type and source of the antigen, particularly in cases of occult or low-level exposure.

## Immunopathogenesis

HP is the result of an immunologically induced inflammation of the lung parenchyma (specifically, the disease involves the alveoli, terminal bronchioli, and interstitium) that occurs in susceptible individuals in response to a variety of antigens [2]. The immunopathogenesis of the disease is likely to be similar, regardless of the causative agent, and both humoral and cellular mechanisms appear to contribute to the development of HP [21]. The genetic basis of HP is poorly understood, and, although some studies suggest that polymorphisms within human leukocyte antigen (HLA) class II genes increase the risk for HP in populations from different genetic backgrounds [22,23], no genetic factors have consistently been associated with the disease. If exposed to agents capable of inducing HP, most individuals develop immune tolerance, and inhalation of the antigen may result in a mild increase in local lymphocytes, without clinical significance. However, according to a “two-hit” hypothesis, the coexistence of inducing factors (eg, antigens) and promoting factors (eg, genetic abnormalities or additional environmental exposures) may lead to the development of an exaggerated immune reaction that results in marked lung inflammation [2]. In acute HP, lung inflammation appears to be mediated by immune complexes, as suggested by the presence of high titers of antigen-specific precipitating IgG in the serum, and an increase in lung neutrophils primed for an enhanced respiratory burst [24]. Conversely, subacute and chronic HP is characterized by an exaggerated T cell–mediated immune response, in which increased T-cell migration, local proliferation, and decreased apoptosis contribute to the characteristic T-lymphocytic alveolitis [25,26]. This process is dependent on the transcription factor STAT-4 and T-bet, a major regulator of T<sub>H</sub>1 lineage [27]. A number of studies have also shown that the immune response in HP is polarized toward a T<sub>H</sub>1-like pattern of differentiation, which is largely mediated by IL-12 and IFN- $\gamma$  [26,28]. However, it has also been shown that, following chronic exposure to *Saccharopolyspora rectivirgula*, CD4<sup>+</sup> T cells display a preferential T<sub>H</sub>17 polarization with differential expression of IL-17A and IL-22 [29], suggesting that this polarization, together with upregulation of T<sub>H</sub>17 signature cytokines, may play an important role in the pathogenesis of HP.

The immune processes that lead to persistent disease and progression to fibrosis are less clear. However, features associated with chronic HP include an increase in CD4<sup>+</sup> T cells and in the CD4<sup>+</sup>/CD8<sup>+</sup> ratio, a skewing toward T<sub>H</sub>2 T-cell differentiation and cytokine profile as well as an exhaustion of CD8<sup>+</sup> T cells [26]. Increased T<sub>H</sub>17 cells following chronic inhalation of aerosolized antigens may also contribute to the development of lung fibrosis (by promoting collagen

deposition) [30], as shown by the protective effect against the disease of both genetic deletion of IL-17 and antibody-depletion of IL-17 [31].

## The “Protective” Role of Cigarette Smoking

Smoking is less prevalent in patients with HP compared with unaffected controls with similar antigenic exposure [8,32,33]. Moreover, when exposed to high levels of HP antigens, smokers have lower levels of specific antibodies to the causative antigen. The mechanisms that account for the “protective” effect of smoking are poorly understood, but nicotine is thought to inhibit macrophage activation and lymphocyte proliferation and function [34]. In fact, mice challenged with *S rectivirgula* and simultaneously treated with nicotine have shown a significant decrease in lung inflammation [34]. Although more common in nonsmokers, when it occurs in smokers, HP is associated with a more chronic and severe course and higher mortality [35].

## Disease Classification

HP has been conventionally classified as acute, subacute, and chronic [36], although there are no widely accepted criteria to distinguish the various forms. In addition, clinical manifestations of each form are highly variable due to a number of factors, including the intensity and duration of exposure, the nature of the antigen, and host factors; yet there may be significant overlap between these forms. The observation of considerable overlap between the clinical manifestations of farmer’s lung (considered the prototype of acute HP) and pigeon breeder’s lung or bird fancier’s lung (considered the prototype of subacute and chronic HP, respectively) suggests that the pattern of antigen exposure may be as important as the antigen itself in determining disease manifestations [11,37]. Although the classification scheme described above is widely used, it applies only to typical cases, and can be misleading when, for instance, acute and chronic disease coexist in the same patient, or when the clinical presentation and disease course are difficult to define. In this regard, Selman [38] proposed an alternative classification scheme based primarily on disease behavior, distinguishing between acute nonprogressive and intermittent disease, acute progressive/subacute disease; chronic nonprogressive disease, and chronic progressive disease. Recently, Lacasse and colleagues [39] used data from the HP study and divided patients (n=168) with differing clinical patterns into a limited number of categories (“clusters”). The variables included in this cluster analysis were derived from clinical history, physical examination, blood testing, chest radiograph, high-resolution computed tomography (HRCT), and bronchoalveolar lavage (BAL). A 2-cluster solution best fit the data, with patients in cluster 1 (n=41) having more frequent recurrent systemic symptoms and normal chest radiographs, and those in cluster 2 (n=127) displaying more frequent digital clubbing, hypoxemia, restrictive ventilator defect on pulmonary function tests (PFTs), and fibrosis on HRCT scans. The results of this analysis differed considerably from results based on the current classification of HP and, again, subacute HP was particularly

difficult to define. This new classification scheme, however, needs to be validated prospectively.

## Diagnosis

Various diagnostic criteria have been proposed for HP, but none of these has been validated. As such, diagnosis relies on the integration of a variety of factors, including history of antigen exposure, precipitating antibodies to the offending antigen, clinical features, inhalation challenge, BAL, and radiological and pathologic abnormalities [17]. However, in the appropriate setting, a high index of suspicion remains of critical importance and may obviate the need for more invasive testing [40]. A clinical prediction model for a diagnosis of HP has also been developed (Table 2). If all 6 predictors in the model are present, the probability of having HP is 98% [11].

Table 2. Clinical Predictors for the Diagnosis of Hypersensitivity Pneumonitis

| Variable                              | OR   | 95% CI     |
|---------------------------------------|------|------------|
| Exposure to a known offending antigen | 38.8 | 11.6-129.6 |
| Positive precipitating antibodies     | 5.3  | 2.7-10.4   |
| Recurrent episodes of symptoms        | 3.3  | 1.5-7.5    |
| Inspiratory crackles                  | 4.5  | 1.8-11.7   |
| Symptoms 4-8 hours after exposure     | 7.2  | 1.8-28.6   |
| Weight loss                           | 2.0  | 1.8-28.6   |

Source: Adapted from Lacasse et al. [11].

## Serum Precipitins

Serum can be assayed for precipitating IgG antibodies (precipitins) against various potential antigens [41], but precipitins are only a marker of exposure. Indeed, up to 40% of farmers have positive serum precipitins to common causes of HP in the absence of clinically significant disease and without long-term sequelae [42,43]. The prevalence of serum precipitins in asymptomatic bird breeders is even higher, probably due to more intense and prolonged exposure to inciting antigens [44]. Nevertheless, in the appropriate clinical setting, a positive test supports the diagnosis of HP. Conversely, the absence of serum precipitins does not rule out HP, primarily because most commercial assays test for only a small fraction of the potential causative antigens. Furthermore, in acute and chronic HP (particularly if the underlying pathology is usual interstitial pneumonia [UIP]), the test tends to lose sensitivity, even if the correct antigen is included [45].

## Inhalation Challenge

Re-exposure of the patient to the suspected inciting agent after a period of avoidance can reveal a relationship between the exposure being analyzed and the development of symptoms and laboratory and functional abnormalities, thus supporting a diagnosis of HP. A positive test is characterized by cough,

dyspnea, fever, and decreased forced vital capacity (FVC) and oxygen saturation a few hours (8-12) after exposure. Because the magnitude of the attack is unpredictable, the patient should be monitored closely for at least 24 hours. In the appropriate clinical setting, a positive inhalation challenge is virtually diagnostic, although false negative results may occur [46,47]. Owing to a lack of standardization (both in the inhalation protocols and the criteria used to define a positive response) and because of the risk of severe reactions, the test should only be performed in selected patients by qualified personnel in specialized centers [38].

## Imaging

Chest radiography is usually the first step in the evaluation of a patient with suspected HP. As in other ILDs, the chest radiograph reveals nonspecific findings, particularly in acute and subacute phases of the disease, and it may also be normal [48-50]. However, a variable combination of fine nodular opacities and widespread ground glass opacity (GGO) may be observed. Pulmonary abnormalities associated with chronic HP may be more specific; indeed, the upper lobe predominance of fibrotic changes (eg, reticular opacities and honeycombing) is almost invariably present in chronic fibrotic HP [48].

HRCT may either show typical findings, which may be virtually diagnostic of HP in the appropriate clinical setting, or provide important clues that may suggest a correct diagnosis [49,51]. HRCT findings vary widely based on the stages of the disease. Only a few reports have described HRCT abnormalities in acute HP, as HRCT is seldom performed at this stage due to the rapid resolution of symptoms [2]. However, in cases with severe clinical manifestations (eg, acute respiratory failure), acute HP on HRCT scans may resemble the exudative phase of diffuse alveolar damage (DAD) [52, 53]. GGO primarily reflects the presence of diffuse lymphocytic interstitial infiltration, and the differential diagnosis with other disorders manifesting with diffuse GGO (eg, opportunistic infections, pulmonary edema, and cellular nonspecific interstitial pneumonia [NSIP]) may not



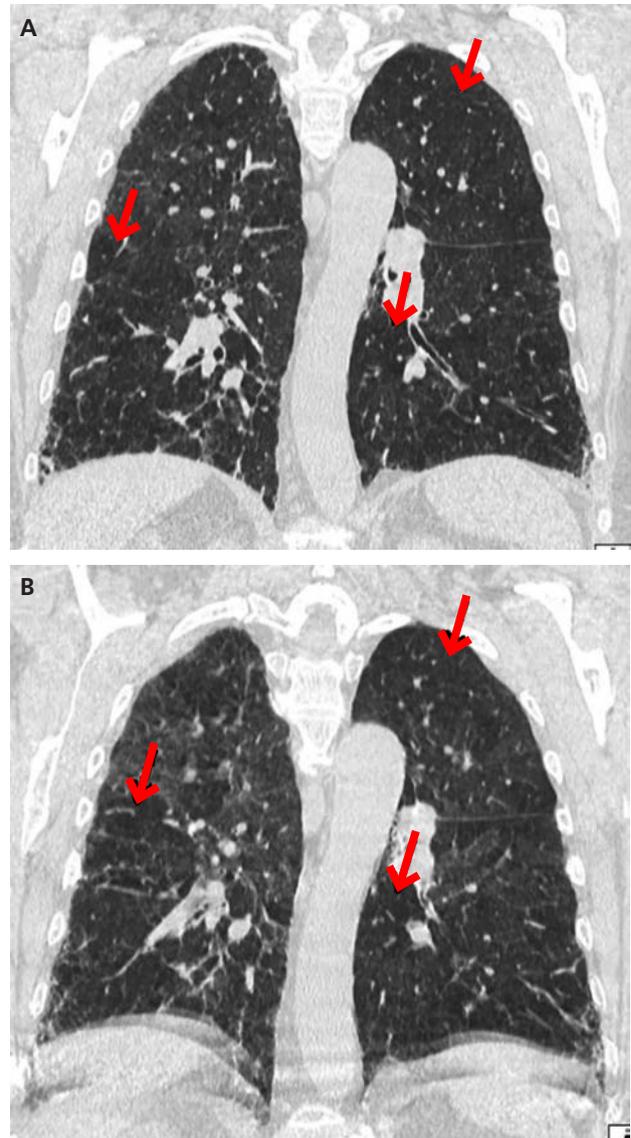
Figure 1. Chronic hypersensitivity pneumonitis. High-resolution computed tomography showing a reticular pattern with subpleural distribution and distortion of the lung parenchyma suggestive of established fibrosis. Diffuse ground glass opacity admixed with areas of lobular decreased attenuation suggests an acute exacerbation in this patient who presented with acute respiratory failure.

be straightforward [54-56]. Furthermore, GGO superimposed on a background of chronic changes may be observed in acute exacerbation of chronic HP or in chronic cases following intense exposure to antigens (Figure 1) [57]. Conversely, HRCT abnormalities observed in the subacute phase of the disease may be more specific, and include poorly defined nodules, GGO, and areas of decreased attenuation (Figure 2) [58,59]. Poorly defined nodules may be the predominant or only abnormality in patients with subacute HP. They are less than 5 mm in diameter and are generally numerous and have a typical centrilobular distribution, although few nodules with an atypical distribution may sometimes be seen. The nodules may be seen throughout the lungs, although they typically predominate in the mid to upper zones. Centrilobular nodules produce a characteristic appearance that narrows the differential diagnosis to either smoking- or occupation-related lung disorders, thus making the patient's history critical for securing a final diagnosis. However, in smoking-related ILD the nodules are typically more patchy and less widespread [49,58-60]. Areas of decreased attenuation are distributed in a lobular fashion, mirroring the air trapping on expiratory CT that is caused by antigen deposition in the small airways (Figures 1,3). Although this HRCT pattern may be observed in up to 90% of patients, it is usually limited in extent and less pronounced than in obliterative bronchiolitis associated with other conditions. The variable combination of areas of decreased attenuation, GGO, and normal lung may produce the so-called head-cheese pattern, which is highly suggestive of HP, although it may also be observed in respiratory bronchiolitis-associated ILD [51,61-64]. Coexisting thin-walled lung cysts have been reported in 13% of patients with subacute HP [49,58,59,65], and are believed to be caused by partial bronchiolar obstruction by peribronchiolar lymphocytic infiltration. These cysts are usually few in number, range in size from 3 to 25 mm, and resemble those seen in lymphocytic interstitial pneumonia (LIP). However, LIP is often associated with other conditions, such as connective tissue diseases or lymphatic disorders (eg, human immunodeficiency virus infection, lymphoma), and the GGO is usually more patchy [49,58,66,67].



**Figure 2.** Subacute hypersensitivity pneumonitis. High-resolution computed tomography showing profuse poorly defined, relatively low attenuation nodules and ground glass opacity in the middle lung zones.

Consolidation is an unusual finding, and may represent foci of organizing pneumonia or superimposed infection. Irregular nodules larger than 10 mm in diameter may also represent focal areas of organizing pneumonia [49,63]. HP classically occurs in nonsmokers; yet, it may be associated with emphysema. Indeed, emphysema has been reported as a frequent (about one-third of cases) and prominent finding in patients with farmer's lung. Emphysema associated with chronic airflow obstruction may be related to massive intermittent exposure, whereas chronic low-level exposure, as in bird fancier's lung, usually causes a restrictive ventilatory defect [49,68].



**Figure 3.** Chronic hypersensitivity pneumonitis. A, Coronal reformatted computed tomography (CT) image obtained at suspended inspiration shows a reticular pattern predominant in the lower lobes; areas of decreased attenuation are also seen (arrows); B, The intensity and extent of the areas of decreased attenuation increase on expiratory CT (arrows) indicating small airway involvement, an almost invariable finding in hypersensitivity pneumonitis. In this case, CT findings led clinicians to re-evaluate the case and discover a previously unappreciated exposure to avian antigens.

The chronic stage of HP is characterized by fibrotic changes, although evidence of active disease (eg, superimposed centrilobular fluffy nodules and GGO) may still be present. HRCT findings include intralobular and interlobular septal thickening, traction bronchiectasis, and honeycombing [69]. Often, but not invariably, the fibrotic abnormalities show mid to upper lung zone predominance. Patients with HP may exhibit histologic and imaging features of NSIP or UIP, and thus the radiological overlap with idiopathic pulmonary fibrosis (IPF) and idiopathic NSIP may be substantial (Figure 3) [65,70,71]. Imaging features that favor HP over IPF and idiopathic NSIP include an upper or mid zone predominance, extensive GGO, centrilobular nodules, and conspicuous air trapping [65,72]. Silva and co-workers [73] assessed the accuracy of thin-section CT in distinguishing chronic HP from IPF and NSIP [73]. Lobular areas of mosaic attenuation were seen significantly more frequently in patients with chronic HP (80% of cases) than in IPF (43%) or NSIP (34%). Similarly, centrilobular nodules were more common in patients with chronic HP (56%) than in those with IPF (15%) or NSIP (14%). Finally, thin-walled cysts were also more common in patients with chronic HP (39%) than in those with IPF (0%) or NSIP (12%). Notably, the frequency of honeycombing was similar in chronic HP (64%) and IPF (67%) [73]. On the other hand, Sverzellati and co-workers [74] showed that 12% of biopsy-proven IPF cases resembled chronic HP on HRCT, thus suggesting that a diagnosis of IPF should not be excluded based on HRCT appearance alone. Widespread areas of mosaic attenuation with lobular areas of decreased attenuation and vascularity associated with parenchymal distortion and fibrosis that resemble chronic HP may also be observed in fibrotic sarcoidosis [75,76].

## Histologic findings

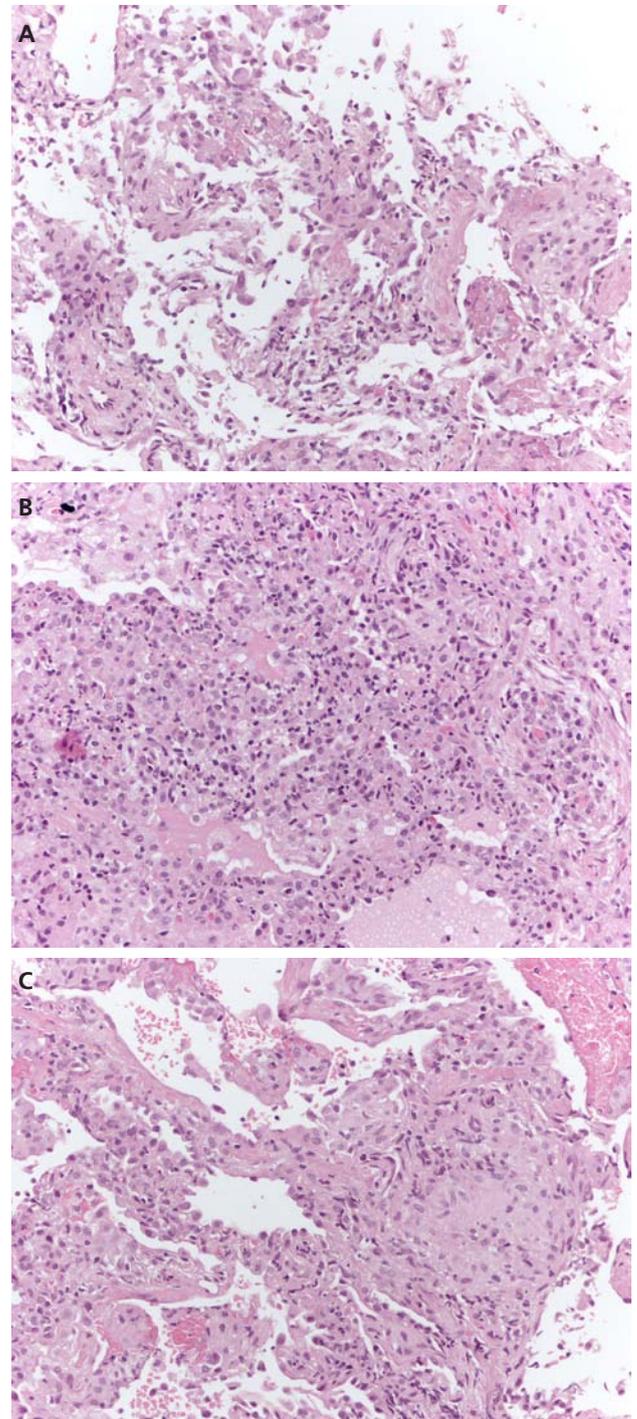
### Acute HP

Histologic studies in acute HP are scanty as lung biopsy is generally not necessary for diagnosis. In the few reported cases, the main abnormalities were fibrin deposition and neutrophils (mostly interstitial and sometimes with features of capillaritis), variably associated with findings of subacute HP (see below) [77]. Figure 4 illustrates a case of acute HP. The differential diagnosis includes any cause of acute lung injury and infections in particular should be carefully excluded. The variable combination of fibrin, neutrophils, cellular infiltrates, and tiny granulomas may be sufficient to raise the suspicion of acute HP, but a compatible clinical scenario remains of critical diagnostic importance.

### Subacute HP

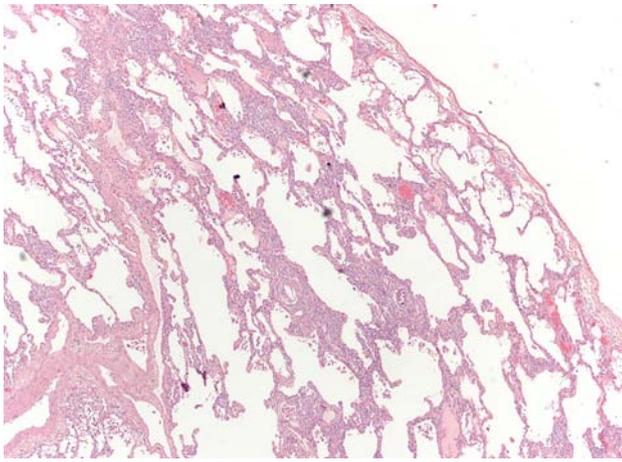
The classic “histologic triad” of subacute HP includes interstitial infiltrate, cellular bronchiolitis, and poorly formed granulomas [78-81] (Figure 5). This triad is present in up to 75% of cases, and any of these features may be the predominant one [1]. The interstitial infiltrate is mainly composed of lymphocytes and plasma cells, which account for the striking cellularity appreciated at low magnification. Descriptively, many cases can be classified as having a cellular NSIP pattern.

The infiltrate tends to be more pronounced in the centrilobular regions, thus leading to cellular bronchiolitis; occasionally, bronchiolitis may be isolated without an associated interstitial infiltrate. Features of chronic bronchiolar damage are

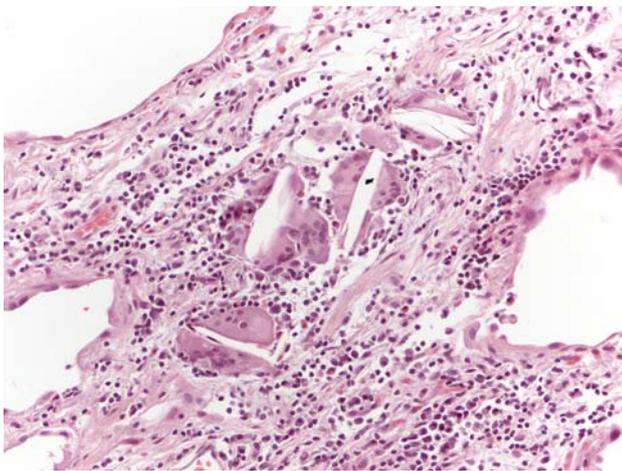


**Figure 4.** Transbronchial biopsy in a young farmer who presented with fever and severe dyspnea shortly after working in a cowshed. The biopsy shows intra-alveolar fibrin (A) associated with cellular interstitial infiltrate consisting of lymphocytes, plasma cells and neutrophils (B). A single tiny granuloma is seen (C). The patient recovered promptly after institution of steroid therapy (hematoxylin-eosin, original magnification x100).

frequently present, including peribronchiolar metaplasia, bronchiolectasis, and bronchiolar wall fibrosis. Accordingly, the histologic boundaries between subacute and chronic HP may be blurred. An indirect feature of bronchiolitis, which is present in some cases of HP and quite characteristic, is a microscopic obstructive pneumonia consisting of focal accumulation of foamy macrophages in the peribronchiolar airspaces. The typical granulomas of HP are present in about 80% of surgical biopsies, and consist of loose collections of histiocytes or scattered giant cells, frequently with cholesterol clefts (Figure 6), or other nonspecific cytoplasmic inclusions, such as Schaumann bodies and oxalate crystals. The latter are birefringent and should not be misinterpreted as exogenous material. Interstitial Schaumann bodies may be the only evidence of pre-existing granulomas. Although traditionally considered exclusively interstitial, granulomas in HP may also be intra-alveolar [81]. Occasionally, well-formed granulomas can be found, but numerous compact granulomas are not



**Figure 5.** A classic example of subacute hypersensitivity pneumonitis characterized by a cellular infiltrate with centrilobular accentuation. A few small granulomas can be seen even at low magnification (hematoxylin-eosin, original magnification x40).



**Figure 6.** Granulomas of hypersensitivity pneumonitis frequently consist of scattered giant cells with cholesterol clefts, as in this case (hematoxylin-eosin, original magnification x200).

a feature of HP and their presence should suggest other diagnostic possibilities. Other findings frequently present in HP are foci of organizing pneumonia and lymphoid follicles, sometimes with germinal centers. Eosinophils can be present as well, but they are never prominent. When present, the histologic triad described above strongly supports the diagnosis of HP. However, because drug reactions and autoimmune diseases may occasionally have a similar histology, the diagnosis always requires a compatible clinical setting. When the histologic findings are less compelling (for example, when the biopsy shows only cellular NSIP [82]), the support from the clinical data needs to be particularly strong.

### Chronic HP

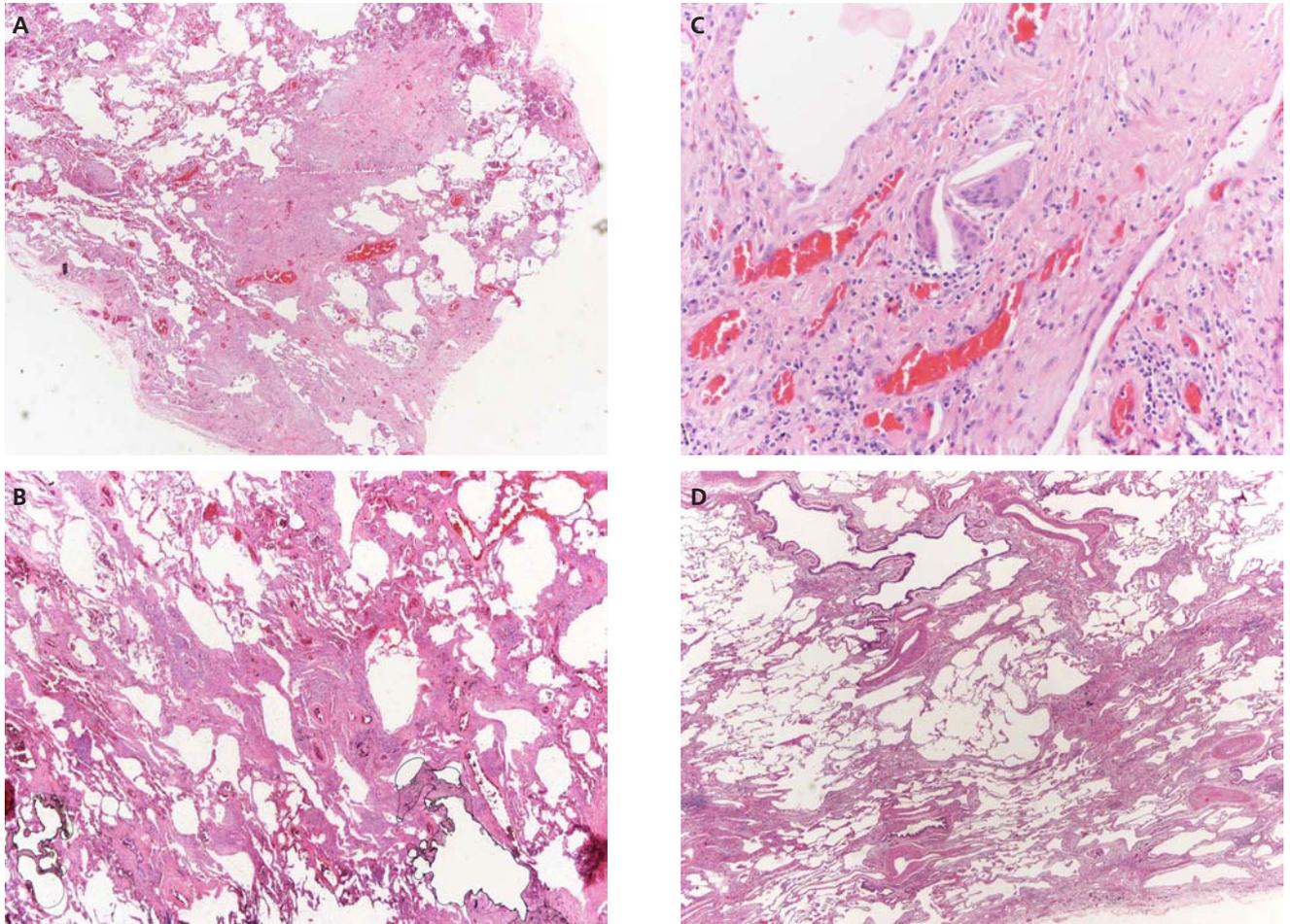
In chronic stages, HP may be particularly difficult to diagnose, and pathology plays a key role in this regard. Histologically, chronic HP may overlap with other ILDs, including fibrosing NSIP [82], airway-centered interstitial fibrosis [83], and UIP [45,84-90]. In particular, chronic HP may have a combination of findings characteristic of UIP, including patchy fibrosis with subpleural/paraseptal distribution, fibroblastic foci, and honeycombing. The main ancillary features for differentiating chronic HP from IPF are centrilobular fibrosis/inflammation (sometimes with “bridging” fibrosis, consisting of a fibrotic net connecting bronchioles with each other and with pleural/septal regions), a significant lymphoid/plasmacytic infiltrate (particularly outside the fibrotic areas), and small granulomas/giant cells (Figure 7). While these findings are often evident, in some cases they are subtle and need to be carefully searched for. A variable combination of the ancillary findings mentioned above is present in the vast majority of cases of chronic HP, particularly if biopsies are taken from at least 2 different lobes [85], with only rare cases being histologically indistinguishable from IPF.

Similarly to other forms of fibrotic lung disease, chronic HP can undergo acute exacerbation [91-94], consisting histologically of areas of acute lung injury (DAD or organizing pneumonia) superimposed on chronic changes. A histologic pattern of UIP is associated with an increased risk of acute exacerbation [92].

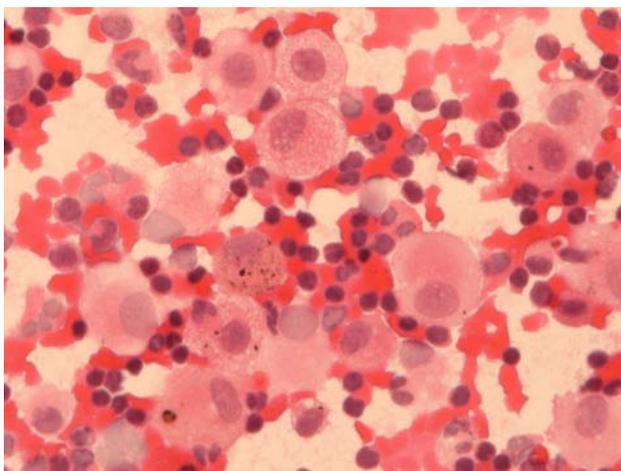
## Diagnostic Role of Bronchoscopic Techniques

### Bronchoalveolar lavage

BAL is the most sensitive tool to detect alveolitis in patients suspected of having HP [95]. The total cell yield is usually very high, more than 20 million from a BAL of 100 mL total instillation [1], and the most typical pattern is a marked lymphocyte-rich alveolitis (>20% and often >50% of the total cells recovered) [96]. Lymphocyte count is usually higher than 50% in subacute HP (Figure 8), and accompanied by an increase of CD8<sup>+</sup> T cells [96]. The presence of mast cells, plasma cells, and foamy macrophages in the BAL are additional features in support of a diagnosis of HP. In patients with chronic HP under corticosteroid treatment, the BAL lymphocytosis is less marked, while neutrophil count tends



**Figure 7.** Histologic features of chronic hypersensitivity pneumonitis. Figure A, illustrates a case of chronic hypersensitivity pneumonitis with a usual interstitial pneumonia (UIP) pattern characterized by patchy fibrosis and fibroblastic foci indistinguishable from the UIP seen in idiopathic pulmonary fibrosis (hematoxylin-eosin, original magnification x40). Other areas of the same biopsy show some degree of cellularity (B, hematoxylin-eosin, original magnification x40) and a few interstitial giant cells (C, hematoxylin-eosin, original magnification x200) that suggest the correct diagnosis. Another example of chronic hypersensitivity pneumonitis is shown in panel D (hematoxylin-eosin, original magnification x40). In this case, the key diagnostic feature is the presence of a fibrotic net linking bronchioles with each other and with the periphery of the lobule (bridging fibrosis).



**Figure 8.** Bronchoalveolar lavage fluid showing some foamy macrophages and lymphocytic alveolitis (hematoxylin-eosin, original magnification x200).

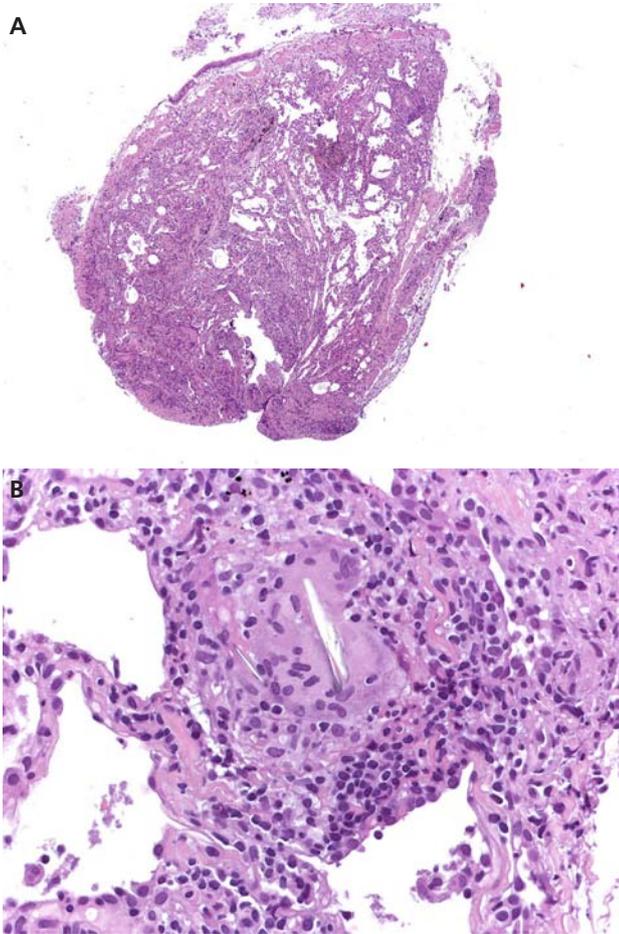
to increase (particularly in patients with a UIP pattern of lung fibrosis), but a cutoff level of 30% for lymphocytes confidently differentiates chronic HP from IPF [45,97].

#### *Transbronchial biopsy*

Not infrequently, transbronchial biopsy may reveal some—and sometimes all—of the typical histologic findings of HP (Figure 9). In the appropriate clinical setting, this may be sufficient to establish a diagnosis. Transbronchial cryobiopsy is an innovative technique that provides larger samples of lung parenchyma [98], thus increasing the sensitivity of transbronchial biopsy in the diagnosis of ILDs, including HP, particularly in its chronic form.

### **Clinical Features**

Acute HP, which generally results from intense exposure to an inciting agent, is characterized by flu-like symptoms (eg,



**Figure 9.** Transbronchial biopsy showing cellular interstitial infiltrate (A, hematoxylin-eosin, original magnification x25) and a few interstitial giant cells with cholesterol clefts (B, hematoxylin-eosin, original magnification x200). In the correct clinical context, this combination of findings can be sufficient to correctly diagnose hypersensitivity pneumonitis).

chills, fever, sweating, myalgias, and headache), which start a few hours after exposure, peak within 6 to 24 hours, and last for hours or days (but often recur after re-exposure). Respiratory symptoms such as cough, chest tightness, and dyspnea are common but not universal. Physical examination usually reveals diffuse fine crackles. However, acute HP may also be associated with wheezing and bronchial hyperresponsiveness but with a normal chest radiograph; in such cases, the main differential diagnosis is occupational asthma. A characteristic clinical sign of HP is represented by isolated, short, high-pitched end-inspiratory sound (squawks), which were first described in 1967 [99]. Although a high-pitched inspiratory wheeze may also occur in other airway diseases (eg, bronchiolitis obliterans associated with rheumatoid disease), squawks in HP are characterized by higher frequency, shorter duration, and later onset. It has been postulated that this sound is produced by the rapid oscillation of small airways, which open late in inspiration, and reflects widespread bronchiolar involvement [100]. During symptomatic episodes, PFT usually reveals a restrictive ventilatory defect, but an obstructive pattern is found in some cases. In general, the acute form is

intermittent, does not progress, and tends to improve following antigen avoidance [2]. Subacute HP results from prolonged low-level antigen exposure, and is characterized by an insidious onset of cough, dyspnea, fatigue, and weight loss that develop over several weeks to a few months. PFTs generally reveal a restrictive or mixed (obstructive and restrictive) ventilator defect accompanied by a reduced diffusing capacity of the lung for carbon monoxide (DLCO). As with other ILDs, the main role of PFTs in HP is to assess disease severity at baseline, evolution over time and response to treatment, although functional data from follow-up studies are limited [2]. Broadly speaking, subacute HP is a progressive disease, with cough and dyspnea becoming persistent and often requiring corticosteroid therapy along with antigen avoidance. An unrecognized and untreated subacute episode may progress to chronic disease, but it is unclear how often this occurs. Chronic HP often has an insidious onset over a period of months to years with a slowly progressive cough, exertional dyspnea, fatigue, and weight loss. Patients may lack a history of acute episodes. Removal of the offending agent at this stage results in only partial improvement, and steroid therapy is often required. Digital clubbing occurs frequently in advanced disease, and may be predictive of clinical worsening [101]. Chronic HP may progress to end-stage fibrosis and pulmonary hypertension, which are associated with increased mortality [102,103]. Due to the insidious presentation and the absence of recognizable acute episodes, chronic forms that progress to irreversible fibrosis may be mistaken for other forms of ILD, particularly IPF [74,104]. In a recent study by Morell and colleagues [90], almost half (20/46) of the patients diagnosed with IPF based on the 2011 guidelines were subsequently diagnosed with chronic HP after additional testing, including the administration of a standardized questionnaire designed to look for occult exposure, inhalation challenge to the putative antigen, BAL, and surgical lung biopsy. The authors observed that most of these cases were due to exposure to occult avian antigens from commonly used feather bedding.

## Management

Avoidance of exposure to a suspected or confirmed causative agent is the cornerstone of HP management and a major determinant of prognosis, as progression is largely, though not invariably, preventable with appropriate antigen avoidance. On the other hand, a number of studies have shown that farmers with HP may not progress, even if they do not change their employment [105,106], suggesting that the phenotypic expression of the disease is likely to depend on a complex interaction between environmental and host/genetic factors [107]. In cases in which elimination of antigen exposure does not result in full recovery, treatment with systemic corticosteroids may be warranted. Corticosteroids may be indicated for acute symptomatic relief and in patients with subacute progressive and chronic disease, but they do not appear to impact on the long-term outcome [108]. There is no universally agreed upon treatment regimen. A reasonable empiric treatment scheme may consist of prednisone 0.5-1 mg/kg/d (up to a maximum daily dose of 60 mg) for 1 to 2 weeks in acute HP or for 4 to 8 weeks in subacute/chronic HP, followed

by a gradual taper to off or a maintenance dose of approximately 10 mg/d [38]. Long-term treatment should be guided by clinical response, pulmonary function, and radiographic improvement. Progressive pulmonary fibrosis that characterizes chronic advanced HP does not respond to treatment, and lung transplantation should be considered in such cases.

Determining the inciting antigen is also critically important in patients with chronic HP. In a recent study of 142 such cases, inability to identify the offending agent was a significant predictor of shortened survival, even after adjusting for other important variables, such as age, presence of fibrosis, FVC, DLCO, and smoking history, with median survival dropping from 8.75 to 4.88 years when the inciting antigen was not identified [109]. Yet, identifying the causative exposure remains challenging, particularly in chronic forms of HP, and this was possible in only approximately half of the cases in 2 of the largest series published to date [109,110]. The main reasons for missed diagnosis include lack of a clear temporal relationship between antigen exposure and the onset of symptoms and inadequate questioning of patients about persistent low-level exposure (eg, feather pillows). HRCT studies provide very similar mortality estimates when comparing patients with and without radiological evidence of fibrosis, and demonstrate a dose-response effect of the severity of fibrosis on mortality [69,111,112]. However, the prognosis of fibrotic HP remains better than that of IPF, even if the causative agent is not identified [109,113].

## Outcome

Patients with acute HP, if correctly and timely diagnosed and treated, generally have an excellent prognosis. Conversely, patients with subacute/chronic disease, particularly those with bird fancier's lung (due to the high levels of bird antigens that can be detected in the home environment for prolonged periods of time even after bird removal and environmental cleanup [114]) may progress to pulmonary fibrosis and die within few years of the diagnosis [115]. Factors associated with worse prognosis include duration of exposure (eg, individuals exposed for a shorter period have a more favorable outcome than those with a longer exposure) [116]; a histologic pattern of either fibrotic NSIP or UIP [45,93]; digital clubbing [101]; older age [117]; greater intensity of exposure [118]; and greater severity of traction bronchiectasis and increased extent of honeycombing on HRCT [69].

## Conclusions

Hypersensitivity pneumonitis is a complex pulmonary syndrome characterized by diffuse inflammation of lung parenchyma and airways in response to the inhalation of antigens to which the individual has been previously sensitized. The disease has protean clinical manifestations and substantial overlap with other ILDs. Disease pathogenesis is not fully understood and identification and removal of the offending agents remains the cornerstone of treatment and a major determinant of prognosis. Finally, and perhaps most importantly, chronic HP should always be considered and

excluded before making a diagnosis of idiopathic fibrotic ILD.

## Future perspectives

The diagnosis of HP is often difficult and effective treatments in progressive forms are lacking. There is an urgent need for an expert consensus statement in order to improve disease definition, establish acceptable and validated diagnostic criteria, define factors that affect both the occurrence and natural history of the disease, and develop a battery of standardized and easily available antigens to be used in clinical and research settings. As with other ILDs, diagnosis and management of HP requires multidisciplinary expertise, for instance for interpreting HRCT findings and deciding whether histological confirmation of the diagnosis is needed. Occupational physicians should be part of the multilevel discussion. Novel emerging data from genomics, epigenetics, and proteomics will hopefully provide new candidate biomarkers to predict disease outcome, or drive therapeutic decisions. To this end, the establishment of multicenter collaborative networks, including tissue and imaging repository, is essential.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest related to the present study.

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